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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

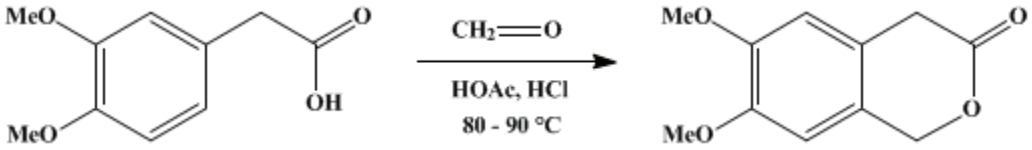
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.055.0045

Organic Syntheses, Coll. Vol. 6, p.471 (1988); Vol. 55, p.45 (1976).

6,7-DIMETHOXY-3-ISOCHROMANONE

[3*H*-2-Benzopyran-3-one, 1,4-dihydro-6,7-dimethoxy-]



Submitted by J. Finkelstein[1] and A. Brossi[1,2].
Checked by Yoshinori Hamada and Wataru Nagata.

1. Procedure

A 500-ml., round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, and a reflux condenser is charged with 49.0 g. (0.250 mole) of 3,4-dimethoxyphenylacetic acid (Note 1) and 125 ml. of acetic acid. The solution is stirred and heated at 80° on a steam bath, while 40 ml. of concentrated hydrochloric acid is added rapidly and followed immediately with 40 ml. of formalin (37% formaldehyde, by weight, in water) (Note 2) and (Note 3). The yellow solution is stirred and heated on a steam bath for 1 hour, during which time the reaction temperature reaches 90° (Note 4) and the solution assumes a dark-brown color. After cooling to room temperature the solution is poured, with stirring, into a mixture of 650 g. of chipped ice and 650 ml. of cold water. The mixture is transferred to a 2-l. separatory funnel, and the organic material is extracted with four 300-ml. portions of chloroform (Note 5). The combined chloroform extracts are washed with 250-ml. portions of aqueous 5% sodium hydrogen carbonate until neutral (Note 6), then with two, 250-ml. portions of water, and finally dried over anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator with a water bath up to a temperature of 55° (Note 7), yielding 43.5–44.2 g. (83.7–85.1%) of crude 6,7-dimethoxy-3-isochromanone, m.p. 95–100°, as a yellow solid suitable for general synthetic purposes. A purer product is obtained by recrystallization from 55 ml. of ethanol (Note 8),(Note 9),(Note 10), giving 26–27.6 g. of white crystals which, after drying at 80°, melt at 106–108° (Note 11). Upon concentration of the mother liquor to a smaller volume, an additional 1.7–3.2 g. of the isochromanone, m.p. 103–105°, is obtained. The total yield is 29.2–29.3 g. (56.2–56.4%).

2. Notes

1. The 3,4-dimethoxyphenylacetic acid was purchased from Matheson, Coleman and Bell. The checkers prepared material of m.p. 97–98° according to the procedure described in *Org. Synth.*, **Coll. Vol. 2**, 333 (1961).
2. "Baker Analyzed" reagent grade formaldehyde solution obtained from J. T. Baker Chemical Company was used. The checkers used material purchased from Wako Pure Chemical Industries, Ltd., Japan.
3. About 30 seconds each is needed for the additions of concentrated hydrochloric acid and formalin.
4. The temperature of the reaction mixture falls to 68° on addition of the reagents but rises again within 10 minutes.
5. Fisher Scientific Company Certified A.C.S. chloroform was used. The checkers used reagent grade chloroform purchased from Wako Pure Chemical Industries, Ltd., Japan.
6. The wash solution should be neutral to litmus. The checkers observed that the pH values of the first and the second wash solutions were 5–5.5 and 7.5, respectively.
7. The viscous, syrupy residue crystallizes on standing at room temperature or by addition of a small amount of methanol.
8. Anhydrous ethanol (Type 2B) was used.
9. Recrystallization can conveniently be performed with the initial syrupy residue.
10. The checkers found that a mixture of dichloromethane and ether was a more suitable solvent for crystallization of the product. The pure sample obtained from this solvent system melts at 108–109°.

11. The product has the following spectral properties; IR ($CHCl_3$) cm.$^{-1}$: 3040, 1750, 1616, 1520, 1253, and 1118; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.63 (s, 2H, CH_2CO_2), 3.88 (s, 6H, $2OCH_3$), 5.25 (s, 2H, CH_2OCO), 6.72 (s, 1H, aromatic *H*), 6.77 (s, 1H, aromatic *H*).

3. Discussion

The reaction is essentially that described by the submitters.[3] The procedure illustrates a convenient method for the synthesis of a type of lactone which could serve as an important intermediate in the synthesis of isoquinolones, tetrahydroisoquinolines, and isoquinoline alkaloids. Several analogous and closely related lactones have been reported.

The parent, unsubstituted isochromanone reacts with a variety of aromatic amines, giving *N*-substituted 1,4-dihydro-3(2*H*)-isoquinolones,[4] and with amines, giving amides.[5] 6,7-Methylenedioxy-3-isochromanone was used as an intermediate in the synthesis of protopine and its allied alkaloids,[6] and in the synthesis of the berberine ring system.[7] The 6-methoxy analog was prepared as a potential intermediate in a camptothecin synthesis[8] and 8-methoxy-4,5,6,7-tetramethyl-3-isochromanone was used as an intermediate in the synthesis of sclerin.[9]

The compound described herein was the basis of a facile synthesis of (±)-xylopinins,[10] and its reaction with hydrazine has been reported.[11] The compound was also used in the synthesis of pseudoberberine,[12] and when reacted with 1-methyltryptamine, 1-methyl-15,16,17,18,19,20-hexahydroyohimban was obtained.[13] When isochroman-3-ones are treated with tryptamine, the synthesis of the yohimban skeleton is achieved.[14] The preparation of α-methyldopa in a rigid framework is described.[15]

The procedure may have considerable scope, as shown by the synthesis of a heterocyclic lactone, an important intermediate in the synthesis of *d,l*-desoxycamptothecin, which on oxidation gave camptothecin.[16] A new synthesis of benzocyclobutenes by the thermal and electron impact-induced decomposition of 3-isochromanones was described.[17]

3-Isochromanone was allowed to react with phenol ethers in polyphosphoric acid, yielding dibenzo [*a,d*] tropylium salts, but in formic acid homoveratric acids were obtained.[18]

The nonaromatic lactones derived from *cis*-[19] and *trans*-2-hydroxymethylcyclohexaneacetic acid[20] are important intermediates in the synthesis of indole alkaloids.

References and Notes

1. Chemical Research Department, Hoffmann-LaRoche, Inc., Nutley, New Jersey 07666.
2. Present address: Section on Medicinal Chemistry, U.S. Public Health Service, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.
3. J. Finkelstein and A. Brossi, *J. Heterocycl. Chem.*, **4**, 315 (1967).
4. Y. Shoo, E. C. Taylor, K. Mislow, and M. Rabian, *J. Am. Chem. Soc.*, **89**, 4910 (1967).
5. G. A. Swan, *J. Chem. Soc.*, 1720 (1949).
6. T. S. Stevens, *J. Chem. Soc.*, 178 (1927).
7. T. S. Stevens, *J. Chem. Soc.*, 663 (1935).
8. T. A. Bryson, *Abstr. Pap., Div. Org. Chem., Am. Chem. Soc., 164th Nat. Meet.*, New York, Aug. 27–Sept. 1, 1972, No. 136.
9. T. Kubota, T. Tokoroyama, T. Nishikawa, and S. Maeda, *Tetrahedron Lett.*, 745 (1967).
10. W. Meise and F. Zymalkowski, *Tetrahedron Lett.*, 1475 (1969).
11. G. Rosen and F. D. Popp, *Can. J. Chem.*, **47**, 864 (1969).
12. F. Shinada and T. Kono, Japan. Pat. Kokai 74 96,000 [*Chem. Abstr.*, **82**, P57993y (1975)].
13. W. Meise and H. Pfister, *Arch. Pharm.*, **310**, 495 (1977).
14. W. Meise and H. Pfister, *Arch. Pharm.*, **310**, 501 (1977).
15. S. N. Rostogi, J. S. Bindra, and N. Anand, *Indian J. Chem.*, **9**, 1175 (1971).
16. R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Am. Chem. Soc.*, **93**, 5576

(1971); S. Danishefsky, S. J. Etheredge, R. Volkmann, J. Eggler, and J. Quick, *J. Am. Chem. Soc.*, **93**, 5575 (1971).
17. R. J. Spangler, B. G. Beckmann, and J. H. Kim, *J. Org. Chem.*, **42**, 2989 (1977).
18. A. V. Bicherov, G. N. Dorofeenko, and E. V. Kuznetsov, *Zh. Org. Khim.*, **15**, 588 (1979).
19. G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **76**, 949 (1954).
20. E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, **76**, 950 (1954).

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

d,l-desoxycamptothecin

camptothecin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

formaldehyde,
formalin (50-00-0)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

formic acid (64-18-6)

hydrazine (302-01-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

3,4-dimethoxyphenylacetic acid (93-40-3)

6,7-Dimethoxy-3-isochromanone,
3H-2-Benzopyran-3-one, 1,4-dihydro-6,7-dimethoxy- (16135-41-4)

6,7-Methylenedioxy-3-isochromanone

8-methoxy-4,5,6,7-tetramethyl-3-isochromanone

1-methyltryptamine

1-methyl-15,16,17,18,19,20-hexahydroyohimban

tryptamine (61-54-1)

3-Isochromanone (4385-35-7)

trans-2-hydroxymethylcyclohexaneacetic acid