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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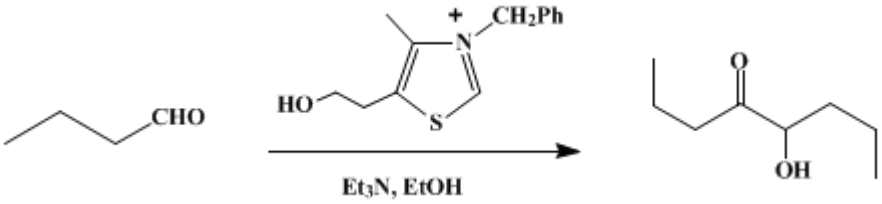
ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN

[4-Octanone, 5-hydroxy-]



Submitted by H. Stetter and H. Kuhlmann[1].
Checked by Sharbil J. Firsan and Robert M. Coates.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube. The flask is charged with 13.4 g (0.05 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 72.1 g (1.0 mol) of butyraldehyde (Note 2), 30.3 g (0.3 mol) of triethylamine (Note 2), and 300 mL of absolute ethanol. A slow stream of nitrogen (Note 3) is begun, and the mixture is stirred and heated in an oil bath at 80°C. After 1.5 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. The residual yellow liquid is poured into 500 mL of water contained in a separatory funnel, and the flask is rinsed with 150 mL of dichloromethane which is then used to extract the aqueous mixture. The aqueous layer is extracted with a second 150-mL portion of dichloromethane. The combined organic phases are washed with 300 mL of saturated sodium bicarbonate and with 300 mL of water. The dichloromethane is removed by rotary evaporation under slightly diminished pressure. Distillation through a 20-cm Vigreux column gives 51–54 g (71–74%) of product as a colorless to light-yellow liquid, n_D^{20} 1.4309, bp 90–92°C (13–14 mm) (Note 4) and (Note 5).

2. Notes

1. The catalyst, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, is supplied by Fluka AG, Buchs, Switzerland, and by Tridom Chemical, Inc., Hauppauge, New York. The thiazolium salt may also be prepared as described below[2] [3] by benzylation of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, which is commercially available from E. Merck, Darmstadt, West Germany, and Columbia Organic Chemicals Co., Inc., Columbia, SC. The acetonitrile used by the checkers was dried over Linde 3A molecular sieves[4] and distilled under nitrogen, bp 77–78°C. The same yield of thiazolium salt was obtained by the checkers when benzyl chloride and acetonitrile from commercial sources were used without purification.

A 250-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a stopper. The flask is charged with 14.3 g (0.1 mol) of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, 12.7 g (0.1 mol) of freshly distilled benzyl chloride, and 50 mL of dry acetonitrile. The mixture is heated at reflux for 24 hr and cooled to room temperature. Crystallization is induced by scratching or seeding. The solid is collected by suction filtration, washed colorless with two 50-mL portions of acetonitrile, and dried partially in the air. Drying is completed under reduced pressure by gentle rotation on a rotary evaporator heated with a water bath at about 90°C. The yield of thiazolium salt, mp 141–143°C, is 18.2–19.6 g (67–73%).

2. Butyraldehyde is supplied by Aldrich Chemical Co., Inc. and Eastman Organic Chemicals. The aldehyde was freshly distilled before use. Triethylamine was dried over potassium hydroxide pellets and distilled.

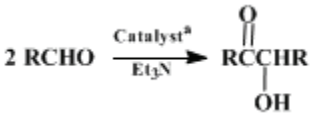
3. The submitters recommend that the nitrogen stream be passed through a bubbler and that the flow rate be adjusted to ca. one bubble per second. If the nitrogen flow is too fast, some of the butyraldehyde

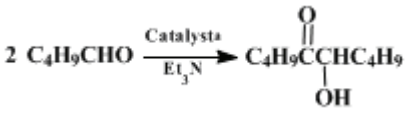
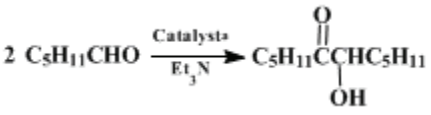
will be swept out of the flask.
4. The procedure may be conducted on a larger scale, in which case the proportion of catalyst and base are reduced. The submitters report that they obtained 169 g (78%) of butyroin from 216.3 g (3.0 mol) of butyraldehyde, 26.8 (0.1 mol) of thiazolium catalyst, 60.6 g (0.6 mol) of triethylamine, and 600 mL of absolute ethanol. Although the scale may be increased further, appropriate precautions should be taken to control the reaction. For example, the aldehyde may be added in portions or the flask may be cooled initially.
5. The product obtained by the checkers boiled at 86–87.5°C (15–16 mm). A boiling point of 85–87°C (12–13 mm) and an index of refraction n_D^{20} 1.4325 have been recorded for butyroin.[5] The product exhibits the following spectral characteristics: IR (neat) cm^{-1}: 3505 and 1704; ^1H NMR (CCl_4) δ: 0.94 (unsymmetrical t, 6 H, 2 CH_3), 1.18–1.56 (m, 4 H, 2 CH_2), 1.64 (sextet, 2 H, J = 7, $CH_2CH_2C{=}O$), 2.41 (t, 2 H, J = 7, $CH_2C{=}O$), 3.31 (s, 1 H, OH), 3.98 (m, 1 H, C*H*OH).

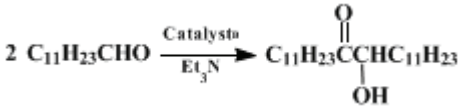
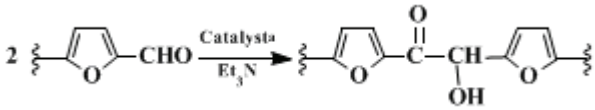
3. Discussion

This procedure is representative of a new general method for the preparation of noncyclic acyloins by thiazolium-catalyzed dimerization of aldehydes in the presence of weak bases (Table I).[6] The advantages of this method over the classical reductive coupling of esters[7] [8] or the modern variation, in which the intermediate enediolate is trapped by silylation,[5,9] are the simplicity of the procedure, the inexpensive materials used, and the purity of the products obtained. For volatile aldehydes such as acetaldehyde and propionaldehyde the reaction is conducted without solvent in a small, heated autoclave. With the exception of furoin the preparation of benzoins from aromatic aldehydes is best carried out with a different thiazolium catalyst bearing an *N*-methyl or *N*-ethyl substituent, instead of the *N*-benzyl group.[6] Benzoins have usually been prepared by cyanide-catalyzed condensation of aromatic and heterocyclic aldehydes.[10,11,12] Unsymmetrical acyloins may be obtained by thiazolium-catalyzed cross-condensation of two different aldehydes.[13] The thiazolium ion-catalyzed cyclization of 1,5-dialdehydes to cyclic acyloins has been reported.[14]

TABLE I
ACYLOINS PREPARED BY THIAZOLIUM ION-CATALYZED CONDENSATION OF ALDEHYDES[6]



R	Yield (%)	Bp or mp (°C)
C_4H_9	 79	83 (2.2 mm)
C_5H_{11}	 81	90 (1.5 mm)
C_7H_{15}		39

		83[b]	
C_9H_{19}			53
		85[b]	
$C_{11}H_{23}$			62
		83[b]	
			136
		80[c,d]	

[a] 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride.

[b] The product was isolated by pouring the ethanolic solution into well-stirred, ice-cold water, filtering, and recrystallizing from aqueous ethanol. The solutions should be ice-cold for the isolation of the low-melting acyloins. The products may also be isolated by extraction as described for butyroin.

[c] In this case furoin crystallized from the ethanolic solution on cooling.

[d] The following somewhat simpler procedure may also be used. A solution of 13.4 g (0.05 mol) of catalyst, 96.1 g (1.0 mol) of 2-furaldehyde, 300 mL of absolute ethanol, and 30.3 g (0.3 mol) of triethylamine is stirred at room temperature for 12 hr. The product (84.5 g, 88%) crystallizes directly from solution and is isolated by filtration.

Although the catalysts of the dimerization of aldehydes to acyloins by thiazolium ion has been known for some time,[15] [16] [17] the development of procedures using anhydrous solvents which give satisfactory yields of acyloins on a preparative scale was first realized in the submitters' laboratories.[6] The mechanism proposed by Breslow[15] for the thiazolium ion-catalyzed reactions is similar to the Lapworth mechanism[18] for the benzoin condensation with a thiazolium ylide replacing the cyanide ion. Similar mechanisms are involved in many important enzyme-catalyzed transformations that require thiamine as a cofactor. The combination of thiazolium salts and weak bases has also been utilized to catalyze the conjugate addition of aldehydes to electron-deficient double bonds.[2,3]

Butyroin has been prepared by reductive condensation of ethyl butyrate with sodium in xylene,[8] or with sodium in the presence of chlorotrimethylsilane,[9] and by reduction of 4,5-octanedione with sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate in the presence of magnesium chloride,[19] or with thiophenol in the presence of iron polyphthalocyanine as electron transfer agent.[20] This acyloin has also been obtained by oxidation of (*E*)-4-octene with potassium permanganate[21] and by reaction of propylmagnesium bromide with nickel tetracarbonyl.[22]

Acyloins are useful starting materials for the preparation of a wide variety of heterocycles (e.g., oxazoles[23] and imidazoles[24]) and carbocyclic compounds (e.g., phenols[25]). Acyloins lead to 1,2-diols by reduction, and to 1,2-diketones by mild oxidation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 620

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

iron polyphthalocyanine

ethanol (64-17-5)

acetaldehyde (75-07-0)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

potassium permanganate (7722-64-7)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

Benzoin (119-53-9)

potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

butyraldehyde (123-72-8)

xylene (106-42-3)

2-Furaldehyde (98-01-1)

dichloromethane (75-09-2)

Thiophenol (108-98-5)

Butyroin,
4-Octanone, 5-hydroxy- (496-77-5)

magnesium chloride (7786-30-3)

triethylamine (121-44-8)

CHLOROTRIMETHYLSILANE (75-77-4)

nickel tetracarbonyl

propylmagnesium bromide

3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride

5-(2-hydroxyethyl)-4-methyl-1,3-thiazole (137-00-8)

furoin (552-86-3)

thiamine (59-43-8)

ethyl butyrate (105-54-4)

4,5-octanedione (5455-24-3)

sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate

(E)-4-octene (14850-23-8)