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Microwave-assisted, solvent-free synthesis of 1-(α- or β-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines by the Mannich reaction

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Abstract—As a new extension of the Mannich reaction of naphthols, 1-(hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinolines were synthesized by the nucleophilic addition of 1- or 2-naphthol to 3,4-dihydroisoquinolines under solvent-free conditions, using microwave irradiation. The additions to 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline proved to be a highly diastereoselective processes, resulting in the cis isomers as the main or the only products.

The frequent occurrence of the 1-substituted isoquinoline nucleus in alkaloids and in a number of physiologically active compounds has led to considerable interest in the synthesis of variously functionalized and saturated representatives of this type of compounds.[1,2] Nucleophilic additions to the C=N double bond of 3,4-dihydroisoquinolines are often used for the construction of the 1-substituted 1,2,3,4-tetrahydroisoquinoline skeleton, and numerous methods have been devised to increase the yield and/or the stereoselectivity of the reaction by using various catalysts or chiral additives.[1,3]

Electron-rich naphthols are known to be good *C*-nucleophiles with the ability to undergo ready addition to C=N double bonds in modified Mannich condensations. The aminomethyl-substituted naphthol derivatives obtained in this way have proved to be easily resolvable, difunctional synthons towards naphthalene-condensed 1,3-heterocycles.[4–6]

In view of the wide-ranging synthetic utility of both 1-substituted tetrahydroisoquinolines and aminomethyl-substituted naphthols, we studied the reactions connecting these structural elements by the nucleophilic addition of 1- or 2-naphthol to 3,4-dihydroisoquinolines.

When 3,4-dihydroisoquinoline **1**[7] or 6,7-dimethoxy-3,4-dihydroisoquinoline **2**[8] was left to stand with 2-naphthol in acetonitrile at ambient temperature for 14 days, 1-(2-hydroxy-1-naphthyl)-1,2,3,4-tetrahydroisoquinolines **3** and **4** were isolated in moderate yields (35% and 40%) on evaporation of the solvent followed by crystallization from methanol (Scheme 1).[9,10] Improved yields could not be achieved either by refluxing the acetonitrile solutions or by heating a solvent-free mixture of the corresponding naphthol and dihydroisoquinoline at 90–100 °C; this may be explained by the rapid thermal decomposition of the addition products.

Microwave irradiation is a process often applied to accelerate organic reactions.[11] In many cases, microwave irradiation has been successfully applied in solvent-free heterogeneous reactions, which is especially advantageous from an environmental aspect.[12] When the naphthol additions to 3,4-dihydroisoquinolines were attempted using microwave agitation, hydroxynaphthyl-substituted tetrahydroisoquinolines **3** and **4** were isolated in considerably improved yields (65% for **3** and 56% for **4**) (Scheme 1).[13] It was found that gradient microwave irradiation furnished the addition products in better yields (85% and 72%, respectively). The initial

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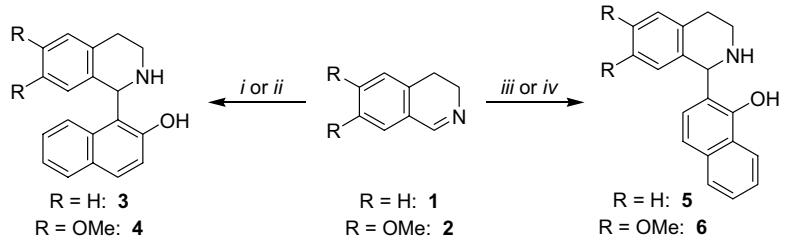
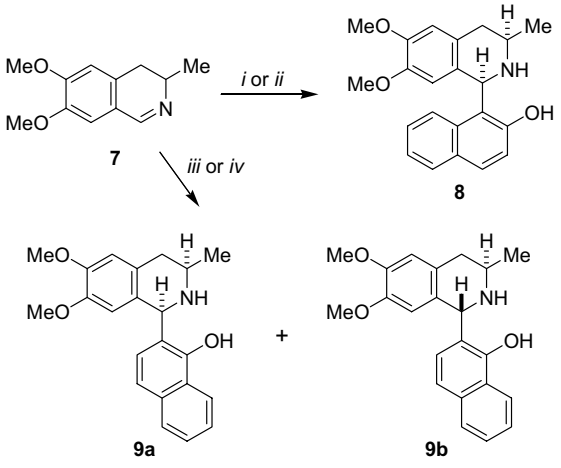


Scheme 1. Reagents and conditions: (i) 2-naphthol, MeCN, rt, 14 days (**3**: 40%, **4**: 35%); (ii) 2-naphthol, microwave irradiation, 90 °C, 20 min, then 70 °C, 30 min (**3**: 65%, **4**: 56%); (iii), 1-naphthol, MeCN, rt, 10 days (**5**: 65%, **6**: 56%); (iv) 1-naphthol, microwave irradiation, 100 °C, 20 min, then 80 °C, 40 min (**5**: 85%, **6**: 72%).

use of higher energies ensured that the melting temperature of the mixture was reached, but keeping the mixture at the same temperature led to decomposition of the product.

2-Aminomethyl-1-naphthol derivatives obtained by Mannich condensation of 1-naphthol are generally relatively unstable compounds and can consequently be isolated only in considerably lower yields than the corresponding 1-aminomethyl-2-naphthol regioisomers.[14] Surprisingly, both the addition performed at ambient temperature and that induced by microwave irradiation of the solvent-free mixture gave 1-(1-hydroxy-2-naphthyl)-substituted 1,2,3,4-tetrahydroisoquinolines **5** and **6** from 1-naphthol and 3,4-dihydroisoquinolines **1** and **2** in higher yields than those observed from 2-naphthol (Scheme 1).[9,10,13]

To investigate the steric effect of a methyl substituent at position 3 of the dihydroisoquinoline, naphthol additions to 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline **7**[15] were also attempted. Substituents adjacent to the C=N bonds proved to exert significant chiral inductive effects on the asymmetric aminoalkylations of 2-naphthol when aromatic aldehydes and (*R*)-1-phenylethylamine[16] or (*S*)-*N*,α-dimethylbenzylamine were used.[17]



Scheme 2. Reagents and conditions: (i) 2-naphthol, MeCN, rt, 13 days (40%); (ii) 2-naphthol, microwave irradiation, 10 min, 90 °C, then 30 min, 70 °C (61%); (iii) 1-naphthol, MeCN, rt, 10 days (60%, **9a**:**9b** = 3:1); (iv) 1-naphthol, microwave irradiation, 20 min, 90 °C, then 40 min, 70 °C, (84%, **9a**:**9b** = 2.6:1).

In the reaction of 2-naphthol and **7** in acetonitrile at ambient temperature, *cis*-1-(2-hydroxy-1-naphthyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline **8** was isolated in moderate yield (40%). No traces of the corresponding trans isomer could be detected in the crude product (Scheme 2). Microwave irradiation of the solvent-free mixture resulted in an increase in the yield (61%) whilst the high stereoselectivity remained the same.[9,10,13] The relative configurations of C-1 and C-3 were determined by NOE measurements.

Analogous additions of 1-naphthol to **7** were accomplished with higher yields (60% in acetonitrile and 84% on the use of microwave irradiation), but with lower stereoselectivities.[9,10,13] The cis (major product) and trans isomers of 1-(1-hydroxy-2-naphthyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (**9a** and **9b**) were separated by column chromatography, and their relative configurations were deduced by NOE measurements.

In conclusion, a new extension of the Mannich reaction was applied to prepare 1-(α- or β-hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinoline derivatives by the nucleophilic addition of 2- or 1-naphthol to 3,4-dihydroisoquinolines. The moderate yields of the reactions performed at ambient temperature could be significantly increased by applying solvent-free microwave heating. The naphthol additions of 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline proved to be highly diastereoselective processes, resulting in the cis isomers as the main or the only products. Further investigations on the synthetic applications of the 1-(hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinolines are in progress.

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9. *General procedure for the synthesis of 1-(α- or β-hydroxynaphthyl)isoquinoline derivatives*: Equivalent amounts of 2- or 1-naphthol (0.22 g, 1.5 mmol) and the corresponding dihydroisoquinoline (1.5 mmol) were dissolved in acetonitrile (20 mL). The reaction mixture was stirred at room temperature for 10–14 days. After evaporation of the solvent, the crude product was recrystallized from *i*-Pr_2O–EtOAc (2:1). Yields: **3**: 0.16 g (40%); **4**: 0.18 g (35%); **5**: 0.27 g (65%); **6**: 0.28 g (56%); **8**: 0.21 g (40%); **9**: 0.31 g (60%, **9a**:**9b** = 3:1), **9a** and **9b** were separated by column chromatography, with EtOAc–*n*-hexane (3:1) as eluent.
10. All new compounds gave correct elemental analyses: Compound **3**: Mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.91 (1H, d, $J = 14.10$ Hz); 3.22–3.36 (2H, m); 3.48–3.56 (1H, m); 6.04 (1H, s); 6.63 (1H, d, $J = 7.55$ Hz); 6.88 (1H, t, $J = 7.05$ Hz); 7.07–7.16 (3H, m); 7.34 (1H, t, $J = 7.55$ Hz); 7.50 (1H, t, $J = 7.55$ Hz); 7.74 (1H, d, $J = 9.06$ Hz); 7.82 (1H, d, $J = 8.06$ Hz); 8.03 (1H, d, $J = 8.06$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 29.9; 44.6; 56.3; 115.6; 120.9; 122.1; 123.3; 126.9; 127.4; 127.6; 129.0; 129.4; 129.6; 130.4; 134.2; 134.6; 136.9; 137.1; 156.7.
Compound **4**: Mp 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.21 (2H, t, $J = 9.80$ Hz); 3.26 (3H, s); 3.48 (1H, t, $J = 6.1$ Hz); 3.80 (3H, s); 3.88 (1H, d, $J = 8.56$ Hz); 5.96 (1H, s); 6.14 (1H, s); 6.60 (1H, s); 7.07 (1H, d, $J = 9.06$ Hz); 7.31 (1H, t, $J = 7.32$ Hz); 7.49 (1H, t, $J = 7.32$ Hz); 7.72 (1H, d, $J = 8.56$ Hz); 7.79 (1H, d, $J = 8.04$ Hz); 8.01 (1H, d, $J = 9.06$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 29.6; 44.6; 56.0; 56.5; 61.6; 111.0; 112.1; 121.0; 121.9; 123.2; 123.4; 123.8; 126.9; 127.5; 128.3; 128.9; 129.6; 130.4; 134.0; 148.6; 156.7.
Compound **5**: Mp 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.80–2.91 (1H, m); 3.08–3.21 (2H, m); 3.31–3.42 (1H, m); 5.30 (1H, s); 6.88 (1H, d, $J = 7.55$ Hz); 6.98–7.06 (1H, m); 7.13 (2H, d, $J = 4.03$ Hz); 7.20 (1H, d, $J = 8.06$ Hz); 7.33 (1H, d, $J = 8.06$ Hz); 7.36–7.46 (2H, m); 7.76 (1H, d, $J = 7.55$ Hz); 8.20 (1H, d, $J = 9.06$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 29.6; 42.9; 61.4; 118.7; 120.2; 123.1; 125.5; 126.5; 126.7; 126.9; 127.5; 127.9; 128.2; 128.3; 129.7; 134.5; 134.8; 136.8; 153.8.
Compound **6**: Mp 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.75–2.80 (1H, m); 3.05–3.18 (2H, m); 3.33–3.38 (1H, m); 3.61 (3H, s); 3.84 (3H, s); 5.28 (1H, s); 6.41 (1H, s); 6.62 (1H, s); 7.19 (1H, d, $J = 8.56$ Hz); 7.32 (1H, d, $J = 8.06$ Hz); 7.39–7.46 (2H, m); 7.76 (1H, d, $J = 7.05$ Hz); 8.23 (1H, d, $J = 7.05$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 29.2; 42.8; 56.4; 56.5; 61.1; 111.3; 112.2; 118.6; 120.2; 123.1; 123.5; 125.5; 126.4; 126.8; 127.8; 127.9; 128.8; 134.7; 148.0; 148.7; 153.9.
Compound **8**: Mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.39 (3H, d, $J = 5.41$ Hz); 2.45–2.56 (1H, m); 2.88 (2H, m); 3.30 (3H, s); 3.84 (3H, s); 6.11 (1H, s); 6.19 (1H, s); 6.62 (1H, s); 7.11 (1H, d, $J = 5.56$ Hz); 7.35 (1H, t, $J = 6.04$ Hz); 7.53 (1H, t, $J = 8.06$ Hz); 7.75 (1H, d, $J = 9.06$ Hz); 7.83 (1H, d, $J = 8.56$ Hz); 8.08 (1H, d, $J = 8.56$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 23.0; 37.8; 50.6; 56.2; 56.5; 64.2; 110.7; 111.8; 118.8; 120.9; 121.9; 123.2; 126.9; 127.5; 128.6; 129.0; 129.6; 130.4; 134.0; 148.2; 148.7; 156.6.
Compound **9a**: Mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (3H, d, $J = 6.04$ Hz); 2.72–2.90 (2H, m); 3.20–3.30 (1H, m); 3.51 (3H, s); 3.80 (3H, s); 5.27 (1H, s); 6.32 (1H, s); 6.37 (1H, s), 7.32–7.47 (4H, m); 7.27 (1H, d, $J = 8.06$ Hz); 8.17 (1H, d, $J = 8.06$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 22.7; 37.7; 49.0; 56.1; 56.2; 62.7; 110.4; 111.5; 118.6; 122.8; 125.3; 126.6; 127.7; 127.8; 128.6; 129.3; 131.0; 131.5; 134.4; 143.5; 144.6; 153.4.
Compound **9b**: Mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.24 (3H, d, $J = 7.55$ Hz); 2.43–2.54 (1H, m); 2.85–2.93 (1H, m); 3.14–3.23 (1H, m); 3.81 (3H, s); 3.89 (3H, s); 5.49 (1H, s); 6.63 (1H, s); 6.66 (1H, s); 6.87 (1H, d, $J = 8.56$ Hz); 7.20 (1H, d, $J = 8.06$ Hz); 7.40–7.47 (2H, m); 7.69–7.75 (1H, m); 8.27–8.33 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 22.6; 36.3; 50.5; 56.8; 56.8; 58.3; 110.5; 112.0; 113.5; 113.7; 115.0; 119.6; 126.7; 128.4; 130.9; 132.5; 134.7; 134.8; 139.0; 140.0; 154.3; 156.4.
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