



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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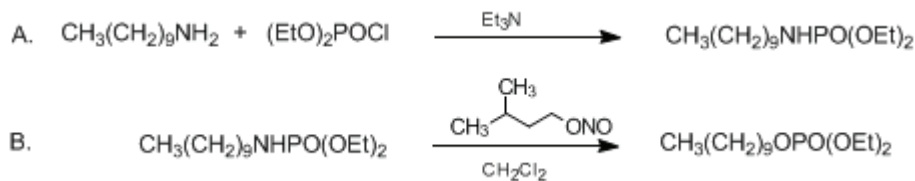
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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CONVERSION OF AMINES TO PHOSPHO ESTERS: **DECYL DIETHYL PHOSPHATE**

[Phosphoric acid, decyl diethyl ester]



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1. Procedure

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

- All glassware was oven-dried for at least 24 hr at 130°C, assembled hot, and cooled under a stream of argon.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).
- 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 benzophenone 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, CDCl_3) δ : 0.78 (t, 3 H, $J = 6.4$, CH_3), 1.17–1.25 (m, 20 H, $-\text{[CH}_2\text{]}_7-\text{OCH}_2\text{CH}_3$), 1.39 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 2.79 (m, 3 H, NH, CH_2N), 3.96 (m, 4 H, OCH_2CH_3); 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.³

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, CDCl_3) δ : 0.82 (t, 3 H, $J = 6.8$, CH_3), 1.24–1.33 (m, 20 H, $-\text{[CH}_2\text{]}_7-\text{OCH}_2\text{CH}_3$), 1.63 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OP}$), 3.96–4.13 (m, 6 H, OCH_2-); 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, CDCl_3) δ : 0.80–1.05 (m, 9 H, $\text{C[CH}_3\text{]}_2$, $-\text{CH}_3$), 1.12–1.80 (m, 19 H, $[\text{CH}_2]_8$, $-\text{OC}-\text{CH}_2\text{CH}$), 3.41 (q, 4 H, $J = 6.6$, OCH_2); (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.⁴ Here, a general procedure for the conversion of amines into phospho esters is described,⁵ 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

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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