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Reaction of 5-aryloxazolidines with arylmagnesium bromides as a new route to *N*-benzyl-β-hydroxyphenethylamines as starting materials for the preparation of 4-aryl-1,2,3,4-tetrahydroisoquinolines

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ABSTRACT

Benzaldehydes react smoothly with the non-stabilized azomethine ylide derived from sarcosine and formaldehyde to form 5-aryloxazolidines as intermediates, which undergo ring-opening to give *N*-benzyl-β-hydroxyphenethylamines in good yields by the action of arylmagnesium bromides. Their subsequent acid-catalyzed cyclization into 4-aryl-1,2,3,4-tetrahydroisoquinolines was performed in moderate to good yields.

The chemistry of 4-aryl-1,2,3,4-tetrahydroisoquinolines has attracted considerable attention from the synthetic community due to their distribution in Nature and various biological activities.[1] *Amaryllidaceae* alkaloids such as cherylline (**1**) and latifine (**2**) have been isolated from *Crinum latifolium* and other *Crinum* species.[2] Nomifensine (**3**), a serotonin–norepinephrine–dopamine reuptake inhibitor, was marketed as an antidepressant in the 1970–1980s.[3] Furthermore, a large number of 4-aryltetrahydroisoquinolines[4] and their hetero analogs[5] have been proposed as triple monoamine reuptake inhibitors, anti-ulcer and antihistamine drugs, for example, 4-(4-bromophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4**)[6] (Fig. 1).

Due to the important applications of this class of compounds, their synthesis has been studied extensively. There are several routes for the preparation of 4-aryltetrahydroisoquinolines, with most of them being completed via the intramolecular cyclization of *N*-benzyl-β-hydroxyphenethylamines.[4–7] The latter are obtained by the reaction of phenacyl bromides and benzylamines followed by a reduction step,[4a–d,6,7a] or from styrene oxides and benzylamines.[7b,c] In addition, there are a number of alternative methods based on Pictet-Spengler cyclization of 2,2-diarylethylamines,[8] the addition of lithium benzylamides to acetophenone enols,[9] direct deprotonation of C-4 in 1,2,3,4-tetrahydroisoquinolines using *sec*-butyllithium, and subsequent arylation using aryl halides via aryne intermediates.[10]

In connection with our interest in the development of azomethine ylide chemistry,[11] we have developed a convenient, one-pot method for the preparation of 2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ols **5** from aromatic aldehydes bearing electron-donating substituents and an azomethine ylide derived from sarcosine and

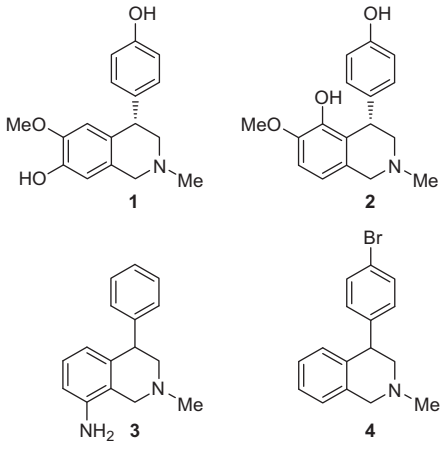

Figure 1. Some natural alkaloids and drugs containing a 4-aryltetrahydroisoquinoline framework.

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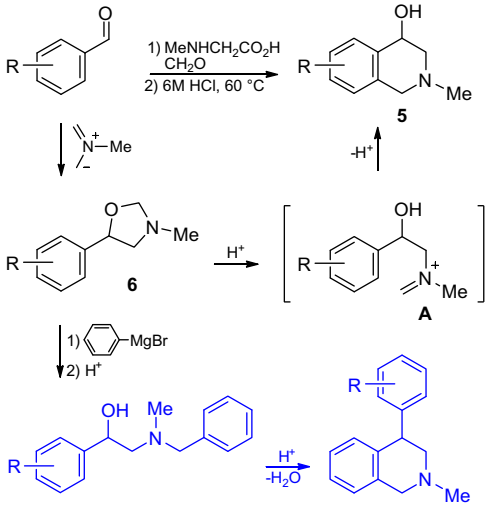
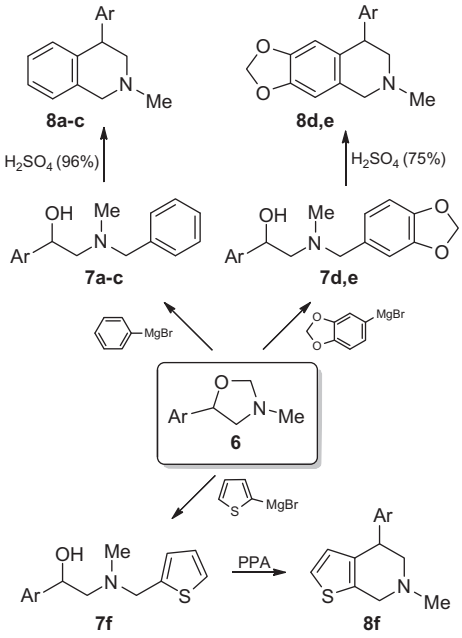


Scheme 1. One-pot syntheses of substituted tetrahydroisoquinolines.

formaldehyde, via a novel aryloxazolidine–tetrahydroisoquinoline rearrangement.[12] In this intramolecular electrophilic substitution reaction, intermediate iminium cation **A** reacts with the nucleophilic arene with formation of the tetrahydroisoquinoline ring system **5**. Taking into account this result, we envisaged that the ring-opening of oxazolidine **6** by an external nucleophilic arene would produce the corresponding *N*-benzyl-β-hydroxyphenethylamine, the key intermediate for our 4-aryl-1,2,3,4-tetrahydroisoquinoline synthesis. To the best of our knowledge, no such reactions have been reported to date (Scheme 1).



Scheme 2. Synthesis of *N*-benzyl-β-hydroxyphenethylamines **7** and 4-aryltetrahydroisoquinolines **8**.

We found that refluxing an aromatic aldehyde (1.0 mmol), sarcosine (1.5 mmol), and paraformaldehyde (3.0 mmol), in benzene or toluene for 6–8 h with azeotropic removal of water, allowed

Table 1
Yields and melting points of *N*-benzyl-β-hydroxyphenethylamines **7** and 4-aryltetrahydroisoquinolines **8**

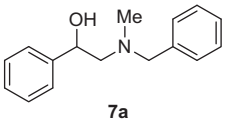
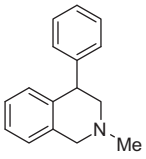
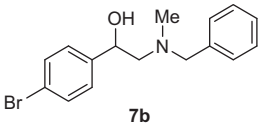
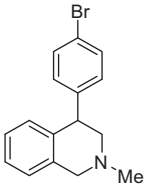
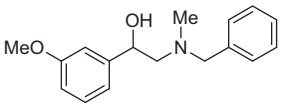
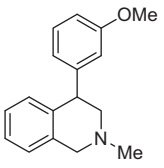
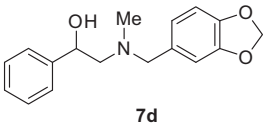
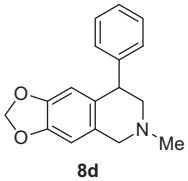
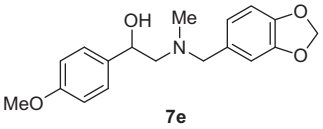
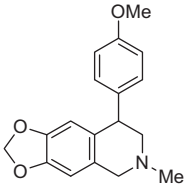
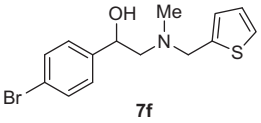
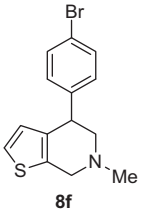
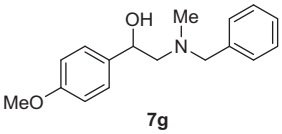
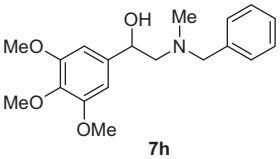
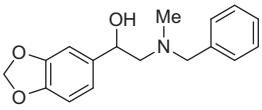
Amino alcohol	Yield (%)	Tetrahydroisoquinoline	Yield[a] (%)	Mp[b] (°C)
 **7a**	71	 **8a**	56	167–172[c]
 **7b**	82	 **8b**	60	247–252[d]
 **7c**	76	 **8c**	32	207–215[e]
 **7d**	58	 **8d**	37	237–240[f]

Table 1 (*continued*)

Amino alcohol	Yield (%)	Tetrahydroisoquinoline	Yield[a] (%)	Mp[b] (°C)
 **7e**	54	 **8e**	39	230–235
 **7f**	79	 **8f**	65	217–224
 **7g**	65	–	–	–
 **7h**	79	–	–	–
 **7i**	88	–	–	–

[a] Overall yield of the hydrochlorides based on the starting aromatic aldehyde.
[b] Mp of the hydrochlorides, uncorrected.
[c] Mp 169–174 °C (Ref. 7a).
[d] Mp 245–250 °C (Ref. 6b).
[e] This compound was recrystallized from *i*-PrOH–Et_2O; reported in Ref. 10 as a free base.
[f] Mp 237–239 °C (Ref. 7c), 212–214 °C (Ref. 7a).

us to obtain 5-aryloxazolidines **6** in high yields.[12,13] The crude oily products were sufficiently pure according to the ^{1}H NMR spectra, and were used in the next stage without purification. Arylmagnesium bromides were prepared from aryl bromides (1.5 mmol) and magnesium (1.5 mmol) in THF according to the standard technique. To our delight, simple addition of oxazolidine **6** to a solution of the arylmagnesium bromide resulted in full opening of cyclic aminal **6**, and subsequent acidification led to the desired 2-(benzylmethylamino)-1-arylethanols **7a–i** (Scheme 2, Table 1).[14] The hydrochlorides of these compounds had different solubilities in water, so the best technique for their purification involved direct precipitation as a mixture with the magnesium salt from the THF–toluene solution, followed by washing to remove non-basic organic side products, and final basification of the salt mixture with concentrated aqueous NH_3.

Intramolecular cyclization of *N*-benzyl-β-hydroxyphenethylamines **7a–c** was performed under previously described conditions (CH_2Cl_2, RT, H_2SO_4;[6,7a–c] for **7c**—$AlCl_3$[4e,f]) to give 4-aryltetrahydroisoquinolines **8a–c** in moderate to good yields based on the starting aromatic aldehyde. Similarly, compounds **8d**,**e** bearing an electron-donating methylenedioxy substituent on the aromatic ring were obtained in 37% and 39% yields, respectively.[15,16] Application of this reaction to 2-thienylmagnesium bromide led to a three-step synthesis of 4-(4-bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**8f**)[17] in 65% yield, as a potential selective 5-HT reuptake inhibitor.[5c] In this case, the cyclization step was performed under the action of PPA[7f,g] (Scheme 2). It should be noted that the structure of thienopyridine **8f** needed additional confirmation because of the known possibility of isomerization via a spirocyclic rearrangement.[7g] This compound was thus identified by comparison of its ^{1}H NMR spectral data with those reported in the literature (the chemical shift of the H-3 thienyl proton at δ 6.52 showing an upfield shift due to shielding by the phenyl ring).

In a few cases (amino alcohols **7g–i**), recognizable products could not be isolated, presumably due to the stabilizing effect of the *p*-alkoxy group on the initial benzylic carbocation intermediate, which makes cyclization difficult and facilitates intermolecular side reactions leading to the formation of resinous products. In the course of this study, *N*-benzyl-β-hydroxyphenethylamines **7c**,**e**,**f** and 4-aryltetrahydroisoquinolines **8e**,**f** have been synthesized for the first time, while the other compounds were previously known. The results are compiled in Table 1.

It is worth noting that compared with the previously known approaches for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines, the present method does not require the use of a reducing

agent, and does not involve working with hazardous compounds, an inert atmosphere, or chromatographic purification of the intermediate liquid products, and thereby greatly facilitates the preparation of the target tetrahydroisoquinolines.

In conclusion, we have developed a new, three-step route to 4-aryl-1,2,3,4-tetrahydroisoquinolines from aromatic aldehydes, sarcosine, and formaldehyde via a 5-aryloxazolidine intermediate, followed by the reaction with an arylmagnesium bromide and final acid-catalyzed cyclization. This method allows easy access to biologically important tetrahydroisoquinoline derivatives. Further application of this reaction for the construction of substituted tetrahydroisoquinolines and their hetero analogs is underway in our laboratory and the results will be reported in due course.

Acknowledgment

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14. *General procedure for the preparation of 4-aryl-1,2,3,4-tetrahydroisoquinolines* ***8***. A mixture of the substituted benzaldehyde (1.0 mmol), finely ground sarcosine (0.13 g, 1.5 mmol), and paraformaldehyde (0.09 g, 3.0 mmol) was refluxed in dry benzene (3.3 mL), with magnetic stirring and removal of formed water by means of a Dean–Stark trap, for 6–8 h. The resulting solution was evaporated in vacuo to give the oily 5-aryl-3-methyloxazolidine **6**. This was dissolved in toluene (1 mL) and quickly added to a solution of ArMgBr prepared from ArBr (1.5 mmol) and Mg (0.04 g, 1.5 mmol) in THF (2 mL) at 0 °C with vigorous stirring. The mixture was left overnight at room temperature. Concentrated HCl (0.25 mL, 3.0 mmol) and toluene (3 mL) were added with stirring to the cooled solution (−5 °C). The organic layer was decanted and the precipitate additionally washed with toluene and Et_2O. After basification with an excess of aq NH_3, extraction with CH_2Cl_2 (2×2 mL), drying over Na_2SO_4, and evaporation, the corresponding *N*-benzyl-β-hydroxyphenethylamine **7** was obtained. This was dissolved in CH_2Cl_2 (2 mL) and treated dropwise with concd H_2SO_4 (2 mL) (96%—for **7a**,**b**, 75%—for **7d**,**e**) over 5 min. After stirring for 2 h, ice chips were added and the aq solution made basic with aq NaOH solution. The mixture was extracted with CH_2Cl_2 (2×2 mL) and the combined organic extracts dried over anhydrous Na_2SO_4, filtered through a thin layer of silica gel and concentrated in vacuo. Amino alcohols **7c** and **7f** were cyclized using $AlCl_3$ in CH_2Cl_2 (4.0 equiv, reflux, 1.5 h) and polyphosphoric acid (1.1 g of PPA—1 mmol of **7f**, 80–90 °C, 1.5 h), respectively. The free bases were converted into hydrochloride salts with anhydrous ethereal HCl solution generated in situ from *i*-PrOH (1.3 equiv) and AcCl (1.1 equiv).
15. 4-(4-Bromophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**8b**≡**4**). White powder, yield 60% (overall yield based on the starting aromatic aldehyde), mp 247–252 °C (245–250 °C in Ref. 6b).
16. *8-(4-Methoxyphenyl)-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline hydrochloride (**8e**).* White powder, yield 39%, mp 230–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$, free base) δ 2.40 (s, 3H, MeN), 2.47 (dd, *J* = 11.3, 8.8 Hz, 1H, 7-C*H*H), 2.96 (dd, *J* = 11.3, 5.5 Hz, 1H, 7-CH*H*), 3.50 (d, *J* = 14.5 Hz, 1H, 5-C*H*H), 3.63 (d, *J* = 14.5 Hz, 1H, 5-CH*H*), 3.79 (s, 3H, MeO), 4.11 (t, *J* = 7.0 Hz, 1H, H-8), 5.85 (s, 2H, H-2), 6.32 (s, 1H, H-9), 6.52 (s, 1H, H-4), 6.83 (d, *J* = 8.6 Hz, 2H, Ar), 7.10 (d, *J* = 8.6 Hz, 2H, Ar); ^{13}C NMR (126 MHz, DMSO-d_6, for the hydrochloride) δ 41.0, 42.2, 53.6, 55.1, 55.9, 101.2, 105.9, 107.8, 114.3, 122.2, 128.8, 130.0, 132.7, 146.3, 146.9, 158.6. Anal. Calcd for $C_{18}H_{20}ClNO_3 \cdot 0.25H_2O$: C, 63.90; H, 6.11; N, 4.14. Found: C, 63.76; H, 6.20; N, 4.08.
17. *4-(4-Bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride (**8f**).* Light yellow powder, yield 65%, mp 217–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$, free base) δ 2.46 (s, 3H, MeN), 2.51 (dd, *J* = 11.6, 8.0 Hz, 1H, 5-C*H*H), 3.00 (dd, *J* = 11.6, 5.5 Hz, 1H, 5-CH*H*), 3.66 (d, *J* = 14.5 Hz, 1H, 7-C*H*H), 3.77 (d, *J* = 14.5 Hz, 1H, 7-CH*H*), 4.10 (dd, *J* = 8.0, 5.5 Hz, 1H, H-4), 6.52 (d, *J* = 5.1 Hz, 1H, H-3), 7.04–7.08 (m, 1H, H-2), 7.07 (d, *J* = 8.2 Hz, 2H, Ar), 7.41 (d, *J* = 8.2 Hz, 2H, Ar); ^{13}C NMR (126 MHz, DMSO-d_6, for the hydrochloride) δ 39.9, 42.3, 50.9, 55.7, 120.8, 125.6, 126.2, 128.0, 130.6, 131.7, 135.3, 139.3. Anal. Calcd for $C_{14}H_{15}BrClNS$: C, 48.78; H, 4.39; N, 4.06. Found: C, 49.08; H, 4.36; N, 4.08.