Three-component reaction between 3-hydroxy-2-naphthoic acid, aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid: synthesis of 4-(acetylaminoarylmethyl)-3-hydroxy-2-naphthoic acid

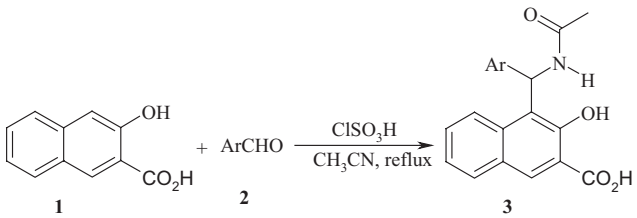
Mohammad Anary-Abbasinejad*, Alireza Hassanabadi, Fatemeh Ghanee and Nahid Tahmasbnia

Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran

The one-pot, three-component reaction between 3-hydroxy-2-naphthoic acid, aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid leads to 4-(acetylaminoarylmethyl)-3-hydroxy-2-naphthoic acids in excellent yields.

Keywords: chlorosulfonic acid, 3-hydroxy-2-naphthoic acid, three-component reaction, aryl aldehydes

Multi-component reactions (MCR) have been examined because they can be employed for the rapid assembly of a series of diverse structures.[1-6] The three–component reaction between an enolic system such as, acetophenone or β-dicarbonyl compounds, an aryl aldehyde and acetonitrile has been recently used to synthesise β-acetamidoketones. This reaction is usually carried out in the presence of excess acetyl chloride and is catalysed by an acid.[7] A three-component reaction between acetophenone or β-ketoesters, aryl aldehydes and acetonitrile was also carried out in the presence of excess trimethylchlorosilane and catalysed by heteropoly acids.[8] Recently we reported that a similar reaction can be carried out between other enolic systems such as 4-hydroxycoumarin[9] or 2-naphthol,[10] aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid without the need to use any other catalyst or activator. In continuation of our work, we now report that the three-component reaction between 3-hydroxy-2-naphthoic acid aromatic aldehydes and acetonitrile can be carried out in the presence of chlorosulfonic acid. Thus, when a mixture of 3-hydroxy-2-naphthoic acid and 4-chlorobenzaldehyde was stirred in boiling acetonitrile in the presence of two equivalents of chlorosulfonic acid, a clean reaction took place and was complete within 1 h (determined by TLC). After pouring the reaction mixture into ice-water 4-(acetylamino4-chlorophenylmethyl)-3-hydroxy-2-naphthoic acid **3a** was obtained as a white powder which was pure on the basis of NMR spectral data. It could be further purified by recrystallisation from an ethyl acetate–hexane mixture. As shown in Scheme 1, this reaction can be carried out with different aromatic aldehydes to yield 4-(acetylaminoarylmethyl)-3-hydroxy-2-naphthoic acid derivatives **3a–i** in excellent yields.



1 **2** **3**

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

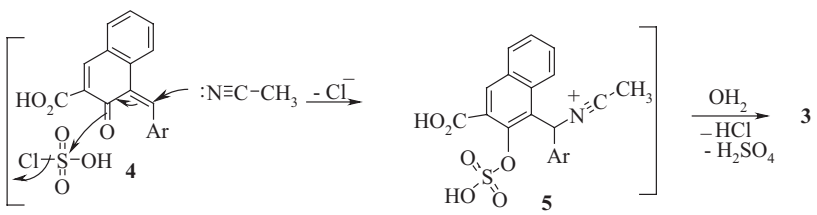
*Isolated yield.

Scheme 1

Compounds **3a–i** were new and their structures were deduced by elemental and spectroscopic analysis. The ^{1}H NMR spectrum of **3a** exhibited a sharp line at δ = 1.9 ppm for the protons of the methyl group. The methine and NH protons coupled to each other and two doublets were observed for them at 7.1 and 8.7 ppm, respectively. When the ^{1}H NMR spectrum was recorded after the addition of some D_2O to the d_6-DMSO solution of **3a** the doublet related to NH proton was disappeared and the doublet related to methine proton was converted to a singlet. The protons of the hydroxy groups resonate in the range of 12.00–13.00 ppm as a very broad signal which in some cases were broadened and were not observed. The ^{13}C NMR spectrum of compound **3a** showed 18 distinct signals consistent with the proposed structure.

A reasonable mechanism for the formation of compounds **3a–i** is presented in Scheme 2. Acetonitrile attacks to condensation product of 3-hydroxy-2-naphthoic acid and the aldehyde in the presence of chlorosulfonic acid to afford the cation **5** which is hydrolysed to from product **3**.

In summary, we report a simple and efficient one-pot synthesis of 4-(arylacetylaminomethyl)-3-hydroxy-2-naphthoic acids by a one-pot, three-component reaction between 3-hydroxy-2-naphthoic acid, aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid, in excellent yields. The advantages of this method are readily available starting materials, short reaction times, easy and clean work-up and excellent yields.



Scheme 2

* Correspondent. E-mail: mohammadanary@yahoo.com

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 for solutions 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 3-hydroxy-2-naphthoic acid (3 mmol) and aldehyde (3 mmol) in acetonitrile (15 ml) was added chlorosulfonic acid (6 mmol) at room temperature. The reaction mixture was then refluxed for 1 h. The reaction 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.

4-[Acetylamino(4-chlorophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3a**): Yellow powder, m.p. 262–264°C, IR (KBr) (ν_{max} cm^{-1}): 3350, 3125–2605, 1725, 1669. Analyses: Calcd. for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36; N, 3.79. Found: C, 65.00; H, 4.28; N, 3.85%. MS (*m/z*, %): 369 (11). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.98 (3 H, s, C*H*$_3$), 7.11 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.25–8.62 (9 H, m, aromatic), 8.76 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.74 (2 H, broad s, 2 OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.97 (*C*H$_3$), 47.48 (*C*H), 120.58, 124.08, 128.32, 128.50, 129.17, 129.35, 130.99, 131.29, 133.50 and 153.06 (naphthol moiety), 114.82, 127.41, 135.27 and 141.52 (phenyl moiety), 169.98,172.71 (2C=O).

4-[Acetylamino(3-chlorophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3b**): Yellow powder, m.p. 258–260°C, 95%; IR (KBr) (ν_{max} cm^{-1}): 3385, 3155–2615, 1708, 1668. Analyses: Calcd. for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36; N, 3.79. Found: C, 65.00; H, 4.28; N, 3.85%. MS (*m/z*, %): 369 (8). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.99 (3 H, s, C*H*$_3$), 7.01 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.27–8.63 (9 H, m, aromatic), 8.71 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.73(2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.95 (*C*H$_3$), 47.60 (*C*H), 120.41, 123.51, 124.13, 125.23, 126.11, 126.78, 130.10, 130.49, 133.59 and 154.92 (naphthol moiety), 114.87, 127.39, 131.01, 133.42, 135.26 and 145.16 (phenyl moiety), 170.07,172.70 (2C=O).

4-[Acetylamino(2-chlorophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3c**): Yellow powder, m.p. 246–248°C, 95%; IR (KBr) (ν_{max} cm^{-1}): 3390, 3130–2580, 1729, 1667. Analyses: Calcd. for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36; N, 3.79. Found: C, 65.00; H, 4.28; N, 3.85%. MS (*m/z*, %): 369 (10). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.94 (3 H, s, C*H*$_3$), 7.15 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.23–8.62 (9 H, m, aromatic), 8.74 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.63 (2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.76 (*C*H$_3$), 47.76 (*C*H), 119.34, 123.35, 123.93, 126.95, 128.84, 129.75, 129.86, 130.21, 132.66 and 155.38 (naphthol moiety), 114.65, 127.25, 131.01, 133.55, 135.81 and 139.57 (phenyl moiety), 169.29,172.84 (2C=O).

4-[Acetylamino(4-methylphenyl)methyl]-3-hydroxy-2-naphthoic acid (**3d**): White powder, m.p. 228–230°C, IR (KBr) (ν_{max} cm^{-1}): 3350, 3182–2630, 1721, 1669. Analyses: Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.34; H, 5.40; N, 4.05%. MS (*m/z*, %): 349 (10). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.97 (3 H, s, CH$_3$), 2.22 (3 H, s, C*H*$_3$), 6.95 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.21–8.61 (9 H, m, aromatic), 8.75 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.73(2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 20.99 and 23.03 (2 *C*H$_3$), 47.71 (*C*H), 121.24, 123.96, 126.41, 127.12, 129.13, 129.78, 130.90, 133.21, 135.41 and 154.80 (naphthol moiety), 114.75, 127.39, 135.73 and 139.32 (phenyl moiety), 169.75,172.78 (2C=O).

4-[Acetylamino(4-nitrophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3e**): Yellow powder, m.p. 253–255°C, 90%; IR (KBr) (ν_{max} cm^{-1}): 3380, 3134–2580,1729, 1671. Analyses: Calcd. for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.36. Found: C, 63.20; H, 4.30; N, 7.40%. MS (*m/z*, %): 380 (8). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.96 (3 H, s, C*H*$_3$), 7.12 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.25–8.65 (9 H, m, aromatic), 8.72 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.76(2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.88 (*C*H$_3$), 47.96 (*C*H), 120.05, 123.38, 123.77, 124.20, 127.43., 130.25, 131.05, 133.83, 135.23 and 155.00 (naphthol moiety), 114.92, 127.56, 146.47 and 150.85 (phenyl moiety), 170.28,172.66 (2C=O).

4-[Acetylamino(3-nitrophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3f**)**:** Yellow powder, m.p. 250–252°C, 94%; IR (KBr) (ν_{max} cm^{-1}): 3385, 3136–2527, 1723, 1672. Analyses: Calcd. for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.36. Found: C, 63.20; H, 4.30; N, 7.40%. MS (*m/z*, %): 380 (7). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.01 (3 H, s, C*H*$_3$), 7.24–8.65 (10 H, m, aromatic and NCH), 8.77 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.74(2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.92 (*C*H$_3$), 47.70 (*C*H), 119.10, 120.81, 121.92, 123.32, 124.25, 130.17, 130.33, 133.85, 135.20 and 155.38 (naphthol moiety), 114.91, 127.25, 131.07, 133.25, 145.08 and 148.22 (phenyl moiety),170.28,172.65 (2C=O).

4-[Acetylamino(4-bromophenyl)methyl]-3-hydroxy-2-naphthoic acid (**3g**): Yellow powder, m.p. 235–237°C, 90%; IR (KBr) (ν_{max} cm^{-1}): 3385, 3150–2590, 1740, 1663. Analyses: Calcd. for $C_{20}H_{16}BrNO_4$: C, 57.99; H, 3.89; N, 3.38. Found: C, 58.06; H, 3.95; N, 3.40%. MS (*m/z*, %): 414 (9). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.99 (3 H, s, C*H*$_3$), 7.01 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.31–8.61 (9 H, m, aromatic), 8.72 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.70(2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.97(*C*H$_3$), 47.55 (*C*H), 119.77, 120.53, 124.27, 126.40, 128.70, 129.49, 129.70, 131.40, 132.99 and 156.50 (naphthol moiety), 115.67, 127.10, 137.68 and 141.97 (phenyl moiety), 170.03,172.05 (2C=O).

4-[Acetylamino(3-methoxyphenyl)methyl]-3-hydroxy-2-naphthoic acid (**3h**): Yellow powder, m.p. 224–226°C, IR (KBr) (ν_{max} cm^{-1}): 3385, 3118–2521, 1732, 1664. Analyses: Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.10; H, 5.30; N, 3.80%. MS (*m/z*, %): 365 (11). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.98 (3 H, s, C*H*$_3$), 3.66 (3 H, s, OCH$_3$), 6.70 (1 H, d, $^3J_{HH}$ = 8 H$_Z$, NCH), 7.11–8.61 (9 H, m, aromatic), 8.70 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.75 (2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.99 (*C*H$_3$), 47.81 (*C*H), 55.35 (OCH$_3$), 118.86, 119.75, 121.05, 124.00, 127.37, 129.69, 130.92, 133.29, 135.40, and 154.80 (naphthol moiety), 111.33, 112.95, 114.75, 129.88, 144.06 and 159.64 (phenyl moiety), 169.81,172.75 (2C=O).

4-[Acetylamino(2-methoxyphenyl)methyl]-3-hydroxy-2-naphthoic acid (**3i**): Yellow powder, m.p. 244–246°C, IR (KBr) (ν_{max} cm^{-1}): 3395, 3130–2570, 1703, 1669. Analyses: Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.10; H, 5.30; N, 3.80%. MS (*m/z*, %): 365 (9). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.93 (3 H, s, C*H*$_3$), 3.58 (3 H, s, OCH$_3$), 7.12–8.61 (10 H, m, aromatic and NCH), 8.74 (1 H, d, $^3J_{HH}$ = 8 Hz, N*H*), 11.64 (2 H, broad s, 2OH). ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.76 (*C*H$_3$), 47.75 (*C*H), 53.75 (OCH$_3$), 119.33, 123.34, 123.93, 126.95, 128.84, 129.75, 129.87, 130.21, 132.65 and 155.37 (naphthol moiety), 114.64, 127.24, 131.01, 133.55, 135.80 and 139.57 (phenyl moiety), 169.27, 172.83 (2C=O).

Received 5 February 2008; accepted 24 February 2008
Paper 08/5072 *doi: 10.3184/030823408X293224*

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