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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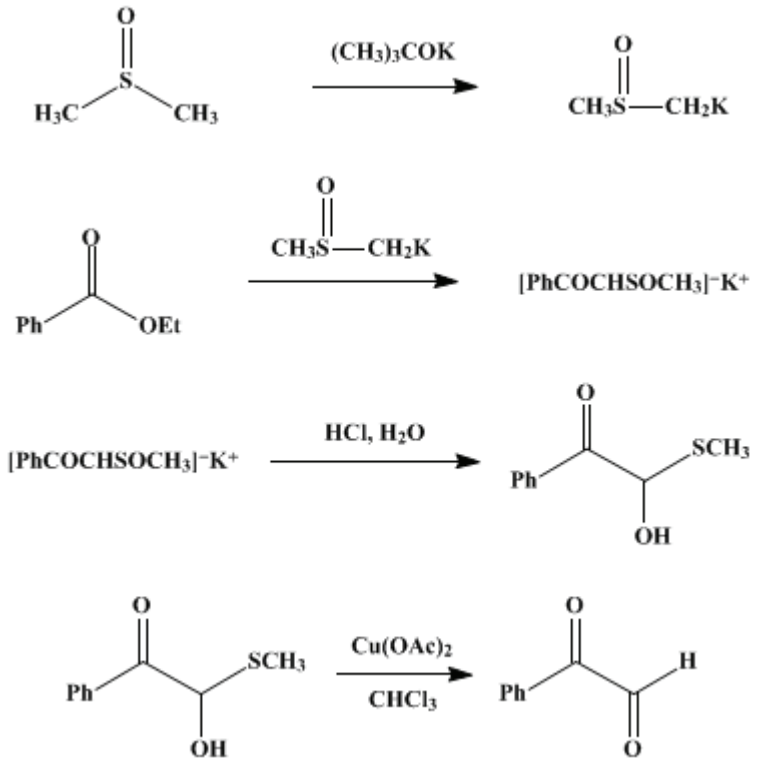
PHENYLGLYOXAL

[Glyoxal, phenyl-]



Submitted by Gerard J. Mikol and Glen A. Russell[1].
Checked by William G. Dauben, Michael H. McGann, and Noel Vietmeyer.

1. Procedure

A. *Phenylglyoxal hemimercaptal*. In a 1-l. three-necked flask equipped with an all-glass mechanical stirrer, a 125-ml. dropping funnel, and a condenser fitted with a nitrogen-inlet tube are placed 90 ml. (99 g., 1.27 moles) of dry dimethyl sulfoxide (Note 1), 120 ml. of dry *t*-butyl alchohol (Note 1), and 57.4 g. (0.51 mole) of potassium *t*-butoxide (Note 2) and (Note 3). The mixture is warmed to 80°; when all the solid has dissolved, the heating is discontinued, and 72 ml. (75 g., 0.50 mole) of dry ethyl benzoate (Note 1) is added slowly from the dropping funnel. The reaction mixture is stirred at room temperature for 4 hours, and the solvent is removed at 80–90° under reduced pressure until the volume of the reaction mixture has been reduced to 150 ml. (Note 4). The residue is poured into 500 ml. of an ice-water slurry. The resulting aqueous solution is extracted with three 100-ml. portions of ether, and the ethereal extracts are discarded (Note 5). The aqueous solution is acidified with a solution of 190 ml. of concentrated hydrochloric acid in 675 ml. of water, and the mixture is allowed to stand at room temperature for 30 hours. The pale yellow precipitate is removed by suction filtration, washed with 500 ml. of cold water, and air-dried to yield 69–74 g. (76–81%) of phenylglyoxal hemimercaptal, m.p. 103–105°.

B. *Phenylglyoxal*. The phenylglyoxal hemimercaptal prepared as described in procedure A (69–74 g.) is dissolved in 400 ml. of warm chloroform, and 60 g. (0.30 mole) of powdered cupric acetate monohydrate is added in one portion to the well-stirred solution. The mixture is stirred at room temperature for 1 hour; the solids are removed by suction filtration and washed with two 75-ml. portions of chloroform. The combined chloroform filtrate and washings are shaken in a separatory funnel with 75 ml. of water; 20 g. of powdered sodium carbonate is added in small portions to the funnel, and the

chloroform solution is shaken with the neutralized aqueous solution. *(Caution! Carbon dioxide is evolved.)* The aqueous layer is separated and extracted with four 30-ml. portion of chloroform. The chloroform solutions are combined and dried with anhydrous magnesium sulfate, and the chloroform is removed under reduced pressure. The residue is fractionally distilled under reduced pressure to yield 43–49 g. (64–73%, based on ethyl benzoate) of anhydrous phenylglyoxal as a yellow liquid, b.p. 63–65° (0.5 mm.).

2. Notes

1. The presence of water results in very rapid saponification of ethyl benzoate. Dimethyl sulfoxide (Crown Zellerbach Corp.) may be dried by stirring with calcium hydride for 4–8 hours, followed by distillation under reduced pressure at 80–90° without filtration. Commercial *t*-butyl alcohol and ethyl benzoate are conveniently dried by stirring for 2–4 hours with calcium hydride followed by filtration.
2. Potassium *t*-butoxide was obtained from Mine Safety Appliances Corp.
3. The potassium salt of dimethyl sulfoxide can also be prepared in the following manner. In a 1-l. three-necked flask equipped with an all-glass mechanical stirrer, a 125-ml. dropping funnel containing 90 ml. of dry dimethyl sulfoxide (Note 1), and a Claisen distillation head and condenser is placed 425 ml. of dry *t*-butyl alcohol (Note 1). The system is flushed with dry nitrogen, and 20 g. (0.51 g. atom) of potassium is added (Note 6). The system is closed to the atmosphere by a mineral oil bubbler through which the evolved hydrogen escapes. The mixture is stirred at 80° until the potassium has dissolved. After cooling, the unreacted alcohol is removed by distillation under reduced pressure until a thick slurry of potassium *t*-butoxide remains (Note 7). The dimethyl sulfoxide is added from the dropping funnel, and the mixture is heated to 80–90° to dissolve all the solid. The solution is maintained at this temperature, and additional *t*-butyl alcohol is removed under reduced pressure until the volume of the solution is reduced to 300 ml.
4. Since the volume of the solution at this point is critical, the reaction flask should be calibrated.
5. The aqueous solution can be used to prepare 2-(methylsulfinyl)acetophenone by the following procedure. The solution is acidified to pH 1–2 (Hydrion paper) by the slow addition of concentrated hydrochloric acid with vigorous stirring and is extracted immediately with two 100-ml. portions of chloroform. The chloroform extracts are combined, washed with 75 ml. of saturated aqueous sodium carbonate and two 75-ml. portions of water, and dried over anhydrous magnesium sulfate. The chloroform is removed under reduced pressure, and the resulting solid is pulverized, slurried with 100 ml. of ether, collected by filtration, and air-dried. The 2-(methylsulfinyl)acetophenone weighs 75–77 g. (82–85%); m.p. 85–86°. It can be converted to phenylglyoxal hemimercaptal by treatment with dilute hydrochloric acid in dimethyl sulfoxide solution at room temperature (2 ml. of dimethyl sulfoxide, 2 ml. of concentrated hydrochloric acid, and 15 ml. of water per gram of the keto sulfoxide). The solution is allowed to stand at room temperature for 30 hours, after which the phenylglyoxal hemimercaptal can be isolated as described in procedure A.
6. The potassium should be free of oxide and/or hydroxide to avoid subsequent saponification of ethyl benzoate.
7. A heating mantle may be used, but care must be taken to avoid decomposition on the walls of the flask due to overheating during the later stages of the distillation.

3. Discussion

Phenylglyoxal has been prepared from isonitrosoacetophenone via the bisulfite compound[2] and by treatment with nitrosyl sulfuric acid[3] or nitrous acid.[4] It has also been prepared by oxidation of benzoylcarbinol with cupric acetate,[5] by heating or aqueous hydrolysis of 2-acetoxy-2-bromoacetophenone,[6] by selenium dioxide oxidation of acetophenone,[7] by oxidation of phenacyl bromide with dimethyl sulfoxide,[8] by oxidative bromination of phenylglyoxal diethyl mercaptal,[9] and by treatment of 2,2-dibromoacetophenone with morpholine followed by acidic hydrolysis.[10] Excellent yields of phenylglyoxal hemihydrate can be obtained on a small scale by the hydrolysis of phenylglyoxal hemimercaptal with boiling dilute hydrochloric acid[11] or in one step from 2-(methylsulfinyl) acetophenone by hydrolysis with boiling 8% phosphoric acid.

4. Merits of the Preparation

This procedure provides a convenient synthesis of phenylglyoxal from readily available starting materials. In addition the method described appears to have general utility for the synthesis of glyoxals. It has been used for the synthesis of *p*-tolylglyoxal, *p*-methoxyphenylglyoxal, *p*-bromophenylglyoxal, and cyclohexylglyoxal. Since β-keto sulfoxides are readily alkylated in basic solution to yield α-alkyl β-keto sulfoxides,[12] it would appear possible to extend the scope of the reaction to yield a variety of α-diketones.

References and Notes

1. Department of Chemistry, Iowa State University, Ames, Iowa 50010.
2. H. von Pechmann, *Ber.*, **20**, 2904 (1887); H. Müller and H. von Pechmann, *Ber.*, **22**, 2556 (1889); A. Pinner, *Ber.*, **35**, 4131 (1902); **38**, 1531 (1905); I. Smedley, *J. Chem. Soc.*, **95**, 218 (1909).
3. C. Neuberg and E. Hofmann, *Biochem. Z.*, **229**, 443 (1930).
4. C. Neuberg and E. Hofmann, *Biochem. Z.*, **239**, 495 (1931); S. Cusmano, *Gazz. Chim. Ital.*, **68**, 129 (1938).
5. J. U. Nef, *Ann.*, **335**, 269 (1904); M. Henze, *Z. Physiol. Chem.*, **198**, 82 (1931); **200**, 232 (1931).
6. W. Madelung and M. E. Oberwegner, *Ber.*, **65**, 931 (1932).
7. H. L. Riley, J. F. Morely, and N. A. C. Friend, *J. Chem. Soc.*, 1875 (1932); H. L. Riley, Brit. Patent 354,798 (1930) [*C.A.*, **26**, 3804 (1932)]; U.S. Patent 1,955,890 (1934) [*C.A.*, **28**, 4067 (1934)]; H. A. Riley and A. R. Gray, *Org. Syntheses*, Coll. Vol., **2**, 509 (1943); R. Bousset, *Bull, Soc. Chim. France*, [5] **6**, 986 (1939).
8. N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
9. F. Weygand and H. J. Bestmann, *Ber.*, **90**, 1230 (1957).
10. M. Kerfanto, *Compt. Rend*, **254**, 493 (1962).
11. H.-D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).
12. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **86**, 1639 (1964); **87**, 1345 (1965).

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

Phenylglyoxal hemimercaptal

t-butyl alchohol

potassium salt of dimethyl sulfoxide

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

nitrous acid (7782-77-6)

carbon dioxide (124-38-9)

Acetophenone (98-86-2)

selenium dioxide (7446-08-4)

phosphoric acid (7664-38-2)

Phenylglyoxal,
Glyoxal, phenyl- (1074-12-0)

potassium (7440-09-7)

cupric acetate (142-71-2)

ethyl benzoate (93-89-0)

nitrosyl sulfuric acid (7782-78-7)

magnesium sulfate (7487-88-9)

Phenacyl bromide (70-11-1)

isonitrosoacetophenone

benzoylcarbinol (582-24-1)

2-acetoxy-2-bromoacetophenone

cupric acetate monohydrate (6046-93-1)

morpholine (110-91-8)

2,2-dibromoacetophenone

dimethyl sulfoxide (67-68-5)

t-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

2-(methylsulfinyl)acetophenone,
2-(methylsulfinyl) acetophenone (26524-93-6)

phenylglyoxal diethyl mercaptal

cyclohexylglyoxal

potassium t-butoxide (865-47-4)

p-tolylglyoxal

p-methoxyphenylglyoxal

p-bromophenylglyoxal