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FACULTY OF SCIENCE
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Laboratory of Organometallic Chemistry and Homogeneous Catalysis
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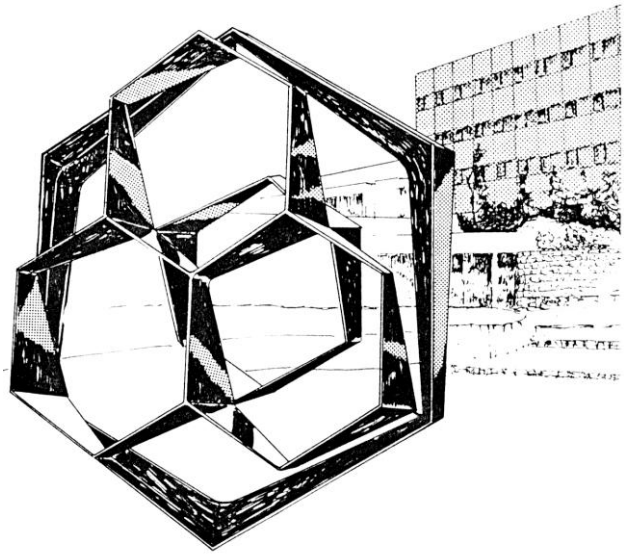
Synthesis and Characterization of N-Heterocyclic Carbene Precursors Derived from Theophylline



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Master in Chemistry

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1. Introduction

1.1. N-heterocyclic carbenes (NHCs)

N-heterocyclic carbenes (NHCs) are ubiquitous ligands in organometallic chemistry and homogeneous catalysis. These species are neutral (generally five-membered) heterocycles[1] bearing a divalent carbene center connected directly to at least one nitrogen atom within the ring structure.[2]

In 1968, Öfele first reported the existence of N-heterocyclic carbenes.[3] However, Wanzlick found that these species dimerized easily and quickly (Figure 1).[4] This behavior led him to formulate the following conclusion: NHCs are too reactive and unstable for organic synthesis! They can, however, be stabilized by transition metals and therefore be used as ligands.[1]

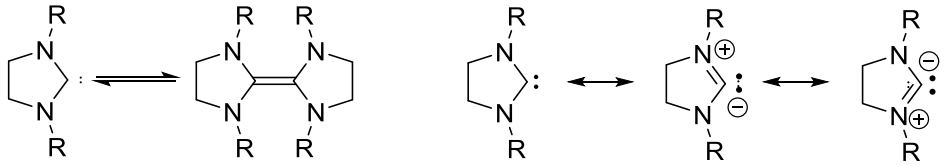


Figure 1: Wanzlick equilibrium and the resonance forms of NHCs

In 1991, Arduengo and co-workers successfully isolated and characterized the first thermodynamically and kinetically stable N-heterocyclic carbene. The "bottle-able" 1,3-di-1-adamantyl-imidazol-2-ylidene (IAd) even formed colourless crystals that could be analyzed by X-ray diffraction analysis to confirm its identity. This carbene is stable under an inert atmosphere but quickly decomposes in the presence of oxygen and moisture. Arduengo et al. obtained it by deprotonating 1,3-di-1-adamantylimidazolium chloride with sodium hydride and a catalytic amount of DMSO in THF at room temperature (Figure 2).[5]

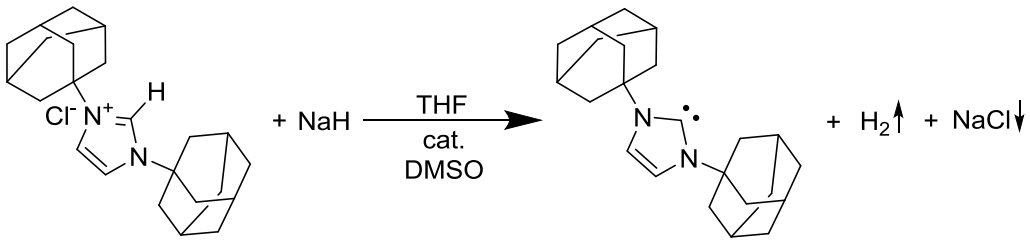


Figure 2: Synthesis of 1,3-di-1-adamantylimidazol-2-ylidene by Arduengo

The carbene obtained by this method is stable thanks to the two bulky adamantyl groups on its nitrogen atoms. In fact, these bulky groups prevent the dimerization of IAd into the corresponding olefin (Wanzlick equilibrium). In addition, an electronic stabilization of the carbene center also takes place in imidazol-2-ylidenes due to the presence of σ-electron-withdrawing and π-electron-donating nitrogen atoms next to it (Figure 3).[6] The combination of these two effects stabilizes the N-heterocyclic carbene by lowering the energy of its occupied σ-orbital with an inductive effect and by donating electron density into its empty p-orbital with a mesomeric effect. The latter effect leads to

different forms of resonance in which the positive charge is delocalized on the imidazole ring. Hence, the C^2 carbon atom depicted in Figure 3 is stabilized and therefore reactive.

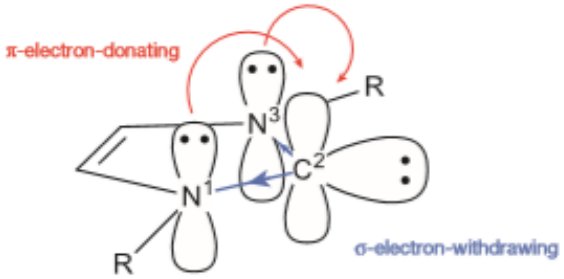


Figure 3: Ground-state electronic structure of imidazole-2-ylidenes[6]

Unlike traditional carbenes, which are electron-deficient, N-heterocyclic carbenes are electron-rich nucleophilic species due to the lone pair located in the plane of their heterocyclic ring. Their nucleophilicity and their strong σ-electron-donating properties allow NHC ligands to form stronger bonds with metal centers than most classical 2-electron donor species, such as the phosphines. Indeed, in 1993, Nolan et al. emphasized that "in general NHC ligands behave as better donors than the best phosphine donor ligands with the exception of the sterically demanding (adamantyl) carbene".[2,3]

NHCs are usually obtained by deprotonating imidazolium or imidazolinium salts with a strong base. The reaction is often carried in situ and leads to the formation of imidazol-2-ylidene or imidazolin-2-ylidene scaffolds. Therefore, the azolium salts are de facto the most common stable ionic precursors of NHCs. In order to synthesize a symmetric aromatic imidazolium salt (Figure 4, equation 1), the first step consists in a condensation between glyoxal and two equivalents of an amine ($R\text{-}NH_2$). The intermediate diimine obtained is then cyclised with paraformaldehyde in the presence of trimethylsilyl chloride. In order to synthesize a symmetric imidazolinium salt (Figure 4, equation 2), the first step is the same as for the imidazolium salt but, in this case, the intermediate diimine is reduced into a diaminium salt by $NaBH_4$ in the presence of an acid (HCl). This second intermediate is treated with triethyl orthoformate and a strong base to give an imidazolinium salt.[7]

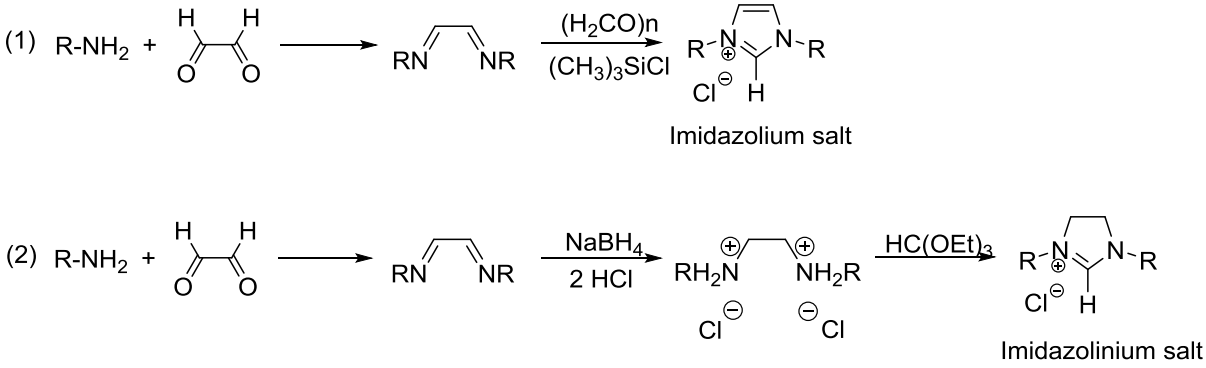


Figure 4: Synthesis of imidazolium and imidazolinium salts

Two options are available to fine-tune the electronic and steric properties of NHCs. First, the substituents on the nitrogen atoms can be modified in a symmetric ($R^1 = R^2$) or asymmetric fashion

($R^1 \neq R^2$). Second, the nature of the core heterocycle can be changed (imidazole, triazole or thiazole).[8] A library of analogous NHC ligands can therefore be prepared and studied. All these characteristics explain well why NHCs have become ubiquitous ligands in organometallic chemistry and homogeneous catalysis.

The applications of NHCs in modern chemistry may be split in three categories: (a) NHCs coordinated to transition metals, (b) NHCs coordinated to p-block elements, and (c) NHCs as organocatalysts.[6] In the Laboratory of Organometallic Chemistry and Homogeneous Catalysis, the NHC ligands are coordinated to transition metal in two different ways: (1) either directly through the carbene center or (2) through heteroatoms after they are transformed into zwitterionic adducts (neutral molecules with charge-separated forms) via a nucleophilic attack (Figure 5).[9, 10] Indeed, the NHCs are strong nucleophiles that can easily form stable zwitterions upon reaction with allenes and heteroallenes X=C=Y. The two methods lead to the formation of a complex with a transition metal. For the second approach, CS_2, a simple heteroallene, may be used as an electrophile to synthesize azolium dithiocarboxylate NHC·CS_2 adducts, which are very strong chelating ligands that bind to metals via their two sulphur atoms.[11]

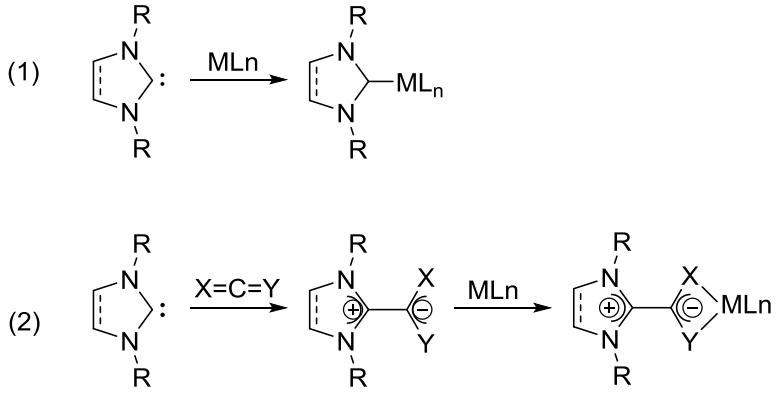


Figure 5: Possible uses of NHCs to form complexes with a transition metal

The coordination between a transition metal and a NHC ligand to form a complex is used in a wide range of applications across the chemical sciences and is illustrated in Figure 6.[6] Metal-NHC complexes usually display remarkable catalytic activities due to the strong electron donating abilities of their carbene ligands.[8] In particular, ruthenium complexes bearing NHC ligands are probably the most efficient catalysts known to date for olefin metathesis.[12] This reaction is particularly well studied in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis. Concerning the cross-coupling reactions, the catalysts used are palladium complexes bearing NHC ligands. Since gold- or silver-NHC complexes have antibacterial and anticancer properties, they are widely studied in the field of metallopharmaceuticals. Metal-organic frameworks (MOFs) are composed of metal ions coordinated to organic ligand to form a three-dimensional structure. Roland et al. synthesized well-defined MOF subunits in which metal-NHC complexes are covalently bound to the carboxylate linkers. MOFs are polymeric in nature and their use to induce selective reactions will be explored in the future.[13] In another part of this study, metal-NHC complexes are also included within polymeric materials using Pd and Pt-NHC-based coordination polymers. These porous materials can act as robust and efficient heterogeneous molecular catalysts.

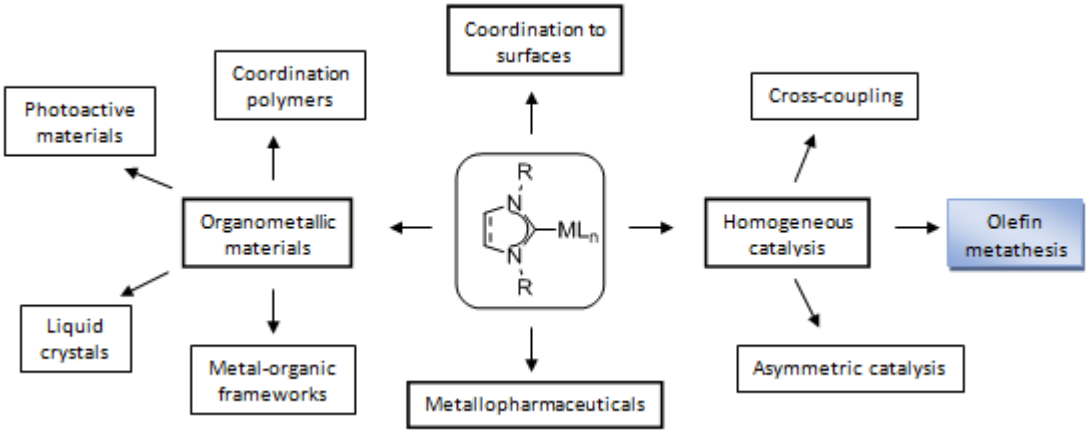


Figure 6: Applications of NHCs coordinated to transition metals[6]

1.2. Olefin metathesis

Olefin metathesis has emerged as a powerful tool for organic synthesis[14] and has been used for the manufacture of various industrial chemicals, such as petrochemicals,[15] oleochemichals,[16] polymers, and fine chemicals. It is a transition metal catalyzed reaction in which a mutual exchange of unsaturated carbon-carbon bonds takes place, as shown in Figure 7.[17] In other words, olefin metathesis is a catalytic method involving the cleavage and the formation of C=C double bonds between similar interacting chemical species. The reaction is reversible and limited to an equilibrium. Therefore, a statistical mixture of reagents and products is usually obtained, unless it is possible to drive the equilibrium toward completion.[18]

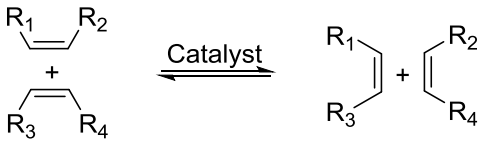


Figure 7: The principle of olefin metathesis

As in many cases in chemistry, this unexpected transformation was discovered by accident.[19] Thus, in the late 1950s, industrial chemists observed the disproportionation of olefins during the study of Ziegler-Natta polymerizations. In 1967, Calderon *et al*. first introduced the term "olefin metathesis" to describe transalkylidenation reactions.[16] The generally accepted mechanism for this reaction was postulated by Chauvin and his student Hérisson in 1971. In the "Chauvin mechanism", olefin metathesis proceeds by a [2+2] cycloaddition between the olefin and a metal carbene complex to form a metallacyclobutane intermediate (Figure 8). This intermediate subsequently reverts to the initiating species or is cleaved into ethylene and a new metal alkylidene. The latter reacts with a new alkene molecule to yield another metallacyclobutane intermediate, which can decompose into the metathesis product and the initial metal carbene. This reversible process leads to a thermodynamic equilibrium between the reagents and the products but if ethylene is removed, the reaction is shifted toward the products.[12]

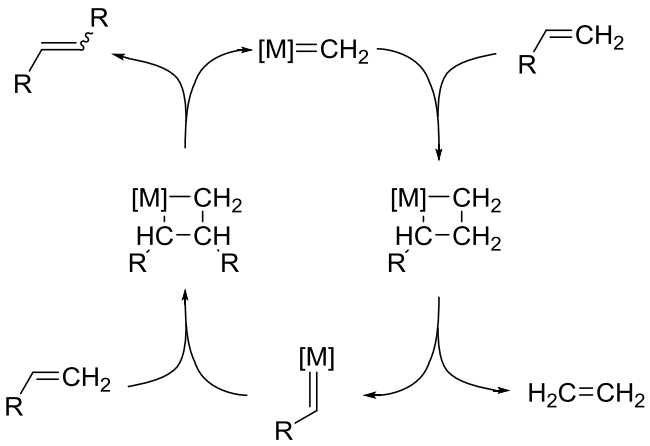


Figure 8: Mechanism of metathesis proposed by Chauvin

Following the seminal discovery by Chauvin and Hérisson that metal carbene species should be efficient catalysts for olefin metathesis, many scientists synthesized transition metal complexes bearing alkylidene fragments to probe their catalytic activity. Ruthenium-based compounds quickly emerged as promising candidates for these transformations. Furthermore, these complexes have a reasonable stability against oxygen, water and impurities in the solvent compared to other species based on early transition metals, such as molybdenum or tungsten.[18]

The first well-defined ruthenium-alkylidene catalyst for olefin metathesis was reported by Grubbs and co-workers in 1991 (Figure 9a). However, this complex was poorly active and only polymerized strained cycloolefins such as norbornene. In the second complex (Figure 9b), the two triphenylphosphine ligands (PPh_3) are replaced by two tricyclohexylphosphine ligands (PCy_3). The latter trialkylphosphine is more electron-donating than a triarylphosphine, that is why this complex is a much more efficient metathesis promoter. The complex $RuCl_2(=CHPh)(PCy_3)_2$ is referred to as the first generation Grubbs catalyst. When, in complex b, one PCy_3 ligand is substituted by an N-heterocyclic carbene (a better σ-donor than the phosphine) the activity and the stability of the complex increase. This modification leads to the second-generation Grubbs catalyst (Figure 9c). The last complex (Figure 9d) contains a chelating oxygen. This oxygen stabilizes the complex compared to those of Grubbs. This complex is known as the second-generation Hoveyda-Grubbs catalyst.[16, 19]

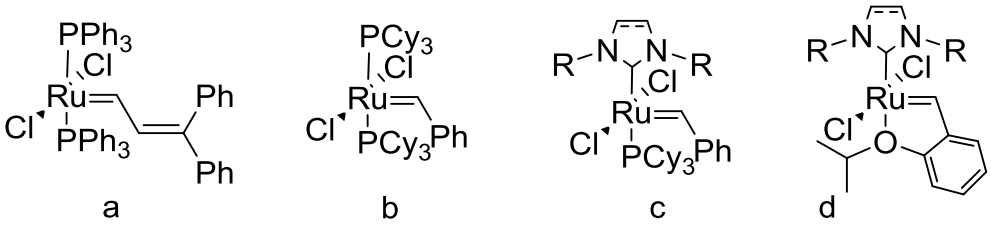


Figure 9: Common well-defined, ruthenium-based olefin metathesis catalysts

Depending on the type of olefinic reagents used as starting materials and on the outcome of the reaction, several types of olefin metathesis reactions have been defined. They include cross-metathesis (CM), ring-closing metathesis (RCM), ring-opening cross-metathesis (ROCM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis polymerization (ADMET) (Figure 10).[16]

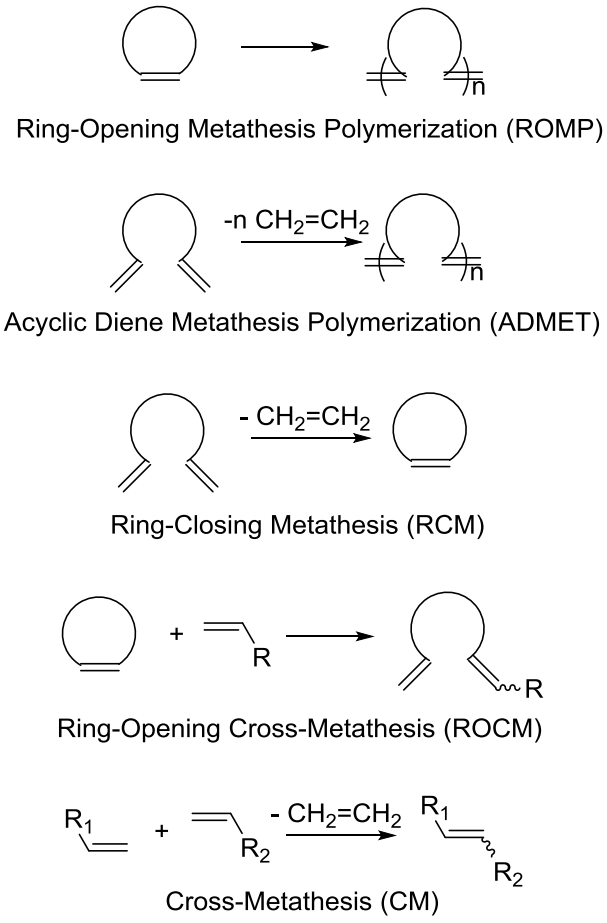


Figure 10: Different types of olefin metathesis reactions[12]

Recently, green chemistry and the synthesis of non-symmetrical NHC ligands have received a sustained attention from the scientific community. Sustainable chemistry is an emerging area of chemistry and chemical engineering. It focussed on the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry is based on 12 principles that must be respected as much as possible (Table 1).[20]

Table 1: 12 principles of green chemistry

Principles	Meaning
Prevention	It is better to prevent waste than to treat or clean up waste after it has been created.
Atom economy	Synthetic method should be designed to maximize incorporation of all materials used in the process into the final product.
Less hazardous chemical synthesis	Wherever practicable, synthetic method should be design to use and generate substances that possess little or no toxicity to human health and the environment.
Designing safer chemicals	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
Safer solvents and auxiliaries	The use of auxiliary substances should be made unnecessary wherever possible and, innocuous when used.
Design for energy efficiency	Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic method should be conducted at ambient temperature and pressure.
Use of renewable feedstock	A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
Reduce derivatives	Unnecessary derivatization should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
Catalysis	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
Design for degradation	Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
Real-time analysis for pollution prevention	Analytical methodologies need to be further developed to allow for real-time, in process monitoring and control prior to the formation of hazardous substances.
Inherently safer chemistry for accident prevention	Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

On one hand, green chemistry is becoming increasingly important in all the fields of chemistry. Natural seed oils and their ester derivatives are attractive bioresources due to their low cost and availability. Olefin metathesis can be used in the refining of plant oils.[15, 21] On the other hand, the synthesis of ruthenium catalysts bearing non-symmetrical NHC has become a hot topic in research.[22] These catalysts have a high activity and selectivity in olefin metathesis. This principle is used in Z-selective cross-metathesis [23] and ethenolysis which is a cross-metathesis of ethylene.[14, 21]

1.3. Theophylline as a precursor of N-heterocyclic carbenes

1.3.1. Generalities

Theophylline, which is also known as 1,3-dimethylxanthine, is a natural alkaloid with the molecular formula $C_7H_8N_4O_2$. This molecule belongs to the xanthine family and is closely related to caffeine and theobromine. The three compounds are called methylxanthines (Figure 11a). According to IUPAC rules, the numbers assigned to the various positions of these heterocycles are determined by first counting the atoms of the 6-membered ring with the number 1 corresponding to the nitrogen between the two carbonyl groups. The numbers then increase toward the second nitrogen atom. The last remaining numbers are added for the 5-membered ring, with the number 7 assigned to the nitrogen atom close to carbon 5 and then increasing until 9. Xanthine derivatives are neutral products and contain two types of rings: a 5-membered imidazole ring and a 6-membered pyrimidinedione ring (Figure 11b).[24] These bicyclic compounds are part of a larger family called purines. A purine consists of a pyrimidine ring fused with an imidazole ring (Figure 11c). Xanthines have two carbonyl groups added on the pyrimidine ring of purine to form the pyrimidinedione ring. Therefore, caffeine, theophylline and theobromine are purine bases.

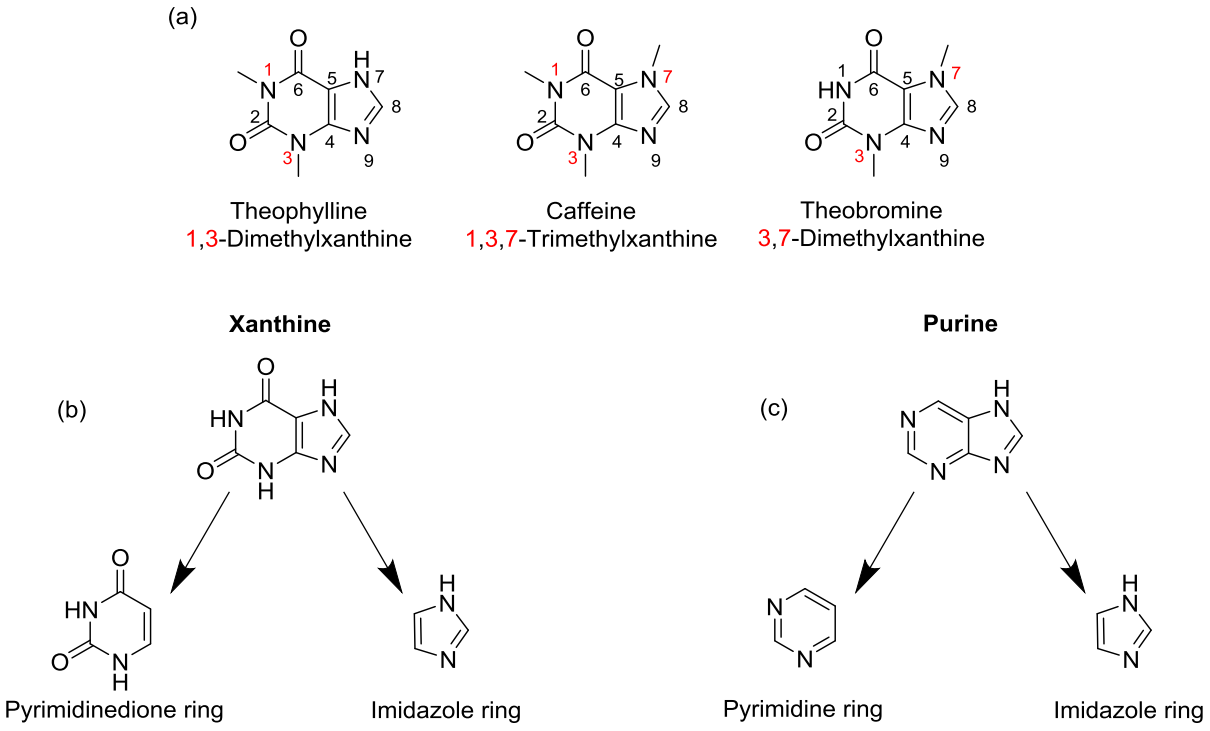


Figure 11: (a) Structures of three xanthine derivatives, (b) Structure of xanthine with its pyrimidinedione and imidazole rings, (c) Structure of purine with its pyrimidine and imidazole rings

Theophylline is widely available from a diverse range of sustainable agricultural products (tea leaves, cocoa beans, etc) (Figure 12). Tea leaves contain three alkaloids: caffeine, theophylline and theobromine. Caffeine represents approximately 6.2% of the dry matter of tea leaves, while their theobromine content varies between 0.01 and 0.26%, and theophylline represents 0.01 to 0.15%.[25] For cocoa beans, the caffeine content is 0.6% in the raw powder. Theobromine is present in a 4.2% proportion and theophylline at 0.02%.[26] In both cases, caffeine is present in greater quantity than theophylline. The extraction of methylxanthines from tea leaves or coffee beans can be achieved using supercritical CO_2 and a high-pressure system. Liquid CO_2 is pumped until the specified extraction pressure is reached at a given temperature. The supercritical fluid is depressurized after a 3 h period to reach equilibrium, while pressure is maintained constant is the extractor. This leads to a precipitated fraction, which is collected in a flask placed in a cooling bath.[27] After this extraction, theophylline can be separated from caffeine on an anion exchange column. The column is first loaded with an alkaline solution in order to adsorb theophylline and caffeine. It is then treated with a diluted acid solution (HCl) for the theophylline elution. Caffeine can be eluted by lowering the pH of the eluent. This method is used because theophylline has an acidic proton unlike caffeine which has a methyl group. Therefore, a quantitative extraction of theophylline can be accomplished.[28] The annual production of theophylline is estimated between 1 and 10 tons.[29] The theophylline used in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis was purchased from TCI at a price of 60 euros for 500 g.[30]

Figure 12: Two natural sources of theophylline: tea leaves (left) and cocoa beans (right)

Although, it has a low toxicity, theophylline is a biologically active substance that is used in medicine for the therapy of respiratory diseases, such as asthma.[31] Indeed, theophylline has bronchodilator properties causing the relaxation of smooth bronchial muscles. However, many side effects are present (tachycardia, tremor, nausea, vomiting, etc).

In coordination chemistry, theophylline has been sporadically used as a ligand. Research into theophylline complexes shows that this purine based is mostly bonded to the metal ions via its N7 atom, although it can also act as a bidentate ligand, in which N7 and O6 atoms are bonded to the metal (Ni(II), Cu(II) or Co(II)) via an N7/O6 chelation. This type of complexes has been tested for antibacterial applications.[32] Another study reports the synthesis of complexes using mixed ligands (theophylline, nicotinamide and thiocyanate). In this case, theophylline is bonded to the metal ions

(Ni(II), Cu(II) or Co(II)) via its N9 atom to form mixed ligand complexes, which have antimicrobial and antioxidant activities.[33]

Why not use theophylline in the field of N-heterocyclic carbenes? Indeed, its low toxicity and its great availability make theophylline an interesting substrate for synthetic applications. In addition, its structure can be associated with that of an NHC.

The synthesis of N-heterocyclic carbene precursors illustrated in Figure 4[7] uses various non-renewable reagents and several steps. It does not comply with the principles of green chemistry. Furthermore, most NHCs obtained through these reactions are symmetrical. In this context, the use of theophylline as a starting material is attractive for several reasons. First, this natural alkaloid is a substrate of choice thanks to its large availability and low cost of extraction. Second, a comparison between the structures of an NHC and theophylline shows that the latter alkaloid also contains heterocyclic rings with two nitrogen atoms encompassing a potential carbene center (Figure 13a). Indeed, it is possible to transform a xanthine derivative into an imidazolium salt (via its 5-membered cycle) or into a hypoxanthinium salt (via its 6-membered ring) (Figure 13b).[34] In this work, we shall focus only on functionalizing the 5-membered ring of theophylline. Third, some substituents can be added on the N7 and N9 nitrogen atoms of theophylline, which leads to symmetrical or non-symmetrical salts.[24,35] In the previous sentence, symmetrical means with the same substituents on the N7 and N9 and non-symmetrical means with two different substituents. It should be pointed out, however, that the whole molecule of theophylline is not symmetrical due to its pyrimidinedione ring. This lack of symmetry can modify the properties of the complex with a transition metal.

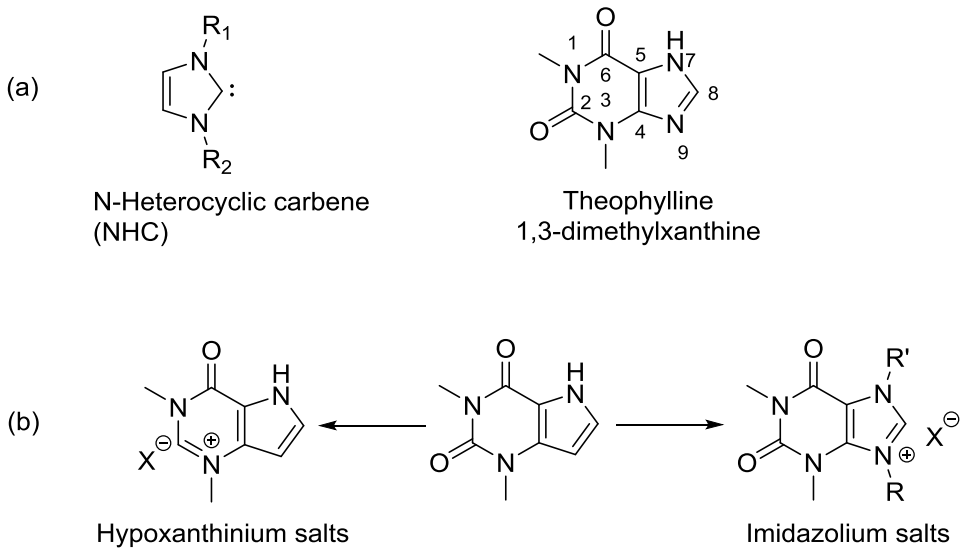


Figure 13: (a) Structure of an imidazol-2-ylidene carbene and of theophylline; (b) Hypoxanthinium and imidazolium salts derived from theophylline

1.3.2. Alkylation of theophylline on its N7 and N9 positions

An ongoing study carried out in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis aims at introducing various alkyl groups on the N7 and N9 atoms of theophylline to synthesize a small library of non-symmetrical dialkylimidazolium salts. The NHCs derived from these precursors will be tested as ancillary ligands on various transition metal complexes to develop new

families of homogeneous catalysts. The strategy adopted in this study to prepare imidazolium salts derived from theophylline is depicted in Figure 14.

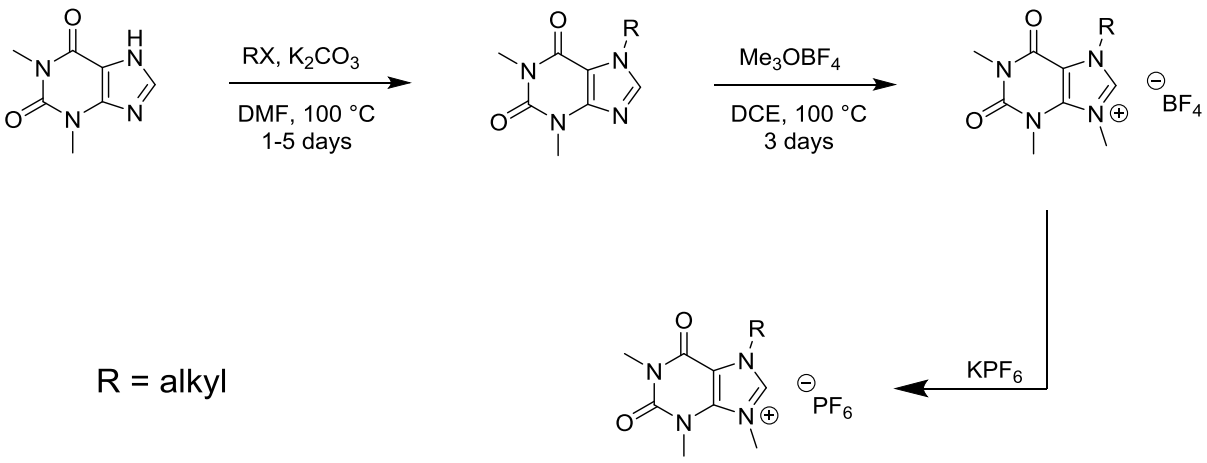
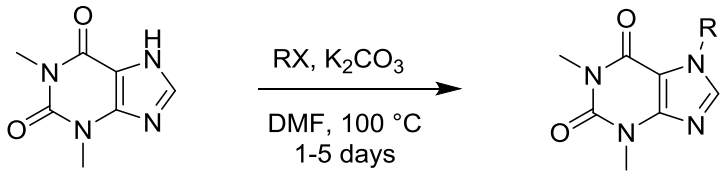


Figure 14: Strategy to obtain pure imidazolium salts derived from theophylline

The first step consists in the alkylation of theophylline on its N7 position with an alkyl halide in the presence of potassium carbonate K_2CO_3 using standard experimental conditions for this type of nucleophilic substitution: heating at 100 °C in *N,N*-dimethylformamide. Eleven alkylating agents were employed to afford the corresponding 7-alkyl-1,3-dimethylxanthine derivatives in moderate to good yields (Table 2). Cyclohexyl bromide, which is bulky and less activated, did not react at all. Surprisingly, triphenylmethyl bromide (trityl bromide) also failed to react under these conditions.[36]

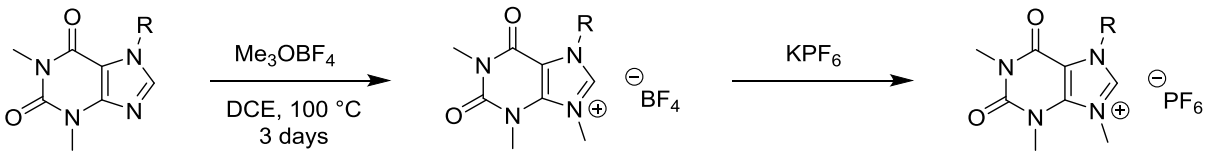
Table 2: Alkylation of theophylline on its N7 position (R = alkyl chain)



Alkyl halide	Reaction time	Temperature (°C)	Yield (%)
Ethyl iodide	17 h	35	67
Propyl iodide	24 h	100	83
Isopropyl iodide	22 h	100	34
Isobutyl iodide	48 h	100	78
Pentyl iodide	24 h	100	88
Cyclohexyl bromide	24 h	100	/
Heptyl iodide	16 h	100	50
Hexadecyl iodide	5 days	100	97
Octadecyl iodide	4.5 days	100	70
Benzyl iodide	4 h	100	87
Trityl bromide	24 h	100	/

The second step is the methylation of these alkylated intermediates on their N9 position using trimethyloxonium tetrafluoroborate, Me_3OBF_4, in dichloroethane at 100 °C for three days in order to synthesise 7-alkyl-1,3,9-trimethylxanthinium salts. Despite the fact that this strong alkylating agent was introduced in excess (2.5 equivalents) and that ample time was allowed for the reaction to proceed (3 days), unreacted 7-alkyl-1,3-dimethylxanthine was still present along with the desired tetrafluoroborate salts in most cases. It was therefore necessary to purify these compounds. This was accomplished by selective precipitation of the hexafluorophosphate salts upon addition of aqueous KPF_6. Yields comprised between 44 and 82% were achieved, depending on the group on N7. However, the reaction did not work with the hexadecyl and octadecyl groups. Due to the presence of long hydrophobic alkyl chains, these salts were not very soluble in water and it was quite difficult to achieve a selective precipitation in this solvent (Table 3).[36]

Table 3: Methylation of 7-alkyl-1,3-dimethylxanthine on its N9 position (R = alkyl chain)



N7 substituent	Reaction time	Temperature (°C)	Yield (%)
Ethyl	3 days	100	44
Propyl	3 days	100	49
Isopropyl	3 days	100	46
Isobutyl	3 days	100	82
Pentyl	3 days	100	82
Heptyl	3 days	100	57
Hexadecyl	3 days	100	/
Octadecyl	3 days	100	/
Benzyl	3 days	100	44
3-Phenylpropyl	3 days	100	/

1.3.3. Ethylation of 7-alkyl-1,3-dimethylxanthine on its N9 position

Another reaction carried out in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis aims at introducing an ethyl substituent on the N9 position of 1,3,7-trimethylxanthine. The reaction leads to 9-ethyl-1,3,7-trimethylxanthinium hexafluorophosphate (Figure 15). This product was obtained by adding to caffeine, two equivalents of triethyloxonium tetrafluoroborate, Et_3OBF_4, in dichloroethane. The reaction mixture was heated at 100 °C during 3 days. However, unreacted caffeine was still present. Therefore, a purification step was needed. This was accomplished by selective precipitation of the hexafluorophosphate salts upon addition of aqueous KPF_6. The yield obtained for this reaction is 45 %.[36]

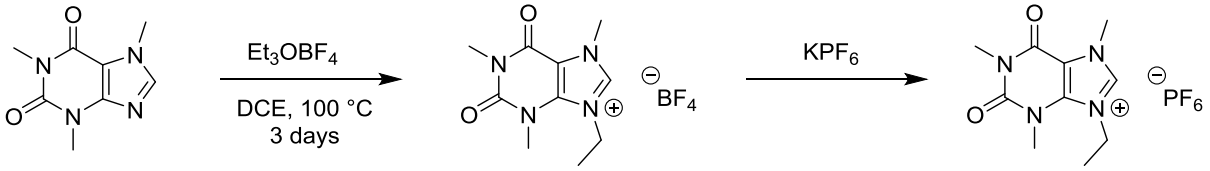


Figure 15: Ethylation of 1,3,7-trimethylxanthine on its N9 position

1.3.4. Arylation of theophylline

The arylation of theophylline has already been described in the literature for preparing 7-(4-methoxyphenyl)-1,3-dimethylxanthine (Figure 16a) and 1,3-dimethyl-7-phenylxanthine (Figure 16b).[24, 37] The common point between these two syntheses is the use of a copper catalyst. Thus, the synthesis of 7-(4methoxyphenyl)-1,3-dimethylxanthine was described in 2010 to ultimately prepare a kinase inhibitor. In this case, theophylline reacts with 4-methoxyphenylboronic acid in CH_2Cl_2 at 40 °C for 24 h in the presence of copper(II) acetate and two equivalents of pyridine (the base). The yield of this reaction is 60%. The synthesis of 1,3-dimethyl-7-phenylxanthine was carried out in 2014 to convert this product into an NHC ligand that was used to prepare copper, palladium, silver, and gold complexes. These complexes have antimicrobial and antitumour activities. The key step is an Ullmann coupling in which theophylline, 2-isobutyrylcyclohexanone, Cs_2CO_3 and copper(I) iodide were placed in a Schlenk flask and degassed. Anhydrous dimethylsulfoxide and iodobenzene were added and the mixture was heated at 130 °C for 24 h. The product was isolated in 34% yield.

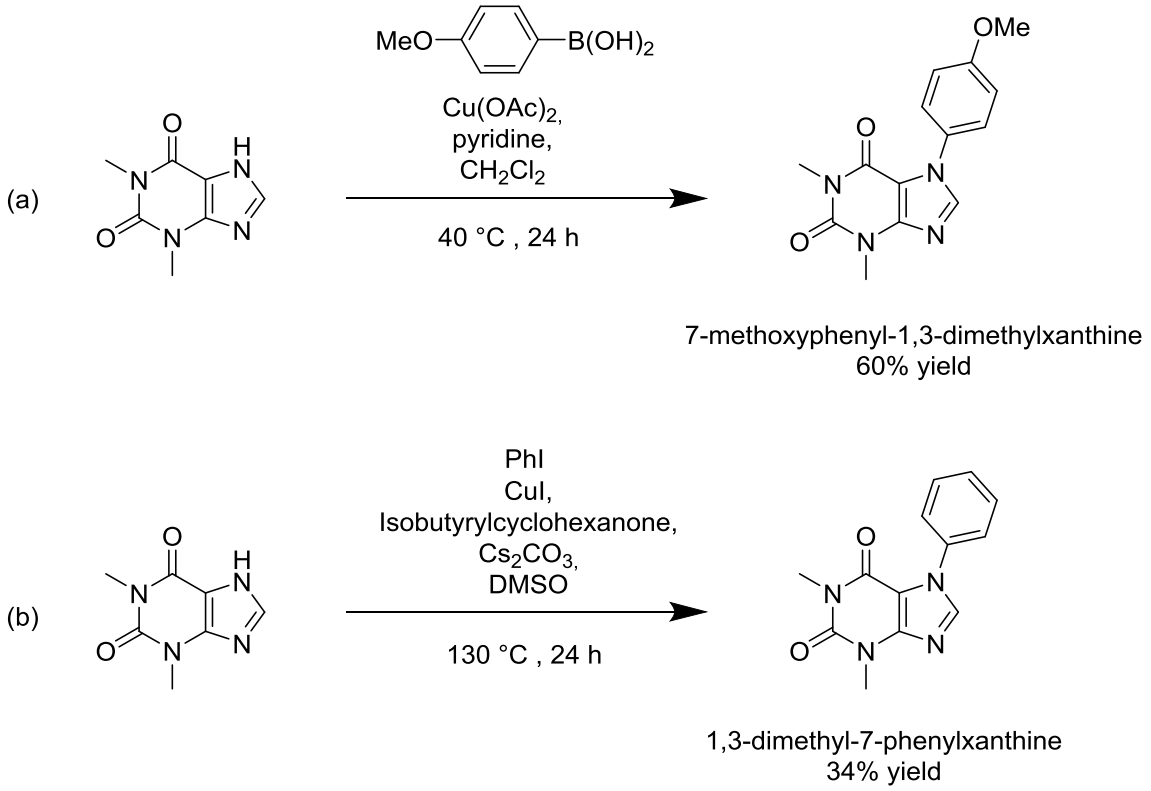


Figure 16: Synthesis of 7-(4-methoxyphenyl)-1,3-dimethylxanthine and 1,3-dimethyl-7-phenylxanthine

In 2014, Larsen *et al.* reported the first coupling of theophylline with an aryl bromide using a copper catalyst like in the two previous methods. In a reaction tube, CuBr, a ligand, sodium ascorbate, theophylline and KOH were added with a magnetic stirring bar. The tube was sealed with a rubber septum, evacuated and back-filled three times with nitrogen. Then DMF/H_2O (4:1) and PhBr were added with a syringe. The mixture was heated to 120 °C for 2 days. After work-up, the crude product was purified by column chromatography to afford pure 1,3-dimethyl-7-phenylxanthine (Figure 17). The yield of this reaction was 78%, which is good for an organic synthesis. However, the synthesis of the ligand is quite expensive.[38,39]

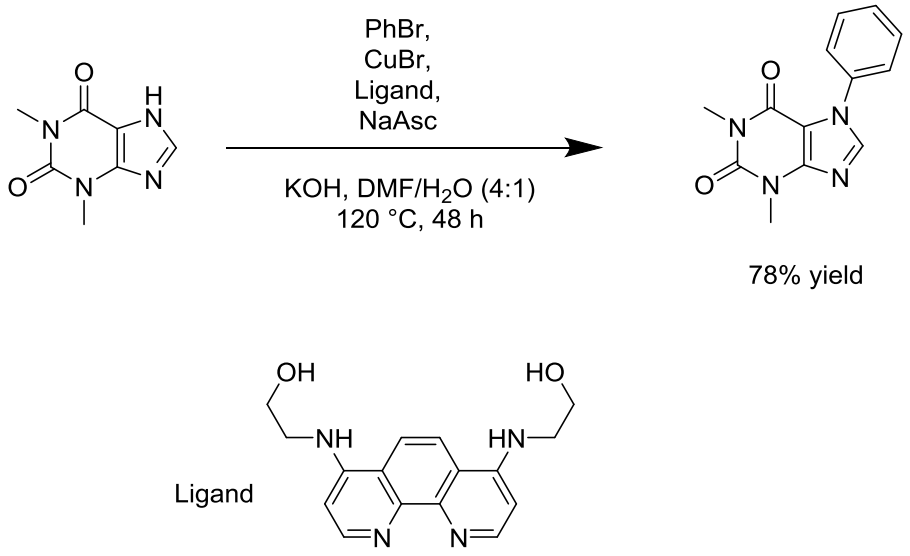


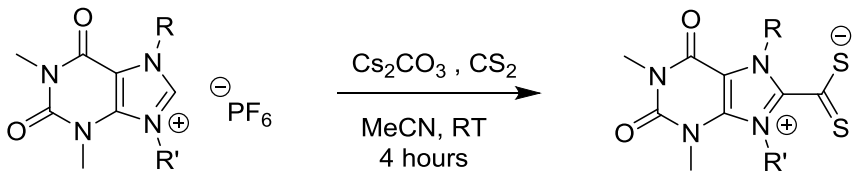
Figure 17: Synthesis of 1,3-dimethyl-7-phenylxanthine with an aryl bromide

The arylation of theophylline is not a widely discussed topic in the literature. However, the three methods presented above deal with this topic and seem simple to reproduce in our laboratory. The products obtained are pure and the yields vary from medium (34%) to good (60 and 78%).

1.3.5. Synthesis of NHC·CS_2 zwitterions derived from 7-alkyl-1,3-dimethyl-xanthine

An ongoing study carried out in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis aims at synthesizing dithiocarboxylate zwitterions starting from different xanthinium salts. Two compounds derived from caffeine and five from theophylline (cf. Table 2) were already obtained by mixing the imidazolium salt with 1.5 equivalents of cesium carbonate, Cs_2CO_3, which is a soft base. Acetonitrile, MeCN, and carbon disulfide, CS_2 (10 equiv.), are then added quickly to form a suspension, which is stirred for 4 h at room temperature. After an aqueous work-up to remove the inorganic salts, the desired NHC·CS_2 betaines were obtained in acceptable yields (Table 4).[36]

Table 4: Synthesis of NHC·CS_2 zwitterions (R = alkyl chain, R' = methyl or ethyl group)



N7/N9 substituent	Reaction time	Temperature (°C)	Yield (%)
Methyl/Methyl	4 h	RT	59
Methyl/Ethyl	4 h	RT	31
Ethyl/Methyl	4 h	RT	18
Propyl/Methyl	4 h	RT	59
Isopropyl/Methyl	4 h	RT	46
Isobutyl/Methyl	4 h	RT	49
Benzyl/Methyl	4 h	RT	68

2. Objectives and strategies

The first objective of our research project consists in the synthesis of non-symmetrical imidazolium salts derived from theophylline by adding various aryl substituents on its N7 position and an alkyl substituent on its N9 atom. In this context, non-symmetrical means that two different substituents are added on N7 and N9. This would lead to new NHC ligand precursors for the synthesis of second-generation ruthenium catalysts that could be used for promoting various types of olefin metathesis reactions.

Our strategy to achieve this goal will consist in arylating theophylline on its N7 position, using different reagents (ArX) and catalytic systems described in the literature to build up a small library of 7-aryl-1,3-dimethylxanthine derivatives (Figure 18). Next, these 7-aryl-1,3-dimethylxanthine derivatives will be alkylated (RX) on their N9 position to yield mixed alkyl,aryl-imidazolium salts. The alkylation is limited to a methylation or an ethylation based on the reactions already performed in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis.[36] This step leads to 7-aryl-1,3,9-trimethylxanthinium salts in case of a methylation or 7-aryl-9-ethyl-1,3-dimethylxanthiunium salt for the ethylation.

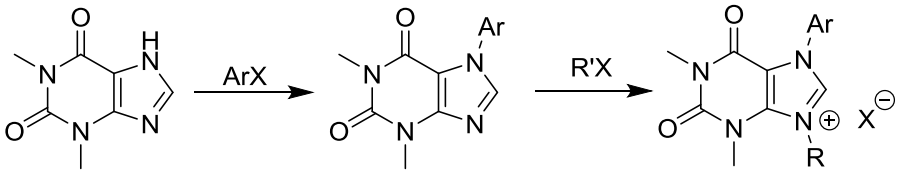


Figure 18: Synthesis of 7-aryl-1,3,9-trimethylxanthinium salts or 7-aryl-9-ethyl-1,3-dimethylxanthiunium salts, where Ar is an aryl substituent and R is methyl or ethyl group

The second objective of our research project consists in the synthesis of dithiocarboxylate inner salts based on the reactions already performed in the laboratory.[36] To carry out this step, the mixed alkyl,aryl-imidazolium salts will be converted into NHC·CS_2 zwitterions upon reaction with carbon disulfide and a base under mild aerobic conditions (Figure 19). The dithiocarboxylate inner salts obtained are expected to behave as strong chelating ligands that bind to metals via their two sulphur atoms.

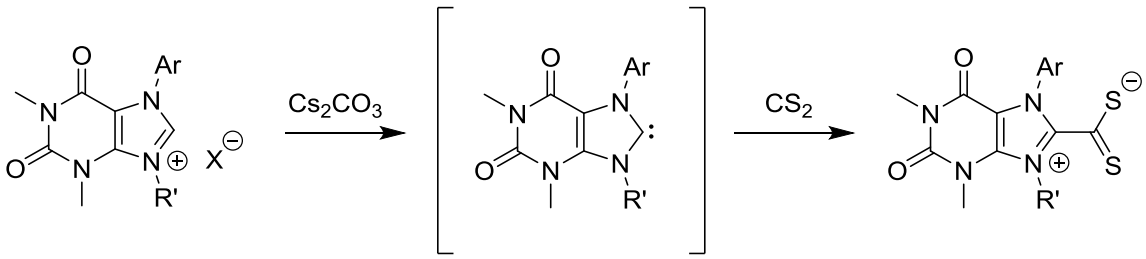


Figure 19: Synthesis of imidazolium dithiocarboxylate zwitterions from xanthinium salts

A final and third objective of this research consists in the synthesis of ruthenium-arene complexes bearing the chelating NHC·CS_2 ligands. Such a reaction can be easily accomplished upon cleavage of the $[RuCl_2(p\text{-cymene})]_2$ dimer with one equivalent of zwitterions (Figure 20).

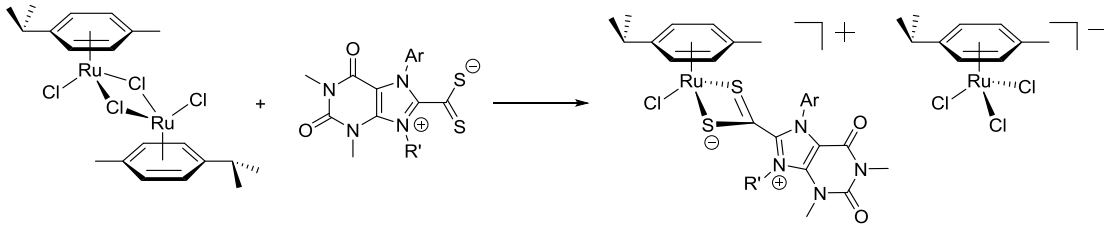


Figure 20: Syntheses of ruthenium-arene complexes with NHC·CS_2 ligand

3. Results and discussion

3.1. Synthesis of imidazolium salts derived from theophylline

The basis of this research relies on the study carried out in the Laboratory of Organometallic Chemistry and Homogeneous Catalysis to introduce various alkyl groups on the N7 and N9 atoms of theophylline in order to synthesize a small library of non-symmetrical dialkylimidazolium salts. To continue in this way, we decided to focus on grafting various aryl substituents on the N7 position and an alkyl on the N9 atom of theophylline. This strategy leads to the synthesis of non-symmetrical alkyl,arylimidazolium salts. More specifically, in this project, four aryl substituents were used: 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl (mesityl), and 2,6-diisopropylphenyl groups.

For a practical point of view, our revised strategy to obtain mixed alkyl,arylimidazolium salts derived from theophylline can be split in two steps (Figure 21). First, we have to arylate regioselectively theophylline on its N7 position using a metal cross-coupling reaction to form the C–N bond. Second, we need to achieve a methylation or an ethylation of the arylated intermediate on its N9 position using the commercially available, highly electrophilic trimethyloxonium or triethyloxonium tetrafluoroborate salts Me_3OBF_4 or Et_3OBF_4. This step can also be carried out with other alkylating agents, such as iodomethane (CH_3I) or iodoethane (CH_3CH_2I), in which case the counter ion will be I^-.

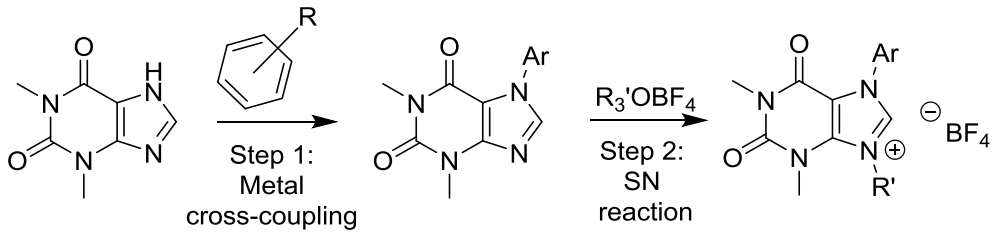


Figure 21: Strategy to obtain mixed alkyl,arylimidazolium salts derived from theophylline

In the next subsections, we shall present step by step the experimental results that we have obtained for the synthesis of imidazolium salts derived from theophylline according to the strategy outlined above.

3.1.1. Arylation of theophylline on its N7 position

Our initial attempts to arylate theophylline on its N7 position involved a Buchwald-Hartwig coupling. The first test aimed at coupling theophylline and bromobenzene. The procedure consisted in adding theophylline, palladium(II) acetate, triphenylphosphine , sodium *tert*-butoxide and bromobenzene in a Schlenk tube. The solvent used was toluene and the mixture was heated at 80 °C during 20 h (Figure 22).[40]

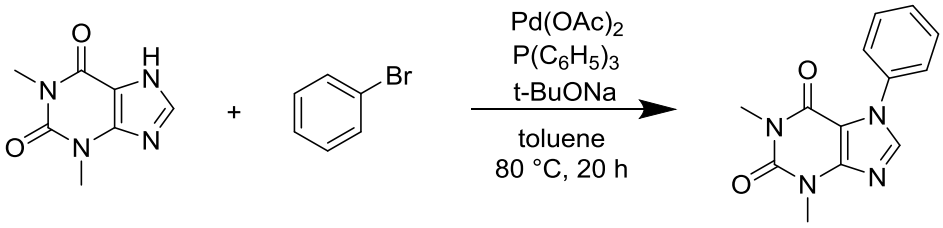
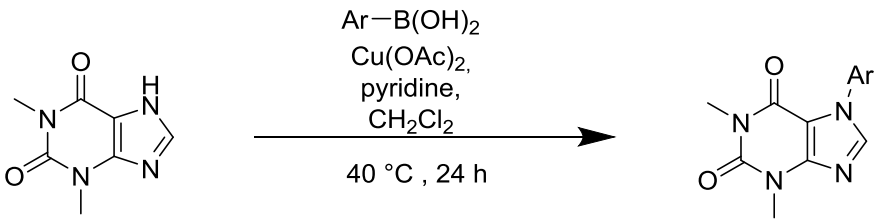


Figure 22: Buchwald-Hartwig coupling to synthesize 1,3-dimethyl-7-phenylxanthine

Several reactions were performed, but the 1,3-dimethyl-7-phenylxanthine product always contained a lot of impurities. Thus, some modifications were applied to the original procedure in order to improve the purity of the product.
We replaced the solvent toluene by acetonitrile, CH_3CN and we used 10 mol% of $Pd(OAc)_2$ instead of 5 mol%. However, a TLC showed that the reaction did not take place because the reagents were present after heating. We also kept toluene as the solvent and we replaced the base *t*-BuONa with cesium carbonate, Cs_2CO_3, while using 10 mol% of $Pd(OAc)_2$. After work-up, a yellow solid was obtained but it was impure.
Another base, potassium carbonate, K_2CO_3 was used. However, the result was the same as with Cs_2CO_3. We also changed the reaction temperature by lowering it to 40 °C or increasing it to 120 °C. However, the ^{1}H NMR analyses did not show the presence of the product. The last test consisted in keeping all the original conditions except for the quantity of catalyst, which was significantly increased (20 mol%). Unfortunately, the result was the same as for the other tests. With this Buchwald-Hartwig coupling, the pure product could never be isolated. Therefore, another method had to be developed.

The first step of the new procedure consisted in a regioselective N7-arylation of theophylline with an arylboronic acid in the presence of copper(II) acetate $Cu(OAc)_2$ and pyridine using standard experimental conditions for this type of nucleophilic substitution (heating at 40 °C in dichloro-methane, CH_2Cl_2). It is a coupling reaction with a copper catalyst to form a nitrogen-carbon bond. This procedure was described by Kim et al.[37] Regarding copper(II) acetate, the anhydrous salt was replaced by the monohydrate. The product was also obtained under these conditions, which is a good thing because $Cu(OAc)_2{\cdot}H_2O$ is less expensive than $Cu(OAc)_2$. A total of four arylating agents were investigated in these experiments (Table 5). The four substituents are: 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl (mesityl), and 2,6-diisopropylphenyl groups. The purity of the products was determined by ^{1}H NMR spectroscopy. The presence of the right number of aromatic protons indicates the presence of the product.

Table 5: Copper-catalyzed arylation of theophylline on its N7 position



Entry	**Aryl substituent**	Reaction time	Temperature (°C)	Yield (%)
1	4-Methoxyphenyl	24 h	40	31
2	Phenyl	24h	40	14
3	Mesityl	24 h	40	/
4	2,6-Diisopropylphenyl	24 h	40	/

The arylation of theophylline on its N7 position with various arylboronic acid afforded quite disappointing results. As can be seen from Table 4, the reaction with 4-methoxyphenylboronic acid led to the best result with a 31% yield (Entry 1). Attempts to optimize this reaction were carried out in different ways such as: change of temperature (60 °C), change of solvent (CH_3CN, H_2O), replacement of the chromatographic column used to remove the copper salts by a treatment with ammonia to form the $Cu(NH_3)_4$ complex. However, all these trials on the 4-methoxyphenyl group led either to yields lower than 31% or to impure products.

It is noteworthy that phenylboronic acid gave a lower yield than 4-methoxyphenylboronic acid (Entry 2). This result is difficult to explain. Mesitylboronic acid and 2,6-diisopropylphenylboronic acid did not react at all (Entries 3 and 4). This might be due to the steric hindrance of mesityl and 2,6-diisopropylphenyl groups. However, the reaction with the 2,6-diisopropylphenyl group was only performed once and further testing would be required to confirm this hypothesis of steric hindrance.

A summary of our attempts to prepare some 7-aryl-1,3-dimethylxanthine derivatives by arylation of theophylline is presented in Figure 23.

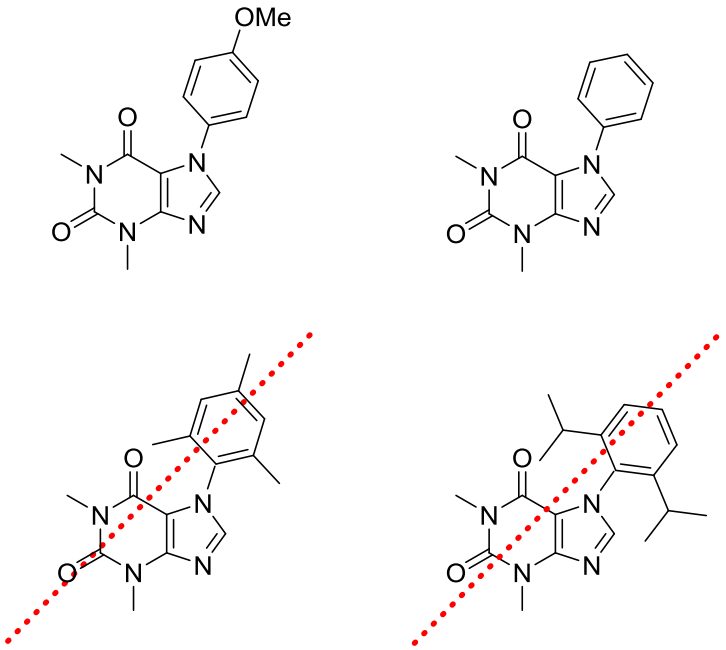


Figure 23: Structures of 7-aryl-1,3-dimethylxanthine derived from theophylline targeted in this work

The mechanism of this coupling reaction has been studied and is known. The arylation of purines has been described in the literature,[41,42] more particularly the arylation of theophylline.[37] Theil [41] and Evans[42] proposed a mechanism for the copper(II)-promoted coupling of boronic acid with phenols (Figure 24). The initial step is the transmetallation of the boronic acid residue with the copper salt. On this intermediate, the deprotonated phenol is added to the copper. A reductive elimination then follows to give the final product where the aryl group of boronic acid is transferred to the phenol. This mechanism can be used for our reaction. The phenol would then be replaced by theophylline.

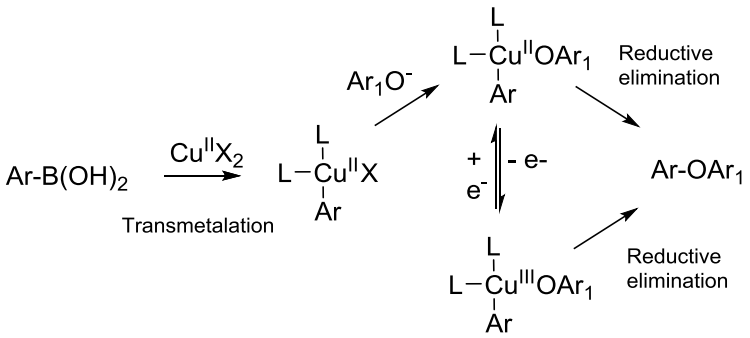


Figure 24: Mechanism proposed by Theil and Evans for the copper(II)-promoted coupling of boronic acids with phenols

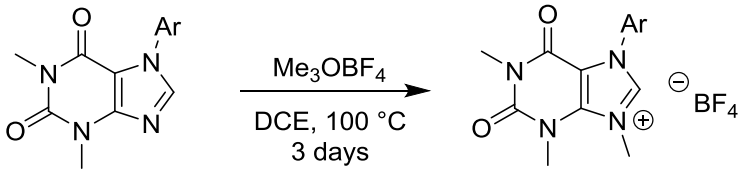
A comparison with the alkylation of theophylline on its N7 position can be done.[36] The alkylation, performed with various alkyl halides in the presence of potassium carbonate K_2CO_3 at 100 °C in DMF, afforded satisfactory results. Indeed, the yields vary between 34 and 97% (cf. Table 2). However, the arylation of theophylline on its N7 position gave much lower yields (Table 5). This difference in yields

is also explained by the use of two different methods. Indeed, when the substituent on the N7 is an alkyl chain, it is a nucleophilic substitution (S_N2), whereas when the substituent is an aryl group, it is a coupling reaction. We can conclude the coupling reaction gives poorer yields than nucleophilic substitution.

3.1.2. Methylation of 7-aryl-1,3-dimethylxanthine on their N9 position with Me_3OBF_4

The two 7-aryl-1,3-dimethylxanthine derivatives that we were able to isolate in pure form were converted into imidazolium salts by methylating them on their N9 position with trimethyloxonium tetrafluoroborate, Me_3OBF_4 (Table 6). Despite the fact that this strong alkylating agent was introduced in excess (2.5 equiv.) and that ample time was allowed for the reaction to proceed (4 days), significant amounts of unreacted reagent were still present along with the desired tetra-fluoroborate salts. It was therefore necessary to purify the products by washing them two times with dichloromethane CH_2Cl_2 and ethanol CH_3CH_2OH. Under these conditions, the product was not isolated in pure form but the purity was relatively close to 100%. Even if these two compounds are not pure, they will be used for the next step, which is the synthesis of imidazolium dithiocarboxylate zwitterions. During this reaction, the impurities present may be removed. The purity of these products was determined by ^1H NMR spectroscopy. The shift of the C8-H peak from 8 ppm, which corresponds to 7-aryl-1,3-dimethylxanthine, to 9-10 ppm indicates the presence of the salt.

Table 6: Methylation of 7-aryl-1,3-dimethylxanthines on their N9 position with Me_3OBF_4



Entry	Aryl substituent (N7)	Alkyl subsituent (N9)	Reaction time	Temperature (°C)	Purity (%)	Yield (%)
1	4-Methoxyphenyl	Methyl	3 days	100	90	53
2	Phenyl	Methyl	3 days	100	94	44

The N9-methylation of 7-aryl-1,3-dimethylxanthines with Me_3OBF_4 led to disappointing results. In fact, the products obtained could not be isolated in pure form. When the N7 substituent is a 4-methoxyphenyl group, the product isolated had a purity of 90% and a yield of 53% (Entry 1). With a phenyl ring in position 7, the product obtained had a purity of 94% and a yield of 44% (Entry 2). A recrystallization is underway to try to purify these two products. This reaction was repeated and we

were able to obtain pure 1,3,9-trimethyl-7-phenylxanthinium tetrafluoroborate but with a yield of 14% only.

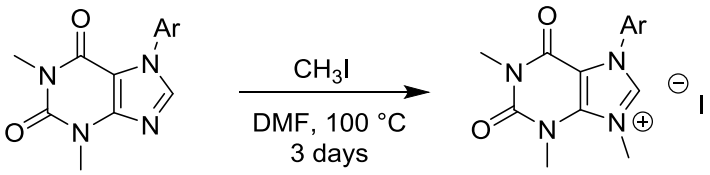
For the 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium tetrafluoroborate, the poor purity and the yield of 50% can be explained by the presence of a methoxy group. In fact, Me_3OBF_4 is a very powerful alkylating agent and can lead to the formation of an oxonium group on the aryl substituent of the molecule. This might result in a decrease in purity by the presence of by-products. The use of a less powerful alkylating agent such as iodomethane, CH_3I, could improve the purity.

A comparison of the results obtained for the methylation of 7-alkyl or 7-aryl-1,3-dimethylxanthine derivatives with Me_3OBF_4 showed a big difference.[36] With an alkyl group on position 7 of theophylline, the imidazolium salts obtained are pure and the yield varies from 44 to 82% (Table 2), whereas with an aryl group, the compounds are not pure and the yield is lower. This means that the nucleophilic substitution on the N9 is more difficult with an aryl substituent on the N7 and therefore, the electron pair on N9 is less available than with an alkyl group. This can be explained by the phenomenon of resonance. In fact, the electronic nitrogen doublet can also be delocalized in the aromatic ring present on the N7. This gives nitrogen 9 a less marked nucleophilic character. And so, the alkylation is more complicated. Attempts to improve the yield and the purity by increasing the reaction temperature (120 °C) and time (4 days) remained mostly unsuccessful.

3.1.3. Methylation of 7-aryl-1,3-dimethylxanthine on their N9 position with CH_3I

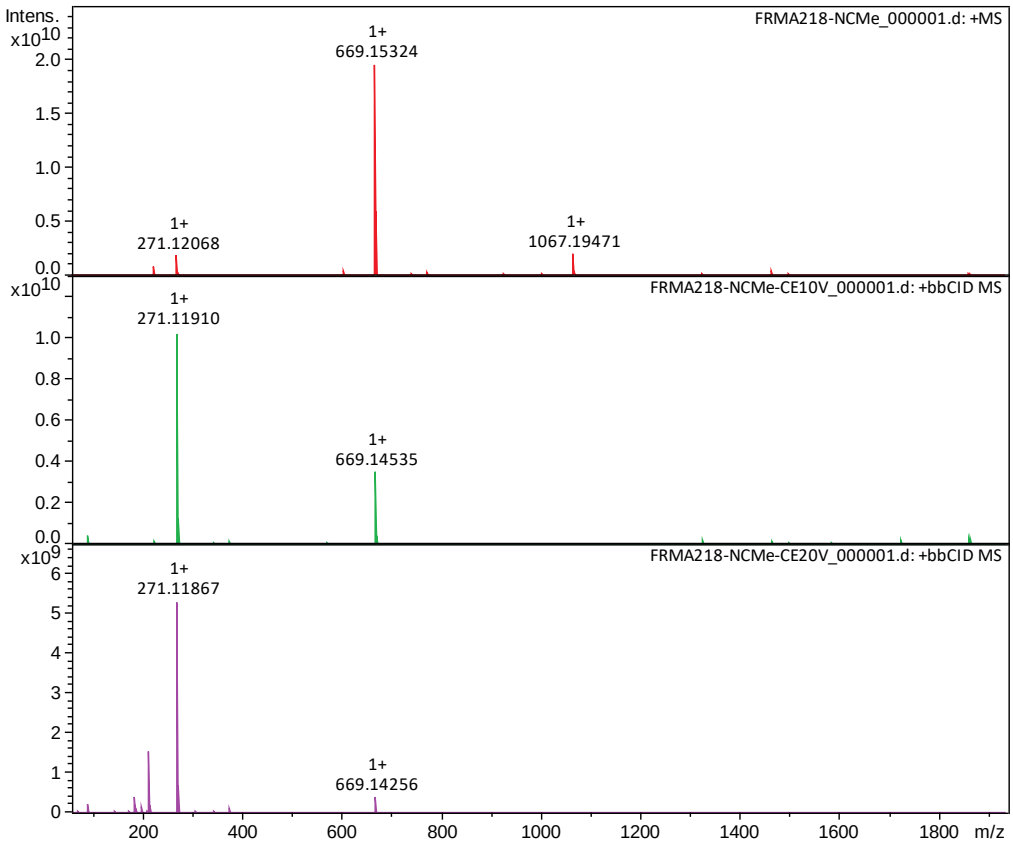
Another method to methylate 7-aryl-1,3-dimethylxanthine derivatives consists in using iodomethane as an alkylating agent. This method can lead to a pure product because CH_3I is less powerful than Me_3OBF_4. The 7-aryl-1,3,9-trimethylxanthinium iodide products were obtained by following a procedure of Luo *et al.* that involves the use of methyl iodide as the alkylating agent and *N,N*-dimethylformamide (DMF) as the solvent (Table 7).[43] The reaction mixture was heated at 100 °C for 3 days. After cooling to room temperature, ethyl acetate was added and the solution was heated to precipitate the product. The purity of these products was determined by ^1H NMR spectroscopy. The shift of the C8-H peak from 8 ppm, which corresponds to 7-aryl-1,3-dimethylxanthine, to 9-10 ppm indicates the presence of the salt.

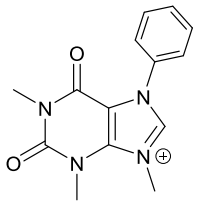
Table 7: Methylation of 7-aryl-1,3-dimethylxanthines on their N9 position with CH_3I



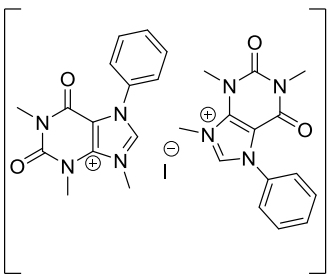
Entry	Aryl substituent (N7)	Alkyl subsituent (N9)	Reaction time	Temperature (°C)	Purity (%)	Yield (%)
1	4-Methoxyphenyl	Methyl	3 days	100	"98"	39
2	Phenyl	Methyl	3 days	100	"100"	44

This method of methylation makes it normally possible to obtain the pure products. The yields of these reactions are not excellent but remain acceptable. The desired compounds were isolated and their identity and purity were determined by ^{1}H and ^{13}C NMR spectroscopies. However, for 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium iodide, an additional methyl was detected. The presence of this additional peak is difficult to explain. Three hypotheses may be invoked: (1) the presence of an impurity present in large quantities, (2) an impurity present on the cation or (3) an impurity on the counter-ion. For 1,3,9-trimethyl-7-phenylxanthinium iodide, two additional peaks were detected (a large one, which integrates for two protons and another one, which integrated for six). In this case, a mass spectrometry analysis was carried out and a COSY spectrum was recorded (Figure 25, a and b). The mass spectrum tells us that the product is present. The different fragments were successfully identified: the peak at m/z = 271.119 corresponds to the cation. The signal at m/z = 669.143 is for two cations associated with one anion I^- and the last one at m/z = 1067.17 can be assigned to an assembly of three cations and two anions I^-. The COSY spectrum shows a correlation between the two additional peaks. One hypothesis explaining these peaks is the presence of impurities originating from the decomposition of DMF since the broad peak indicates that the two protons are carried by a heteroatom. A recrystallisation is underway to try to purify these two products. Even if these two compounds are not pure, they will be used for the next step, which is the synthesis of imidazolium dithiocarboxylate zwitterions. During this reaction, the impurities present may be removed.

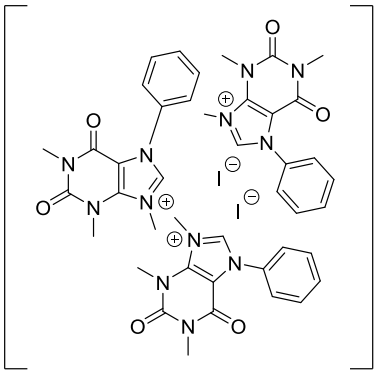




Exact Mass: 271,119



Exact Mass: 669,143



Exact Mass: 1067,17

Figure 25 a: Mass spectrum of 1,3,9-trimethyl-7-phenylxanthinium iodide with the structures of the different fragments observed

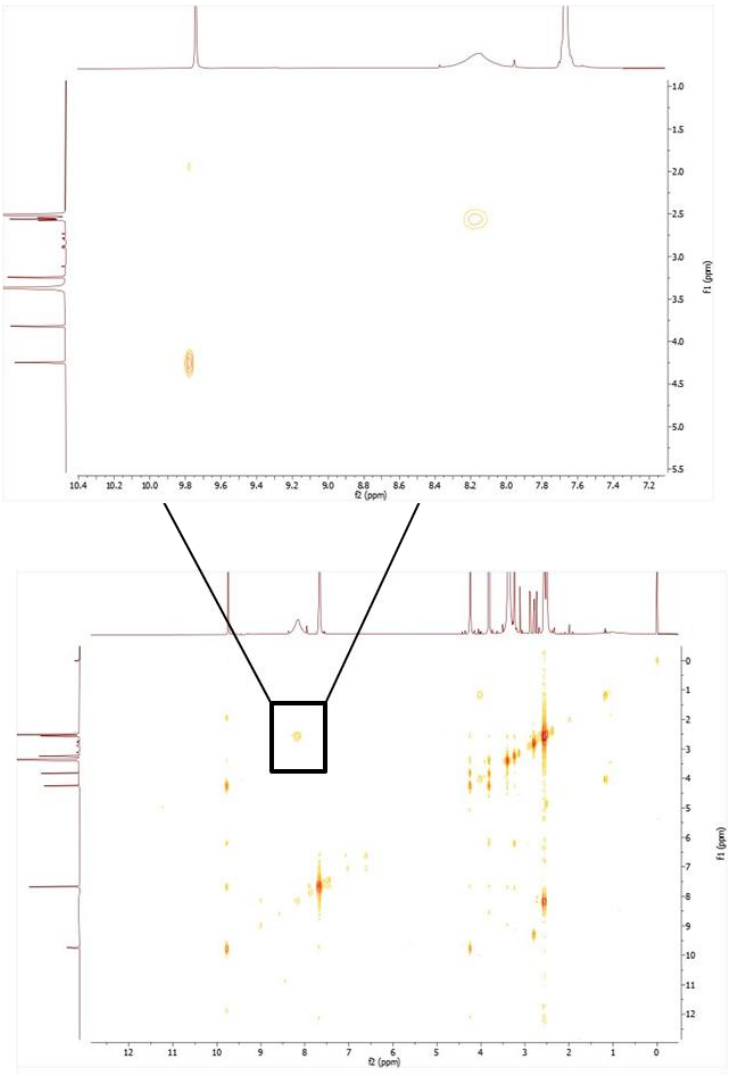


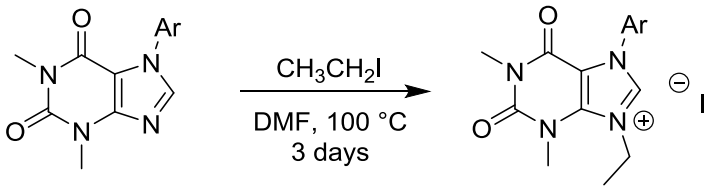
Figure 25 b: COSY spectrum of 1,3,9-trimethyl-7-phenylxanthinium iodide

A comparison between the methylation of 1,3,7-trimethylxanthine with CH_3I and our results showed a difference. With a methyl substituent on position 7 of theophylline, the imidazolium salts obtained was pure and the yield was 66%.[36] With an aryl group present on N7, the compounds are not pure and the yield is lower, 39 and 44% (Entries 1 and 2). This result can be explained by the resonance due to the aryl group on the N7, which gave to the nitrogen N9 a less marked nucleophilic character. That is why the nucleophilic substitution is more difficult to achieve.

3.1.4. Ethylation of 7-aryl-1,3-dimethylxanthine on their N9 position with CH_3CH_2I

In this section, we focus on the ethylation in position 9 of 7-aryl-1,3-dimethylxanthine derivatives. This method corresponds to the same procedure as a methylation with CH_3I. It therefore consists in using iodoethane as the alkylating agent and *N,N*-dimethylformamide (DMF) as the solvent (Table 8).[41] The reaction mixture was heated at 100 °C for 3 days. After cooling to room temperature, ethyl acetate was added and the solution was heated to precipitate the product. The purity of these products was determined by ^{1}H NMR spectroscopy. The shift of the C8-H peak from 8 ppm, which corresponds to 7-aryl-1,3-dimethylxanthine, to 9-10 ppm indicates the presence of the salt.

Table 8: Ethylation of 7-aryl-1,3-dimethylxanthines on their N9 position with CH_3CH_2I



Entry	Aryl substituent (N7)	Alkyl subsituent (N9)	Reaction time	Temperature (°C)	Purity (%)	Yield (%)
1	4-Methoxyphenyl	Ethyl	3 days	100	100	13
2	Phenyl	Ethyl	3 days	100	/	/

Although the yield obtained for 9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium iodide was low, ^{1}H and ^{13}C NMR analyses showed that the compound was pure (Entry 1). Unlike in the methylation with CH_3I, there were no additional peaks on the spectra. This low yield can be explained by the resonance and a lower nucleophilic character of N9, which made the nucleophilic substitution difficult. Furthermore, iodoethane is a less powerful alkylating agent than iodomethane. The formation of 9-ethyl-1,3-dimethyl-7-phenylxanthinium iodide was evidenced by ^{1}H NMR spectroscopy: the C_8H singlet signal around 9 ppm seemed to be present (Entry 2). However, we did not find a way to purify this product in a solvent. Therefore, it could not be isolated in pure form.

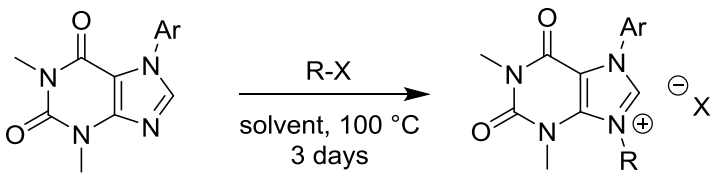
3.1.5. Comparison of the three methods used to alkylate 7-aryl-1,3-dimethyl-xanthines on their N9 position

In sections 3.1.2 to 3.1.4, we described three different methods for alkylating 7-aryl-1,3-dimethyl-xanthine derivatives into imidazolium salts. The three alkylating agents used in this project are trimethyloxonium tetrafluoroborate (Me_3OBF_4), iodomethane (CH_3I) and iodoethane (CH_3CH_2I). The

same experimental procedure was followed for iodomethane and iodoethane. A comparison between the method with Me_3OBF_4 and CH_3I/CH_3CH_2I showed the use of the same temperature (100 °C) and reaction time (3 days) (Table 9). The solvent, on the other hand, is different. It can be seen that the more powerful the alkylating agent is, the higher is the yield, but the strongest alkylating agent Me_3OBF_4 leads to the formation of by-products and therefore lowers the purity (Entries 1 and 2). Remember that the low yields are due to the less nucleophilic nature of nitrogen because of the delocalization in the cycle (on N7) of its electronic doublet. Therefore, the nucleophilic substitution is more difficult.

The two methylation methods gave rather frustrating results. In fact, the methylation with Me_3OBF_4 gave acceptable yields but impure products (Entries 1 and 2), whereas the methylation with CH_3I gave the expected products, with excess peaks on the NMR spectra. These peaks are difficult to explain and the most probable hypothesis is the presence of impurities.

Table 9: Alkylation of the N9 position of 7-aryl-1,3-dimethylxanthine under various conditions



Entry	Aryl (N7)	Alkyl (N9)	X^-	Reaction time	Temperature (°C)	Purity (%)	Yield (%)
1	4-$MeOC_6H_4$	Me	BF_4^-	3 days	100	90	53
2	Ph	Me	BF_4^-	3 days	100	94	44
3	4-$MeOC_6H_4$	Me	I^-	3 days	100	“98”	39
4	Ph	Me	I^-	3 days	100	“100”	44
5	4-$MeOC_6H_4$	Et	I^-	3 days	100	100	13
6	Ph	Et	I^-	3 days	100	/	/

A summary of all your attempts to prepare imidazolium salts by methylation or ethylation of 7-aryl-1,3-dimethylxanthine derivatives is presented on the Figure 26.

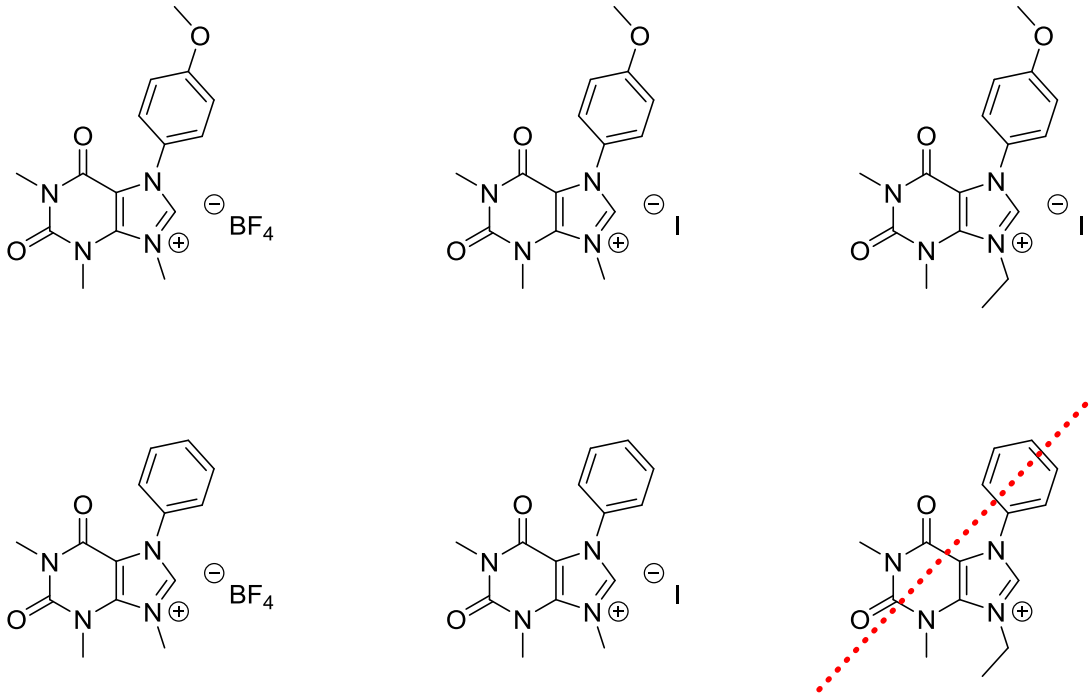


Figure 26: Structures of the imidazolium salts derived from theophylline targeted in this work

3.2. Synthesis of imidazolium dithiocarboxylate zwitterions from imidazolium salts

The second objective of our research project consists in the synthesis of dithiocarboxylate inner salts. To do that, the method successfully used with imidazolium salts bearing two alkyl groups on N7 and N9 was applied to our mixed alkyl,aryl derivatives.[36] To carry out this step, the imidazolium salts (1 equiv.) were reacted with carbon disulfide, CS_2 (10 equiv.) and a base, which is cesium carbonate, Cs_2CO_3 (1.5 equiv.) under mild aerobic conditions. The solvent was acetonitrile and the suspension was stirred for 4 hours at room temperature (Figure 27). This reaction consists of an acid-base reaction to form the carbene followed by a nucleophilic addition.

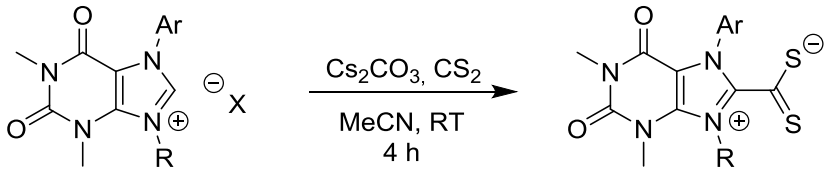


Figure 27: Synthesis of imidazolium dithiocarboxylate zwitterions from imidazolium salts at room temperature (R = methyl or ethyl group and X^- = counter ion)

Although we tried several times, the desired NHC·CS_2 zwitterions were never obtained using this method. Inspired by the literature, we devised a new procedure for this type of acid-base reaction and nucleophilic addition.[44,45] It involves the use of an imidazolium salt (1 equiv.), sodium *tert*-

butoxide, NaO*t*Bu (10 equiv.) as a base, carbon disulfide, CS_2 (20 equiv.) and dry tetrahydrofuran (THF) as the solvent (Table 10). The reaction mixture was heated at 60 °C for a few minutes and was concentrated under reduced pressure. Dichloromethane (CH_2Cl_2) was then added to precipitate by-products and the filtrate was concentrated under reduced pressure obtain the NHC·CS_2 zwitterions. By this method, most of the imidazolium dithiocarboxylate zwitterions were obtained quickly and without any difficulty, and their identity and purity were confirmed by ^{1}H and ^{13}C NMR analyses in $CDCl_3$. In the ^{1}H spectrum, the C8-H peak disappeared and in the ^{13}C spectrum, the CS_2 peak appeared at 220 ppm. These two indications confirm the incorporation of a dithiocarboxylate moiety.

For each NHC·CS_2 obtained, ^{1}H NMR spectroscopy showed the pure product. However, the ^{13}C NMR spectrum showed an additional peak at 30.9 ppm. After reflexion, we concluded that it was *t*-BuOH still present (Figure 28). In order to remove this by-product, the solid was dried overnight under high vacuum.

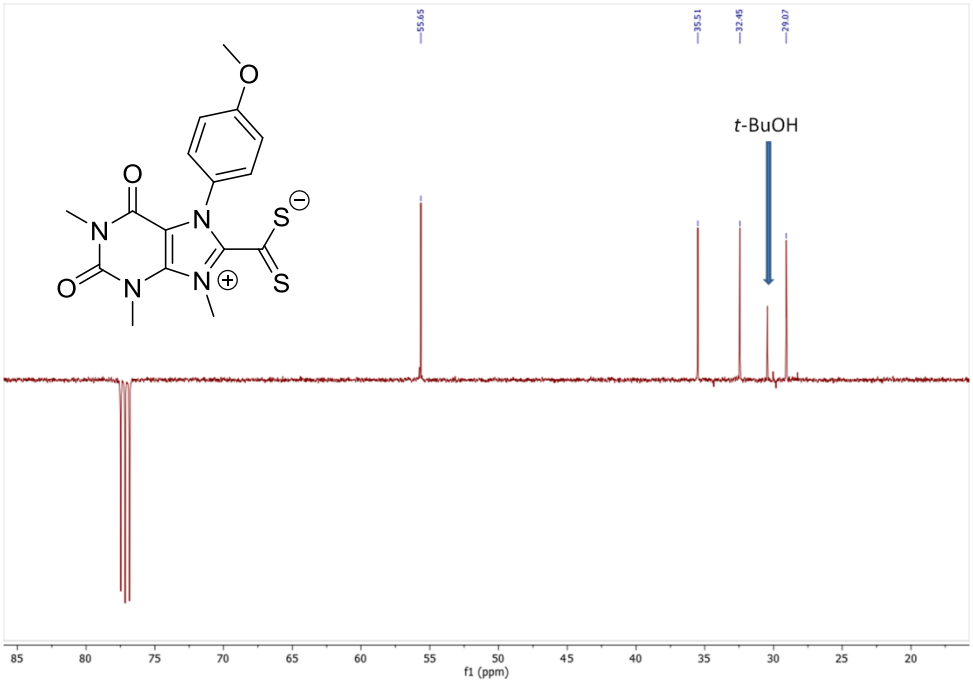
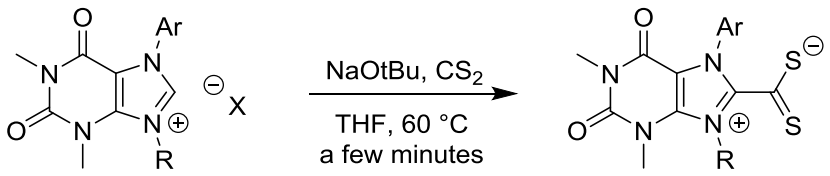


Figure 28: ^{13}C NMR of an NHC·CS_2 zwitterion showing the presence of *t*-BuOH

Table 10: Synthesis of imidazolium dithiocarboxylate zwitterions from imidazolium salts at 60 °C (R = methyl or ethyl group and X^- = counter ion)



Entry	Aryl substituent (N7)	Alkyl substituent (N9)	Counter ion (reagent)	Reaction time	Temperature (°C)	Yield (%)
1	4-Methoxyphenyl	Methyl	BF_4^-	8 min	60	/
2	Phenyl	Methyl	BF_4^-	10 min	60	59
3	4-Methoxyphenyl	Methyl	I^-	8 min	60	23
4	Phenyl	Methyl	I^-	/	60	/
5	4-Methoxyphenyl	Ethyl	I^-	10	60	66

A mixture of products is obtained for 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate (Entry 1). The purity is 78% and the impurity can be identified and corresponds to (7-(4-methoxyphenyl)-1,3-dimethylxanthine. It is therefore an impurity that remains from the previous step. The product therefore cannot be isolated in pure form. This is due to the fact that the reagent used for this method itself was not pure. The reaction to form the NHC·CS_2 zwitterions did not allow purification. A recrystallization is underway to try to purify the product. However, when 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium iodide was used as a reagent, the NHC·CS_2 product was isolated in pure form (Entry 3). The additional peaks present in the spectra of the imidazolium salt were no longer present in the spectra of the product. The impurities were therefore removed during this reaction, which eliminates the hypothesis of an impurity on the cation. A recrystallization is underway to obtain some crystals, which will be subjected to an X-ray diffraction analysis in order to determine the molecular structure of the product.

With a phenyl ring on N7, opposite results were obtained depending on the nature of the counter ion. Thus, when 1,3,9-trimethyl-7-phenylxanthinium tetrafluoroborate is used as the reagent, the NHC·CS_2 product was isolated in pure form with a yield of 67% (Entry 2). A recrystallization is underway to obtain some crystals, which will be studied by X-ray diffraction analysis. However, with the 1,3,9-trimethyl-7-phenylxanthinium iodide, the pure product was not isolated (Entry 4). This step did not allow a purification. A recrystallization is underway to try to purify the product. The highest yield was obtained with 9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium iodide (Entry 5). This result is not surprising since it is the only reaction where the NHC·CS_2 is obtained from a pure reagent. A recrystallization is also underway to obtain some crystals suitable for X-ray diffraction analysis.

A summary of all your attempts to prepare imidazolium dithiocarboxylate zwitterions from imidazolium salts is presented in Figure 29.

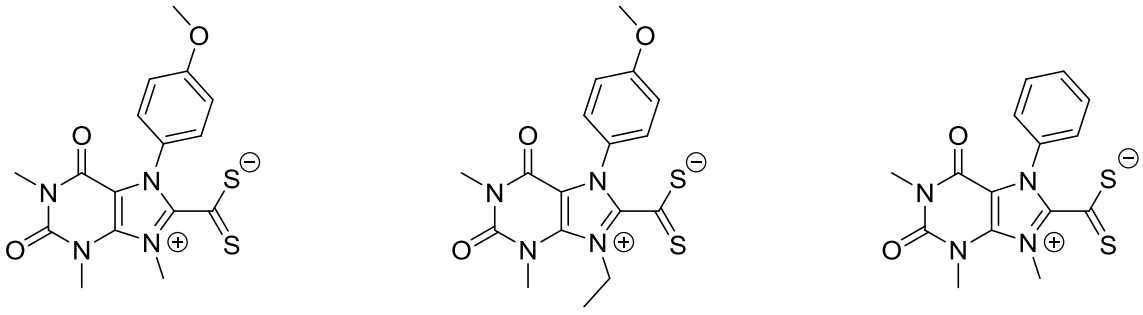


Figure 29: Structures of imidazolium dithiocarboxylate zwitterions

A comparison with the imidazolium dithiocarboxylate zwitterions bearing an alkyl group on their N7 can be done.[36] The synthesis of these NHC·CS_2 zwitterions was carried out with Cs_2CO_3 at room temperature for 4 hours and the yield obtained varied between 18 and 68% (cf. Table 4). The advantage of this method is that it uses a weak inorganic base under mild aerobic conditions, whereas the method adopted in this project required a strong organic base and dry and degassed solvents. The yields are quite similar between the two methods since they vary in the same area. The chemical shift of the CS_2 carbon on ^{13}C NMR spectroscopy can also be compared between these two methods (Figure 30). When the substituent on N7 is an alkyl chain, the carbon of the CS_2 resonates at 224 ppm. When it is an aryl group, the same CS_2 signal is shifted downfield to 220 ppm.

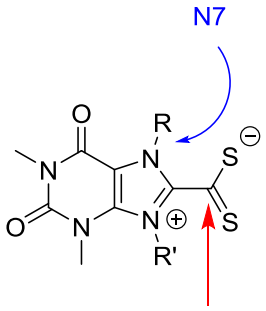


Figure 30: Influence of the nature of the N7 substituent on the chemical shift of the CS_2 moiety

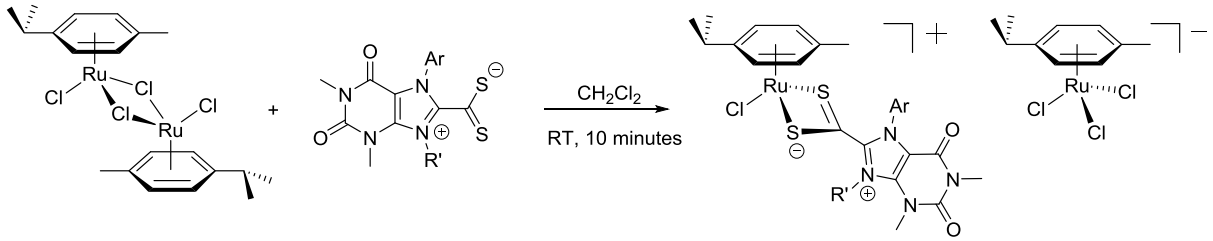
3.3. Synthesis of Ruthenium-arene complexes

Our last objective to complete this research project consists in the synthesis of ruthenium complexes using the NHC·CS_2 ligands that we prepared. Indeed, the dithiocarboxylate inner salts obtained are very strong chelating ligands that bind to metals via their two sulphur atoms. As a proof of concept, we have investigated their reactivity toward the $[RuCl_2(p\text{-cymene})]_2$ dimer.

The complexes are synthesized when one equivalent of an NHC·CS_2 ligand and one equivalent of the ruthenium dimer are used. In this case, the counter ion is bearing a ruthenium atom and its structure is $[RuCl_3(p\text{-cymene})]$. The procedure followed consists in adding imidazolium dithiocarboxylate zwitterions (1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ dimer (1 equiv.), and dichloromethane (CH_2Cl_2) using

simple conditions for this type of ligand substitution: room temperature for 10 minutes (Table 11). The two complexes synthesised were obtained without any difficulty and with very good yields. The purity of these products was determined by ^{13}C NMR spectroscopy. The shift of the CS_2 peak from 220 ppm, which corresponds to the dithiocarboxylate, to 200-210 ppm indicates the presence of the complex. A recrystallisation is underway for to obtain some crystal, which will be subjected to X-ray diffraction analysis.

Table 11: Synthesis of [RuCl(*p*-cymene)(S_2C·NHC)][$RuCl_3$(*p*-cymene)] complexes



Entry	Aryl substituent (N7)	Alkyl substituent (N9)	Reaction time	Temperature (°C)	Yield (%)
1	4-Methoxyphenyl	Methyl	10 min	RT	75
2	4-Methoxyphenyl	Ethyl	10 min	RT	91

Two different complexes were synthesised, both with the 4-methoxyphenyl group on N7. The difference is in the group on the N9, one with a methyl group and the other is an ethyl group. The results obtained are quite positive with good to very high yields. The [RuCl(*p*-cymene)(7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate)][$RuCl_3$(*p*-cymene)] complex was obtained with a yield of 75% (Entry 1). For the [RuCl(*p*-cymene)(9-ethyl-7-(4-methoxyphenyl)-1,3-dimethyl-xanthinium-8-dithiocarboxylate)][$RuCl_3$(*p*-cymene)] complex, the yield was 91% (Entry 2).

A summary of all your attempts to prepare this type of complexes from imidazolium dithiocarboxylate zwitterions is presented in Figure 31.

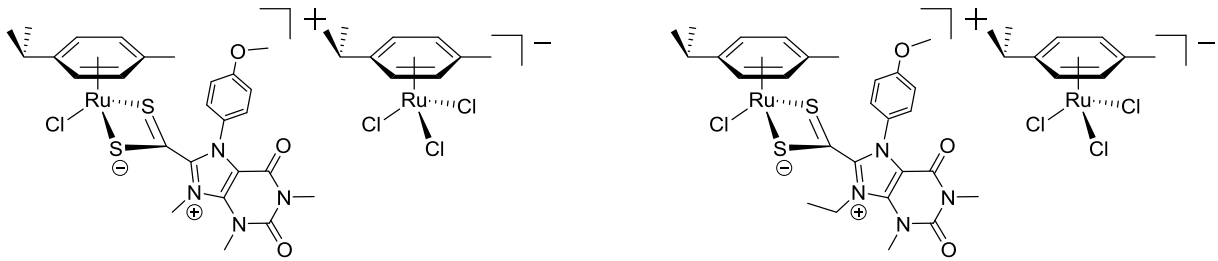


Figure 31: Structures of [RuCl(*p*-cymene)(S_2C·NHC)][$RuCl_3$(*p*-cymene)] complexes

4. Conclusion and perspectives

As mentioned in the objectives and strategies of this dissertation, our aim was to synthesize a small library of non-symmetrical N-heterocyclic carbene precursors by adding various aryl substituents on the N7 position and an alkyl substituent on the N9 atom of theophylline, which is a cheap and abundant natural alkaloid.

Despite numerous attempts, we were only able to arylate the N7 position of theophylline by a coupling reaction with 4-methoxyphenyl- or phenylboronic acid and copper(II) acetate. Next, a methylation or an ethylation was carried out to obtain imidazolium salts bearing an aryl group on the N7 position and a methyl or ethyl groups on the N9. These two reactions did not give good yields because the aryl groups make the nitrogen less nucleophile. Three different imidazolium dithio-carboxylate zwitterions were isolated in pure form with moderate to good yields. Two of them were used to synthesize ruthenium complexes. This last step gave very good yields.

In order to continue this study, two other types of ruthenium complexes bearing NHC·CS_2 ligands could be easily synthesized to further explore the coordination chemistry of the zwitterions that we prepared. First, cationic ruthenium–arene complexes could be obtained from the reaction of two equivalents of an NHC·CS_2 ligand with one equivalent of the $[RuCl_2(p\text{-cymene})]_2$ dimer (Figure 32a). In this case, the counter ion is PF_6^- because the reaction occurs in the presence of KPF_6. Alternatively, dicationic homoleptic complexes could also be prepared by reacting six equivalents of an NHC·CS_2 ligand with one equivalent of the ruthenium dimer in the presence of KPF_6 (Figure 32b). In addition, the synthesis of the three complexes can be done with a phenyl on N7 and a methyl on N9 group. We did not have time to synthesize the first type of complex with this NHC·CS_2 ligand.

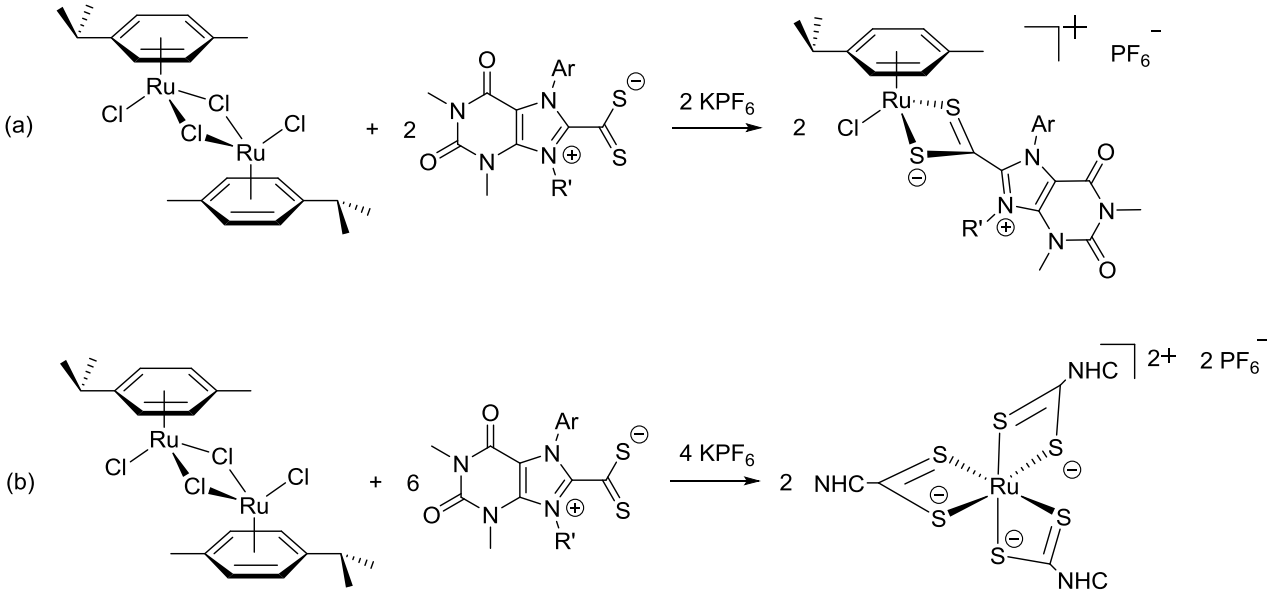


Figure 32: Two other types of ruthenium complexes than can be synthesized with NHC·CS_2 ligands

Another line of research to extend this study would be to deprotonate the xanthinium salts that we have obtained to generate free NHCs and to use these carbon-based ligands for synthesizing ruthenium-alkylidene complexes analogous to the second-generation Grubbs (Figure 33a) and Hoveyda-Grubbs catalysts (Figure 33b). Next, the catalytic activity and the selectivity of these complexes will be evaluated in olefin metathesis reactions.

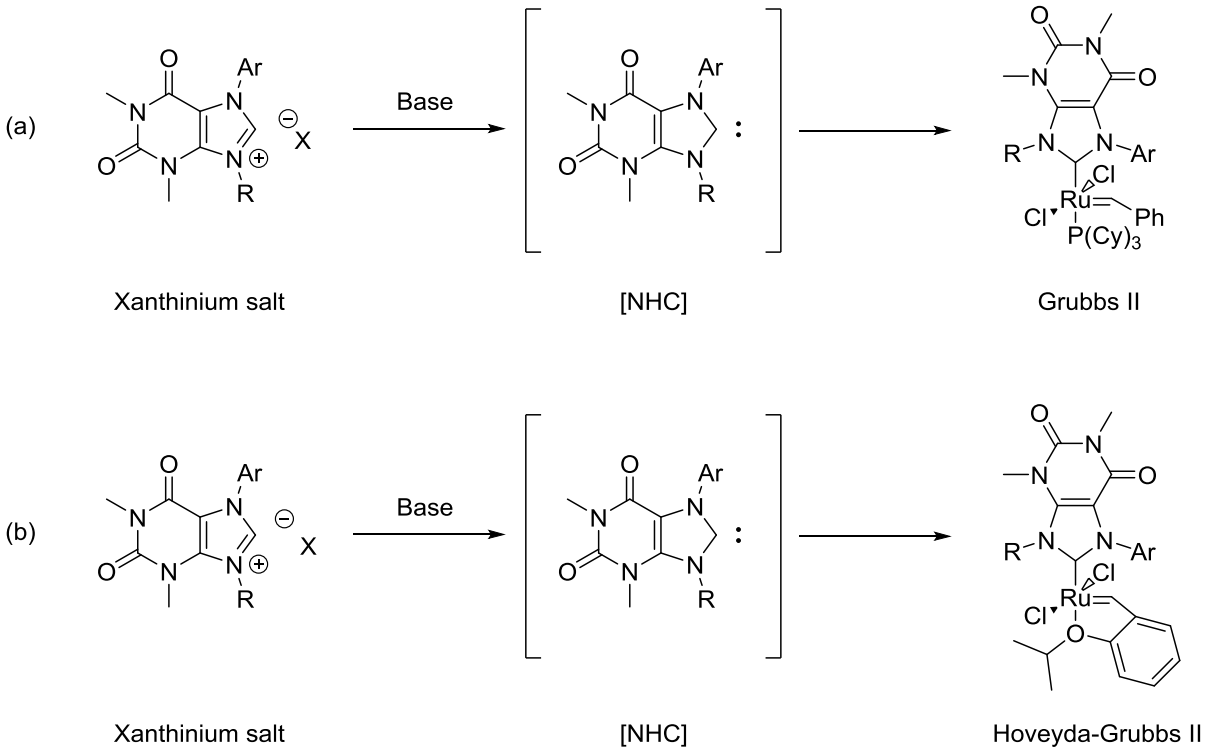


Figure 33: Synthesis of ruthenium-alkylidene complexes analogous to the second-generation Grubbs (a) and Hoveyda-Grubbs (b) catalysts

5. Experimental section

5.1. General information

Reagents were purchased from Merck or TCI and used without any further purification. Solvents were purchased from VWR. ^{1}H and ^{13}C NMR spectra were recorded at 298 K with a Bruker DRX 400 spectrometer operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are listed in parts per million downfield from TMS and are referenced from the solvent peaks or TMS.

5.2. Synthesis of imidazolium salts derived from theophylline

5.2.1. Synthesis of 7-aryl-1,3-dimethylxanthine from theophylline and arylboronic acid

7-(4-Methoxyphenyl)-1,3-dimethylxanthine

A round-bottom flask equipped with a magnetic stir bar was loaded with theophylline (5 g, 27.75 mmol, 2 equiv.), 4-methoxyphenylboronic acid (2.11 g, 13.88 mmol, 1 equiv.) and copper(II) acetate (5.54 g, 30.53 mmol, 2.2 equiv.). Dichloromethane (70 mL) and pyridine (5.59 mL, 69.38 mmol, 5 equiv.) were added. The reaction mixture was stirred and heated in an oil bath at 40 °C for 24 hours. The solution was then filtered through a pad of Celite, and the blue filtrate was concentrated under reduced pressure. A purification by column chromatography on silica gel was carried out to recover the product with the eluent CH_2Cl_2/MeOH (20:1). This organic phase was washed two times with 50 mL of water and concentrated under reduced pressure. Recrystallization of the orange solid in ethyl acetate was carried out in order to obtain the pure product. The solution was cooled to room temperature and left in the freezer overnight. A white powder is obtained and the yield is 24% (1.25 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H, C8-H), 7.44 – 7.32 (m, 2H, aromatics), 7.06 – 6.94 (m, 2H, aromatics), 3.86 (s, 3H, O-CH_3), 3.65 (s, 3H, N3-CH_3), 3.40 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.12 (aromatic), 154.51 (C6), 151.61 (C2), 149.40, 141.13, 127.74 (aromatic), 126.50 (aromatic), 114.42 (aromatic), 107.57 (C5), 55.68 (O-CH_3), 30.00 (N3-CH_3), 28.19 ppm (N1-CH_3).

1,3-Dimethyl-7-phenylxanthine (article 33)

A round-bottom flask equipped with a magnetic stir bar was loaded with theophylline (3 g, 16.65 mmol, 2 equiv.), phenylboronic acid (1.02 g, 8.33 mmol, 1 equiv.) and copper(II) acetate (3.33 g, 18.32 mmol, 2.2 equiv.). Dichloromethane (30 mL) and pyridine (3.35 mL, 41.63 mmol, 5 equiv.) were added. The reaction mixture was stirred and heated in an oil bath at 40 °C for 24 hours. The solution was then filtered through a pad of Celite, and the blue filtrate was concentrated under reduced pressure. A purification by column chromatography on silica gel was carried out to recover the product with the eluent CH_2Cl_2/MeOH (20:1). The product obtained was not pure and a second chromatographic column was carried out with the eluent AcOEt/petroleum ether (4:1).

Recrystallization of the white solid in ethyl acetate was carried out in order to obtain the pure product. The solution was cooled to room temperature and left in the freezer overnight. A white powder is obtained and the yield is 14% (0.29g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, C8-H), 7.58 – 7.38 (m, 5H, aromatics), 3.65 (s, 3H, N3-CH_3), 3.39 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.43 (C6), 151.58 (C2), 149.68, 141.26, 134.85 (aromatic), 129.30 (aromatic), 129.15 (aromatic), 125.11 (aromatic), 107.22 (C5), 29.98 (N3-CH_3), 28.23 ppm (N1-CH_3).

7-Mesityl-1,3-dimethylxanthine

A round-bottom flask equipped with a magnetic stir bar was loaded with theophylline (2.25 g, 12.49 mmol, 2 equiv.), phenylboronic acid (1.02 g, 6.24 mmol, 1 equiv.) and copper(II) acetate (2.5 g, 13.74 mmol, 2.2 equiv.). Dichloromethane (30 mL) and pyridine (2.51 mL, 31.22 mmol, 5 equiv.) were added. The reaction mixture was stirred and heated in an oil bath at 40 °C for 24 hours. The solution was then filtered through a pad of Celite, and the blue filtrate was concentrated under reduced pressure. A purification by column chromatography on silica gel was carried out to recover the product with the eluent CH_2Cl_2/MeOH (20:1). The product obtained was not pure and a second chromatographic column was carried out with the eluent AcOEt/petroleum ether (4:1). Fractions containing a product were concentrated under reduced pressure and an NMR analysis was performed. However, the NMR spectrum showed the presence of an unidentifiable product.

7-(2,6-Diisopropylphenyl)-1,3-dimethylxanthine

A round-bottom flask equipped with a magnetic stir bar was loaded with theophylline (1.75 g, 9.71 mmol, 2 equiv.), 2,6-diisopropylphenylboronic acid (1 g, 4.86 mmol, 1 equiv.) and copper(II) acetate monohydrate (2.13 g, 10.68 mmol, 2.2 equiv.). Dichloromethane (50 mL) and pyridine (1.96 mL, 24.28 mmol, 5 equiv.) were added. The reaction mixture was stirred and heated in an oil bath at 40 °C for 24 hours. The solution was then filtered through a pad of Celite and a TLC was performed on this blue filtrate. It showed only one product. This organic phase was washed two times with 50 mL of water and concentrated under reduced pressure. Recrystallization of the brown solid in ethyl acetate was carried out in order to obtain the pure product. The solution was cooled to room temperature and left in the freezer overnight. However, there was no precipitation of a solid.

5.2.2. Methylation of 7-aryl-1,3-dimethylxanthine on their N9 position with Me_3OBF_4

7-(4-Methoxyphenyl)-1,3,9-trimethylxanthinium tetrafluoroborate

A Schlenk flask equipped with a magnetic stir bar was loaded with 7-(4-methoxyphenyl)-1,3-dimethylxanthine (0.5 g, 1.75 mmol, 1 equiv.), trimethyloxonium tetrafluoroborate (0.7 g, 4.37 mmol, 2.5 equiv.), and 1,2-dichloroethane (20 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solvent was evaporated under vacuum. The remaining solid was washed with dichloromethane until the filtrate was colourless. To increase the purity of this salt, the solid was washed with hot ethanol. The solid

was dried under high vacuum to afford pure 7-(4-methoxyphenyl)-1,3-dimethylxanthinium tetrafluoroborate. The white powder was pure at 90% and the yield was 53% (0.357 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H, C8-H), 7.64 – 7.53 (m, 2H, aromatics), 7.21 – 7.13 (m, 2H, aromatics), 4.22 (s, 3H, N9-CH_3), 3.86 (s, 3H, O-CH_3), 3.80 (s, 3H, N3-CH_3), 3.24 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.26 (aromatic), 152.85 (C6), 150.71 (C2), 140.62, 140.18, 127.77 (aromatic), 126.02 (aromatic), 114.91 (aromatic), 108.35 (C5), 56.25 (O-CH_3), 37.65 (N9-CH_3), 31.89 (N3-CH_3), 29.05 ppm (N1-CH_3).

1,3,9-Trimethyl-7-phenylxanthinium tetrafluoroborate

A Schlenk flask equipped with a magnetic stir bar was loaded with 1,3-dimethyl-7-phenylxanthine (0.490 g, 1.91 mmol, 1 equiv.), trimethyloxonium tetrafluoroborate (0.707 g, 4.78 mmol, 2.5 equiv.), and 1,2-dichloroethane (10 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solvent was evaporated under vacuum. The remaining solid was washed with dichloromethane until the filtrate was colourless. To increase the purity of this salt, the solid was washed with hot ethanol. The solid was dried under high vacuum to afford pure 1,3,9-trimethyl-7-phenylxanthinium tetrafluoroborate. The white powder was pure at 94% and the yield was 44% (0.3 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H, C8-H), 7.66 (s, 5H, aromatics), 4.23 (s, 3H, N9-CH_3), 3.81 (s, 3H, N3-CH_3), 3.24 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.27 (C6), 150.15 (C2), 140.34, 139.77, 132.75 (aromatic), 130.83 (aromatic), 129.39 (aromatic), 125.81 (aromatic), 107.59 (C5), 37.24 (N9-CH_3), 31.44 (N3-CH_3), 28.60 ppm (N1-CH_3).

5.2.3. Methylation of 7-aryl-1,3-dimethylxanthine on their N9 position with CH_3I

7-(4-Methoxyphenyl)-1,3,9-trimethylxanthinium iodide

A Schlenk flask equipped with a magnetic stir bar was loaded with 7-(4-methoxyphenyl)-1,3-dimethylxanthine (1 g, 3.49 mmol, 1 equiv.), iodomethane (4.5 mL, 69.86 mmol, 20 equiv.), and *N,N*-dimethylformamide (15 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solution was poured into 30 mL of ethyl acetate and heated to boiling. A yellow precipitate appeared and was recovered by filtration. The pale yellow product was dried under high vacuum to afford pure 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium iodide (white powder, 0.58 g, 39 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H, C8-H), 7.61 – 7.55 (m, 2H, aromatics), 7.22 – 7.13 (m, 2H, aromatics), 4.22 (s, 3H, N9-CH_3), 3.86 (s, 3H, O-CH_3), 3.81 (s, 3H, N3-CH_3), 3.24 (s, 3H, N1-CH_3), 3.10 ppm (s, 3H, impurity). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.16 (aromatic), 152.78 (C6), 150.62 (C2), 140.53, 140.10, 127.73 (aromatic), 125.94 (aromatic), 114.85 (aromatic), 108.34 (C5), 56.29 (O-CH_3), 54.87 (impurity), 37.83 (N9-CH_3), 32.01 (N3-CH_3), 29.06 ppm (N1-CH_3).

1,3,9-Trimethyl-7-phenylxanthinium iodide

A Schlenk flask equipped with a magnetic stir bar was loaded with 1,3-dimethyl-7-phenylxanthine (0.16 g, 624.35 µmol, 1 equiv.), iodomethane (0.7 mL, 12.49 mmol, 20 equiv.), and *N,N*-dimethylformamide (2 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solution was poured into 20 mL of ethyl acetate and heated to boiling. A yellow precipitate appeared and was recovered by filtration. The yellow product was dried under high vacuum to afford pure 1,3,9-trimethyl-7-phenylxanthinium iodide (white powder, 0.11 g, 44 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H, C8-H), 7.67 (s, 5H, aromatics), 4.25 (s, 3H, N9-CH_3), 3.82 (s, 3H, N3-CH_3), 3.25 (s, 3H, N1-CH_3), 2.56 ppm (t, *J* = 5.5 Hz, 6H, impurity). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.27 (C6), 150.12 (C2), 140.18, 139.77, 132.75 (aromatic), 130.79 (aromatic), 129.33 (aromatic), 125.84 (aromatic), 107.73 (C5), 37.46 (N9-CH_3), 34.42 (impurity), 31.56 (N3-CH_3), 28.61 ppm (N1-CH_3).

5.2.4. Ethylation of 7-aryl-1,3-dimethylxanthine on their N9 position with CH_3CH_2I

9-Ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium iodide

A Schlenk flask equipped with a magnetic stir bar was loaded with 7-(4-methoxyphenyl)-1,3-dimethylxanthine (0.6 g, 2.10 mmol, 1 equiv.), iodoethane (3.37 mL, 41.92 mmol, 20 equiv.), and *N,N*-dimethylformamide (10 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solution was poured into 30 mL of ethyl acetate and heated to boiling. A yellow precipitate appeared and was recovered by filtration. The white solid was dried under high vacuum to afford pure 9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium iodide (white powder, 0.1212 g, 13 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H, C8-H), 7.59 (d, *J* = 8.9 Hz, 2H, aromatics), 7.17 (d, *J* = 9.0 Hz, 2H, aromatics), 4.63 (q, *J* = 7.2 Hz, 2H, N9-CH_2-CH_3), 3.86 (s, 3H, O-CH_3), 3.78 (s, 3H, N3-CH_3), 3.23 (s, 3H, N1-CH_3), 1.59 ppm (t, *J* = 7.2 Hz, 3H, N9-CH_2-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.76 (aromatic), 152.39 (C6), 150.40 (C2), 139.32, 139.20, 127.44 (aromatic), 125.65 (aromatic), 114.33 (aromatic), 108.05 (C5), 55.83 (O-CH_3), 45.66 (N9-CH_2CH_3), 31.90 (N3-CH_3), 28.61 (N1-CH_3), 15.15 ppm (N9-CH_2CH_3).

9-Ethyl-1,3-dimethyl-7-phenylxanthinium iodide

A Schlenk flask equipped with a magnetic stir bar was loaded with 1,3-dimethyl-7-phenylxanthine (0.11 g, 429.24 µmol, 1 equiv.), iodoethane (0.7 mL, 8.58 mmol, 20 equiv.), and *N,N*-dimethylformamide (2.5 mL). A septum was strongly attached to the flask. The reaction mixture was heated in an oil bath at 100 °C for 3 days. After cooling down, the solution was poured into 20 mL of ethyl acetate and heated to boiling. No precipitate appeared.

5.3. Synthesis of imidazolium dithiocarboxylate zwitterions from imidazolium salts

7-(4-Methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate

A round-bottom flask equipped with a magnetic stir bar was loaded with 7-methoxyphenyl-1,3,9-trimethylxanthinium tetrafluoroborate (0.357 g, 919.8 µmol, 1 equiv.), sodium *tert*-butoxide (0.884 g, 9.2 mmol, 10 equiv.), carbone disulfide (1.11 mL, 18.4 mmol, 20 equiv.), and dry and degassed tetrahydrofuran (30 mL). A septum was attached to the flask. The reaction mixture was heated in an oil bath at 60 °C for 8 minutes and was concentrated under reduced pressure. Dichloromethane (50 mL) was added to precipitate by-products and a filtration was carried out. The filtrate was concentrated under reduced pressure. The red solid was dried under high vacuum. NMR analysis showed a mixture of products.

A round-bottom flask equipped with a magnetic stir bar was loaded with 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium iodide (0.2688 g, 627.7 µmol, 1 equiv.), sodium *tert*-butoxide (0.6033 g, 6.28 mmol, 10 equiv.), carbone disulfide (0.76 mL, 12.55 mmol, 20 equiv.), and dry and degassed tetrahydrofuran (20 mL). A septum was attached to the flask. The reaction mixture was heated in an oil bath at 60 °C for 8 minutes and was concentrated under reduced pressure. Dichloromethane (50 mL) was added to precipitate by-products and a filtration was carried out. The filtrate was concentrated under reduced pressure. The red solid was dried under high vacuum to afford pure 7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate (0.0529 g, 22.5% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.0 Hz, 2H, aromatics), 6.94 (d, *J* = 9.0 Hz, 2H, aromatics), 4.14 (s, 3H, N9-CH_2-CH_3), 3.88 (s, 3H, O-CH_3), 3.82 (s, 3H, N3-CH_3), 3.36 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.66 (CS_2), 161.11 (aromatic), 152.65 (C6), 150.51 (C2), 150.01, 137.84, 128.37 (aromatic), 124.96 (aromatic), 114.46 (aromatic), 105.96 (C5), 55.65 (O-CH_3), 35.51 (N9-CH_3), 32.45 (N3-CH_3), 29.07 ppm (N1-CH_3).

1,3,9-Trimethyl-7-phenylxanthinium-8-dithiocarboxylate

A round-bottom flask equipped with a magnetic stir bar was loaded with 1,3,9-trimethyl-7-phenylxanthinium tetrafluoroborate (0.28 g, 781.9 µmol, 1 equiv.), sodium *tert*-butoxide (0.75 g, 7.82 mmol, 10 equiv.), carbon disulfide (0.95mL, 15.64 mmol, 20 equiv.), and dry and degassed tetra-hydrofuran (20 mL). A septum was attached to the flask. The reaction mixture was heated in an oil bath at 60 °C for 10 minutes and was concentrated under reduced pressure. Dichloromethane (40 mL) was added to precipitate by-products and a filtration was carried out. The filtrate was concentrated under reduced pressure. The red solid was washed with water and diethyl ether and was dried under high vacuum to afford pure 1,3,9-trimethyl-7-phenylxanthinium-8-dithiocarboxylate (0.16 g, 59%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.44 (m, 5H, aromatics), 4.07 (s, 3H, N9-CH_3), 3.80 (s, 3H, N3-CH_3), 3.17 ppm (s, 3H, N1-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.25 (CS_2), 152.47 (C6), 150.41 (C2), 148.36, 138.65, 132.88 (aromatic), 130.19 (aromatic), 128.78 (aromatic), 127.26 (aromatic), 105.06 (C5), 35.01 (N9-CH_3), 31.70 (N3-CH_3), 28.43 (N9-CH_3).

A round-bottom flask equipped with a magnetic stir bar was loaded with 1,3,9-trimethyl-7-phenylxanthinium iodide (0.097 g, 243.59 µmol, 1 equiv.), sodium *tert*-butoxide (0.234 g, 2.44 mmol, 10 equiv.), carbon disulfide (0.3 mL, 4.88 mmol, 20 equiv.), and dry and degassed tetrahydrofuran (10 mL). A septum was attached to the flask. The reaction mixture was heated in an oil bath at 60 °C for 10 minutes and was concentrated under reduced pressure. Dichloromethane (40 mL) was added to precipitate by-products and a filtration was carried out. The filtrate yellow was concentrated under reduced pressure but no precipitate appeared.

9-Ethyl-7-methoxyphenyl-1,3-dimethylxanthinium-8-dithiocarboxylate

A round-bottom flask equipped with a magnetic stir bar was loaded with 9-ethyl-7-methoxyphenyl-1,3-dimethylxanthinium iodide (0.12 g, 271.34 µmol, 1 equiv.), sodium *tert*-butoxide (0.26 g, 2.71 mmol, 10 equiv.), carbon disulfide (0.33 mL, 5.43 mmol, 20 equiv.), and dry and degassed tetrahydrofuran (10 mL). A septum was attached to the flask. The reaction mixture was heated in an oil bath at 60 °C for 10 minutes and was concentrated under reduced pressure. Dichloromethane (40 mL) was added to precipitate by-products and a filtration was carried out. The filtrate was concentrated under reduced pressure. The solid was washed with petroleum ether (20 mL). The supernatant was removed after decantation. The red solid was dried under high vacuum to afford pure 9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium-8-dithiocarboxylate (0.07 g, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H, aromatics), 6.92 (d, *J* = 8.5 Hz, 2H, aromatics), 4.62 (q, *J* = 7.2 Hz, 2H, N9-CH_2-CH_3), 3.85 (s, 3H, O-CH_3), 3.80 (s, 3H, N3-CH_3), 3.34 (s, 3H, N1-CH_3), 1.68 ppm (t, *J* = 7.2 Hz, 3H, N9-CH_2-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.85 (CS_2), 160.94 (aromatic), 152.59 (C6), 150.60 (C2), 149.95, 137.32, 128.40 (aromatic), 124.96 (aromatic), 114.30 (aromatic), 106.23 (C5), 55.58 (O-CH_3), 43.99 (N9-CH_2CH_3), 31.87 (N3-CH_3), 28.95 (N1-CH_3), 16.66 ppm (N9-CH_2CH_3).

5.4. Synthesis of Ruthenium-arene complexes

[RuCl(*p*-cymene)(7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate)][$RuCl_3$(*p*-cymene)]

The [$RuCl_2$(*p*-cymene)]$_2$ dimer (0.0599 g, 98.02 µmol, 1 equiv.), 7-(4-methoxyphenyl)-1,3,9-trimethyl-xanthinium-8-dithiocarboxylate (0.0369 g, 98.02 µmol, 1 equiv.) were mixed together. Dichloro-methane (3 mL) was added and the reaction mixture was stirred at room temperature for 10 minutes. The solvent was removed on a rotary evaporator. The residue was taken up with a minimum amount of dichloromethane and was poured dropwise in 10 mL of diethyl ether. A brown solid appeared and the supernatant was removed. The brown solid was dried under high vacuum to afford the pure complex (0.0729 g, 75% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57 (d, *J* = 8.9 Hz, 2H, aromatics from aryl), 6.97 (d, *J* = 8.9 Hz, 2H, aromatics from aryl), 5.74 (d, *J* = 6.3 Hz, 2H, aromatics from *p*-cymene), 5.56 (d, *J* = 6.1 Hz, 2H, aromatics from *p*-cymene), 5.11 – 5.03 (m, 2H, aromatics from *p*-cymene), 4.23 (s, 3H, N9-CH_3), 3.88 (s, 3H, O-CH_3), 3.84 (s, 3H, N3-CH_3), 3.26 (s, 3H, N1-CH_3), 3.06 – 2.93 (m, 1H, CH from *p*-cymene), 2.66 (h, *J* = 6.9 Hz, 1H, CH from *p*-cymene), 2.23 (s, 3H, CH_3-Ar from *p*-cymene), 2.16 (s, 3H, CH_3-Ar from *p*-cymene), 1.29 (d, *J* = 7.2 Hz, 6H, $(CH_3)_2$-CH from *p*-cymene), 1.11 ppm (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$-CH from *p*-cymene). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 215.20 (CS_2), 161.86 (aromatic), 153.15 (C6), 150.99

(C2), 142.64, 140.02, 129.78 (aromatic), 125.02 (aromatic), 114.46 (aromatic), 109.31, 107.26, 105.04, 96.93, 86.44, 86.21, 82.26, 81.58, 80.86, 79.64, 56.09 (O-CH_3), 38.59 (N9-CH_3), 33.44, 32.53, 31.07 (N3-CH_3), 29.05 (N1-CH_3), 22.83, 22.38, 22.19, 19.56 ppm.

[RuCl(*p*-cymene)(9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium-8-dithiocarboxylate)]-[$RuCl_3$(*p*-cymene)]

The [$RuCl_2$(*p*-cymene)]$_2$ dimer (0.0512 g, 179.27 µmol, 1 equiv.) and 9-ethyl-7-(4-methoxyphenyl)-xanthinium-8-dithiocarboxylate (0.0327 g, 179.27 µmol, 1 equiv.) were mixed together. Dichloromethane (3 mL) was added and the reaction mixture was stirred at room temperature for 10 minutes. The solvent was removed on a rotary evaporator. The residue was taken up with a minimum amount of dichloromethane and was poured dropwise in 10 mL of diethyl ether. A brown solid appeared and the supernatant was removed. The brown solid was dried under high vacuum to afford the pure complex (0.076 g, 91% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.59 (d, *J* = 8.6 Hz, 2H, aromatics from aryl), 6.97 (d, *J* = 8.5 Hz, 2H, aromatics from aryl), 5.74 (d, *J* = 5.9 Hz, 2H, aromatics from *p*-cymene), 5.57 (d, *J* = 6.0 Hz, 2H, aromatics from *p*-cymene), 5.35 (d, 2H, aromatics from *p*-cymene), 5.05 (d, *J* = 5.5 Hz, 2H, aromatics from *p*-cymene), 4.74 (q, *J* = 7.2 Hz, 2H, N9-CH_2-CH_3), 3.87 (s, 3H, O-CH_3), 3.85 (s, 3H, N3-CH_3), 3.27 (s, 3H, N1-CH_3), 2.98 (dq, *J* = 11.9, 6.1, 5.1 Hz, 1H, CH from *p*-cymene), 2.62 (sept, *J* = 7.0 Hz, 1H, CH from *p*-cymene), 2.21 (s, 3H, CH_3-Ar from *p*-cymene), 2.15 (s, 3H, CH_3-Ar from *p*-cymene), 1.50 (t, *J* = 7.0 Hz, 3H, N9-CH_2-CH_3), 1.27 (dd, *J* = 9.5, 6.9 Hz, 6H, $(CH_3)_2$-CH from *p*-cymene), 1.07 ppm (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$-CH from *p*-cymene). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 215.79 (CS_2), 161.82 (aromatic), 153.07 (C6), 151.12 (C2), 142.53, 139.09, 129.79 (aromatic), 125.08 (aromatic), 114.45 (aromatic), 109.69, 107.17, 105.08, 86.44, 86.02, 82.29, 81.56, 80.86, 79.60, 56.09 (O-CH_3), 45.63 (N9-CH_2CH_3), 32.77, 32.51, 31.06 (N3-CH_3), 29.08 (N1-CH_3), 22.78, 22.40, 22.19, 19.54, 19.08, 18.85, 17.34 ppm (N9-CH_2CH_3).

6. Bibliography

[1] Cazin, C. S. J. (ed.) N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis; *Springer, Dordrecht*, **2011**. https://doi.org/10.1007/978-90-481-2866-2

[2] Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. Synthetic Routes to N-Heterocyclic Carbene Precursors. *Chem. Rev*. **2011**, *111*, 2705–2733. https://doi.org/10.1021/cr100328e

[3] Herrmann, W. A. N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem. Ind. Ed*. **2002**, *41*, 1290–1309. https://doi.org/10.1002/1521-3773(20020415)41:8<1290::AID-ANIE1290>3.0CO;2-Y

[4] Böhm, V. P. W.; Herrmann, W. A. The Wanzlick Equilibrium. *Angew. Chem. Ind. Ed*. **2000**, *39*, 4036–4038. https://doi.org/10.1002/1521-3773%2820001117%2939%3A22<4036%3A%3AAID-ANIE4036>3.0.CO%3B2-L

[5] Arduengo, A. J.; Harlow, R.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361-363. https://doi.org/10.1021/ja00001a054

[6] Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*(7506), 485–496. https://doi.org/10.1038/nature13384

[7] Hans, M.; Lorkowski, J.; Demonceau, A.; Delaude, L. Efficient Synthetic Protocols for the Preparation of Common N-Heterocyclic Carbene Precursors. *Beilstein J. Org. Chem.* **2015***, 11*, 2318–2325. https://doi.org/10.3762/bjoc.11.252

[8] Islam SK.A.; Kundu, K.; Kundu, P. K. Azobenzene-Isomerization Induced Photomodulation of Electronic Properties of N-Heterocyclic Carbene. *Chem. Eur. J*. **2020**, *26*, 4214–4219. https://doi.org/10.1002/chem.201905161

[9] Delaude, L. Betaine Adducts of N-Heterocyclic Carbenes : Synthesis, Properties, and Reactivity. *Eur. J. Inorg. Chem*. **2009**, 1681–1699. https://doi.org/10.1002/ejic.200801227

[10] Delaude, L.; Sauvage, X.; Demonceau, A.; Wouters, J. Synthesis and Catalytic Evaluation of Ruthenium-Arene Complexes Generated Using Imidazol(in)ium-2-carboxylates and Dithiocarboxylates. *Organometallics*, **2009**, *28*, 4056–4064. https://doi.org/10.1021/om9002363

[11] Beltrán, T. F.; Delaude, L. Recent Advances in Small Clusters and Polymetallic Assemblies Based on Transition Metals and Dithiocarboxylate Zwitterions Derived from N-Heterocyclic carbenes. *J. Clust. Sci*. **2017**, *28*, 667–678. https://doi.org/10.1007/s10876-017-1174-4

[12] Samojlowicz, C.; Bieniek, M.; Grela, K. Ruthenium-Based Olefin Metathesis Catalysts Bearing N-Heterocyclic Carbene Ligands. *Chem. Rev*. **2009**, *109*, 3708–3742. https://doi.org/10.1021/cr800524f

[13] Roland, S. ; Suarez, J.M. ; Sollogoub, M. Confinement of Metal–N-Heterocyclic Carbene Complexes to Control Reactivity in Catalytic Reactions. *Chem. Eur. J*. **2018**, *24,* 12464–12473. https://10.1002/chem.201801278

[14] Engl, P. S.; Fedorov, A.; Cope, C.; Togni, A. N-Trifluoromethyl NHC Ligands Provide Selective Ruthenium Metathesis Catalysts. *Organometallics* **2016**, *35*, 887–893. https://doi.org/10.1021/acs.organomet.6b00028

[15] Chikkali, S.; & Mecking, S. Refining of Plant Oils to Chemicals by Olefin Metathesis. *Angew. Chem. Int. Ed*. **2012**, *51*, 5802–5808. https://doi.org/10.1002/anie.201107645

[16] Rybak, A.; Fokou, P. A. ; Meier, M. A. R. Metathesis as a Versatile Tool in Oleochemistry. *Eur. J. Lipid Sci. Technol*. **2008**, *110*, 797–804. https://doi.org/10.1002/ejlt.200800027

[17] Schuster, M.; Blechert, S. Olefin Metathesis in Organic Chemistry. *Angew. Chem. Int. Ed*. **1997**, *36*, 2036–2056. https://doi.org/10.1002/anie.199720361

[18] Fürstner, A. Olefin Metathesis and Beyond. *Angew. Chem. Int. Ed*. **2000**, *39*, 3012–3043. https://doi.org/10.1002/1521-3773(20000901)39:17<3012::AID-ANIE3012>3.3.CO;2-7

[19] Grubbs, R. H. Olefin metathesis. *Elsevier Ltd,* **2004**, *60*, 7117–7140. https://doi.org/10.1016/j.tet.2004.05.124

[20] American Chemical Society ACS, Web Site, consulted on 28/12/2020 https://www.acs.org/content/acs/en.html

[21] Schrodi, Y.; Ung, T.; Vargas, A.; Mkrtumyan, G.; Lee, C. W.; Champagne, T. M.; Container, L. Ruthenium Olefin Metathesis Catalysts for the Ethenolysis of Renewable Feedstocks, *Clean*, **2008**, *36*, 669–673. https://doi.org/10.1002/clen.200800088

[22] Paradiso, V.; Bertolasi, V.; Grisi, F. Novel Olefin Metathesis Ruthenium Catalysts Bearing Backbone-Substituted Unsymmetrical NHC Ligands, *Organometallics* **2014**, *33*, 5932–5935. https://doi.org/10.1021/om500731k

[23] Hamad, F. B.; Sun, T.; Xiao, S.; Verpoort, F. Olefin Metathesis Ruthenium Catalysts Bearing Unsymmetrical Heterocylic Carbenes. *Coord. Chem. Rev.*, **2013**, *257*, 2274–2292. https://dx.doi.org/10.1016/j.ccr.2013.04.015

[24] Mohamed, H. A.; Lake, B. R. M.; Laing, T.; Phillips, R. M. Willans, C. E. Synthesis and Anticancer Activity of Silver(I)-N-Heterocyclic Carbene Complexes Derived from the Natural Xanthine Products Caffeine, Theophylline and Theobromine. *Dalton Trans*. **2015**, *44*, 7563–7569. https://doi.org/10.1039/c4dt03679d

[25] Friedman, M.; Levin, C. E.; Choi, S. H.; Kozukue, E.; Kozukue, N. HPLC Analysis of Catechins, Theaflavins , and Alkaloids in Commercial Teas and Green Tea Dietary Supplements: Comparison of Water and 80 % Ethanol/Water Extracts. *J.Food Sci.*, **2006**, *71*, 328–337. https://doi.org/10.1111/j.1750-3841.2006.00090.x

[26] Coco, F. Lo.; Lanuzza, F.; Micali, G.; Cappellano, G. Determination of Theobromine, Theophylline, and Caffeine in by-Products of Cupuacu and Cacao Seeds by High-Performance Liquid Chromatography. *J. Chromatogr. Sci.*, **2007**, *45*, 273–275. https://doi.org/10.1093/chromsci/45.5.273

[27] Saldana, M. D. A.; Mohamed, R. S.; Baer, M. G.; Mazzafera, P. Extraction of Purine Alkaloids from Mate (Ilex paraguariensis) Using Supercritical CO_2. *J. Agric. Food Chem.*, **1999**, *47*, 3804−3808. https://doi.org/10.1021/jf981369zCCC:$18.00

[28] Dockendorff, B.; Holman, D. A.; Christian, G. D.; Ruzicka, J.; August, R.; October, A. Automated Solid Phase Extraction of Theophylline by Sequential Injection on Renewable Column. *Anal. Commun.*, **1998**, *35*, 357–359. https://doi.org/10.1039/A806471G

[29] European Chemistry Agency ECHA, Web Site, consulted on 11/04/2020 https://echa.europa.eu/fr/home

[30] TCI Europe N.V, Web Site, consulted on 11/04/2020 https://www.tcichemicals.com/fr/be/

[31] Barnes, P. J. Pulmonary Perspectives, Theophylline, *Am. J. Respir. Crit. Care Med.*, **2013**, *188*, 901–906. https://doi.org/10.1164/rccm.201302-0388PP

[32] Ismail, A.H.; Al-Bairmani, H.K.; Abbas, Z.S.; Rheima, A.M. Nano-synthesis, spectroscopic characterisation and antibacterial activity of some metal complexes derived from Theophylline. *Egypt. J. Chem*, **2020**, *Vol. 63, No. 12*, 4951–4962. https://10.21608/EJCHEM.2020.32582.2690

[33] Altun, O.; Suözer, M. Synthesis, spectral analysis, stability constants, antioxidant and biological activities of Co (II), Ni (II) and Cu (II) mixed ligand complexes of nicotinamide, theophylline and thiocyanate. *Journal of Molecular Structure*, 2017, *1149*, 307–314. https://doi.org/10.1016/j.molstruc.2017.07.069

[34] Makhloufi, A.; Frank, W.; & Ganter, C. Converting Caffeine to Electronically Different N-Heterocyclic Carbenes with a Hypoxanthine Backbone. *Organometallics* **2012**, *31*, 7272–7277. https://doi.org/10.1021/om300836w

[35] Schweiger, M. J.; Beck, W. Metal Complexes of Biologically Important Ligands, Part CLXXVIII. Addition of the Pentacarbonylrhenium Cation $[(OC)_5Re]^+$ to the Xanthine Alkaloids Caffeine, Theophylline, and Theobromine. *Z. Anorg. Allg. Chem*. **2017**, *643*, 1335–1337. https://doi.org/10.1002/zaac.201700218

[36] Mazars, F.; Delaude, L. Manuscript in Preparation

[37] Kim, D.; Jun, H.; Lee, H.; Hong, S.; Hong, S. Development of New Fluorescent Xanthines as Kinase Inhibitors, *Org. Lett* **2010**, *12,* 1212–1215. https://doi.org/10.1021/ol100011n

[38] Larsen, A. F.; Ulven, T. Direct N9-Arylation of Purines with Aryl Halides. *Chem. Commun.* **2014**, *50*, 4997–4999. https://doi.org/10.1039/c3cc48642g

[39] Li, B. ; Shi, Y., Fu, Z. Schiff Base as a Novel Kind of Catalyst for Reversible Complexation-Mediated Radical Polymerization of Methyl Methacrylate. *J. Polym. Sci. A: Polym. Chem.*. **2019**, *57*, 1653–1663. https://doi.org/10.1002/pola.29430

[40] Heravi, M.M.; Kheilkordi, Z. ; Zadsirjan, V. ; Heydari, M. ; Malmir, M. Buchwald-Hartwig reaction: An overview. *Journal of Organometallic Chemistry*, **2018**, *861*, 17–104. https://doi.org/10.1016/j.jorganchem.2018.02.023

[41] Theil, F. Synthesis of Diaryl Ethers: A Long-Standing Problem Has Been Solved. *Angew. Chem. Int. Ed*. **1999**, *38*, 2345–2347. https://doi.org/10.1002/9783527619986.ch2

[42] Evans, D.A.; Katz, J.L.; West, T.R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.*. **1998**, *39,* 2937–2940. https://doi.org/10.1016/S0040-4039(98)00502-4

[43] Luo, F. ; Lo, H. Short Synthesis of Bis-NHC-Pd Catalyst Derived from Caffeine and Its Applications to Suzuki, Heck, and Sonogashira Reactions in Aqueous Solution. *J. Organomet. Chem*. **2011**, 696, 1262–1265. https://doi.org/10.1016/j.jorganchem.2010.11.002

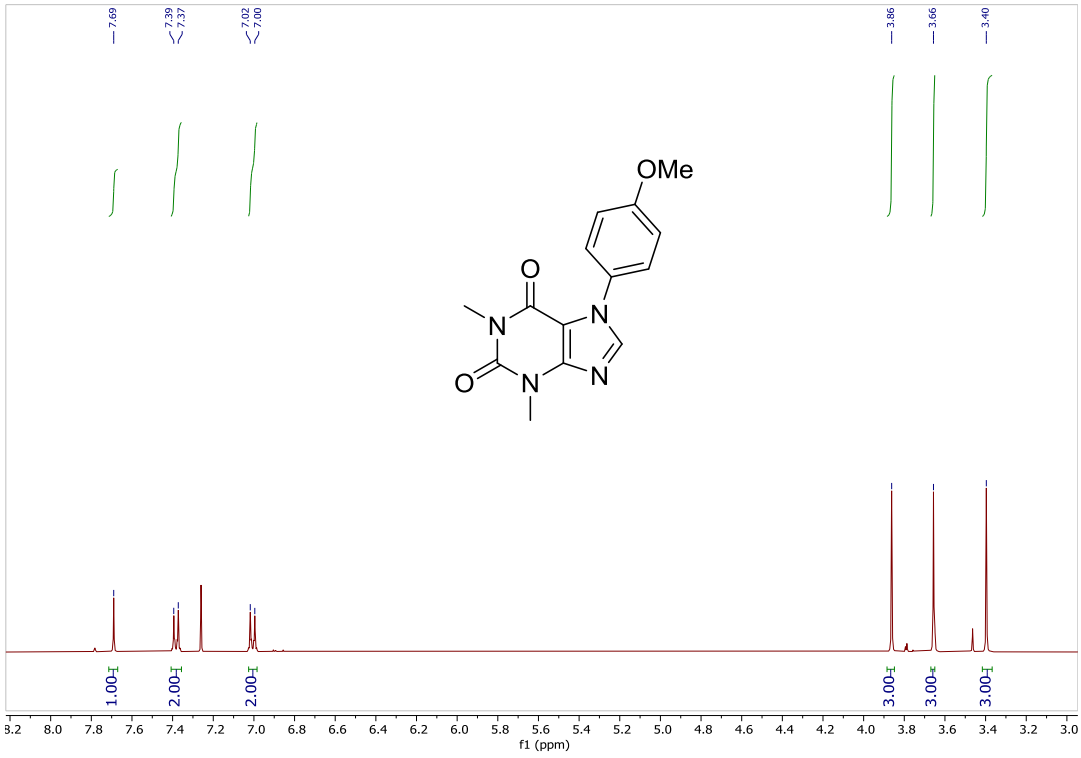
[44] Fèvre, M; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, T. Imidazol(in)ium Hydrogen Carbonates as a Genuine Source of N-Heterocyclic Carbenes (NHCs): Applications to the Facile Preparation of NHC Metal Complexes and to NHC-Organocatalyzed Molecular and Macromolecular Syntheses, *J. Am. Chem. Soc*. **2012**, *134*, 6776−6784. https://doi.org/10.1021/ja3005804

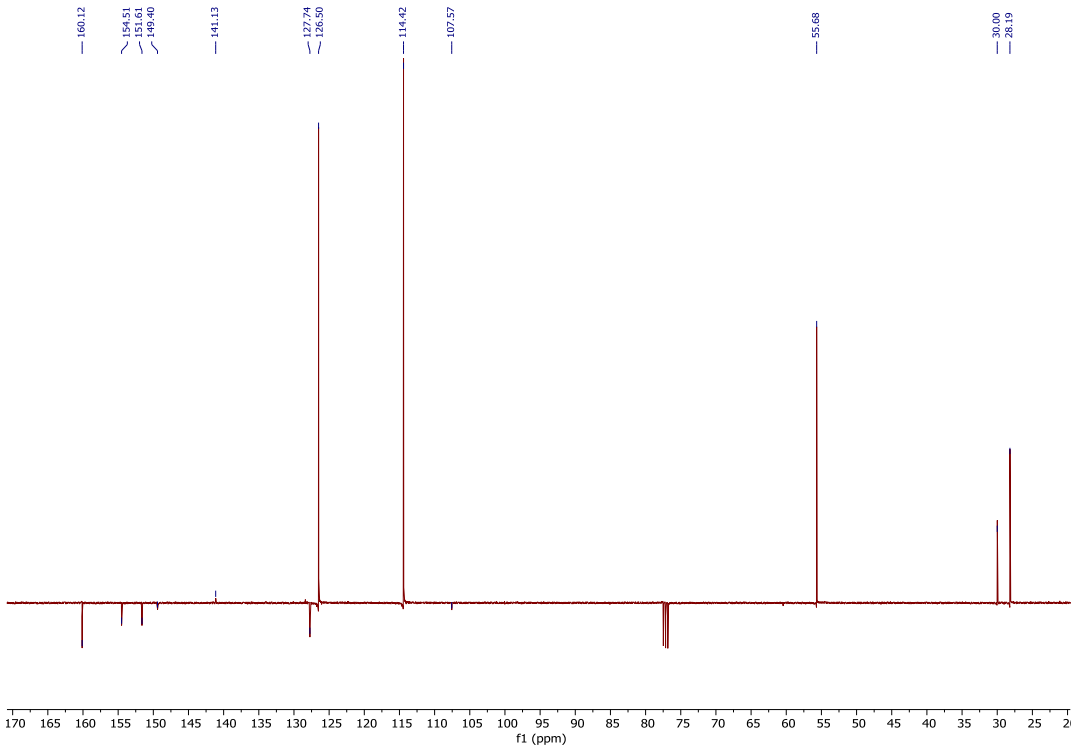
[45] Delaude, L.; Demonceau, A.; Wouters, J. Assessing the Potential of Zwitterionic NHC·CS_2 Adducts for Probing the Stereoelectronic Parameters of N-Heterocyclic Carbenes. *Eur. J. Inorg. Chem.* **2009**, 1882–1891. https://doi.org/10.1002/ejic.200801110

7. Appendix

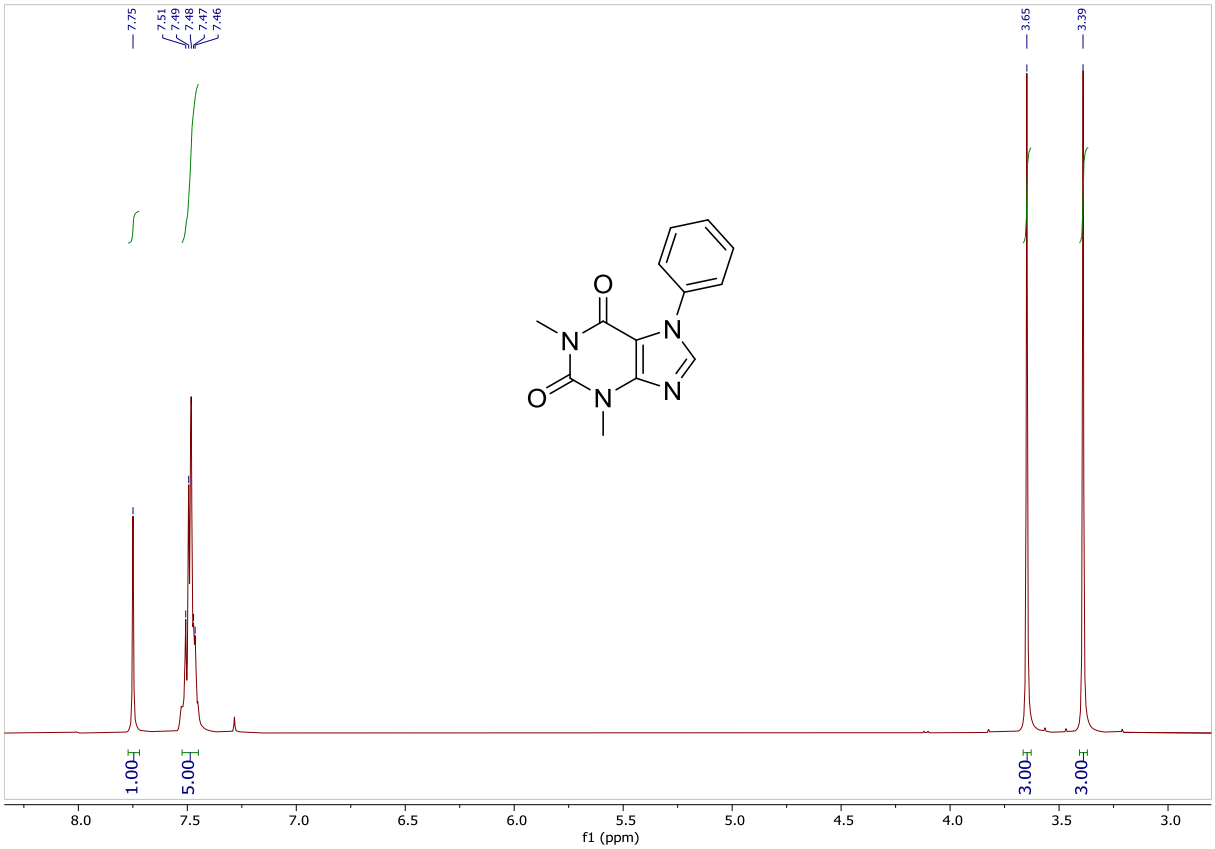
7.1. ^{1}H and ^{13}C NMR spectra of 7-aryl-1,3-dimethylxanthine derivatives

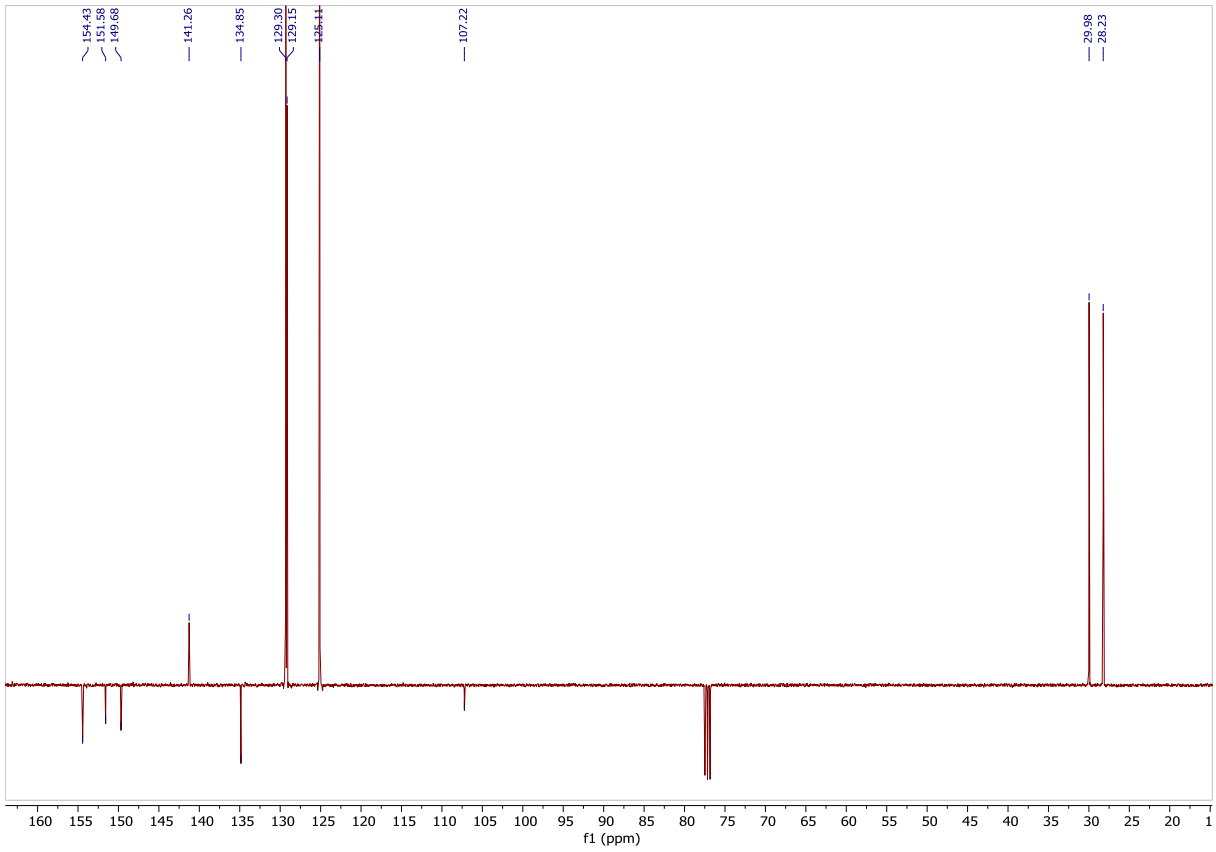
7-(4-Methoxyphenyl)-1,3-dimethylxanthine





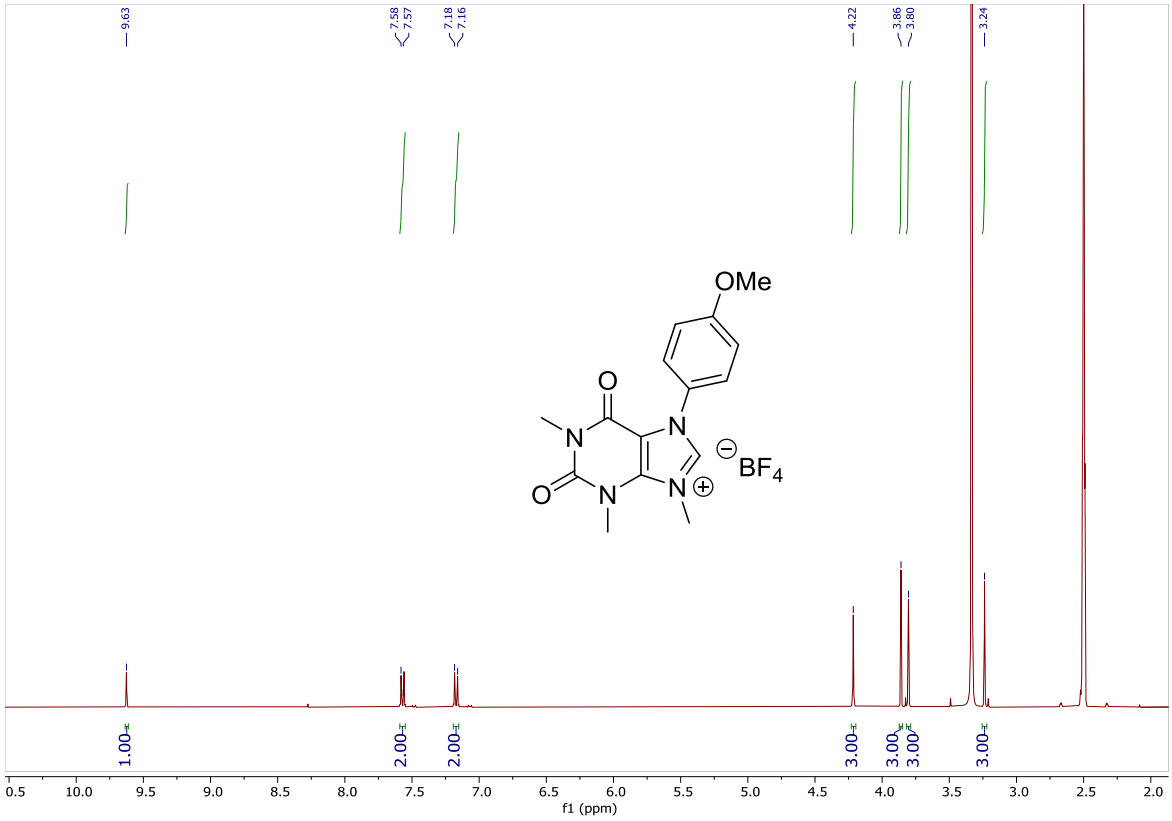
1,3-Dimethyl-7-phenylxanthine

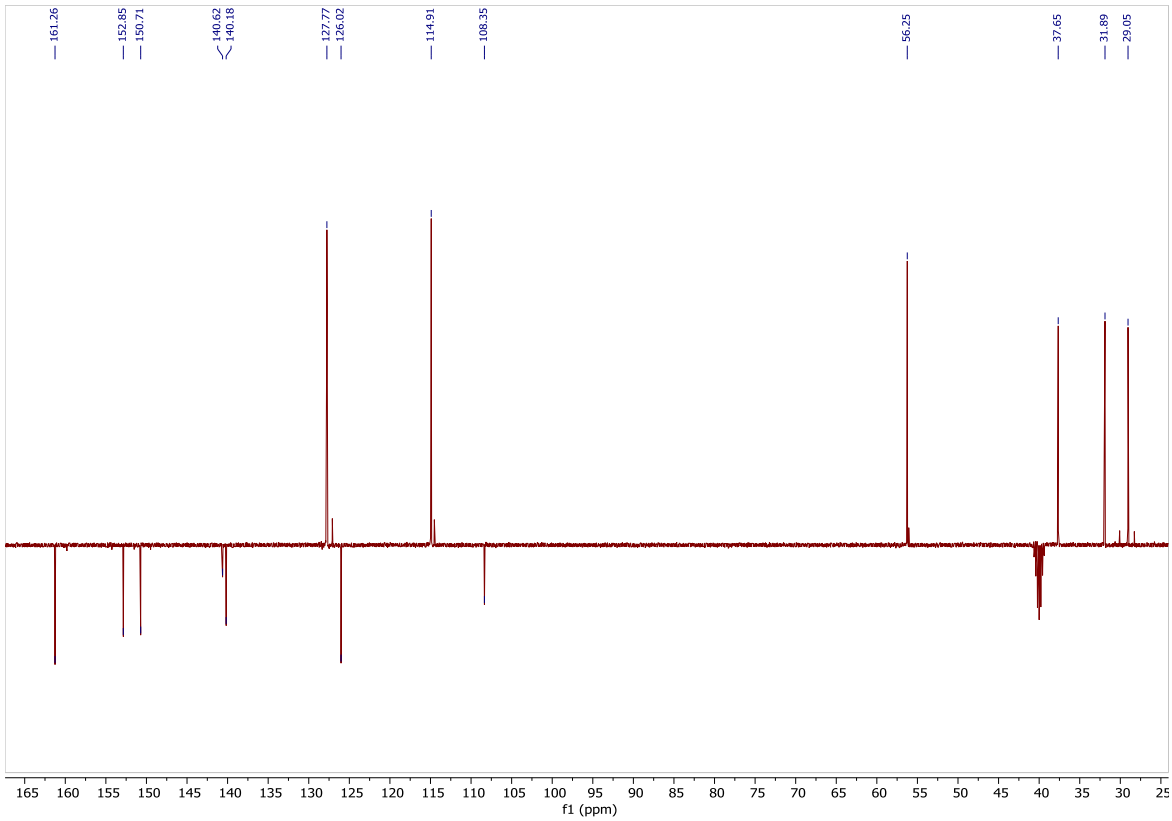




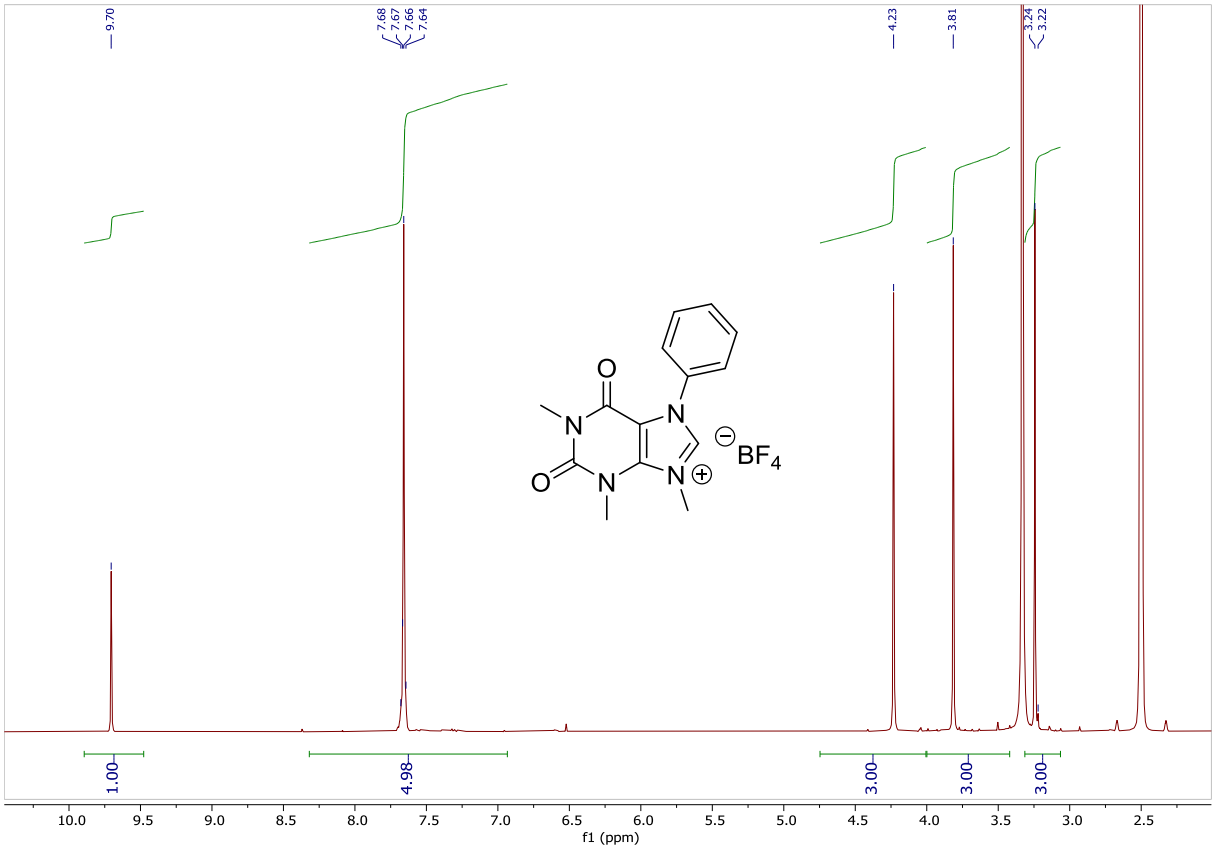
7.2. ^{1}H and ^{13}C NMR spectra of 7-aryl-1,3,9-trimethylxantinium salts

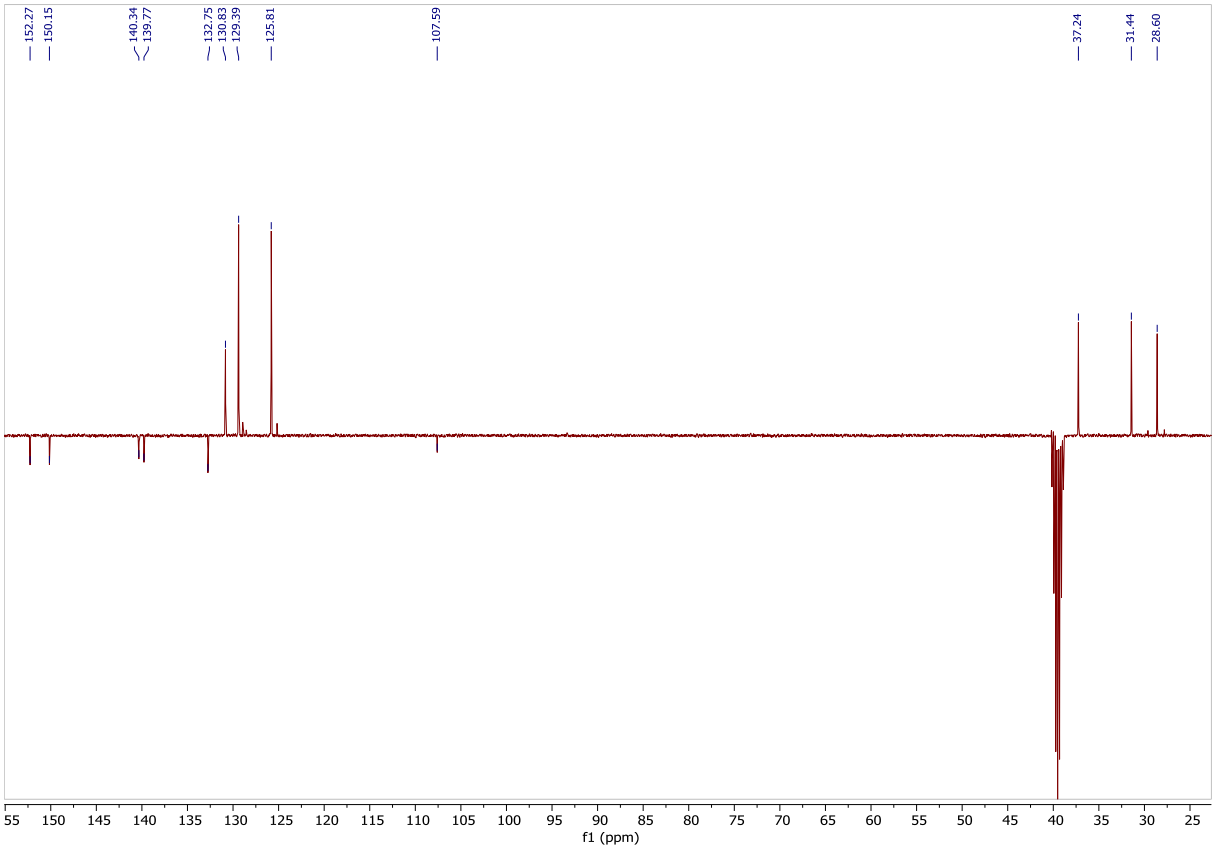
7-(4-Methoxyphenyl)-1,3,9-trimethylxanthinium tetrafluoroborate



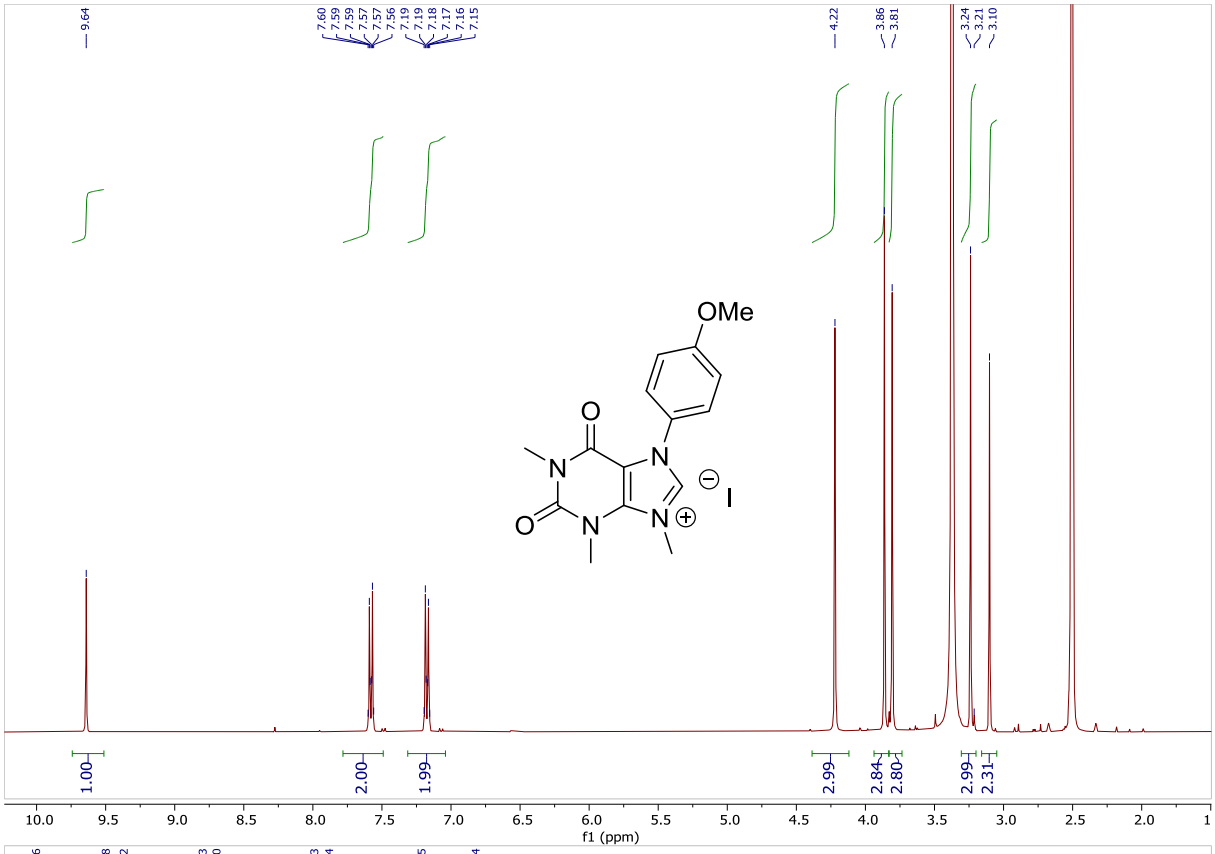


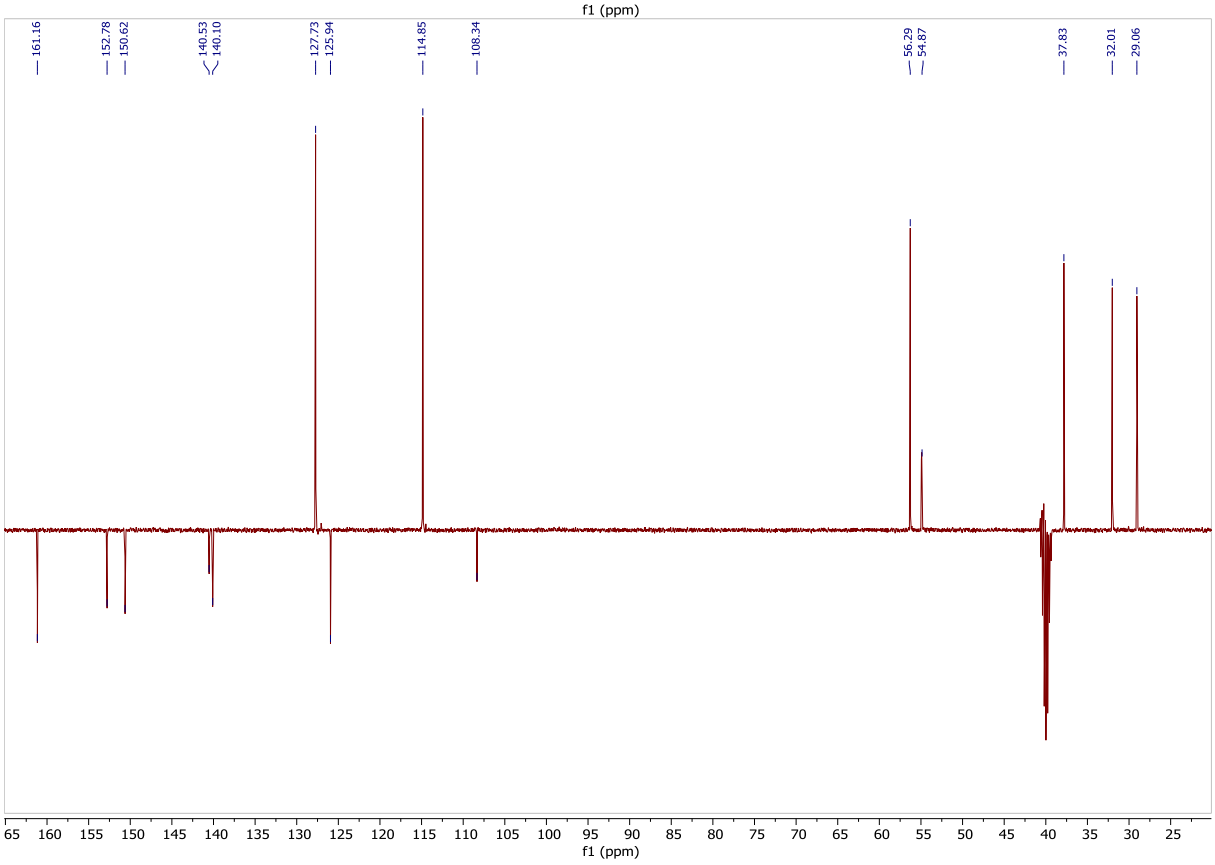
1,3,9-Trimethyl-7-phenylxanthinium tetrafluoroborate



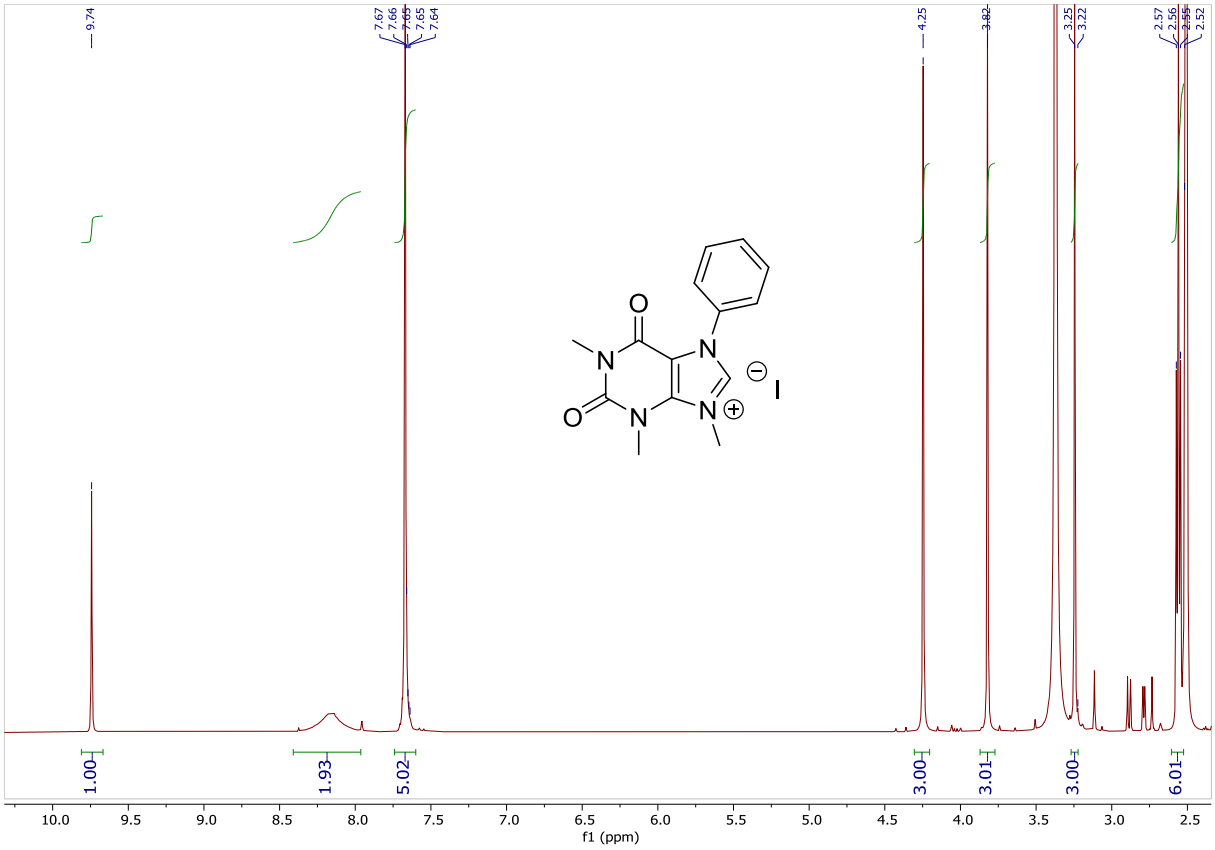


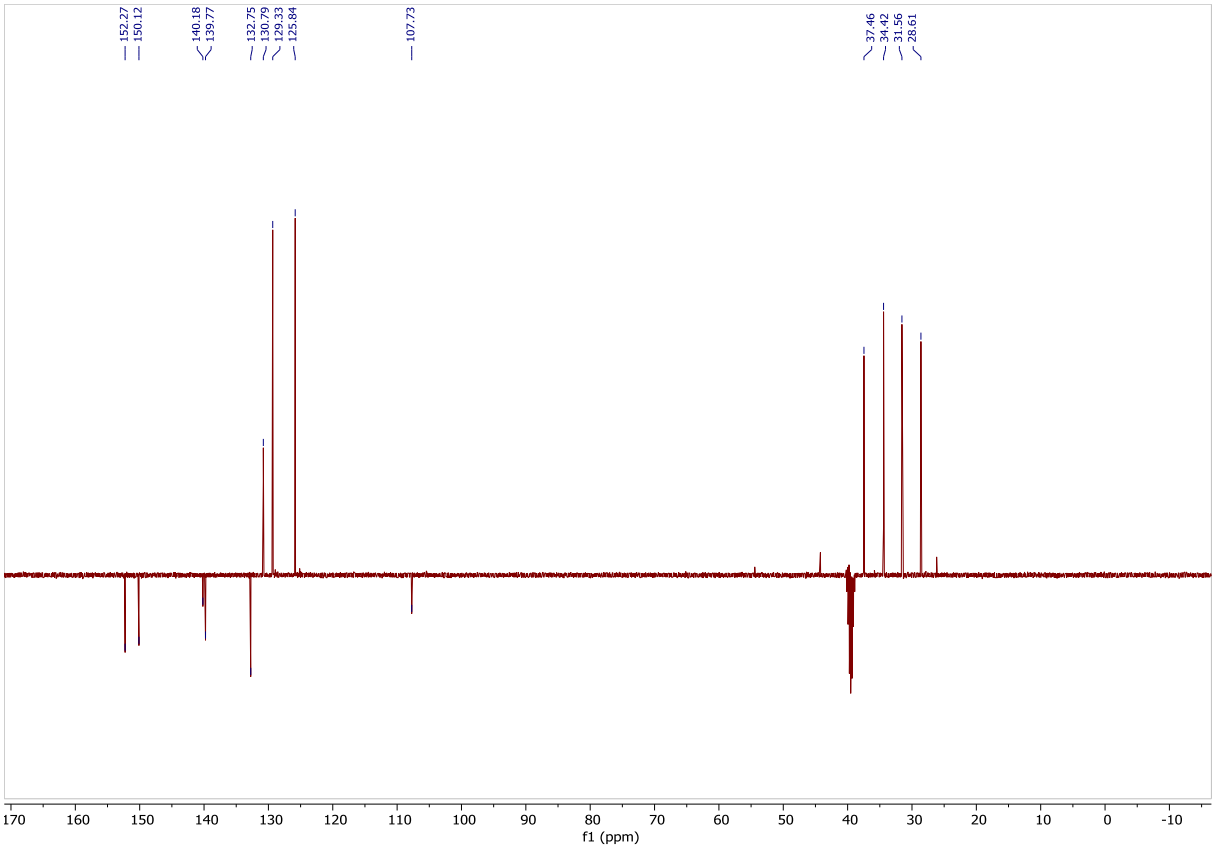
7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium iodide



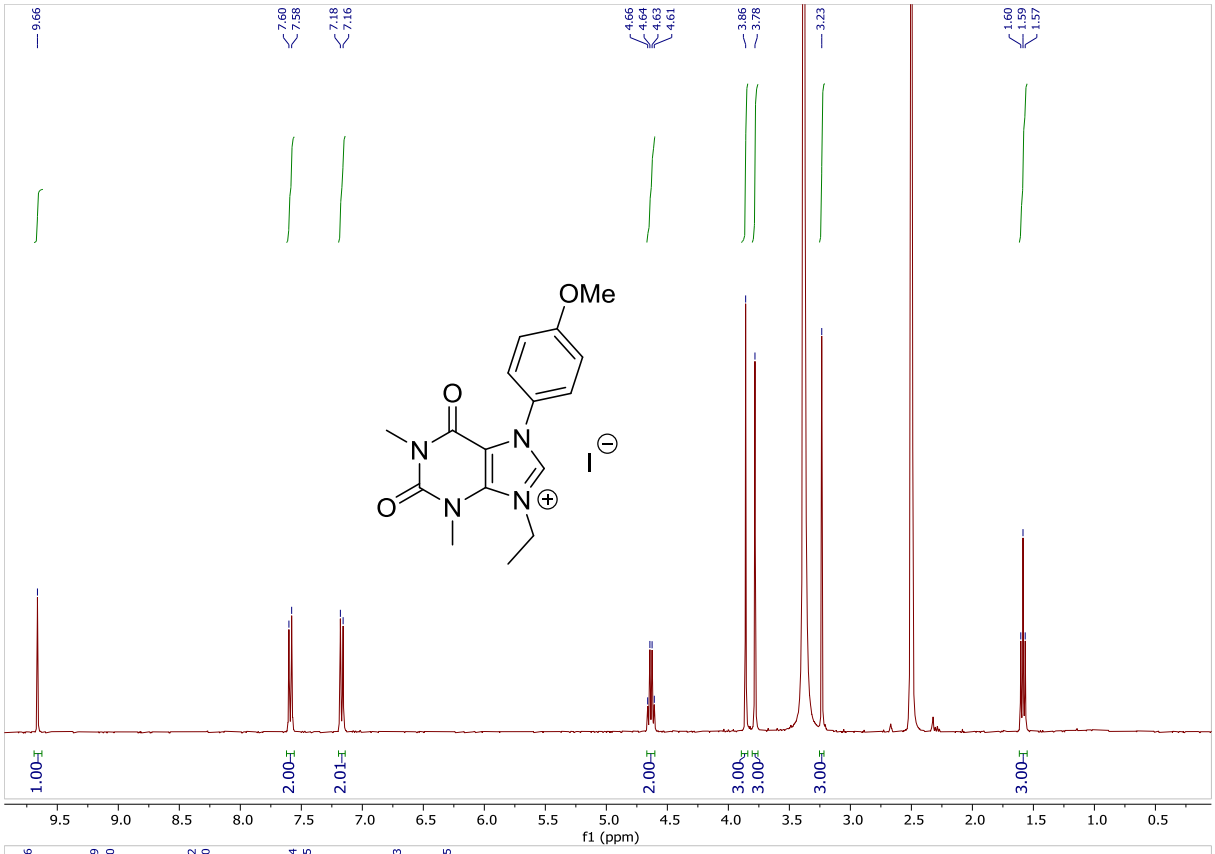


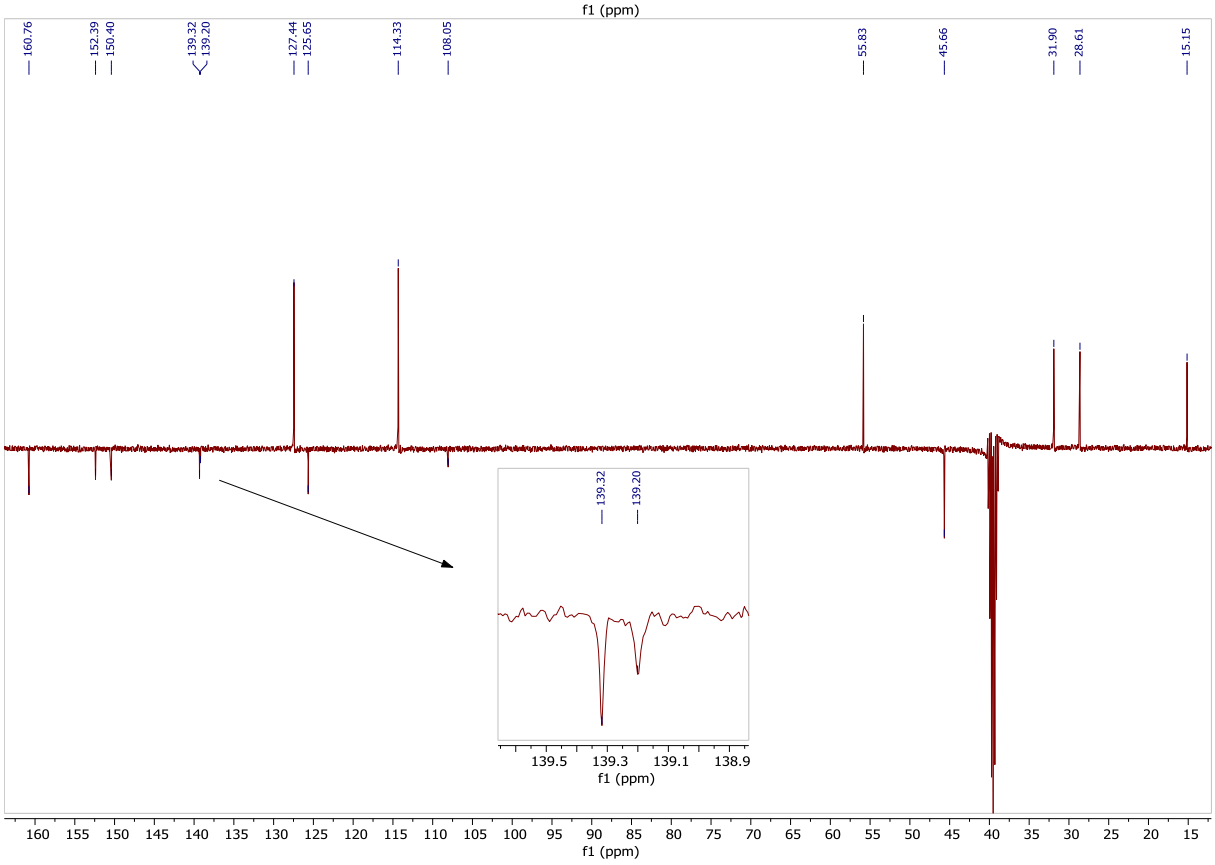
1,3,9-Trimethyl-7-phenylxanthinium iodide





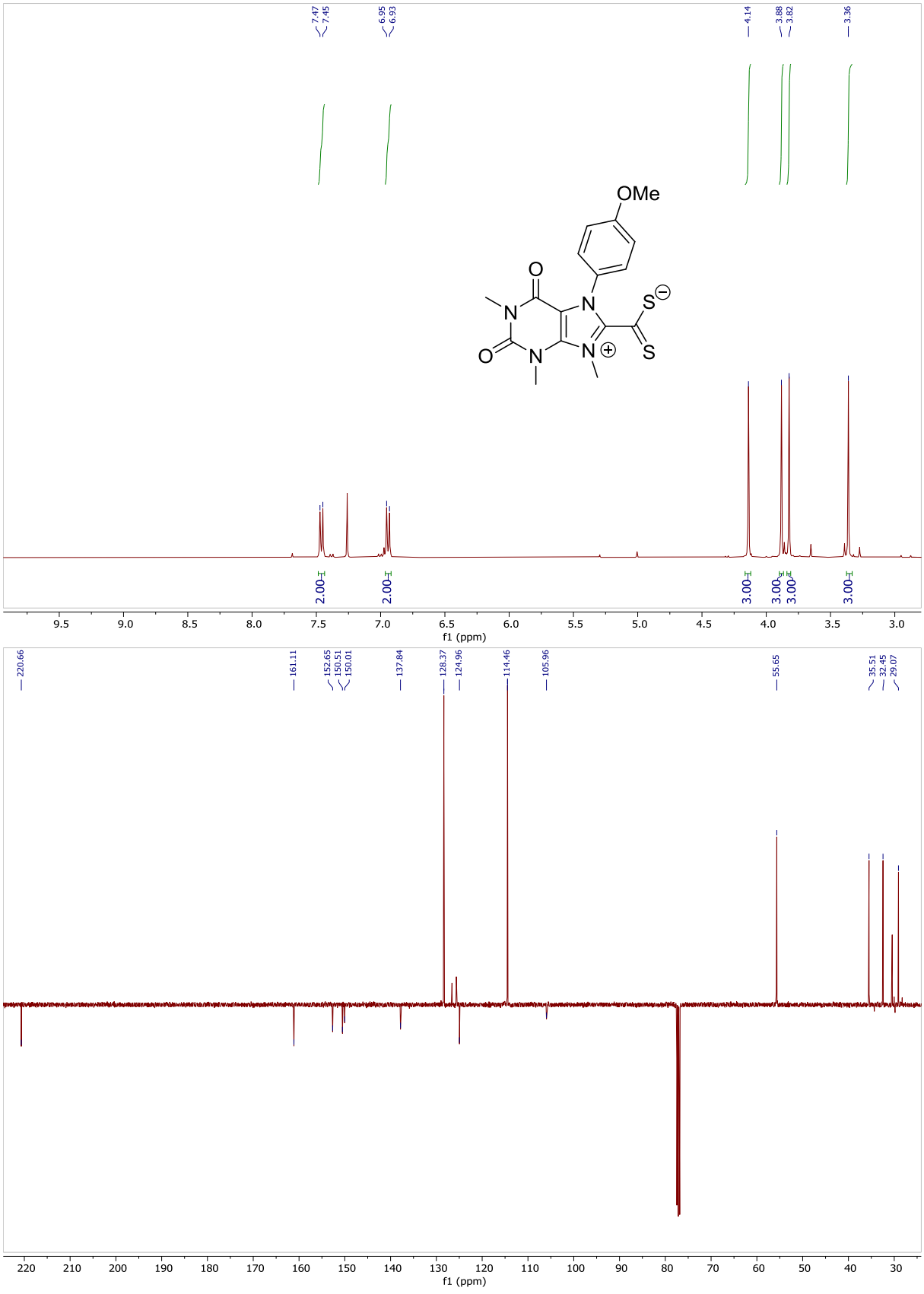
9-Ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium iodide



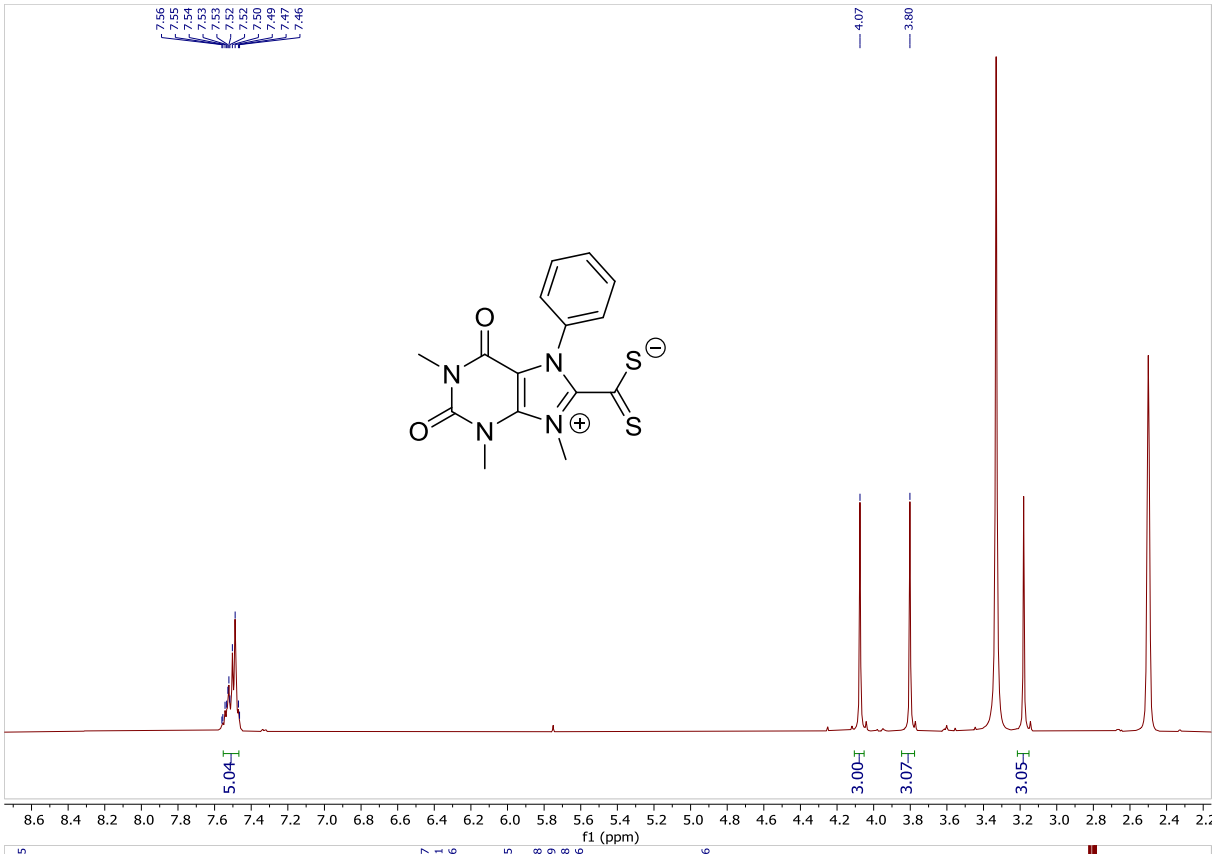


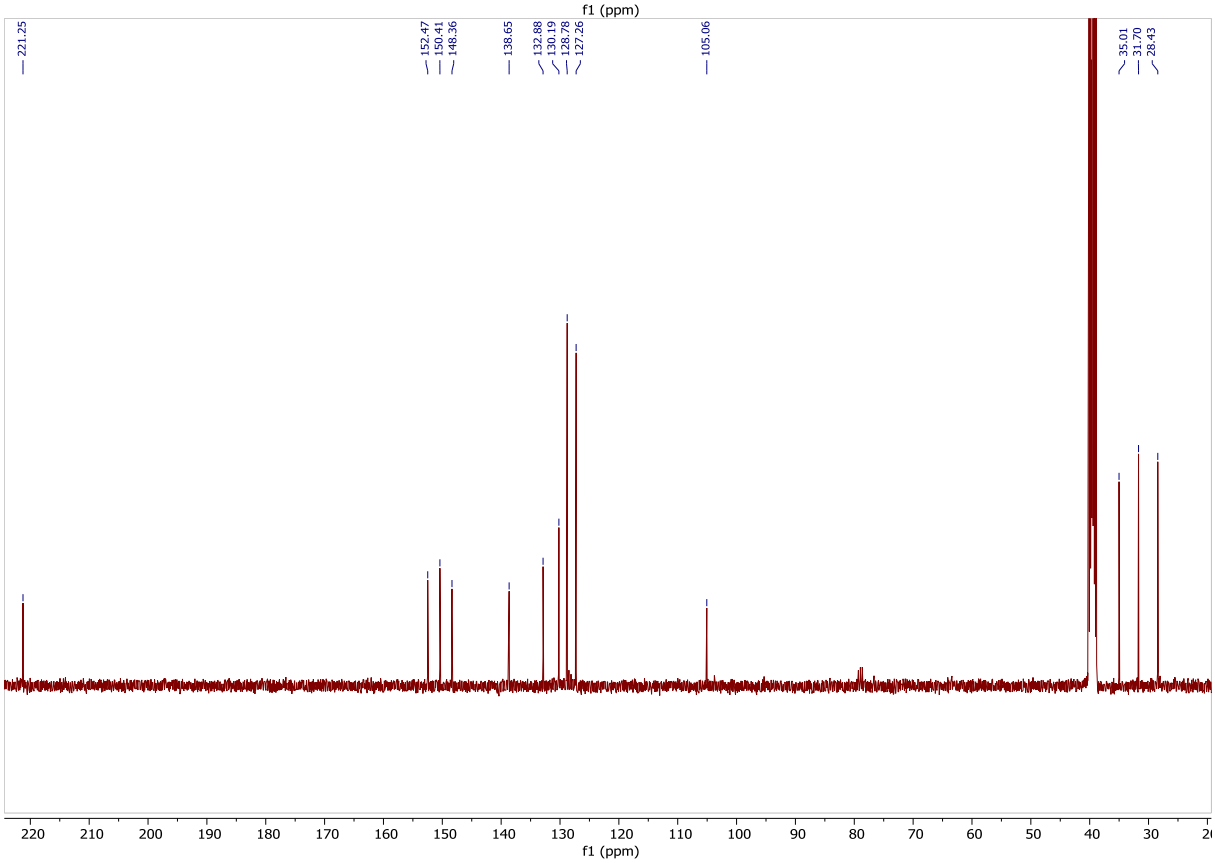
7.3. ^{1}H and ^{13}C NMR spectra of imidazolium dithiocarboxylate zwitterions

7-(4-Methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate

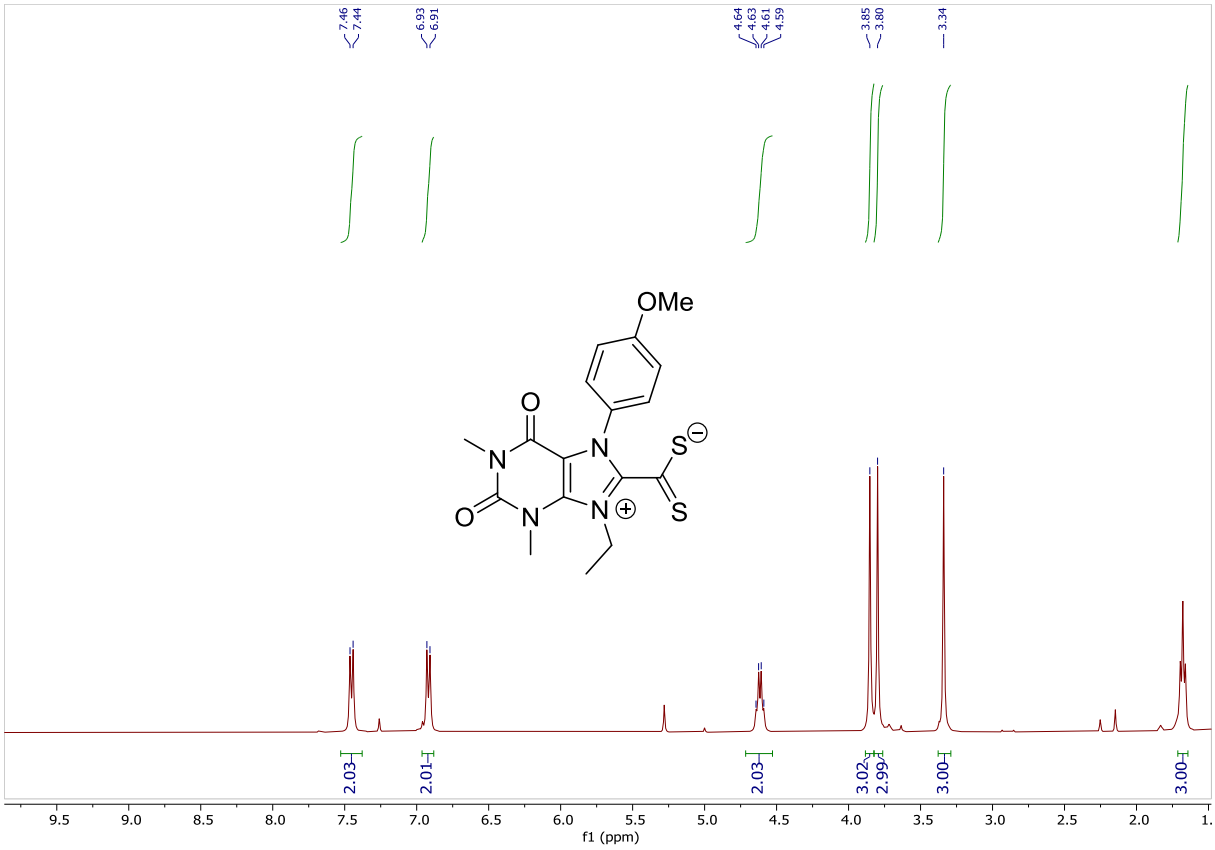


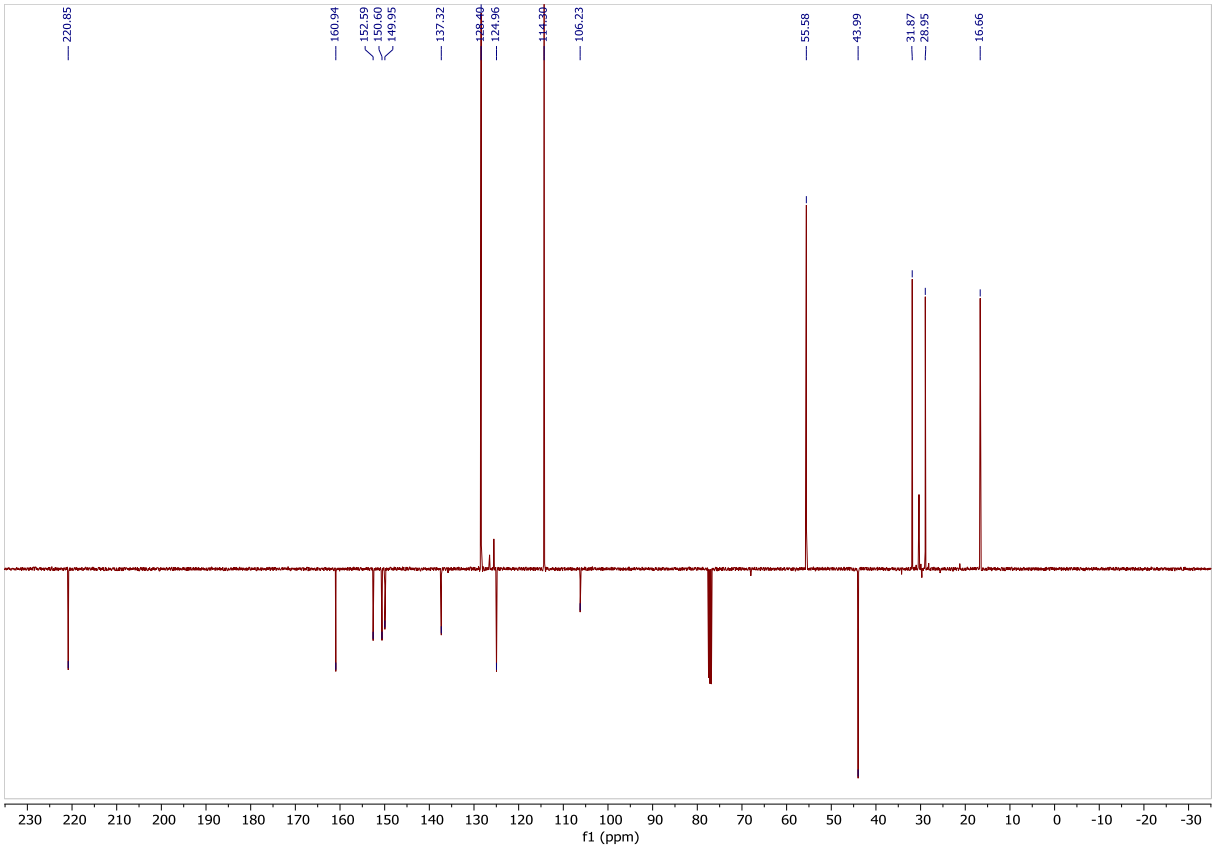
1,3,9-Trimethyl-7-phenylxanthinium-8-dithiocarboxylate





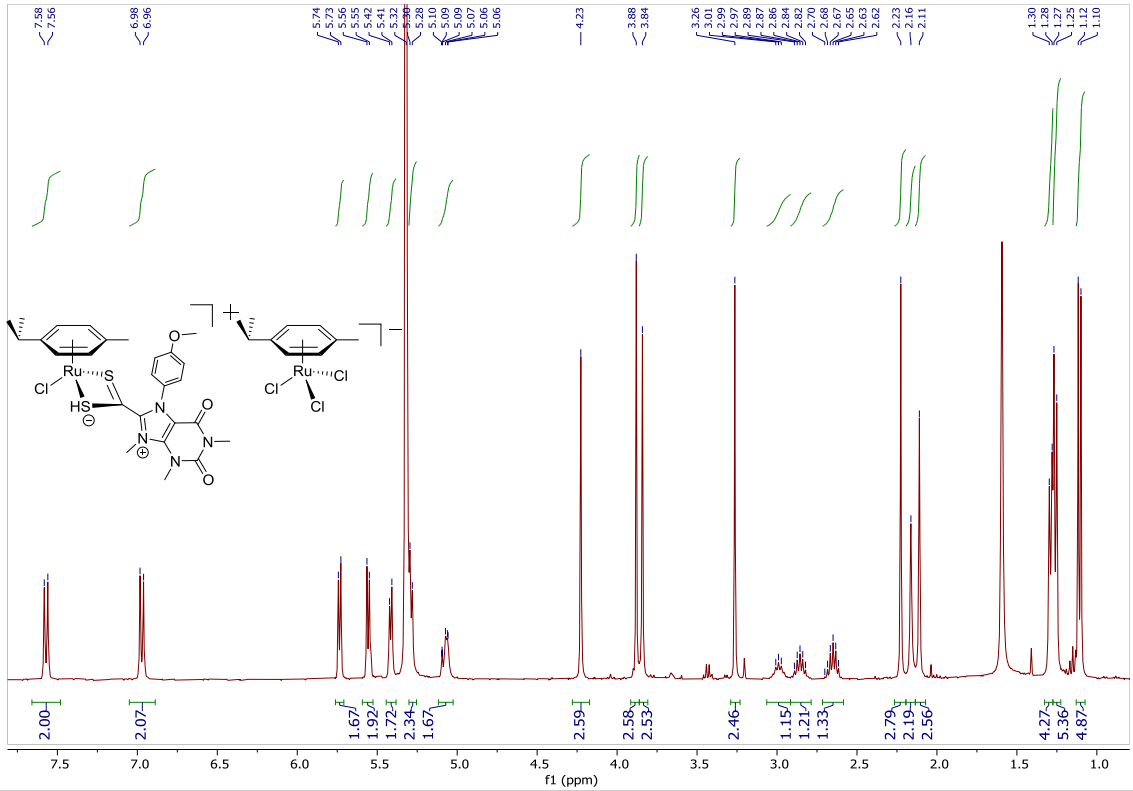
9-Ethyl-7-(4-Methoxyphenyl)-1,3-dimethylxanthinium-8-dithiocarboxylate

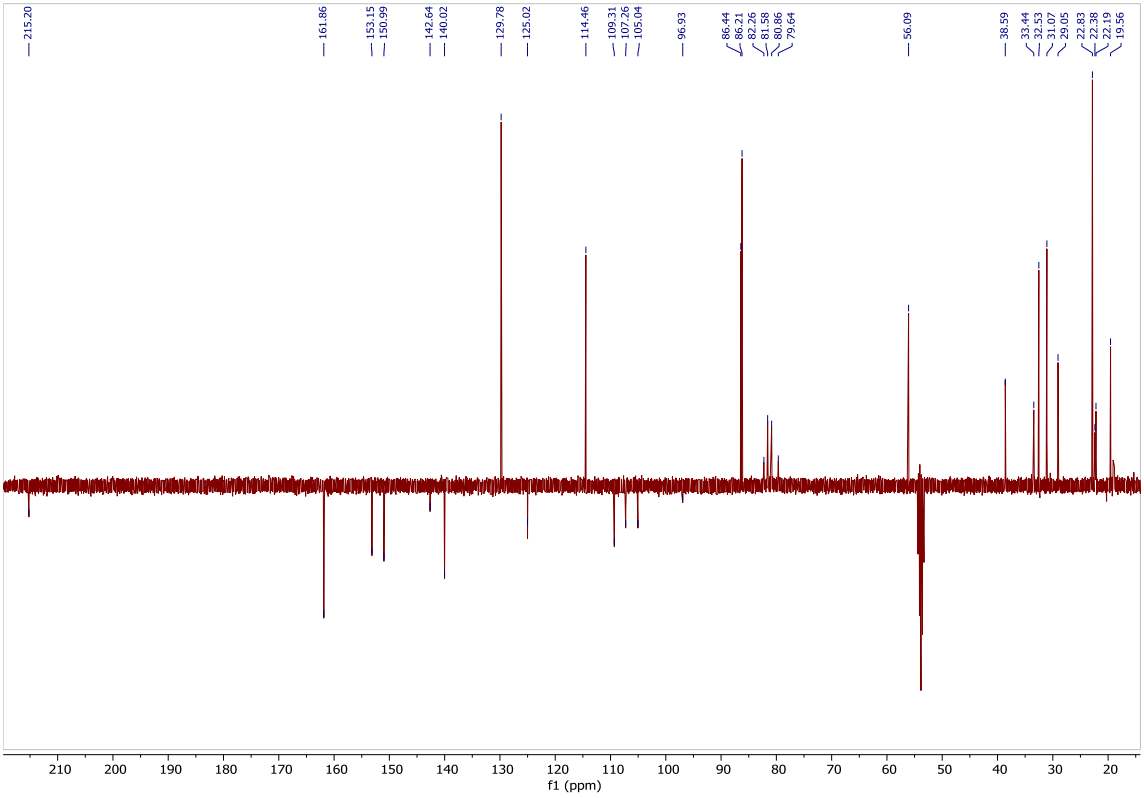




7.4. ^{1}H and ^{13}C NMR spectra of [RuCl(*p*-cymene)(S_2C·NHC)][$RuCl_3$(*p*-cymene)] complexes

[RuCl(*p*-cymene)(7-(4-methoxyphenyl)-1,3,9-trimethylxanthinium-8-dithiocarboxylate)][$RuCl_3$(*p*-cymene)]





[RuCl(*p*-cymene)(9-ethyl-7-(4-methoxyphenyl)-1,3-dimethylxanthinium-8-dithiocarboxylate)]-[$RuCl_3$(*p*-cymene)]