A Convenient Synthesis of 2-Aminonaphthalene-1-thiol

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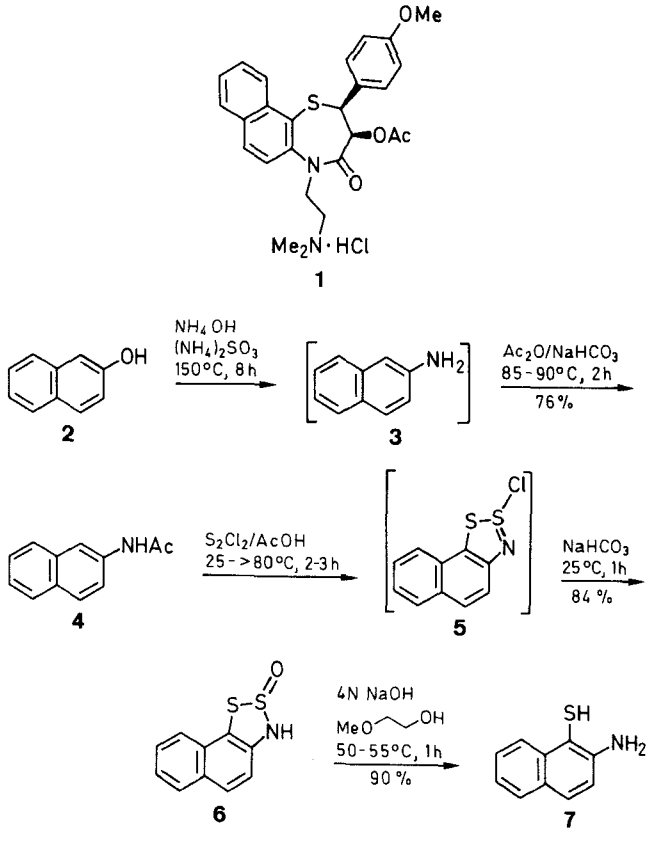
Reaction of 2-acetamidonaphthalene with sulfur monochloride gives the corresponding naphthothiazathiolium chloride, which on sequential hydrolyses with sodium bicarbonate and sodium hydroxide affords 2-aminonaphthalene-1-thiol.

In connection with a synthesis of the novel calcium channel blocker **1**,[1] we needed a practical and inexpensive synthesis of 2-aminonaphthalene-1-thiol (**7**). Because the reported[2] synthesis of **7** from 2-naphthylamine proceeded in low yield and used reaction conditions that were considered unsuitable for large-scale work, we examined a number of synthetic routes to **7**. Of these, that starting from the readily available 2-acetamido-1-naphthalenesulfonic acid[3] appeared to be the most attractive. However, various attempts to prepare the corresponding sulfonyl chloride and to reduce it to the thiol **7** were unsuccessful. A satisfactory route to **7** from 2-naphthol (**2**) was subsequently achieved, and is the subject of the present paper.



A Bucherer reaction[4] between **2** and ammonia in the presence of ammonium sulfite gave 2-naphthylamine, which, without isolation, was immediately acetylated to afford 2-acetamidonaphthalene (**4**). The latter in acetic acid was treated with sulfur monochloride (Herz reaction)[5] to give the crude naphthothiazathiolium chloride **5**, hydrolysis of which with sodium bicarbonate furnished the crystalline naphthodithiazole **6** in 84% yield from **4**.

Further hydrolysis of **6** with 4 N sodium hydroxide gave, after acidification with acetic acid, **7** in 57% overall yield from **2**. It should be noted that we obtained **7** as an oil rather than as a crystalline solid (m.p. 110 °C) as reported by Gupta and Jain.[2] One explanation for the discrepancy, despite an apparently compatible IR spectrum, is the possibility that these workers isolated the corresponding disulfide (m.p. 117–120 °C).

2-Acetamidonaphthalene (4):
Sulfur dioxide (112 g) is bubbled into cold (0 °C), concentrated NH_4OH and the resulting ammonium sulfite is added to a 3.5-L glass-lined autoclave containing 2-naphthol (**2**, 144.17 g, 1.00 mol). The mixture is heated at 150 °C for 8 h, allowed to cool to r.t. and is transferred to a 3-L, 3-necked, round-bottomed flask (*caution:* **3** is a potent carcinogen). $NaHCO_3$ (100 g, 1.19 mol) is added, the stirred mixture is warmed to 85 °C, and then treated, via an addition funnel, with Ac_2O (100 mL, 1.06 mol). After *ca.* 5 minutes, 400 mL of Ac_2O is added during 30 min. The mixture is stirred at 90 °C for 2 h, and then at r.t. overnight. It is extracted with EtOAc (2 × 600 mL), and the extract is dried ($MgSO_4$), evaporated, slurried with Et_2O (400 mL), and left at 0 °C overnight to give **4**; yield: 141.2 g (76.3%); mp 133–135 °C (Lit.[4] mp 137 °C).

3*H*-Naphtho[2,1-*d*]-1,2,3-dithiazole 2-Oxide (6):
Sulfur monochloride (Aldrich, 100 mL, 1.25 mol) is added under Ar to **4** (92.61 g, 0.5 mol) in AcOH (400 mL) and the mixture is stirred at r.t. for 2 h (during which the original yellow solution changed into an orange, heterogeneous mixture) and then at 75–80 °C for 3 h. The mixture, now deep red, is cooled, and diluted with toluene (800 mL), and the precipitated product is collected by filtration and washed with toluene and dried *in vacuo* to give crude **5**; yield: 154.56 g. To a stirred mixture of **5** in water (1.0 L) is added sat. $NaHCO_3$ (400 mL). The mixture (pH 4.0) is stirred at r.t. for 1 h, and the product is collected by filtration. It is washed with water (250 mL), dissolved in THF (1.0 L), and stirred with Darco G-60 decolorizing charcoal (50 g) for 15 min. The charcoal is removed by filtration over Celite, and the Celite is washed with THF (4 × 200 mL). The filtrate and washing are diluted with toluene (500 mL), some water (*ca.* 100 mL) is separated, and the mixture is evaporated *in vacuo* at 40 °C. To this residue is added toluene (*ca.* 500 mL), and the mixture is evaporated again *in vacuo* until *ca.* 200 mL of distillate is collected. The resultant slurry is cooled (ice bath) for 0.5 h, and the product is collected by filtration. It is washed with some toluene and is dried *in vacuo* overnight to give **6**; yield: 93.0 g (84%); mp 142–143 °C.

$C_{10}H_7NOS_2$	calc.	C 54.28	H 3.19	N 6.33	S 28.98
(221.3)	found	54.54	3.16	6.38	28.68

IR (KBr): ν = 3220, 1082 cm^{-1}.

UV (EtOH): λ_{max} (ε): 217 (21200), 240 (48300), 275 (3870), 288 (4320), 299 (3770), 331 (2110), 340 (2220) nm.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.58 (m, 2H), 7.64 (t, 1H, J = 7 Hz), 7.65 (d, 1H, J = 7 Hz), 7.88 (d, 1H, J = 7 Hz), 7.98 (d, 1H, J = 7 Hz), 11.36 (s, 1H, NH).

MS: m/z = 280 (M^+, 100).

2-Aminonaphthalene-1-thiol (7):
To a de-aerated mixture of 4 N NaOH (420 mL) in methyl cellosolve (420 mL) is added portion-wise under Ar **6** (93.0 g, 0.42 mol). The mixture is stirred under Ar at 50–55 °C for 1 h, cooled to r.t., diluted with water (840 mL) and extracted with Et_2O (2 × 800 mL, oxygen-free). The aqueous phase is acidified to pH 5.5 with AcOH (84 mL), extracted with EtOAc/toluene (1:1, 3 × 800 mL), and the extract is dried ($MgSO_4$) and evaporated (45 °C at 33 mm Hg followed by 25 °C at 0.1 mm Hg) to give **7** as an amber-colored oil that failed to crystallize; (Lit.[2] mp 110 °C); yield: 72.5 g (90%).

$C_{10}H_9NS$ 175	calc.	C 68.54	H 5.19	N 7.99	S 18.29
(175)	found	68.50	4.89	7.96	18.12

IR ($CHCl_3$): ν = 3485, 3385, 2535 cm^{-1}.

UV (EtOH): λ_{max} = 235 (27500) nm.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.65 (br s, 1 H, SH), 4.55 (br s, 2 H, NH_2), 6.97 (d, 1 H, J = 8 Hz), 7.51 (t, 1 H, J = 4 Hz), 7.62 (d, 1 H, J = 8 Hz), 7.67 (d, 1 H, J = 8 Hz), 8.30 (d, 1 H, J = 8 Hz).

MS: m/z = 175 (M, 100).

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