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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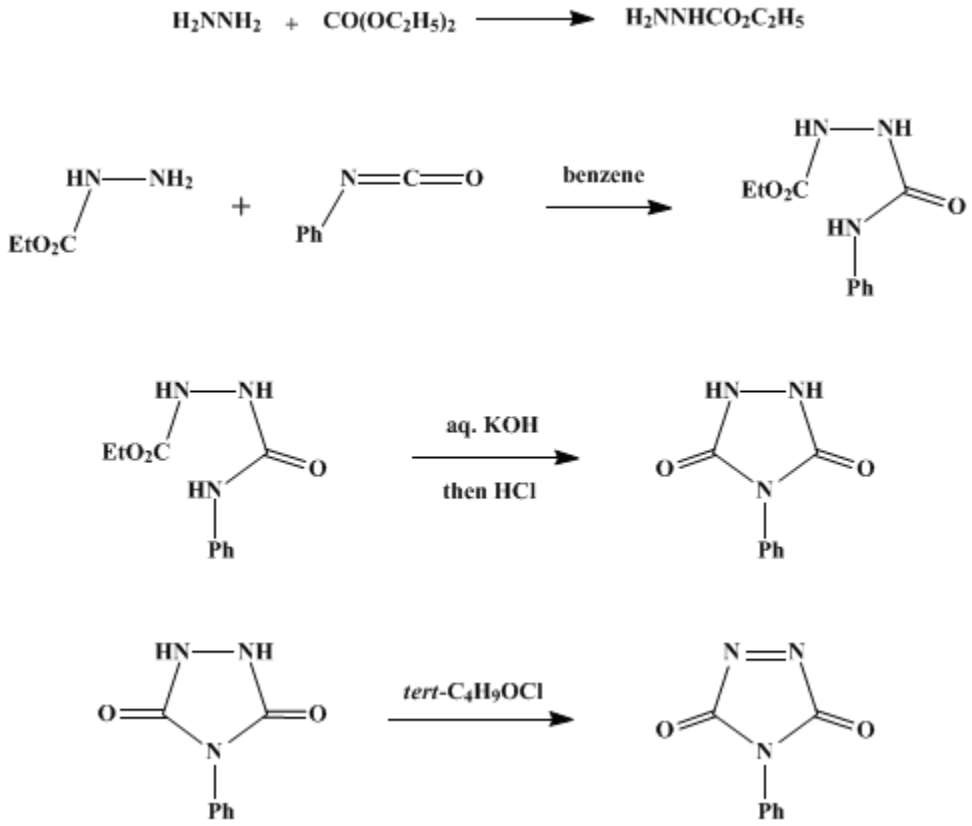
# 4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE

## [3*H*-1,2,4-Triazole-3,5(4*H*)-dione, 4-phenyl-]

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## 1. Procedure

*Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

A. *Ethyl hydrazinecarboxylate.* To 100 g. (96.9 ml., 2.00 moles) of 100% hydrazine hydrate, contained in a 1-l., round-bottomed flask, is added 236 g. (243 ml., 2.00 moles) of diethyl carbonate (Note 1). The flask is fitted with a calcium chloride-containing drying tube and shaken vigorously, mixing the two liquids. After about 5 minutes, the milky emulsion becomes warm, and shaking is continued until a clear solution is obtained (approximately 20 minutes). The flask is equipped with a reflux condenser fitted with a calcium chloride-containing drying tube and heated on a steam bath for 3.5 hours. The reaction mixture is transferred to a 500-ml., round-bottomed flask and is distilled through a 15-cm. Vigreux column under reduced pressure, yielding 161–176 g. (77–85%) of a colorless liquid collected at 102–103° (18 mm.) or 117–118° (40 mm.) (Note 2), $n_D^{22}$ 1.4495; IR $cm^{-1}$ 1640, 1725, 3350. The product, which may crystallize on standing, m.p. 45–47°, need not be purified for the next step.

B. 4-*Phenyl*-1-*carbethoxysemicarbazide.* A 1-l., three-necked, round-bottomed flask equipped with a liquid-sealed mechanical stirrer (Note 3), a constant-pressure dropping funnel, and a reflux condenser fitted with a drying tube containing silica gel is charged with a solution of 52 g. (0.50 mole) of ethyl

hydrazinecarboxylate in 550 ml. of dry benzene (Note 4). After the solution is cooled with an ice bath, stirring is begun and 59.7 g. (54.5 ml., 0.501 mole) of phenyl isocyanate is added dropwise to the solution over a 45-minute period. After about one-half of the isocyanate has been added, a white precipitate of the product appears, and the reaction mixture becomes progressively thicker. After addition is complete the ice bath is removed; the mixture is stirred at room temperature for 2 hours, then heated under reflux for 2 hours. The suspension is allowed to cool to room temperature, and 4-phenyl-1-carbethoxysemicarbazide is isolated by suction filtration, washed with 500 ml. of benzene, and dried in a vacuum desiccator, yielding 108 g. (97%) of 4-phenyl-1-carbethoxysemicarbazide, m.p. 151–152°. The product is not further purified for use in the next step, but may be recrystallized from ethyl acetate to yield white crystals, m.p. 154–155°; IR $cm.^{-1}$ 1645, 1687, 1797, and 3300 (Note 6).

C. 4-*Phenylurazole.* A 250-ml. Erlenmeyer flask is charged with 100 ml. of aqueous 4 *M* potassium hydroxide and 44.6 g. (0.200 mole) of 4-phenyl-1-carbethoxysemicarbazide. The suspension is warmed on a steam bath, the flask being swirled occasionally to wash the solid off the sides. After 1.5 hours most of the solid has dissolved, and the hot solution is filtered. After cooling to room temperature, the solution is acidified with concentrated hydrochloric acid (about 33 ml. is required). The mixture is again cooled to room temperature and the precipitated 4-phenylurazole is isolated by suction filtration. The mother liquor is evaporated to dryness on a rotary evaporator, and the residue is extracted twice with 100-ml. portions of boiling absolute ethanol (Note 7). The ethanol solutions are combined, filtered, and evaporated to dryness on a rotary evaporator, and the additional 4-phenylurazole recovered is combined with that obtained above. The product is crystallized from 95% ethanol (about 80 ml.), yielding 30.0–33.5 g. (85–95%) of 4-phenylurazole, m.p. 209–210°; IR $cm.^{-1}$ 1685 and 3120 (Note 8),(Note 9), and (Note 10).

D. 4-*Phenyl*-1,2,4-*triazoline*-3,5-*dione.* A 100-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a gas-inlet tube, a calcium chloride-containing drying tube, and a magnetic stirrer is flushed with oxygen-free nitrogen (Note 11) and charged with 12 ml. of ethyl acetate (Note 12) and 4.4 g. (0.025 mole) of 4-phenylurazole (Note 13). The stirrer is started, and 2.5 g. (2.8 ml., 0.023 mole) of *tert*-butyl hypochlorite (Note 14) and (Note 15) is added to the flask over a period of approximately 20 minutes, the reaction mixture being maintained close to room temperature with a cold-water bath (Note 16) and (Note 17). After the addition is complete, the resulting suspension is stirred for 40 minutes at room temperature. The reaction mixture is transferred to a 100-ml., round-bottomed flask, and the solvent is removed on a rotary evaporator, keeping the temperature below 40°. The last traces of solvent are removed with a high-vacuum pump (about 0.1 mm.). The product is sublimed (Note 18) onto an ice-cooled cold finger under vacuum (100° at 0.1 mm.), yielding 2.7–2.8 g. (62–64%) of the triazoline as carmine-red crystals which decompose (165–175°) before melting; IR $cm.^{-1}$ 1760 and 1780; UV (dioxane) nm (ε) 247 (2300), 310 (1020), and 532 (171) (Note 19) and (Note 20).

## 2. Notes

1. Both the hydrazine hydrate and diethyl carbonate were British Drug Houses Ltd. or Matheson Laboratory reagent grade and used without further purification.
2. A forerun of approximately 100 ml., boiling below 80° (18 mm.), containing ethanol, water, and unreacted starting materials, is also collected.
3. An efficient stirrer should be employed, since the reaction mixture becomes quite viscous. If efficient mixing is not maintained a violent reaction can occur. This is especially important when using aliphatic isocyanates.
4. British Drug Houses Ltd. or Amend Drug & Chemical Co., Inc., reagent grade benzene, dried over sodium wire, is adequate.
5. British Drug Houses Ltd. or Matheson Laboratory reagent grade phenyl isocyanate was used without further purification. When using other isocyanates, care should be taken to ensure their purity as the yield is greatly dependent upon this, commercially available 4-nitrophenyl isocyanate being a case in point.
6. The submitters report a similar yield on a scale three times that illustrated here. This method has been employed for the preparation of the 4-methyl- (100%, m.p. 143° from ethyl acetate), 4-*tert*-butyl- (100%, m.p. 147° from ethyl acetate), and 4-(4-nitrophenyl)-1-carbethoxysemicarbazide (90%, m.p.

219° from methanol). Because of the impure nature of commercial 4-nitrophenyl isocyanate, the product from that reaction may be contaminated with 4-nitrophenylurea. It can be used in the impure form for preparing the corresponding urazole, as the contaminant is alkali insoluble.
7. The extraction procedure increases the yield of 4-phenylurazole by about 6%. This step is unnecessary when preparing 4-(4-nitrophenyl)urazole, as it is insoluble in water.
8. This method has been used to prepare 4-methyl- (90%, m.p. 240° from methanol) and 4-(4-nitrophenyl)urazole (80%, m.p. 264° from ethanol).
9. 4-*tert*-Butyl-1-carbethoxysemicarbazide can be cyclized by refluxing with 4% sodium ethoxide in ethanol for 4 hours, followed by acidification with an ethanolic solution of hydrogen chloride. Filtration, evaporation of the filtrate, and crystallization from ethyl acetate yields 4-*tert*-butylurazole (89%, m.p. 168°).
10. 4-Benzalaminourazole (m.p. 255°) can be prepared from 4-aminourazole[2] by condensation with benzaldehyde.
11. A gentle stream of nitrogen is maintained through the apparatus during the entire reaction. Hydrogen chloride is evolved and adequate precautions should be taken to prevent exposure to the gas.
12. Ethyl acetate was purified by Fieser's method.[3]
13. The 4-phenylurazole should be ground with a pestle and mortar before use.
14. *tert*-Butyl hypochlorite was prepared by the method described in *Org. Synth.*, **Coll. Vol. 4**, 125 (1963).
15. An excess of *tert*-butyl hypochlorite should not be used, as it cannot be removed and interferes with the sublimation of the product.
16. When preparing the 4-(4-nitrophenyl)- and 4-benzalamino- analogs, the reaction mixture should be maintained at 0–5°.
17. As soon as the first drop of hypochlorite is added, the reaction mixture becomes red in color, with the color deepening as the addition proceeds.
18. The impure material has a limited stability and should be sublimed as quickly as possible. The scale of the reaction should not be greatly increased unless an efficient large subliming apparatus is available. The submitters report similar yields on experiments four times this scale.
19. The product has a shelf life of several months if stored in the dark in a refrigerator.
20. This method has been used to prepare 4-methyl- [sublimed at 50° (0.1 mm.), 85%, m.p. 104°], 4-*tert*-butyl- [50° (0.1 mm.). 80%, m.p. 119°], 4-(4-nitrophenyl)- [100° (0.1 mm.), 25%, m.p. 130°], and 4-benzalamino-1,2,4-triazoline-3,5-dione [100° (0.1 mm.), 75%].

## 3. Discussion

Ethyl hydrazinecarboxylate has been prepared from hydrazine hydrate and ethyl *N*-tricarboxylate in good yield.[4] The method described here is comparable in efficiency, but has the added advantage that both starting materials are commercially available.

Methods for preparing 4-phenyl-1-carbethoxysemicarbazide and 4-phenylurazole have been described in principle by Zinner and Deucker.[5] 4-Phenylurazole has also been prepared from biurea and aniline hydrochloride;[6,7] however, the method is unreliable, with yields varying from 0 to 20%. 4-Substituted urazoles have also been made by heating the corresponding *N,N'*-disubstituted diamides of hydrazodicarboxylic acid,[8] but the results are difficult to reproduce.

4-Phenyl-1,2,4-triazoline-3,5-dione has been prepared by oxidizing 4-phenylurazole with lead dioxide,[6] and with ammoniacal silver nitrate followed by treatment with an ethereal solution of iodine.[7] The yields are low for both methods. 4-Substituted triazolinediones can also be made by oxidation of the corresponding urazole with fuming nitric acid[8] or dinitrogen tetroxide.[9] Oxidation with *tert*-butyl hypochlorite in acetone has also been described;[10,11] however, it yields an unstable product, even after sublimation. Dioxane[11] and ethyl acetate are preferred as solvents for the reaction, since the product is obtained in a stable form. The latter solvent is superior since 4-phenylurazole has a greater solubility in it.

In common with other azodicarboxylic acid derivatives, 4-phenyl-1,2,4-triazoline-3,5-dione has many uses. It undergoes Diels-Alder reactions with most dienes[10,11,12,13] and is, in fact, the most reactive dienophile so far reported.[14,15] As with the formation of all Diels-Alder adducts the reaction is

reversible, and in the case of the adduct with 3β-acetoxy-17-cyano-5,14,16-androstatriene, the reverse reaction can be made to proceed under especially mild conditions.[13] An instance has also been reported of the dione photochemically catalyzing other retro Diels-Alder reactions.[16] Along with the proved use of azodicarboxylic ester,[17,18] the dione should be potentially important in the preparation of strained ring compounds.

4-Phenyl-1,2,4-triazoline-3,5-dione also undergoes "addition-abstraction" reactions (*e.g.*, with acetone[16]). As would be expected for such a species, it will oxidize alcohols to the corresponding aldehydes or ketones.[19] This oxidation is especially mild (room temperature in benzene, chlorobenzene or ethyl acetate) and is, as such, a valuable method of oxidizing or preparing compounds sensitive to acid, base, or heat.

## References and Notes


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

dinitrogen tetroxide

Ethyl N-tricarboxylate

oxygen-free nitrogen

ethanol (64-17-5)

hydrogen chloride,

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

aniline hydrochloride (142-04-1)

benzaldehyde (100-52-7)

iodine (7553-56-2)

acetone (67-64-1)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

sodium wire (13966-32-0)

sodium ethoxide (141-52-6)

hydrazine hydrate (7803-57-8)

phenyl isocyanate (103-71-9)

dioxane (123-91-1)

diethyl carbonate (105-58-8)

Ethyl hydrazinecarboxylate (4114-31-2)

urazole (3232-84-6)

4-Phenyl-1,2,4-triazoline-3,5-dione,
4-Phenylurazole (15988-11-1)

4-Phenyl-1-carbethoxysemicarbazide

4-nitrophenyl isocyanate (100-28-7)

4-(4-nitrophenyl)-1-carbethoxysemicarbazide

4-nitrophenylurea

4-(4-nitrophenyl)urazole,
4-(4-Nitrophenyl)-1,2,4-triazoline-3,5-dione

4-Benzalaminourazole,
4-benzalamino-1,2,4-triazoline-3,5-dione

4-aminourazole

biurea (110-21-4)

3β-acetoxy-17-cyano-5,14,16-androstatriene

lead dioxide

tert-Butyl hypochlorite (507-40-4)

4-tert-Butyl-1-carbethoxysemicarbazide

4-tert-butylurazole

3H-1,2,4-Triazole-3,5(4H)-dione, 4-phenyl- (4233-33-4)