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Hydrogen bond assisted activation of a dinitrile towards nucleophilic attack

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1. Materials and instrumentation

^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II + 300 (UltraShield™ Magnet) spectrometer operating at 300.130 and 75.468 MHz for proton and carbon-13, respectively. The chemical shifts are reported in ppm using tetramethylsilane as the internal reference. The infrared spectra ($4000\text{--}400\text{ cm}^{-1}$) was recorded on a BIO-RAD FTS 3000MX instrument in KBr pellets. Carbon, hydrogen, and nitrogen elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. All of the synthetic work was performed in air and at room temperature. Electrospray mass spectra were carried out with an ion-trap instrument (Varian 500-MS LC Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. The solutions in acetone were continuously introduced into the mass spectrometer source with a syringe pump at a flow rate of $10\ \mu\text{L}/\text{min}$. The drying gas temperature was maintained at $350\text{ }^\circ\text{C}$ and dinitrogen was used as nebulizer gas at a pressure of 35 psi. Scanning was performed from $m/z = 50$ to 1500.

2. Synthesis of 2-(2-(dicyanomethylene)hydrazinyl)benzenesulfonic acid (1)

1 was synthesized via the Japp-Klingemann reaction⁷ between 2-sulfophenyldiazonium chloride and malononitrile in an ethanolic solution containing sodium acetate.

Diazotization: 2-aminobenzenesulfonic acid (3.46 g, 20 mmol) was dissolved in 50 mL water, and (0.80 g, 20 mmol) of NaOH was added. The solution was cooled in an ice bath to 273 K and 1.38 g (20 mmol) of NaNO_2 was added; 4.00 mL HCl were then added in 0.5 mL portions for 1 h. The temperature of the mixture should not exceed 278 K.

Azocoupling: CH_3COONa (4.10 g, 50 mmol) was added to a mixture of 1.32 g (20 mmol) of malononitrile with 50 mL of ethanol. The solution was cooled in an ice bath to *ca.* 273 K, and a suspension of 2-sulfophenyldiazonium chloride (see above) was added in three portions under vigorous stirring for 1 h. The formed yellow precipitate of **1** was filtered off, washed with acetone and dried in air.

1. Yield 90 % (based on malononitrile), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $\text{C}_9\text{H}_6\text{N}_4\text{O}_3\text{S}$ ($M = 250.23$): C, 43.20; H, 2.42; N, 22.39. Found: C, 43.29; H, 2.10; N, 22.00. MS (ESI): m/z : 251 $[\text{M}+\text{H}]^+$. IR (KBr, selected bands, cm^{-1}): 3099 $\nu(\text{NH})$, 2218 and 2227 $\nu(\text{C}\equiv\text{N})$ and 1587 $\nu(\text{C}=\text{N})$. ^1H NMR (300.13 MHz, $\text{DMSO-}d_6$), δ : 7.09–7.93 (4H, Ar–H), 13.33 (1H, NH). $^{13}\text{C}\{^1\text{H}\}$ NMR (75.468 MHz, $\text{DMSO-}d_6$), 87.2 (C=N), 109.0 (CN), 113.6 (C≡N), 115.5, 125.3, 127.7 and 131.0 (Ar–H), 134.1 (Ar– SO_3H), 136.0 (Ar–NH–N).

3. Reactions of 1

Synthesis of 2. 0.25 g (1 mmol) of **1** was dissolved in 25 mL methanol and the solution stirred and heated under solvent reflux for 1 h. The reaction mixture was then cooled to room temperature and 0.11 mL (1.0 mmol) HCl (33 % w/w) was added. The yellow product **2** precipitated for 10 min, whereupon it was filtered off, washed with methanol on filter and dried in air.

2. Yield 92 % (based on **1**), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $C_{10}H_{11}ClN_4O_4S$ ($M = 318.74$): C, 37.68; H, 3.48; N, 17.58. Found: C, 36.96; H, 3.30; N, 17.16. MS (ESI): m/z : 283 $[M-Cl]^+$. IR (KBr, selected bands, cm^{-1}): 2955 and 3018 $\nu(NH)$, 2213 $\nu(C\equiv N)$, 1535 and 1594 $\nu(C=N)$. 1H NMR (300.13 MHz, DMSO- d_6), δ : 3.81 (3H, OCH₃), 4.80 (H, HN=C), 6.94–7.65 (4H, Ar-H), 12.66 (1H, NH). $^{13}C\{^1H\}$ NMR (75.468 MHz, DMSO- d_6), 52.4 (OCH₃), 105.3 (C=N), 110.3 (C \equiv N), 114.7, 123.9, 127.2 and 130.4 (Ar-H), 133.5 (Ar-SO₃H), 136.3 (Ar-NH-N), 160.5 (CH₃OC=N).

Synthesis of 3. Method 1 (Route III, Scheme 2). To 0.25 g (1 mmol) of **1** were added 0.24 mL (4 mmol) propylamine and 25 mL methanol (or water), in this order, and the system was stirred at room temperature for 30 min. The solvent was evaporated under vacuum and the residue was dissolved in acetone. Addition of a moderate excess (0.17 mL, 1.5 mmol) of HCl (33 % w/w) leads to the precipitation of the product **3**, which is then filtered off, washed with acetone on filter and dried in air.

Method 2 (Route II, Scheme 2). To 0.28 g (1 mmol) of **2** were added 0.24 mL (4 mmol) propylamine and 25 mL methanol. The reaction mixture was stirred at room temperature for 30 min, and then the solvent was evaporated and the residue was dissolved in acetone. Upon addition of 0.17 mL (1.5 mmol) HCl (33 % w/w) the yellow product **3** was allowed to precipitate for 10 min, whereafter it was filtered off, washed with acetone on filter and dried in air. The yields of **3** prepared by both methods are similar, ca. 80 %.

3. Yield 80 % (based on **1**), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $C_{12}H_{16}ClN_5O_3S$ ($M = 345.80$): C, 41.68; H, 4.66; N, 20.25. Found: C, 41.00; H, 5.07; N, 19.76. MS (ESI): m/z : 310 $[M-Cl]^+$. IR (KBr, selected bands, cm^{-1}): 2969 and 3091 $\nu(NH)$, 2210 $\nu(C\equiv N)$, 1668 and 1619 $\nu(C=N)$. 1H NMR (300.13 MHz, DMSO- d_6), δ : 0.89–0.94 (3H, CH₃), 1.60–1.62 (2H, CH₂), 3.36–3.38 (2H, CH₂), 7.19–8.00 (4H, Ar-H), 9.11–9.60 (3H, NH₃), 13.04 (1H, NH). $^{13}C\{^1H\}$ NMR (75.468 MHz, DMSO- d_6), 11.0 (CH₃), 21.0 (CH₂), 44.0 (CH₂), 102.8 (C=N), 109.2 (C \equiv N), 116.5, 125.0, 127.6 and 130.6 (Ar-H), 134.1 (Ar-SO₃H), 136.3 (Ar-NH-N), 155.1 (C=N).

Synthesis of 4. To 0.28 g (1 mmol) of **2** were added 0.24 mL (4 mmol) ethylenediamine, 15 mL water and the mixture was stirred for 30 min, at room temperature. The solvent was then evaporated under vacuum, the residue was dissolved in acetone and 0.11 mL (1.0 mmol) HCl (33 % w/w) were added. The yellow compound **4** was filtered off, washed with acetone on filter and dried in air.

4. Yield 71 % (based on **2**), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $C_{11}H_{14}ClN_5O_4S$ ($M = 347.78$): C, 37.99; H, 4.06; N, 22.14. Found: C, 37.94; H, 4.32; N, 20.45. MS (ESI): m/z : 312 $[M-Cl]^+$. IR (KBr, selected bands, cm^{-1}): 2914, 2887, 2795 and 2587 $\nu(NH)$, 1666 $\nu(C=O)$, 1581 and 1509 $\nu(C=N)$. 1H NMR (300.13 MHz, DMSO- d_6), δ : 4.00 (H, HN=C), 7.01–7.90 (4H, Ar-H), 8.15–8.44 (3H, NH₃), 9.90 and 13.11 (1H, NH). $^{13}C\{^1H\}$ NMR (75.468 MHz, DMSO- d_6), 36.6 (CH₂), 44.5 (CH₂), 115.6, 119.4, 123.1 and 127.4 (Ar-H), 130.4 (Ar-SO₃H), 133.6 (C=N), 138.1 (Ar-NH-N), 161.2 (C=N), 161.44 (C=O).

Synthesis of 5. To 0.25 g (1 mmol) of **1** was added 0.22 g (4 mmol) of potassium hydroxide and 15 mL water, and the mixture was stirred for 30 min at room temperature. The solvent was then evaporated under vacuum, the residue was dissolved in methanol and 0.17 mL (1.5 mmol) HCl (33 % w/w) was added. The yellow product **5** was allowed to precipitate for 10 min, whereafter it was filtered off and dried in air.

5. Yield 83 % (based on **1**), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $C_9H_9ClN_4O_4S$ ($M = 304.78$): C, 35.48; H, 2.98; N, 18.39. Found: C, 34.91; H, 2.68; N, 18.34. MS (ESI): m/z : 269 $[M-Cl]^+$. IR (KBr, selected bands, cm^{-1}): 3128, 2852 and 2727 $\nu(NH)$, 2226 $\nu(C\equiv N)$, 1676 $\nu(C=O)$, 1637 $\nu(C=N)$. 1H NMR (300.13 MHz, DMSO- d_6), δ : 7.09–7.79 (4H, Ar-H), 9.87–10.04 (3H, NH₃), 14.42 (1H, NH). $^{13}C\{^1H\}$ NMR (75.468 MHz, DMSO- d_6), 106.7 (C=N), 114.8 (C≡N), 116.5, 123.5, 127.3 and 130.2 (Ar-H), 134.4 (Ar-SO₃H), 137.8 (Ar-NH-N), 162.3 (C=O).

Synthesis of 6. To 0.35 g (1 mmol) of **3** was added 0.29 mL (4 mmol) butylamine and 25 mL methanol, and the mixture was stirred for 30 min at room temperature. The solvent was evaporated and the product was dissolved in acetone and 0.11 mL (1.0 mmol) HCl (33 % w/w) were added. The yellow compound **6** precipitated for 10 min, whereafter it was filtered off, washed with acetone on filter and dried in air.

6. Yield 62 % (based on **3**), yellow powder soluble in methanol, ethanol, water. Anal. Calcd for $C_{16}H_{27}ClN_6O_3S$ ($M = 418.94$): C, 45.87; H, 6.50; N, 20.06. Found: C, 46.28; H, 6.88; N, 20.07. MS (ESI): m/z : 383 $[M-Cl]^+$. IR (KBr, selected bands, cm^{-1}): 2873, 2934 and 2962 $\nu(NH)$, 1634, 1594 and 1545 $\nu(C=N)$. 1H NMR (300.13 MHz, DMSO- d_6), δ : 0.84–0.93 (6H, 2CH₃), 1.29–1.40 (2H, CH₂), 1.52–1.68 (4H, 2CH₂), 3.27–3.37 (4H, 2CH₂), 7.04–8.00 (4H, Ar-H), 9.00–9.71 (2H, NH₂), 10.02–10.52 (3H, NH₃), 11.89 (1H, NH). $^{13}C\{^1H\}$ NMR (75.468 MHz, DMSO- d_6), 13.6 and 13.8 (2CH₃), 19.4 and 19.8 (2CH₂), 28.5 (CH₂), 42.0 and 43.4 (2CH₂), 114.9 (Ar-H), 120.4 (Ar-SO₃H), 122.9, 127.4 and 130.3 (3Ar-H), 133.0 (C=N), 137.3 (Ar-NH-N), 152.7 and 154.7 (2C=N).