Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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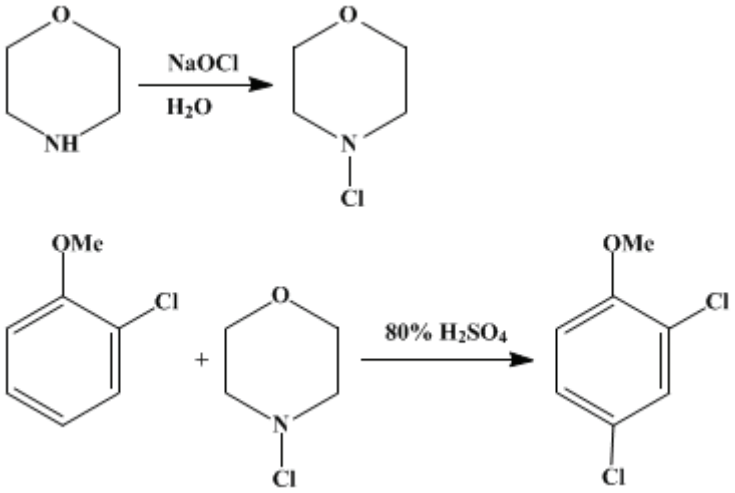
4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS: 2,4-DICHLOROMETHOXYBENZENE

[Benzene, 2,4-dichloro-1-methoxy-]



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Checked by Yasushi Morita and Ryoji Noyori.

1. Procedure

A. *N-Chloromorpholine.* A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a thermometer is charged with 250 mL of 1.5 *M* sodium hypochlorite solution (Note 1). The solution is stirred and the temperature is maintained below 10°C while 30 mL (0.34 mol) of morpholine (Note 2) is added dropwise. The resulting mixture is stirred for 5 min before the *N*-chloromorpholine is extracted with four 50-mL portions of diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator (Note 3). The concentrate is distilled at reduced pressure (Note 4) to afford 35.5–36.5 g (86–88%) of *N*-chloromorpholine, bp 63–64°C (36–38 mm) (Note 5).

B. *2,4-Dichloromethoxybenzene.* A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a thermometer is charged with 250 mL of 80% (v/v) sulfuric acid (Note 6) and cooled in an ice bath before 16 g (0.11 mol) of 2-chloromethoxybenzene (Note 7) is added with stirring. The stirring and cooling are maintained while 14.5 g (0.12 mol) of *N*-chloromorpholine is added dropwise (Note 8). The cooling bath is removed and stirring is continued for 1 hr. The reaction mixture is carefully poured into a mixture of 150 mL of distilled water and 100 g of crushed ice in a 1-L flask cooled at 0°C (Note 9). The aromatic products are extracted with a 100-mL portion, followed by four 50-mL portions, of diethyl ether. The combined ether extracts are washed with 100 mL of water containing 0.5 g of potassium iodide, 2 g of sodium thiosulfate and 2 mL of acetic acid (Note 10) followed by 50 mL of 8% (w/v) aqueous sodium hydroxide (Note 11), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure to afford 15.2–16.0 g (77–81%) of 2,4-dichloromethoxybenzene, bp 110–111°C (10 mm) [lit.[2] bp 125°C (10 mm), 233°C (740 mm)]. The product after distillation is 98.9–99.2% pure; the major impurities are 2,6-dichloromethoxybenzene (0.4–0.5%) and 2,4,6-trichloromethoxybenzene (0.4–0.6%) (Note 12) and (Note 13). If this above purity is insufficient, it can be improved to >99.9% by recrystallization (Note 14) and (Note 15).

2. Notes

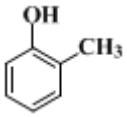
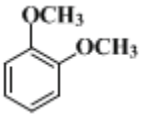
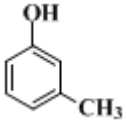
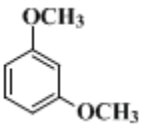
1. Solutions of sodium hypochlorite of different concentrations can be used with a corresponding change in the volume. The submitters purchased sodium hypochlorite solution from BDH Chemicals Ltd., England. The material initially contains 10–14% available chlorine, but it deteriorates on standing over a period of weeks. The checkers used the material (chlorine content 9–14%) purchased from Nakarai Chemicals, Ltd., Japan.
2. Gold Label-grade morpholine (≥99%) was obtained from Aldrich Chemical Company, Inc., and used as supplied.
3. Since *N*-chloromorpholine has a low boiling point, the water-bath temperature should not exceed 30° C.
4. It is recommended that a water or oil bath, or a hot-air blower, be used for this distillation to avoid the risk of local overheating.
5. *N*-Chloromorpholine should be handled with extreme care at all times. On standing at room temperature it slowly decomposes, forming crystals of morpholine hydrochloride. However, it can be stored for several weeks at −18°C. Vigorous decomposition of *N*-chloromorpholine has been reported when it is distilled at atmospheric pressure.[3] The checkers removed the small quantity of salt contamination by filtration through a glass filter and used the pure liquid in the subsequent chlorination reaction.
6. Trifluoroacetic acid, 100 mL, obtainable from Aldrich Chemical Company, Inc., can be used instead of aqueous sulfuric acid (see Discussion).
7. 2-Chloromethoxybenzene was obtained from Aldrich Chemical Company, Inc., and was distilled prior to use, bp 195–196°C or 112°C (41 mm).
8. Since the dissolution of *N*-chloromorpholine in sulfuric acid (or trifluoroacetic acid) and the subsequent reaction between protonated *N*-chloromorpholine and 2-chloromethoxybenzene are both exothermic processes, the addition of the chloramine should be carried out at such a rate as to keep the reaction temperature below 5°C. The checkers found that a reaction run at 8°C gave product of only 93% purity.
9. If the reaction is carried out in trifluoroacetic acid, the product mixture is made basic by adding it cautiously, with cooling and stirring, to a cold solution of 50 g of sodium hydroxide in 150 mL of distilled water. The aromatic products are then extracted with diethyl ether as described in the main text.
10. If trifluoroacetic acid is used, more acetic acid may be required to ensure that the aqueous layer is acidic. Should any iodine remain, more sodium thiosulfate should be added until all of the iodine has been converted to iodide.
11. The aqueous layer should remain basic after washing with sodium hydroxide. If it is still acidic, this wash should be repeated.
12. If trifluoroacetic acid is used as solvent, the purity is 98–99% and the impurities are mainly 2,6-dichloro- and 2,4,6-trichloromethoxybenzene.
13. The purity of the product can be determined by gas–liquid chromatography using a column packed with 10% (w/w) Carbowax 20 M on Celite (80–100 mesh) at 195°C, nitrogen carrier gas flow rate 35 mL/min.
14. Eighteen grams of 2,4-dichloromethoxybenzene is dissolved in 20 mL of light petroleum ether and chilled to −18°C. Crystallization can be induced by either scratching or seeding. The mixture is kept at −18°C for 1 hr to maximize the yield before the crystals are filtered with a Büchner funnel and washed with 10 mL of chilled light petroleum ether. The crystals are sucked dry, and then dried in a vacuum desiccator. The recrystallized yield of 2,4-dichloromethoxybenzene is 12.8 g (55–58% overall), mp 25.5–26.5°C, lit.[2] mp 28°C.
15. The product had the following spectral properties: IR (neat) cm^{-1}: 1483, 1288, 1254, 1055, 700; ^1H NMR (CCl_4, 60 MHz) δ: 3.77 (s, 3 H, OCH_3), 6.70 (d, 1 H, J = 9.0, H_6), 7.05 (dd, 1 H, J = 9.0 and 2.5, H_5), 7.27 (d, 1 H, J = 2.5, H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ: 56.2 (q), 112.7 (d), 123.3 (s), 125.6 (s), 127.5 (d), 129.9 (d), 153.9 (s); mass spectrum (70 eV) *m/e* (relative intensity): 178 (M^+ + 2, 66), 176 (M^+, 100), 163 (47), 161 (58), 135 (23), 133 (43). Mass spectrum calcd, for $C_7H_6OCl_2$ (M^+): 175.9797. Found: 175.9809.

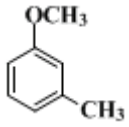
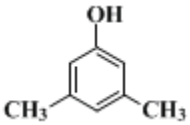
3. Discussion

Chlorine or hypochlorous acid has been used traditionally for the chlorination of aromatic compounds and, when required, the reactivity of these reagents can be increased with a Lewis or protic acid, respectively.[4] However, these reactions are rarely selective for one monochlorinated product (site-

selective[5]) and, furthermore, with some substrates di- and polychlorination can also occur. The increasing need for isomerically pure chloroaromatics in recent years has led to the development of more selective chlorinating agents, particularly for electron-rich aromatic compounds (e.g., phenol).[6] In this respect the submitters have found that *N*-chlorodialkylamines in strongly acidic solution are efficient and very selective monochlorinating agents for aromatic compounds containing a π-donor (+ M) substituent.[7] Thus, normally the addition of the *N*-chloramine to an equimolar quantity of the substrate in acid leads rapidly and almost exclusively to the *para*-chlorinated product (Table I). Although most of the reactions have been studied on a small scale (< 1 g of substrate) for reasons of economy, the submitters have had no difficulty in scaling up the chlorinations to use 20 g of substrate. The two acidic media that have been used with success are trifluoroacetic acid and aqueous sulfuric acid [commonly 80% (v/v) sulfuric acid]. The advantages of the former are that the reactions are homogeneous and can, if necessary, be carried out at low temperature (< 0°C) and can be monitored readily by ^{1}H NMR spectroscopy. However, trifluoroacetic acid is relatively expensive and is highly toxic. (The reactions must be carried out in a well-ventilated hood.) In situations where these disadvantages outweigh the advantages, aqueous sulfuric acid is generally a cheap and less toxic alternative. The fact that the reactions in aqueous sulfuric acid are not homogeneous is not a serious problem. Thus, with efficient stirring the chlorinations occur rapidly; furthermore, solid substrates can be added as solutions in diethyl ether (e.g., with *N*-chloromorpholine, phenol gave 93% of 4-chloro- and 7% of 2-chlorophenol, and 2-methylphenol gave 95% of 4-chloro- and 5% of 6-chloro-2-methylphenol). The major disadvantage in the use of aqueous sulfuric acid arises with the most reactive substrates (e.g., some phenols) from competing aromatic sulfonation. However, this can be reduced to a minor side reaction by keeping the reaction mixture cold (below 8°C the 80% sulfuric acid reaction mixtures will begin to freeze) and by minimizing the time between the addition of the substrate and of the chloramine to the aqueous sulfuric acid.

TABLE I
YIELD AND PRODUCT DISTRIBUTIONS FROM THE CHLORINATION OR AROMATIC COMPOUNDS IN TRIFLUOROACETIC ACID[a]

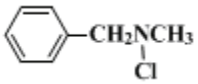
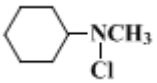
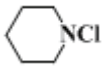
Substrate	Chlorinating Agent	Yield[b] (%)	Product	Product Distribution (%)
C_6H_5OMe	NCP[c]	97	2-Chloromethoxybenzene	1
			4-Chloromethoxybenzene	99
C_6H_5OH	NCP	98	2-Chlorophenol	3
			4-Chlorophenol	97
	NCP	84	6-Chloro-2-methylphenol	1.5
			4-Chloro-2-methylphenol	98.5
	NCTA[d]	80	4-Chloro-1,2-dimethoxybenzene	100
	NCP	89	4-Chloro-3-Methylphenol	98
			4,6-Dichloro-3-methylphenol	2
	NCP	79	4-Chloro-1,3-dimethoxybenzene	91

			4,6-Dichloro-1,3-dimethoxybenzene	9
	NCP	85	4-Chloro-3-methylmethoxybenzene	100
	NCTA[e]	95	4-Chloro-3,5-dimethylphenol	96
			2,4-Dichloro-3,5-dimethylphenol	4

[a]Equimolar quantities of substrate and *N*-chloro compound
[b]Yield of products isolated from reaction, based on *N*-chloro compound
[c]NCP = *N*-chloropiperidine
[d]NCTA = *N*-chlorotriethylammonium chloride.[8]
[e]Twofold excess of substrate, reaction temperature −17°C

The structure of the *N*-chlorodialkylamine markedly affects its reactivity and to a lesser extent its selectivity (Table II). Thus with 2-chloromethoxybenzene as substrate, *N*-chloromorpholine is approximately 17,000 times more reactive than *N*-chloropiperidine and yet it is only slightly less selective for *para*-chlorination of methoxybenzene. For most substrates the shorter reaction times (less chance of other side reactions) of the more reactive *N*-chloroamines more than compensates for any small decrease in selectivity.

TABLE II
RELATIVE REACTIVITY AND SELECTIVITY OF *N*-CHLORINATED AMINES IN TRIFLUOROACETIC ACID

N-Chloro Compound	Reactivity Relative to NCP[a]	Ratio of 4- to 2-Chlorination[b]
	160,000	6.0
	17,000	20
	200	48
	9	66
	1	99
	0.2	500

[a]Determined from chlorination of 2-chloromethoxybenzene. NCP = *N*-chloropiperidine
[b]From the chlorination of methoxybenzene

References and Notes

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

petroleum ether

2,6-dichloro- and 2,4,6-trichloromethoxybenzene

93% of 4-chloro- and 7% of 2-chlorophenol

95% of 4-chloro- and 5% of 6-chloro-2-methylphenol

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

methoxybenzene (100-66-3)

iodine (7553-56-2)

chlorine (7782-50-5)

hypochlorous acid (7790-92-3)

2-methylphenol (95-48-7)

sodium hypochlorite (7681-52-9)

chloro

magnesium sulfate (7487-88-9)

2-chlorophenol (95-57-8)

iodide (20461-54-5)

chloramine,
N-chloramine (10599-90-3)

morpholine (110-91-8)

trifluoroacetic acid (76-05-1)

2-chloromethoxybenzene,
4-Chloromethoxybenzene

4-Chlorophenol (106-48-9)

N-Chloropiperidine (2156-71-0)

2,4-Dichloromethoxybenzene,
Benzene, 2,4-dichloro-1-methoxy- (553-82-2)

2,6-dichloromethoxybenzene (1984-65-2)

2,4,6-trichloromethoxybenzene (87-40-1)

6-chloro-2-methylphenol (87-64-9)

4-Chloro-2-methylphenol (1570-64-5)

4-Chloro-1,2-dimethoxybenzene (16766-27-1)

4-Chloro-3-Methylphenol (59-50-7)

4,6-Dichloro-3-methylphenol (1124-07-8)

4-Chloro-1,3-dimethoxybenzene (7051-13-0)

4,6-Dichloro-1,3-dimethoxybenzene

4-Chloro-3-methylmethoxybenzene (3260-85-3)

4-Chloro-3,5-dimethylphenol (88-04-0)

2,4-Dichloro-3,5-dimethylphenol (133-53-9)

N-Chloromorpholine (23328-69-0)

N-chlorotriethylammonium chloride

morpholine hydrochloride