Simple Synthetic Route to 4-Aminobenzaldehydes from Anilines

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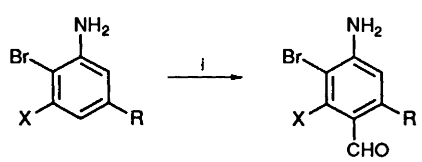
Anilines unsubstituted at the 4-position react under mild conditions in Me_2SO–HCl solvent (H^+ = 0.6 mol dm^{-3}) to give substituted 4-aminobenzaldehydes in high yields; although addition of $CuCl_2$ gives a cleaner product, it is not essential for the reaction. Chloromethyl methyl sulfoxide is thought to be the active species in the reaction.

There are few simple methods for preparing aminobenzaldehydes in high yield from anilines. The present method describes replacement of H by CHO in a position *para* to the amino group, a reaction which takes place in the dark.

Results

The present method has been examined with bromo and/or methyl substituted anilines in dimethyl sulfoxide (DMSO)–HCl solvent. A reaction time of 5–10 h at 90 °C is optimum, longer periods giving rise to dialdehydes and ring chlorinated products.

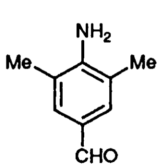
2-Bromoaniline gave 4-amino-3-bromobenzaldehyde **1** (98%) and 2,3-dibromo- and 2,3-dibromo-5-methyl-aniline, gave 4-amino-2,3-dibromo- **2** and 4-amino-2,3-dibromo-6-methylbenzaldehyde **3**, respectively, in high yields (Scheme 1). 2-Substitution gave traces of 2-aminobenzaldehydes in these cases (^{1}H NMR, MS).



1 X = H, R = H
2 X = Br, R = H
3 X = Br, R = Me

Scheme 1 *Reagents:* i, DMSO–HCl (aq), $CuCl_2$

2,6-Dimethyl- and 2-methyl-aniline gave 4-amino-3,5-dimethyl- **4** (55%) and 4-amino-3-methyl-benzaldehyde **5** (45%), respectively together with *ca.* 20% of ring chlorinated by-products. 3-Methylaniline yielded only a dialdehyde after 5 h.



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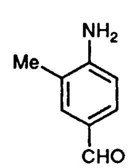


5

$MeSOCH_2Cl$

6

Me_2SO_2

7

Attempted reactions with 4-substituted anilines (*e.g.* 4-bromo- and 4-methyl-aniline) and 2- and 4-bromophenol were unsuccessful.

Products from the DMSO–HCl solvent, identified (^{1}H NMR, ^{13}C NMR and mass spectra) in the reaction mixture or compared with authentic samples, were chloromethyl methyl sulfoxide **6**, dimethyl sulfone **7** and methyl methanethiosulfonate **8** (judging from the spectra) together with formaldehyde, methanethiol and dimethyl sulfide. Although no intermediate aromatic compound was isolated or observed, prolonged reaction times gave ring chlorination.

The reaction of chloromethyl methyl sulfoxide **6**, prepared according to Tsuchihashi and Ogura,[11] with 2-bromoaniline has been examined in dimethylformamide (DMF) (HCl and $CuCl_2$ added, see Experimental section). After *ca.* 100 min at 90 °C the main product was 4-amino-3-bromobenzaldehyde **1** (^{1}H NMR, MS).

The ^{1}H NMR spectrum of chloromethyl methyl sulfoxide **6** indicated the presence of at least two conformations, arising from rotation about the S–CH_2Cl bond[1] and with different chemical shifts and patterns for the CH_2 proton signal.

Discussion

DMSO, an polar aprotic solvent with excellent solvating power for organic substances, acts as a nucleophile at either the oxygen or sulfur atom, and can be used as both a reducing and an oxidizing agent.[2–5] With DMSO as the oxidant in aldehyde syntheses,[6] overoxidation to the corresponding acid does not occur even with sensitive aldehydes.

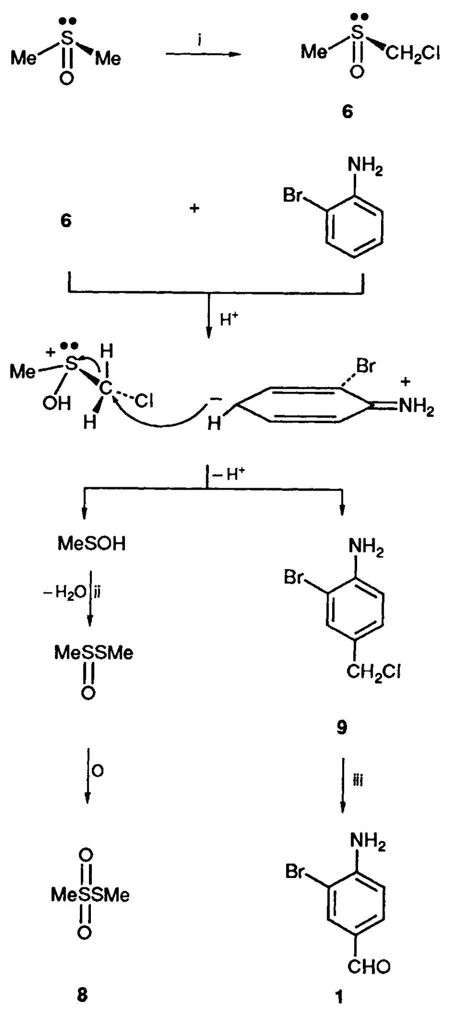
The following speculation as to the mechanism for the DMSO–HCl induced reactions is based upon the observed products.

The known activation by an NH_2 group of the *ortho* and *para* positions to electrophilic attack seems in the present reaction to favour the *para*-position, probably because of reduced steric crowding in the intermediate state.

Smythe[7] reported that dibenzyl sulfoxide reacted with hydrochloric acid to give benzaldehyde (30%) and benzyl chloride, whilst Kornblum *et al.*[6] showed that benzyl halides in DMSO at 100–150 °C for <5 min were converted into aldehydes (yield 65–85%). Further, Sato *et al.*[8] reported that salicylaldehyde was formed in moderate yield from phenol and chloromethyl methyl sulfoxide with thionyl chloride as an activator whilst Gross and Matthey[9] synthesized aromatic aldehydes from aromatic hydrocarbons and dichloromethyl methyl sulfide with a $TiCl_4$ or $AlCl_3$ catalyst, *e.g.* toluene gave *p*-tolualdehyde (56%).

Rynbrandt[10] showed that sulfoxides in dichloromethane reacted with anhydrous HCl in diethyl ether, *e.g.* DMSO was converted into chloromethyl methyl sulfide (73%). Tsuchihashi and Ogura[11] reported that chlorination of DMSO with *N*-chlorosuccinimide in CH_2Cl_2 in the presence of pyridine gave chloromethyl methyl sulfoxide (87%) while DMSO with nitrosyl chloride–pyridine in chloroform[12] also produced chloromethyl methyl sulfoxide (61%); higher concentrations of nitrosyl chloride and pyridine gave dichloro sulfoxides. Chlorine reacted with DMSO in carbon tetrachloride with triethylamine as a proton acceptor to give chloromethyl methyl sulfoxide (60%)[13] whilst chlorinated Lewis acids react with DMSO *via* a chlorosulfonium salt and a Pummerer rearrangement to chloromethyl methyl sulfide, which readily oxidized to methyl methanethiosulfonate.[14]

In the present investigation with DMSO–HCl (H^+ = 0.6 mol dm^{-3}) the only observed and identified chlorinated compound was chloromethyl methyl sulfoxide **6**. We differed from Rynbrandt (*vide supra*) in using 37% aqueous HCl. Although it is possible for a CH_2Cl carbon to undergo electrophilic attack by chloromethyl methyl sulfoxide, after an oxidative cleavage of the carbon–sulfur bond with the aromatic amine (Scheme 2), the



Scheme 2 *Reagents and conditions:* i, DMSO–HCl (aq); ii, MeSOH; iii, DMSO

possibility of another reactive species, derived from the chloromethyl methyl sulfoxide, being the reactive principle in the aldehyde synthesis cannot be excluded. The conversion of the chloromethylated amine **9** into an aldehyde by DMSO is a known reaction.[6] The sulfenic acid, MeSOH, produced is an unstable intermediate and the presumed $MeSO_2SMe$ **8**, which appeared in the reaction mixture, could be produced by further reaction of the former.

Experimental

M.p.s were determined with a Kofler hot-stage microscope and are uncorrected. The ^1H NMR and ^{13}C NMR spectra were obtained on a Varian XL-400 NMR spectrometer in $CDCl_3$ with Me_4Si as internal standard and *J*-values in Hz (21 °C). Mass spectra (GCMS) were recorded on a Finnigan 1020 instrument (EI 70 eV) and IR spectra on a Perkin-Elmer 1600 FT infrared spectrometer. The elemental analysis was performed by Mikro Kemi AB, Uppsala. High resolution mass spectra for exact mass calculations were carried out at the Department of Medical Biochemistry, Göteborg.

General Procedure.—Reactions of aromatic amines in DMSO–HCl (H^+ = 0.6 mol dm^{-3}) to produce amino aldehydes were carried out at 90 °C. Thus, a mixture of the aromatic amine (0.5 mmol) dissolved in DMSO (10.0 cm^3) (distilled under reduced pressure over CaH_2 or alternately of commercial analytical grade), conc. aqueous HCl (0.5 cm^3) and dried $CuCl_2$ (1 mmol, 0.135 g) in a flask with reflux condenser was immersed in a thermostatted water bath for the stated time. The reaction was quenched with ice–water, the pH of the mixture adjusted to *ca.* 8 [NaOH solution (10%)] and the mixture extracted with ether (3 × 100 cm^3). The solvent was evaporated and the residue, containing the aldehyde, dried *in vacuo* to constant weight. The yield was quantitative. The purity of the title compounds was judged to be 98–84% by ^1H NMR spectral determinations. The products, originating from the DMSO–HCl solvent, were isolated by fractional vacuum distillation of the crude reaction mixture.

4-*Amino-3-bromobenzaldehyde* **1**.—This compound was prepared from 2-bromoaniline (Fluka) (*ca.* 300 min; 98% yield); m.p. 101.0–101.8 °C (vacuum sublimation) (lit.,[15] 109–110 °C); ν_{max}(KBr)/cm^{-1} 3389, 3319, 3201, 2837, 2747 and 1677; δ_H(400 MHz; $CDCl_3$) 7.95 (d, *J* 1.8 2-H), 7.64 (q, *J* 8.2, 1.8, 6-H), 6.80 (d, *J* 8.2, 5-H), 4.73 (2 H, s, NH_2) and 9.71 (1 H, s, CHO); *m/z* 199 (57%), 201 (56), 198 (−H, 100) and 200 (−H, 98). The compound obtained was also compared to an authentic sample. This reaction also gave *ca.* 1% of another unpurified isomer (probably 2-amino-3-bromobenzaldehyde); *m/z* 199, 201.

4-*Amino-2,3-dibromobenzaldehyde* **2**.—This aldehyde was prepared from 2,3-dibromoaniline[16] (10 h; 93%); m.p. 160.6–162.3 °C (vacuum sublimation) (Found: M − H, 277.863. $C_7H_5{}^{79}Br^{81}BrNO$ requires *M* − 1, 277.8638); ν_{max}(KBr)/cm^{-1} 3461, 3348, 3196, 2923, 2855 and 1663; δ_H(400 MHz; $CDCl_3$) 7.75 (d, *J* 8.4, 6-H), 6.75 (d, *J* 8.4, 5-H), 4.93 (2 H, s, NH_2) and 10.12 (1 H, s, CHO); *m/z* 277 (38%), 279 (67), 281 (33), 276 (−H, 53), 278 (−H, 100) and 280 (−H, 49). About 2% of another unpurified isomer (probably 2-amino-3,4-dibromobenzaldehyde) was detected; *m/z* 277, 279, 281.

4-*Amino-2,3-dibromo-6-methylbenzaldehyde* **3**.—The compound was obtained from 2,3-dibromo-5-methylaniline[16] (5 h 50 min; 84%). It was purified by column chromatography on silica gel (Merck Kieselgel S, 0.063–0.2 mm) with toluene as eluent; m.p. 169.6–170.3 °C (Found: C, 33.15; H, 2.5; N, 4.85. $C_8H_7Br_2NO$ requires C, 32.8; H, 2.4; N, 4.8%; M − H, 291.883. $C_8H_7{}^{79}Br^{81}BrNO$ requires *M* − 1, 291.880); ν_{max}(KBr)/cm^{-1} 3461, 3317, 3181, 2923 and 1664; δ_H(400 MHz; $CDCl_3$) 6.54 (s, 5-H), 2.51 (3 H, s, CH_3), 4.76 (2 H, s, NH_2) and 10.33 (1 H, s, CHO); *m/z* 291 (31%), 293 (59), 295 (28), 290 (−H, 52), 292 (−H, 100) and 294 (−H, 52).

4-*Amino-3,5-dimethylbenzaldehyde* **4**.—2,6-Dimethylaniline subjected to the currect reaction gave 55% of compound **4** after 5 h. The aldehyde was not purified but was identified from its ^1H NMR and mass spectra; δ_H(400 MHz; $CDCl_3$) 7.47 (s, 2-H and 6-H), 2.23 (6 H, s, CH_3), 4.22 (2 H, s, NH_2) and 9.73 (1 H, s, CHO);[15] *m/z* 149 (80%), 148 (−H, 100) and 120 (47).

4-*Amino-3-methylbenzaldehyde* **5**.—Compound **5** (45%) was obtained from 2-methylaniline after 6 h. The compound was not purified but was identified from its ^1H NMR and mass spectra; *ca.* 30% of starting material remained; δ_H(400 MHz; $CDCl_3$) 6.7 (d, *J* 7.6, 5-H), 7.57 (q, 6-H), 7.59 (d, 2-H), 2.22 (3 H, s, CH_3), 4.2 (2 H, s, NH_2) and 9.74 (1 H, s, CHO);[18] *m/z* 135 (70%), 134 (−H, 100) and 106 (50).

In the syntheses of compounds **4** and **5** we also obtained *ca.* 20% of ring chlorinated by-products.

Dialdehyde of 3-*Methylaniline*.—The reaction of 3-methylaniline with DMSO–HCl solvent gave after 5 h 40% of a dialdehyde, not purified; δ_H(400 MHz; $CDCl_3$) 7.95 (1 H, s), 6.46 (1 H, s), 9.95 (1 H, s, CHO) and 9.87 (1 H, s, CHO).

Chloromethyl methyl sulfoxide **6**.—δ_H(400 MHz; $CDCl_3$) 2.7 (3 H, s, CH_3) and 4.39 (2 H, s, CH_2) or 4.52, 4.44 (2 H, d, d, *J* 11, CH_2) arising from two conformations;[1,11,13] δ_C($CDCl_3$) 58.4 (CH_2) and 36.5 (CH_3); *m/z* 112 (18%), 114 (7) and 49 (100).

Reaction of Chloromethyl Methyl Sulfoxide **6** *with* 2-*Bromoaniline*.—The amine (0.25 mmol, 0.045 g) was dissolved in DMF (5 cm^3) at 90 °C. Compound **6** (2 mmol, 0.22 g) conc. HCl (0.2 cm^3) and dried $CuCl_2$ (0.5 mmol, 0.070 g) were added. After 100 min 4-amino-3-bromobenzaldehyde **1** was obtained (40%) (yield after 5 h, was 55%).

Dimethyl Sulfone **7**.—δ_H(400 MHz; $CDCl_3$) 2.99 (6 H, s, CH_3); δ_C($CDCl_3$) 42.7 (CH_3); *m/z* 94 (45%), 79 (100) and 47 (30).

Methyl methanethiosulfonate **8**.—δ_H(400 MHz; $CDCl_3$) 3.32 (3 H, s, CH_3) and 2.7 (3 H, s, SCH_3); δ_C($CDCl_3$) 48.8 (CH_3) and 18.7 (SCH_3);[14,17] *m/z* 126 (15%), 128 (1), 81 (45), 79 (30) and 47 (100).

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