A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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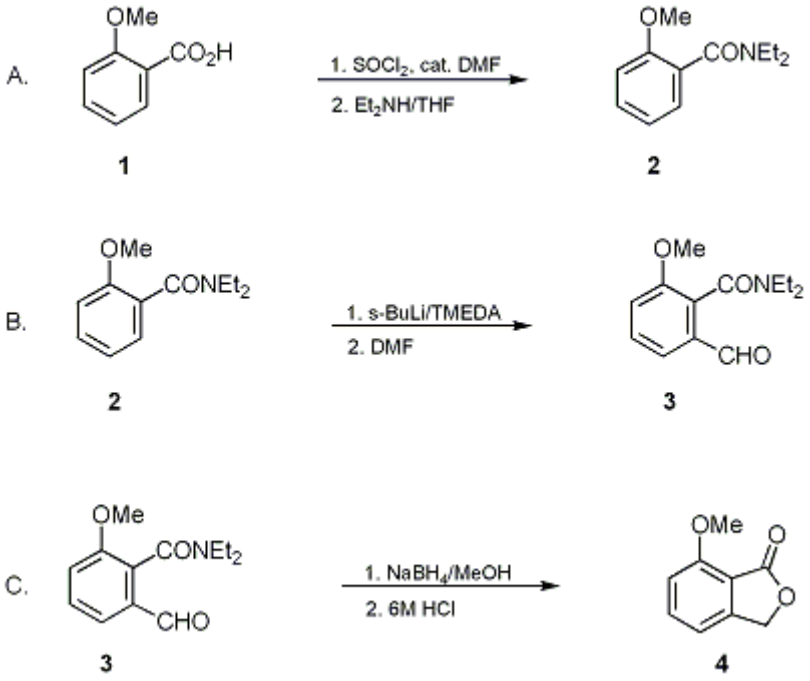
7-METHOXYPHTHALIDE

[1(3H)-Isobenzofuranone, 7-methoxy-]



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Checked by Chris Limberakis and Stephen F. Martin.

1. Procedure

A. *N,N-Diethyl-2-methoxybenzamide* **(2)**. An oven-dried, two-necked, 500-mL flask equipped with a septum cap, nitrogen bubbler, and magnetic stirrer is charged with 2-methoxybenzoic acid (20 g, 0.13 mol) (Note 1) under nitrogen. Thionyl chloride (135 mL, 220 g, 1.85 mol) (Note 2) is added with stirring, resulting in slow effervescence. Dimethylformamide (DMF, 0.34 mL, 320 mg, 4.4 mmol) (Note 3),(Note 4) is added dropwise via syringe after which effervescence becomes much more vigorous *(CAUTION: Sulfur dioxide and hydrogen chloride are evolved)*. The solution is stirred for 0.5 hr, at which time no further effervescence is visible. Half of the thionyl chloride is removed under reduced pressure on a rotary evaporator, toluene (100 mL) is added, and the mixture is evaporated to dryness. A further 100 mL of toluene is added and the process of evaporation is repeated twice more to ensure complete removal of all excess thionyl chloride (Note 5). The colorless oil is dissolved in dry tetrahydrofuran (THF, 150 mL) (Note 6), the resulting solution is cooled in an ice water bath, and treated slowly with diethylamine (50 mL, 35.3 g, 0.48 mol) (Note 7), with stirring to prevent the reaction from becoming too vigorous. A copious white precipitate forms.

When all the diethylamine has been added the mixture is stirred for a further 10 min and then concentrated under reduced pressure. The residue is dissolved in methylene chloride (200 mL), washed with water (2 × 200 mL) and saturated brine (2 × 50 mL), and concentrated under reduced pressure to give an orange oil. The oil is distilled at reduced pressure to give 23.5–24.5 g (86–90%) of N,N-diethyl-2-methoxybenzamide (118–120°C/0.1 mm) as a straw-colored liquid.

B. *N,N-Diethyl-2-formyl-6-methoxybenzamide* **(3)**. An oven-dried, three-necked, 1-L flask equipped with a 100-mL, pressure-equalizing, dropping funnel, nitrogen bubbler, internal low temperature thermometer pocket, and overhead stirrer is flamed under reduced pressure and allowed to cool under a

stream of nitrogen. The flask is charged with 500 mL of THF (Note 6) and cooled to an internal temperature of −72°C. N,N,N',N'-Tetramethylethylenediamine (TMEDA) (Note 8) (23.5 mL, 0.156 mol) followed by 128.7 mL (0.157 mmol) of 1.22 M sec-butyllithium in cyclohexane (Note 9) are then added. The internal temperature rises a little as the reagents are added. The fluorescent yellow solution is allowed to recool to an internal temperature of −73°C. N,N-Diethyl-2-methoxybenzamide **(2)** 24.9 g (0.121 mmol) is dissolved in 100 mL of THF and added dropwise via the dropping funnel, while the internal temperature is maintained below −68°C. The solution is stirred for 1 hr during which time the color changes from fluorescent yellow to yellow with a white precipitate. Dimethylformamide (DMF, 11.2 mL) is added via the dropping funnel, and the cooling bath is removed after 2 min. The solution is allowed to warm to room temperature over 16 hr after which time the solution is yellow. The reaction mixture is concentrated under reduced pressure to 150 mL, and the residue is cooled to 0°C and made acidic (pH 4–5) by the addition of 90 mL of 6 M aqueous hydrochloric acid. The solution is extracted with ethyl acetate (5 × 100 mL) (Note 10), the combined organic layers are washed with water (100 mL) and brine (2 × 200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual, yellow oil is dried overnight under reduced pressure to give 26.9 g of crude product [2](Note 11).

C. *7-Methoxyphthalide* **(4)**. The crude product from Step B (26.9 g), in a 1-L, one-necked, round-bottomed flask with a magnetic stirring bar, is dissolved in 465 mL of absolute methanol (Note 12). To this solution, cooled to 0°C, is added 7.4 g (0.20 mol) of powdered sodium borohydride, in small portions (Note 13), and the mixture is stirred at room temperature for 18 hr. The reaction mixture is cooled in an ice water bath and taken to pH 4–5 with about 35 mL of 6 M aqueous hydrochloric acid. A further 48 mL (0.288 mol) of 6 M hydrochloric acid is added, the flask is fitted with a reflux condenser and the reaction mixture is heated under reflux for 12 hr. The reaction mixture is then allowed to cool to room temperature and most of the methanol is evaporated under aspirator pressure. The residue is dissolved in 400 mL of methylene chloride, the phases are separated, and the organic fraction is washed with saturated ammonium chloride (3 × 200 mL) and water (1 × 100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The pale yellow solid is recrystallized from ethyl acetate-hexane (1:1) (Note 10) to give 15.4 g (81% overall from **2**) of 7-methoxyphthalide, mp 106–108°C, lit[3] mp 107–109°C (Note 14).

2. Notes

1. 2-Methoxybenzoic acid, purchased from Lancaster Synthesis Ltd., was used as received.
2. Thionyl chloride, purchased from J.T.Baker Ltd., was used as received.
3. Dimethylformamide was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen.
4. The use of DMF to accelerate the formation of acid chlorides from carboxylic acids has been reviewed previously,[4] and is believed to occur via an imidoyl chloride intermediate.[5]
5. The removal of excess thionyl chloride by formation of an azeotrope with benzene was used in a previous *Organic Syntheses* procedure;[6] however, toluene is much less toxic than benzene and is therefore recommended.
6. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
7. The use of acid chlorides in the preparation of amides has been reviewed.[7] The diethylamine was distilled from calcium hydride prior to use.
8. N,N,N',N'-Tetramethylethylenediamine was distilled from calcium hydride and stored under nitrogen.
9. sec-Butyllithium purchased from Aldrich Chemical Company, Inc., was standardized by titration using 2,5-dimethoxybenzyl alcohol as indicator.[8]
10. Reagent grade ethyl acetate, methylene chloride, and hexane purchased from British Drug House, Inc., were distilled before use.
11. N,N-Diethyl-2-formyl-6-methoxybenzamide may be purified by silica gel (mesh 230-400) column chromatography using ethyl acetate-hexane (1:1) eluent. The compound shows the following physical and spectral data: bp 134–136°C (0.05 mm); IR ($CHCl_3$) ν (max) cm^{-1}: 1705, 1620 ; ^1H NMR ($CDCl_3$) δ: 1.01 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.11 (q, 2 H, J = 7.2), 3.49–3.61 (m, 1 H), 3.67–3.82 (m, 1 H), 3.86 (s, 3 H), 7.16 (dd, 1 H, J = 1.3, 7.8), 7.43–7.55 (m, 2 H), 9.99 (s, 1 H); MS, m/z (rel intensity) 235 (M^+, 5), 206 (100); Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 67.44; H,

7.69; N, 5.75.
12. Absolute methanol, purchased from British Drug House, Inc., was used as received.
13. Sodium borohydride, purchased from Aldrich Chemical Company, Inc., was used as received.
14. 7-Methoxyphthalide shows the following spectral data : IR ($CHCl_3$) ν (max) cm^{-1}: 1755; ^1H NMR ($CDCl_3$) δ: 4.01 (s, 3 H), 5.23 (s, 2 H), 6.95 (d, 1 H, J = 8.2), 7.01 (d, 1 H, J = 8.2), 7.65 (t, 1 H, J = 8.2).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

7-Methoxyphthalide has also been prepared by nonregioselective bromination of substituted benzenes,[9] by L-Selectride reduction[10,11] of 3-methoxyphthalic anhydride,[12,13] by metalation of 3-methoxybenzyl alcohol[14,15] and its chromium tricarbonyl complex,[15,16] by metalation of N,N-dimethyl-3-methoxybenzylamine,[17,18] and by Diels-Alder reaction of methoxycyclohexadiene with propargylic esters.[19] The isomeric 4-methoxyphthalide, that is also available by the present method,[2] has been prepared by methods that, in part, overlap those used for the synthesis of 7-methoxyphthalide: by bromination of o-toluic acids and o-xylenes,[9,19,20] by metal hydride reduction[21] of 3-methoxyphthalic anhydride, and by metalation of 3-methoxyphenyloxazoline.[22] Some of these methods[19,23,24] as well as others, have been used for the preparation of a variety of other methoxy-substituted phthalides.

The directed ortho metalation reaction has been widely applied for the preparation of phthalides.[25,26,27] Since it lends itself well to the regiospecific construction of contiguously substituted aromatic compounds, the approach via metalation of N,N-diethylbenzamides has been particularly extensively adapted.[28,29] The present procedure uses a readily available and inexpensive starting benzoic acid, proceeds in reproducible, high yields, does not require chromatographic separation, and furnishes usually crystalline phthalide products in high purity. A comparison of yields shows that 7-methoxyphthalide has been obtained by metalation of 3-methoxybenzyl alcohol (78%),[14] Diels-Alder reaction of methoxycyclohexadiene with a propargylic ester (55%),[19] and reduction of 3-methoxyphthalic anhydride (quantitative).[10] The latter two methods are lengthy and require a several stage synthesis of precursors. The metalation method complements the present procedure, but has not been optimized. Based on the reported preparation of 4-methoxyphthalide,[22] the synthesis of 7-methoxyphthalide via metalation of 2-methoxyphenyloxazoline would undoubtedly be successfully achieved, but would require the more expensive oxazoline.

Phthalides constitute a relatively minor class of natural products.[25,30] However, their value as synthetic intermediates is shown by an extensive list of applications. The use of phthalides derived from metalation of N,N-diethylbenzamides in the synthesis of anthraquinones, anthracyclones, isocoumarins, fluorenones, phenanthrenes, several classes of alkaloids, and polycyclic aromatic hydrocarbons has been summarized.[27] Phthalides derived by other methods have served as intermediates in the construction of anthraquinones,[15,20,31,32,33] benzophenones,[34] cervicarcin,[35] dibenzofurans,[36,37] lignans,[22] naphthalenes and naphthoquinones,[15,24,38,39,40,41] and polyketides.[14,42,43]

References and Notes

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

benzophenone ketyl

brine

imidoyl chloride

o-toluic acids

o-xylenes

N,N-diethylbenzamides

anthraquinones

anthracyclones

isocoumarins

fluorenones

phenanthrenes

benzophenones

cervicarcin

dibenzofurans

naphthalenes

naphthoquinones

hydrogen chloride,
hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

cyclohexane (110-82-7)

toluene (108-88-3)

sodium (13966-32-0)

diethylamine (109-89-7)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

oxazoline

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

ethyl acetate-hexane (2639-63-6)

sec-butyllithium (598-30-1)

methoxycyclohexadiene

chromium tricarbonyl

2,5-dimethoxybenzyl alcohol (33524-31-1)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

7-Methoxyphthalide,
1(3H)-Isobenzofuranone, 7-methoxy- (28281-58-5)

N,N-Diethyl-2-methoxybenzamide (51674-10-3)

2-methoxybenzoic acid (579-75-9)

N,N-Diethyl-2-formyl-6-methoxybenzamide (70946-17-7)

4-methoxyphthalide

3-methoxyphthalic anhydride

3-methoxybenzyl alcohol (6971-51-3)

2-methoxyphenyloxazoline

N,N-dimethyl-3-methoxybenzylamine (15184-99-3)

3-methoxyphenyloxazoline