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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

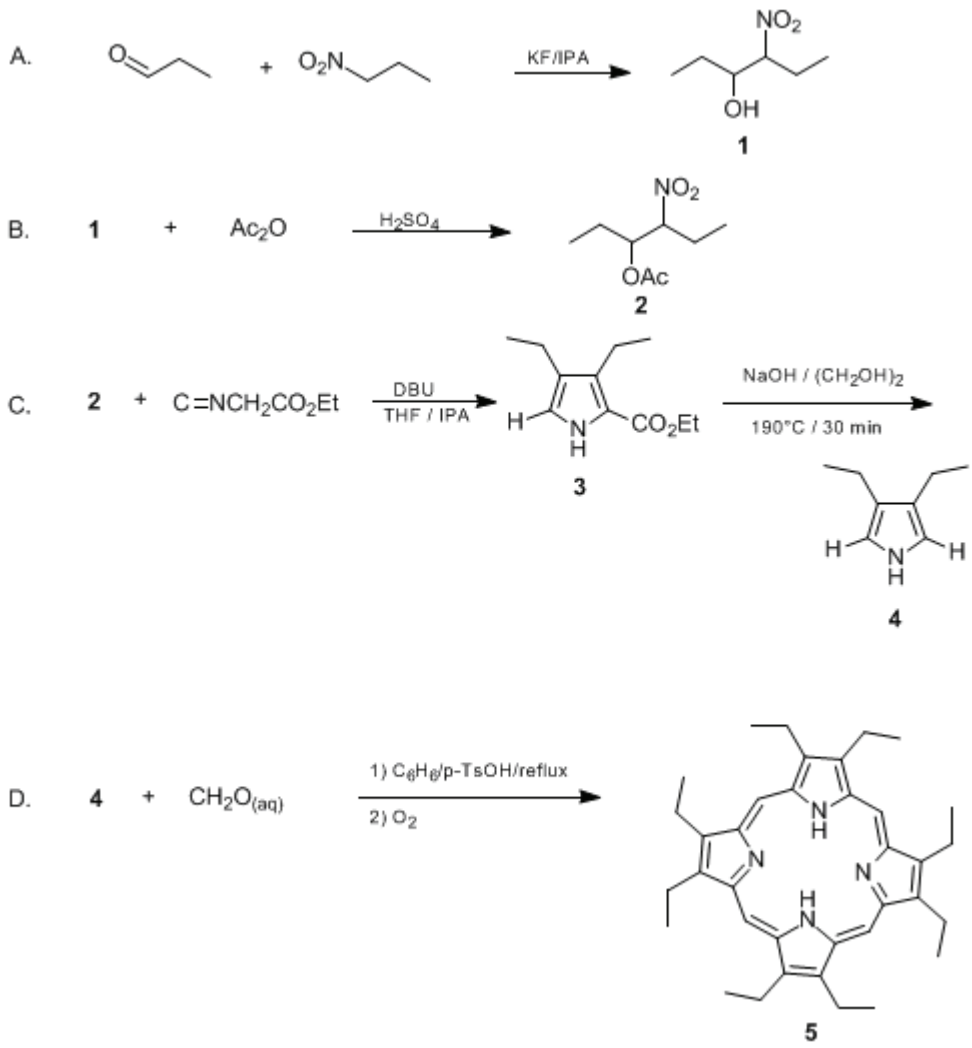
*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

DOI:10.15227/orgsyn.070.0068

*Organic Syntheses, Coll. Vol. 9, p.242 (1998); Vol. 70, p.68 (1992).*

# 3,4-DIETHYLPYRROLE AND 2,3,7,8,12,13,17,18-OCTAETHYLPORPHYRIN

## [Pyrrole, 3,4-diethyl and 21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-]




Submitted by Jonathan L. Sessler[1], Azadeh Mozaffari, and Martin R. Johnson.
Checked by Jürgen Fischer and Ekkehard Winterfeldt.

## 1. Procedure

A. *4-Nitro-3-hexanol* **(1)**.[2] To a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, dropping funnel, and drying tube are added propionaldehyde (174 g, 3 mol) and isopropyl alcohol (IPA) (450 mL) (Note 1). The solution is stirred while finely ground potassium fluoride (25 g, 0.15 mol) is added to the flask. 1-Nitropropane (267.3 g, 3 mol) (Note 1) is then added dropwise with stirring, and the temperature is kept below 40°C with the aid of an ice bath (Note 2). The ice bath is removed about 30 min after the addition of 1-nitropropane is complete. The flask contents are stirred for an additional 18 hr. The catalyst is then removed by filtration and the filtrate is concentrated under reduced pressure. The residue is poured into water (500 mL) and the oil is extracted with ether (3 × 300 mL). The ethereal layer is dried over anhydrous sodium sulfate ($Na_2SO_4$), and the solvent is removed under reduced pressure. The remaining liquid is distilled under reduced pressure and the fraction boiling at 88–90°C/2 mm is collected in a tared, 1-L round-bottomed flask,

yielding 3-nitro-4-hexanol (330 g, 2.24 mol, 65%) (Note 3). The flask containing the product is used directly in the next step.

B. *4-Acetoxy-3-nitrohexane* **(2)**.[3] To the above flask, containing 3-nitro-4-hexanol (330 g, 2.24 mol), is added a magnetic stirring egg and 1 mL of concd sulfuric acid. The contents of the flask are stirred in an ice bath and acetic anhydride (240 g, 2.35 mol) is added in portions, keeping the temperature of the reactants below 60°C. After the addition of the acetic anhydride is complete, the contents of the flask are stirred for 1 hr. The flask is then equipped for vacuum distillation. The lower boiling components ($Ac_2O$ and AcOH) are removed at 25 mm by gently heating the stirred contents of the flask (≤ 100°C bath temperature). After these reagents have been removed, the system is cooled, attached to a vacuum pump, and carefully heated. The fraction boiling at 105–107°C/10 mm is collected, affording 4-acetoxy-3-nitrohexane (379 g, 2.0 mol, 90%) (Note 4).

C. *Ethyl 3,4-diethylpyrrole-2-carboxylate* **(3)**[4] *and 3,4-Diethylpyrrole* **(4)**. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, dropping funnel, thermometer, and drying tube, and charged with 4-acetoxy-3-nitrohexane (103 g, 0.54 mol), ethyl isocyanoacetate (50.7 g, 0.45 mol, (Note 5)), anhydrous tetrahydrofuran (320 mL), and anhydrous isopropyl alcohol (IPA) (130 mL) (Note 1). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 152 g, 1 mol) (Note 6) & (Note 7) is then added, taking care to maintain the temperature at 20°C to 30°C at all times with the aid of an ice bath (Note 8). When addition of DBU is complete, the orange solution is stirred for 4 hr at room temperature. The solvent is completely removed under reduced pressure (50°C bath temp, 20–40 mm) and the residue is poured into a 1-L beaker and diluted with warm water (300 mL). To this biphasic mixture is added diethyl ether (300 mL). The contents of the beaker are poured into a separatory funnel. The aqueous layer is drawn off and extracted with an additional two portions of ether (300 mL). The ether layers are combined and washed with aqueous 10% hydrochloric acid (2 × 300 mL) and dried over magnesium sulfate ($MgSO_4$). The ether is removed under reduced pressure in a 1-L round-bottomed flask, leaving approximately 95 g of crude ethyl 3,4-diethylpyrrole-2-carboxylate **(3)** (Note 7). This material is not isolated, but is decarboxylated directly as follows: To the crude product **3** (95 g) is added sodium hydroxide (30 g, 0.75 mol) and ethylene glycol (300 mL). The contents are held at reflux under nitrogen for 1 hr, cooled, transferred to a 2-L separatory funnel, and diluted with water (500 mL) and hexane (600 mL). The layers are separated, and the aqueous layer is extracted further with hexane (3 × 300 mL). The hexane layers are combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue is distilled under reduced pressure, and the fraction boiling at 100°C/25 mm is collected, yielding 3,4-diethylpyrrole (21.14–22.00 g, 0.17–0.177 mol, 38.1–40%) (Note 9).

D. *2,3,7,8,12,13,17,18-Octaethylporphyrin* **(5)**. A 500-mL, round-bottomed flask is wrapped with aluminum foil and equipped with a reflux condenser with a Dean-Stark trap, mechanical stirrer, and nitrogen inlet. The flask is charged with 3,4-diethylpyrrole (1 g, 8.1 mmol), benzene (300 mL) (Note 10), a 37% solution of aqueous formaldehyde (0.73 mL, 8.9 mmol), and *p*-toluenesulfonic acid (0.03 g, 1.7 mmol). The mixture is stirred and heated at reflux under nitrogen using an oil bath, and the water is removed by means of the Dean-Stark trap. After 8 hr, the solution is cooled, and the Dean-Stark trap and condenser are replaced with a fritted glass aerator/bubbler. Oxygen is bubbled through the brown mixture while it is stirred for 12–24 hr. Benzene is removed from the flask by distillation under reduced pressure, and the residue is dissolved in chloroform (20 mL) (Note 11). The solution is washed with 1 N sodium hydroxide (40 mL) and water (2 × 20 mL). The chloroform solution is concentrated to 5 mL in a 100-mL, round-bottomed flask, carefully layered over with methanol (≈70 mL), and allowed to stand for 48 hr. The resulting solid is collected by filtration and dried under reduced pressure for 24 hr. The crude material is recrystallized twice from chloroform-hexanes [effected by dissolving in chloroform (≈ 10 mL), layering over with hexanes (≈70 mL), and allowing to stand overnight]. The final precipitate is collected by filtration and dried under reduced pressure for 48 hr to yield analytically pure 2,3,7,8,12,13,17,18-octaethylporphyrin (720 mg, 1.34 mmol, 66.4%) as a purple, amorphous powder (Note 12).

## 2. Notes

1. Propionaldehyde and 1-nitropropane were obtained from Aldrich Chemical Company, Inc., and used as received. Isopropyl alcohol and tetrahydrofuran were obtained from J.T. Baker and used as received.

2. It is necessary to cool the reaction vessel to prevent the volatile propionaldehyde from evaporating.
3. The literature boiling point is reported[2] as 89°C (2 mm).
4. The spectral and analytical properties are as follows: $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.99 (m, 6 H, $CH_3$), 1.62 and 1.80 (2 × m, 2 H, $O_2NCHCH_2CH_3$), 1.99 and 2.12 (2 × m, 2 H, $CH_3CO_2CHCH_2CH_3$), 2.06 (m, 3 H, $CH_3CO_2$), 4.56 (m, 1 H, $CHNO_2$), 5.16 and 5.24 (2 × m, 1 H, $CH_3CO_2CH$); C.I. MS, $(M+1)^+$ 190 (calcd for $C_8H_{15}NO_4 \cdot H$: 190). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.98; H, 8.14; N, 7.01.
5. A disadvantage of the present procedure is that it requires the use of the relatively foul-smelling substance, ethyl isocyanoacetate. Although this material is commercially available (from, e.g., Aldrich Chemical Company, Inc.), it is moderately expensive. The authors have found that the existing preparative procedure (Hartman, G. D.; Weinstock, L. M. *Org. Synth., Coll. Vol VI* **1988**, 620) can be improved by the use of trichloromethyl chloroformate (Kurita, K.; Iwakura, Y. *Org. Synth., Coll. Vol. VI* **1988**, 715) rather than phosphoryl chloride. This substitution simplifies purification of the isocyanoacetate by eliminating the aqueous portion of the workup.
6. DBU was obtained from Aldrich Chemical Company, Inc. and used as received.
7. Two equivalents of DBU are used here. One equivalent of DBU eliminates acetate from one of the reactants to form 3-nitro-3-hexene in situ, which goes on to form the pyrrole. The intermediate ethyl 3,4-diethylpyrrole-2-carboxylate can also be prepared directly from ethyl isocyanoacetate and 3-nitro-3-hexene in good yield (86%) under conditions similar to those outlined here.[5] Although this alternative requires a further manipulative step, it requires only half as much DBU.
8. It is important not to allow the temperature to drop below 20°C because the reaction slows down considerably. Unreacted DBU then builds up. As a result, when the temperature does climb, it does so rapidly (often to as high as 65°C). This results in a significantly lower yield.
9. The spectral and physical properties are as follows: $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.16 (t, 6 H, $CH_2CH_3$), 2.47 (q, 4 H, $CH_2CH_3$), 6.42 (d, 2 H, pyrrole CH), 7.65 (s, 1 H, pyrrole NH); MS m/e (relative intensity) 123 (46), 108 (100), 93 (37); bp 100°C/25 mm; 69°C/7 mm (lit.[6] bp, 83°C/10 mm).
10. Benzene is a known carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.
11. Chloroform is a suspected carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.
12. The spectral and analytical properties are as follows: $^1$H NMR (300 MHz, $CDCl_3$) δ: −3.72 (s, 2 H, NH), 1.95 (t, 24 H, $CH_2CH_3$), 4.12 (q, 16 H, $CH_2CH_3$), 10.12 (s, 4 H, meso CH); HRMS, $M^+$ 534.37351 (calcd for $C_{36}H_{46}N_4$: 534.37225). Anal. Calcd for $C_{36}H_{46}N_4$: C, 80.85; H, 8.67; N, 10.48. Found: C, 80.89; H, 8.56; N, 10.37; UV-vis ($CHCl_3$-MeOH 95:5 vv.) $\lambda_{max}$ (log ε): 398 (5.20), 498 (4.10), 533 (4.00), 565 (3.79), 618 (3.68) nm.

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

Octaethylporphyrin (OEP) and tetraphenylporphyrin (TPP) remain among the most widely used of an increasingly diverse set of available synthetic porphyrins. The inherently high symmetry and relatively good solubility properties of these systems often combine to make them the models of choice for a wide range of biological modeling and inorganic chemical applications.[7] Recently, an optimized synthesis of TPP and related tetraarylporphyrins has been developed by Lindsey and co-workers.[8,9,10] At present, however, the synthesis of OEP **(5)** remains problematic: Although numerous strategies have been reported,[5,11,12,13,14,15,16,17,18,19] no convenient, high-yield procedure currently exists.

Traditionally, octaethylporphyrin has been prepared by the self-condensation of 2-N,N'-diethylaminomethyl-3,4-diethylpyrrole,[11,12,13] ethyl 5-N,N'-diethylaminomethyl-3,4-diethylpyrrole-2-carboxylate,[14,15] or 3,4-diethyl-5-hydroxymethylpyrrole-2-carboxylic acid under oxidative conditions.[16] It has also been prepared on a small scale directly from 3,4-diethylpyrrole in 65% yield by condensation with aqueous formaldehyde under acid-catalyzed conditions,[17,18] using conditions similar to those which have proved useful for preparing the corresponding octamethylporphyrin analogue.[20] All of these

syntheses derive from the same, initial pyrrole precursor, namely, ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate, prepared from the classic, reverse-sense Knorr reaction of ethyl propionylacetate with 2,4-pentanedione, and they require several steps before the ultimate porphyrin-forming condensation. Octaethylporphyrin has also been prepared recently by the reduction of 2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin by diborane,[17,18] and by the condensation of 3,4-diethylpyrrole-N-carboxylic acid with formaldehyde in refluxing acetic acid/pyridine.[19] Neither of these procedures, however, truly overcomes the problem associated with preparing the initial pyrrole.

The synthesis reported here circumvents many of the problems associated with existing preparative methods. Specifically, it makes use of a new procedure of Barton and Zard[4] in the key pyrrole-forming step. This method, which gives an α-unsubstituted pyrrole ester (e.g., **3**) directly in good yield, provides a substantial saving in labor when compared to the Knorr approach, and it is very flexible with regard to the kinds of β-substitution allowed. Since the remaining α-ester group can be conveniently removed by saponification and subsequent decarboxylation (often, as is the case here, without isolation of the initial pyrrole product), this method provides a quick and easy means of preparing 3,4-dialkylated pyrroles. Simple acid-catalyzed condensation of the resulting 3,4-dialkylpyrroles with formaldehyde and subsequent oxidation is then all that is required to complete the synthesis of an octaalkylporphyrin.[21,22] We have found that these latter transformations may be readily effected using aqueous formaldehyde under acid-catalyzed dehydrating conditions, followed by simple air-induced oxidation. In the specific case of octaethylporphyrin, when the reaction is run on a 1-g scale, a 75% yield of analytically pure product is obtained following workup and purification (which involves only simple recrystallizations and no chromatographic separations). This procedure can be conveniently scaled up by a factor of ten. Under these conditions, it still gives a good yield (55%) of pure product. It does, however, require relatively large amounts of benzene (3 L for a reaction carried out with 10 g of 3,4-diethylpyrrole), which could present a health hazard. However, if due caution is exercised with regard to this point, the present method provides an easy way to prepare large quantities of octaethylporphyrin. As such it represents a considerable advance over earlier methods in terms of both ease and convenience.

## References and Notes


1. Department of Chemistry, University of Texas at Austin, Austin, TX 78712.
2. Procedure of Kambe and Yasuda: Kambe, S.; Yasuda, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1444.
3. Procedure of Tindall: Tindall, J. B. *Ind. Eng. Chem.* **1941**, *33*, 65.
4. Procedure of Barton and Zard: Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098.
5. Ono, N.; Maruyama, K. *Chem. Lett.* **1988**, 1511.
6. Fischer, H.; Guggemos, H.; Schäfer, A. *Ann. Chem.* **1939**, *540*, 30.
7. "The Porphyrins"; Dolphin, D., Ed.; Academic Press: New York, 1978–1979; Vols. I-VII.
8. Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969;
9. Lindsey, J. B.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827;
10. Wagner, R. W.; Lawrence, D. S.; Lindsey, J. S. *Tetrahedron Lett.* **1987**, *28*, 3069.
11. Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733;
12. Eisner, U.; Linstead, R. P.; Parkes, E. A.; Stephen, E. *J. Chem. Soc.* **1956**, 1655.
13. Whitlock, H. W.; Hanauer, R. *J. Org. Chem.* **1968**, *33*, 2169.
14. Paine, J. B., III; Kirshner, W. B.; Moskowitz, D. W.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 3857.
15. Wang, C.-B.; Chang, C. K. *Synthesis* **1979**, 548.
16. Inhoffen, H. H.; Fuhrhop, J. H.; Voight, H.; Brockmann, H., Jr. *Ann. Chem.* **1966**, *695*, 133.
17. Cheng, D. O.; LeGoff, E. *Tetrahedron Lett.* **1977**, 1469;
18. LeGoff, E.; Cheng, D. O. In "Porphyrin Chemistry Advances"; F. R. Longo, Ed.; Ann Arbor Science Publishers, 1979; pp. 153–156.
19. Callot, H. J.; Louati, A.; Gross, M. *Bull. Soc. Chim. Fr.* **1983**, 317; Callot, H. J.; Louati, A.; Gross, M. *Angew. Chem., Inter. Ed. Engl.* **1982**, *21*, 285.
20. Treibs, A.; Häberle, N. *Justus Liebigs Ann. Chem.* **1968**, *718*, 183.
21. Alternatively, the ethyl 3,4-diethylpyrrole-2-carboxylate may be carried on directly to give

octaethylporphyrin,[5] although the yields reported (ca. 40%) are not quite as good as those obtained by the present procedure. Similarly, this substance or the 3,4-diethylpyrrole produced by the present procedure could conceivably serve as the basis for an an improved synthesis via a Mannich base-type approach such as that outlined in refs. 9–12.

**22.** The procedure reported here appears to be quite general. We have, for example, used it to prepare a β-substituted tetrakis-fused cyclohexylporphyrin (1,2,3,4,8,9,10,11,15,16,17,18,22, 23,24,25-hexadecahydro-29H,31H-tetrabenzo[BGLQ]porphine) in 51% overall yield starting from 1-nitrocyclohexene.

---

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

hexanes

diborane

2,3,7,8,12,13,17,18-Octaethylporphyrin

DBU

Pyrrole, 3,4-diethyl and 21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-

Octaethylporphyrin (OEP)

tetraphenylporphyrin (TPP)

TPP

octaethylporphyrin

ethyl 5-N,N'-diethylaminomethyl-3,4-diethylpyrrole-2-carboxylate

2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

formaldehyde (50-00-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

pyridine (110-86-1)

isopropyl alcohol (67-63-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

2,4-pentanedione (123-54-6)

potassium fluoride (7789-23-3)

hexane (110-54-3)

1-nitropropane (108-03-2)

p-toluenesulfonic acid (104-15-4)

Trichloromethyl chloroformate (503-38-8)

phosphoryl chloride (10025-87-3)

Ethyl isocyanoacetate (2999-46-4)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

3,4-Diethylpyrrole (16200-52-5)

4-Nitro-3-hexanol,

3-nitro-4-hexanol (5342-71-2)

4-Acetoxy-3-nitrohexane (3750-83-2)

Ethyl 3,4-diethylpyrrole-2-carboxylate (97336-41-9)

3-nitro-3-hexene (4812-22-0)

3,4-diethyl-5-hydroxymethylpyrrole-2-carboxylic acid

ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate (16200-50-3)

ethyl propionylacetate (4949-44-4)

3,4-diethylpyrrole-N-carboxylic acid

1-nitrocyclohexene

2-N,N'-diethylaminomethyl-3,4-diethylpyrrole