A Novel Three-Component One-Pot Reaction Involving β-Naphthol, Aldehydes, and Urea Promoted by TMSCl/NaI

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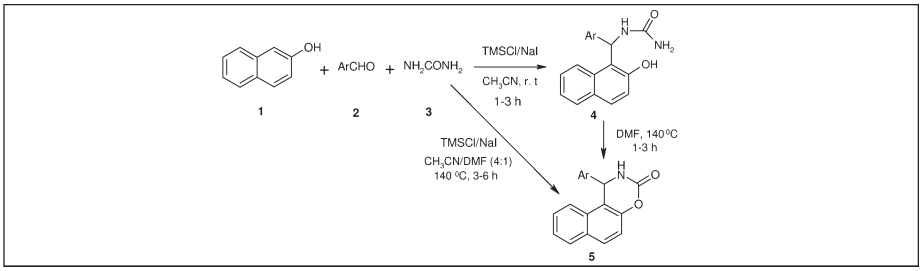

Amidoalkyl naphthol derivatives have been synthesized in good yields in a one-pot condensation of β-naphthol, aromatic aldehydes and urea in presence of TMSCl/NaI at room temperature. Ring closure of amidoalkyl naphthol derivatives occurred at 140°C to afford 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazin-3-one derivatives.

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INTRODUCTION

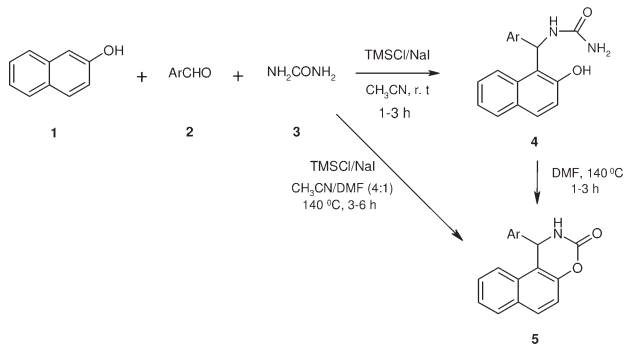
Multicomponent reactions have emerged as powerful strategies with the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules, which provide maximum diversity are encouraging on economy and environmental grounds [1]. One such example is the reaction of β-naphthol and aldehydes with urea to produce amidoalkyl naphthols or oxazinone derivatives. Benzoxazin-4-one derivatives are an important class of heterocyclic compounds [2–5], which exibit many industrial, research, and clinical applications. Naphthalene condensed oxazinone derivatives are known to possess interesting pharmacological and reported as antibacterial agents [6]. These compounds have also been used in the preparation of chiral amino phosphine ligands for asymmetric catalysis [7]. Even though a large number of methods [8–15] were reported for the preparation of intermediate compounds (amidoalkyl naphthols), ring closure reactions to give naphthalene condensed oxazinone derivatives have not been thoroughly investigated [16–19]. This has stimulated significant interest and there is always considerable demand in exploring more milder, convenient, practical, and efficient reagents for their synthesis using multicomponent reactions. Therefore, the development of simple, convenient, and practical procedures for the synthesis of naphtho[1,2-e][1,3]oxazin-3-one derivatives continue to be a challenging endeavor in synthetic organic chemistry.

RESULTS AND DISCUSSION

TMSCl/NaI combination has been explored in various organic transformations [19]. In continuation of our efforts to explore the synthetic utility of TMSCl/NaI combination [20], herein we report a three-component approach for the one-pot synthesis of a series of amidoalkyl naphthols and naphthoxazinones under different reaction conditions using TMSCl/NaI (Scheme 1).

Initially, we examined the reaction of naphthol (**1**), benzaldehyde (**2**), and urea (**3**) in the presence of TMSCl/NaI in CH_3CN at room temperature and found to give the corresponding intermediate amidoalkyl naphthol derivative **4a** in 81% yield. The structure of the product was confirmed by spectral data and compared with the authentic sample. Similarly, other aromatic aldehydes were also reacted to give the intermediate compounds in good yields at room temperature (Scheme 2) and the results are presented in Table 1. Under present conditions, formation of side products, such as, dibenzoxanthenes was not observed. When an intermediate amidoalkyl naphthol derivative **4a** was heated in DMF at 140°C for 1.2 h cyclization occurred to produce the naphthoxazinone **5a**. Encouraged by this result, the reaction of β-naphthol (**1**), benzaldehyde (**2**), and urea (**3**) in the presence of TMSCl/NaI in CH_3CN/DMF (4:1) was directly heated at 140°C and found to give the cyclized product, naphthoxazinone **5a** exclusively within 1 h, without isolating the intermediate **4a**. To find out the scope and generality of this reaction, we turned our attention to various substituted aldehydes.

Scheme 1



The aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the desired products. All the reactions were clean at 140°C and the corresponding cyclized products **5b–m** were obtained in good yields without isolating intermediate compounds **4**. The results are summarized in Table 2. The products were characterized by spectral data and known compounds were compared with the authentic samples data.

In summary, we have demonstrated an efficient protocol for the synthesis of amidoalkyl naphthols and naphthoxazinone derivatives using TMSCl/NaI as promoter. The notable features of this method are mild reaction conditions, greater selectivity, simplicity in operation, which make it an attractive and very useful process for the synthesis of amidoalkyl naphthol and naphthoxazinone derivatives of biological importance.

EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded onVarian-unity 300 spectrometer in CDCl3 using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the synthesis of amidoalkyl naphthol derivatives 4 and naphthoxazinones 5. To a mixture of 1 equiv. of β-naphthol, 1 equiv. of aromatic aldehyde and 1.5 equiv. of urea in acetonitrile (10 mL) was added 1.5 equiv. of TMSCl and 1.5 equiv. of NaI at 0°C and stirred at room temperature (see Table 1). After completion, followed by TLC, acetonitrile was removed and ethyl acetate was added to the residue. Ethyl acetate was washed with water, sodium thiosulfate, and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford the pure product **4**.

Scheme 2

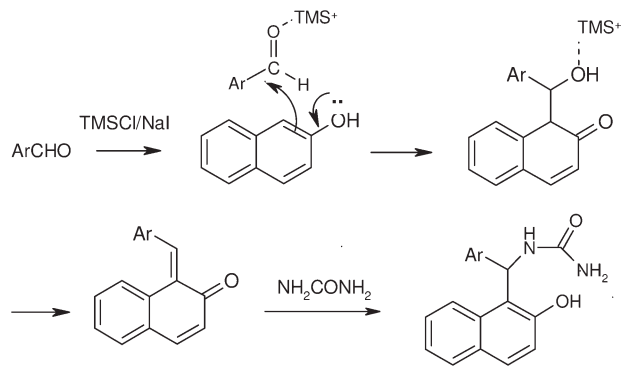
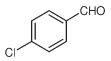
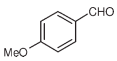
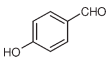
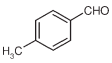


Table 1

TMSCl/NaI catalyzed synthesis of amidoalkyl naphthols (**4**).[a,b]

Entry	Aldehyde	Time (h)	Yield (%)	mp (°C)
4a		1.5	81	212
4b		1.8	79	208
4c		1.2	78	193
4d		3	78	198
4e		2.3	81	179

[a] All products were confirmed by their spectral data and compared with authentic samples.
[b] Isolated yields after purification.

A mixture of intermediate amidoalkyl naphthol derivative **4** in DMF was heated at 140°C for 1–3 h. After completion of cyclization reaction, followed by TLC, water was added and extracted with ether. The organic layer was washed with water and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford naphthoxazinone product **5**.

General procedure for the one-pot synthesis of naphthoxazinones 5. To a mixture of 1 equiv. of β-naphthol, 1 equiv. of aromatic aldehyde and 1.5 equiv. of urea in acetonitrile/dimethyl formamide (6 mL:1.5 mL; 4:1) was added 1.5 equiv. of TMSCl and 1.5 equiv. of NaI at 0°C and stirred at 140°C (see Table 2). After completion, followed by TLC, solvent mixture was removed by rotary evaporation and ethyl acetate was added to the residue. Ethyl acetate was washed with water, sodium thiosulfate, and brine solution, dried, and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford the pure product **5**.

Spectral data of amidoalkyl naphthol derivatives 4.

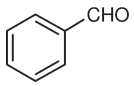
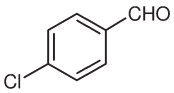
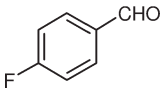
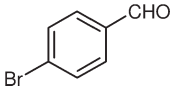
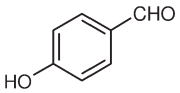
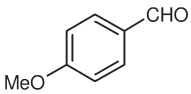
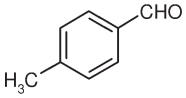
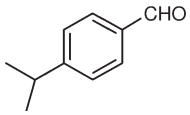
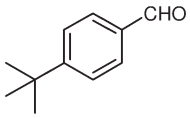
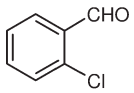
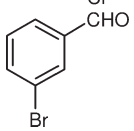
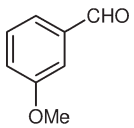
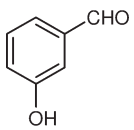
Compound 4a. mp 212°C; ^{1}H NMR (300 MHz, DMSO): 5.55 (s, 2H), 7.22.7.51 (m, 9H), 7.63–7.81 (m, 2H), 7.94–8.20 (d, J = 7.8 Hz, 2H), 9.80 (s, 1H). IR (KBr): 3450, 3210, 1640, 1575, 1510, 1425, 1360, 1242, 816 cm^{-1}. ESI MS: m/z 292 (M^+).

Compound 4b. mp 208°C; ^{1}H NMR (200 MHz, DMSO): 5.61 (s, 2H), 7.05–7.42 (m, 8H), 7.65–7.83 (d, J = 11.2 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 9.95 (s, 1H). IR (KBr): 3420, 3320, 1651, 1570, 1520, 1420, 1362, 1242, 815 cm^{-1}. ESI MS: m/z 326 (M^+).

Compound 4c. mp 193°C; ^{1}H NMR (300 MHz, DMSO): 3.75 (s, 3H), 5.53 (s, 2H), 7.52–7.81 (m, 8H), 7.95–8.12 (m, 2H), 8.24 (d, J = 8.2 Hz, 2H), 9.65 (s, 1H). IR (KBr): 3410, 3320, 1650, 1578, 1523, 1425, 1362, 1240, 780 cm^{-1}. ESI MS: m/z 322 (M^+).

Table 2

TMSCI/NaI catalyzed synthesis of naphtho[1,2-e][ ] benzoxazinones (**5**).[a,b]

Entry	Aldehyde	Time (h)	Yield (%)	mp (°C)
5a		2	78	219
5b		2.6	86	208
5c		1.5	86	203
5d		1.9	79	221
5e		2.4	89	182
5f		1.6	78	187
5g		2.4	86	166
5h		3	81	172
5i		2.5	80	178
5j		4	62	199
5k		3.2	68	222
5l		4.9	66	172
5m		5	71	189

[a] All products were characterized by spectral data and compared with the authentic samples.
[b] Isolated pure products.

Compound 4d. mp 198°C; ^{1}H NMR (300 MHz DMSO): 5.65 (s, 2H), 7.52–7.65 (m, 8H), 7.72–7.96 (m, 2H), 8.34 (d, J = 8.3 Hz, 2H), 9.73 (s, 1H). IR (KBr): 3445, 3322, 1646, 1575, 1530, 1415, 1360, 1242, 816, 780 cm^{-1}. ESI MS: m/z 308 (M^+).

Compound 4e. mp 179°C; ^{1}H NMR (200 MHz, DMSO): 2.13 (s, 3H), 5.56 (s, 2H), 6.92–7.85 (m, 8H), 7.93–8.13 (m, 2H), 8.34 (d, J = 8.3 Hz, 2H), 9.63 (s, 1H). IR (KBr): 3420, 3326, 1652, 1572, 1475, 1365, 1241, 860, 781 cm^{-1}. ESI MS: m/z (%) 306 (M^++1).

Spectral data of naphthoxazines 5.

Compound 5a. mp 219°C; ^{1}H NMR (300 MHz, DMSO): 6.12 (d, J = 2.26 Hz, 1H), 7.24–8.12 (m, 3H), 8.88 (brs, 1H). IR (KBr): 3296, 1721, 1517, 720 cm^{-1}. ESI MS: m/z 275 (M^+).

Compound 5b. mp 208°C; ^{1}H NMR (300 MHz, DMSO): 6.21 (s, 1H), 7.26–8.10 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3229, 3142, 1734, 1517, 747 cm^{-1}. ESI MS: m/z 310 (M^++1).

Compound 5c. mp 203°C; ^{1}H NMR (200 MHz, $CDCl_3$): 6.23 (s, 1H), 7.31–8.02 (m, 10H), 8.94 (brs, 1H). IR (KBr): 3126, 1751, 1509, 736 cm^{-1}. ESI MS: m/z (%) 293 (M^+).

Compound 5d. mp 221°C; ^{1}H NMR (200 MHz, DMSO): 6.21 (s, 1H), 7.20–8.13 (m, 10H), 8.90 (brs, 1H). IR (KBr): 3229, 3146, 1730, 1515, 723 cm^{-1}. ESI MS: m/z 377 (M^++Na).

Compound 5e. mp 182°C; ^{1}H NMR (300 MHz, DMSO): 5.6 (s, 1H), 7.32–8.20 (m, 10H), 8.55 (brs, 1H), 11.10 (s, 1H). IR (KBr): 3673, 3215, 1701, 1551, 746 cm^{-1}. ESI MS: m/z 291 (M^+).

Compound 5f. mp 187°C; ^{1}H NMR (200 MHz, DMSO): 3.76 (s, 3H), 6.24 (s, 1H), 7.20–8.01 (m, 10H), 8.65 (brs, 1H). IR (KBr): 3149, 2942, 1733, 1607, 1510, 842, 723 cm^{-1}. ESI MS: m/z 305(M^+).

Compound 5g. mp 166°C; ^{1}H NMR (300 MHz, DMSO): 2.03 (s, 3H), 6.26 (s, 1H), 7.26–8.05 (m, 10H), 8.86 (brs, 1H). IR (KBr): 3148, 2921, 1735, 1512, 723 cm^{-1}. ESI MS: m/z 289 (M^+).

Compound 5h. mp 172°C; ^{1}H NMR (300 MHz DMSO): 1.25 (s, 6H), 2.56 (m, 1H), 6.01 (d, J = 2.86 Hz, 1H), 7.24–8.08 (m, 10H), 8.82 (brs, 1H). IR (KBr): 3281, 2924, 1729, 1513, 830 cm^{-1}. ESI MS: m/z 317 (M^+).

Compound 5i. mp 178°C; ^{1}H NMR (200 MHz, DMSO): 1.24 (s, 6H), 1.31 (s, 3H), 6.30 (s, 1H), 7.40–8.19 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3203, 2959, 1727, 1515, 828, 740 cm^{-1}. ESI MS: m/z (%) 332 (M^++1).

Compound 5j. mp 199°C; ^{1}H NMR (300 MHz, DMSO): 6.13 (s, 1H), 7.21–8.06 (m, 10H), 8.92 (brs, 1H). IR (KBr): 3220, 3142, 1729, 1513, 820, 748 cm^{-1}. ESI MS: m/z 309 (M^+).

Compound 5k. mp 222°C; ^{1}H NMR (200 MHz, DMSO): 6.20 (s, 1H), 7.18–8.06 (m, 10H), 8.91 (brs, 1H). IR (KBr): 3252, 3140, 1730, 1512, 823, 758 cm^{-1}. ESI MS: m/z 355 (M^++1).

Compound 5l. mp 172°C; ^{1}H NMR (200 MHz, $CDCl_3$): 3.78 (s, 3H), 6.12 (s, 1H), 7.03–8.06 (m, 10H), 8.93 (s, 1H). IR (KBr): 3149, 1733, 1510, 814, 743 cm^{-1}. ESI MS: m/z 306 (M^++1).

Compound 5m. mp 191°C; ^{1}H NMR (200 MHz, DMSO): 6.01 (d, J = 3.38 Hz, 1H), 6.98–8.01 (m, 10H), 8.56 (brs, 1H). IR (KBr): 3423, 3299, 1730, 1515, 812, 743 cm^{-1}. ESI MS: m/z 292 (M^++1).

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