



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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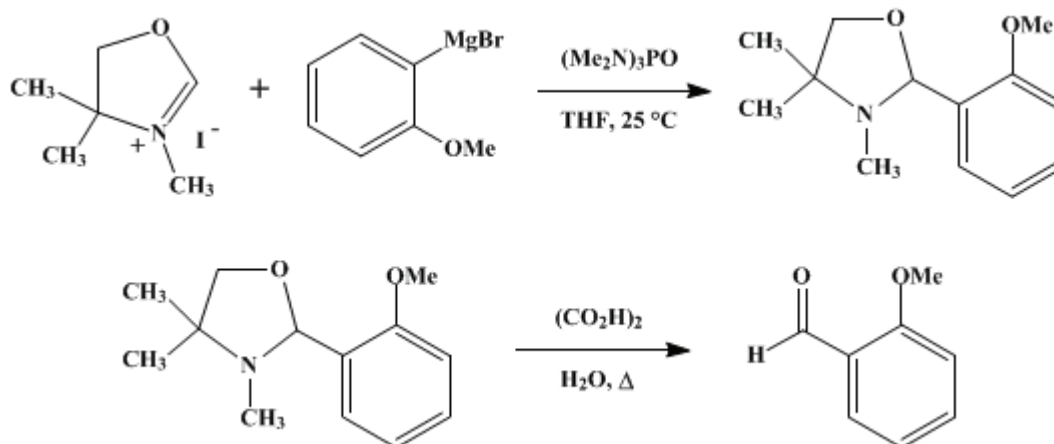
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.64 (1988); Vol. 54, p.42 (1974).

ALDEHYDES FROM 4,4-DIMETHYL-2-OXAZOLINE AND GRIGNARD REAGENTS: *o*-ANISALDEHYDE

[Benzaldehyde, 2-methoxy-]



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1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.² All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists³ has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A 1-l., three-necked, round-bottomed flask equipped with a 500-ml. dropping funnel (Note 1), a mechanical stirrer, and an argon inlet tube is charged with 80 g. (0.33 mole) of *N*,4,4-trimethyl-2-oxazolinium iodide (Note 2). The system is flushed with argon; 150 ml. of dry tetrahydrofuran (Note 3) is added, and the stirred suspension is cooled in an ice bath. Meanwhile, to a cooled solution of freshly prepared 2-methoxyphenylmagnesium bromide (0.414 mole) (Note 4) is added 150 g. (146 ml., 0.828 mole) of dry hexamethylphosphoric triamide (Note 5). This solution is then transferred under an argon atmosphere to the 500-ml. dropping funnel with the aid of an argon-pressurized siphon. The solution is slowly run into the cooled suspension, whereupon the methiodide salt dissolves. When the addition is complete, the reaction mixture is stirred at room temperature overnight.

The suspension is slowly poured into 600 ml. of saturated ammonium chloride solution which has previously been cooled to 10–15°, and the mixture is extracted with three 250-ml. portions of diethyl ether. Concentration of the combined extracts gives the crude addition product (Note 6), which is added to 200 ml. of ice-cold water and quickly acidified with cold 3 *N* hydrochloric acid. The acidic solution is rapidly extracted with 300 ml. of cold hexane, and the extract is discarded. The aqueous solution is then made basic by the addition of aqueous 20% sodium hydroxide solution (Note 7), and the mixture is

extracted with three 250-ml. portions of ether. Concentration of the combined ethereal extracts affords 70–75 g. of crude oxazolidine (Note 8).

A 1-l., round-bottomed flask is charged with 72 g. of the crude oxazolidine in 600 ml. of water, and 201.6 g. (1.6 moles) of hydrated oxalic acid is added. The mixture is heated under reflux for 1 hour, cooled, treated with 600 ml. of water to dissolve precipitated oxalic acid, and extracted with three 100-ml. portions of ether. The combined ethereal extracts are washed with 50 ml. saturated sodium hydrogen carbonate, dried over anhydrous potassium carbonate, and concentrated, giving 30–35 g. of crude aldehyde. Distillation of this material at 70–75° (1.5 mm.) gives pure *o*-anisaldehyde (22.8–26.3 g.; 51–59%), m.p. 35.5–38° (Note 9).

2. Notes

1. The dropping funnel should be equipped so that the transfer of the Grignard reagent to it can be carried out under a positive nitrogen pressure.

2. 4,4-Dimethyl-2-oxazoline is commercially available from Columbia Organic Chemicals, 912 Drake Street, Columbia, South Carolina, or may be prepared as follows. A 250-ml., three-necked flask is charged with 89.14 g. (1.001 mole) of 2-amino-2-methylpropanol and cooled in an ice bath. The amine is carefully neutralized with 52.3 g. (1.25 mole) of 90.6% formic acid over a 1-hour period. A magnetic stirring bar is added, the flask is fitted with a short path distillation head, and the reaction mixture is placed in a silicon oil bath which is rapidly heated to 220–250°. The azeotropic mixture of water and oxazoline distills over a period of 2–4 hours and is collected in an ice-cooled flask containing ether. The aqueous layer is separated, saturated with sodium chloride, and extracted with three 50-ml. portions of ether. The combined ethereal extracts are dried over potassium carbonate and filtered. The ether is removed at 35–40° at atmospheric pressure, and 4,4-dimethyl-2-oxazoline is collected as the temperature rises above 85°, yielding 56.7–62.7 g. (57–63%) of a colorless mobile liquid, b.p. 99–100° (758 mm.).

The checkers found that if the azeotropic mixture is distilled more slowly from the reaction mixture at a pot temperature of 175–195°, the yield is greatly reduced and large amounts of polymeric material are formed.

N,4,4-Trimethyl-2-oxazolinium iodide is prepared by adding 49.5 g. (0.500 mole) of 4,4-dimethyl-2-oxazoline to an excess of cold methyl iodide (182 g., 78.2 ml., 1.28 moles) in a 500-ml. flask and stirring at room temperature under argon for 20 hours. The light brown solid is suction filtered and dissolved in 350 ml. of dry acetonitrile. The methiodide salt is precipitated by the addition of 750 ml. of dry ether to this acetonitrile solution. The purified salt is again suction filtered, and the white solid is washed with 250 ml. of dry ether and finally dried under vacuum, giving 96 g. (80%) of the methiodide, m.p. 215° (dec.). The salt can be stored in an inert atmosphere without deterioration.

3. Tetrahydrofuran was dried by distillation from lithium aluminium hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976, 1973, for a warning concerning the purification of tetrahydrofuran.

4. 4,2-Methoxyphenylmagnesium bromide was prepared from 77.5 g. (0.414 mole, distilled from calcium hydride) of *o*-bromoanisole and 11 g. (0.46 g.-atom) of magnesium turnings in 100 ml. of dry tetrahydrofuran. The solution of this Grignard reagent is heated to reflux for 30 minutes prior to use.

5. Hexamethylphosphoric triamide was dried by distillation from calcium hydride.

6. If pure oxazoline is required, residual amounts of hexamethylphosphoric triamide can be removed by elution of the ethereal solution through silica gel (20–40 mesh).

7. Ice may be added to keep the mixture cool during the neutralization.

8. If this step is omitted, the *o*-anisaldehyde obtained after hydrolysis of the oxazolidine is contaminated with 5–10% *o*-bromoanisole.

9. *o*-Anisaldehyde is commercially available from Aldrich Chemical Co. and Eastman Organic Chemicals, Eastman Kodak Co.

3. Discussion

The conversion of a Grignard or an organolithium reagent to an aldehyde has been accomplished by a variety of reagents. The methods utilize such reagents as *N*-ethoxymethylethaniline;⁴ ethyl orthoformate;⁴ 4-dimethylaminobenzaldehyde;⁵ *N,N*-dimethylformamide;⁶ a dihydroquinazolinium salt;⁷ and, more recently, a *tert*-alkyl isonitrile.⁸

This procedure illustrates a general method for the preparation of aryl, benzyl, alkynyl, and vinyl aldehydes.⁹ Table I gives the aldehydes which have been prepared from the corresponding Grignard reagents by conditions similar to those described here.

TABLE I
ALDEHYDES FROM *N*,4,4-TRIMETHYL-2-OXAZOLINIUM
IODINE

Grignard Reagent	Aldehyde	Yield, %
C ₆ H ₅ MgBr	C ₆ H ₅ CHO	69
C ₆ H ₅ CH ₂ MgCl	C ₆ H ₅ CH ₂ CHO	87
C ₆ H ₅ CH=CHMgBr	C ₆ H ₅ CH=CHCHO	64
C ₆ H ₅ C≡CMgBr	C ₆ H ₅ C≡CCHO	51
2-CH ₃ OC ₆ H ₄ MgBr	2-CH ₃ OC ₆ H ₄ CDO	70 ^a

^a From 2-deuterio-*N*,4,4-trimethyl-2-oxazolinium iodide.

This method does not allow the formylation of aliphatic Grignard or organolithium reagents, since in these cases, the enhancement in base strength in the presence of hexamethylphosphoric triamide produces side reactions due to proton abstraction.

The present method is simple, proceeds easily and in good yield. The starting materials are readily available. The method is of particular value for the ready preparation of C-1 deuterated aldehydes using the 2-deuterio-*N*,4,4-trimethyl-2-oxazolinium iodide.⁹ Also, since ¹⁴C-labeled formic acid is routinely available, this provides easy access to isotopically labeled aldehydes.

References and Notes

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2. J. A. Zapp, *Science*, **190**, 422 (1975).
3. American Conference of Governmental Industrial Hygienists (ACGIH), "Documentation of Threshold Limit Values," 3rd ed., Cincinnati, Ohio, 1971, p. 166.
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether,

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

formic acid (64-18-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Methyl iodide (74-88-4)

Ethyl orthoformate

Tetrahydrofuran (109-99-9)

N-ethoxymethylaniline (6780-49-0)

lithium aluminium hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

2-amino-2-methylpropanol (124-68-5)

hexane (110-54-3)

oxazoline

argon (7440-37-1)

calcium hydride (7789-78-8)

Benzaldehyde, 2-methoxy-,
o-Anisaldehyde (135-02-4)

4-dimethylaminobenzaldehyde (100-10-7)

hexamethylphosphoric triamide (680-31-9)

4,4-DIMETHYL-2-OXAZOLINE (30093-99-3)

2-methoxyphenylmagnesium bromide

oxazolidine

4.2-Methoxyphenylmagnesium bromide

o-bromoanisole (578-57-4)

N,4,4-trimethyl-2-oxazolinium iodide (30093-97-1)

2-deuterio-N,4,4-trimethyl-2-oxazolinium iodide