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Grau de Química

Treball Final de Grau

Palladium-Catalyzed C–H bond functionalization for the synthesis of tetrahydroisoquinolines

Funcionalització d'enllaços C–H catalitzada per pal·ladi per a la síntesi de tetrahidroisoquinolines.

Pau Guillamon Daimiel

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Marie Curie

En primer lloc sento la necessitat d'agrair especialment al doctor Xavier Ariza l'oportunitat brindada al seu grup de recerca, així com l'especial atenció prestada tan a mi com a aquest projecte.

De la mateixa manera, donar les gràcies als meus companys de laboratori Luis, Víctor, Javier, Roberto i Marc pel seu suport, ajut i atenció així com pel seu humor i amè ambient de treball i, evidentment, per la seva paciència en moments difícils.

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REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (ODS)

Since this project turns around the synthesis of potential biological useful structures via a cyclization process based on Pd(II) C–H activation it would mainly fit properly in the **Good Health and well-Being** category.

The discovery and expansion of biological useful structures' libraries and the development of new synthetic routes to approach them is a key step to warranty the sufficient drug availability, especially in those countries with resource shortage. In fact, the increase of alternatives for the synthesis of new medicines warranties the accessibility to those countries since both, more optimal methods, and more efficient substances, causes an immediate reduction of the price of manufacture.

Besides that, the opening of a new front of synthetic possibilities also means making easy to find new necessary drugs in a shorter period of time. In future situations, this additional swiftness in compound production might make a huge difference by better preparation of the community to tackle new possible situations similar to the pandemic caused by COVID-19.

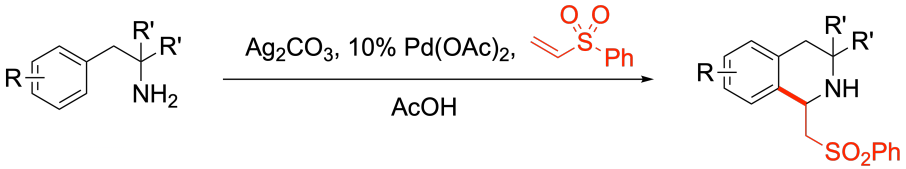
CONTENTS

1. SUMMARY

The synthesis of new bioactive compounds is always a challenge for chemists, particularly in areas where the appearance of resistant strains to specific drugs is becoming important. Even with the technology and knowledge available, drug discovery is not trivial and hit rates tend to be unfavourable. For this reason, the discovery of privileged bioactive scaffolds that allow multiple structural variations seems to be an appropriate strategy to tackle these issues. In this sense, tetrahydroisoquinoline, a heterocycle that is present in many natural sources, is part of a family of compounds with multiple biological activities that fits with these features.

One way to access these heterocycles is by metal-catalyzed cyclization of 2-phenylethylamine derivatives by a C–H activation process. However, the use of unprotected primary amines as a cyclization precursors was almost unprecedented: the elevated reactivity and strong coordination of primary amines to metals difficults their use in metal-catalyzed processes.

In this context, to avoid the aforementioned coordination to the metal, the addition of steric hindrance next to the nitrogen was suggested and tested. The results showed that hindered primary amines can be used in this type of cyclization with Pd(II) as a catalyst. Thus, a general synthetic route for the obtention of tetrahydroisoquinoline derivatives coming from primary amines is reported in this project where the additional carbon atom necessary to form the THIQ is introduced through a conjugated addition of a C–H activated carbon to a phenyl vinyl sulfone.



General scheme for the THIQ obtention process by cyclization of phenylethylamines

The synthetized compounds have a common THIQ skeleton and vary their aromatic substituents and the steric hindrance around the amine. In this work, two different methods for the preparation of the starting amines are reported as well as its cyclization to THIQs.

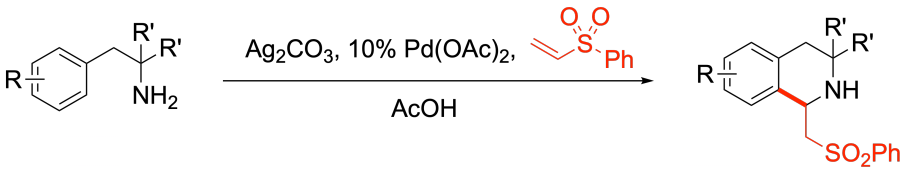
Keywords: tetrahydroisoquinolines, primary amines, vinyl sulfones, C–H activation, palladium catalysis.

2. RESUM

La síntesi de nous compostos bioactius ha estat sempre un repte pels químics, particularment quan l'aparició de resistència a medicaments específics es troba en augment. Tot i la tecnologia i coneixements que es té a l'abast, el descobriment de nous fàrmacs és un procés complicat i amb una molt baixa taxa d'èxit. És per això que el descobriment d'estructures privilegiades les quals admeten diverses variacions estructurals sembla ser una estratègia adient per abordar el problema. En aquest sentit, la tetrahidroisoquinolina, un heterocicle present en diverses fonts naturals, és part d'un grup de compostos amb activitat biològica diversa que sembla complir amb les característiques desitjades.

Una possibilitat sintètica per aquests heterocicles es mitjançant l'activació d'un enllaç C-H catalitzada per un metall de transició. De totes maneres, l'ús d'amines primàries com a precursors té pocs precedents degut a la seva reactivitat i el fort caràcter coordinant que té amb els metalls complicant així el seu ús en reaccions catalitzades per aquests.

Així doncs, per evitar aquesta coordinació esmentada, es proposa i prova l'addició de grups voluminosos que impedeixin estèricament l'amina. En aquesta línia, els resultats avalen l'ús d'amines primàries impedides en aquest tipus de ciclacions amb catalitzadors de Pd(II). Així doncs, en aquest projecte es detalla una ruta sintètica per l'obtenció de tetrahidroisoquinolines a partir d'amines primàries on el carboni extra necessari ve donat per l'addició conjugada d'un enllaç C–H activat al carboni d'una sulfona de fenil i vinil.



Esquema general del procediment d'obtenció de THIQs per ciclació de feniletilamines

Els compostos sintetitzats tenen una estructura comú de THIQ amb les seves respectives variacions en els substituents de l'anell aromàtic i l'impediment estèric al voltant de l'amina. En aquest treball es proposen dos mètodes per la preparació de les amines de partida, les quals han estat posteriorment ciclades donant lloc a les THIQ desitjades.

Paraules clau: tetrahidroisoquinolines, amines primàries, sulfones de vinil, activació C–H, catàlisi per pal·ladi.

3. INTRODUCTION

3.1. TETRAHYDROISOQUINOLINE (THIQ): A PRIVILEGED SCAFFOLD FOR BIOACTIVE COMPOUNDS

Nowadays chemists have many options and advanced technologies to synthetize a huge number of different compounds in a relatively short period of time. Some of these methods are widely used to find useful structures from large libraries of compounds. As it might be supposed, this systematic work implies a considerably low hit rate since only a few are critical discoveries[1].

With the analysis of bioactive compounds isolated from natural sources, recent studies have proven the presence of a repeated structure in some of them: tetrahydroisoquinolines. For this reason, THIQ is considered a privileged scaffold and, furthermore, THIQ-based libraries of compounds have shown a significantly better hit rate[2].

In Figure 1 some of the multiple examples of bioactive compounds with a THIQ scaffold are depicted and, due to the relevance of this structure, many routes for the preparation of these heterocycles are being studied[3], [4].

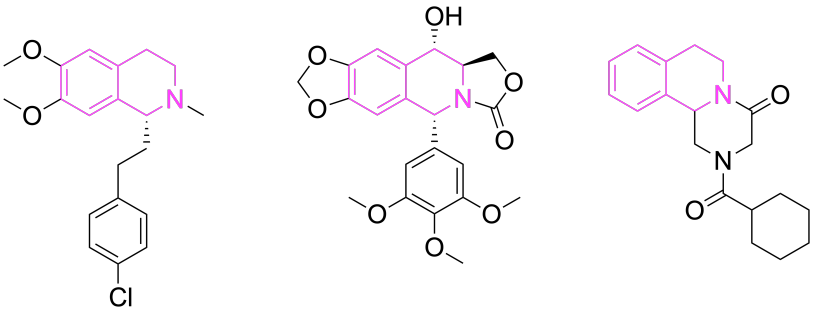
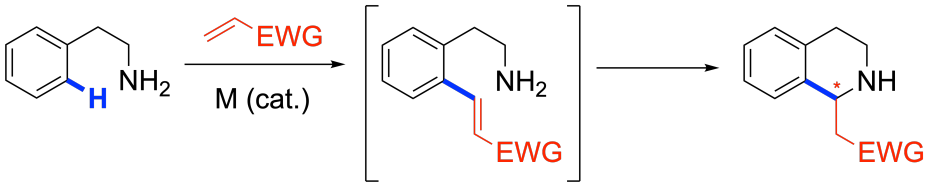


Figure 1. Example of bioactive THIQ-based structures

In addition, the fact that antibacterial resistance is becoming a worldwide threat, increases the demand of novel antibiotics raising, even more, the importance of this project as THIQs are proven to be particularly good as antibacterial agents responding to this global demand of new modified structures[5].

3.2. METAL-CATALYZED C–H ACTIVATION: A POWERFUL SYNTHETIC TOOL

Carbon-carbon bond formation is a key process in synthetic organic chemistry. In the last decade, metal-catalyzed C–H activation has become a common transformation to form, among others, new C–C bonds. We envisioned that this type of processes can be used to form the THIQ skeleton by cyclilzating phenylethylamines as shown in Scheme 1[6].



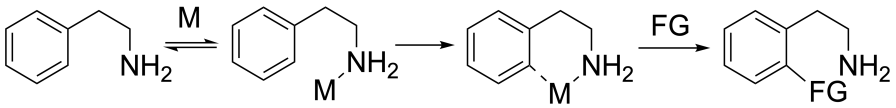
Scheme 1. Obtention of a generic THIQ by a phenylethylamine cyclization reaction via metal catalyzed C–H activation

As the reader may notice, apart from the new bond created (marked in blue) along the process, a new carbon atom has been added from the reagent (red structure). The catalyzed activation mentioned before showed to be useful creating new C–C bonds with Michael acceptors, which consist in products with an α,β-unsaturated electron withdrawing group. In previous research of the group, acrylates were already tested as Michael acceptors in this type of cyclizations[6].

In a general vision of the proposed reaction, the Michael acceptor should coordinate to the catalyst as the phenylethylamine does, leading to an insertion creating the desired C–C bond with the subsequent intramolecular conjugated addition of the amino group to this α,β-unsaturated EWG (structure in brackets).

3.2.1. Selectivity

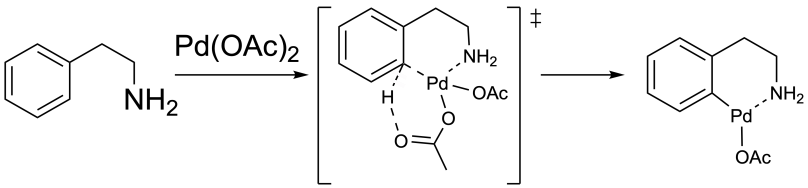
The development of selective processes is one of the main challenges in chemistry. In this particular case, many C–H bonds are present in the structure and most of them have similar properties and reactivity[7]. For this reason, even if there are many reported reagents to activate these kind of bonds, only a few will present the selectivity needed for the desired functionalization. One way to select a particular C–H bond is with the use of internal directing groups[8, 9]: in our approach, the amine should direct the aromatic hydrogen *ortho* to the ethylamino group[10]. As it is shown in Scheme 2, the amine present in the phenylethylamine acts as the desired directing group (DG) due to the lone electron pair capacity to complex metals. The use of nitrogen functional groups as DG is well-stablished, but examples of primary amines are scarcer[11, 12].



Scheme 2. Use of an ethylamino substituent as a directing group

3.2.2. Palladium-catalyzed synthesis of novel modified THIQs

Several transition metals such as iridium[13], rhodium[14] or palladium have been used as catalysts in these type of transformations but $Pd(OAc)_2$[15] has showed a broader scope. The coordination of the nitrogen sets the catalyst near an *ortho* hydrogen directing the C_{Ar}–H bond activation only through this position as shown in Scheme 3. Furthermore, in this case, the acetate ligand helps to accelerate the hydrogen abstraction.



Scheme 3. Palladium acetate activation with a generic phenylethylamine

3.2.3. Primary amines bonded to a quaternary carbon as parent structures

The main problem of this kind of activation with primary amines lies in the strong coordinating behaviour of the basic nitrogen to palladium and so, the difficulty to use it as a catalyst. As a result of this property, bis-coordination products like the ones shown in Figure 2 were detected giving rise to the subsequent catalyst poisoning[16].

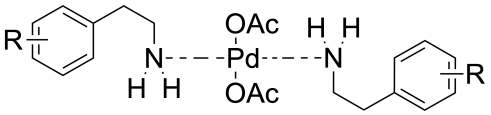


Figure 2. Palladium catalyst poisoning by bis-coordination of primary amines

This bis-coordination product prevents the C–H activation process, which is needed for the successful mechanism development. To sort this undesired pathway, an increase of the amine steric hindrance by the addition of alkyl groups in the closest C_{sp^3} was suggested and checked allowing, this way, the obtention of, not only new structures to expand the library of THIQ-based compounds, but a new and more efficient method to reach them[6]. For this reason and to evaluate this C–H functionalization, a series of α,α-disubstituted phenylethylamines was needed.

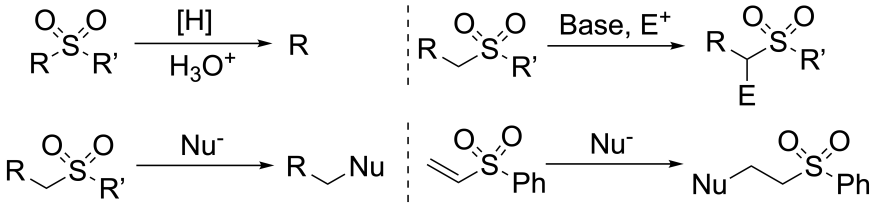
Figure 3. General skeleton for the target amines

In addition, it is expected that this double α substitution to the amino group would help the Michael-type addition by a Thorpe-Ingold effect[15].

3.2.4. Vinyl sulfones: a versatile Michael acceptor

Once the skeleton of the parent amines is defined, the selection of the Michael acceptor used for the cyclization must be a suitable choice considering the future possible modifications to the THIQ obtained.

As it can be deduced from section 3.1, THIQ-based bioactive compounds require further modifications after the cyclization as THIQs by themselves are not biologically useful. For this reason, sulfones, concretely phenyl vinyl sulfone, was chosen as an EWG owing to its availability and versatility (Scheme 4)[17].

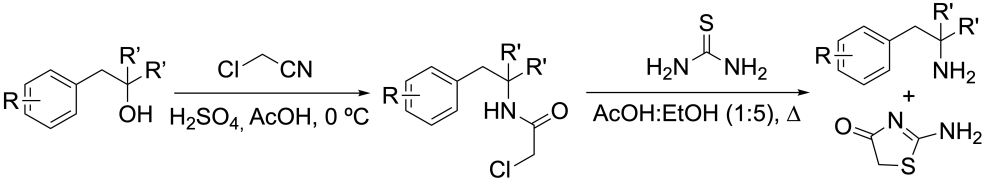


Scheme 4. Sulfone reactivity

Due to this wide range of possibilities and its combinations, when possible, diverse functionalization of the THIQs obtained is not risky and, in fact, is the key to be able to swiftly obtain an even more accurate library of compounds.

3.2.5. Previous results of the group

Along last years, our research group has been working in C–H bond activation for the synthesis of modified THIQs and proposed a Ritter reaction, which is detailed in further sections, for the preparation of the starting phenylethylamines. The use of 2-chloroacetonitrile, instead of acetonitrile, allows an easier method for the amide hydrolysis with thiourea[18].

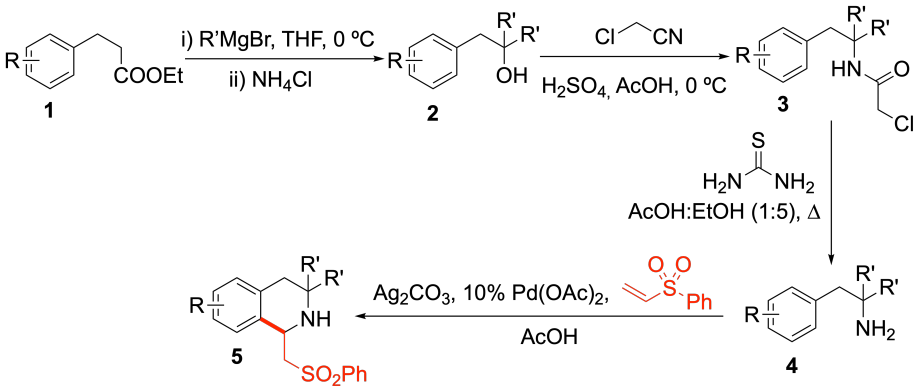


Scheme 5. General method for the amine synthesis via a Ritter reaction

4. OBJECTIVES

The aim of this project is to test a standard method based on a Ritter reaction for the synthesis of primary amines with a suitable steric hindrance in order to successfully obtain a series of the desired tetrahydroisoquinolines according to Scheme 6.

THIQs with different nature R groups will be synthetized and characterized. In cases of significantly lower yield an alternative synthetic route will be designed.



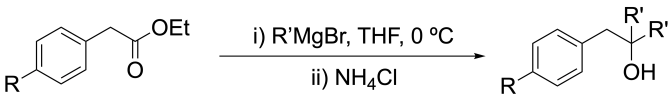
Scheme 6. General sequence for the obtention of THIQs

5. DISCUSSION OF RESULTS

5.1. Obtention of the starting amines via a Ritter reaction

5.1.1. Synthesis of tertiary alcohols

Tertiary alcohols are the first necessary intermediates to obtain the desired amines. Despite some of them are commercially available, many others are not and can easily be synthetized by the complete addition of the desired organomagnesium containing R' over the corresponding ester (nucleophilic attack).



1a (R=Me)
1b (R=H)
1c (R=OMe)

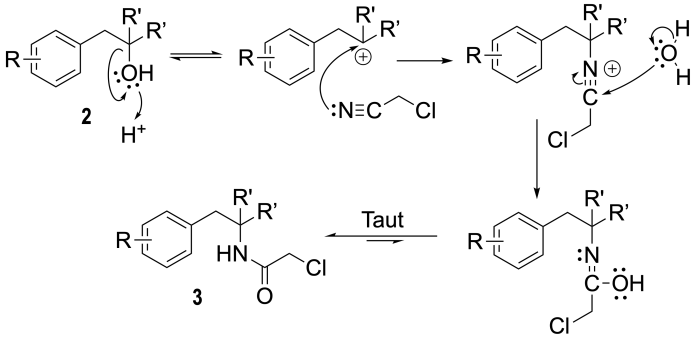
2a (R=R'=Me) 100%
2b (R=H, R'=Et) 93%
2c (R=OMe, R'=Me) 100%

Scheme 7. Tertiary alcohol synthesis

The reaction is carried out with organomagnesium excess and inert atmosphere: if there were water traces the Grignard excess would react leading to magnesium hydroxide. As there are not any possible byproducts, yields tend to be favourable. The excess of magnesium compound is eliminated while quenching in slightly acidic aqueous medium so only the desired product is extracted to the organic layer.

5.1.2. Synthesis of chloroacetamides

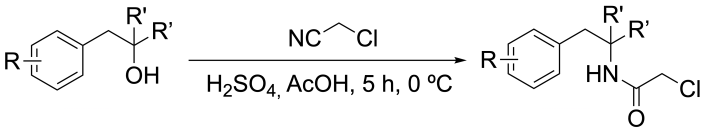
In strong dehydrating acidic medium, tertiary alcohols form easily relatively stable carbocations susceptible to the nucleophilic attack of nitrile. For this reason, the addition of chloroacetonitrile leads to a Ritter reaction which is necessary to obtain the desired intermediates: chloroacetamides.



Scheme 8. Chloroacetamide formation mechanism (Ritter reaction)

As shown in Scheme 8, the intermediate in aqueous medium adds water obtaining an imide which will quickly tautomerize leading to the desired chloroacetamide.

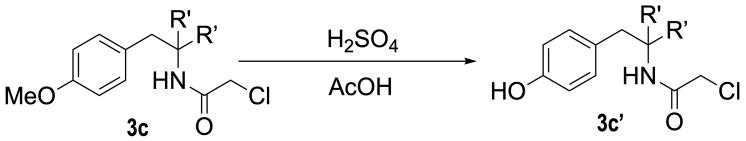
With the tertiary alcohols prepared (**2a**, **2b**, **2c**) and commercially available alcohols (**2d**, **2e**) the above conditions were applied to afford the corresponding 2-chloroacetamides (Scheme 9). To purify the product, the excess of chloroacetonitrile was eliminated at reduced pressure (bp(atm) 123-124ºC).



2a (R=*p*-Me, R'=Me)	**3a** (R=*p*-Me, R'=Me)	66%
2b (R=H, R'=Et)	**3b** (R=H, R'=Et)	85%
2c (R=*p*-OMe, R'=Me)	**3c** (R=*p*-OMe, R'=Me)	24%
2d (R=H, R'=Me)	**3d** (R=H, R'=Me)	93%
2e (R=*o*-Me, R'=Me)	**3e** (R=*o*-Me, R'=Me)	60%

Scheme 9. Chloroacetamide synthesis

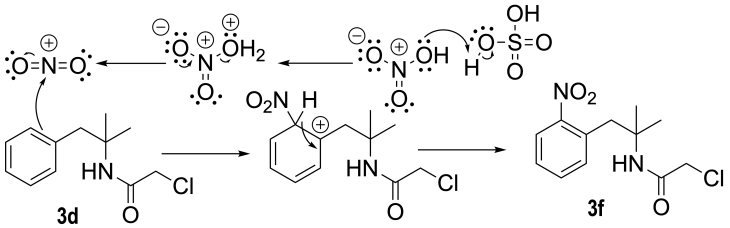
Chloroacetamide **3c** contains an aryl ether and the reaction, as mentioned, takes place in extremely acidic dehydrating medium which favours the obtention of the demethylation product shown in Scheme 10. To avoid this undesirable process, a new method based on a Curtius rearrangement is detailed in further sections.



Scheme 10. Aryl ether hydrolysis in acidic conditions

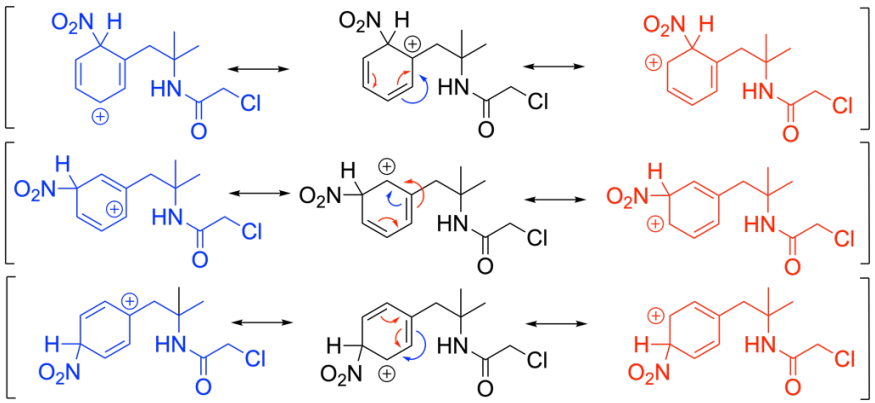
5.1.3 Nitration

To obtain both *ortho* and *para* nitro-compounds, an aromatic nitration process starting from chloroacetamide **3d** was carried out. The mechanism shown in Scheme 11 will only lead to *ortho* and *para* nitration and both isomers must be separated by LC before any further step.



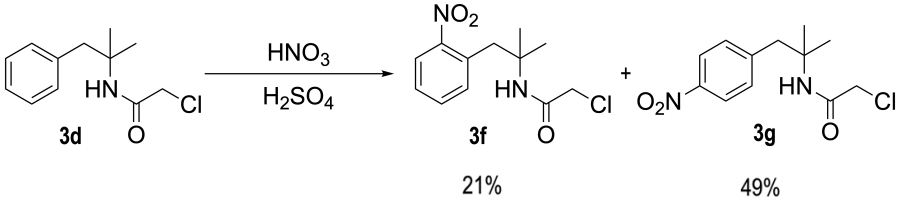
Scheme 11. Aromatic nitration mechanism

As shown, the mechanism involves the formation of a carbocation and so only the compounds which go through the most stable one will be obtained. In Scheme 12 the resonance of each intermediate is depicted which explains the obtention of only two of the three possible isomers.



Scheme 12. Resonance forms of *ortho*, *meta* and *para* (from top to bottom) carbocation intermediates

Meta nitro-compound will not be formed as tertiary carbocations (black figure for *orhto* and blue figure for *para*) are much more stable than secondary ones. Moreover, steric hindrance also plays an important role considering the size of the group bonded to the aromatic ring: a considerably lower proportion of *ortho* nitro-compound was obtained.

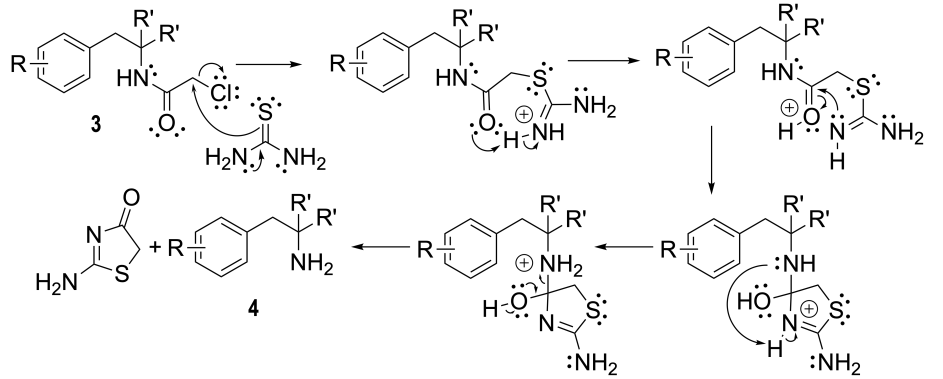


Scheme 13. Nitration process

Even if yields might seem lower than expected, it should be considered that the obtention of two isomers comes from a single starting reagent. Thus, the overall yield for the nitration process is 70% in a 30:70 proportion between *ortho* and *para* nitro-compounds.

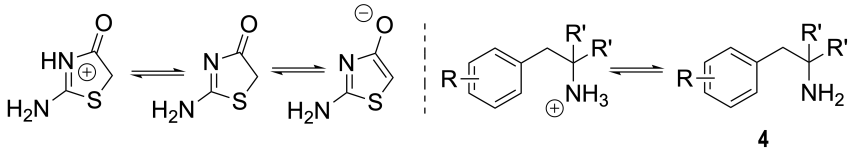
5.1.4. Hydrolysis of amides

Amines are obtained by heating the previous chloroacetamides in acidic medium and presence of thiourea by the following mechanism (Scheme 14). In this step the formation of 2-aminothiazol-4-one can be considered the driving force of the reaction to obtain the desired amine. The heterocycle and the excess of thiourea must be eliminated during the work-up, which is possible due to the acid-base properties of each compound.



Scheme 14. Amine formation mechanism

As the pK_a of general amino compounds is ~9-10 (It will variate between amines with different R and R' groups) and the pK_a of protoned aminothiazoles is around 5[19], the first clean-up of the 2 M hydrochloric acid aqueous phase with DCM will remove thiourea remaining only the desired amine and 2-aminothiazol-4-one in the aqueous phase.



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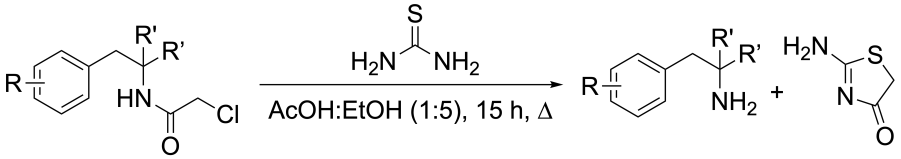
Scheme 15. Acid base equilibrium of 2-aminothiazol-4-one and amines

In a further step, when the medium is basified with NaOH to pH 12, the amine will be in its neutral form, being successfully extracted with DCM from the aqueous phase. On the other side, 2-aminothiazol-4-one, will remain in the aqueous phase as its pK_a is lower than 12.



Entry	R	R'	Product	Yield
3a	*p*-Me	Me	**4a**	65%
3b	H	Et	**4b**	45%
3d	H	Me	**4d**	40%
3e	*o*-Me	Me	**4e**	53%
3f	*o*-NO_2	Me	**4f**	95%
3g	*p*-NO_2	Me	**4g**	89%

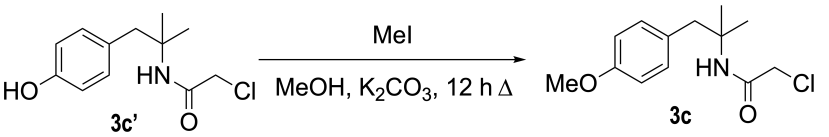
Table 1. Amine synthesis

Analyzing the yield data in Table 1 it is easy to notice that nitro-compound deprotection reactions are more efficient. This effect can be explained by the strong electron withdrawing behaviour of nitro groups, which increases the electrophilia of the carbonyl and so it favours the nucleophilic attack of the thiourea already shown in Scheme 15.

5.2. An alternative route to amines via a Curtius rearrangement

Compound **3c** contain an aryl ether, which is a labile functional group when strong acidic conditions are used. When compound **4c** is synthetized by the standard method developed significantly low yields are obtained. In step 2, when forming the chloroacetamide, the ether stays 5 h in strong dehydrating acidic medium (96% H_2SO_4 in acetic acid), conditions which are proven by ^{1}H-NMR to demethylate 80% of the product due to the aryl ether hydrolysis.

To solve that, a methylation with iodomethane in slightly basic medium[20] was firstly suggested:

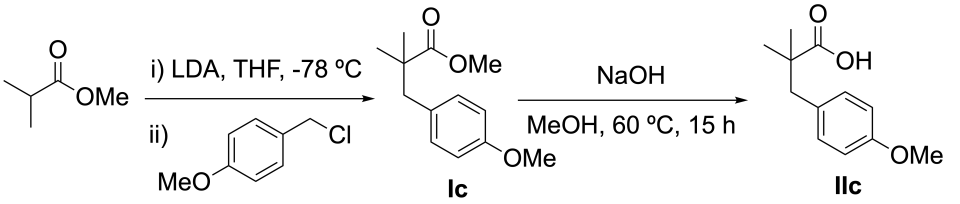


Scheme 16. Methylation conditions

When the crude residue was analysed, the result of this procedure was a mixture of several unknown products. Although the target methylation was significant, other methylated products and dimers due to the basic medium were also significant.

However, as the objective was to optimize the synthetic plan, this reaction was rejected. The resulting theorical yields were not significantly better and two more steps were added to the route, the methylation itself and the necessary liquid chromatography purification of the crude mixture, which was not carried out.

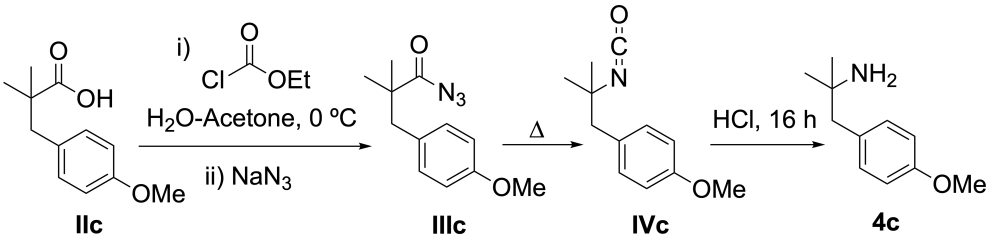
A second alternative and completely different route was developed and explored. In a first step, the carbon skeleton of the molecule was synthesized[21] obtaining an ester which was hydrolysed leading to its corresponding carboxylic acid as shown in Scheme 17.



Scheme 17. Carboxylic acid synthesis

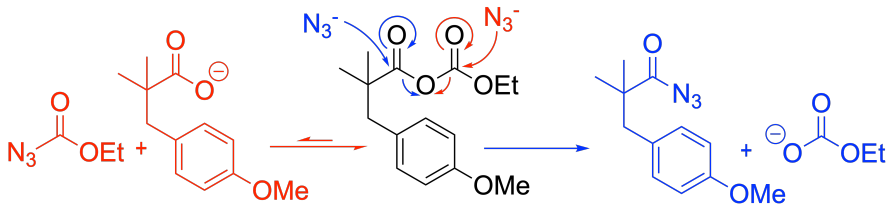
100%

It is important to consider the kinetic conditions when generating the methyl isobutyrate enolate: LDA is used as a non-nucleophilic strong base and the dropwise addition of the compound over the base avoids the dimer formation by intermolecular attack to the carbonyl group. Once we have **IIc**, the carboxyl was activated with ethyl chloroformate to obtain the corresponding acyl azide[22] which was rearranged to an isocyanate and hydrolysed to the desired amine:



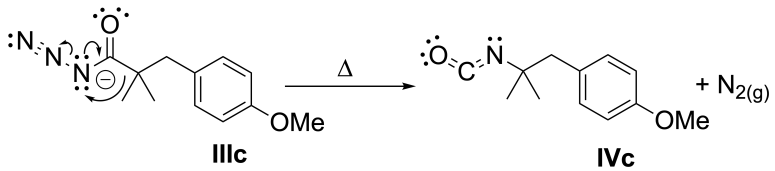
Scheme 18. Curtius rearrangement conditions

As the mixed anhydride has two carbonyl groups, the final product obtained will be the one which generates the best leaving group: the weaker conjugated base stabilized by resonance (blue path in Scheme 19).



Scheme 19. Possible nucleophilic attacks to the activated carboxyl

When **IIIc** is heated, a Curtius rearrangement takes place eliminating $N_{2(g)}$ and generating the isocyanate **IVc**. The global mechanism is described in Scheme 20.



Scheme 20. Curtius rearrangement mechanism

As azides are potentially explosive compounds, **IIIc** was heated in an oil bath to warranty the full control of the temperature. The reaction was followed by IR spectroscopy (Figure 4, ~2110 cm^{-1} band for the acyl azide and ~2230 cm^{-1} band for the isocyanate) to avoid unnecessary long reaction times which might yield to decomposition of the expected products.

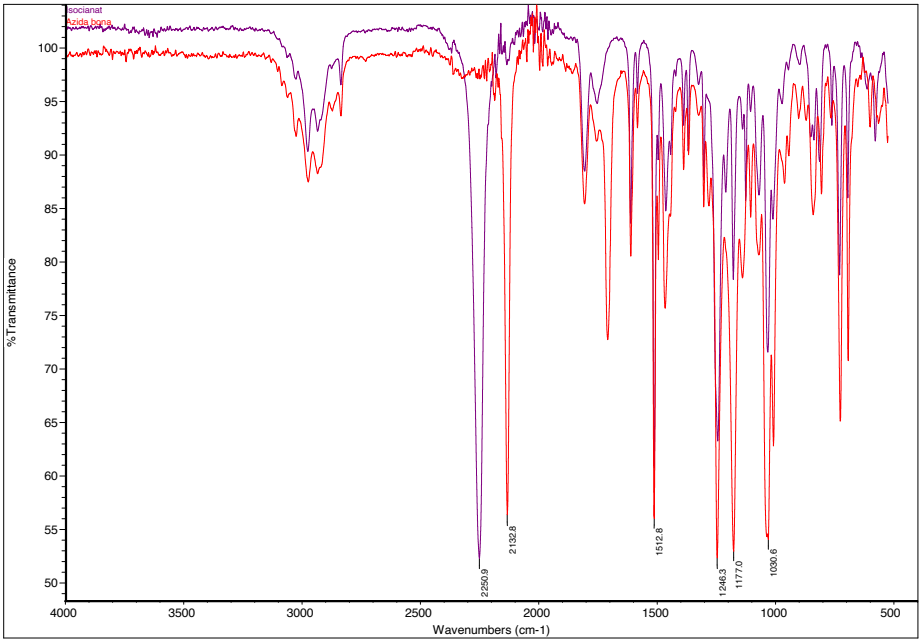
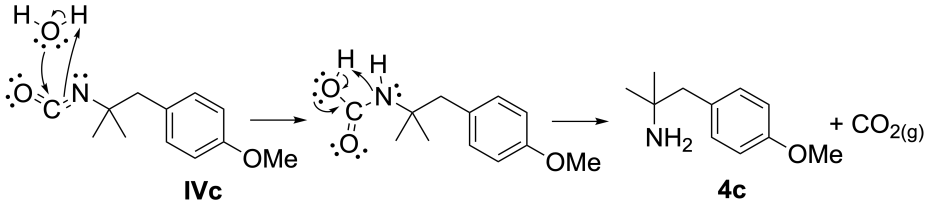


Figure 4. Acyl azide IR spectra (red) and isocyanate IR spectra (blue)

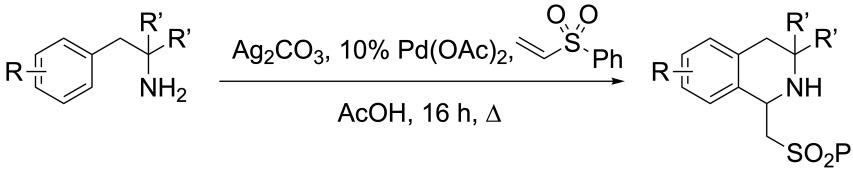
The last step consists in the isocyanate hydrolysis in acidic medium obtaining the desired amine **4c**[23] by the elimination of $CO_{2(g)}$ (Scheme 21). It is important to be aware of the differences between these acidic conditions and the ones used in the initial procedure. In this case, 15% aqueous HCl in acetic acid was used which are less drastic conditions even when it is heated.



Scheme 21. Aqueous isocyanate hydrolysis

5.3. Palladium-catalyzed obtention of THIQs

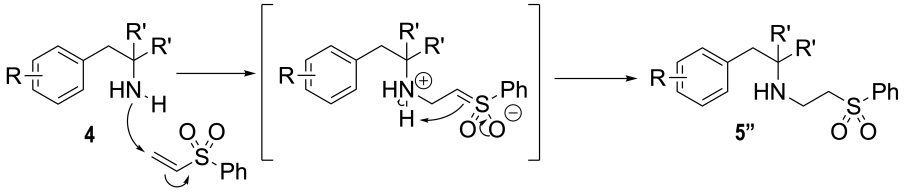
The synthetized amines are the main reagent used to obtain the target compounds of this project, tetrahydroisoquinolines. To reach these structures, an aromatic carbon-hydrogen bond must be activated to allow the formation of a new C_{Ar}–C_{sp^3} bond leading to the desired bicyclic compound which necessarily involves the use of a catalyst. In this case, $Pd(OAc)_2$ was used in a 10% molar ratio using Ag_2CO_3 as an oxidating agent to recovery the reduced palladium[6].



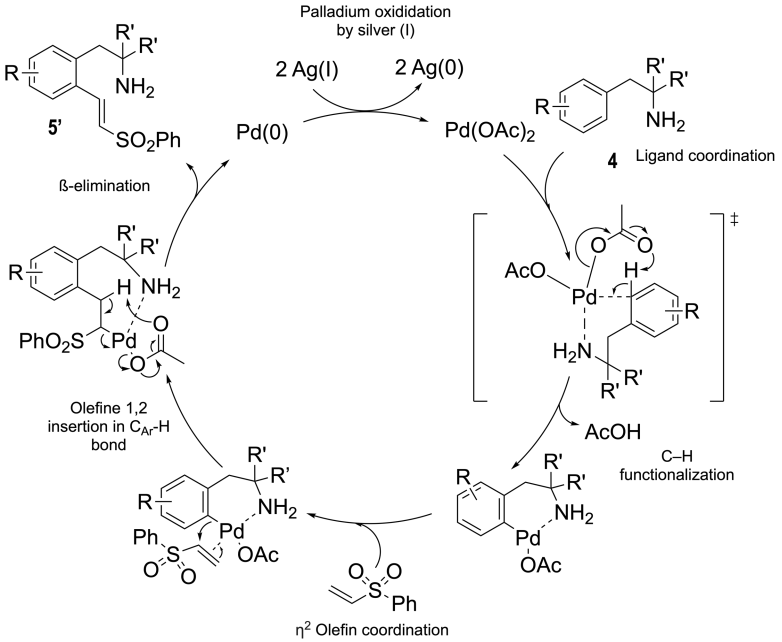
Entry	R	R'	Product	Yield
4a	*p*-Me	Me	**5a**	51%
4b	H	Et	**5b**	57%
4c	*p*-OMe	Me	**5c**	56%
4d	H	Me	**5d**	59%
4e	*o*-Me	Me	**5e**	45%
4f	*o*-NO_2	Me	**5f**	24%
4g	*p*-NO_2	Me	**5g**	33%

Table 2. THIQ synthesis

The mechanism[6] is not trivial and many byproducts were obtained which furthermore involves the pertinent purification by LC. Even if amines are strongly coordinating groups, before the organometallic compound containing amine **4** is formed, intermolecular conjugated attack from the amine to the phenyl vinyl sulfone significantly occurs.

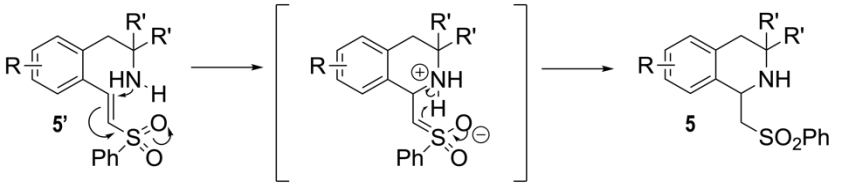


Scheme 22. Intermolecular conjugated attack



Scheme 23. Palladium catalytic cycle for the olefin 1,2 insertion in a C_{Ar}–H bond[6]

Since amines are strongly coordinating groups, the desired coordination is favourable and once the corresponding **5'** type molecule is released from the metal, intramolecular conjugated addition is much faster than any other secondary reaction (Scheme 24).



Scheme 24. Intramolecular conjugated attack

To sum up, the lower yields obtained in this step can be understood by the multiple byproducts the reaction yields to but, in any case, THIQs were successfully synthetized as all those and the starting materials were separated by LC leading to extremely pure compounds checked by ^{1}H and ^{13}C-NMR as well as HRMS.

6. EXPERIMENTAL SECTION

General methods. ^{1}H-NMR and ^{13}C–NMR spectra were recorded using a Bruker 400 MHz or a Bruker 500 Hz spectrometer (indicated in each case). The coupling constants (*J*) are reported in Hz and the chemical shifts (δ) in ppm. The multiplicity of signals is abbreviated as: singlet (s), doublet (d), triplet (t), multiplet (m). $CDCl_3$ (99.8%) was used as solvent and $SiMe_4$ as a reference. Column chromatography was carried out using as stationary phase VWR BDH Chemicals silica gel (technical grade, 40-63 μm particle size). The eluents are indicated in each case. High-resolution mass spectra HRMS (ESI+) were recorded on ThermoFinnigan GC/MS TRACE DSQ at Servei d'Espectrometria de Masses de la Universitat de Barcelona. IR spectra were collected on a Nicolet 6700 Thermo Scientific.

6.1. GENERAL PROCEDURES

6.1.1. General procedure for the alcohol synthesis

The corresponding ester **1** (1 eq) was dissolved in anhydrous THF (30 mL). The mixture was cooled to 0 ºC and a 3 M solution of the organomagnesium reagent in Et_2O (3.5 eq) was added. After the addition, the mixture was stirred for 1.5 h at rt and a saturated ammonium chloride solution was added carefully until no changes were observed. Then, ethyl acetate was added, the organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. The collected organic phase was washed with brine and dried over anhydrous magnesium sulfate. Finally, the solvent was evaporated under reduced pressure to obtain the desired alcohol[6].

6.1.2. General procedure for the chloroacetamide synthesis

The corresponding alcohol **2** (1 eq) was dissolved in acetic acid (2.7 mL) and 2-chloroacetonitrile (6 eq) was added. The mixture was cooled to 0 ºC, and concentrated sulfuric acid (2.7 mL) was added dropwise. It was stirred for 5 h at rt and ice was added carefully until no changes were observed. The aqueous phase was extracted three times with Et_2O, and the

resulting organic phases were washed twice with a saturated solution of Na_2CO_3 and once with brine. The organic phase was dried over anhydrous magnesium sulfate, and it was evaporated under reduced pressure to obtain the desired chloroacetamide impurified with 2-chloroacetonitrile that was removed under reduced pressure (<1 mmHg) at 70 ºC[6].

6.1.3. General procedure for the amine synthesis

The corresponding chloroacetamide **3** (1 eq) was added to a solution of thiourea (1.2 eq) in 5:1 ethanol/acetic acid (60 mL). The mixture was heated to reflux for 15 h (overnight), it was cooled down and the ethanol was evaporated at reduced pressure. 2 N Hydrochloric acid was added to the obtained oily solution and the aqueous phase was washed twice with DCM. The resulting aqueous phase was basified to pH 12 with the necessary amount of solid NaOH and it was extracted three times with DCM. The organic phase was dried over anhydrous sodium sulfate and was evaporated at reduced pressure to obtain the desired amine[6].

6.1.4. General procedure for the THIQ synthesis

The corresponding amine **4** (1 eq) was dissolved in acetic acid (20 mL) and Ag_2CO_3 (1.1 eq) and $Pd(OAc)_2$ (0.1 eq) were added. Then, phenyl vinyl sulfone (1.2 eq) was added, and the mixture was stirred for 16 h at 110 ºC. Toluene was added and the result was filtered through celite. Solvents were evaporated at reduced pressure and the crude oil was dissolved in DCM. A saturated solution of Na_2CO_3 was added. The aqueous phase was extracted three times with DCM, the combined organic layer was dried over anhydrous $MgSO_4$ and evaporated at reduced pressure obtaining the crude **THIQ 5**[8].

6.2. SPECIFIC PROCEDURES

6.2.1. Nitration

The chloroacetamide **3d** (1.577 g, 6.17 mmol) was cooled to 0 ºC. Concentrated sulfuric acid (15.9 mL) and concentrated nitric acid (20.4 mL) were added. The mixture was stirred 30 min at rt and was diluted with water carefully . The resulting solution was extracted three times with DCM, and the organic phase was washed twice with a saturated solution of Na_2CO_3 and once with brine.

After that, the combined organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated at reduced pressure to obtain both **3f** and **3g** nitro-compounds[6].

6.2.2. Curtius rearrangement

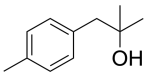
LDA was freshly prepared by adding dropwise a 1.6 M solution of butyllithium (65 mL, 104 mmol) over diisopropylamine (14.8 mL, 105 mmol) under nitrogen atmosphere. The mixture was cooled to -78 ºC and methyl isobutyrate (11.5 mL, 101 mmol) was added carefully. The mixture was stirred for 1 h at -78 ºC and 1-(chloromethyl)-4-methoxybenzene was added dropwise (13.5 mL, 92 mmol). The reaction was quenched with water at 0 ºC, it was extracted with Et_2O and washed with brine. The organic phase was dried over anhydrous $MgSO_4$ and was evaporated at reduced pressure to obtain the ester **Ic**. A 2 M solution of NaOH (30 mL) and methanol (30 mL) were added, and the mixture was stirred at 60 ºC overnight. The mixture was acidified to pH 9 and washed with DCM. The resulting aqueous phase was acidified to pH 2 and extracted twice with ethyl acetate and washed with brine. The organic phase was dried over $MgSO_4$ and evaporated at reduced pressure to obtain the carboxylic acid **IIc**[21].

Triethylamine (3.7 mL, 29 mmol) and **IIc** (5.213 g, 25 mmol) were dissolved in water (10 mL) at 0 ºC and enough acetone was added to solubilize them (15 mL). Ethyl chloroformate (3.2 mL, 33 mmol) in acetone (40 mL) was added over a period of 30 min followed by the dropwise addition of NaN_3 (2.074 g, 32 mmol) in water (30 mL). The mixture was allowed to warm to rt and stirred for 45 min to obtain the acyl azide **IIIc**, which was extracted with toluene (100 mL), washed with water, and dried over anhydrous $MgSO_4$. The organic layer was analyzed by IR spectroscopy which showed a strong absorption at 2133 cm^{-1}(azide band). The solution was and heated at 100 ºC until nitrogen formation stopped obtaining the isocyanate **IVc**. The crude mixture showed a strong absorption at 2251 cm^{-1} by an IR analysis (isocyanate band). Toluene was removed under vacuum and the isocyanate **IVc** was obtained[22].

A mixture of **IVc**, hydrochloric acid (15%, 10 mL) and acetic acid (10 mL) was stirred overnight at rt. The aqueous phase was washed with Et_2O and was added dropwise over a cooled NaOH solution (10%, 100 mL). Then the solution was extracted three times with Et_2O, and the organic phase was washed with water and brine and then dried over anhydrous Na_2SO_4 and concentrated at reduced pressure obtaining the amine **4c**[23].

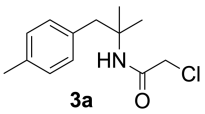
6.3. Characterization of the starting amines and its intermediates

6.3.1. 2-Methyl-1-*(p-methylphenyl)*-2-propanamine



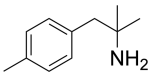
2a

Obtained from **Ethyl-2-*(p-methylphenyl)*acetate** (1 mL, 5.61 mmol) and Methylmagnesium bromide (6.5 mL) following standard procedure 1. Colorless oil, 100% (922 mg, 5.61 mmol). **^{1}H-NMR**[24] (400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 4H, ArH), 2.73 (s, 2H, $ArCH_2$), 2.33 (s, 3H, $ArCH_3$), 1.22 (s, 6H, $C(CH_3)_2$).



3a

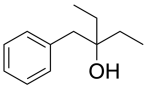
Obtained from alcohol **2a** (922 mg, 5.61 mmol) following standard procedure 2. White solid, 66% (897 mg, 3.74 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.11 (d, *J*= 8.1Hz, 2H, ArH), 7.03 (d, *J*= 8.1Hz, 2H, ArH), 3.94 (s, 2H, CH_2Cl), 2.98 (s, 2H, $ArCH_2$), 2.33 (s, 3H, $ArCH_3$), 1.37 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.14, 136.17, 134.08, 130.31, 128.87, 54.54, 45.00, 43.01, 26.76, 21.04. **HRMS (ESI+)** *m/z* calculated for $C_{13}H_{18}NOCl$ $[M+H]^+$= 240.1150 found= 240.1154.



4a

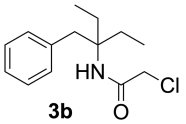
Obtained from chloroacetamide **3a** (897 mg, 3.74 mmol) following standard procedure 3. Colorless oil, 65% (395 mg, 2.41 mmol). **^{1}H-NMR**[6] (400 MHz, $CDCl_3$): δ 7.11 (d, *J*= 8.1Hz, 2H, ArH), 7.07 (d, *J*= 8.1Hz, 2H, ArH), 2.62 (s, 2H, $ArCH_2$), 2.33 (s, 3H, $ArCH_3$), 1.11 (s, 6H, $C(CH_3)_2$).

6.3.2. 3-Benzylpentan-3-amine



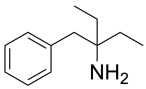
2b

Obtained from **Methyl-2-phenylacetate** (2 mL, 13.3 mmol) and Ethylmagnesium bromide (16 mL, 47 mmol) following standard procedure 1. Colorless oil, 100% (2.361g, 13.3 mmol). **^{1}H-NMR**[25] (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, ArH), 2.73 (s, 2H, $ArCH_2$), 1.45 (q, *J*= 6.0 Hz, 4H, $C(CH_2)_2$), 0.92 (t, *J*= 5.9 Hz, 6H, CH_3).



3b

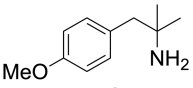
Obtained from alcohol **2b** (2.361 g, 13.3 mmol) following standard procedure 2. Yellow oil, 85% (2.816 g, 11.1 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.30-7.19 (m, 3H, ArH), 7.14-7.10 (m, 2H, ArH), 3.93 (s, 2H, CH_2Cl), 3.04 (s, 2H, $ArCH_2$), 1.5-1.9 (m, 4H, $C(CH_2)$), 0.90 (t, *J*= 6.0, 6H, CH_3) **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.07, 137.24, 130.33, 128.13, 126.49, 60.49, 43.01, 39.37, 26.53, 7.65. **HRMS (ESI+)** *m/z* calculated for $C_{14}H_{21}NOCl$ $[M+H]^+$= 254.1306 found= 254.1312.



4b

Obtained from chloroacetamide **3b** (2.816 g, 11.1 mmol) following standard procedure 3. Red oil, 45% (893 mg, 5.05 mmol). **^{1}H-NMR**[6] (400 MHz, $CDCl_3$): 7.33-7.18 (m, 5H, ArH), 2.65 (s, 2H, $ArCH_2$), 1.28-1.47 (m, 4H, $C(CH_2)_2$), 0.93 (t, *J*= 7.6, 6H, CH_3).

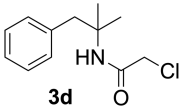
6.3.3. 2-Methyl-1-*(p-methoxyphenyl)*-2-propanamine



4c

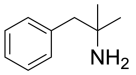
Obtained from **Methyl isobutyrate** (11.46 mL, 100 mmol) and **1-(chloromethyl)-4-methoxybenzene** (11.35 mL, 100 mmol) following the Curtius rearrangement procedure. Yellow oil, 67% (2.685 g, 15 mmol). **^{1}H-NMR**[6] (400 MHz, $CDCl_3$): δ 7.11-7.06 (m, 2H, ArH), 6.86-6.81 (m, 2H, ArH), 3.77 (s, 3H, ArOMe), 2.58 (s, 2H, $ArCH_2$), 1.19-1.28 (s, 2H, NH_2), 1.09 (s, 6H, $C(CH_3)_2$).

6.3.4. 2-Methyl-1-phenyl-2-propanamine



3d

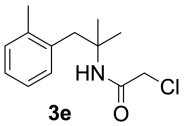
Obtained from **2-Methyl-1-phenylpropan-2-ol** (5.085 g, 33.17 mmol) following standard procedure 2. White solid, 93% (7.366 g, 30.72 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 3H, ArH), 7.18-7.16 (m, 2H, ArH), 3.97 (s, 2H, CH_2Cl), 3.06 (s, 2H, $ArCH_2$), 1.41 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.29, 137.32, 130.46, 128.16, 126.62, 54.52, 45.16, 43.04, 26.86. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{16}NOCl$ $[M+H]^+$= 226.0993 found= 226.0997.



4d

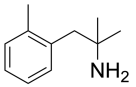
Obtained from chloroacetamide **3d** (5.085 g, 33.17 mmol) following standard procedure 3. Colorless oil, 40% (1.972 g, 12.08 mmol). **^{1}H-NMR**[6] (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, ArH), 2.67 (s, 2H, $ArCH_2$), 1.12 (s, 6H, $C(CH_3)_2$).

6.3.5. 2-Methyl-1-*(o-methylphenyl)*-2-propanamine



3e

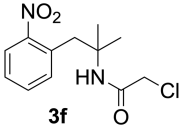
Obtained from **2-methyl-1-*(o-methylphenyl)*2-propanol** (0.888 g, 5.41 mmol) following standard procedure 2. Yellow oil, 64% (777 mg, 3.24 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.23-7.09 (m, 4H, ArH), 4.00 (s, 2H, CH_2Cl), 3.11 (s, 2H, $ArCH_2$), 2.39 (s, 3H, $ArCH_3$), 1.49 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.15, 137.21, 135.67, 131.29, 130.71, 126.72, 125.62, 55.63, 43.04, 41.41, 26.87, 20.39. **HRMS (ESI+)** *m/z* calculated for $C_{13}H_{18}NOCl$ $[M+H]^+$= 240.1150 found= 240.1162.



4e

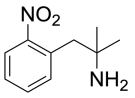
Obtained from chloroacetamide **3e** (545 mg, 2.28 mmol) following standard procedure 3. Yellow oil, 53% (197 mg, 1.21 mmol). **^{1}H-NMR**[6] (400 MHz, $CDCl_3$): δ 7.18-7.12 (m, 4H, ArH), 2.73 (s, 2H, $ArCH_2$), 2.36 (s, 3H, $ArCH_3$), 1.15 (s, 6H, $C(CH_3)_2$).

6.3.6.- 2-Methyl-1-*(o-nitrophenyl)*-2-propanamine



3f

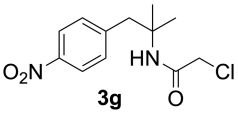
Obtained from chloroacetamide **3d** (1.577 g, 6.17 mmol) following the nitration procedure. Orange oil, 21% (388 mg, 1.30 mmol). Separated from p-nitro compound by column silica gel liquid chromatography (hexane/ethyl acetate 80:20). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.85-7.81 (m, 1H, ArH), 7.54-7.50 (m, 1H, ArH), 7.43-7.38 (m, 1H, ArH), 7.31-7.27 (m, 1H, ArH), 3.98 (s, 2H, CH_2Cl), 3.55 (s, 2H, $ArCH_2$), 1.37 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.61, 148.08, 139.53, 136.52, 128.99, 124.95, 121.79, 54.44, 53.47, 43.75, 27.00. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{15}ClN_2NaO_3$ $[M+Na]^+$= 293.0663 found= 293.0670.



4f

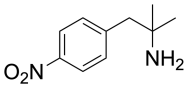
Obtained from chloroascetamide **3f** (388 mg, 1.30 mmol) following standard procedure 3. Orange oil, 95% (239 mg, 1.23 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.84-7.82 (m, 1H, ArH), 7.53-7.49 (m, 1H, ArH), 7.40-7.34 (m, 2H, ArH), 3.13 (s, 2H, $ArCH_2$), 1.10 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 151.02, 133.70, 132.93, 131.91, 127.37, 124.61, 51.27, 45.31, 30.64. **HRMS (ESI+)** *m/z* calculated for $C_{10}H_{15}N_2O_2$ $[M+H]^+$= 195.1128 found= 195.1134.

6.3.7. 2-Methyl-1-*(p-nitrophenyl)*-2-propanamine



3g

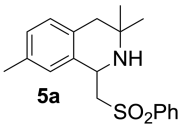
Obtained from chloroacetamide **3d** (1.577 g, 6.17 mmol) following the nitration procedure. Orange oil, 49%. (898 mg, 3.00 mmol). Separated from o-nitro compound by column silica gel liquid chromatography (hexane/ethyl acetate 80:20). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.17-8.15 (m, 2H, ArH), 7.30-7.28 (m, 2H, ArH), 3.98 (s, 2H, CH_2Cl), 3.24 (s, 2H, $ArCH_2$), 1.39 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 165.53, 146.85, 145.39, 131.14, 123.26, 54.49, 44.09, 42.88, 27.12. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{15}ClN_2NaO_3$ $[M+Na]^+$= 293.0663 found= 293.0668.



4g

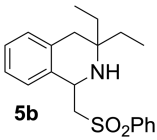
Obtained from chloroacetamide **3g** (898 mg, 3.00 mmol) following standard procedure 3. Orange oil, 89% (798 mg, 2.67 mmol). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.18-8.16 (m, 2H, ArH), 7.38-7.36 (m, 2H, ArH), 2.77 (s, 2H, $ArCH_2$), 1.14 (s, 6H, $C(CH_3)_2$). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 146.75, 146.49, 131.17, 125.03, 50.82, 50.31, 30.58. **HRMS (ESI+)** *m/z* calculated for $C_{10}H_{15}N_2O_2$ $[M+H]^+$= 195.1128 found= 195.1133.

6.4. Characterization of THIQs



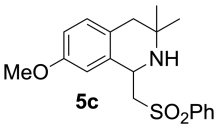
5a

Obtained from amine **4a** (242 mg, 1.48 mmol) following standard procedure 4. Yellow oil, 51% (248 mg, 0.75 mmol). Purified by column silica gel liquid chromatography (DCM/Methanol 97:3). **^{1}H-NMR[6]** (500 MHz, $CDCl_3$): δ 7.98 (d, *J*= 7.4 Hz, 2H, ArH), 7.65 (t, *J*= 7.4 Hz, 1H, ArH), 7.57 (t, *J*= 7.6 Hz, 2H, ArH), 6.93 (m, 2H, ArH), 6.73 (s, 1H, ArH), 4.65 (d, *J*= 9.2 Hz, 1H, ArCHNH), 3.72 (dd, *J*= 14.3, 1.9 Hz, 1H, $ArCHCH_AH_B$), 3.48 (dd, *J*= 14.3, 9.2 Hz, 1H, $ArCHCH_BH_A$), 2.75 (d, *J*= 15.6 Hz, 1H, $ArCHH_A$), 2.43 (dd, *J*= 15.6 Hz, 1H, $ArCHH_B$), 2.23 (s, 3H, $ArCH_3$), 1.22 (s, 3H, CH_3), 1.04 (s, 3H, CH_3).



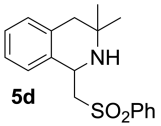
5b

Obtained from amine **4b** (310 mg, 1.65 mmol) following standard procedure 4. Brown oil, 57%. (321 mg, 0.94 mmol). Purified by column silica gel liquid chromatography (Hexane/ethyl acetate 85:15 0.1% Et_3N). **^{1}H-NMR[6]** (500 MHz, $CDCl_3$): δ 8.02-7.98 (m, 2H, ArH), 7.70-7.55 (m, 3H, ArH), 7.15-7.02 (m, 3H, ArH), 6.92 (d, *J*= 8.4 Hz, 1H, ArH), 4.55 (d, *J*= 9.4 Hz, 1H, ArCHNH), 3.75 (dd, *J*= 14.3, 1.8 Hz, 1H, $ArCHCH_AH_B$), 3.47 (dd, *J*= 14.3, 9.4 Hz, 1H, $ArCHCH_BH_A$), 2.74 (d, *J*= 15.8 Hz, 1H, $ArCH_AH_B$), 2.48 (d, *J*= 15.8 Hz, 1H, $ArCH_BH_A$), 1.30-1.50 (m, 4H, $C(CH_2)_2$), 0.89 (t, *J*= 7.5 Hz, 3H, CH_3), 0.82 (t, *J*= 7.5 Hz, 3H, CH_3).



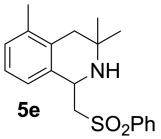
5c

Obtained from amine **4c** (300 mg, 1.67 mmol) following standard procedure 4. Yellow oil, 56% (321 mg, 0.93 mmol). Purified by column silica gel liquid chromatography (Hexane/ethyl acetate 50:50 0.1% Et_3N). **^{1}H-NMR[6]** (500 MHz, $CDCl_3$): δ 7.96 (d, *J*= 7.4 Hz, 2H, ArH), 7.65 (m, 1H, ArH), 7.56 (m, 2H, ArH), 6.95 (d, *J*= 8.4 Hz, 1H, ArH), 6.69 (d, *J*= 8.4 Hz, 1H, ArH), 6.46 (s, 1H, ArH), 4.63 (dd, *J*= 8.9, 1.6 Hz, 1H, ArCHNH), 3.73 (dd, *J*= 14.3, 1.6 Hz, 1H, $ArCHCH_AH_B$), 3.72 (s, 3H, ArOMe), 3.49 (dd, *J*= 14.3, 9 Hz, 1H, $ArCHCH_BH_A$), 2.71 (d, *J*= 15.4 Hz, 1H, $ArCHH_A$), 2.41 (d, *J*= 15.4 Hz, 1H, $ArCHH_B$), 1.21 (s, 3H, CH_3), 1.03 (s, 3H, CH_3).



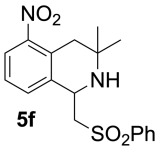
5d

Obtained from amine **4d** (1.2 g, 8 mmol) following standard procedure 4. Yellow oil, 59% (1.48 g, 4.70 mmol). Purified by column silica gel liquid chromatography (DCM/Methanol 97:3). **^{1}H-NMR[6]** (500 MHz, $CDCl_3$): δ 8.00 (d, *J*= 7.3 Hz, 2H, ArH), 7.66 (t, *J*= 7.4 Hz, 1H, ArH), 7.60 (t, *J*= 7.5 Hz, 2H, ArH), 7.15-6.95 (m, 4H, ArH), 4.69 (dd, *J*= 9.3, 1.7 Hz, 1H, ArCHNH), 3.72 (dd, *J*= 14.3, 1.7 Hz, 1H, $ArCHCH_AH_B$), 3.49 (dd, *J*= 14.3, 9.3 Hz, 1H, $ArCHCH_BH_A$), 2.81 (d, *J*= 15.8 Hz, 1H, $ArCHH_A$), 2.48 (d, *J*= 15.8 Hz, 1H, $ArCHH_B$), 1.24 (s, 3H, CH_3), 1.06 (s, 3H, CH_3).



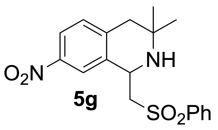
5e

Obtained from amine **4e** (176 mg, 1.08 mmol) following standard procedure 4. Yellow oil, 45% (162 mg, 0.49 mmol).[1] Purified by column silica gel liquid chromatography (DCM/Methanol 97:3). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H, ArH), 7.69-7.64 (m ,1H, ArH), 7.55-7.61 (m, 2H, ArH), 6.99 -7.02 (m, 2H, ArH), 6.80-6.84 (m, 1H, ArH), 4.70 (d, *J*= 9.3 Hz, 1H, ArCHNH), 3.72 (dd, *J*= 12, 1.8 Hz, 1H, $ArCHCH_AH_B$), 3.45 (dd, *J*= 14.22, 9.3 Hz, 1H, $ArCHCH_BH_A$), 2.56 (d, *J*= 15.4 Hz, 1H, $ArCHH_A$), 2.42 (d, *J*= 16.2 Hz, 1H, $ArCHH_B$), 2.19 (s, 3H, $ArCH_3$), 1.27 (s, 3H, CH_3), 1.07 (s, 3H, CH_3).



5f

Obtained from amine **4f** (350 mg, 1.80 mmol) following standard procedure 4. Orange oil, 24% (153 mg, 0.43 mmol). Purified by column silica gel liquid chromatography (Hexane/ethyl acetate 50:50 0.1% Et_3N). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H, ArH), 7.75-7.72 (m, 1H, ArH), 7.71-7.67 (m, 1H, ArH), 7.62-7.57 (m, 2H, ArH), 7.32-7.25 (m, 2H, ArH), 4.80 (d, *J*= 8.5 Hz, 1H, ArCHNH), 3.66 (dd, *J*= 14.25 Hz, 2.1 Hz, 1H, $ArCHCH_AH_B$), 3.53 (dd, *J*= 14.35 Hz, 8.7 Hz, 1H, $ArCHCH_BH_A$), 2.97 (d, *J*= 17.2 Hz, 1H, $ArCHH_A$), 2.66 (d, *J*= 17.2 Hz, 1H, $ArCHH_B$), 1.27 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 150.50, 139.57, 137.49, 134.07, 130.90, 130.16, 128.00, 126.31, 123.11, 64.30, 48.84, 48.26, 38.91, 31.20, 24.51. **HRMS (ESI+)** *m/z* calculated for $C_{18}H_{21}N_2O_4S$ $[M+H]^+$= 361.1217 found= 361.1218.



5g

Obtained from amine **4g** (330mg, 1.70 mmol) following standard procedure 4. Orange solid, 33% (200 mg, 0.56 mmol) Purified by column silica gel liquid chromatography (Hexane/ethyl acetate 50:50 0.1% Et_3N). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 8.00 -7.93 (m, 3H, ArH), 7.85-7.82 (m, 1H, ArH), 7.70-7.64 (m, 1H, ArH), 7.61-7.55 (m, 2H, ArH), 7.22 (d, *J*= 8.4 Hz, 1H, ArH), 4.76 (d, *J*= 8.7 Hz, 1H, ArCHNH), 3.74 (dd, *J*= 13.8 Hz, 2.1 Hz, 1H, $ArCHCH_AH_B$), 3.56 (dd, *J*= 14.2 Hz, 8.9 Hz, 1H, $ArCHCH_BH_A$), 2.88 (d, *J*= 16.5 Hz, 1H, $ArCHH_A$), 2.62 (d, *J*= 16.5 Hz, 1H, $ArCHH_B$), 1.30 (s, 3H, CH_3), 1.08 (s, 3H, CH_3). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 146.24, 143.78, 139.57, 135.71, 134.07, 130.96, 129.51, 127.94, 121.82, 120.54, 62.90, 48.88, 42.45, 31.08, 24.50. **HRMS (ESI+)** *m/z* calculated for $C_{18}H_{21}N_2O_4S$ $[M+H]^+$= 361.1217 found= 361.1226**.**

7. CONCLUSIONS AND FINAL SUMMARY

In conclusion, the method used for the general amine synthesis showed to be robust and reproducible but, in cases of failure, a new successful method for the phenylethylamine synthesis has been developed increasing the number of functionalization possibilities. Moreover, the C–H functionalization procedure also performed in a robust and reproducible way.

The above list analyses more in depth every transformation carried out by summarizing the work done during this project:

- The synthesis of the first intermediates (alcohol **2**), when necessary, is confirmed to work properly leading to high yields (90-100%).
- Transforming alcohols **2** into chloroacetamides **3** is also a good-working reaction as yields tended to be good.
- The reaction to obtain amines **4** is considerably affected by the electron withdrawing behaviour of the R group bonded to the aromatic ring: electronically poor rings lead to better yields.
- The methylation of compound **3c'** as a solution to the significantly lower yield obtained for **e** series was a failure but a completely new, different, and efficient method has been developed to obtain amine **4c** from **1c** ester with an overall 67% yield.
- Even if cyclization reactions to obtain THIQs **5** lead to many different byproducts, > 40% yields can be achieved for the pure compound and only a 10% molar proportion of catalyst is needed.

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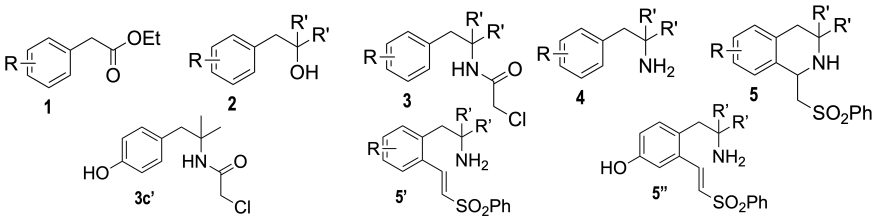
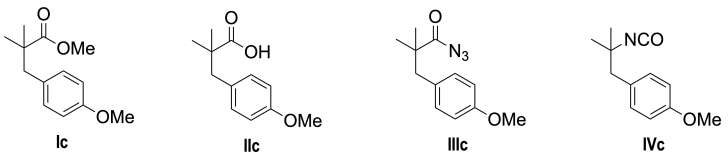
9. ACRONYMS AND COMPOUND NUMBERING

AcOH	Acetic acid
Ar	Aryl
atm	Atmospheric pressure
Bp	Boiling point
Com	Commercially
DCM	Dichloromethane
DG	Directing group
E^+	Electrophile
eq	Equivalent
ESI	Electrospray
Et	Ethyl
EWG	Electron Withdrawing Group
[H]	Reducting agent
HRMS	High resolution mass spectrum
IR	Infrared
LC	Liquid Chromatography
LDA	Lithium diisopropylamine
Me	Methyl
min	Minutes
NMR	Nuclear magnetic resonance
Nu^-	Nucleophile
Ph	Phenyl
rt	Room temperature
sat	Saturated
Taut	Tautomerism
THF	Tetrahydrofuran
THIQ	Tetrahydroisoquinoline

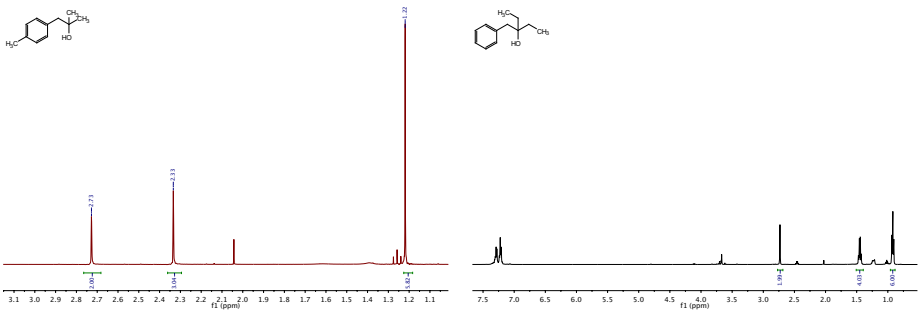
R	*p*-Me	H	*p*-OMe	H	*o*-Me	*o*-NO_2	*p*-NO_2
R'	Me	Et	Me	Me	Me	Me	Me
	a	**b**	**c**	**d**	**e**	**f**	**g**



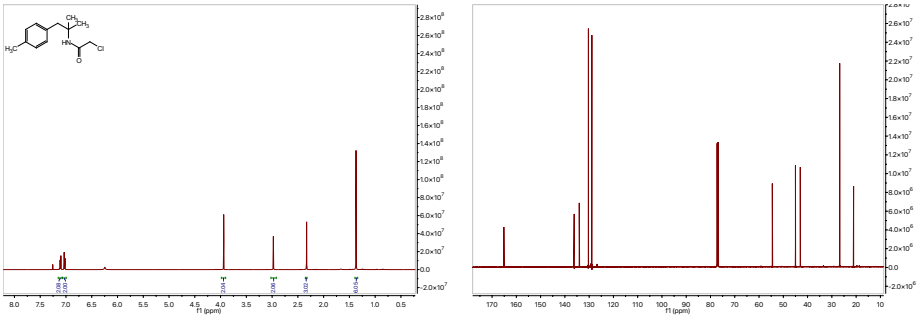


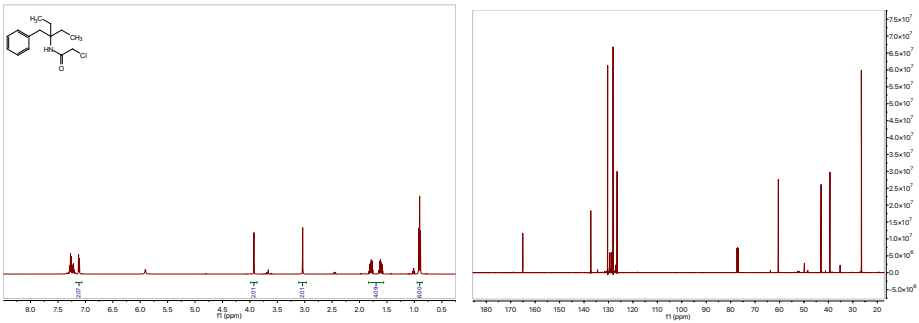
APPENDICES

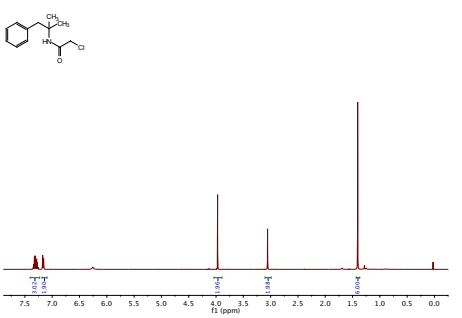
APPENDIX 1: ALCOHOL CHARACTERIZATION (^{1}H-NMR)

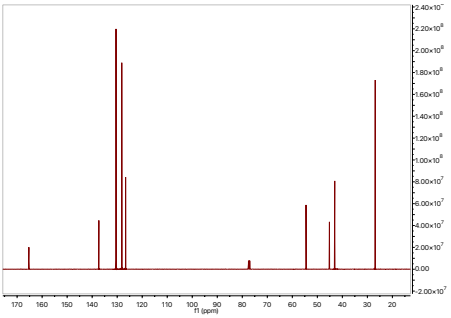


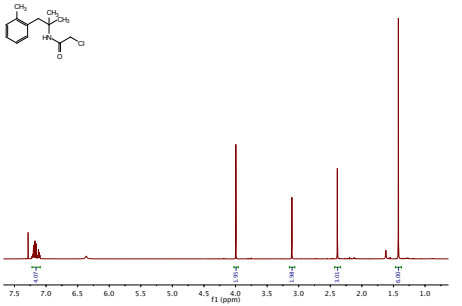
APPENDIX 2: CHLOROACETAMIDE CHARACTERIZATION (^{1}H-NMR + ^{13}C-NMR)

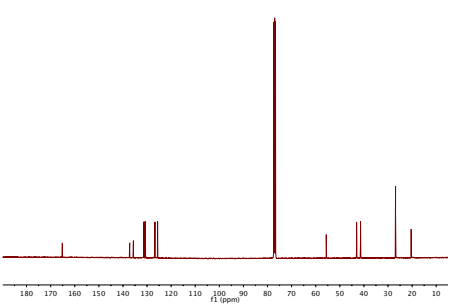


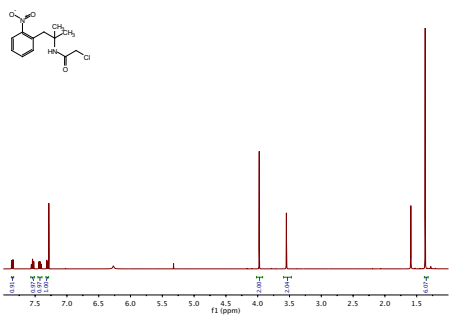


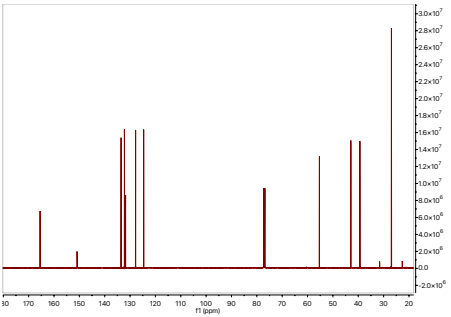


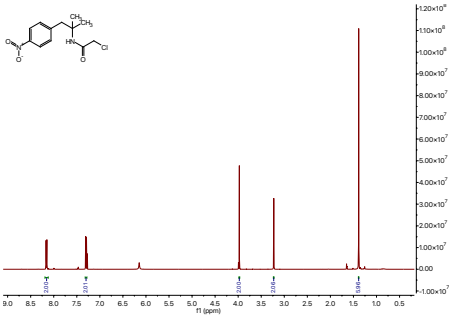








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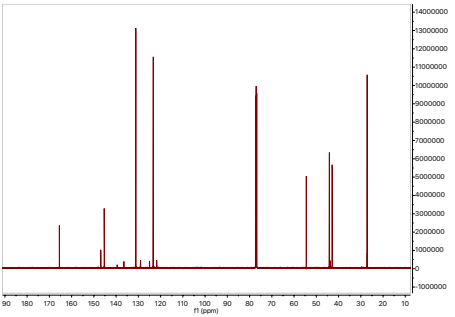
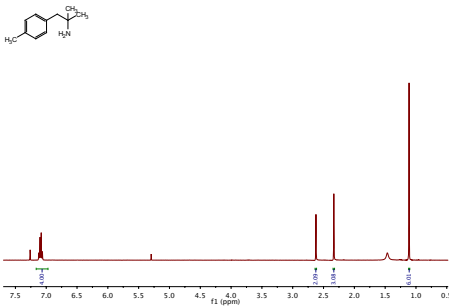
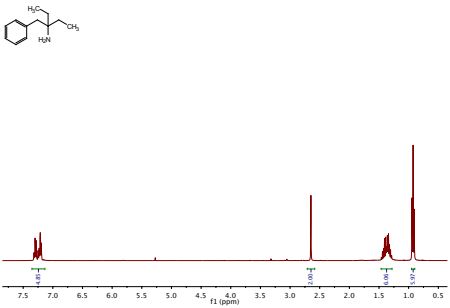
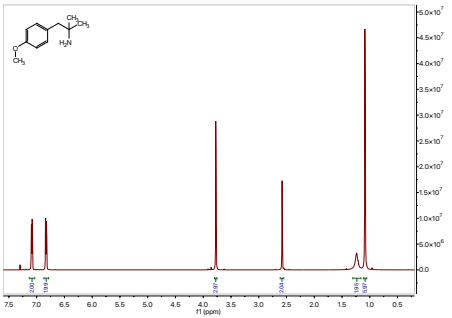
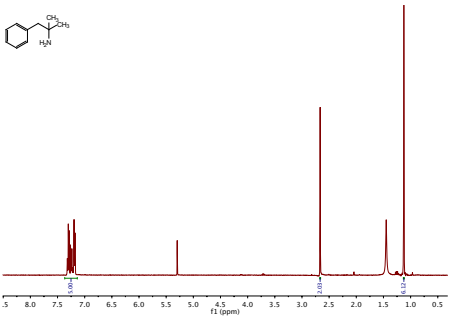

f1 (ppm)

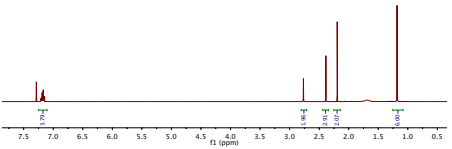
APPENDIX 3: AMINE CHARACTERIZATION (^{1}H-NMR + 4F AND 4G ^{13}C-NMR)

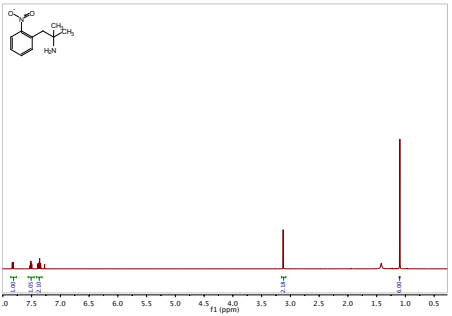


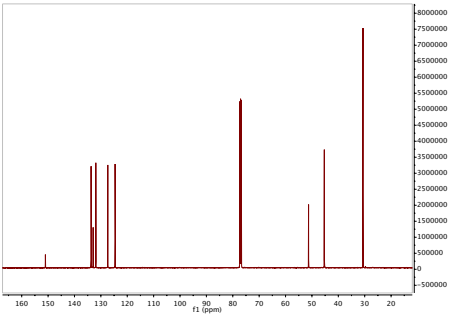







3.07
1.96
2.01
2.00
6.00
f1 (ppm)


f1 (ppm)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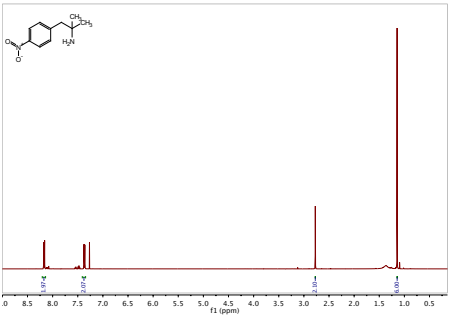
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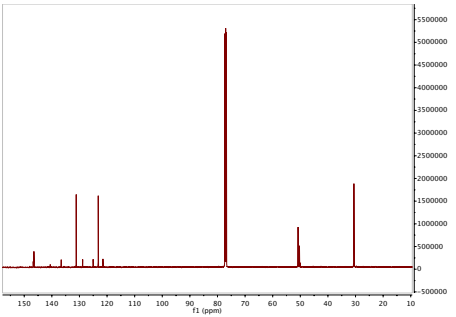
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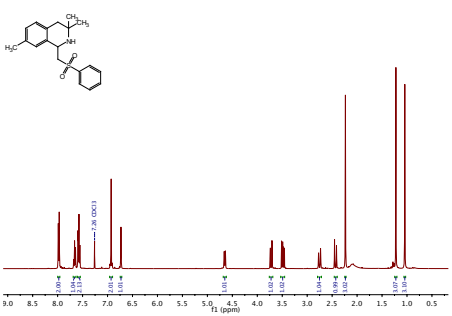
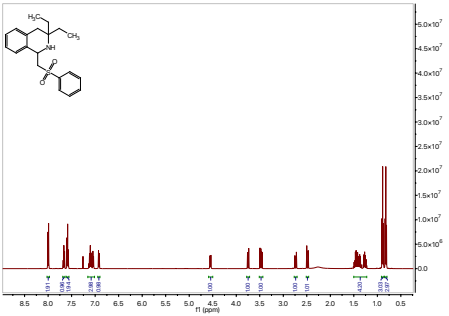
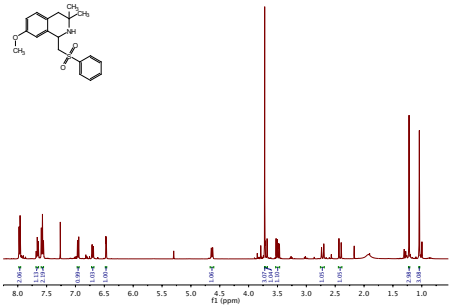
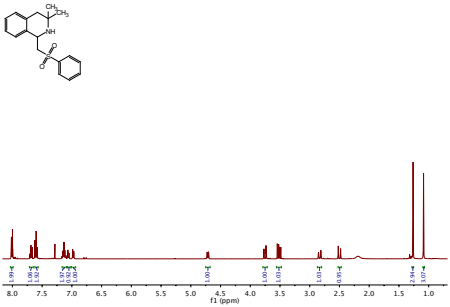
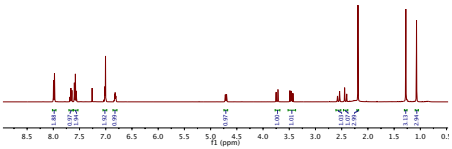
APPENDIX 4: THIQ CHARACTERIZATION (^{1}H-NMR + 5F AND 5G ^{13}C-NMR)

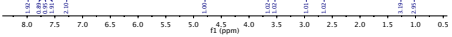


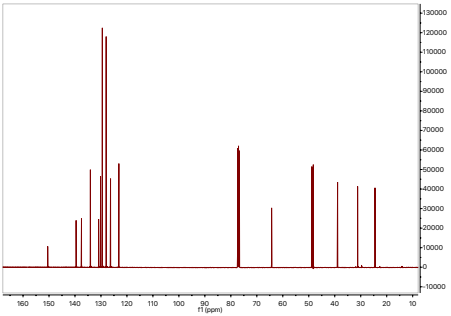




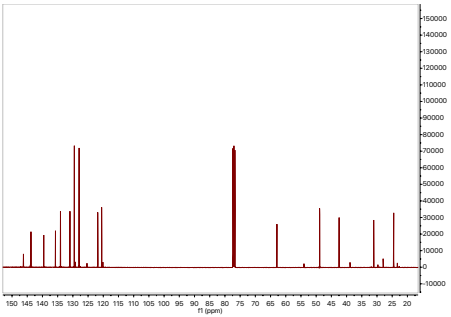



f1 (ppm)


f1 (ppm)


f1 (ppm)

f1 (ppm)


f1 (ppm)