An Improved Synthesis of Amidoalkyl Phenols Involving a Ritter-Type Reaction[1]

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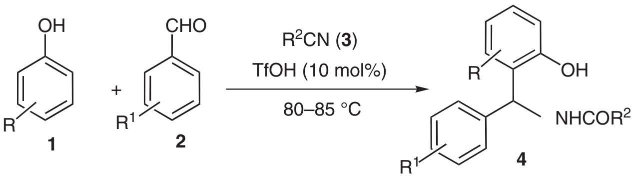
Abstract: Three-component condensation of phenols, aromatic aldehydes and alkyl nitriles in the presence of a catalytic amount of triflic acid yielded the corresponding amidoalkyl phenols involving a Ritter-type reaction. The products were formed in high yields and in short reaction times.

Keywords: amidoalkyl phenol, three-component condensation, *ortho*-quinone methide, Ritter reaction

Multicomponent reactions have gained considerable attention in recent years for generating molecular complexity in a single synthetic operation.[2] In this context, *ortho*-quinone methides have been utilized in many tandem processes.[3] The condensation of phenols with aldehydes under acid or base catalysis is believed to proceed via *ortho*-quinone methide intermediates.[4] Recently the reaction of 2-naphthol and benzaldehydes in the presence of *p*-toluenesulfonic acid (PTSA)[5a] or I_2[5b] has been employed for the synthesis of dibenzoxanthenes involving these intermediates. In these reaction when amides and urea were used as nucleophiles to react with the in situ generated *ortho*-quinone methides the products were found to be amidoalkyl naphthols.[6] We felt that in the reaction of phenols and benzaldehydes if alkyl nitriles were used, Ritter-type reaction[7] involving *ortho*-quinone methide intermediates and alkyl nitriles might take place to form the corresponding amidoalkyl phenols (Scheme 1).

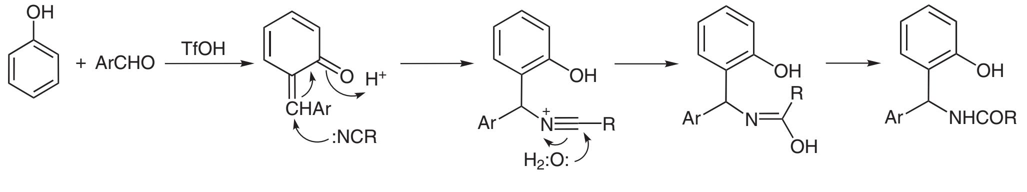


Scheme 1

Our expectation was fulfilled when a mixture of 2-naphthol and 4-chlorobenzaldehyde was heated in MeCN under reflux for 1.5 hours using triflic acid as a catalyst to form the corresponding amidoalkyl naphthol **4e** (Table 1, entry **e**). The product was formed in a yield of 91%. 1,3-Aminooxygenated moieties are frequently found in various bioactive natural products and important drug molecules.[8] The present method provides a simple route to such moieties. Initially, we attempted the above reaction with different catalysts, such as triflic acid, PTSA and iodine to prepare **4e** but in terms of the reaction times and yields the first one was found to be the best. Subsequently this catalyst was used to prepare a series of amidoalkyl phenols from various phenols, aromatic aldehydes and acetonitrile or acrylonitrile (Table 1). Benzaldehydes containing both electron-donating and electron-withdrawing groups worked well. 2-Naphthaldehyde (entry **i**) also underwent the conversion smoothly. Phenol and its derivatives and 2-naphthol were applied for the reaction. 2-Naphthol required shorter reaction times and the yields were also comparatively high. Using acetonitrile the reaction was complete within 1.5–5 hours and the yields were good to excellent (50–91%), while with acrylonitrile the reaction times were somewhat longer (4.5–6 h) and the yields were somewhat lower (60–67%). When this work was ready for submission, a report appeared[9] on the preparation of acetamido phenols using $Ce(SO_4)_2$ as a catalyst but the reaction times were long (16–48 h). The catalyst was used in equivalent amount and the conversion was studied only with acetonitrile.

The formation of amidoalkyl phenols possibly takes place by Ritter-type reaction involving alkyl nitriles and *ortho*-quinone methides formed by interaction of phenols and aromatic aldehydes (Scheme 2).

In conclusion, we have developed an efficient method for the synthesis of amidoalkyl phenols utilizing triflic acid



Scheme 2

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catalyzed one-pot three-component condensation of phenols, aromatic aldehydes and alkyl nitriles involving a Ritter-type reaction. The simple experimental procedure, high yields and short reaction times are the notable advantages of the protocol.

Table 1 Synthesis of Amidoalkyl Phenols[a,10]

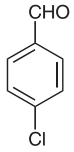
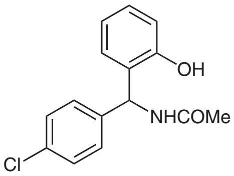
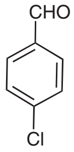
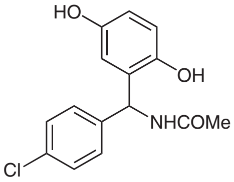
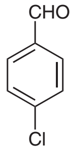
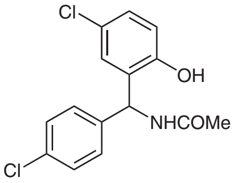
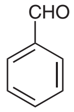
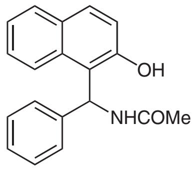
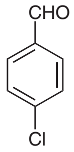
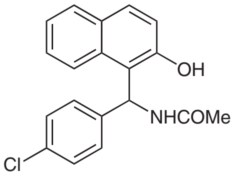
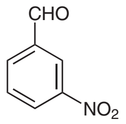
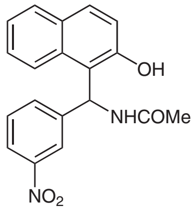
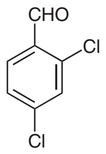
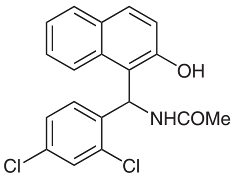
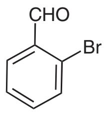
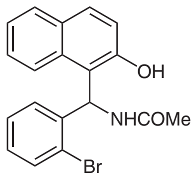
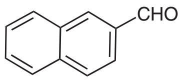
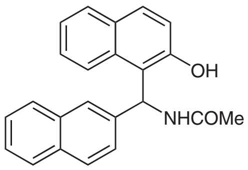
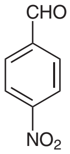
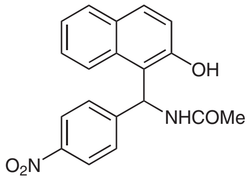
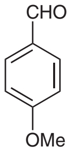
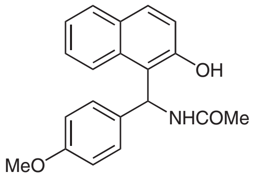
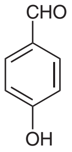
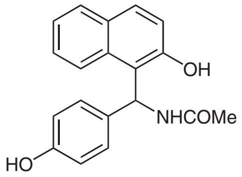
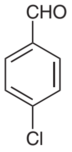
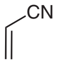
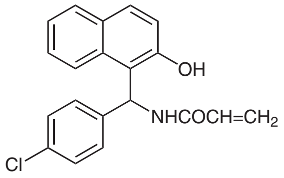
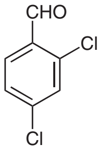
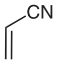
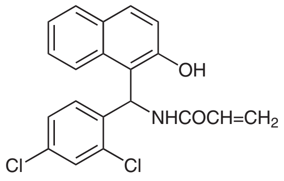
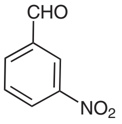
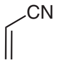
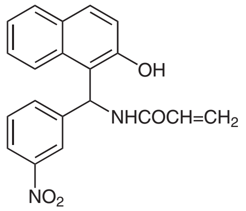
Entry	Phenol	Aldehyde	Nitrile	Time (h)	Product	Isolated yields (%)
a	PhOH		MeCN	4.5		56
b	4-HOC_6H_4OH		MeCN	5		50
c	4-ClC_6H_4OH		MeCN	5		58
d	2-naphthol		MeCN	2		90
e	2-naphthol		MeCN	1.5		91
f	2-naphthol		MeCN	2.25		89
g	2-naphthol		MeCN	2.5		86
h	2-naphthol		MeCN	2.5		82

Table 1 Synthesis of Amidoalkyl Phenols[a,10] (continued)

Entry	Phenol	Aldehyde	Nitrile	Time (h)	Product	Isolated yields (%)
i	2-naphthol		MeCN	3		89
j	2-naphthol		MeCN	2.25		86
k	2-naphthol		MeCN	3.25		81
l	2-naphthol		MeCN	3.5		75
m	2-naphthol			4.5		63
n	2-naphthol			5		60
o	2-naphthol			6		67

[a] The structures of the products were determined from their spectral (IR, ^1H and ^{13}C NMR and MS) data.

Acknowledgment

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References and Notes

(1) Part 118 in the series ‘Studies on novel synthetic methodologies’.

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(10) **General Experimental Procedure**: To a mixture of a phenol (1 mmol) and aromatic aldehyde (1 mmol) in MeCN or acrylonitrile (5 mL), triflic acid (10 mol%) was added. The mixture was heated under reflux and the reaction was monitored by TLC. After completion of the reaction, H_2O (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The extract was dried and concentrated. The residue was subjected to column chromatography (silica gel; eluent: hexane–EtOAc, 4:1) to obtain the pure amidoalkyl phenol.

The spectral (IR, ^{1}H and ^{13}C NMR and MS) data of some representative products are given below.

Compound **4a**: IR (KBr): 3422, 1654, 1511, 1460, 1376, 1269 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 8.99 (br s, 1 H), 8.01 (m, 1 H), 7.90 (br s, 1 H), 7.44–7.52 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 3 H), 6.68 (d, *J* = 8.0 Hz, 3 H), 1.92 (s, 3 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 23.0, 55.4, 115.8, 121.8, 122.3, 129.3, 130.4, 132.2, 134.4, 146.1, 148.2, 157.1, 169.3. MS (FAB): *m/z* (%) = 278 (2), 276 (6) $[M + H]^{+\cdot}$, 184 (33), 182 (100).

Compound **4i**: IR (KBr): 3409, 1644, 1537, 1370, 1330, 1272 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 9.82 (br s, 1 H), 8.26 (m, 1 H), 8.02 (m, 1 H), 6.62–7.76 (m, 6 H), 7.32–7.41 (m, 3 H), 7.18–7.25 (m, 4 H), 2.06 (s, 3 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 22.9, 48.0, 118.4, 119.1, 122.5, 123.3, 123.4, 123.9, 125.1, 125.3, 126.4, 126.7, 127.2, 127.9, 128.7, 128.8, 128.9, 131.3, 132.2, 132.9, 140.6, 153.2, 169.1. MS (FAB): *m/z* (%) = 342 (2) $[M + H]^{+\cdot}$, 198 (100).

Compound **4k**: IR (KBr): 3425, 1647, 1513, 1462, 1274 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 9.65 (br s, 1 H), 9.12 (d, *J* = 8.0 Hz, 1 H), 8.00 (m, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.36 (m, 1 H), 7.06–7.22 (m, 5 H), 6.64 (d, *J* = 8.0 Hz, 2 H), 3.64 (s, 3 H), 2.02 (s, 3 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 23.2, 48.2, 55.5, 113.9, 119.0, 119.5, 122.9, 126.8, 127.8, 129.0, 129.6, 132.8, 134.9, 153.6, 158.2, 169.6. MS (FAB): *m/z* (%) = 322 (3) $[M + H]^{+\cdot}$, 178 (100).

Compound **4m**: IR (KBr): 3446, 1657, 1622, 1514, 1337, 1276 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 9.61 (br s, 1 H), 8.22 (m, 1 H), 8.00 (m, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.41 (m, 1 H), 7.10–7.28 (m, 7 H), 6.21–6.38 (m, 2 H), 5.61 (m, 1 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.5, 117.5, 118.0, 121.8, 122.2, 125.0, 125.8, 127.0, 127.2, 127.5, 128.5, 128.7, 130.6, 130.9, 131.9, 140.1, 152.4, 164.0. MS (FAB): *m/z* (%) = 340 (2), 338 (6) $[M + H]^{+\cdot}$, 196 (33), 194 (100).