A Simple and Efficient Procedure for the Synthesis of Amidoalkyl Naphthols by *p*-TSA in Solution or under Solvent-Free Conditions

Mohammad Mehdi Khodaei,* Ahmad Reza Khosropour,* Hassan Moghanian

Department of Chemistry, Razi University, Kermanshah 67149, Iran
Fax +98(831)4223306; E-mail: mmkhoda@razi.ac.ir; E-mail: arkhosropour@razi.ac.ir

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Abstract: An efficient and direct procedure for the synthesis of amidoalkyl naphthols has been described that employs a three-component condensation reaction in one pot using aromatic aldehydes, β-naphthol and ureas or amides in the presence of *p*-toluene sulfonic acid in 1,2-dichloroethane at room temperature or under solvent-free conditions at elevated temperature.

Key words: amidoalkyl naphthol, one-pot reaction, condensation, β-naphthol, aryl aldehyde, solvent-free

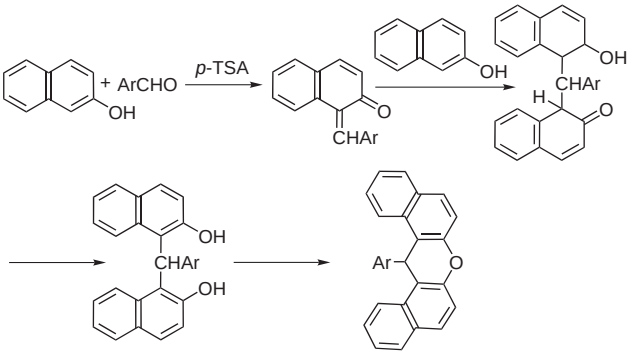
Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without need to isolate any intermediate during their processes; this reduces time and saves both energy and raw materials.[1] They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and bulding up complex molecules. Bigenilli,[2] Ugi,[3] Passerini[4] and Mannich[5] reactions are some examples of MCRs. Nevertheless, development and discovery of new MCRs is still in demand.

In this context, *ortho*-quinone methides (O-QMs) have been used in many tandem processes,[6] but only limited work has appeared with their reaction with nucleophiles.[7]

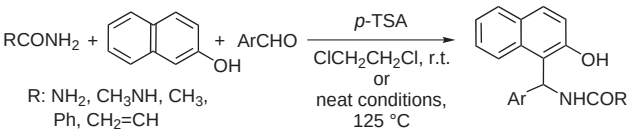
Very recently, we reported a simple and convenient method for the synthesis of dibenzoxanthenes by the condensation of aldehydes with β-naphthol in the presence of *p*-toluene sulfonic acid (*p*-TSA) as a catalyst.[8] It seems, the intermediate O-QMs reacted further with another molecule of β-naphthol (molar ratio of β-naphthol to aryl aldehyde is 2:1) to afford the corresponding benzoxanthenes (Scheme 1).

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 novel compounds. The reaction of equimolar amounts of β-naphthol, aryl aldehyde and ureas or amides in 1,2-dichloroethane at room temperature or under solvent-free conditions at 125 °C catalyzed by catalytic amount of *p*-TSA were examined (Scheme 2).

First we chose 4-chlorobenzaldehyde and urea as the substrates and examined the reaction with several catalysts in



Scheme 1



Scheme 2

1,2-dichloroethane at room temperature (Table 1). The best result was obtained when *p*-TSA was used (Table 1, entry 6).

We then examined the above reaction in different solvents (Table 2). We found that 1,2-dichloroethane was the best choice. Several aromatic aldehydes with β-naphthol and urea in 1,2-dichloroethane using *p*-TSA at room temperature reacted to afford the corresponding products in good to excellent yields.

Table 1 Catalyst Effect on the Reaction of 4-Chlorobenzaldehyde, β-Naphthol and Urea

Entry	Catalyst	Time (h)	Yield (%)
1	$BiCl_3$	12	–
2	$Bi(NO_3)_3{\cdot}5H_2O$	12	–
3	$Bi(OTf)_3$	12	<30
4	$Zn(OTf)_2$	12	<30
5	$CuCl_2{\cdot}4H_2O$	12	–
6	CH_3SO_3H	12	75
7	$4\text{-}CH_3C_6H_4SO_3H$	12	93

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Table 2 Solvent Effect on the Reaction of 4-Chlorobenzaldehyde, β-Naphthol and Urea Catalyzed by *p*-TSA

Entry	Solvent	Time (h)	Yield (%)
1	$ClCH_2CH_2Cl$	12	93
2	MeCN	12	30
3	MeOH	12	78
4	C_2H_5OH	12	70
5	$CHCl_3$	12	85
6	CH_2Cl_2	12	87
7	$HCON(CH_3)_2$	12	<10
8	1,4-Dioxane	12	80

In all cases, amido naphthols were the sole products and no by-product was observed. The results are summarized in Table 3. Similar results were obtained under the same reaction conditions when *N*-methyl urea was used in place of urea.

The reactions of aromatic aldehydes with β-naphthol and different amides including acetamide, benzamide and propenionamide in 1,2-dichloroethane under similar reaction conditions also provided the corresponding amido naphthols in high yields (Table 3).

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. It was shown that the aromatic aldehydes with electron-withdrawing groups reacted faster than the aromatic aldehyde with electron releasing group as would be expected.

Table 3 Synthesis of Amidoalkyl Naphthols[11] in the Presence of Substoichiometric Amounts of *p*-TSA[a]

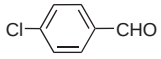
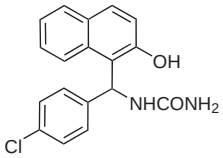
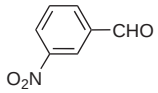
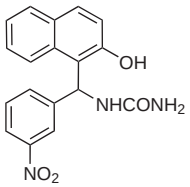
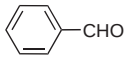
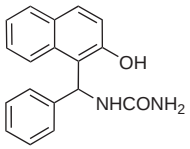
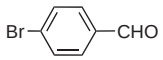
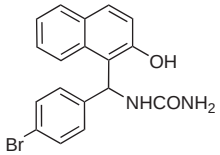
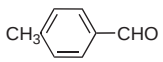
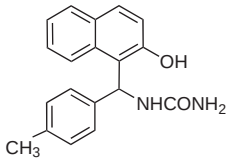
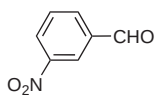
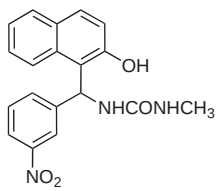
Entry	Aldehyde	Urea or amide	Product	Method A[9]		Method B[10]	
				Time (h)	Yield (%)	Time (h)	Yield (%)
1		H_2NCONH_2		12	93	4	91
2		H_2NCONH_2		12	95	3	90
3		H_2NCONH_2		15	90	4	88
4		H_2NCONH_2		15	89	4	87
5		H_2NCONH_2		18	85	6	83
6		$CH_3NHCONH_2$		10	96	4	93

Table 3 Synthesis of Amidoalkyl Naphthols[11] in the Presence of Substoichiometric Amounts of *p*-TSA[a] (continued)

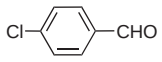
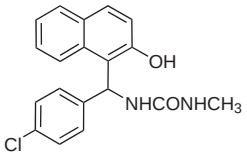
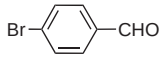
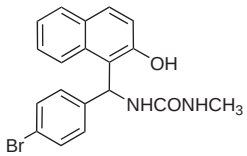
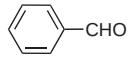
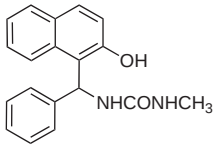
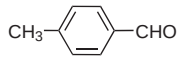
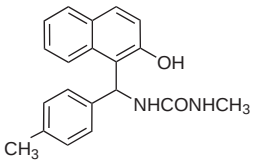
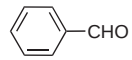
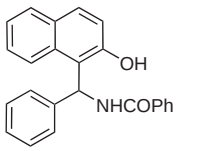
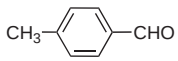
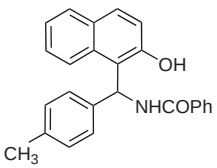
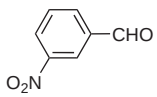
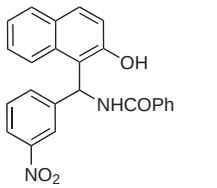
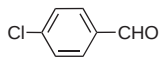
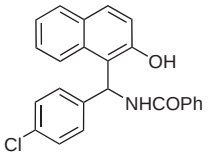
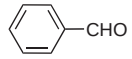
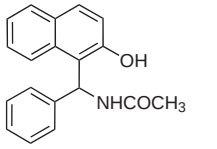
Entry	Aldehyde	Urea or amide	Product	Method A[9]		Method B[10]	
				Time (h)	Yield (%)	Time (h)	Yield (%)
7		$CH_3NHCONH_2$		10	95	5	95
8		$CH_3NHCONH_2$		12	92	6	90
9		$CH_3NHCONH_2$		15	90	6	89
10		$CH_3NHCONH_2$		15	87	8	85
11		$PhCONH_2$		15	89	6	86
12		$PhCONH_2$		18	83	8	80
13		$PhCONH_2$		12	87	5	87
14		$PhCONH_2$		12	89	6	90
15		CH_3CONH_2		12	90	5	88

Table 3 Synthesis of Amidoalkyl Naphthols[11] in the Presence of Substoichiometric Amounts of *p*-TSA[a] (continued)

Entry	Aldehyde	Urea or amide	Product	Method A[9]		Method B[10]	
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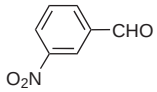
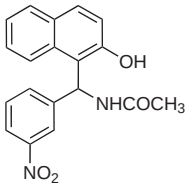
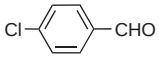
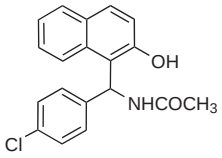
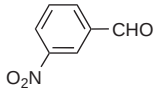
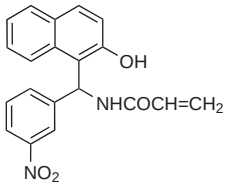
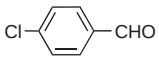
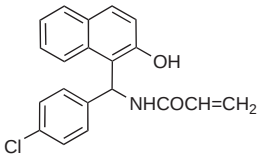
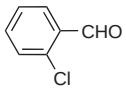
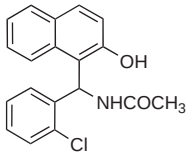
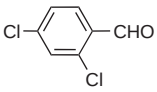
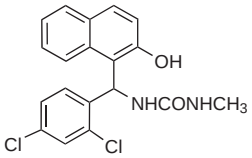
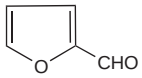
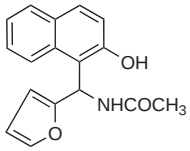
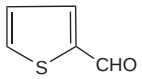
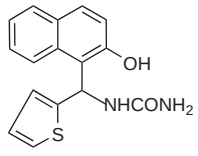
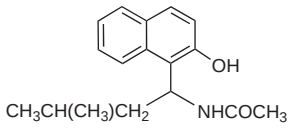
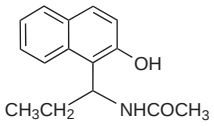
16		CH_3CONH_2		9	93	4	90
17		CH_3CONH_2		10	91	4	90
18		$CH_2=CHCONH_2$		12	94	5	91
19		$CH_2=CHCONH_2$		12	90	6	89
20		CH_3CONH_2		30	65	5	62
21		$CH_3NHCONH_2$		18	71	4	69
22		CH_3CONH_2		24	20	10	0
23		NH_2CONH_2		24	<5	10	0
24	$CH_3CH(CH_3)CH_2CHO$	NH_2CONH_2		24	<5	10	<10
25	CH_3CH_2CHO	NH_2CONH_2		24	<5	10	<10

To demonstrate the scope and limitations of the procedure, the reactions of *ortho*-substituted aromatic aldehydes such as 2-chlorobenzaldehyde and 2,4-dichlorobenzaldehyde, and heteroaromatic aldehydes including furfural and thiophene-2-carbaldehyde were studied and the results were collected in Table 3. Aliphatic aldehydes like isovaleraldehyde and propionaldehyde were also examined but their yields were not satisfactory at all, even after 24 hours at room temperature or 10 minutes at 125 °C (Table 3). 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.

The reactions carried out under solvent-free conditions were examined and the corresponding products obtained in high yields with very much lower reaction times (Table 3). No reaction occurred at room temperature under neat conditions and thus the reactions were followed at 125 °C.

In conclusion, a novel and highly efficient methodology for the synthesis of amidoalkyl naphthols by the straightforward three-component condensation in one pot using aromatic aldehyde, β-naphthol and ureas or amides in organic solvent (method A) and neat conditions (method B) is reported. The simplicity, low cost and the speed of the reactions under solvent-free conditions and mildness of the reactions under organic solvent conditions are other merits.

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(9) **General Experimental Procedure (Method A).** A mixture of aromatic aldehyde (1 mmol), β-naphthol (1 mmol), urea or amide (1.1 mmol) and *p*-TSA (0.1 mmol) in 1,2-dichloroethane (2 mL) at r.t. was stirred for the time as shown in Table 3. The progress of the reaction was monitored by TLC. On completion, the reaction mixture was filtered and the precipitate washed with H_2O. The crude products were purified by recrystallization from EtOH–H_2O (1:3) and the pure products were obtained in 83–96% yields.

(10) **General Experimental Procedure (Method B).** A mixture of aromatic aldehyde (1 mmol), β-naphthol (1 mmol), urea or amide (1.1 mmol) and *p*-TSA (0.1 mmol) was magnetically stirred at 125 °C for the appropriate time as indicated in Table 3. The reaction was followed by TLC. After completion, the reaction mixture was washed with H_2O. The pure products were obtained by recrystallization using EtOH–H_2O (1:3) in 80–95% yields.

(11) **Selected Characterization Data.**
Table 3, entry 1: IR (neat): ν_{max} = 3456, 3360, 3200–2240, 1632, 1580, 1513, 1430, 1370, 1238, 816 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 10.30 (s, 1 H), 7.88–7.71 (m, 3 H), 7.45–7.10 (m, 7 H), 6.90 (s, 2 H), 5.85 (s, 2 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 159.4, 153.7, 144.4, 132.9, 131.2, 130.1, 129.5, 129.2, 129.0, 128.7, 128.5, 127.5, 123.4, 120.5, 119.3, 48.5. MS (EI): *m/z* (%) = 266 (6), 231 (14), 202 (10), 172 (18), 144 (100), 115 (57), 60 (52), 44 (70).
Table 3, entry 6: IR (neat): ν_{max} = 3380, 3250–2800, 1625, 1580, 1535, 1430, 1360, 1240, 815 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 8.07–6.96 (m, 12 H), 6.43 (s, 1 H), 2.61 (d, *J* = 3.72 Hz, 3 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 159.4, 153.8, 148.5, 148.0, 133.5, 132.9, 130.5, 130.4, 129.6, 129.2, 127.8, 123.5, 123.3, 122.0, 121.0, 120.1, 119.3, 49.0, 27.2. MS (EI): *m/z* (%) = 260 (4), 229 (17), 207 (100), 144 (23), 115 (33), 77 (40), 58 (70).
Table 3, entry 19: IR (neat): ν_{max} = 3390, 3300–2800, 1648, 1620, 1517, 1418, 1322, 1262, 1062, 970, 820 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 8.80 (d, *J* = 7.91 Hz, 1 H), 7.91–7.78 (m, 3 H), 7.44–7.18 (m, 8 H), 6.75–6.60 (m, 1 H), 6.10 (d, *J* = 16.99 Hz, 1 H), 5.60 (d, *J* = 10.40 Hz, 1 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 165.0, 154.2, 142.3, 133.1, 132.5, 131.7, 130.5, 129.5, 129.3, 128.9, 128.8, 127.4, 126.8, 124.0, 123.4, 119.3, 119.0, 48.5. MS (EI): *m/z* (%) = 339 (2) [M + 2], 337 (7) [M], 266 (40), 231 (64), 202 (54), 144 (64), 115 (54), 101 (63), 71 (25), 55 (100).