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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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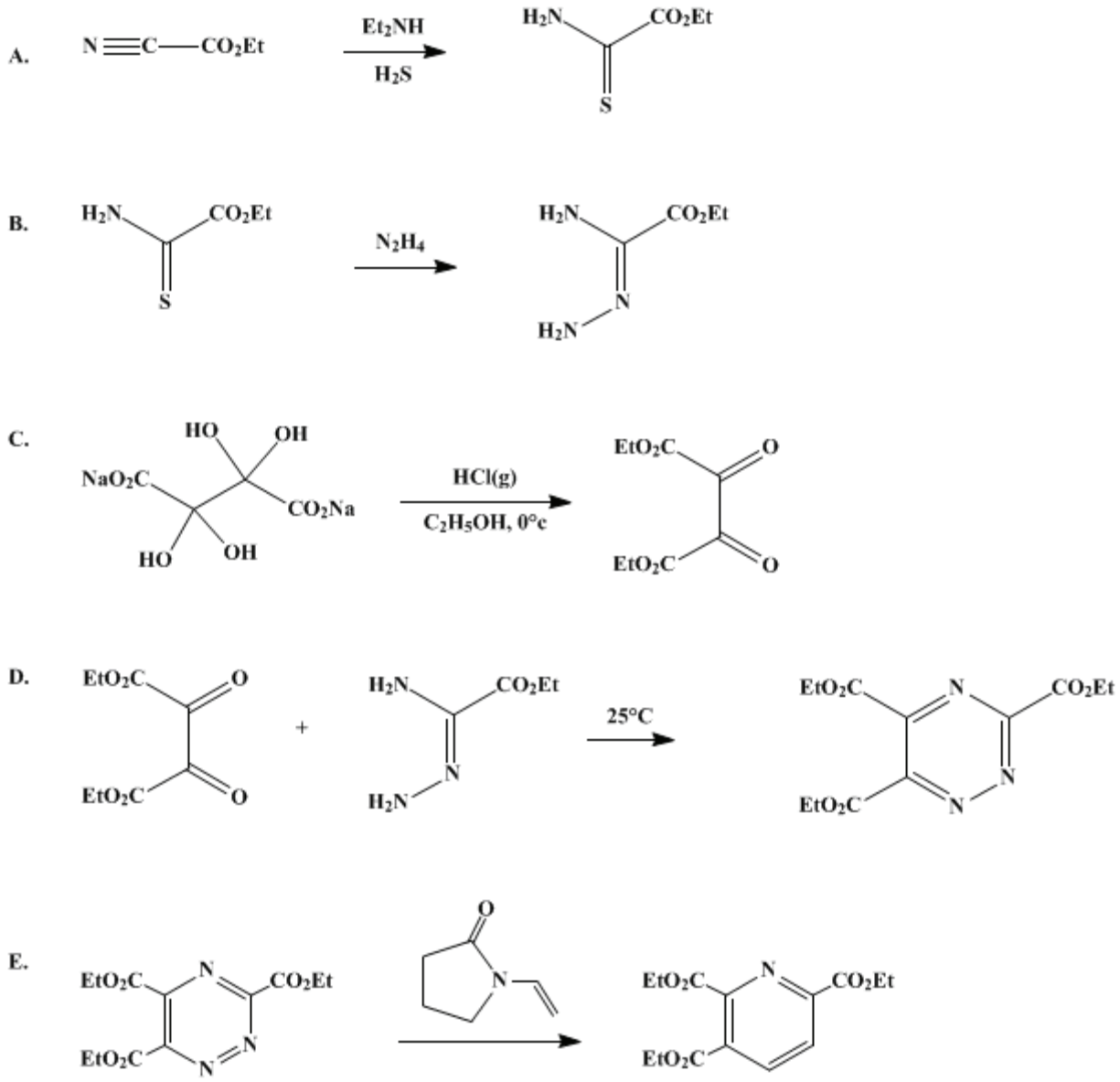
PREPARATION AND INVERSE-ELECTRON-DEMAND DIELS–ALDER REACTION OF AN ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE AND 2,3,6-TRICARBOETHOXYPYRIDINE

[1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester]



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Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

[2]

Caution! Hydrogen sulfide is highly toxic and a stench. Steps A and B must be run in an efficient fume hood.

A. *Ethyl thioamidooxalate.*[3] A 100-mL, round-bottomed flask is fitted with a magnetic stirring bar. Ethyl cyanoformate (20 g, 0.20 mol, (Note 1)) in benzene (25 mL) is added to the reaction vessel and the mixture is cooled to 0°C with an ice bath. Diethylamine ((Note 2), 0.4 g, 5.5 mmol, 0.57 mL) is added to the stirring reaction mixture (0°C) and hydrogen sulfide (Note 3) is then bubbled into the reaction for an additional 15–20 min. The reaction mixture is allowed to stir at 25°C (14–16 hr). The crude product is collected by filtration (Note 4) and washed with benzene (2 × 3 mL) to give 20.96 g (78%) of pure ethyl thioamidooxalate. The filtrate is concentrated under reduced pressure and the crude product subjected to chromatography on silica gel (30% ether–hexane eluant) to give an additional 1.57 g of ethyl thioamidooxalate. The total amount of ethyl thioamidooxalate isolated as a bright-yellow solid is 22.53 g (84%); mp 63–66°C (Note 5).

B. *Ethyl oxalamidrazonate.* A 1-L, round-bottomed flask is equipped with a magnetic stirring bar and fitted with a 125-mL addition funnel. A solution of anhydrous hydrazine (4.8 g, 0.15 mol) in ethanol (75 mL) is added dropwise (10 min) to a stirred solution of ethyl thioamidooxalate (20.0 g, 0.15 mol) in ethanol (450 mL) at 25°C. The reaction mixture is stirred at 25°C (3.0 hr). The solvent is removed under reduced pressure and the reddish-orange solid is triturated with ethanol (350 mL). The ethanolic solution containing the oxalamidrazonate is concentrated under reduced pressure to afford 13.90 g (71%) of ethyl oxalamidrazonate as a yellow solid (Note 6).

C. *Diethyl dioxosuccinate.* A 1-L, round-bottomed flask equipped with a magnetic stirring bar is charged with dihydroxytartaric acid disodium salt hydrate (100 g, 0.44 mol, (Note 7)) and absolute ethanol (750 mL, (Note 8)). The suspension is cooled to 0°C with an ice bath and anhydrous hydrogen chloride gas (Note 9) is bubbled into the reaction mixture with stirring (0°C, ca. 30 min). The reaction mixture is stoppered and placed in the refrigerator for 72 hr. The mixture is filtered using a Büchner funnel and the filtrate is concentrated under reduced pressure. The crude diethyl dioxosuccinate is distilled under reduced pressure to afford 39.60 g (44%) of pure diethyl dioxosuccinate is (Note 10), bp 109–116°C (6–8 mm); lit.[4] bp 109–114°C (6 mm).

D. *Triethyl 1,2,4-triazine-3,5,6-tricarboxylate*. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 500-mL addition funnel, and a nitrogen inlet. A solution of ethyl oxalamidrazonate (11.6 g, 88.0 mmol) in absolute ethanol (350 mL) is added dropwise (40–45 mi) to a stirring solution of diethyl dioxosuccinate (23.1 g, 114.0 mmol) in absolute ethanol (86 mL) at 25°C under nitrogen. After the addition is complete, the reaction mixture is stirred at 25°C (16 hr). A reflux condenser is fitted onto the three-necked, round-bottomed flask and the reaction mixture is warmed at reflux for 2.0 hr. The reaction mixture is cooled and the solvent is removed under reduced pressure. Purification of the product is effected by gravity chromatography (Note 11) on a 5.20 × 40.0-cm column of silica gel (10–40% ether–hexane gradient elution), collecting 100-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (40% ether–hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 14.70 g (56%) of pure triethyl 1,2,4-triazine-3,5,6-tricarboxylate as a viscous, yellow oil[2,5] (Note 12).

E. *2,3,6-Tricarboethoxypyridine.* A 50-mL, round-bottomed flask is fitted with a magnetic stirring bar and a reflux condenser. Triethyl 1,2,4-triazine-3,5,6-tricarboxylate (1.49 g, 5.0 mmol) and chloroform (22.7 mL. (Note 13)) are added to the reaction vessel. *N*-Vinyl-2-pyrrolidone (2.22 g, 20 mmol, 2.3 mL, (Note 14)) is added to the solution and the reaction mixture is warmed at 60°C under an atmosphere of nitrogen for 26 hr. The solvent is removed under reduced pressure and the crude product subjected to gravity chromatography (Note 11) on a 2.7 × 32-cm column of silica gel (40–50% ether–hexane gradient elution), collecting 50-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (50% ether–hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 1.01–1.35 g (68–92%) of 2,3,6-tricarboethoxypyridine as a yellow oil (Note 15).

2. Notes

1. The submitters employed, without purification, ethyl cyanoformate purchased from Aldrich Chemical Company, Inc.
2. The submitters employed, without purification, diethylamine purchased from Aldrich Chemical Company, Inc.

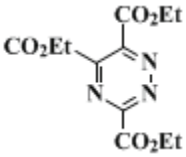
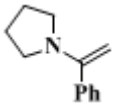
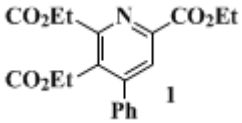
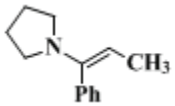
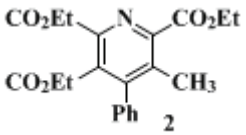
3. Hydrogen sulfide gas was purchased from Burnox, Kansas City, MO. This reaction should be run in a fume hood.
4. In some instances, it is necessary to cool the flask (ice bath) containing the ethyl thioamidooxalate to promote crystallization of the product.
5. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.39 (t, 3 H, J = 8, CH_3), 4.33 (q, 2 H, J = 8, CH_2), 7.30–8.30 (br s, 2 H, NH_2), mp 63–66°C, lit.[2,5] mp 64–65°C.
6. *Caution: This reaction should be carried out in a fume hood. Ethyl oxalamidrazonate cannot be stored in solution for prolonged periods of time.*
7. The submitters employed dihydroxytartaric acid disodium salt hydrate purchased from Aldrich Chemical Company, Inc.
8. Ethanol was dried by distillation from magnesium turnings immediately before use.
9. Anhydrous hydrogen chloride gas purchased from Burnox, Kansas City, MO was employed.
10. The ^{1}H NMR spectrum of this compound is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, 3 H, J = 8, CH_3), 4.4 (q, 2 H, J = 8, CH_2).
11. The checkers used flash chromatography for these steps.
12. The spectral properties of this product (orange oil) are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3 H, J = 7, CH_3), 1.48 (t, 3 H, J = 7, CH_3), 1.51 (t, 3 H, J = 7, CH_3); 4.38–4.68 (3 overlapping q, 6 H, three CH_2); IR (film) cm^{-1}: 2986, 1757, 1738, 1518, 1468, 1408, 1383, 1302, 1217, 1177, 1155, 1099, 1017, 857.
13. The submitters employed chloroform obtained from Fisher Chemical Co.
14. The submitters employed, without purification, *N*-vinyl-2-pyrrolidone obtained from GAF Corporation.
15. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, 3 H, J = 7, CH_3), 1.41 (t, 3 H, J = 7, CH_3), 1.43 (t, 3 H, J = 7, CH_3), 4.38 (q, 2 H, J = 7, CH_2), 4.44 (q, 2 H, J = 7, CH_2), 4.47 (q, 2 H, J = 7, CH_2), 8.16 (d, 1 H, J = 8, aromatic), 8.30 (d, 1 H, J = 8, aromatic); IR (film) cm^{-1}: 2986, 1728, 1586, 1570, 1468, 1455, 1406, 1387, 1370, 1321, 1283, 1239, 1152, 1071, 1021, 853, 762.

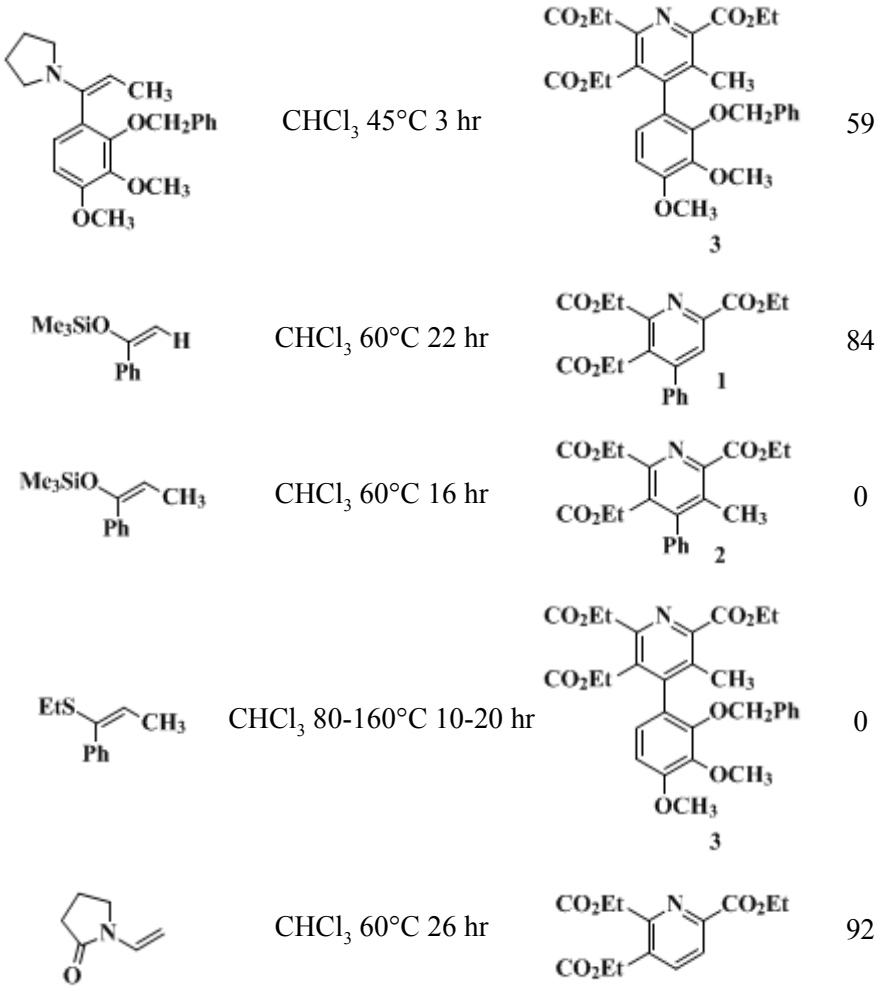
3. Discussion

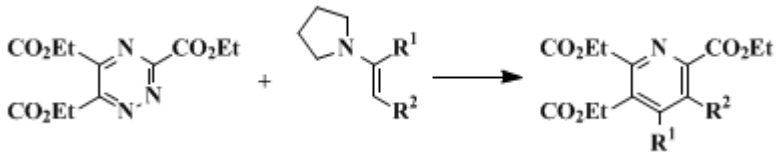
This procedure describes the preparation of an electron-deficient heterocyclic azadiene suitable for use in inverse-electron-demand ($LUMO_{diene}$ controlled)[6] Diels–Alder reactions with electron-rich dienophiles.

Table 1[6,7] details representative examples of the [4 + 2] cycloaddition of triethyl 1,2,4-triazine-3,5,6-tricarboxylate with pyrrolidine enamines and related electron-rich olefins. Cycloaddition occurs across carbon-3 and carbon-6 of the 1,2,4-triazine nucleus, and the nucleophilic carbon of the dienophile attaches to carbon-3 (Eq. 1). Loss of nitrogen from the initial adduct and aromatization with loss of pyrrolidine affords pyridine products.

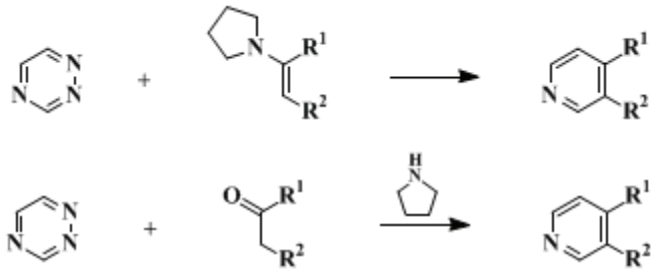
TABLE 1
DIELS-ALDER REACTION OF TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE

	Dienophile	Conditions: Solv., Temp., Time	Product	Yield (%)
		$CHCl_3$ 60°C 18 hr	 1	79
		$CHCl_3$ 45°C 8 hr	 2	73





Similar reactivity and regioselectivity is observed with the parent system, 1,2,4-triazine (Eq. 2).[8] Reduction of this process to a catalytic Diels–Alder reaction with in situ generation of the pyrrolidine enamine does not alter these observations (Eq. 3).[9]



The number and position of electron-withdrawing substituents on the 1,2,4-triazine nucleus and the reactivity of the electron-rich dienophile determine the mode of cycloaddition (additions across C-5/N-2 as well as C-3/C-6 of the 1,2,4-triazine nucleus have been observed) as well as the regioselectivity.[8,9,10] A survey of the reported Diels–Alder reactions of 1,2,4-triazines including triethyl 1,2,4-triazine-3,5,6-

tricarboxylate has been compiled.[11]

[12]

References and Notes

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

Ethyl thioamidooxalate

Ethyl oxalamidrazonate

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

carbon (7782-42-5)

pyridine (110-86-1)

diethylamine (109-89-7)

hydrazine (302-01-2)

ethyl cyanoformate (623-49-4)

hexane (110-54-3)

Triethyl 1,2,4-triazine-3,5,6-tricarboxylate,
1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester (74476-38-3)

2,3,6-Tricarboethoxypyridine (122509-29-9)

dihydroxytartaric acid disodium salt hydrate

Diethyl dioxosuccinate (59743-08-7)

N-Vinyl-2-pyrrolidone (88-12-0)