



## Synthesis of active pharmaceutical ingredient atomoxetine *via* desulfurative halogenation

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### ARTICLE INFO

#### Keywords:

Desulfurative halogenation  
Atomoxetine  
Phenyl sulfides  
Pummerer's fragmentation

### ABSTRACT

An innovative preparation of the Active Pharmaceutical Ingredient (API) Atomoxetine has been developed. Key advantages of the synthetic procedure include: a one-pot preparation of a 1,3-bis-electrophilic phenyl-propionic synthon obtained *via* desulfurative chlorination of an easy to make thiophenyl sulfide; an unreported strategy for the preparation of secondary amines. The synthesis involves a total of four consecutive steps from unexpensive and readily available reagents and employs mild conditions.

### Introduction

Atomoxetine **1** (Fig. 1) is a second-generation anti-depressant drug sold commercially as Strattera, [1,2] used as a treatment for attention deficit hyperactivity disorder (ADHD) [3]. There is a vivid interest of pharmaceutical companies in identifying methods of preparation of active pharmaceutical ingredients. To decrease costs of manufacture, those syntheses employing inexpensive reagents, short linear sequences, and producing limited wastes are particularly desirable [4].

Atomoxetine **1** (Fig. 1) possesses a phenylpropionic scaffold which is

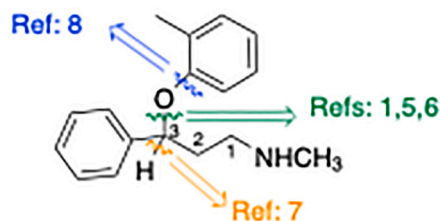
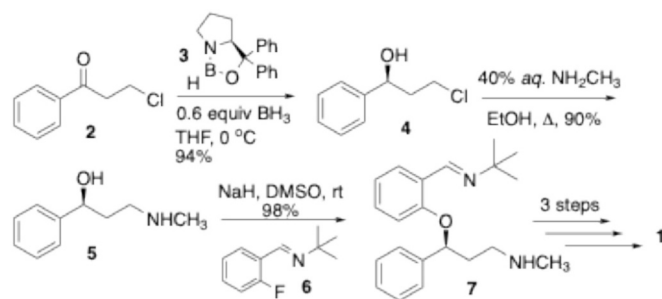


Fig. 1. Active Pharmaceutical Ingredient (API) Atomoxetine **1**.

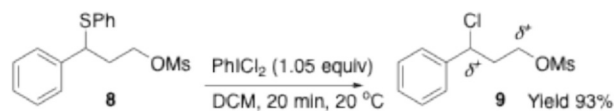
decorated with an amine at C<sub>1</sub> and an alcohol at C<sub>3</sub> respectively. Reported synthetic routes to make **1** can be summarized under three individual disconnections (Fig. 1). Molloy [1] described the synthesis of **1** where the key C<sub>3</sub>-OAr bond was formed *via* nucleophilic displacement of an opportune *N*-protected 3-halo-3-phenylpropylamine by a phenoxide; similarly, Sharpless [5] and Brown [6] took advantage of a variant of the Mitsunobu reaction that, starting from a 3-hydroxy-3-phenylpropylaldehyde provided the required C<sub>3</sub>-OAr linkage. In an alternative design, a phenylpropionic scaffold was prepared *via* a preformed C<sub>3</sub>-C<sub>2</sub> enolether, which subsequent reduction using Rhodium chiral complexes provided a synthetic intermediate on route to **1** [7]. The current method of manufacture of **1** involves the formation of an O-Aryl bond *via* nucleophilic aromatic substitution of an aryl fluoride by the 3-hydroxyl, under strongly basic conditions (Scheme 1) [8]. Stereoselective reduction of 3-chloro-1-phenylpropanone **2** with Corey's CBS reagent **3**, provided benzylic alcohol **4**. Amination of **4** produces *N*-methyl-3-phenyl-3-hydroxy propylamine **5**, which was then used to install the aryl ether *via* reaction with 2-fluorobenzaldehyde derivative **6**. Three further steps are then required to convert **7** to Atomoxetine **1**. We have recently developed a new reaction by which phenylthioethers, for example **8** (Scheme 2), were converted to the corresponding benzylic chlorides **9** [9], or bromides [10–12] in high yields and in reaction times as short as 5–10 min.

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Scheme 1. Current method of manufacture of Atomoxetine **1** [8].



Scheme 2. Exemplification of desulfurative halogenation.

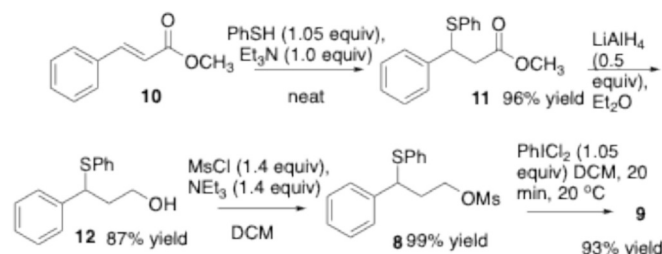
This reaction, that we named desulfurative halogenation, is mechanistically an example of Pummerer fragmentation [13] operating in an  $S_N2$  mode, it requires very short reaction times and is tolerant of several functional groups. Key to the established functional group tolerance is the preferential oxidation of a sulfide compared to other electronrich functional groups such as alcohols, aldehydes or amines [9–12]. Hence, desulfurative halogenation can be run in presence of many other groups, voiding the need of protection deprotection and facilitating, in many instances, a shorter synthetic route.

Phenylpropionic derivatives such as **9** possess an organic framework which is common to many bioactive molecules, such as Atomoxetine **1**, Duloxetine, Pinostrobin and Tephrowatsin E [7]. Moreover, compound **9**, containing two opportunely positioned electrophilic centers, is an ideal intermediate on route to all of the above-mentioned bioactive compounds. Herein, we report on the development of a racemic synthesis of Atomoxetine **1** that: (i) avails of desulfurative halogenation; (ii) makes use of a modified Gabriel procedure for the introduction of monoalkylated amines; (iii) features a one-pot procedure that by combining four steps into a single operation shortened the preparation of Atomoxetine **1** to just four steps.

## Results and discussion

We have already reported the preparation of compound **8–9** and **11–12** (Scheme 3) [9–12]. Reaction of neat methyl cinnamate **10** with equimolar amounts of thiophenol and triethylamine provided desired thioether **11** in high isolated yields. Subsequent reduction of **11** with  $LiAlH_4$  in diethyl ether gave alcohol **12** that was then reacted with mesyl chloride and triethylamine to give mesylate **8**.

Desulfurative halogenation carried out on compound **9** gave desired **9** in high isolated yields. To be commercially competitive as part of the synthesis of an API, the preparation of compound **9** should be executable in a single step. Hence, each step required for the preparation of **9** has



Scheme 3. Reported synthesis of intermediate **9**.

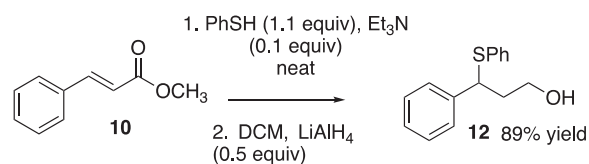
been reoptimized to use a single solvent and to be executed as a one-pot procedure. This required to change the solvent for the reaction of **11** to **12** from diethyl ether to dichloromethane and to incorporate acids or bases or alter the number of equivalents of reagents required to merge multiple steps into a single operation. This optimization was executed stepwise, *i.e.* combining the first two and then adding a next one in a follow-up experiment.

An initial experiment was run where equimolar amounts of cinnamate **10**, thiophenol and triethylamine were allowed to react to generate *in situ* compound **11** (Scheme 4); at this point, the reaction mixture was diluted with dichloromethane, cooled to 0 °C,

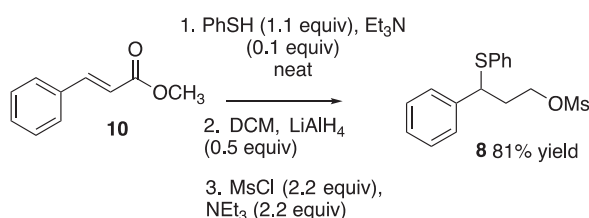
then  $LiAlH_4$  was added in portions under cooling (0 °C) and the reduction carried out for the time required. Delightfully, in this experiment compound **12** was obtained in 89 % isolated yield.

In the next experiment, we have tried preparing compound **8** directly from **10** (Scheme 5). This involved repeating the preparation of **12** (Scheme 4), followed by the addition of an excess of  $MsCl$  (2.2 equiv) and an additional amount of triethylamine (1.2 equiv). This experiment gave compound **8** in 81 % isolated yields. Finally, we have attempted the one-pot preparation of compound **9** directly from compound **10**.

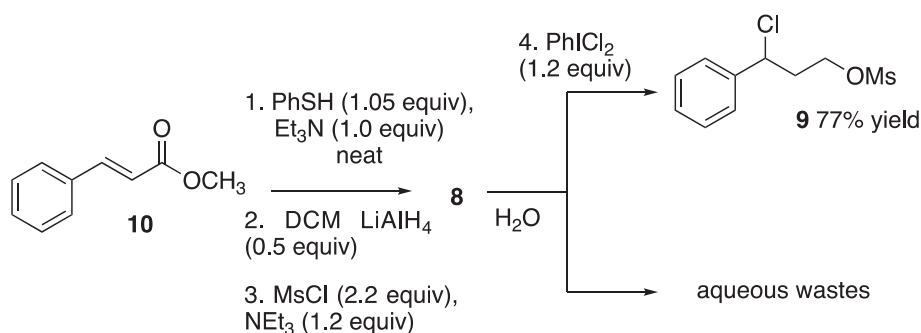
In a first experiment, compound **10** was carried through the thia-Michael addition, reduction and mesylation to generate crude compound **8** (Scheme 6) which was then reacted with  $PhICl_2$  to prepare desired **9**. This experiment gave compound **9** in a low 22 % yield. However, when the same reaction sequence was repeated on the crude **8** in DCM after an aqueous work up, compound **9** was obtained in 77 % yield. In summary, we have demonstrated that steps from **10** to **11**, **11** to **12**, **12** to **8** and **8** to **9** (Scheme 6) could be run as a single operation; this was possible by changing the following reaction parameters from the stepwise process: (i) replacing the solvent from  $Et_2O$  to DCM in the conversion of **10** to **11**; (ii) adding an extra amount of mesyl chloride and  $NET_3$  in the reaction of **12** to **8** and (iii) adding an aqueous phase and an aqueous treatment before the reaction of **8** to **9**. Having optimized the preparation of 3-chloro-3-phenylpropyl methanesulfonate **9**, we then turned our attention to the following steps leading to Atomoxetine **1**. It was reasoned that soft nucleophiles would react preferentially at  $C_1$ -OMs than the  $C_3$ -Cl electrophile. Initially, we have reacted compound **9** with a solution of methylamine in THF hoping to obtain the required secondary amine in a single operation. Unfortunately, no conversion to **9** to the desired amine was observed, even when the reaction was protracted for long times and at 50 °C. However, when **9** was reacted with one equivalent of potassium phthalimide **13** – a reagent used in the Gabriel synthesis [14] – the correspondent  $C_1$  aminated compound **14** was obtained in 42 % isolated yields. Delightfully, when 2 equivalents of **13** were used, desired **14** was obtained in 82 % isolated yields (Scheme 7).



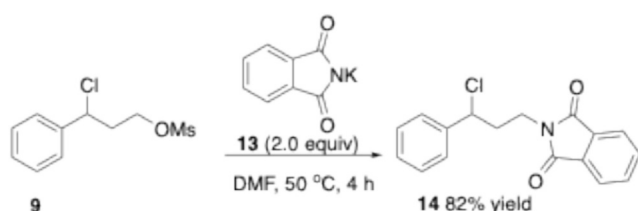
Scheme 4. One-pot preparation of alcohol **12**



Scheme 5. One-pot preparation of mesylate **8**



Scheme 6. One-pot preparation of key compound 9



Scheme 7. Conversion of mesyl ester 9 into phthalimide 14.

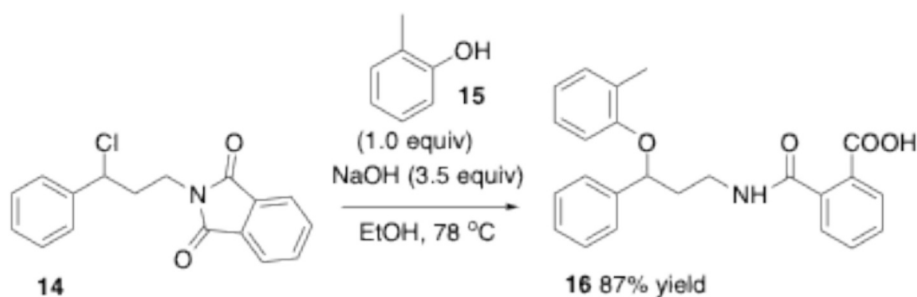
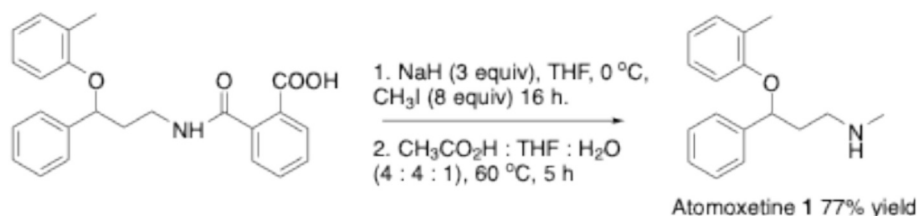
The next step involved the formation of the C<sub>3</sub>—O bond, which was realized by reacting compound 14 and *o*-cresol under basic conditions (Scheme 8). This reaction not only provided the required C<sub>3</sub>—O bond, but also resulted in the conversion of the phthalimide moiety into a carboxyl benzamido group. This transformation was attempted using several combinations of solvents and bases; the substitution was unsuccessful using a solution 1.0 M of *o*-cresol in EtOH or DMF, or employing NaH, K<sub>2</sub>CO<sub>3</sub>, or CsCO<sub>3</sub> as the base. However, when NaOH was employed as the base and this latter reagent increased from 1.0 to 3.0 equivalents, desired substitution at C<sub>3</sub> occurred and compound 16 obtained in 87 % isolated yields. Significantly, no traces of intermediates holding an intact phthalimide unit was detected in the crude reaction

mixture.

Compound 16 was particularly useful for the execution of the mono-methylation required to prepare Atomoxetine 1, which would have been difficult if carried out on a primary amine. The step-wise methylation of compound 16 using CH<sub>3</sub>I and various bases generated a complex mixture where the desired *N*-methyl derivative was contaminated by several side products. However, when the *N*-methylation and the subsequent *N*-debenzylation of 16 were carried out as a single operation, compound 1 was obtained in high yields. This novel route to secondary amines derivatives, based on the monoalkylation of carboxyl benzamides, can be employed for the synthesis of a vast number of secondary amines starting from alkyl halides or other alkanes bearing a good leaving group. Hence, when 16 was treated with an excess of CH<sub>3</sub>I and NaH as the base, followed by treatment with a solution of acetic acid in tetrahydrofuran (THF) and water, desired Atomoxetine 1 was obtained in 77 % isolated yields (Scheme 9).

## Conclusion

In conclusion, we have reported a new synthetic route for the synthesis of Atomoxetine that required four linear steps, three steps shorter compared to currently manufacturing route (Scheme 1). Key findings reported herein are: a new one-pot procedure to obtain 9; an

Scheme 8. *O*-Arylation of 14 and conversion of phthalimido moiety into a carboxyl benzamido group

Scheme 9. Preparation of Atomoxetine 1.

unprecedented monoalkylation *via* Gabriel synthesis; desulfurative halogenation demonstrated as a viable tool for the preparation of APIs. We believe this work will be of interest to those involved in synthetic route scouting and in drug manufacture.

#### CRedit authorship contribution statement

**Giovanni Roviello:** Methodology. **Caterina Cioffi:** Methodology, Investigation. **Maria Moccia:** Project administration, Data curation. **Malachi W. Gillick-Healy:** Methodology, Investigation, Funding acquisition. **Brian G. Kelly:** Supervision, Funding acquisition. **Mauro F. A. Adamo:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

#### Acknowledgments

We Acknowledge Horizon TRANSPHARM, grant agreement No 101057816 for support to MFAA, BGK and MWGH; and the Irish Research Council (IRC) grant No EPSPG2016185 for support to CC.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2025.155800>.

#### Data availability

Data will be made available on request.

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