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Minimizing Tertiary Amine Byproducts in Reductive Amination: a Microwave-Assisted Study of the $InCl_3/Et_3SiH/MeOH$ System

Gabriel A. S. de Aquino,[a,b] *Rayanne L. N de Lima,*[a] *Floriano P. Silva-Jr.*[b] *and Sabrina B. Ferreira*[*,a]

[a]*Laboratório de Síntese Orgânica e Prospecção Biológica, Instituto de Química, Universidade Federal do Rio de Janeiro, 21941-909 Rio de Janeiro-RJ, Brazil*

[b]*Laboratório de Bioquímica Experimental e Computacional de Fármacos, Instituto Oswaldo Cruz, Fiocruz, 21040-900 Rio de Janeiro-RJ, Brazil*

This study describes the development and optimization of a microwave-assisted reductive amination protocol for the synthesis of secondary amines using the $Et_3SiH/InCl_3/MeOH$ catalytic system. Initially aimed at establishing a robust route for secondary amine derivatives, the investigation revealed a significant competitive pathway leading to the formation of tertiary amine byproducts through over-alkylation. A systematic screening of reaction conditions, using 2-bromobenzaldehyde as a model substrate, demonstrated that microwave irradiation significantly reduces reaction times compared to conventional heating methods while maintaining high conversion rates. The reaction profile was rigorously monitored using high performance liquid chromatography coupled to diode array detection and mass spectrometry (UHPLC-DAD-MS), which allowed for the identification and relative quantification of the product distribution. The substrate scope investigation showed that the selectivity and reaction rates are strongly influenced by the electronic and steric properties of the aromatic substituents, particularly at the *ortho*-position. Several of the identified tertiary amines were isolated and characterized as novel compounds, as they are not previously described in the literature as byproducts for this system. These findings provide a strategic framework for controlling selectivity in reductive aminations and highlight the importance of detailed byproduct analysis in methodology development, offering new chemical entities for future applications in chemistry.

Keywords: reductive amination, microwave-assisted synthesis, selectivity enhancement, overalkylation, one-pot reaction

Introduction

Reductive amination is a key reaction in organic synthesis that involves the formation of amines from carbonyl compounds, such as aldehydes and ketones, through the addition of amines and a reducing agent, as shown in Figure 1.[1,2] This methodology, which can be performed directly or indirectly, involves the reaction between a carbonyl compound and an amine, followed by reduction, resulting in the formation of secondary or tertiary amines, respectively. Direct reductive amination occurs in a single vessel ("one-pot"), where the formation of the intermediate imine or enamine and its subsequent reduction happens without isolation of the intermediate, while in indirect reductive amination, the N-condensation product is first isolated and subsequently reduced.[2] This process is highly important due to its atomic economy, tolerance to various functional groups, the ability to form C –N bonds selectively, and it also allows the introduction of structural diversity in complex molecules, making it an indispensable tool in synthetic organic chemistry.[3]

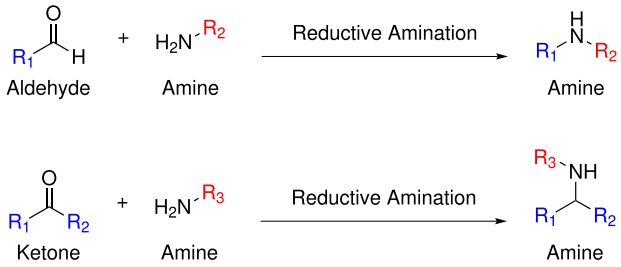

Figure 1. Reductive aminations reactions using aldehyde or ketone.

*e-mail: sabrinab@iq.ufrj.br
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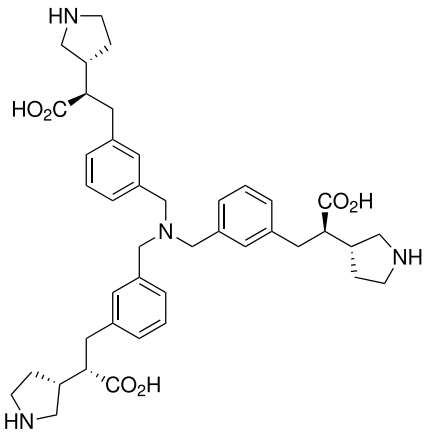
Many different reducing agents have been used in these reductive amination reactions, each offering specific advantages in terms of selectivity, reaction conditions, and compatibility with functional groups. Among the most common are: sodium cyanoborohydride ($NaCNBH_3$), which is widely used due to its stability in acidic medium (pH 3-4), where the reduction of the imine is favored over direct reduction of the carbonyl; sodium triacetoxyborohydride (STAB, $NaBH(OAc)_3$), which shows greater selectivity for imine reduction compared to carbonyls and is less toxic than $NaCNBH_3$, making it an attractive alternative; sodium borohydride ($NaBH_4$), which, although less selective, is often employed under modified conditions, such as in the presence of Lewis acids or additives that increase its selectivity; and lithium aluminum hydride ($LiAlH_4$), which is a more potent reducing agent and is generally reserved for cases where the reactivity of other agents is insufficient, although its high reactivity may compromise selectivity.[4-8]

In addition to these, some alternative reduction systems have been explored to overcome the limitations of conventional reducing agents, such as the reductive amination of aldehydes and ketones using triethylsilane in the presence of palladium catalysts on activated carbon, demonstrating the versatility of this system in organic syntheses under mild conditions, and the $InCl_3/Et_3SiH$/MeOH system, which has proven efficient for a wide range of substrates such as cyclic, acyclic, aromatic, and aliphatic amines, with the advantage of being tolerant to the presence of water and compatible with various functional groups, such as esters and carboxylic acids.[9-11]

A significant challenge in reductive amination reactions is controlling selectivity, mainly due to preventing overalkylation, which can lead to the undesired formation of tertiary amines when the objective is to obtain secondary amines. This problem is very important when using ammonia or primary amines as reagents, as the initial product, which is a primary or secondary amine, may be more nucleophilic than the starting material, leading to consecutive reactions. Because of this, several studies have addressed this issue through the development of reaction conditions that favor mono-alkylation, such as using an excess of the amine component, careful control of reaction conditions, or employing more selective reducing agents.[12-14]

In this context, the application of microwaves in reductive amination reactions has emerged as a promising strategy to accelerate reactions and improve yields, as microwave energy acts directly on solvents and reagents, resulting in rapid and uniform heating of the reaction mixture, thus offering significant advantages compared to conventional heating methods. Additionally, since the containers are sealed during the reaction, it is possible to work at temperatures well above the boiling point of the solvent, which frequently leads to drastically reduced reaction times. Potter and co-workers[15] provide an example of a rapid reductive amination (10 min) of anilines with ketones at 140 °C in 1,2-dichloroethane using microwaves, obtaining yields of 64-95%. Another example is provided by Dong *et al.*,[16] who demonstrated that the conversion of ketones to primary amines using ammonium acetate and $NaCNBH_3$ under microwave conditions occurred in just 2 min, while the same reaction under conventional heating would take hours. Van der Eycken and co-workers[17] provide yet another example using a one-pot strategy for the formation of tertiary amines needed to synthesize Buflavine analogues, where microwave-assisted imine formation occurred in just 3 min at 175 °C, while the same reaction under conventional reflux would require 3 h.[16-18]

Thus, reductive amination is very important for the preparation of secondary amines, which are fundamental precursors for the development of pharmaceuticals, agrochemicals, and industrial chemicals. And the controlled formation of tertiary amines through reductive amination is of particular interest in the synthesis of complex bioactive compounds, where a notable example is muvalaplin (**1**), Figure 2, an inhibitor of microsomal triglyceride transfer protein (MTTP) developed for the treatment of dyslipidemia. Its structure contains a tertiary amine with aromatic rings, whose synthesis requires precise control to avoid the formation of unwanted byproducts. With this, the application of selective reductive amination conditions, possibly microwave-assisted, could offer a more efficient synthetic route for this and other pharmaceutical compounds containing tertiary amines.[9,15,19-21]



Muvalaplin
(1)

Figure 2. Structure of muvalaplin, an inhibitor of microsomal triglyceride transfer protein, which contains a tertiary amine and its synthesis could be improved by microwave assistance.

Experimental

All solvents and reagents were purchased from commercial suppliers and used without further purification. Dry solvents were treated for water removal according to literature procedures.[21] Reaction progress was monitored by thin-layer chromatography (TLC) using aluminum-backed silicagel 60F-254 sheets (0.25 mm thickness) with a UV indicator (254 nm). Eluent systems were prepared on a volume-to-volume (v/v) basis. Compounds were visualized under a UV lamp or by staining with a sulfuric vanillin solution followed by heating. Purification was performed through flash column chromatography using silicagel F60 (40-65 μm). Automated flash chromatography was also performed on a Teledyne CombiFlash NextGen 300+ system for selected samples. Solvents were partially removed under reduced pressure using an IKA RV 10 Control rotary evaporator equipped with an IKA HB 10 Control heated water bath. Complete removal of volatile residues was achieved under high vacuum. Melting points were determined using a Fisatom 430 D digital apparatus. Microwave-assisted reactions were performed in a Biotage Initiator+ Microwave System with power range of 400 W from magnetron at 2.45 GHz. Intermediate confirmation was performed via ultra-high performance liquid chromatography coupled to diode array detection and mass spectrometry (UHPLC-DAD-MS) on a Shimadzu LCMS-2020 system equipped with a Hypersil Gold C18 column (1.9 μm, 50 × 2.1 mm). The mobile phase consisted of water containing 0.1% formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B). A linear gradient elution from 5 to 95% B was applied within a total run time of 3.0 min. The injection volume was 1 μL and was run before work-up of the reaction. Structural determination was performed using ^{1}H and ^{13}C nuclear magnetic resonance (NMR). NMR spectra were recorded on Bruker AVHD 9.40 T (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) and AVIII 11.75 T (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C) spectrometers and NMR spectra were processed using TopSpin software (version 4.1.4, Bruker BioSpin GmbH). Chemical shifts (δ) are reported in parts *per* million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are reported in hertz (Hz). Signal multiplicities are described as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), and m (multiplet). Samples (10-25 mg) were dissolved in 0.6 mL of $CDCl_3$, DMSO-d_6 (dimethylsulfoxide-d_6) or MeOD (methanol-d_4), depending on solubility, and measured in 5 mm diameter tubes.

General procedure for microwave-assisted reductive amination

To a microwave vial, the corresponding aldehyde (**2a**-**2h**) (1 mmol), 2-thiophenemethylamine (**3**) (1 mmol), triethylsilane (2.5 mmol), and indium(III) chloride (0.3 mmol) were added in dry methanol (2.5 mL). The reaction mixture was irradiated in a microwave reactor at 90 °C for the appropriate time (25 min-12 h). After completion, the solvent was evaporated under reduced pressure, and a saturated sodium bicarbonate solution (10 mL) was added. The resulting salt was filtered off, and the aqueous layer was extracted with dichloromethane or methylene chloride (DCM) (3 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using an ethyl acetate/hexane gradient to afford products (**4a**-**4h**) and (**5a**-**5e**).

General procedure for reductive amination under reflux

To a round-bottom flask the corresponding aldehyde (**2a**-**2h**) (1 mmol), 2-thiophenemethylamine (**3**) (1 mmol), triethylsilane (2.5 mmol), and indium(III) chloride (0.3 mmol) were added in dry methanol (2.5 mL). The reaction mixture was heated under reflux for 24 h. The solvent was evaporated under reduced pressure, and a saturated sodium bicarbonate solution (10 mL) was added. The resulting salt was filtered off, and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using an ethyl acetate/hexane gradient to afford products (**4a**-**4h**) and (**5a**-**5e**).

N-Benzyl-1-(thiophen-2-yl)methanamine (**4a**)

Yellow oil; 50% yield; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.78 (s, 1H, H-8), 3.70 (s, 2H, H-9), 3.85 (s, 2H, H-7), 6.95-6.96 (m, 2H, H-11 and H-12), 7.22 (t, *J* 6.9 Hz, 1H, H-3), 7.30-7.34 (m, 4H, H-1, H-2, H-4 and H-5), 7.38 (dd, *J* 4.8 and 0.5 Hz, 1H, H-13); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 145.1, 140.5, 128.1, 127.9, 126.6, 124.4, 124.3, 51.8, 46.9.

N-(2-Bromobenzyl)-1-(thiophen-2-yl)methanamine (**4b**)

White solid; 49% yield; m.p. 210-214 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.28 (s, 1H, H-8), 3.94 (s, 2H, H-7), 4.01 (s, 2H, H-9), 6.96-6.97 (m, 2H, H-12 and H-13), 7.14 (td, *J* 7.7, 1.7 Hz, 1H, H-2, H-3, H-4 or H-5), 7.24 (dd, *J* 4.8, 1.6 Hz, 1H, H-11), 7.30 (td, *J* 7.5, 1.1 Hz, 1H, H-2, H-3, H-4 or H-5), 7.42 (dd, *J* 7.6, 1.6 Hz, 1H, H-2, H-3, H-4 or H-5), 7.56 (dd, *J* 8.0, 1.1 Hz, 1H, H-2, H-3, H-4

or H-5); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 144.0, 139.0, 133.0, 130.5, 128.8, 127.5, 126.7, 125.1, 124.6, 124.2, 52.8, 47.6; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 283.2, found: 283.6, t_R 1.19 min (96.2%, DAD).

N-(4-Bromobenzyl)-1-(thiophen-2-yl)methanamine (**4c**)

White solid; 45% yield; m.p. 200-204 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.68 (s, 1H, H-8), 3.79 (s, 2H, H-7), 3.99 (s, 2H, H-9), 6.92-6.93 (m, 1H, H-11), 6.95-6.97 (m, 1H, H-12 or H-13), 7.22-7.24 (m, 3H, H-1, H-5 and H-12 or H-13), 7.44-7.47 (m, 2H, H-2 and H-4); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.1, 139.2, 131.6, 130.0, 126.8, 125.1, 124.6, 120.9, 52.2, 47.7; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 283.2, found: 283.7, t_R 1.11 min (94.2%, DAD).

2-(((Thiophen-2-ylmethyl)amino)methyl)phenol (**4d**)

White solid; 42% yield; m.p. 250-253 °C; ^{1}H NMR (400.13 MHz, MeOD) δ 4.11 (s, 2H, H-7), 4.32 (s, 2H, H-9), 6.86 (m, 2H, H-12 and H-13), 7.07 (dd, *J* 3.6, 1.5 Hz, 1H, H-11), 7.22 (m, 3H, H-2, H-3, H-4 or H-5), 7.50 (d, *J* 5.1 Hz, 1H, H-2, H-3, H-4 or H-5), 8.52 (bs, 1H, H-14); ^{13}C NMR (100.61 MHz, MeOD) δ 157.7, 135.5, 132.1, 131.7, 130.9, 128.6, 128.5, 120.8, 120.1, 116.4, 48.0, 45.9; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 219.3, found: 219.8, t_R 1.05 min (99.3%, DAD).

4-(((Thiophen-2-ylmethyl)amino)methyl)phenol (**4e**)

White solid; 35% yield; m.p. 250-253 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.76 (s, 2H, H-7), 4.01 (s, 2H, H-9), 4.24 (s, 2H, H-8 and H-14), 6.72 (d, *J* 8.5 Hz, 2H, H-2 and H-4), 6.96 (m, 2H, H-11 and H-12 or H-13), 7.15 (d, *J* 8.5 Hz, 2H, H-1 and H-5), 7.22 (dd, *J* 4.8, 1.5 Hz, 1H, H-12 or H-13); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 155.3, 143.5, 131.4, 129.9, 126.9, 125.5, 124.8, 115.8, 52.2, 47.3; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 219.3, found: 220.0, t_R 0.89 min (96.2%, DAD).

Methyl 4-(((thiophen-2-ylmethyl)amino)methyl)benzoate (**4f**)

White solid; 56% yield; m.p. 215-219 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.76 (s, 1H, H-8), 3.89 (s, 2H, H-7), 3.91 (s, 3H, H-15), 3.99 (s, 2H, H-9), 6.92 (m, 1H, H-11), 6.96 (m, 1H, H-12 or H-13), 7.22 (dd, *J* 5.0, 1.2 Hz, 1H, H-12 or H-13), 7.42 (d, *J* 8.5 Hz, 2H, H-1 and H-5), 8.0 (d, *J* 8.3 Hz, 2H, H-2 and H-4); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.1, 145.5, 144.0, 129.9, 129.1, 128.1, 126.8, 125.1, 124.6, 52.5, 52.1, 47.7; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 261.4, found: 262.0, t_R 1.01 min (99.6%, DAD).

N-(2-Allylbenzyl)-1-(thiophen-2-yl)methanamine (**4g**)

Yellow solid; 26% yield; m.p. 183-186 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.48 (s, 1H, H-8), 3.36-3.38 (m, 2H, H-14), 3.73 (s, 2H, H-7), 3.91 (s, 2H, H-9), 4.84-4.88 (m, 1H, H-16), 4.93-4.95 (m, 1H, H-16), 5.83-5.92 (m, 1H, H-15), 6.84-6.87 (m, 2H, H-2, H-3, H-4, H-5, H-11, H-12 or H-13), 7.07-7.13 (m, 4H, H-2, H-3, H-4, H-5, H-11, H-12 or H-13), 7.23-7.25 (m, 1H, H-2, H-3, H-4, H-5, H-11, H-12 or H-13); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.5, 138.5, 138.0, 137.6, 130.0, 129.4, 127.4, 126.7, 126.5, 124.9, 124.5, 115.7, 50.5, 48.2, 37.0; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 243.4, found: 243.9, t_R 1.20 min (85.8%, DAD).

3-Fluoro-4-(((thiophen-2-ylmethyl)amino)methyl)phenol (**4h**)

Brown solid; 22% yield; m.p. 265-267 °C; ^{1}H NMR (500.13 MHz, MeOD) δ 3.71 (s, 2H, H-9), 3.92 (s, 2H, H-7), 6.50 (dd, *J* 11.9, 2.3 Hz, 1H, H-5), 6.57 (dd, *J* 8.3, 2.3 Hz, 1H, H-4), 6.95-6.98 (m, 2H, H-12, and H-13), 7.15 (t, *J* 8.6 Hz, 1H, H-11), 7.28-7.29 (m, 1H, H-2); ^{13}C NMR (125.76 MHz, MeOD) δ 163.2 (d, *J* 243.3 Hz), 159.7 (d, *J* 12.0 Hz), 143.5, 132.5 (d, *J* 6.6 Hz), 127.7, 127.0, 125.7, 117.6 (d, *J* 15.6 Hz), 112.3 (d, *J* 2.7 Hz), 103.5 (d, *J* 25.0 Hz), 47.6, 46.1; ^{19}F NMR (125.76 MHz, MeOD) δ 119.7; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 237.3, found: 237.8, t_R 0.95 min (96.6%, DAD).

N,*N*-Dibenzyl-1-(thiophen-2-yl)methanamine (**5a**)

Beige solid; 1% yield; m.p. 224-227 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.61 (s, 4H, H-7 and H-7'), 3.78 (s, 2H, H-8), 6.92-6.95 (m, 2H, H-10 or H-11 or H-12), 7.22-7.25 (m, 3H, H-3, H-3' and H-10 or H-11 or H-12), 7.32 (t, *J* 7.5 Hz, 4H, H-2, H-4, H-2', H-4'), 7.43 (d, *J* 7.3 Hz, 4H, H-1, H-5, H-1' and H-5'); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 143.4, 139.5, 128.9, 128.4, 127.1, 126.5, 125.6, 124.8, 57.7, 52.3.

N,*N*-bis(2-Bromobenzyl)-1-(thiophen-2-yl)methanamine (**5b**)

Yellow oil; 4% yield; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.80 (s, 4H, H-7 and H-7'), 3.89 (s, 2H, H-8), 6.95-6.96 (m, 2H, H-10 and H-12), 7.09 (t, *J* 7.8 Hz, 2H, H-3 and H-3' or H-4 and H-4'), 7.22-7.24 (m, 1H, H-11), 7.31 (t, *J* 7.5 Hz, 2H, H-3 and H-3' or H-4 and H-4'), 7.51 (d, *J* 8.0 Hz, 2H, H-2 and H-2' or H-5 and H-5'), 7.73 (d, *J* 7.5 Hz, 2H, H-2 and H-2' or H-5 and H-5'); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 142.6, 138.4, 132.8, 130.3, 128.5, 127.6, 126.7, 126.1, 125.0, 124.4, 57.3, 53.0; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 451.2, found: 452.0, t_R 2.47 min.

N,*N*-bis(4-Bromobenzyl)-1-(thiophen-2-yl)methanamine (**5c**)

Yellow oil; 7% yield; ^{1}H NMR (500.13 MHz, $CDCl_3$)

δ 3.53 (s, 4H, H-7 and H-7'), 3.74 (s, 2H, H-8), 6.89-6.90 (m, 1H), 6.94 (dd, *J* 5.1, 3.4 Hz, 1H), 7.24 (dd, *J* 5.1, 1.1 Hz, 1H), 7.28 (d, *J* 8.4 Hz, 4H), 7.43-7.46 (m, 4H).

2,2'-(((Thiophen-2-ylmethyl)azanediyl)bis(methylene)) diphenol (**5d**)

Yellow oil; 10% yield; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.77 (s, 2H, H-8), 4.00 (s, 2H, H-7b), 4.01 (s, 2H, H-7a), 5.63 (s, 2H, H-13 and H-13'), 6.77-6.87 (m, 3H, H-Ar), 6.93-7.00 (m, 4H, H-Ar), 7.10-7.19 (m, 2H, H-Ar), 7.23-7.28 (m, 2H, H-Ar); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 158.2, 156.4, 141.4, 129.0, 128.8, 127.1, 126.3, 125.2, 119.3, 116.6, 54.5, 51.5, 46.7; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 325.4, found: 326.0, t_R 1.28 min.

4,4'-(((Thiophen-2-ylmethyl)azanediyl)bis(methylene)) diphenol (**5e**)

Yellow oil; 2% yield; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.48 (s, 4H, H-7 and H-7'), 3.72 (s, 2H, H-8), 4.63 (s, 2H, H-13 and H-13'), 6.87 (d, *J* 3.0 Hz, 1H, H-10), 6.91 (dd, *J* 5.0, 3.4 Hz, 1H, H-11 or H-12), 7.19 (dd, *J* 5.0, 1.2 Hz, 1H, H-11 or H-12), 7.23 (d, *J* 8.4 Hz, 4H, H-2, H-4, H-2' and H-4'), 7.76 (d, *J* 8.5 Hz, 4H, H-1, H-5, H-1' and H-5'); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 154.7, 143.4, 131.4, 130.2, 126.5, 125.6, 124.8, 115.3, 56.7, 51.9; UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 325.4, found: 326.0, t_R 1.21 min.

Dimethyl 4,4'-(((thiophen-2-ylmethyl)azanediyl) bis(methylene))dibenzoate (**5f**)

UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 409.5, found: 410.0, t_R 2.11 min.

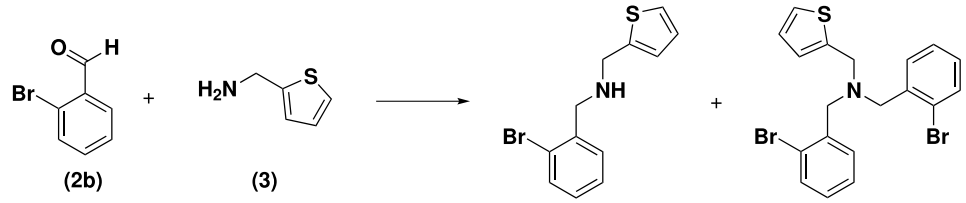
4,4'-(((Thiophen-2-ylmethyl)azanediyl)bis(methylene)) bis(3-fluorophenol) (**5h**)

UHPLC-DAD-MS *m/z*, calcd. for $[M + H]^+$: 361.4, found: 362.0, t_R 1.24 min.

Results and Discussion

Initially, our synthetic efforts were directed toward the preparation of secondary amines via reductive amination between different aldehydes (**2a**-**2h**) and 2-thiophenemethylamine (**3**) using sodium triacetoxyborohydride as reducing agent. However, preliminary results indicated that the product was not being formed. To overcome this situation, different methodologies were conducted, investigating the influence of different reagents, molar ratios, and heating methods (conventional reflux *vs.* microwave irradiation) to favor the formation of the desired secondary amines (**4a**-**4h**) as indicated at Table 1. The reaction progress and ratio between secondary and tertiary amines were monitored by relative percentage area using UHPLC-DAD-MS analysis and 2-bromobenzaldehyde (**2b**) was the model used to test such reactions.

Table 1. Optimization of reaction conditions and relative percentage of crude mixture for the secondary and tertiary amines formation



(2b) (3) (4b) (5b)

entry	Condition	Relative area (UHPLC-DAD-MS) / %		
		2b	**4b**	**5b**
1	STAB, acetic acid, DCM, r.t., 72 h	52.7	–	–
2	$NaBH_4$, molecular sieves, MeOH, r.t., 24 h	85.7	–	
3	Et_3SiH (2 eq), $InCl_3$ (0.15 eq), MeOH, r.t., 42 h	71.6	28.4	3.6
4	Et_3SiH (2.5 eq), $InCl_3$ (0.3 eq), MeOH r.t., 24 h	6.8	42.0	15.9
5	Et_3SiH (4 eq), $InCl_3$ (0.5 eq), MeOH, r.t., 24 h	–	73.4	13.9
6	Et_3SiH (2.5 eq), $InCl_3$ (0.5 eq), MeOH, reflux, 24 h	–	58.8	19.9
7	Et_3SiH (2.5 eq), $InCl_3$ (0.5 eq), MeOH, MW, 100 ºC, 30 min	–	75.3	11.8
8	Et_3SiH (2.5 eq), $InCl_3$ (0.5 eq), MeOH, MW, 80 ºC, 20 min	71.9	16.2	1.5
9	Et_3SiH (2.5 eq), $InCl_3$ (0.5 eq), MeOH, MW, 100 ºC, 10 min	30.0	46.2	6.9
10	Et_3SiH (2.5 eq), $InCl_3$ (0.5 eq), MeOH, MW, 90 ºC, 25 min	5.5	72.0	10.5

STAB: sodium triacetoxyborohydride; DCM: methylene chloride; MW: microwave; UHPLC-DAD-MS: ultra-high performance liquid chromatography coupled to diode array detection and mass spectrometry.

Initially, sodium triacetoxyborohydride was replaced by sodium borohydride, and molecular sieves were added to maintain anhydrous conditions, as the presence of water could interfere with the reduction step. However, UHPLC-MS analysis indicated that the intermediate imine was not formed, suggesting that the initial condensation between the amine and the aldehyde, which is an essential step for the subsequent reduction, was not occurring.

In a third approach, the reaction was performed using triethylsilane and indium(III) chloride in methanol, varying reaction times, temperatures and reagent concentrations, based on the methodology described by Lee *et al.*[9] Under these conditions, the formation of the desired product was observed. Nevertheless, a tertiary amine byproduct (**5a**-**5e**), arising from the condensation of two aldehydes and one amine was also formed, as illustrated in Table 1. Interestingly, the formation of the byproducts occurred even when a lower equivalent of aldehyde was used. Initially, the reactions were performed at room temperature while varying the stoichiometric ratios of the reagents and reaction times (ranging from 24 to 42 h). However, the yields remained unsatisfactory due to the formation of a substantial amount of tertiary amine byproduct. To drive the reaction forward, the temperature was increased to reflux for 24 h; unfortunately, this modification further promoted the formation of the tertiary amine and consequently decreased the yield of the desired product. In order to decrease the time of the reaction, the same methodology was tested under microwave irradiation, a variation not previously reported in the literature for the $InCl_3$/Et_3SiH/MeOH system.

After evaluating the different parameters, entry 10 was selected as the optimal procedure for obtaining derivative (**4b**), as it provided the highest aldehyde conversion with minimal formation of the tertiary byproduct (**5b**) in a lower temperature and time, which can be interesting for sensitive aldehydes. Consequently, the methodology was expanded to a range of aldehydes using Et_3SiH (2.5 eq) and $InCl_3$ (0.5 eq). The reaction time was individually adjusted for each substrate to ensure maximum conversion, and it was possible to relate the electronic and steric effects of the substituent attached to the aromatic ring with the time the reaction took to finish. Benzaldehyde (**2a**), the only unsubstituted substrate in the series, was the exception and was reacted under condition 5 because the aldehyde underwent significant degradation under microwave irradiation, even on lower temperatures. The specific reaction times, along with the relative percentages of residual aldehyde, desired product, and tertiary amine byproducts determined at the end of the reaction, are summarized in Table 2.

Our results show longer reaction times with belzaldehydes containing substituents at the *ortho*-position, which makes sense as this position typically exerts greater steric hindrance, which usually hampers the nucleophilic attack of the amine during imine formation. However, the electron-withdrawing nature of the bromine atom increases the electrophilicity of carbonyl carbon compared to hydroxylated benzaldehydes, potentially explaining the observed reaction rates. In contrast, the hydroxyl group acts as an electro-donating group through resonance, which decreases the electrophilicity of the carbonyl carbon and subsequently slows down the nucleophilic attack by the amine. Furthermore, aldehydes with *ortho*-substitutions showed a higher tendency toward tertiary amine formation. The exception was 2-allylbenzaldehyde (**2g**), for which no tertiary amine was detected. Among those that did form byproducts, 2-hydroxybenzaldehyde (**2d**) yielded significantly higher amounts of the tertiary amine compared to the other substrates. It suggests that the hydroxyl group at the *ortho*-position may have an important role with its H-bonds at the reaction, as this interaction promotes an efficient polarization of the carbonyl π-system, thereby

Table 2. Reaction time for the aldehyde series and relative percentage area after the end of the reaction

entry	Aldehyde	time	Relative area (UHPLC-DAD-MS) / %		
			2	**4**	**5**
1	benzaldehyde (**2a**)[a]	–	–	–	–
2	2-bromobenzaldehyde (**2b**)	25 min	5.48	72.0	10.5
3	4-bromobenzaldehyde (**2c**)	1 h	5.49	80.5	–
4	2-hydroxybenzaldehyde (**2d**)	50 min	–	42.2	45.1
5	4-hydroxybenzaldehyde (**2e**)	2 h	–	83.3	4.3
6	4-(methoxycarbonyl)benzaldehyde (**2f**)	50 min	–	74.0	8.5
7	2-allylbenzaldehyde (**2g**)	12 h	–	66.8	–
8	2-fluoro-4-hydroxybenzaldehyde (**2h**)	90 min	–	68.8	18.9

[a]Reaction with benzaldehyde was performed under reflux due to its degradation under microwave irradiation; UHPLC-DAD-MS: ultra-high performance liquid chromatography coupled to diode array detection and mass spectrometry.

enhancing the partial positive charge on the carbonyl carbon. Consequently, the electrophilicity of this center is significantly increased, rendering it more susceptible to the subsequent nucleophilic attack by the amine nitrogen. This cooperative effect might explain the distinct reactivity observed for this substrate which led to significant tertiary amine formation (up to 45.1%) compared to the other *ortho*-substituted benzaldehydes.

Although not all byproducts could be isolated, those that were successfully purified were characterized by ^{1}H and ^{13}C NMR and their yields calculated as shown in Table 3.

Table 3. Calculated yield for the secondary and tertiary amines

entry	Product	Yield / %	Byproduct	Yield / %
1	**4a**	50	**5a**	2
2	**4b**	49	**5b**	4
3	**4c**	40	**5c**	8
4	**4d**	48	**5d**	10
5	**4e**	35	**5e**	2
6	**4f**	56	**5f**	–
7	**4g**	27	**5g**	–
8	**4h**	19	**5h**	–

Tertiary amines for these specific derivatives have not been previously reported in the literature. Indeed, a search of chemical databases reveals a lack of studies identifying these tertiary amines as significant byproducts in this reaction system.

Conclusions

Our findings demonstrated that while microwave-assisted synthesis significantly accelerates reaction rates compared to conventional methods, it also reveals a competitive pathway leading to significant amounts of tertiary amine byproducts. The systematic investigation of the substrate scope showed that the formation of these byproducts is dictated by the balance of electronic and steric effects, with *ortho*-substituted benzaldehydes showing a higher tendency toward the formation of the tertiary amine. By employing UHPLC-DAD-MS for real-time monitoring, it was able to characterize these tertiary amines as novel compounds, filling a notable gap in the existing literature where such byproducts are often overlooked. Future research may focus on further refining catalyst loading to suppress the competitive tertiary pathway for even more demanding substrates. Ultimately, this work not only introduces an optimized microwave-assisted protocol for the reaction of different benzaldehyde and 2-thiophenemethylamine but also establishes the importance of rigorous byproduct analysis in the development of robust synthetic methodologies.

Supplementary Information

Supplementary data (NMR and UHLC-DAD-MS spectra) are available free of charge at http://jbcs.sbq.org.br, as PDF file.

Data Availability Statement

Data is available in the text and in the supplementary information.

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Author Contributions

G. A. S. A. was responsible for development, methodology, investigation, formal analysis and writing; R. L. N. L. for investigation, NMR spectra acquisition, formal analysis and writing; F. P. S.-Jr. for writing, reviewing, editing, funding acquisition, and supervision; S. B. F. for development, methodology, writing, reviewing, editing, funding acquisition, supervision and project management.

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