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Working with Hazardous Chemicals

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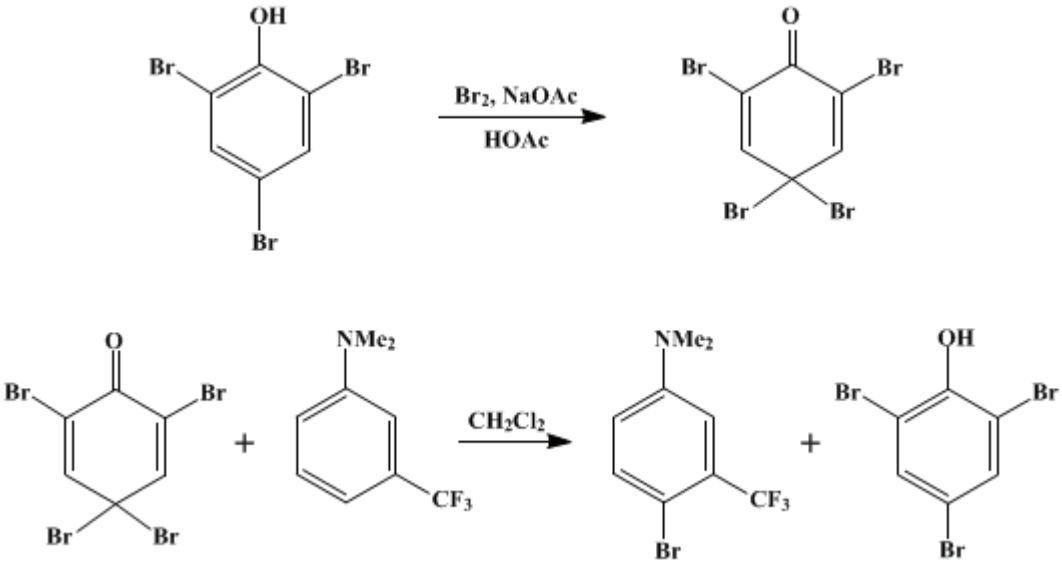
para-BROMINATION OF AROMATIC AMINES: 4-BROMO-*N*,*N*-DIMETHYL-3-(TRIFLUOROMETHYL)ANILINE

[Benzenamine, 4-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)]



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Checked by J. D. Lock, Jr. and S. Masamune.

1. Procedure

Caution! The reaction should be conducted in a hood to avoid inhalation of bromine vapor.

A. 2,4,4,6-*Tetrabromo*-2,5-*cyclohexadien*-1-*one*. A mixture of 66.2 g. (0.200 mole) of 2,4,6-tribromophenol (Note 1), 27.2 g. (0.197 mole) of sodium acetate trihydrate, and 400 ml. of glacial acetic acid is placed in a 1-l. Erlenmeyer flask and warmed (*ca.* 70°) until a clear solution is obtained. The solution is magnetically stirred and cooled to room temperature to produce a finely divided suspension of the phenol, to which a solution of 32 g. (0.20 mole) of bromine in 200 ml. of glacial acetic acid is added dropwise over 1 hour (Note 2). The resulting mixture is kept at room temperature for 30 minutes, then poured onto 2 kg. of crushed ice. The yellow solid which separates is removed by suction filtration after the ice has melted, and the damp crystals are dissolved in the minimum of warm chloroform (Note 3). The upper aqueous layer is removed with a pipet fitted with a suction bulb. The dienone crystallizes from the chloroform solution upon cooling, yielding 50–55 g. (61–67%) of crystals, m.p. 125–130° (dec.), sufficiently pure for use in the next step (Note 4) and (Note 5).

B. 4-*Bromo*-N,N-*dimethyl*-3-(*trifluoromethyl*)*aniline*. A solution of 9.45 g. (0.0500 mole) of *N*,*N*-dimethyl-3-(trifluoromethyl)aniline (Note 6) in 200 ml. of dichloromethane is placed in a 500-ml. Erlenmeyer flask, cooled to −10°, and stirred magnetically as 20.5 g. (0.0500 mole) of finely powdered 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one is added in 0.5-g. portions. During this addition the temperature of the mixture should be maintained between −10° and 0° (Note 7). The cooling bath is removed and the reaction mixture is allowed to warm to room temperature over a 30-minute period and extracted twice with 50 ml. of aqueous 2 *N* sodium hydroxide to remove 2,4,6-tribromophenol (Note 8). The organic layer is washed with 25 ml. of water and dried over anhydrous magnesium sulfate. Removal of the solvent yields 12–12.5 g. of crude 4-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)aniline. Distillation through an 8-cm. Vigreux column provides 11–12 g. (82–90%) of pure bromoamine, b.p. 134–136° (15 mm.), which solidifies, giving colorless crystals, m.p. 29–30° (Note 9) and (Note 10).

2. Notes

1. The submitters used reagent grade 2,4,6-tribromophenol. The checkers recrystallized the practical grade reagent purchased from Fisher Scientific Company. The solvent used was Skelly B, and the melting point of the phenol, after recrystallization, was 93–95°.
2. It is essential to maintain the temperature of the solution below 25° during the addition of the bromine solution. If external cooling is applied, initially with an ice-water bath, the addition can be completed within 20 minutes.
3. Some decomposition of the dienone is observed if the chloroform solution is vigorously refluxed for any length of time; bromine is evolved and there is a reduction in yield. Approximately 400 ml. of chloroform is needed to dissolve the dienone at approximately 60°. The checkers used 450 ml of the solvent.
4. The submitters used 0.5-molar quantities with no reduction in yield.
5. ^{1}H NMR (dioxane-d_8), δ (multiplicity): 7.98 (singlet).
6. The amine was prepared according to the procedure described in *Org. Synth.*, **Coll. Vol. 5**, 1085 (1973).
7. The reaction proceeds satisfactorily over a range between −30° and +20°. At lower temperatures, the reaction proceeds rather slowly.
8. 2,4,6-Tribromophenol may be recovered by acidification of the aqueous alkaline extracts and reused in the preparation of the tetrabromo-compound after crystallization from petroleum ether (b.p. 80–100°).
9. The product can be crystallized from petroleum ether (b.p. 30–40°).
10. ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.94 (s, 6H, 2CH_3), 6.7 (approximate d of d, 1H), 7.0 (approximate d, 1H), 7.5 (approximate d, 1H).

3. Discussion

4-Bromo-*N,N*-dimethyl-3-(trifluoromethyl)aniline has been prepared by the methylation of 4-bromo-3-(trifluoromethyl)aniline with trimethyl phosphate in 70–80% yield.[3] The present method, which effectively uses 3-(trifluoromethyl)aniline as starting material, offers advantages in cost, yield, and ease of purification.

Aromatic amines are usually polybrominated on treatment with bromine. Several mild brominating agents have been introduced in attempts to achieve partial bromination without the necessity of protecting and deprotecting the amino group, but these give variable results when applied to a large variety of amines. Dioxane dibromide[4] monobrominates tertiary aromatic amines, but gives poor yields with primary and secondary aryl amines. The use of *N*-bromosuccinimide[5,6] (1-bromo-2,5-pyrrolidinedione) leads to monobrominated compounds frequently contaminated with decomposition products.

The dienone, which is prepared essentially as described by Benedikt[7] and Caló,[8] monobrominates a wide range of primary, secondary, and tertiary aromatic amines almost exclusively in the *para*-position. The procedure described is of general synthetic utility for the preparation of *para*-brominated aromatic and heteroaromatic amines in high yields and frequently in a high state of purity. The submitters have used this technique to *para*-brominate many compounds in quantities ranging from 0.01–0.1 mole, including the following (yields after one crystallization): aniline (92), *N*-methylaniline (94), *N,N*-dimethylaniline (91), *N,N*-diethylaniline (94), *o*-toluidine (88), *N*,2-dimethylaniline (91), *N,N*,2-trimethylaniline (90), *m*-toluidine (90), *N,N*,3-trimethylaniline (86), 2,3-dimethylaniline (91), 2,5-dimethylaniline (91), 3,5-dimethylaniline (81), 2-chloroaniline (86), 3-chloroaniline (86), 2-bromoaniline (78), 3-bromoaniline (82), 2-nitroaniline (91), 3-nitroaniline (85), *m*-phenylenediamine (82), *o*-anisidine (85), 3-methoxyaniline (58, 4-bromo; 30, 6-bromo), diphenylamine (90), 1-aminonaphthalene (86), 1-dimethylaminonaphthalene (84), 2-(trifluoromethyl)aniline (85), 2-aminopyridine (75), 2-dimethylaminopyridine (70), 3-dimethylaminopyridine (60),[9] 2-amino-6-methylpyridine (76). Where solubility of the amine in dichloromethane is low, chloroform may be used as solvent. For example, 2-aminopyrimidine gave 2-amino-5-bromopyrimidine (82%) in this manner, compared with 41% when the amine is brominated conventionally in aqueous solution.[10] In the case of anthranilic acid, 2-amino-5-bromobenzoic acid (82%) precipitated from the chloroform reaction

medium. In addition to its use with amines, the dienone reagent monobrominates a variety of phenols,[11] and behaves as an oxidizing agent toward sulfides, converting them to sulfoxides.[12]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

acetic acid (64-19-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

bromine (7726-95-6)

N,N-dimethylaniline (121-69-7)

Anthranilic Acid (118-92-3)

N,N-diethylaniline (91-66-7)

dichloromethane (75-09-2)

2-aminopyridine (504-29-0)

1-aminonaphthalene (134-32-7)

diphenylamine (122-39-4)

magnesium sulfate (7487-88-9)

2,4,6-tribromophenol (118-79-6)

N-Methylaniline (100-61-8)

N-bromosuccinimide,
1-bromo-2,5-pyrrolidinedione (128-08-5)

sodium acetate trihydrate (6131-90-4)

2-aminopyrimidine (109-12-6)

2-Nitroaniline (88-74-4)

2-(trifluoromethyl)aniline (88-17-5)

3-Chloroaniline (108-42-9)

o-toluidine (95-53-4)

m-toluidine (108-44-1)

trimethyl phosphate (512-56-1)

2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one (20244-61-5)

4-bromo-3-(trifluoromethyl)aniline (393-36-2)

3-(trifluoromethyl)aniline (98-16-8)

Dioxane dibromide

2,3-dimethylaniline (87-59-2)

2,5-dimethylaniline (95-78-3)

3,5-dimethylaniline (108-69-0)

2-chloroaniline (95-51-2)

2-bromoaniline (615-36-1)

3-bromoaniline (591-19-5)

3-nitroaniline (99-09-2)

3-methoxyaniline (536-90-3)

1-dimethylaminonaphthalene (86-56-6)

2-dimethylaminopyridine (5683-33-0)

3-dimethylaminopyridine

2-amino-6-methylpyridine (1824-81-3)

2-amino-5-bromopyrimidine (7752-82-1)

o-anisidine (90-04-0)

N,N-dimethyl-3-(trifluoromethyl)aniline (329-00-0)

4-Bromo-N,N-dimethyl-3-(trifluoromethyl)aniline,
Benzenamine, 4-bromo-N,N-dimethyl-3-(trifluoromethyl) (51332-24-2)

N,2-dimethylaniline (611-21-2)

N,N,2-trimethylaniline (609-72-3)

N,N,3-trimethylaniline (121-72-2)

m-phenylenediamine (108-45-2)

2-amino-5-bromobenzoic acid (5794-88-7)