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Synthesis of amidoalkyl naphthols by an iodine-catalyzed multicomponent reaction of β-naphthol

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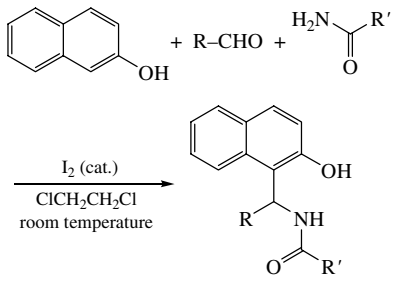
Iodine is an efficient catalyst for the multicomponent condensation reaction of β-naphthol, aromatic aldehydes and urea or an amide to afford the corresponding amidoalkyl naphthols in good yields.

Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without isolating intermediates during the processes; this reduces time and saves both energy and raw materials.[1] They have benefits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules. Biginelli,[2] Ugi,[3] Passerini[4] and Mannich[5] are some examples of MCRs.

In this context, *ortho*-quinone methides (*o*-QMs) have been used in many tandem processes,[6] but only limited work on their reaction with nucleophiles has appeared in the literature.[7,8] Recently, a simple and convenient method for the synthesis of amidoalkyl naphthols by the condensation of aldehydes with β-naphthol and urea or amide in the presence of *p*-toluenesulfonic acid (*p*-TSA) as a catalyst has been reported.[9] To expand this type of tandem process that would permit the condensation of the *in situ* generated *ortho*-quninone methide with nucleophiles other than phenols, we utilized ureas and amides to produce new amidoalkyl naphthol compounds using iodine as a catalyst.

Herein, we report the rapid synthesis of biologically significant amidoalkyl naphthols using a catalytic amount of iodine under extremely mild conditions (Scheme 1).† Firstly, 4-chlorobenzaldehyde was treated with an equimolar amount of β-naphthol and urea in the absence of iodine at room temperature in various solvents, and no desired amidoalkyl naphthol was formed. The introduction of 10 mol% iodine in the reaction of 4-chlorobenzaldehyde with an equimolar amount of β-naphthol and urea in various solvents afforded the desired amidoalkyl naphthol

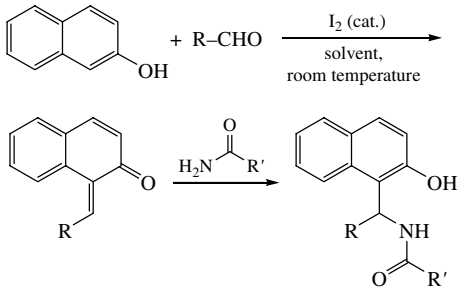


1–10

1 R = 4-ClC_6H_4, R′ = NH_2
2 R = Ph, R′ = NH_2
3 R = 4-$MeOC_6H_4$, R′ = NH_2
4 R = 3-$O_2NC_6H_4$, R′ = NH_2
5 R = 2-furyl, R′ = NH_2
6 R = 2-ClC_6H_4, R′ = NH_2
7 R = 3-$O_2NC_6H_4$, R′ = NHMe
8 R = 3-$O_2NC_6H_4$, R′ = Ph
9 R = 3-$O_2NC_6H_4$, R′ = Me
10 R = Et, R′ = NH_2

Scheme 1

(Table 1). Iodine acts as a Lewis acid catalyst and facilitates the formation of *o*-QMs, which further react with a nucleophile (urea/amide) to form the desired amidoalkyl naphthols (Scheme 2). Chlorinated solvents (dichloroethane > dichloromethane > chloroform) gave the highest yields. Polar protic solvents (methanol >



o-QMs Amidoalkyl naphthols

Scheme 2

Table 1 Solvent effect on the reaction of 4-chlorobenzaldehyde, β-naphthol and urea catalyzed by I_2.

Entry	Solvent	Time/h	Isolated yield of **1** (%)
1	$ClCH_2CH_2Cl$	10	91
2	MeCN	13	52
3	MeOH	13	76
4	EtOH	14	68
5	$CHCl_3$	12	83
6	CH_2Cl_2	12	86
7	DMF	13	25
8	1,4-dioxane	14	78

† Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in [$^2H_6$]DMSO solutions at 200 MHz for ^{1}H and 50 MHz for ^{13}C. Chemical shifts are reported in δ units (ppm) relative to TMS as an internal standard. Electron spray ionization mass spectra (ES-MS) were recorded on a Water-Micromass Quattro-II spectrometer. IR spectra were recorded on a Varian spectrometer. All the reagents of analytical grade were used without further purification.

General procedure. A mixture of an aromatic aldehyde (1 mmol), β-naphthol (1 mmol), urea or amide (1.1 mmol) and I_2 (0.1 mmol) in 1,2-dichloroethane was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (solvent system: MeOH–$CHCl_3$, 1:9). After completion of the reaction, the reaction mixture was filtered and the precipitate was washed with diethyl ether and then with water. The crude compounds were purified by silica gel column chromatography (60–120 mesh silica gel) eluting with chloroform followed by 2% MeOH in chloroform to afford the desired compound in a pure form. All of the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

ethanol) gave higher yields than polar aprotic solvents (dioxane > acetonitrile > DMF). The yields of the end products depend on the polarity of a solvent used, and we found that 1,2-dichloroethane was the best choice.

Amidoalkyl naphthols **1**–**10**‡ were synthesized in excellent yields by the reaction of different aromatic aldehydes with β-naphthol and urea. In all cases, amidoalkyl naphthols were the sole products and no by-product was observed. Similar results were obtained under the same conditions when *N*-methylurea was used in place of urea to give compound **7**.‡ The reaction of 3-nitrobenzaldehyde with β-naphthol and acetamide or benzamide in 1,2-dichloroethane under similar conditions also provided the corresponding amidoalkyl naphthols **8** or **9** in high yields.‡

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. Aromatic aldehydes with electron-withdrawing groups reacted faster than aromatic aldehydes with electron-donating groups, as would be expected. To demonstrate the scope and limitations of the procedure, the reaction of *ortho*-substituted aromatic aldehydes such as 2-chlorobenzaldehyde and furfural were studied. Aliphatic propionaldehyde was also examined, but the yield of **10** was low as compared to those of products from aromatic aldehydes.‡ On the other hand, the reactions with thiourea were considered, but no corresponding products were produced. Also, amines such as ethylamine and aniline were utilized and no aminoalkyl naphthol was obtained.

In conclusion, a highly efficient synthesis of amidoalkyl naphthols by the multicomponent condensation of aromatic aldehydes, β-naphthol and ureas or amides catalysed by iodine is reported. This method offers significant advantages, such as, high conversions, easy handling, cleaner reaction profile and shorter reaction times, which makes it a useful and attractive process for the rapid synthesis of substituted amidoalkyl naphthols.

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‡ *[(4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]urea* **1**: yield 91% in 10 h. ^{1}H NMR, δ: 10.32 (s, 1H), 7.95–7.75 (m, 3H), 7.50–7.10 (m, 7H), 6.80 (s, 2H), 5.80 (s, 2H). ^{13}C NMR, δ: 159.3, 153.6, 144.3, 132.8, 131.1, 130.0, 129.4, 129.1, 128.9, 128.6, 128.4, 127.4, 123.3, 120.4, 119.2, 48.4. IR (neat, ν/cm^{-1}): 3456, 3360, 3200, 2240, 1632, 1580, 1513, 1430, 1370, 1238, 816. ES-MS, *m/z*: 325 (M – H, 100%). Found (%): C, 66.32; H, 4.59; N, 8.62. Calc. for $C_{18}H_{15}ClN_2O_2$ (%): C, 66.16; H, 4.63; N, 8.57.

[(2-Hydroxynaphthalen-1-yl)phenylmethyl]urea **2**: yield 88% in 13 h. ^{1}H NMR, δ: 10.28 (s, 1H), 7.85–7.15 (m, 12H), 6.90 (s, 2H), 5.70 (s, 2H). ^{13}C NMR, δ: 159.3, 153.6, 144.3, 132.8, 131.1, 130.0, 129.4, 129.1, 128.9, 128.6, 128.4, 127.4, 123.3, 120.4, 119.2, 48.4. ES-MS, *m/z*: 291 (M – H, 100%). Found (%): C, 74.51; H, 5.57; N, 9.62. Calc. for $C_{18}H_{16}N_2O_2$ (%): C, 73.96; H, 5.52; N, 9.58.

[(4-Methoxyphenyl)(2-hydroxynaphthalen-1-yl)methyl]urea **3**: yield 85% in 14 h. ^{1}H NMR, δ: 10.30 (s, 1H), 7.60–7.05 (m, 8H), 6.80 (d, 2H), 6.70 (br. s, 2H), 5.70 (s, 2H). ^{13}C NMR, δ: 162.7, 153.5, 142.8, 135.1, 133.5, 129.3, 128.8, 128.3, 126.3, 123.2, 122.3, 118.9, 115.4, 114.8, 51.0. ES-MS, *m/z*: 321 (M – H, 100%). Found (%): C, 70.43; H, 5.61; N, 8.75. Calc. for $C_{19}H_{18}N_2O_3$ (%): C, 70.79; H, 5.63; N, 8.69.

[(3-Nitrophenyl)(2-hydroxynaphthalen-1-yl)methyl]urea **4**: yield 92% in 9 h. ^{1}H NMR, δ: 10.27 (s, 1H), 8.05–7.95 (m, 2H), 7.55–6.85 (m, 8H), 6.75 (br. s, 2H), 5.80 (s, 2H). ^{13}C NMR, δ: 162.5, 153.3, 148.7, 143.5, 133.3, 132.4, 130.2, 128.7, 128.2, 126.2, 124.4, 123.6, 123.1, 119.1, 118.6, 115.7, 50.2. ES-MS, *m/z*: 336 (M – H, 100%). Found (%): C, 64.37; H, 4.53; N, 12.52. Calc. for $C_{18}H_{15}N_3O_4$ (%): C, 64.09; H, 4.48; N, 12.46.

[(Furan-2-yl)(2-hydroxynaphthalen-1-yl)methyl]urea **5**: yield 62% in 16 h. ^{1}H NMR, δ: 10.27 (s, 1H), 7.70–7.05 (m, 7H), 6.75 (s, 2H), 6.40 (br. s, 1H), 6.25 (m, 1H), 6.10 (m, 1H), 5.75 (br. s, 1H). ^{13}C NMR, δ: 162.9, 153.7, 152.7, 142.3, 133.6, 129.1, 128.6, 126.5, 123.4, 122.6, 118.7, 115.6, 110.8, 106.9, 46.1. ES-MS, *m/z*: 281 (M – H, 100%). Found (%): C, 67.89; H, 5.06; N, 9.85. Calc. for $C_{16}H_{14}N_2O_3$ (%): C, 68.08; H, 5.00; N, 9.92.

[(2-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]urea **6**: yield 68% in 24 h. ^{1}H NMR, δ: 10.35 (s, 1H), 7.60–7.45 (m, 2H), 7.30–6.95 (m, 8H), 6.75 (s, 2H), 5.85 (s, 2H). ^{13}C NMR, δ: 163.2, 154.0, 143.9, 134.3, 134.1, 130.1, 129.9, 129.2, 128.8, 127.9, 126.8, 123.2, 119.4, 115.8, 42.3. ES-MS, *m/z*: 325 (M-H, 100%). Found (%): C, 66.02; H, 4.69; N, 8.51. Calc. for $C_{18}H_{15}ClN_2O_2$ (%): C, 66.16; H, 4.63; N, 8.57.

[(3-Nitrophenyl)(2-hydroxynaphthalen-1-yl)methyl]-3-methylurea **7**: yield 93% in 8 h. ^{1}H NMR, δ: 10.30 (s, 1H), 8.10–7.98 (m, 2H), 7.60–6.90 (m, 8H), 6.55 (m, 1H), 5.75 (br. s, 2H), 2.90 (d, 3H). ^{13}C NMR, δ: 157.8, 153.5, 148.9, 143.9, 133.8, 132.9, 130.7, 129.2, 128.7, 126.8, 124.9, 124.1, 123.6, 119.5, 119.1, 116.2, 50.8, 28.9. ES-MS, *m/z*: 350 (M – H, 100%). Found (%): C, 65.20; H, 4.92; N, 12.01. Calc. for $C_{19}H_{17}N_3O_4$ (%): C, 64.95; H, 4.88; N, 11.96.

N-*[(2-Hydroxynaphthalen-1-yl)-(3-nitrophenyl)methyl]benzamide* **8**: yield 84% in 10 h. ^{1}H NMR, δ: 10.30 (s, 1H), 8.10–7.85 (m, 4H), 7.65–6.95 (m, 11H), 6.55 (br. s, 1H), 6.15 (br. s, 1H). ^{13}C NMR, δ: 167.9, 153.5, 148.9, 143.7, 134.4, 134.2, 133.5, 132.2, 130.2, 128.9, 128.8, 128.3, 127.5, 126.3, 123.5, 123.2, 122.5, 118.9, 118.6, 115.4, 48.7. ES-MS, *m/z*: 397 (M – H, 100%). Found (%): C, 72.65; H, 4.61; N, 7.08. Calc. for $C_{24}H_{18}N_2O_4$ (%): C, 72.35; H, 4.55; N, 7.03.

N-*[(3-Nitrophenyl)(2-hydroxynaphthalen-1-yl)methyl]acetamide* **9**: yield 89% in 8 h. ^{1}H NMR, δ: 10.30 (s, 1H), 8.10–7.85 (m, 2H), 7.65–6.95 (m, 8H), 6.60 (br. s, 1H), 5.95 (br. s, 1H), 2.10 (s, 3H). ^{13}C NMR, δ: 171.1, 152.5, 147.8, 142.7, 133.4, 132.5, 129.2, 127.8, 127.3, 125.3, 122.5, 122.2, 121.5, 117.9, 117.5, 114.4, 46.9, 22.6. ES-MS, *m/z*: 335 (M – H, 100%). Found (%): C, 67.42; H, 4.84; N, 8.41. Calc. for $C_{19}H_{16}N_2O_4$ (%): C, 67.85; H, 4.79; N, 8.33.

[1-(2-Hydroxynaphthalen-1-yl)propyl]urea **10**: yield 30% in 24 h. ^{1}H NMR, δ: 10.35 (s, 1H), 7.65–6.95 (m, 6H), 6.45 (br. s, 1H), 5.65 (br. s, 2H), 4.85 (m, 1H), 1.75 (m, 2H), 1.05 (t, 3H). ^{13}C NMR, δ: 160.5, 151.5, 131.3, 126.8, 126.1, 124.5, 121.8, 120.7, 116.4, 113.2, 43.6, 28.1, 16.2. ES-MS, *m/z*: 243 (M – H, 100%). Found (%): C, 69.11; H, 6.64; N, 11.53. Calc. for $C_{14}H_{16}N_2O_2$ (%): C, 68.83; H, 6.60; N, 11.47.