Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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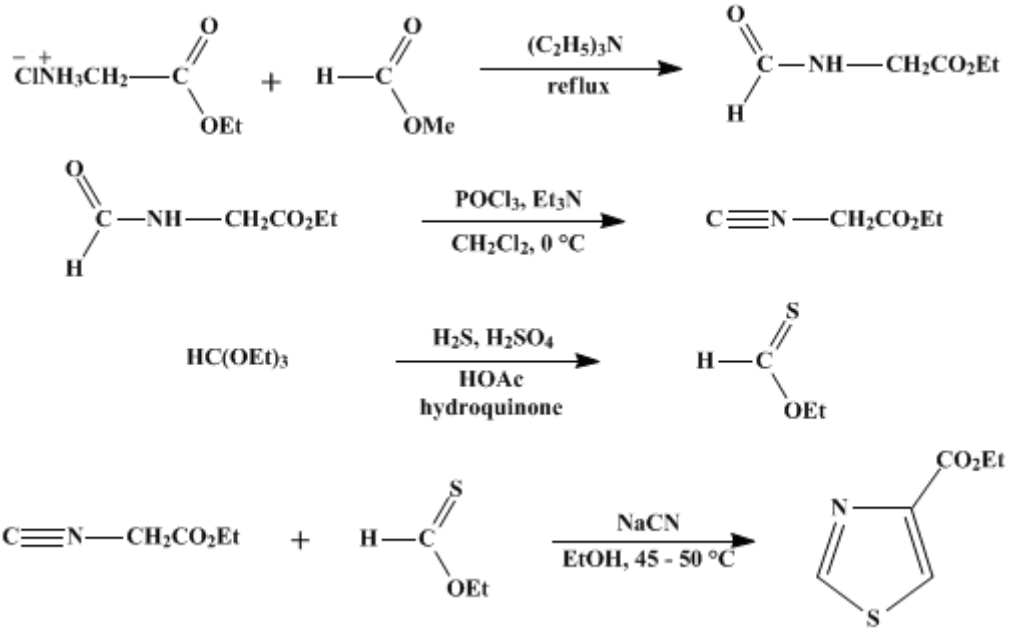
THIAZOLES FROM ETHYL ISOCYANOACETATE AND THIONO ESTERS: ETHYL THIAZOLE-4-CARBOXYLATE

[4-Thiazolecarboxylic acid, ethyl ester]



Submitted by G. D. Hartman and L. M. Weinstock[1].
Checked by Louis E. Benjamin Sr, Norman W. Gilman, and Gabriel Saucy.

1. Procedure

A. N-*Formylglycine ethyl ester*. A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser bearing a calcium chloride drying tube is charged with 69.5 g. (0.495 mole) of glycine ethyl ester hydrochloride and 250 ml. of methyl formate (Note 1). The suspension is stirred and heated at reflux while 55.0 g. (0.544 mole) of triethylamine (Note 1) is added. The resulting mixture is stirred and heated under reflux for 20 hours, cooled to room temperature, and filtered through a Büchner funnel, removing triethylamine hydrochloride. The filtrate is concentrated on a rotary evaporator, and the remaining clear oil is distilled under reduced pressure, yielding 51.7–61.5 g. (79–94%) of *N*-formylglycine ethyl ester, b.p. 94–97° (0.05 mm., (Note 2)).

B. *Ethyl isocyanoacetate*. A 3-l., three-necked, round-bottomed flask equipped with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a nitrogen inlet is charged with 65.5 g. (0.500 mole) of *N*-formylglycine ethyl ester, 125.0 g. (1.234 moles) of triethylamine, and 500 ml. of dichloromethane, and the apparatus is flushed with nitrogen. The resulting solution is stirred and cooled to 0° to −2° in an ice–salt bath, and 76.5 g. (0.498 mole) of phosphorus oxychloride (Note 3) is added dropwise over 15–20 minutes while the temperature is kept at 0°. The mixture becomes reddish brown as it is stirred and cooled at 0° for an additional 1 hour. The ice–salt bath is removed and replaced by an ice-water bath. Stirring is continued as a solution of 100 g. of anhydrous sodium carbonate in 400 ml. of water is added dropwise at a rate such that the temperature of the mixture is maintained at 25–30° (Note 4). The two-phase mixture is stirred for another 30 minutes, after which water is added until the volume of the aqueous layer is brought to 1 l. The aqueous layer is separated and extracted with two 250-ml. portions of dichloromethane. The dichloromethane solutions are combined, washed with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure and distillation of the remaining brown oil

afford 43–44 g. (76–78%) of ethyl isocyanoacetate, b.p. 89–91° (11 mm.) (Note 5).

C. O-*Ethyl thioformate*. *Caution! Hydrogen sulfide gas is highly toxic; this procedure should be conducted in a well-ventilated hood.* A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a gas-inlet tube with a fritted-glass tip extending near to the bottom of the flask, and a gas-outlet connected to a scrubber flask containing 0.5–1.0 l. of aqueous 20% sodium hydroxide (Note 6). The flask is charged with 333 g. (2.25 moles) of triethyl orthoformate (Note 7), 330 ml. of glacial acetic acid, 3.2 g. of hydroquinone, and 0.4 ml. of concentrated sulfuric acid. The resulting solution is stirred and cooled in an ice bath as hydrogen sulfide gas is passed through the gas-inlet tube into the solution (Note 8). After the solution becomes saturated with hydrogen sulfide, the contents of the flask are poured into a 4-l. beaker containing a mechanically stirred mixture of 2.3 l. of ice and 340 ml. of diethyl ether. The mixture is poured into a separatory funnel, and the layers are separated. The organic layer is washed successively with two 100-ml. portions of aqueous saturated sodium hydrogen carbonate solution, two 100-ml. portions of water, three 80-ml. portions of aqueous saturated sodium hydrogen carbonate, and two 80-ml. portions of aqueous saturated sodium chloride. The solution is dried over anhydrous sodium sulfate and distilled at atmospheric pressure through a 45-cm. Vigreux column, affording 60–76.7 g. (30–38%) of *O*-ethyl thioformate as a yellow liquid, b.p. 87–89° (Note 9) and (Note 10).

D. *Ethyl thiazole-4-carboxylate*. A 250-ml., three-necked, round-bottomed flask fitted with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 0.25 g. (0.0051 mole) of sodium cyanide and 10 ml. of absolute ethanol. The suspension is stirred vigorously at room temperature as a solution of 4.52 g. (0.0439 mole) of ethyl isocyanoacetate and 3.60 g. (0.0400 mole) of *O*-ethyl thioformate in 15 ml. of absolute ethanol is added slowly. Because the reaction is exothermic the temperature of the mixture should be kept below 45° by adjusting the addition rate and, if necessary, cooling the flask in an ice bath (Note 11). When the addition is completed, the contents of the flask are stirred and heated at 50° for another 30 minutes. The solvent is removed by rotary evaporation, and the resulting dark oil is extracted with three 60-ml. portions of hot hexane (Note 12). The combined hexane extracts are concentrated with a rotary evaporator until the product begins to separate, and the concentrate is cooled in an ice bath, yielding 5.1–5.5 g. (81–87%) of ethyl thiazole-4-carboxylate as off-white needles, m.p. 52–53° (Note 13).

2. Notes

1. Glycine ethyl ester hydrochloride, methyl formate, and triethylamine were purchased from Aldrich Chemical Company, Inc., and were used without purification.
2. The submitters obtained 63 g. (96%), b.p. 104–106° (0.1 mm).
3. The submitters recommend that phosphorus oxychloride either be taken from a previously unopened bottle or distilled before use.
4. Foaming generally occurs during the addition.
5. Essentially no forerun need be taken prior to collection of the product. The last few milliliters of distillate were slightly yellow, and 2–3 g. of intractable material remained in the distillation flask. A boiling point of 76–78° (4 mm.) has been reported[2] for ethyl isocyanoacetate. The submitters have found the distilled product to be stable for up to 6 months when stored under nitrogen at −20°.
6. The checkers used a gas-inlet tube without a fritted-glass tip and aqueous 30% sodium hydroxide as scrubber solution.
7. Triethyl orthoformate is available from Aldrich Chemical Company, Inc.
8. Hydrogen sulfide is admitted into the flask slowly at first, with bubble formation kept to a minimum. Initially the gas dissolves readily. As the solution becomes saturated, more bubbling action is apparent in the flask and the scrubber.
9. The submitters reported a yield of 56.5 g. (28%), b.p. 90–92°. The product is often contaminated with *ca.* 5% of ethyl formate; however, this impurity does not interfere with Part D. The submitters state that the product is stable when stored under nitrogen at −20°.
10. The checkers found that glassware in which the product was stored acquired a disagreeable odor that was difficult to remove with aqueous sodium hydroxide.
11. Controlling the temperature in this manner prevents discoloration of the final product and improves its yield.

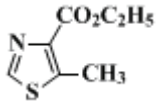
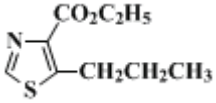
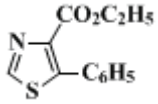
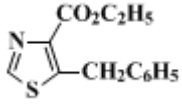
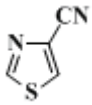
12. The product was obtained as tan needles when boiling hexane was used by the checkers. Off-white needles were isolated when the temperature of the hexane was 50–55°.
13. The submitters reported a yield of 5.8 g. (92%) of product as white needles, m.p. 53–54°. However, the checkers obtained colorless needles only after recrystallizing the product from hexane. The melting points of the discolored needles obtained initially by the checkers and the recrystallized material were identical (lit.,[3,4] m.p. 57° and 52–54°). The spectral properties of the product are as follows: IR ($CHCl_3$) $cm.^{-1}$: 3130, 3030, 1724 (C=O), 1500, 1270; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.39 (t, *J* = 7, 3H, OCH_2CH_3), 4.43 (q, *J* = 7, 2H, OCH_2CH_3), 8.33 (d, *J* = 2.5, 1H, *H* at C-5), 8.98 (d, *J* = 2.5, 1H, *H* at C-2).

3. Discussion

Ethyl thiazole-4-carboxylate has been prepared by hydrogenolysis of ethyl 2-bromothiazole-4-carboxylate with Raney nickel in ethanol,[3] by desulfurization of ethyl 2-mercaptothiazole-4-carboxylate with hydrogen peroxide in concentrated hydrochloric acid,[4] and by condensation of ethyl bromopyruvate with thioformamide in ether.[5,6]

The present procedure is illustrative of a mild and general method for preparing thiazoles substituted at the 4-position with electron-withdrawing substitutents such as ethoxycarbonyl,[7] cyano,[7] and *p*-toluenesulfonyl.[8] Thus, condensation of ethyl isocyanoacetate with various thiono esters affords the parent ethyl thiazole-4-carboxylate as well as a series of analogs bearing substituents in the 5-position (Table I).[7] A similar reaction of α-isocyanoacetonitrile with *O*-ethyl thioformate gave the cyano analog in 23% yield. However, the instability of the latter isocyanide hampers the utility of this reaction.

TABLE I
THIAZOLES FROM CONDENSATION OF ETHYL ISOCYANOACETATE AND α-ISOCYANOACETAMIDE WITH THIONO ESTERS

Thiazole	M.p. or B.p. (°)	Yield(%)
	89–90	82
	85–87 (0.15 mm.)	68
	183–185	22
	49–50	75
	55–56	23

The mechanism of the condensation in Part D probably involves thioformylation of the metallated isocyanoacetate followed by intramolecular 1,1-addition of the tautomeric enethiol to the isonitrile. This

thiazole synthesis is analogous to the formation of oxazoles from acylation of metallated isonitriles with acid chlorides or anhydrides.[9,10] Interestingly, ethyl formate does not react with isocyanoacetate under the conditions of this procedure. Ethyl and methyl isocyanoacetate have been prepared in a similar manner by dehydration of the corresponding *N*-formylglycine esters with phosgene[2] and trichloromethyl chloroformate,[11] respectively. The phosphorus oxychloride method described here was provided to the submitters by Professor U. Schöllkopf[12] and is based on the procedure of Böhme and Fuchs.[13] The preparation of *O*-ethyl thioformate was developed from a report by Ohno, Koizuma, and Tsuchihaski.[14]

4-Substituted thiazoles are important intermediates, as in the synthesis of thiabendazole [2-(4-thiazolyl)benzimidazole], a leading anthelminthic utilized for control of gastrointestinal nematodes in ruminants.[15] Other thiazoles have displayed significant pharmacologic activity as antiinflammatory[16] and antibacterial agents.[17] Recently, 4-substituted thiazoles were implicated as intermediates in the energy transfer mechanism of firefly bioluminescence.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 242

References and Notes

1. Merck, Sharp, and Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pennsylvania 19486.
2. I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Int. Ed. Engl.*, **4**, 472 (1965).
3. H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **28**, 362 (1948).
4. J. J. D'Amico and T. W. Bartram, *J. Org. Chem.*, **25**, 1336 (1960).
5. M. Erne, F. Ramirez, and A. Burger, *Helv. Chim. Acta*, **34**, 143 (1951).
6. For a review, see J. M. Sprague and A. H. Land, "Thiazoles and Benzothiazoles," in R. C. Elderfield, Ed., "Heterocyclic Compounds," Vol. 5, Wiley New York, 1957, pp. 484–722.
7. G. D. Hartman and L. M. Weinstock, *Synthesis*, 681 (1976); G. D. Hartman, U.S. Pat. 4,021,438 (1977) [*Chem. Abstr.*, **87**, 53264s (1977)].
8. O. H. Oldenziel and A. M. Van Leusen, *Tetrahedron Lett.*, 2777 (1972).
9. U. Schöllkopf and R. Schröder, *Angew Chem. Int. Ed. Engl.*, **10**, 333 (1971); R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Justus Liebigs Ann. Chem.*, 533 (1975); M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okumura, and K. Matsumoto, *J. Org. Chem.*, **38**, 3571 (1973); A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
10. For a review on α-metallated isocyanides, see U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.*, **16**, 339 (1977).
11. G. Skorna and I. Ugi, *Angew. Chem. Int. Ed. Engl.*, **16**, 259 (1977).
12. U. Schöllkopf, private communication.
13. H. Böhme and G. Fuchs, *Chem. Ber.*, **103**, 2775 (1970).
14. A. Ohno, T. Koizumi, and G. Tsuchihashi, *Tetrahedron Lett.*, 2083 (1968).
15. H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campbell, and A. C. Cuckler, *J. Am. Chem. Soc.*, **83**, 1764 (1961).
16. D. A. Evans, S. African Pat. 69 04,621 (1970) [*Chem. Abstr.*, **74**, 100028 m (1971)].
17. E. G. Curphey, *Ind. Chem.*, **34**, 85 (1958) [*Chem. Abstr.*, **52**, 9078b (1958)].
18. K. Okada, H. Iio, I. Kubota, and T. Goto, *Tetrahedron Lett.*, 2771 (1974).

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

Glycine ethyl ester hydrochloride, methyl formate

Ethyl and methyl isocyanoacetate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

sodium hydrogen carbonate (144-55-8)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

isonitrile (57-12-5)

Raney nickel (7440-02-0)

Phosphorus Oxychloride (21295-50-1)

phosgene (75-44-5)

hydrogen peroxide (7722-84-1)

triethyl orthoformate (122-51-0)

ethyl formate (109-94-4)

Triethylamine hydrochloride (554-68-7)

methyl formate (107-31-3)

dichloromethane (75-09-2)

Glycine ethyl ester hydrochloride (623-33-6)

thiazole (288-47-1)

hexane (110-54-3)

triethylamine (121-44-8)

Trichloromethyl chloroformate (503-38-8)

Ethyl isocyanoacetate (2999-46-4)

Ethyl thiazole-4-carboxylate,
4-Thiazolecarboxylic acid, ethyl ester (14527-43-6)

ethyl 2-bromothiazole-4-carboxylate

ethyl 2-mercaptothiazole-4-carboxylate

ethyl bromopyruvate (70-23-5)

thioformamide (115-08-2)

α-isocyanoacetonitrile

isocyanoacetate

2-(4-thiazolyl)benzimidazole (148-79-8)

N-Formylglycine ethyl ester (3154-51-6)

O-ethyl thioformate (21071-39-6)