Three-component reaction between 2-naphthol, aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid yields 1-(acetylamino (aryl)methyl)-2-naphthols

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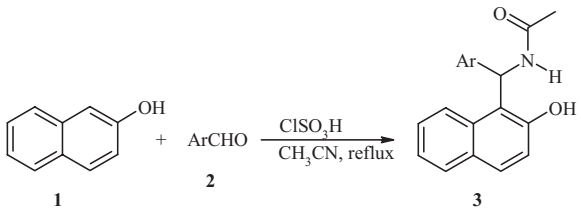
The one-pot, three-component reaction between aryl aldehydes, 2-naphthol, and acetonitrile in the presence of chlorosulfonic acid affords 1-[acetylamino(aryl)methyl]-2-naphthols in excellent yields.

Keywords: chlorosulfonic acid, 2-naphthol, three-component reaction, aryl aldehydes

Multi-component reactions (MCRs) have attracted considerable interest from organic chemists because they can be widely employed for the rapid assembly of arrays with high molecular diversity.[1] These processes are performed without need to isolate any intermediate and this reduces time and saves both energy and row materials.[2] Quinone methides (*o*-QMs) have been employed in many tandem processes,[3] but there are few reports of their reactions with nucleophiles.[4] There are some recent reports on the preparation of 1-aminoalkyl-2-naphthols from the three-component reaction between 2-naphthol, aromatic aldehydes and amides or ureas using different catalysts.[5-8] These reactions have been reported to proceed by the nucleophilic addition of amide or urea derivative on the intermediate *o*-QM. Recently, we have reported the three-component reaction between 4-hydroxycoumarin, aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid to prepare 3-[acetylamino (aryl)methyl]-4-hydroxycoumarins in excellent yields.[9] We have now extended this chlorosulfonic acid driven procedure to prepare 1-[acetylamino(aryl)methyl]-2-naphthols using 2-naphthol, aromatic aldehydes and acetonitrile (Scheme 1). This reaction takes place cleanly with no need to use any other activator or catalyst.



3	Ar	%Yield*
a	Ph	98
b	4-ClC_6H_4	95
c	2-$CH_3C_6H_4$	95
d	2-ClC_6H_4	93
e	3-$NO_2C_6H_4$	94
f	4-FC_6H_4	90
g	4-$CH_3C_6H_4$	95
h	4-BrC_6H_4	90
i	3-$CH_3OC_6H_4$	95
j	2-$CH_3OC_6H_4$	98

*Isolated yield

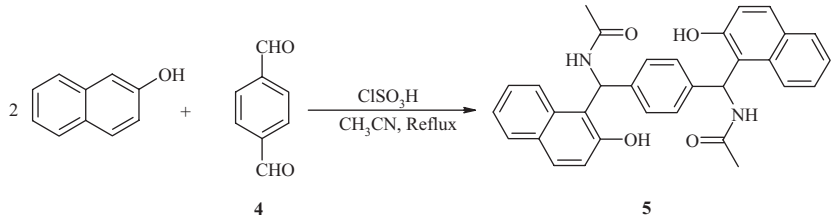
Scheme 1

Compounds **3a–h** were compared with the corresponding compounds prepared by the reported procedures.[5,6] Compounds **3i–j** were new and their structure were deduced by elemental and spectral analysis. The ^{1}H NMR spectrum of **3a** exhibits a sharp line at δ = 1.99 ppm for the protons of the methyl group. The methine and NH protons couple each other and a doublet is observed for NH proton at 8.49 ppm which disappears after addition of some D_2O to the d_6-DMSO solution of **3a**. Two multiplets between 7.09 and 7.78 ppm are observed which are related to aromatic protons and the methine proton.

The four-component reaction between 2 equivalent of 2-naphthol and terphthalaldehyde **4** in acetonitrile in the presence of 3.0 equivalent of chlorosulfonic acid affords the addition product **5** in 91% yield (Scheme 2). ^{13}C NMR spectrum of this compound exhibits two signals at 126.67 and 142.95 ppm for aldehyde subunit. This is consistent with the symmetrical structure of compound **5**.

The three-component reaction between aromatic aldehydes, 2-naphthol and acetonitrile can also be carried out in the presence of phosphorus trichloride. For example, when a mixture of 3-methoxybenzaldehyde and 2-naphthol was stirred in acetonitrile in the presence of 1.2 equivalent of phosphorus trichloride, after work-up, 1-[acetylamino (3-methoxyphenyl)methyl]-2-naphthol **3i** was obtained in 95% yield.

We also tried the reaction between 2-naphthol, 3-methoxy-benzaldehyde and other nitriles, such as benzonitrile and acrilonitrile in solvents such as dichloromethane and acetone, but no product was isolated. The reaction between



Scheme 2

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1-naphthol or 8-hydroxyquinoline, 3-methoxybenzaldehyde and acetonitrile was also tried in the presence of chlorosulfonic acid but no product was obtained.

Although we did not study the mechanism of the reaction, a reasonable possibility is presented in Scheme 3. Acetonitrile attack the condensation product of 2-naphthol and aldehyde in the presence of chlorosulfonic acid or phosphorus trichloride to afford the cation **7** or **8** which is then hydrolysed to product **3**.

In summary, we report here a simple and efficient one-pot synthesis of 1-[acetylamino(aryl)methyl]-2-naphthols by three-component reaction between 2-naphthol, aryl aldehydes and acetonitrile in the presence of chlorosulfonic acid. The advantages of this method are simply available starting materials, short reaction times, easy and clean work-up and excellent yields.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in d_6-DMSO using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

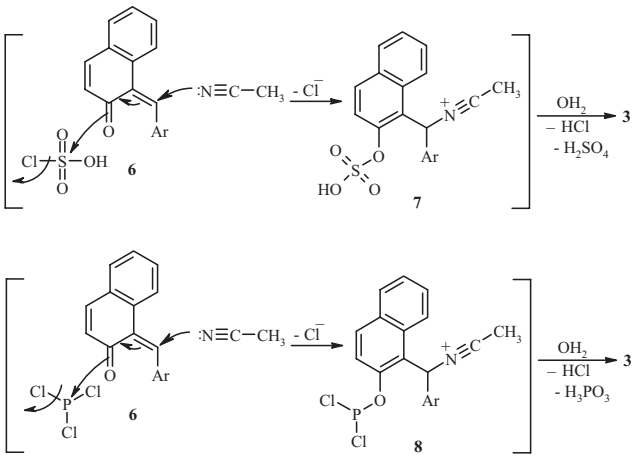
To a magnetically stirred solution of 2-naphthol (3 mmol) and aldehyde (3 mmol) in acetonitrile (15 ml) was added chlorosulfonic acid (6 mmol) at room temperature. The reaction mixture was then stirred at reflux temperature for 3 h. The mixture was poured into 50 ml ice-water. The solid product was filtered, washed with ice-water and recrystallised from ethyl acetate/n-hexane to give the pure product.

1-[acetylamino(phenyl)methyl]-2-naphthol (**3a**): White powder, m.p. 229–230°C, IR (KBr) (ν_{max} cm^{-1}): 3397, 3213–2724, 1631. Analyses: Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.43; H, 5.68; N, 4.85. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.95 (3 H, s, C*H*$_3$), 7.09–7.78 (12 H, m, aromatic and NCH), 8.47 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.12(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.43 (*C*H$_3$), 48.67 (*C*H), 119.21, 119.54, 123.30, 124.02, 127.00, 129.25, 129.41, 130.14, 133.09 and 153.93 (naphthol moiety), 126.81, 127.24, 128.86 and 143.27 (phenyl moiety), 170.43 (NC=O).

1-[acetylamino(4-chlorophenyl)methyl]-2-naphthol (**3b**)**:** White powder, m.p. 232–233°C, IR (KBr) (ν_{max} cm^{-1}): 3403, 3296–2762, 1627. Analyses: Calcd. for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30%. Found: C, 70.38; H, 4.62; N, 4.47. ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.02 (3 H, s, C*H*$_3$), 7.06–7.78 (11 H, m, aromatic and NCH), 8.12 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 9.68(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.43 (*C*H$_3$), 48.67 (*C*H), 119.21, 119.54, 123.30, 124.02, 127.00, 129.25, 129.41, 130.14, 133.09 and 153.93 (naphthol moiety), 126.07, 127.84, 140.15 and 142.19 (phenyl moiety), 170.22 (NC=O).

1-[acetylamino(2-methylphenyl)methyl]-2-naphthol (**3c**)**:** White powder, m.p. 200–202°C, IR (KBr) (ν_{max} cm^{-1}): 3425, 3300–2727, 1642. Analyses: Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%. Found: C, 78.71; H, 6.16; N, 4.62. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.88 (3 H, s, C*H*$_3$), 2.11 (3 H, s, C*H*$_3$), 7.00–7.92 (11 H, m, aromatic and NCH), 8.43 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 9.88(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 21.42 and 23.57 (2 *C*H$_3$), 48.69 (*C*H), 118.04, 118.92, 123.15, 125.08, 126.93, 128.75, 131.38, 131.77, 132.84 and 155.41 (naphthol moiety), 126.38, 128.05, 132.13, 132.65, 140.73 and 142.17 (phenyl moiety), 170.25(NC=O).

1-[acetylamino(2-chlorophenyl)methyl]-2-naphthol (**3d**)**:** White powder, m.p. 194–196°C, IR (KBr) (ν_{max} cm^{-1}): 3404, 3398–2766, 1628. Analyses: Calcd. for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30%. Found: C, 70.38; H, 4.62; N, 4.47. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.89 (3 H, s, C*H*$_3$), 7.01–7.58 (11 H, m, aromatic and NCH), 8.63 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.12(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.09 (*C*H$_3$), 48.44 (*C*H), 117.89, 119.75, 123.56, 124.71, 127.18, 129.12, 130.12, 130.59, 133.54 and 155.18 (naphthol moiety), 125.94, 127.92, 131.01, 133.09, 140.28 and 142.02 (phenyl moiety), 169.88 (NC=O).



Scheme 3

1-[acetylamino(3-nitrophenyl)methyl]-2-naphthol (**3e**)**:** White powder, m.p. 236–237°C, IR (KBr) (ν_{max} cm^{-1}): 3388, 3295–2787, 1621. Analyses: Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33%. Found: C, 68.03; H, 4.60; N, 8.47. ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.00 (3 H, s, C*H*$_3$), 7.15–8.04 (11 H, m, aromatic and NCH), 8.66 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.12(1 H, s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.33 (*C*H$_3$), 48.44 (*C*H), 118.50, 119.19, 123.53, 124.02, 127.70, 129.20, 129.57, 130.48, 133.64 and 154.15 (naphthol moiety), 121.18, 122.15, 130.81, 132.92, 146.09 and 148.53 (phenyl moiety), 170.83 (NC=O**).**

1-[acetylamino(4-fluorophenyl)methyl]-2-naphthol (**3f**)**:** White powder, m.p. 203–205°C, IR (KBr) (ν_{max} cm^{-1}): 3392, 3300–2790, 1626. Analyses: Calcd. for $C_{19}H_{16}FNO_2$: C, 73.77; H, 5.21; N, 4.53%. Found: C, 73.74; H, 5.23; N, 4.49. ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.02 (3 H, s, C*H*$_3$), 7.07–7.81 (11 H, m, aromatic and NCH), 8.52 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.10(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.68 (*C*H$_3$), 48.95 (*C*H), 120.27, 121.06, 123.82, 124.88, 128.05., 130.71, 130.80, 131.24, 134.86 and 155.03 (naphthol moiety), 127.65, 128.11, 142.19 and 148.14 (phenyl moiety), 170.06 (NC=O).

1-[acetylamino(4-methylphenyl)methyl]-2-naphthols (**3g**)**:** White powder, m.p. 174–176°C, IR (KBr) (ν_{max} cm^{-1}): 3423, 3300–2725, 1640. Analyses: Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%. Found: C, 78.71; H, 6.16; N, 4.62. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.76 (3 H, s, CH$_3$), 1.95 (3 H, s, C*H*$_3$), 7.01–8.00 (11 H, m, aromatic and NCH), 8.44 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 21.35 and 23.42 (2 *C*H$_3$), 48.67 (*C*H), 119.22, 119.44, 123.30, 124.12, 127.07, 129.29, 129.31, 130.33, 133.09 and 153.80 (naphthol moiety), 126.81, 128.86, 140.34 and 143.27 (phenyl moiety), 170.77 (NC=O).

1-[acetylamino(4-bromophenyl)methyl]-2-naphthol (**3h**)**:** White powder, m.p. 174–176°C, IR (KBr) (ν_{max} cm^{-1}): 3408, 3293–2760, 1629. Analyses: Calcd. for $C_{19}H_{16}BrNO_2$: C, 61.64; H, 4.36; N, 3.78%. Found: C, 61.87; H, 4.21; N, 3.85. ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.01 (3 H, s, C*H*$_3$), 7.02–7.59 (11 H, m, aromatic and NCH), 8.39 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.02(1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.57(*C*H$_3$), 48.06 (*C*H), 120.04, 120.38, 122.92, 124.15, 127.45, 129.76, 130.24, 130.74, 132.57 and 151.58(naphthol moiety), 126.74, 127.36, 141.58 and 147.83 (phenyl moiety), 170.47 (NC=O).

1-[acetylamino(3-methoxyphenyl)methyl]-2-naphthol (**3i**)**:** White powder, m.p. 213–215°C, IR (KBr) (ν_{max} cm^{-1}): 3413, 3312–2728, 1630. Analyses: Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36%. Found: C, 74.92; H, 5.73; N, 4.43. ^{1}H NMR (500 MHz, d_6-DMSO): δ ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.97 (3 H, s, C*H*$_3$), 3.65 (3 H, s, OCH$_3$), 6.69–7.80 (11 H, m, aromatic and NCH), 8.46 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 10.06 (1 H, broad s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.45 (*C*H$_3$), 48.57 (*C*H), 55.71 (OCH$_3$), 119.30, 119.59, 123.27, 124.01, 127.20, 129.25, 129.39, 130.10, 133.12, and 153.93 (naphthol moiety), 111.48, 113.40, 119.24, 129.95, 145.10 and 159.94 (phenyl moiety), 170.23 (NC=O).

1-[acetylamino(2-methoxyphenyl)methyl]-2-naphthol (**3j**)**:** White powder, m.p. 202–204°C, IR (KBr) (ν_{max} cm^{-1}): 3415, 3312–2734, 1633. Analyses: Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36%. Found: C, 74.92; H, 5.73; N, 4.43. ^{1}H NMR (500 MHz, d_6-DMSO): δ ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.87 (3 H, s, C*H*$_3$), 3.56 (3 H, s,

OCH_3), 6.85–8.14 (11 H, m, aromatic and NCH), 8.31 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 9.81 (1 H, s, OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.40 (*C*H_3), 45.35 (*C*H), 56.10 (OCH_3), 119.34, 119.56, 123.06, 124.16, 126.70, 129.13, 129.27, 129.61, 133.34, and 154.02 (naphthol moiety), 111.63, 120.46, 128.66, 128.99, 130.69 and 157.36 (phenyl moiety), 169.57 (NC=O).

N-{[(acetylamino-(2-hydroxynaphthalen-1-yl)methyl]phenyl}-(2-hydroxynaphthalen-1-yl)methyl]acetamide (**5**)**:** White powder, m.p. 187–189ºC, IR (KBr) (ν_{max} cm^{-1}): 3335, 3261, 1664. Analyses: Calcd. for $C_{32}H_{28}N_2O_4$: C, 76.17; H, 5.59; N, 5.55%. Found: C, 76.37; H, 5.39; N, 5.60. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.89 (6 H, s, 2 C*H*$_3$), 6.83–7.77 (26 H, m, aromatic and 2 NCH), 8.39 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 9.89 (2 H, broad s, 2 OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 23.22 (*C*H$_3$), 48.78 (*C*H), 119.20, 119.28, 123.28, 124.81, 127.00, 129.17, 129.37, 130.09, 133.02 and 153.80 (naphthol moiety), 128.54 and 142.95 (phenyl moiety), 170.32 (NC=O).

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