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Highly efficient synthesis of 3-alkyl/aryl-4-aryl-1,2,3,4-tetrahydroisoquinolines from *N*,*N*-dibenzylaminols†

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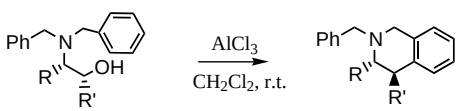
Abstract—Substituted tetrahydroisoquinolines are synthesized in optically pure form using a Grignard reaction of *N*,*N*-dibenzyl aminol and Friedel–Crafts cyclization as the key steps.

Considerable interest has been shown in substituted isoquinolines due to their diverse biological activities. They are constituents of several drugs and natural products.[1] They exhibit broad spectrum calcium antagonistic[2] and cardiovascular to β-adrenergic receptor antagonism,[3] antibacterial[4] and antiplasmodial activity.[5] All these activities are attributed to the substitution pattern on the isoquinoline skeleton. These classes of compounds are traditionally synthesized by the ring closure of iminium intermediates via the well known Pictet–Spengler[6] or Bischler–Napieralski reactions.[7] A few other methods have also been reported for the synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines in both racemic and enantiopure forms.[8] Surprisingly, however, there are few methods known for the stereocontrolled synthesis of 3- or 3,4-disubstituted congeners.[9]



R = Alkyl, Aryl; R' = Aryl

Scheme 1.

Our own interest in the development of new protocols for the synthesis of nitrogen containing heterocycles and amino alcohols[10] prompted us to investigate the feasibility of a Lewis acid mediated Friedel–Crafts type cyclization of *N*,*N*-dibenzyl aminols of the type shown (Scheme 1) for the synthesis of the titled class of compounds. Incidentally, of the Lewis acids examined which included $AlCl_3$, $TaCl_5$ and $BiCl_3$, the conventionally used $AlCl_3$ turned out to be the best. We report a practical and general method for the synthesis of 3,4-disubstituted-1,2,3,4-tetrahydroisoquinolines[11] (Scheme 1 and Table 1).

Initially, the required *N*,*N*-dibenzyl-1,2-aminol **1** (Table 1, entry 1) was prepared from a known alaninal by a Grignard reaction with PhMgBr.[12] The product obtained was treated with 1 equiv. of $AlCl_3$ in dichloromethane to furnish the *trans* isoquinoline derivative **1a** in 82% yield. Mechanistically it is anticipated that the benzylic OH group bearing carbon participates in Friedel–Crafts type cyclization.[9b] A few other aminols were prepared following standard procedures. For instance alaninol derivative **2** obtained by Grignard addition of *p*-bromoanisole yielded 2-*N*-benzyl-3-methyl-4-(methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **2a** in 85% yield. Similarly, the phenylglycine derivatives (entries 4 and 5) underwent smooth intramolecular Friedel–Crafts cyclization to furnish the 3,4-diphenyl-1,2,3,4-tetrahydroisoquinolines **4a** and **5a**, in 90 and 80% yields, respectively. The phenylalaninol **6** also reacted to yield the corresponding isoquinoline **6a** in 75% yield. However, in the serine

Keywords: substituted isoquinolines; Friedel–Crafts cyclization; *N*,*N*-dibenzyl aminol; $AlCl_3$.

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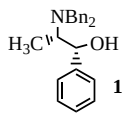
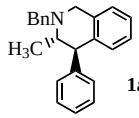
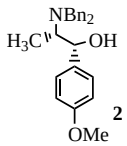
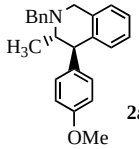
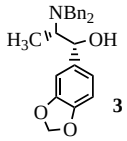
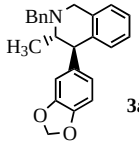
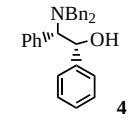
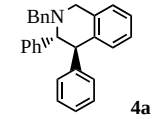
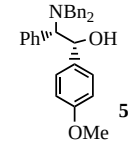
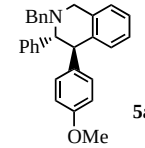
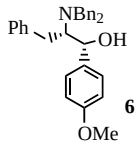
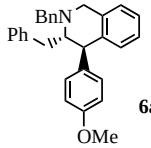
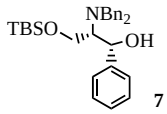
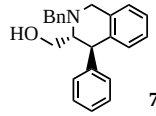
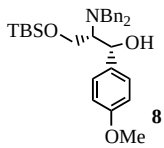
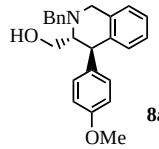
Table 1. $AlCl_3$-mediated synthesis of tetrahydroisoquinolines[a]

Entry	Substrate	Product	Yield(%)[b]
1	 **1**	 **1a**	82
2	 **2**	 **2a**	85
3	 **3**	 **3a**	75
4	 **4**	 **4a**	90
5	 **5**	 **5a**	80
6	 **6**	 **6a**	75
7	 **7**	 **7a**	72
8	 **8**	 **8a**	65

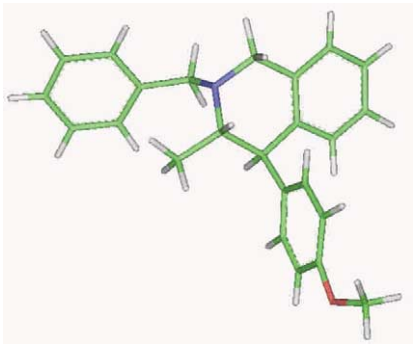
[a]All products were characterized by ^1H NMR and mass spectral data.

[b]Isolated yields

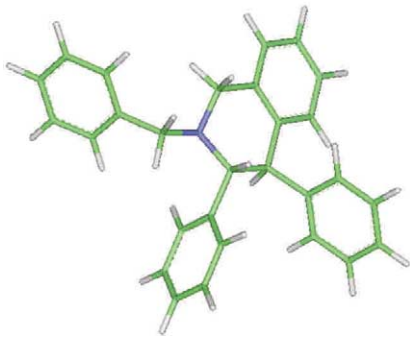
series (entries 7 and 8), the silyl ether was cleaved with concomitant cyclization to produce **7a** and **8a**.

The high stereoselectivity of the cyclization step leading to one diastereomer exclusively was confirmed with the aid of ^1H NMR data,[13] which were also in complete agreement with the predicted stereochemistry as studied by molecular dynamics.[14] The stick models of the minimized energy conformers of the *cis* and *trans* isomers of **2a** and **4a** are shown below. The energy difference between the *trans* and *cis* isomers is of the order of 7.7 kcal/mol in the case of **2a** and 2.1 kcal/mol in the case of **4a** and, assuming these structures to model the transition states which would lead to them, confirm the kinetic control of the products observed (Figs. 1 and 2).

General procedure for cyclization: To the aminol (1 mmol) in CH_2Cl_2 (5 mL) was added anhydrous $AlCl_3$ (1 mmol) and the mixture stirred under an inert atmosphere for 4 h. Ice water (5 mL) was added and the resulting mixture extracted with CH_2Cl_2 (2×10 mL), washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated to furnish the product, which was purified by column chromatography (for yields see Table 1).

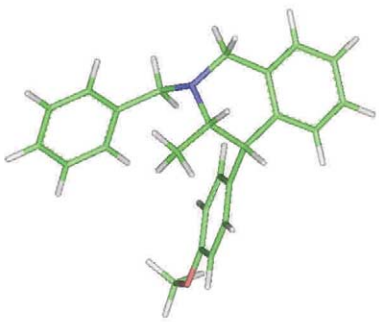


2a (*trans*)

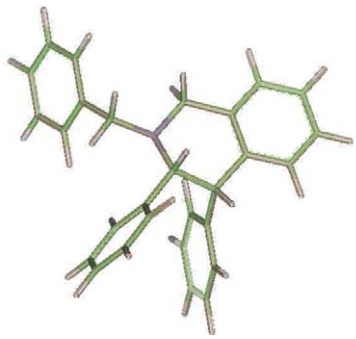


4a (*trans*)

Figure 1. Lower energy diagrams.



2a (*cis*)



4a (*cis*)

Figure 2. Higher energy diagrams.

Acknowledgements

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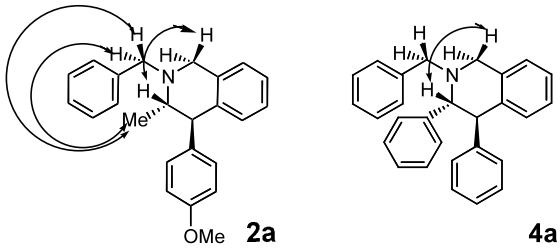
Schmidtz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.

13. ^{1}H NMR of compound **2a** (500 MHz, $CDCl_3$): δ 1.10 (3H, d, $^3J_{Me–H5}=6.5$ Hz), 3.12 (1H, dq, $^3J_{H3–H4}=4.8$ Hz), 3.64 (1H, d, $^2J_{N–CH2(gem)}=13.5$ Hz), 3.69 (1H, d, $^2J_{H1(up)–H1(down)}=15.9$ Hz), 3.71 (1H, d, $^2J_{N–CH2(gem)}=13.5$ Hz), 3.79 (3H, s), 3.81 (1H, d, $^3J_{H4–H3}=4.8$ Hz), 3.83 (1H, d, $^2J_{H1(up)–H1(down)}=15.9$ Hz), 6.83–7.24 (13H, m); ^{13}C NMR 13.2; 29.6; 50.8; 55.2; 57.1; 59.5; 113.3; 125.7; 126.1; 126.3; 128.1; 128.6; 130.0; 130.5; 134.5; 138.5; 139.4; 159.2; FAB MS 343; 342; 328; 252; 210; 179; 165; 135; 109; 91. NOE percentages H_1(up)–$H_3=2.3$; CH_3–NCH_2(up) = 0.7; CH_3–NCH_2(down) = 1.2.

^{1}H NMR of Compound **4a** (500 MHz, $CDCl_3$): δ 3.16 (1H, d, $^2J_{H1(up)–H1(down)}=13.2$ Hz), 3.72 (1H, d, $^2J_{N–CH2(gem)}=13.1$ Hz), 3.75 (1H, d, $^2J_{H1(up)–H1(down)}=13.2$ Hz), 3.78 (1H, d, $^3J_{H3–H4}=6.8$ Hz), 3.82 (1H, d, $^2J_{N–CH2(gem)}=13.1$ Hz), 4.36 (1H, d, $^3J_{H4–H3}=6.8$ Hz), 6.94–7.22 (19H, m); ^{13}C NMR 14.1; 20.8; 53.5; 53.7; 59.5; 60.2; 72.1; 125.7; 25.8; 126.1; 126.3; 126.7; 127.2; 127.7; 127.8; 128.1; 128.4; 128.5; 128.7; 128.9; 129.1; 129.4; 129.5; 134.9; 137.7; 139.0; 40.5; 144.7; FAB MS 375; 374; 298; 284; 206; 179; 91. NOE percentages H_1(up)–H_3 = 18.3.



Characteristic nOe's For Compounds **2a, 4a**

14. MD simulations were performed at constant NVE ensemble, the total run is 500 ps at 1 fs time step and the averages are calculated at 300 K over 0.5 ps.