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# Scalable methodologies for the synthesis of novel unsymmetrically substituted secondary amines

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*Abstract*: Fast, easy, and scalable methodologies for the synthesis of unsymmetrically substituted secondary amines containing naphthalene, indole, pyridine and imidazole moieties through reductive amination were explored. The investigated operating procedures were successful on a 50- to 30-mmol scale, and present a high potential for up-scaling.

*Keywords*: reductive amination; imine; secondary amine; scalability.

## INTRODUCTION

Medicinal chemistry depends significantly on the generation of compound libraries for the discovery of leads, exploration of structure–activity relationship (SAR), and optimization of physical properties. However, the scope of a compound library can be limited by the commercial availability of the starting materials. Several chemical classes of starting materials, such as aldehydes and carboxylic acids, are well represented commercially. Amongst other important scaffolds in the preparation of numerous biologically active substances, a large number of structurally diverse amines are also available. Nonetheless, the significant use of amines as building blocks in drug-like molecules justifies the expansion of the available entities.

In connection with previous work concerning the synthesis,[1,2] reactivity,[3,4] and biological activity[5,6] of Mannich bases derived from *ortho*-hydroxyacetophenones, easy access to novel, biologically relevant secondary amines in 10-gram quantities was required. One-pot, solution-phase reductive alkylation of a primary amine with an aldehyde or a ketone is one of the most widely utilized methods for the synthesis of secondary amines. One of the drawbacks of this approach is the necessity for the removal (usually by column chromatography) of the unreacted primary amine along with other potential by-products, especially

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the alcohol related to the initial carbonyl compound. Both solid-phase synthesis and solution-phase synthesis with resin-bound scavengers/reagents have been used to circumvent the shortcomings of the classical solution-phase synthesis.[7] Although these methodologies allow fast preparation of a virtually infinite number of pure secondary amines (either individually or in parallel synthesis) on a very small scale, the cost of the resins employed makes large- or even medium-scale synthesis prohibitive. Therefore, low-cost, classical, solution-phase synthetic strategies that are amenable to scaling up without the need for chromategraphic separation were considered for the achievement of this synthetic goal. In this paper, two of such strategies were employed for the multi-gram preparation of unsymmetrically substituted secondary amines having naphthalene, indole, pyridine and imidazole moieties in their structure; in addition, the potential for scale-up of these two strategies was explored.

## EXPERIMENTAL

All chemical reagents were obtained from Sigma–Aldrich and were used without prior purification. Analytical thin-layer chromatography was performed on glass-backed SiliCycle precoated silica gel 60 $F_{254}$ plates, and the compounds were visualized by UV illumination (254 nm). Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house, on a PerkinElmer 2400 Series II CHNS/O system. The $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the $^1$H-NMR spectra. The chemical shifts for the carbon atoms are given relative to $CDCl_3$ ($\delta$ = 77.16 ppm), $CD_3OD$ ($\delta$ = 49.00 ppm), or DMSO-$d_6$ ($\delta$ = 39.52 ppm). The high-resolution mass spectra were obtained on an Applied Biosystems/MDS Sciex QSTAR XL spectrometer equipped with an Agilent HP1100 Cap-LC system in the electrospray ionization (ESI) mode.

*General procedure for the synthesis of* N-*(naphthalen-1-ylmethylene)benzylamines* ***1***

A mixture of the required amine (50 mmol) and 1-naphthaldehyde (7.81 g, 50 mmol) in ethanol (20 mL) was treated with 0.5 mL of ethereal HCl and stirred at room temperature for 1 h. The mixture was refrigerated overnight, and then the solid that separated was filtered and recrystallized.

*General procedure for the synthesis of* N-*(naphthalen-1-ylmethyl)benzylamines* ***2***

A solution of *N*-(naphthalen-1-ylmethylene)benzylamine **1** (20 mmol) in methanol (50 mL) was gradually treated with $NaBH_4$ (2.28 g, 60 mmol) at room temperature. The mixture was stirred at room temperature overnight, and then the solvent was removed under reduced pressure and the residue was partitioned between water (80 mL) and ethyl acetate (50 mL). The aqueous layer was further extracted with ethyl acetate (2× 20 mL) and the combined organic phase was washed with water and brine and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to give the pure secondary amine. The hydrochloride was prepared by treating a solution of the free base in diethyl ether with an excess of ethereal HCl. Filtration and recrystallization of the separated solid afforded the crystalline hydrochloride.

*General procedure for the synthesis of* N-*(arylidene)-2-(1*H-*indol-3-yl)ethanamines **3***

A mixture of tryptamine (4.81 g, 30 mmol) and aldehyde (30 mmol) in benzene (60 mL) was heated at reflux temperature for 4 h while the formed water was removed as an azeotrope. At the end of the reaction time, the solvent was removed under reduced pressure to give a residue that was recrystallized from the appropriate solvent.

*Reduction of imines **3** derived from tryptamine to amines **4***

Starting from imines **3** (20 mmol) and $NaBH_4$ (2.28 g, 60 mmol), the reduction was performed in a manner similar to the procedure reported previously for amines **2**. The hydrochlorides were prepared as described for the *N*-(naphthalen-1-ylmethyl)benzylamines **2**.

*General procedure for the one-pot synthesis of* N-*(pyridin-3-ylmethyl)benzylamines **5***

A mixture of 3-(aminomethyl)pyridine (3.24 g, 30.0 mmol) and aldehyde (36 mmol) in methanol (50 mL) was stirred at room temperature for 6 h, and then $NaBH_4$ (3.42 g, 90.0 mmol) was gradually added to the solution, and the mixture was further stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was further extracted with ethyl acetate (2×20 mL); the combined organic phase was washed with water (3×30 mL) and extracted with 1 M HCl (60 mL). The acid extract was washed with ethyl acetate (2×20 mL), and then the pH of the aqueous phase was rendered alkaline with 10 % aqueous $K_2CO_3$ solution. The separated oil was extracted in ethyl acetate (2×30 mL), washed with water and brine, and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to yield the pure amine. The dihydrochlorides were prepared as described for the *N*-(naphthalen-1-ylmethyl)benzylamines **2**.

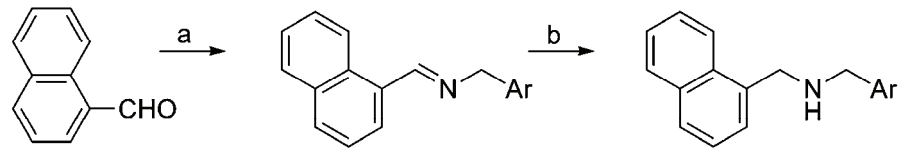
*General procedure for the synthesis of* N-*(3-(1*H-*imidazol-1-yl)propyl)benzylamines **6***

A mixture of 1-(3-aminopropyl)-1*H*-imidazole (1.25 g, 10.0 mmol) and aldehyde (12 mmol) in methanol (20 mL) was stirred at room temperature for 24 h, and then $NaBH_4$ (1.14 g, 30.0 mmol) was gradually added. The mixture was further stirred at room temperature overnight, and then the solvent was removed under reduced pressure and the residue was partitioned between water (50 mL) and ethyl acetate (30 mL). The aqueous phase was further extracted with ethyl acetate (20 mL), and then the combined organic phase was washed with water (3×50 mL) and brine (20 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure to give an oil that was purified by column chromatography. The dihydrochlorides were obtained by treating the solution of the free base in diethyl ether with excess of HCl in diethyl ether.

## RESULTS AND DISCUSSION

The first methodology towards the large-scale synthesis of pure secondary amines investigated in this paper was based on the two-step reductive alkylation of a primary amine, an approach that entails the isolation of the intermediate imine. This methodology is less attractive for the preparation of secondary amines than the one-pot approach owing to the additional step. However, the two-step reductive alkylation becomes acceptable provided that the intermediate imine could be separated from the reaction mixture by filtration, and purified (preferably through recrystallization) prior to its reduction in the subsequent step; in this case, the reduction of the imine could yield the secondary amine in high pu-

rity even in bulk preparations. As a high molecular weight and the presence of fused carbocycles or heterocyles are usually grounds for an organic compound to be in the solid state at room temperature, it was hypothesized that imines having at least one naphthalene moiety could be good candidates for the exploration of this strategy. Furthermore, a naphthalene scaffold could be an interesting structural feature, as proved by its presence in the structure of the biologically active compounds that bind to a highly hydrophobic active site of an enzyme,[8] or by its effectiveness as a pharmacophore required for the binding to melanocortin receptors.[9] A brief search of the literature showed that the available information even on the common *N*-(naphthalen-1-ylmethylene)benzylamine or *N*-benzylidene-1-(naphthalen-1-yl)methylamine is scarce, and that the corresponding secondary amine is available from a limited number of commercial sources at considerable cost. Encouraged by these findings, the synthesis of a series of *N*-(naphthalen-1-ylmethyl)benzylamines **2** was undertaken starting from the commercially available naphthalene-1-carboxaldehyde and substituted benzylamines (Scheme 1). When an equimolar mixture of the starting materials in a small volume of ethanol and in the presence of catalytic amounts of ethereal HCl was stirred at room temperature for 1 hour and subsequently refrigerated overnight, the corresponding imines **1** separated as solids. However, 4-methylbenzylamine and 4-fluorobenzylamine did not lead to solid imines, but produced the Schiff bases as viscous oils that redissolved when the reaction mixture was allowed to warm to room temperature; the experiments with these two benzylamines were not pursued further. The solid imines **1** could be recrystallized from lower alcohols with only a moderate loss of material, except for the Schiff base derived from 4-methoxybenzylamine. Aside from 2-chloro-*N*-(naphthalen-1-ylmethylene)benzylamine **1b**, all other naphthalene-containing Schiff bases are novel, and were fully characterized (the analytic and spectral data are given as supplementary material). As a general feature, the $^1$H-NMR spectra of imines **1** present one singlet integrating for one proton at approximately 9 ppm that can be associated with the




**1** **2**

Ar = 4-$CH_3OC_6H_4$-; 2-$ClC_6H_4$-; 2-$CH_3C_6H_4$-; 2,4-$Cl_2C_6H_3$-; 3,4-$(OCH_2O)C_6H_3$-

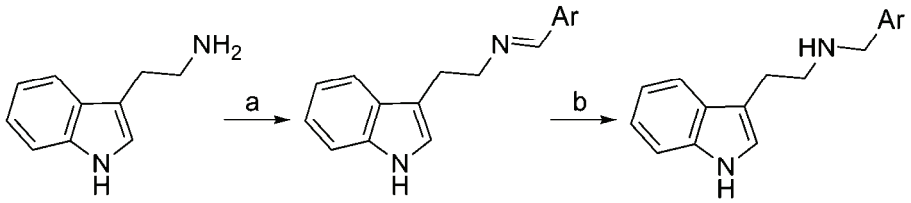
Scheme 1. Synthesis of naphthalene-containing unsymmetrically substituted secondary amines. Conditions: a) substituted benzylamine, 36 % HCl, diethyl ether, rt for 1 h, then –10 °C overnight; b) $NaBH_4$, methanol, rt, overnight.

proton of the imine function, and one singlet integrating for two protons at around 5 ppm, corresponding to the methylene group. The signal of the carbon atom in the imine function just above 160 ppm and the peak of the carbon atom of the methylene group at about 60 ppm can also serve as markers for the validation of the structure of imines **1**.

As expected, the reduction of the pure imines with sodium borohydride in methanol[10] afforded the pure secondary amines **2** almost quantitatively. As the free amines are known to age badly or form carbamic acids in the presence of carbon dioxide from air, the novel compounds were also converted into their hydrochlorides by treating their solution in diethyl ether with ethereal HCl. A comparative inspection of the $^{1}$H-NMR spectra of amines **2** as free bases revealed the presence of a new singlet integrating for two protons at around 4 ppm and the disappearance of the singlet that was noticeable downfield in the spectra of imines **1**. Moreover, an additional peak in the aliphatic region of the $^{13}$C-NMR spectra can be attributed to the aliphatic carbon atom in the naphthalen-1-ylmethyl residue. The $^{1}$H-NMR spectra of the hydrochlorides of amines **2** taken in deuterated DMSO feature a broad singlet at approximately 10 ppm that integrates for two protons. Since the addition of deuterated methanol to the NMR sample resulted in a decrease of the integration for this peak, the signal was attributed to the hydrogen atoms of the protonated secondary nitrogen atom.

The investigation was extended to a second series of secondary amines derived from tryptamine and aromatic aldehydes. A few *N*-benzyltryptamines with sedative, anticonvulsant, analgesic, and neuroleptic action,[11] or active as tuberculostatics[12] have been so far obtained through the condensation of tryptamine with aldehydes followed by the *in situ* reduction of the intermediate imine. On the other hand, imines derived from tryptamine have usually been reported in connection with the synthesis of tetrahydro-*β*-carbolines *via* the Pictet–Spengler reaction.[13] A brief examination of the methods described in the literature for the synthesis of imines **3** derived from tryptamine revealed that the most efficient method is based on the condensation of the reactants in benzene with the removal of the by-product water as an azeotrope (Scheme 2). For example, this method produced a 70 % yield of (2-(1*H*-indol-3-yl)-*N*-(2-thienylmethylene)ethanamine **3d** after recrystallization, whereas a low yield of only 24 % was reported when the same compound was prepared by heating the reactants in ethanol at reflux temperature for 30 min.[14] The analytic and spectral data for imines **3** are given in the Supplementary material to this paper. The $^{1}$H-NMR spectra of the imines **3** showed two triplets around 3.1 and 3.9 ppm, attributable to the protons of the methylene groups originating from tryptamine, whereas the imine proton and the proton at the heterocyclic nitrogen atom were associated with a sharp singlet usually above 8 ppm and a broad singlet at approximately 8 ppm, respectively. In the $^{13}$C-NMR spectra of imines **3**, the carbon atom of the imine function gave a

signal downfield at about 160 ppm. In the subsequent step, the reduction of the pure imines **3** with sodium borohydride in methanol at room temperature afforded, almost quantitatively, the pure secondary amines **4**. Amines **4a** and **4d** were crystalline compounds, whereas amines **4b** and **4c** were dense oils that were characterized both as free bases and as hydrochlorides.

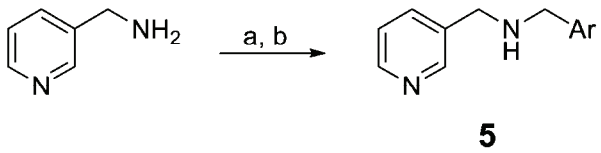



Ar = 4-Br$C_6H_4$-; 3,4-$(CH_3O)_2C_6H_3$-; naphthalen-1-yl; 2-thienyl

Scheme 2. Synthesis of tryptamine-derived unsymmetrically substituted secondary amines. Conditions: a) (hetero)aromatic aldehyde, benzene, reflux, 4 h; b) $NaBH_4$, methanol, rt, overnight.

A second hypothesized strategy that could provide uncomplicated access to multi-gram quantities of secondary amines was also explored in this study. This strategy relies on the association of the standard one-pot reductive alkylation with a procedure allowing the adequate separation of the desired product from the unreacted starting materials and any potential by-products. An inexpensive, fast separation procedure that is applicable for large-scale preparations could be based on the differential solubility of the components in the mixture. Thus, the simple partition of the crude reaction mixture between an organic solvent and an aqueous acid solution would result in the extraction in the latter phase of the basic components only (*i.e.*, the starting primary amine and the desired secondary amine), whereas the unreacted carbonyl compound and the alcohol by-product derived from it remain in the organic phase. Next, the mixture consisting of a hydrophilic primary amine and a more lipophilic secondary amine could be separated owing to their differential solubility in water. In order to test this hypothesis, the water-soluble 3-(aminomethyl)pyridine and 1-(3-aminopropyl)imidazole were selected as starting materials. These two primary amines are also good candidates for the generation of biologically active chemical entities. For example, the 3-pyridinyl moiety is important for the activity of several types of nicotinic acetylcholine receptor agonists,[15–17] or it is present as the pharmacophore in inhibitors of aldosterone synthase[18] or cytochromes P450,[19] whereas imidazole is ubiquitous in azole antifungal agents[20] and inhibitors of hemoenzymes, such as nitric oxide synthase[21] or heme oxygenase.[22]

Treatment of 3-(aminomethyl)pyridine with an excess of aromatic aldehydes in methanol for 6 hours led to the formation of the corresponding imines, which, in turn, were reduced *in situ* with sodium borohydride to the related secondary amines **5** (Scheme 3). Sequential removal of the solvent and partition between ethyl acetate and dilute hydrochloric acid allowed the separation of the basic components from the crude reaction mixture. Subsequent release of the amine (or amines, if unreacted 3-(aminomethyl)pyridine is still present) from their hydrochlorides, followed by extraction with ethyl acetate afforded the pure secondary amine in good yield, as shown by TLC; the unreacted 3-(aminomethyl)-pyridine, if present in the first ethyl acetate extract, appears to have remained in the aqueous phase after the second extraction. The analytic and spectral data for the secondary amines are given in the Supplementary material to this paper. The NMR characterization of the isolated amines **5** confirmed their purity and supported their structure through the two singlets integrating for two protons in the vicinity of 4 ppm in the $^{1}$H-NMR spectra and the two signals around 50 ppm in the $^{13}$C-NMR spectra, which are associated with the two methylene groups adjacent to the nitrogen atom. Inspection of the $^{1}$H-NMR spectra of the salts prepared by treating the free bases of amines **5** with an excess of ethereal HCl revealed that the corresponding dihydrochlorides were obtained in all cases. The protonation of the heterocyclic nitrogen atom was supported by the displacement of the signals of the protons in the pyridine moiety to lower magnetic fields. The peak integrating for two protons noticeable above 10 ppm in $^{1}$H-NMR spectra of the dihydrochlorides in deuterated DMSO confirmed the protonation of the nitrogen atom in the amine function; in contrast, the $^{1}$H-NMR spectrum of dihydrochloride **5d** taken in deuterated methanol lacks this peak.

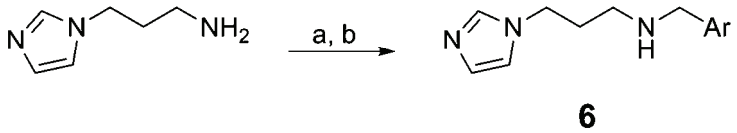



**5**

Ar = 4-Br$C_6H_4$-; 4-$CH_3O C_6H_4$-; 4-biphenylyl; naphthalen-1-yl; 2-thienyl

Scheme 3. Synthesis of pyridine-containing unsymmetrically substituted secondary amines. Conditions: a) (hetero)aromatic aldehyde, methanol, rt, 6 h; b) $NaBH_4$, methanol, rt, overnight.

Under similar reaction conditions, the condensation of 1-(3-aminopropyl)-imidazole with aromatic aldehydes to the corresponding imines (Scheme 4) was less straightforward. TLC analysis of the reaction mixture after 6 h revealed significant amounts of unreacted starting materials; extension of the reaction time to 24 h resulted in a slight improvement of the conversion. *In situ* reduction with sodium borohydride followed by the separation procedure detailed for amines **5**




**6**

Ar = $C_6H_5$-; naphthalen-1-yl; 2-thienyl; 2,4-$(CH_3O)_2C_6H_3$-

Scheme 4. Synthesis of imidazole-containing unsymmetrically substituted secondary amines. Conditions: a) (hetero)aromatic aldehyde, methanol, rt, 24 h; b) $NaBH_4$, methanol, rt, overnight.

led to a mixture of 1-(3-aminopropyl)imidazole and secondary amines **6**, that required additional column chromatographic separation in order to afford modest yields of pure amines **6**. As a result, this strategy does not seem to be appropriate for a fast, medium-scale synthesis of amines derived from 1-(3-aminopropyl)imidazole. The analytic and spectral data of the synthesized amines **6** are given in the Supplementary material. The structure of the imidazole-containing secondary amines **6** was supported by NMR analysis. In the aliphatic region of the $^1$H-NMR spectra, a multiplet at 2 ppm and two triplets at approximately 2.6 and 4 ppm are indicative for the propyl moiety, whereas the aromatic protons in the imidazole ring appear at 6.87, 7.03 and 7.43 ppm. The deliquescent dihydrochlorides of compounds **6a** and **6b** were also prepared and characterized by NMR. Again, the displacement of the protons in the heterocyclic ring towards higher chemical shifts confirmed the protonation of the imidazole, and the peak integrating for two protons at 10 ppm in the spectrum of compound **6b** taken in deuterated DMSO (which was absent in the spectrum of the compound **6a** taken in deuterated methanol) suggested the protonation of the nitrogen atom in the amine function.

## CONCLUSIONS

Novel naphthalene- and indole-containing secondary amines were synthesized by a two-step reductive alkylation process, with the separation of the intermediate imine. The methodology was successfully applied to a 50-mmol scale synthesis of these novel amines, and the procedure could be scaled up for the production of even larger quantities. A second strategy, employing heterocyclic, water-soluble amines, and comprising the usual reductive alkylation process combined with an isolation procedure relying on the differential solubility of the initial primary amine and the resulting secondary amine, was successful only in the case of 3-(aminomethyl)pyridine; the methodology was valid on a 30-mmol scale, and its potential for scalability was high. On the other hand, the application of the same methodology with 1-(3-aminopropyl)imidazole as the starting material required chromatographic separation, making the procedure unsuitable for scaling up.

## SUPPLEMENTARY MATERIAL

Analytical and spectral data of synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

## ИЗВОД

## МЕТОДОЛОГИЈА СИНТЕЗЕ НОВИХ АСИМЕТРИЧНО СУПСТИТУИСАНИХ СЕКУНДАРНИХ АМИНА

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Испитана је брза и једноставна синтеза асиметрично супституисаних секундарних амина који садрже нафталенски, индолски и имидазолски структурни фрагмент. Испитане процедуре успешно су примењене на скали 30 до 50 mmol и имају озбиљан потенцијал за примену на већим скалама.

(Примљено 8. априла, ревидирано 2. јула 2011)

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