



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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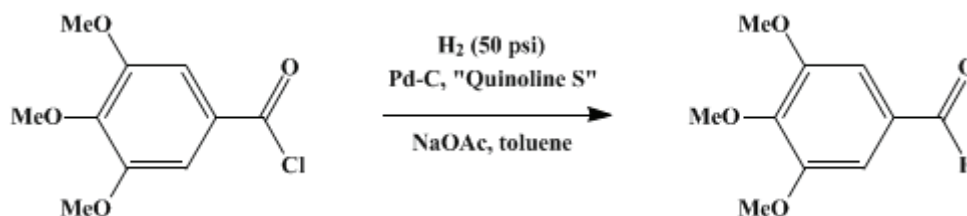
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.1007 (1988); Vol. 51, p.8 (1971).

ALDEHYDES FROM ACID CHLORIDES BY MODIFIED ROSENMUND REDUCTION: 3,4,5- TRIMETHOXYBENZALDEHYDE

[Benzaldehyde, 3,4,5-trimethoxy-]



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Checked by James H. Sherman and Richard E. Benson.

1. Procedure

A pressure vessel (Note 1) is charged in order with 600 ml. of dry toluene (Note 2), 25 g. (0.30 mole) of anhydrous sodium acetate (Note 3), 3 g. of dry, 10% palladium-on-carbon catalyst (Note 4), 23 g. (0.10 mole) of 3,4,5-trimethoxybenzoyl chloride (Note 5), and 1 ml. of Quinoline S (Note 6). The pressure vessel is flushed with nitrogen, sealed, evacuated briefly, and pressured to 50 p.s.i. with hydrogen. The mixture is shaken with 50 p.s.i. of hydrogen for 1 hour at room temperature (Note 7), then heated at 35–40° for 2 hours. Agitation is continued overnight while the reaction mixture cools to room temperature. The pressure on the vessel is released, the vessel is opened, and the mixture is filtered through 10 g. of Celite filter aid, and the insoluble material is washed with 25 ml. of toluene. The combined filtrates are washed successively with 25 ml. of 5% sodium carbonate solution and 25 ml. of water. The toluene solution is dried over 5 g. of anhydrous sodium sulfate and filtered. The filtrate is concentrated by distillation at reduced pressure using a water aspirator. The residue (Note 8) is distilled through a 10-cm. Vigreux column with warm water circulating through the condenser, to prevent crystallization of the distillate, yielding 12.5–16.2 g. (64–83%) of 3,4,5-trimethoxybenzaldehyde, b.p. 158–161° (7–8 mm.), m.p. 74–75° (Note 9) and (Note 10).

2. Notes

- Both glass-lined and stainless-steel autoclaves have been used successfully. The checkers used a 1.2-l., Hastelloy autoclave.
- Reagent grade toluene was heated at reflux to remove a small forerun, then allowed to cool.
- Anhydrous sodium acetate was dried in a vacuum oven at 115° for 48 hours. The use of less than 3 moles of sodium acetate per mole of acid chloride results in a lower yield of product.
- A catalyst available from Engelhard Industries was used after being dried in a vacuum oven at 115° for 48 hours. *Caution! Palladium-on-carbon is pyrophoric, and vacuum drying increases this hazard. Catalysts kept in the oven for longer periods of time were extremely pyrophoric.*
- The acid chloride or the acid may be purchased from Aldrich Chemical Company, Inc. The acid chloride must be pure (99% minimum by GC analysis) whether purchased or prepared. Purification was effected by recrystallization from Skellysolve B.
- Quinoline S was prepared according to the procedure in *Org. Synth., Coll. Vol. 3, 629 (1955)*.
- Repressuring with hydrogen is required during this period. The amount of repressuring required is dependent upon the free space of the pressure vessel. The submitters report lower yields if the pressure falls below 30 p.s.i. No further repressuring is made at the end of 1 hour.
- The crude aldehyde (prior to distillation) is sufficiently pure for most purposes. Isolation of the aldehyde may also be achieved *via* the bisulfite-addition compound.²
- The product shows a strong IR band (KBr) at 1690 cm.⁻¹ (C=O). The ¹H NMR spectrum (CCl₄) has

peaks at δ 3.84 (s, 3H), 3.87 (s, 6H), 7.03 (s, 2H), and 9.76 (s, 1H).

10. The submitters state that the aldehyde is obtained in 78–84% yield when the reaction is conducted on a scale 5 times that described. The amount of catalyst and Quinoline S need not be increased proportionately. The pressure vessel is charged with 3 l. of dry [toluene](#), 123 g. of anhydrous [sodium acetate](#), 10 g. of dry, 10% palladium-on-carbon catalyst, 115 g. of [3,4,5-trimethoxybenzoyl chloride](#), and 4 ml. of Quinoline S.

3. Discussion

[3,4,5-Trimethoxybenzaldehyde](#) has been prepared by the classical Rosenmund^{3,4,5} reduction, by methylation of [5-hydroxyvanillin](#),⁶ and by oxidation of [3,4,5-trimethoxybenzyl alcohol](#).⁷

The normal Rosenmund reduction has often been used for small-scale reactions, but for large preparations it has the following disadvantages: long reaction cycles at elevated temperatures, inefficient use of [hydrogen](#), the hazard of passing [hydrogen](#) through and away from a hot reaction, the use of relatively high catalyst to substrate ratios, and the necessity of monitoring evolved [hydrogen chloride](#) as a means of following the reaction. These shortcomings have been eliminated by carrying out the reaction in a closed system at low pressure in the presence of a [hydrogen chloride](#) acceptor.

The reaction has been carried out on large- and small-scale batches (Note 10). This modification⁸ has been applied by the submitters to the preparation of other aldehydes,⁹ such as [3,4-dimethylbenzaldehyde](#)¹⁰ (90% yield), [3-benzyloxy-4,5-dimethoxybenzaldehyde](#)¹¹ (88% yield, with retention of the benzyl group), and [3-methoxy-4-nitrobenzaldehyde](#)¹² (62% yield, with retention of the nitro group).

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 6, 268](#)
- [Org. Syn. Coll. Vol. 7, 420](#)

References and Notes

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Appendix

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

Quinoline S

palladium-on-carbon

hydrogen chloride (7647-01-0)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

3,4,5-Trimethoxybenzaldehyde,
Benzaldehyde, 3,4,5-trimethoxy- (86-81-7)

3,4,5-trimethoxybenzoyl chloride (4521-61-3)

5-hydroxyvanillin (3934-87-0)

3,4,5-trimethoxybenzyl alcohol (3840-31-1)

3,4-dimethylbenzaldehyde (5973-71-7)

3-benzyloxy-4,5-dimethoxybenzaldehyde

3-methoxy-4-nitrobenzaldehyde