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.
CONVERSION OF AMINES TO PHOSPHO ESTERS: DECYL DIETHYL PHOSPHATE

[Phosphoric acid, decyl diethyl ester]

A. Diethyl decylphosphoramidate. An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-inch magnetic stirring bar is flushed with argon and charged with 10.0 mL (0.05 mol) of decylamine (Note 2) and 35 mL (0.25 mol) of triethylamine (Note 3). The solution is cooled to 0°C in an ice bath with stirring. Using a 10-mL, gas-tight syringe, 7.4 mL (0.05 mol) of diethyl chlorophosphate (Note 4) is added dropwise, whereupon a voluminous white precipitate forms. Upon completion of addition, vigorous stirring is maintained for 30 min at 0°C. The mixture is diluted with 100 mL of ice-cold, anhydrous diethyl ether (Note 5) and filtered through a sintered glass funnel (Note 6) layered with ca. 1 in. of Celite. The solid residue is washed with ca. 50 mL of fresh, cold ether, and the filtrate is concentrated by rotary evaporation (room temperature under aspirator pressure) to give a cloudy white suspension. Another aliquot of cold ether (50 mL) is added and the process of filtration through Celite is repeated at least three times (Note 7). Concentration by rotary evaporation followed by drying under reduced pressure for 1 hr at 0.1 mm provides 14.0–14.5 g (95–99% yield) of a clear, pale yellow oil (Note 8). This compound is stored under argon until used in part B.

B. Decyl diethyl phosphate. An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-in. magnetic stirring bar is flushed with argon and charged with 14 g (0.048 mol) of diethyl decylphosphoramidate and 125 mL of dichloromethane (Note 9). Using a 20-mL gas-tight syringe, 31.9 mL (0.24 mol) of isoamyl nitrite (Note 10) is added successively in two portions (20 mL, 11.9 mL) at 33°C (oil bath) and stirring is continued for 18 hr. At this time, nitrogen evolution is no longer observed and thin layer chromatography (eluting with 3:2 hexanes:ethyl acetate, (Note 11)) indicates the complete disappearance of starting phosphoramidate (R_f = 0.1) and the appearance of a major product spot (R_f = 0.3). The solvent is removed by rotary evaporation (40–50°C under aspirator pressure) to produce 17 g (>100%) of a viscous yellow oil that still contains traces of isoamyl nitrite and other impurities. The crude product is redissolved in 20 mL of ethyl acetate, loaded onto a 1" × 6" column of Silica Gel 60 (Note 12) and eluted under pressure (Note 13) with 150 mL of ethyl acetate into a 500-mL, round-bottomed flask. The solvent is removed by rotary evaporation (room temperature under aspirator pressure), the product is transferred to an ammonia-washed (Note 14), oven-dried, 50-mL, round-bottomed flask and distilled under vacuum to yield 7.7–8.8 g (54–60%) of the phospho triester as a clear, colorless oil (bp 95–105°C/0.15 mm) (Note 15) and (Note 16).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C, assembled hot, and cooled under a stream of argon.2
2. Decylamine was obtained from Aldrich Chemical Company, Inc., and was distilled under reduced pressure prior to use (bp 70°C at 1.9 mm).
3. Reagent grade triethylamine was obtained from Mallinckrodt Inc. and distilled from barium oxide
immediately prior to use (bp 87°C at 1 atm).

4. Diethyl chlorophosphate (97%) was obtained from Aldrich Chemical Company, Inc., and distilled before use (bp 58–60°C at 2 mm). This material is a highly toxic acetylcholinesterase inhibitor and must be handled with caution.

5. Diethyl ether was distilled from sodium benzo phenone ketyl immediately before use.

6. A grade D (10–20 m) sintered glass funnel from Ace Glass Corporation was used.

7. Insufficient filtrations led to solid precipitates after rotary evaporation.

8. The product exhibits the following spectral properties: IR (film) cm⁻¹: 3220, 2970, 2880, 1470, 1240, 1060, 1040; ¹H NMR (300 MHz, CDCl₃) δ: 0.78 (t, 3 H, J = 6.4, CH₃), 1.17–1.25 (m, 20 H, -[CH₂]₇ - OCH₂CH₃), 2.79 (m, 3 H, NH, CH₂N), 3.96 (m, 4 H, OCH₂CH₃); CIMS (isobutane) m/z 294 (M+1, 100%).

9. Dichloromethane was dried and distilled over calcium hydride immediately prior to use.

10. Isoamyl nitrite (97%) was obtained from either Aldrich Chemical Company, Inc., or Fluka AG and used without further purification. Five equivalents of isoamyl nitrite were optimal for complete consumption of starting phosphoramidate. Use of three equivalents of isoamyl nitrite necessitated much longer reaction times (2–3 days) and resulted in incomplete conversions.

11. ACS reagent grade hexanes and ethyl acetate were obtained from Aldrich Chemical Company, Inc. Thin layer chromatography was performed on Silica Gel 60 F-254 precoated plates. Chromatograms were visualized with phosphomolybdic acid reagent from Aldrich Chemical Company, Inc.

12. Silica Gel 60 (230–400 mesh) was obtained from Merck & Company, Inc.

13. The published procedure of flash chromatography was employed.¹

14. The distillation flask was rinsed with 28% ammonium hydroxide solution to neutralize the acidic glass surface, then placed directly in the oven (i.e., with no aqueous rinse).

15. The product exhibits the following spectral properties: IR (film) cm⁻¹: 2940, 2860, 1470, 1395, 1275, 1040, 755; ¹H NMR (300 MHz, CDCl₃) δ: 0.82 (t, 3 H, J = 6.8, CH₃), 1.24–1.33 (m, 20 H, -[CH₂]₇, -OCH₂CH₃), 1.63 (m, 2 H, CH₂CH₂OP), 3.96–4.13 (m, 6 H, OCH₂-); CIMS (isobutane) m/z 295 (M+1, 50%), 155 (100%).

16. The checkers isolated decyl isoamyl ether as a side-reaction product in 2.0–2.3 g (18–20%) yield. This product exhibits the following spectral properties: ¹H NMR (200 MHz, CDCl₃) δ: 0.80–1.05 (m, 9 H, C[CH₃]₂ -CH₃), 1.12–1.80 (m, 19 H, [CH₂]₇, -OC -CH₂CH), 3.41 (q, 4 H, J = 6.6, OCH₂); (bp 80–85°C/0.5 mm).

**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**

Phospho esters are important components of nucleic acids, lipids, and other biologically significant substances. Most existing phospho ester syntheses rely on the direct phosphorylation of alcohols. Here, a general procedure for the conversion of amines into phospho esters is described,³ based on the well-known thermal decomposition of N-nitroso carboxamides to carboxylic esters, that represents one of the few useful synthetic methods for replacing an amine group with oxygen-based functionality.⁶ ⁷ ⁸ ⁹ ¹⁰ ¹¹ ¹² Besides complementing existing methods for synthesizing phospho triesters, the nitrosation of phosphoramidates makes available unnatural phosphates derived from naturally-occurring amino sugars, alkaloids, and amino acids. Phospho monoesters may similarly be prepared by hydrogenolysis of the corresponding alkyl dibenzyl phosphates.¹⁴

**References and Notes**

1. Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853–1301

2. Techniques for handling air-sensitive compounds are reviewed in Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley: New York, 1975: Technical data on air-sensitive compounds is also available in Lane, C. F.; Kramer, G. W.
Aldrichemica Acta 1977, 10, 11–16.

10. For alternative methods, see (a) Katritzky, A. R. Tetrahedron 1980, 36, 679;

Appendix

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

hexanes

sodium benzophenone ketyl

ethyl acetate (141-78-6)

ether,

diethyl ether (60-29-7)

barium oxide

nitrogen (7727-37-9)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

Isoamyl nitrite (110-46-3)

decylamine (2016-57-1)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)
diethyl chlorophosphate (814-49-3)

phosphomolybdic acid (51429-74-4)

Decyl diethyl phosphate,
Phosphoric acid, decyl diethyl ester (20195-16-8)

Diethyl decylphosphoramidate (53246-96-1)

decyl isoamyl ether