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Highly diastereoselective aminoalkylation of naphthols with chiral amines mediated by lithium perchlorate solution in diethyl ether

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Abstract—One-pot, three-component, Mannich reaction of naphthols with in situ prepared imines in 5 M ethereal lithium perchlorate at room temperature affords the corresponding aminoalkylated products in high yields with high diastereoselectivities. The process is exemplified by the reaction of 2-naphthol with (*R*)-1-phenylethylamine and an aromatic aldehyde in concentrated ethereal lithium perchlorate solution, which affords a highly diastereoselective access to the requisite 2-aminoalkylated product.

1. Introduction

New methods for the stereoselective aminoalkylation of electron-rich aromatic compounds are currently of great interest. Although a variety of methods for the aminoalkylation of electron-rich aromatic compounds are available,[1,2] new direct approaches that are stereoselective and mild enough to allow the preparation of single diastereoisomers are continuously attracting interest.[3]

The Mannich reaction is one of the most important multi-component reactions in organic synthesis and biosynthesis.[4] In the course of this three-component aminoalkylation of aldehydes, C–N and C–C single bonds replace the C–O double bond.

Recently, we reported the lithium perchlorate-mediated, one-pot three-component aminoalkylation of aromatic or aliphatic aldehydes with (trimethylsilyl)alkylamines and different nucleophiles, including electron-rich aromatic compounds.[5] Herein we describe an efficient, straightforward and diastereoselective method for the aminoalkylation of naphthols with chiral amines mediated by lithium perchlorate solution in diethyl ether.

2. Results and discussion

In concentrated ethereal lithium perchlorate solution, aldehyde **1** and enantiopure (*R*)-1-phenylethylamine **2** (also readily available commercially as the (*S*) enantiomer) produce the imine **3** as an intermediate at room temperature. Upon addition of β-naphthol or α-naphthol to the reaction mixture, aminoalkylated products **4a**–**k** were formed in moderate to high yields and with diastereoselectivity (dr) from 75 to 99% (Tables 1 and 2).

When a mixture of aromatic aldehyde **1**, (*R*)-1-phenylethylamine, **2**, and β-naphthol, in a molar ratio of 1.0:1.5:1.0, was stirred under an argon atmosphere in 5 M ethereal lithium perchlorate solution at room temperature for 4 h, the desired aminoalkylnaphthol was produced in 20% yield. Reaction of a mixture of aromatic aldehyde **1**, (*R*)-(trimethylsilyl)-1-(phenylethyl)amine and β-naphthol, in a molar ratio of 1.0:1.5:1.0, gave very similar results. When a mixture of **1**, **2** and trimethylsilylchloride (TMSCl) in a molar ratio of 1.0:1.5:0.5, respectively, were stirred for 15 min in ethereal lithium perchlorate solution (4 mL, 5 M) at room temperature under an argon atmosphere, presumably the imine **3**, is formed. By addition of 1 equiv1 of β-naphthol into the reaction mixture and stirring at room temperature for 6 h the 1-aminoalkyl-2-naphthol was produced in >75% yield with a diastereomeric purity of >99%, (Scheme 1, Table 1). The diastereo-

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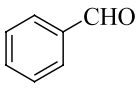
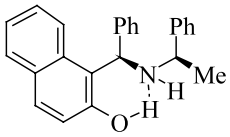
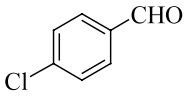
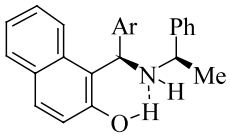
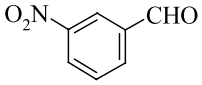
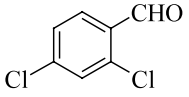
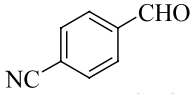
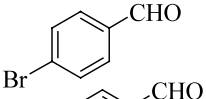
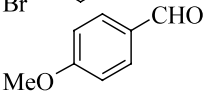
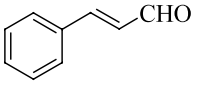
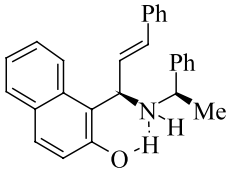
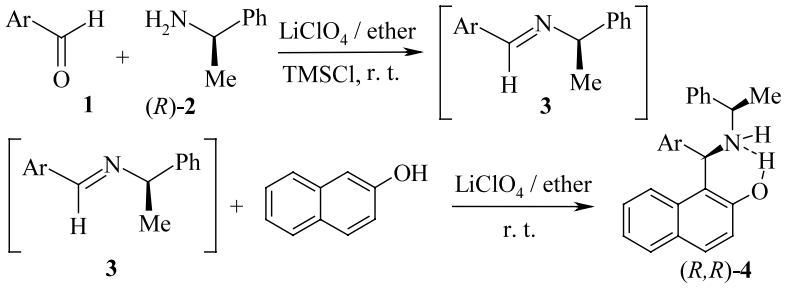
Table 1. $LiClO_4$-mediated stereoselective aminoalkylation of 2-naphthol with chiral amine

Entry	Aldehyde	Product		% Yield	dr[ref]
1			(*R*,*R*)-**4a**	75	99:1[3a]
2			Ar= 4-ClC_6H_4 (*R*,*R*)-**4b**	78	99:1[3a]
3		Ar= 3-$NO_2C_6H_4$	(*R*,*R*)-**4c**	70	90:10[3a]
4		Ar= 2,4-di-ClC_6H_4	(*R*,*R*)-**4d**	70	95:5[3b]
5		Ar= 4-NCC_6H_4	(*R*,*R*)-**4e**	72	95:5[3c]
6		Ar= 4-BrC_6H_4	(*R*,*R*)-**4f**	60	93:7[3f]
7		Ar= 4-$MeOC_6H_4$	(*R*,*R*)-**4g**	55	75:25[3a]
8			(*R*,*R*)-**4h**	60	88:12[3d]

The dr values were determined by ^1H NMR of the crude reaction mixture.

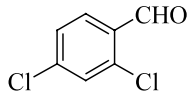
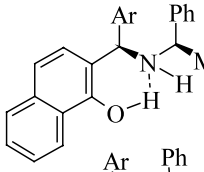
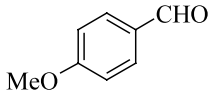
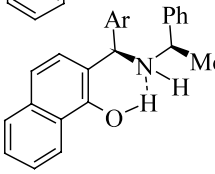
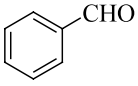
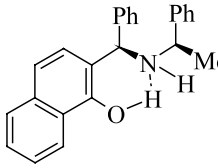
meric purity was determined by ^1H NMR analysis of the product. Completing the reaction over longer times and under different conditions did not effect any improvement in the yield of the 1-aminoalkyl-2-naphthol.

Addition of 1 equiv. of α-naphthol instead of β-naphthol into the mixture of **1**, **2** and trimethylsilyl chloride in a molar ratio of 1.0:1.5:0.5, respectively in 5 M ethereal lithium perchlorate solution at room temperature under an argon atmosphere, gave the 2-aminoalkyl-1-naphthol in 40% yield (Table 2, entries 1–3). In this case the dr was lower than for the β-aminoalkylnaphthols. With isobutyraldehyde, low conversion and dr was observed (20% yield with a diastereomeric purity of 45–55%). When the pre-formed imine **3** was used in a two-step process in ethereal $LiClO_4$ or with Lewis acids such as BF_3-ether, $ZnBr_2$ or

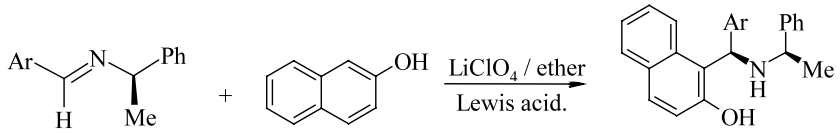


Scheme 1.

Table 2. $LiClO_4$-mediated stereoselective aminoalkylation of 1-naphthol with chiral amine

Entry	Aldehyde	Product	% Yield	dr[ref]
1			44	90:10[3e]
		(*R,R*)-**4i** Ar = 2,4-diClC_6H_4		
2			35	85:15[3g]
		(*R,R*)-**4j** Ar = 4-$MeOC_6H_4$		
3			40	90:10[3a]
		(*R,R*)-**4k**		

The dr values were determined by ^1H NMR of the crude reaction mixture.



Scheme 2.

$AlCl_3$, the dr was not improved and the overall yields of the aminoalkylated products **4** were lower in comparison with the one-pot reaction in the presence of TMSCl (Scheme 2).

The structure of compounds **4a**–**k** were confirmed by their spectral data and were characterized by comparison of IR, NMR (^1H and ^{13}C) and MS spectra with those reported in the literature.[3]

In summary, a one-pot, three-component diastereoselective aminoalkylation of 2-naphthol and 1-naphthol has been achieved in good to moderate yields and with very high to moderate selectivity.

3. Experimental

3.1. General procedure for diastereoselective aminoalkylation of 2-naphthol

A mixture of benzaldehyde (2 mmol, 0.21 g), (*R*)-(+)-1-phenylethylamine (3 mmol, 0.36 g), and 5 M $LiClO_4$ in diethyl ether (4 mL) were placed in a 50 mL flask under argon and stirred for 15 min at room temperature. TMSCl (1 mmol) was added via a syringe. After the addition of TMSCl, a white solid was formed. Then 2-naphthol (2 mmol, 0.29 g) was added. Following the progress of the reaction by TLC and ^1H NMR, the reaction mixture was stirred at room temperature for 6 h. Water (20 mL) and dichloromethane (20 mL) were added. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The crude product was further purified by column chromatography on basic alumina eluting with petroleum ether/ethyl acetate. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) by comparison with those reported in the literature.[3] The same procedure was used for the diastereoselective aminoalkylation of 1-naphthol.

3.2. Selected spectroscopic data for the major diastereoisomers

4a:[3a] ^1H NMR (500 MHz, $CDCl_3$): δ 1.55 (d, $J=6.8$ Hz, 3H), 2.22 (br s, 1H), 3.95 (m, 1H), 5.51 (s, 1H), 7.22–7.80 (m, 16H), 13.80 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.4 (CH_3), 56.9 (CH), 60.6 (CH), 113.2, 120.4, 121.3, 122.7, 126.7, 127.7, 127.9, 128.1, 128.9, 129.0, 129.1, 129.3, 130.0, 130.1, 133.0, 141.9, 143.5, 157.7. IR (KBr), 3220, 1080, cm^{-1}.

4c:[3a] ^1H NMR (500 MHz, $CDCl_3$): δ 1.57 (d, $J=6.9$ Hz, 3H), 2.31 (br s, 1H), 3.91 (q, $J=6.9$ Hz, 1H), 5.94 (s, 3H), 7.13–8.25 (m, 15H), 13.65 (br s, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$): 23.6 (CH_3), 57.9 (CH), 60.1 (CH), 112.4, 120.1, 121.2, 123.7, 127.2, 127.4, 128.4, 128.8, 129.3, 129.7, 130.5, 132.6, 134.4, 142.9, 142.6, 149.0, 158.0. IR (KBr), 3283, 1210, cm^{-1}.

4k:[3a] ^1H NMR (500 MHz, $CDCl_3$): δ 1.54 (d, $J=6.8$ Hz, 3H), 2.32 (br s, 1H), 3.94 (q, $J=6.8$ Hz, 1H), 4.85 (s, 1H), 7.04–7.89 (m, 16H), 12.90 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.8 (CH_3), 56.8 (CH), 65.6 (CH), 116.1, 118.4, 119.3, 120.9, 123.3, 125.3, 126.7, 127.2, 127.8, 128.1, 128.3, 129.4, 129.6, 134.3, 142.8, 143.7, 149.0, 154.9. IR (KBr), 3380, 1095, cm^{-1}.

Caution: Although we did not have any accidents while using $LiClO_4$, it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

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