An Efficient and Convenient Synthesis of 2-Mercaptobenzaldehyde

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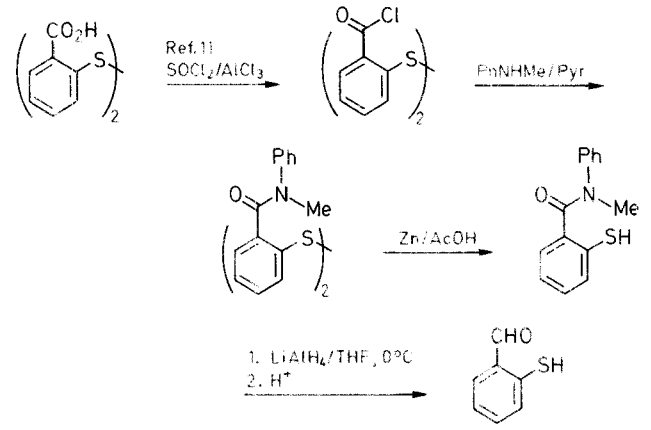
An efficient and convenient synthesis of 2-mercaptobenzaldehyde (**1**) is described.

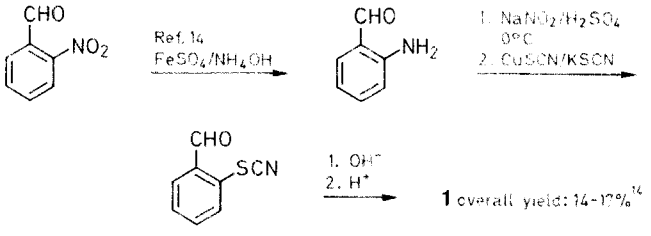
2-Mercaptobenzaldehyde is a valuable precursor in the synthesis of benzo[*b*]thiophenes,[1] 1,2-benzisothiazoles,[2] and iso-π-electronic thia analogues of benzo- and dibenzoazulenes,[3] which have been referred to as "pseudoazulenes".[4] It is also a potentially useful intermediate in the syntheses of a number of important sulfur analogues of known oxygen heterocycles such as 2*H*- and 4*H*-1-benzopyrans,[5,6] 1-benzopyran-2-ones,[7] 1-benzoxepins,[8] and 1-benzoxocins.[9]

Two procedures have been reported for the synthesis of this aldehyde.[10] The first method,[11] shown in Scheme **A**, involves the reduction of the anilide of 2,2'-dithiodibenzoic acid with lithium aluminum hydride in an overall yield of 38% from the corresponding acid chloride. In our experience and according to other investigators,[12] the critical factor in this reduction is the type and amount of the reducing agent employed. We found that with lithium aluminum hydride the yield of the aldehyde **1** was reduced as a result of the formation of the corresponding alcohol.



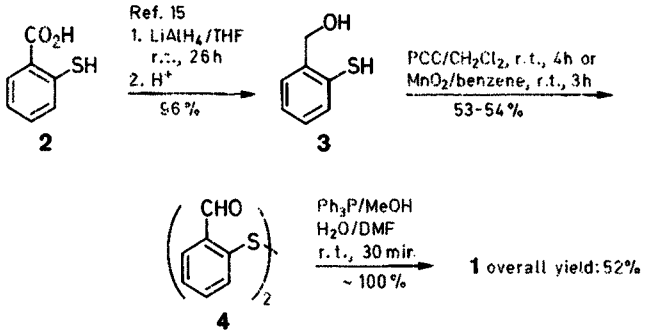
Scheme **A** **1**

The second approach,[13] which was modified by West and coworkers,[14] yields 2-mercaptobenzaldehyde (**1**) in an overall yield of 14–17% from 2-nitrobenzaldehyde (Scheme **B**).



Scheme **B**

We now report an efficient and convenient synthesis of 2-mercaptobenzaldehyde (**1**), in an overall yield of 52%, starting with the readily available 2-mercaptobenzoic acid (**2**) (Scheme **C**).



Scheme C

Reduction of 2-mercaptobenzoic acid (**2**) with lithium aluminum hydride in tetrahydrofuran according to the procedure of Arnoldi and Carughi[15] resulted in 2-mercaptobenzyl alcohol (**3**) in 96% yield. This alcohol, usually obtained as a viscous oil and sometimes as a low melting solid, is sufficiently pure (NMR) to be used in the succeeding step. However, it is air-sensitive and gives rise to the corresponding disulfide at room temperature and under the work-up conditions, if air is not excluded.

Oxidation of **3** with pyridinium chlorochromate (PCC)[16] in dichloromethane at room temperature afforded 2,2'-dithiodibenzaldehyde (**4**)[14,17] in 53% yield. Disulfide **4** was also prepared in 54% yield from the oxidation of **3** with activated manganese dioxide according to the procedure of Goldman.[18] Brown and Meth-Cohn[19] have reported the preparation of **4** in 70–90% yield from the oxidation of **3** with manganese dioxide according to the procedure of Pratt and Van De Castle.[20] However, we obtained **4** in yields lower than 50% when we used this procedure.

Conversion of the disulfide **4** to the desired product **1** required a selective reduction of the disulfide function. Humphrey and Hawkins[21] have reported reductions of a number of substituted aromatic disulfides with triphenylphosphine in aqueous methanol. Their work consisted of polarographic or amperometric study of this reduction and no preparative procedures were given. We found that treatment of **4** with triphenylphosphine in a solvent system composed of methanol, water and dimethylformamide (2:1:2) at room temperature gives the aldehyde **1** quantitatively. Most of the triphenylphosphine oxide formed in this reaction precipitates when the reaction mixture is cooled to 0°C. 2-Mercaptobenzaldehyde, isolated as a yellow ethereal solution, is further purified by chromatography on Florisil.[14] The yield of pure **1** is 80–90%.

2-Mercaptobenzoic acid (**2**), Ph_3P and $LiAlH_4$ were purchased from Aldrich Chemical Co. All solvents were freshly distilled. Deoxygenated solvents were prepared by bubbling N_2 through freshly distilled solvents for 20 min. THF was dried by refluxing over benzophenone/Na. Benzene was distilled from Na metal and stored over molecular sieves (4 Å) prior to use. PCC was prepared according to the published procedure.[16] MnO_2 was prepared by a modified Attenburro procedure[20] and was activated by either the procedure of Pratt and Van De Castle[20] or Goldman.[18] TLC plates were purchased from Eastman Kodak Co. Florisil (100–200 mesh) was obtained from Fisher Scientific. Melting points were taken using a Thomas-Hoover apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Jeol FX-90Q spectrometer.

2-Mercaptobenzyl alcohol (**3**) was prepared in 96% yield according to the published procedure.[15]

2,2'-Dithiodibenzaldehyde (4):

Oxidation of 2-Mercaptobenzyl Alkohol (**3**) *with PCC:* In a 100 mL round-bottomed three-neck flask fitted with a reflux condenser and a magnetic stirrer and filled with N_2, PCC (12.95 g, 60.25 mmol) is suspended in deoxygenated, dry CH_2Cl_2 (50 mL). A solution of alcohol **3** (3.37 g, 24.1 mmol) in deoxygenated CH_2Cl_2 (10 mL) is added by a disposable pipette to the stirred mixture. After stirring for 4 h at room temperature, CH_2Cl_2 (50 mL) is added and the supernatant liquid is decanted from the black gum. The black gum is washed with CH_2Cl_2 (3 × 15 mL) and dry Et_2O (20 mL) whereupon the residue becomes granular. The combined organic solution is passed through a short pad of Florisil. Evaporation of solvent at room temperature and under aspirator pressure gives **4**; yield: 1.76 g (54%); mp 145°C (95% EtOH) (Lit.[14] mp 144°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.24–8.07 (m, 8 H_{arom}); 10.22 (s, 2H, CHO).

Oxidation of 2-Mercaptobenzyl alcohol (**3**) *with MnO_2:* In a 250 mL round-bottomed three-neck flask fitted with a reflux condenser and a magnetic stirrer and filled with N_2, is placed a solution of **3** (1.03 g, 7.36 mmol) in dry benzene (125 mL). Activated MnO_2[18] (10.53 g, 121 mmol) is added in one portion. The mixture is stirred at room temperature for 3 h. The suspension is filtered through a short pad of filter-aid wetted with benzene. The solvent is evaporated under aspirator pressure to give **4**; yield: 0.54 g (54%); mp 145°C (95% MeOH) (Lit.[14] mp 144°C).

2-Mercaptobenzaldehyde (1):

In a N_2 filled round-bottomed three-neck flask (200 mL) is placed a solution of crude 2,2'-dithiodibenzaldehyde, (**4**; 1.76 g, 6.45 mmol) in deoxygenated DMF (54 mL). Deoxygenated MeOH (54 mL) and water (30 mL) are added to the magnetically stirred solution. Ph_3P (2.53 g, 9.68 mmol) is added at a moderate rate and the stirring is continued for 30 min at room temperature. The mixture is cooled in an ice-water bath and stirring is continued at this temperature for 0.5 h. The supernatant is then transferred with a double-tipped needle and under N_2 to a separatory funnel containing cold (0°C) deoxygenated Et_2O (160 mL) and water (120 mL). The yellow orange ethereal solution is separated into a round-bottomed flask filled with N_2. The yellow aqueous layer is extracted twice with deoxygenated Et_2O (100 mL and 70 mL). The combined Et_2O layer is washed with cold (0°C) deoxygenated water (2 × 70 mL) and is dried ($MgSO_4$) at 0°C. All the above transfers are made under N_2 as much as possible. The dried Et_2O solution is filtered under N_2 and is concentrated in a rotary evaporator to a volume of 2–3 mL at 0°C. The light brown solution is then adsorbed on top of a 47 cm × 1.5 cm column of Florisil (100–200 mesh) wet-packed under N_2 with dry Et_2O. Elution with Et_2O (200 mL) gives a yellow solution, which is evaporated at 0°C to afford **1** as a yellow oil; yield: 1.5 g (80%); mp of the 2,4-dinitrophenylhydrazone 267–267.5°C (Lit.[14] mp 269–270°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 5.23 (br s, 1H, 5H); 7.37 (m, 3 H_{arom}); 7.74 (br d, 1 H_{arom}, J = 8.5 Hz); 10.10 (s, 1H, CHO).

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(1) For a review see:
Scrowston, R.M. *Adv. Heterocycl. Chem.* **1981**, *29*, 171.
Rahman, L.K.A., Scrowston, R.M. *J. Chem. Soc. Perkin Trans. 1*, **1983**, 2973.
(2) For a review see:
Davis, M. *Adv. Heterocycl. Chem.* **1985**, *38*, 106.
(3) For oxygen and nitrogen analogues see:
Boyed, G.V. *J. Chem. Soc.* **1958**, 1978.
Los, M., Stafford, W.H. *J. Chem. Soc.* **1959**, 1680.
For sulfur analogue see: Ref. 11.
(4) Mayer, R. *Angew. Chem.* **1957**, *69*, 481.
(5) Varma, R.S., Kabalka, G.W. *Heterocycles* **1985**, *23*, 139.
Liepa, A.J. *Aust. J. Chem.* **1984**, *37*, 2545.
(6) Gupta, R.K., George, M.V. *Tetrahedron* **1975**, *31*, 1265.
Roudier, J.F., Foucaud, A. *Synthesis* **1984**, 159.
(7) Dauzonne, D., Royer, R. *Synthesis* **1983**, 836.
Phadke, C.P., Kelkar, S.L., Wadia, M.S. *Synth. Commun.* **1984**, *14*, 407.
(8) Schweizer, E.E., Berninger, C.J., Crouse, D.M., Davis, R.A., Logothetis, R.S. *J. Org. Chem.* **1969**, *34*, 207.
(9) Schweizer, E.E., Anderson, S.E. *J. Org. Chem.* **1974**, *39*, 3038.

(10) An efficient synthesis of 2-mercapto-3-methoxybenzaldehyde from the corresponding 2-hydroxy compound and *N,N*-dimethylthiocarbamoyl chloride has been described in Ref. 1.
(11) Leaver, D., Smolicz, J., Stafford, W.H. *J. Chem. Soc.* **1962**, 740.
(12) Corrigan, M.F., West, B.O. *Aust. J. Chem.* **1976**, *29*, 1413.
(13) Friedländer, P., Lenk, E. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 2083.
(14) Marini, P.J., Murray, K.S., West, B.O. *J. Chem. Soc. Dalton Trans.* **1983**, 143.
(15) Arnoldi, A., Carughi, M. *Synthesis* **1988**, 155.
(16) Corey, E.J., Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647.
(17) An attempts to prepare the aldehyde **4** from the PCC oxidation of 2,2'-dithiodibenzyl alcohol resulted in a low yield (16%) of **4**.
(18) Goldman, I.M. *J. Org. Chem.* **1969**, *34*, 1979.
(19) Brown, K.J., Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 4069.
(20) Pratt, E.F., Van De Castle, J.F. *J. Org. Chem.* **1961**, *26*, 2973.
(21) Humphrey, R.E., Hawkins, J.M. *Anal. Chem.* **1964**, *36*, 1812.