



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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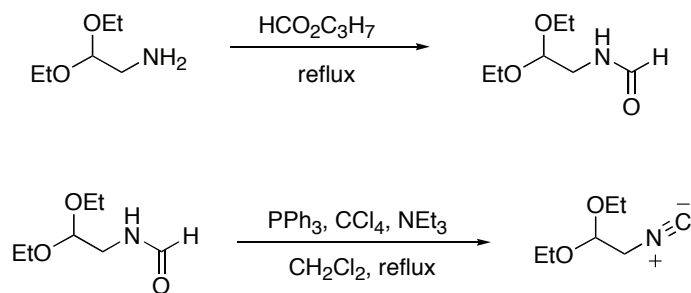
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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2,2-DIETHOXY-1-ISOCYANOETHANE
(2,2-Diethoxyethyl isocyanide, Isocyanoacetaldehyde diethyl acetal)



Submitted by Francesco Amato and Stefano Marcaccini.¹

Checked by Raghuram S. Tangirala and Dennis P. Curran.

1. Procedure

CAUTION: All the operations must be conducted in an efficient hood because the isocyanide has an obnoxious odor.

A. N-(2,2-Diethoxy)ethyl formamide. A 100-mL round-bottomed flask equipped with a magnetic stir bar and fitted with a reflux condenser is charged with aminoacetaldehyde diethyl acetal (28.34 g, 213 mmol, Note 1) and propyl formate (22.48 g, 255 mmol, Note 2). The resulting clear solution is heated at reflux in an oil bath for 3 h (Note 3). After cooling, the reaction mixture is transferred to a 250-mL round-bottomed flask and freed from the 1-propanol and the unreacted propyl formate by rotary evaporation. The residue is transferred to a distillation apparatus equipped with a 10 cm Vigreux column and a two-necked receiver, and distilled under reduced pressure. After a short forerun, the fraction boiling at 110–111 °C (0.5 mmHg) is collected to give 29.3–29.5 g (86% yield) of *N*-(2,2-diethoxy)ethyl formamide (Notes 4, 5).

B. 2,2-Diethoxy-1-isocyanoethane. A 500-mL one-necked flask equipped with a reflux condenser bearing a CaCl_2 trap at the upper end is charged with *N*-(2,2-diethoxyethyl) formamide (24.20 g, 150 mmol), tetrachloromethane (24.61 g, 160 mmol, Note 6), triphenyl phosphine (44.59 g, 170 mmol, Note 7), triethylamine (17.20 g, 150 mmol, Note 8), and 150 mL dichloromethane (Note 9). The clear mixture is heated at reflux in an oil bath, and a precipitate (triphenyl phosphine oxide) begins to appear after 20–30 min. After 3.5 h at reflux, the suspension is cooled to 5 °C and filtered through a Büchner funnel under vacuum from a water aspirator. The

collected solid is washed with 50 mL diethyl ether. The filtrate and the washings are combined and evaporated to dryness, and the residue is stirred with a mixture of 100 mL ethyl ether and 100 mL pentanes (Note 10). The resulting suspension is allowed to stand overnight in the freezer (Note 11), and then filtered through a fritted funnel under vacuum with chilling of the collected filtrate in an ice-sodium chloride bath. The solid residue is washed with 60 mL of pentanes. The filtrate is concentrated on a rotary evaporator in a fume hood and the residue is transferred to a flask equipped with a short path distillation head and a two-necked receiver. Distillation under reduced pressure gives 13.5–13.8 g (63-64%) of 2,2-diethoxy-1-isocyanoethane (Note 12), bp 60-61 °C at 1 mm Hg, as a colorless, vile-smelling liquid (Notes 13, 14).

2. Notes

1. Aminoacetaldehyde diethyl acetal was purchased from Aldrich and used as supplied.

2. Propyl formate (40 mL, purchased from Aldrich) is stirred with 20 mL aq. 5% NaHCO₃ for 2 min. The layers are separated, and the propyl formate layer is washed with 3 x 20 mL of distilled water then dried over magnesium sulfate. After filtration, the filtrate is distilled at atmospheric pressure and the fraction boiling at 80-81 °C is collected for use in Step A.

3. The submitters used an electric shell for heating.

4. The distillation tends to bump, but the Vigreux column prevents overflow into the receiver.

5. IR spectrum (neat) 3304, 1666 cm⁻¹; ¹H NMR (300 MHz, CDCl₃), the formamide is an 6/1 ratio of amide rotamers in this solvent, major rotamer resonances: δ 8.21 (s, 1 H, NCHO), 5.81 (broad s, 1 H, NH), 4.52 (t, *J* = 5.1 Hz, 1 H, O-CH-O), 3.50-3.77 (m, 4 H, CH₂CH₃), 3.45 (t, *J* = 5.4 Hz, 2 H, CH₂N), 1.29 (t, *J* = 7.1 Hz, 3 H, CH₂CH₃), minor rotamer resonances: δ 8.05 (d, *J* = 13.5 Hz, 1 H, NCHO), 4.45 (t, *J* = 6 Hz, 1 H, O-CH-O), 3.31 (t, *J* = 6 Hz, 2 H, CH₂N); ¹³C NMR (75 MHz, CDCl₃) major rotamer resonances: δ 161.3, 100.2, 62.4, 40.1, 14.9, minor rotamer resonances: δ 165.0, 101.3, 63.0, 44.3; LRMS (EI) *m/z* 117 (M – CH₃NO, 10%), 103 (100%), 91 (17%), 84 (55%), 75 (77%); HRMS (EI) *m/z* calcd for C₇H₁₆NO₂ (M + H) 162.1130, found, 162.1126.

6. Tetrachloromethane was purchased from Baker or Fisher and dried over molecular sieves before use.

7. Triphenyl phosphine (99%) was purchased from Aldrich or Acros and used as supplied.

8. Reagent grade triethylamine (Fluka) was dried over calcium hydride pellets and distilled. The fraction boiling at 89 °C was employed.

9. Dichloromethane was stored overnight on 4 Å molecular sieves (submitters) or distilled from calcium hydride (checkers) prior to use.

10. The lumps that formed were carefully broken with a spherical-ended glass rod.

11. The freezer temperature is about -15 °C. If this operation is omitted, then additional solid that precipitates during the distillation makes this process difficult.

12. IR (neat) 2156 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.64 (t, *J* = 5.4 Hz, 1 H, O-CH-O), 3.48-3.71 (m, 2 H, CH₂CH₃), 3.43 (d, *J* = 5.4 Hz, 2 H, CH₂NC), 1.17 (t, *J* = 7.0 Hz, 3 H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 157.8, 99.1, 62.8, 44.3, 14.8.

13. The submitters obtained 71-75% yields. The submitters report that 2,2-diethoxy-1-isocyanoethane can be stored for at least two years at -30 °C under nitrogen without appreciable decomposition. The checkers stored a sample at -20 °C for three months, and the resulting liquid was still clear and exhibited a ¹H NMR spectrum identical to that recorded on the starting sample.

14. The checkers had the impression that this isonitrile smells fouler than phenyl isonitrile and related aryl isonitriles. Glassware can be freed from the isonitrile odor by rinsing with a 1:10 mixture of 37% hydrochloric acid/ethanol.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This synthesis of 2,2-diethoxy-1-isocyanoethane is based on the dehydration of *N*-substituted formamides, which is the most important route to isocyanides.² The combination of triphenylphosphine, carbon tetrachloride and triethylamine allows a smooth dehydration and a facile workup. The formylation of aminoacetaldehyde diethyl acetal employs propyl formate, because of the instability of acetals towards acidic reagents

such as formic acid and formic-acetic anhydride that are usually employed in *N*-formylations.

Hartke³ reported a synthesis of 2,2-diethoxy-1-isocyanoethane in which amino acetaldehyde acetal was transformed initially into the corresponding thioformamide. The thioformamide was then converted into the isocyanide by treatment with diphenylacetyl chloride/diisopropyl carbodiimide/triethylamine. The present method appears to be more convenient, because the experimental procedures are simpler, the yields are higher (62-68% overall) and the reagents are easily available and cheap.

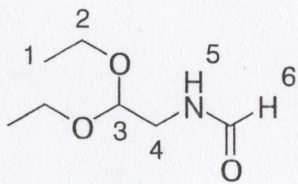
This isocyanide has been employed as C–C–N–C unit in the synthesis of imidazoles, imidazo-imidazoles and aminoisoxazoles.⁴ 2,2-Dimethoxy-1-isocyanoethane can be prepared starting from aminoacetaldehyde dimethyl acetal following this procedure. The yields are similar and the product shows the same reactivity of its ethyl analogues. A procedure for the synthesis of 2,2-dimethoxy-1-isocyanoethane based on the dehydration of the corresponding formamide with POCl₃/NEt₃ has recently been reported.⁵ The dehydration with PPh₃/CCl₄/NEt₃ appears to be a superior method, giving better yields without employing a tedious aqueous work-up. 2,2-Dimethoxy-1-isocyanoethane has been used for the synthesis of 4,5-dihydrothiazoles and thiazoles.⁵

1. Dipartimento di Chimica Organica “Ugo Schiff”, Università di Firenze, via della Lastruccia 13, I-50019 Sesto Fiorentino (FI), Italy.
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Aminoacetaldehyde diethyl acetal: Ethanamine, 2,2-diethoxy-; (645-36-3)
Propyl formate: Formic acid, propyl ester; (110-74-7)
Tetrachloromethane: Methane, tetrachloro-; (56-23-5)
Triphenylphosphine: Phosphine, triphenyl-; (603-35-0)
Triphenylphosphine oxide: Phosphine oxide, triphenyl-; (791-28-6)



Integral

ppm

10

9

8

7

6

5

4

3

2

1

0

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6.3928

CDCl₃

6

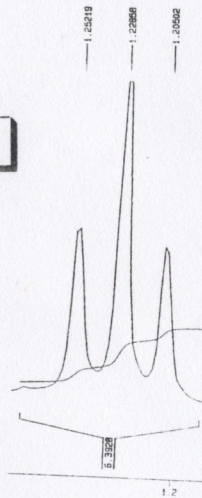
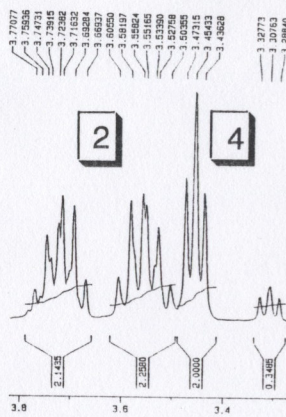
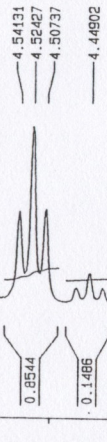
5

3

2

4

1



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