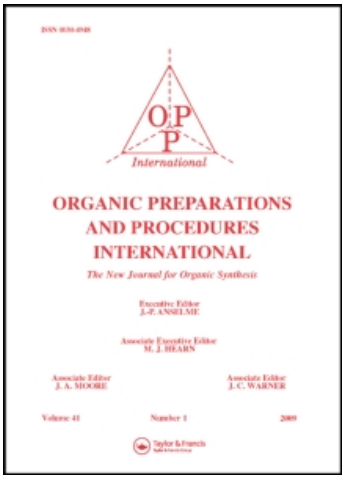

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AN IMPROVED PREPARATION OF 4-AMINO-3-MERCAPTOBENZOIC ACID

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AN IMPROVED PREPARATION OF 4-AMINO-3-MERCAPTOBENZOIC ACID

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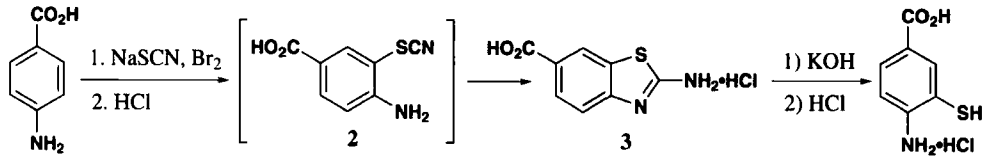
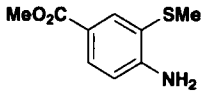
4-Amino-3-mercaptobenzoic acid (**4**) is commonly used as a precursor of 6-carboxybenzothiazole[1] which is heavily utilized by materials chemists[2] and to a lesser extent by medicinal chemists.[3] Two procedures have been reported for the synthesis of **4**; the first involves reaction of sodium sulfide[3b,4] with 4-amino-3-thiocyanatobenzoic acid (**2**), and the second[1a] requires hydrolysis of 1-amino-6-carboxybenzothiazole (**3**), derived from 4-aminobenzoic acid (**1**). Although, the later procedure[1a] can be conducted on large scale and has successfully been repeated by others (*Scheme 1*),[2d,2e,3a] it requires either catalytic[3a] or stoichiometric[1a] amounts of



Scheme 1

tin chloride to reduce/remove the corresponding disulfide by-product from **4**. In view of recent environmental concerns regarding tin compounds, we required either a new method or a new procedure for the synthesis of **4** without the use of tin chloride.

During the course of repeating the most recently reported synthesis of **4**,[2d,3a] which can afford up to 20% of the corresponding disulfide,[3a] it became apparent that if hydrolysis was performed with the exclusion of light and air, disulfide formation could be reduced to trace amounts. Most importantly this modification not only alleviated the use of tin chloride but additionally gave an increase in yield of 46% and 10% respectively to that reported [Chow *et al.*[2d] (33%) and Matsuoka *et al.*[3a] (69%)].[5] Characterization of the products was complicated by the fact that the ^{1}H and ^{13}C nmr spectra of **4** and of the disulfide are nearly identical. However, treatment of the mixture with diazomethane affords derivatives **5** and **6**, thus allowing differentiation of **4** from the disulfide.



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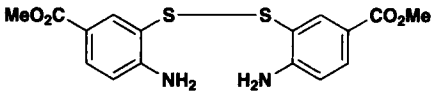

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Finally, it should be noted that **4** displays a unique ^{1}H nmr phenomena depending on the deuterated solvent used. In DMSO-d_6, an additional set of peaks [δ 6.69 (d), 7.52 (dd) and 7.76 (d)] appear in addition to those expected [δ 6.74 (d), 7.45 (d) and 7.61 (dd)]. However, when 5% D_2O is introduced these peaks disappear. At this stage it is unclear why two sets of peaks are observed, however, a thorough investigation will be reported in due course.

In conclusion, a significant improvement on the synthesis of 4-amino-3-mercaptobenzoic acid **4**, to that previously reported, has been developed. This new procedure eliminates the use of tin chloride, which, along with other tin derivatives, has recently raised environmental concerns.[6]

EXPERIMENTAL SECTION

^{1}H and ^{13}C nmr spectra were recorded on a Bruker AV400 instrument. Accurate and low resolution mass spectral data were obtained on a KRATOS MS 25 RFA. Electrospray mass spectrotrometry was performed on a Finnigan MAT 900 XL-Trap. Microanalyses were carried out in-house by the University of Queensland Microanalytical Service. GC/MS data were recorded

on a Hewlett-Packard 5890A chromatograph fitted with a DBS EC-5 Alltech column (30 m x 0.25 mm), coupled to a 5970 series mass spectrometer. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Column chromatography (Flash Silica gel 230–400 mesh, Merck) on silica gel was performed using distilled solvents.

2-Aminobenzothiazole-6-carboxylic Acid Hydrochloride (3).- The published procedure[3a] was followed. To a stirred suspension of sodium thiocyanate (13 g, 0.160 mol) and 4-aminobenzoic acid **3** (20 g, 0.146 mol) in MeOH (75 mL) was slowly added bromine (7.5 mL, 0.146 mol) while the temperature was maintained below –5°C. After addition, the mixture was stirred at –5°C for 2 h. The precipitated solid was collected and washed with water. The isolated solid was suspended in hydrochloric acid (1M, 70 mL), refluxed for 30 mins and then filtered while hot. Conc. hydrochloric acid (30 mL) was added to the filtrate producing a white solid. The solid was collected and dried under vacuum to afford **3** (11.5 g, 34%). The crude product was used without further purification. A sample was recrystallized from methanol, mp. >290°C (dec.). *Lit.*[2d] mp. 288-290°C (dec).

^{1}H NMR (DMSO-d_6): δ 7.54 (d, 1H, H4, J = 8.5 Hz), 7.94 (dd, 1H, H5, J = 8.5, 1.6 Hz), 8.45 (d, 1H, H7, J = 1.6 Hz). ^{13}C NMR (DMSO-d_6): δ 114.6, 124.4, 125.86, 125.91, 128.5, 145.2, 166.6, 170.1. Mass spectrum (EI) m/z (%): 194(M^+ -HCl, 100), 177 (82), 149 (27), 122 (29).

HRMS (ESI): Calcd for $C_8H_7N_2O_2S$ [M+H]: 195.0228; Found: 195.0228.

4-Amino-3-mercaptobenzoic Acid Hydrochloride (4).- A suspension of **3** (6.0 g, 0.026 mol) and potassium hydroxide (26.3 g, 0.469 mol) in rigorously degassed demineralized water (50 mL) was shielded from light (aluminium foil) and then refluxed under nitrogen (or argon) for 4 h. After cooling to room temperature, conc. hydrochloric acid (45 mL) was added dropwise under nitrogen. The resulting mixture was cooled in a cold-water bath (~5°C) and stirred for 30 mins. The precipitate was collected under a nitrogen blanket and dried under vacuum (0.01 mmHg) to give the desired product as a white solid (4.2 g, 79%). Light- and oxygen-free storage (–5°C) is recommended.

^{1}H NMR (DMSO-d_6): δ 6.69 (d, J = 8.4 Hz), 6.74 (d, 1H, H5, J = 8.4 Hz), 7.45 (d, 1H, H2, J = 1.6 Hz), 7.52 (dd, J = 8.4, 1.6 Hz), 7.61 (dd, 1H, H6, J = 8.4, 1.6 Hz), 7.76 (d, J = 1.6 Hz).

^{1}H NMR [D_2O (5%)/DMSO-d_6 (95%)]: δ 6.75 (d, 1H, H5, J = 8.6 Hz), 7.41 (d, 1H, H2, J = 2.1 Hz), 7.61 (dd, 1H, H6, J = 8.6, 2.1 Hz). ^{13}C NMR [D_2O (5%)/DMSO-d_6 (95%)]: δ 114.3, 115.2, 117.8, 133.2, 138.5, 153.8, 167.0.

All attempts to recrystallize the title compound resulted in the formation of *bis*-(2-amino-3-mercaptobenzoic acid) disulfide hydrochloride, mp. 284-286°C (dec.) (methanol). *Lit.*[7] mp. 285°C (dec).

^{1}H NMR (DMSO-d_6): δ 6.28 (s, 2H, NH), 6.74 (d, 1H, H5, J = 8.6 Hz), 7.47 (d, 1H, H2, J = 2.0 Hz), 7.62 (dd, 1H, H6, J = 8.6, 2.0 Hz), 12.15 (bs, 1H, CO_2H). ^{13}C NMR (DMSO-d_6): δ 113.8 (C-5), 114.8 (C-3), 117.5 (C-1), 132.7 (C-6), 138.0 (C-2), 153.6 (C-4), 166.5 (-CO_2H). Mass spectrum (EI) m/z (%): 336 (M^+-2HCl, 28), 194 (36), 177 (18), 169 (55), 168 (100), 152 (28), 124 (46).

HRMS (ESI): Calcd. for $C_{14}H_{12}N_2O_4S_2Na$ [M+Na]: 359.0136; Found: 359.0132.

Methyl 4-Amino-3-methylsulfanylbenzoate (5).- To a solution of **1** (15 mg, 0.073 mmol) in MeOH (0.3 mL) was added a solution of diazomethane in diethyl ether at room temperature until effervescence ceased (performed in fumehood). The unreacted diazomethane was removed by flushing the solution with nitrogen gas, and the solvents were evaporated under reduced pressure affording a yellow colored oily residue. Column chromatography (ethyl acetate/hexane; 1:4) on silica gel gave the title compound (12mg, 83%) as a white solid, mp. 58-60°C.

^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, $SC\underline{H}_3$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 6.66 (d, 1H, H5, J = 8.4 Hz), 7.75 (dd, 1H, H6, J = 8.4, 2.0 Hz), 8.04 (d, 1H, H2, J = 2.0 Hz). ^{13}C NMR ($CDCl_3$): δ 17.8, 51.7, 113.6, 119.5, 120.1, 130.8, 135.5, 151.0, 166.7. GC/MS (EI) m/z (%): 197 (M^+, 100), 182 (53), 166 (87), 151 (16), 138 (12), 123 (14).

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; $M^{+\bullet}$ 197.0510. Found: C, 54.77; H, 5.64; N, 7.01; 197.0503.

***bis*-(Methyl 4-amino-3-mercaptobenzoate) Disulfide (6).**- The same procedure to that directly above afforded the title compound as a yellow solid in near quantitative yield, mp. 166-168°C. All attempts at obtaining an analytical sample failed.

^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H, $CO_2C\underline{H}_3$), 6.68 (d, 1H, H5, J = 8.4 Hz), 7.74 (d, 1H, H2, J = 2.0 Hz), 7.82 (dd, 1H, H6, J = 8.4, 2.0 Hz). ^{13}C NMR ($CDCl_3$): δ 51.7, 114.3, 117.3, 119.7, 133.4, 139.2, 152.2, 166.2. Mass spectrum (EI) m/z (%): 364 (M^+, 28), 197 (6), 183 (39), 182 (100), 152 (33), 124 (14).

HRMS (ESI): Calcd. for $C_{16}H_{17}N_2O_4S_2$ [M+H]: 365.0630; Found: 365.0633.

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IMPROVED SYNTHESIS OF 1,3-DIAZA-6-ADAMANTANONE

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(08/11/03)

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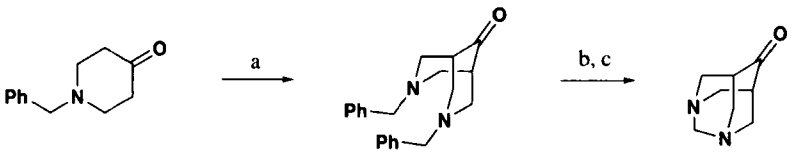
1,3-Diaza-6-adamantanone was first synthesized by oxidation of 1,3-diaza-6-adamantanol.[1] The alcohol synthesis[2] (6 steps, 10%) was later shortened (3 steps, 8%) and the oxidation yield improved.[3] We have synthesized the ketone directly, improving the overall yield (3 steps, 35%) while avoiding the lachrymators and thiols used previously.



a) Benzylamine, $(CH_2O)_n$, HOAc/HCl/MeOH (69%), ref. 4; b) H_2, $Pd(OH)_2/C$, HOAc/MeOH; (c) CH_2O (aq) (51%, two steps)

Mannich condensation of benzylamine, paraformaldehyde, and *N*-benzyl-4-piperidone was performed using a literature procedure.[4] Hydrogenolysis of the *bis*-benzylamine product proceeded slowly under atmospheric pressure. Cyclization of the crude product with aqueous formaldehyde gave 1,3-diaza-6-adamantanone, which was isolated by hot filtration.

EXPERIMENTAL SECTION

Mps were determined on a Mel-temp apparatus and are uncorrected. All reactions were run under an argon atmosphere except where noted. All solvents and reagents were purchased from Aldrich or VWR and used without purification, except for benzylamine and *N*-benzyl-4-piperi-