Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

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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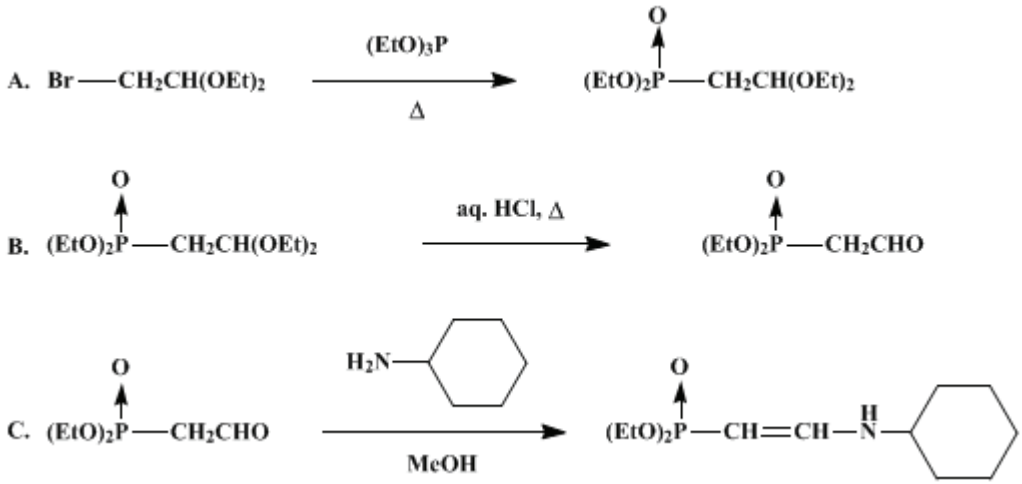
DIETHYL 2-(CYCLOHEXYLAMINO)VINYLPHOSPHONATE

[Phosphonic acid, [2-(cyclohexylamino)ethenyl]-, diethyl ester]



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1. Procedure

A. *Diethyl 2,2-diethoxyethylphosphonate* (Note 1). A 2-l., three-necked, round-bottomed flask fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 410 g. (2.08 moles) of bromoacetaldehyde diethyl acetal (Note 2), and a gentle stream of nitrogen is then passed continuously through the system. To the stirred solution is added dropwise 316 g. (1.90 moles) of triethyl phosphite (Note 3) over a period of 30 minutes, at 110–120°. The mixture is then stirred for 3 hours at 160°. The ethyl bromide evolved is trapped with a condenser and a receiver cooled in an ice bath. The low-boiling material (below 100°) is distilled under reduced pressure (22 mm.). The residual oil is fractionated under reduced pressure, and the fraction boiling at 101–103° (0.8 mm.) is collected, yielding 338 g. (70%) (Note 4).

B. *Diethyl formylmethylphosphonate* (Note 5). A mixture of 192 g. (0.755 mole) of diethyl 2,2-diethoxyethylphosphonate and 670 ml. of 2% hydrochloric acid is refluxed for 10 minutes under a nitrogen atmosphere. To the cooled (20–30°) mixture is added 240 g. of sodium chloride (Note 6). The resulting mixture is extracted with three, 500-ml. portions of dichloromethane. The combined organic extracts are washed successively with 40 ml. of 5% aqueous sodium hydrogen carbonate solution (Note 7) and 300 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at water bath temperatures (60–70°). The resulting residue, weighing approximately 125 g., is fractionated under reduced pressure, and the fraction boiling at 100–103° (0.8 mm.) is collected, yielding 104 g. (76%) (Note 8) and (Note 9).

C. *Diethyl 2-(cyclohexylamino)vinylphosphonate*. A 1-l., two-necked, round-bottomed flask fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 90.0 g. (0.500 mole) of diethyl formylmethylphosphonate and 400 ml. of dry methanol. Under a nitrogen atmosphere, 49.6 g. (0.501 mole) of cyclohexylamine (Note 10) is added in portions to the stirred solution, over a period of 5 minutes. During the addition the temperature is maintained at 0–5° with an ice bath. The mixture is stirred for an additional 10 minutes at room temperature, and then the methanol is distilled from the mixture under reduced pressure (10–35 mm.) at water bath temperatures (25–30°). The residue is dissolved in 300 ml. of dry diethyl ether (Note 11), dried over anhydrous potassium carbonate (70 g.) (Note 12), and evaporated to dryness. The residual oil is fractionated under reduced pressure in the presence of 300 mg. of anhydrous potassium carbonate (Note 13), and the fraction boiling at 126–141°

(0.08 mm.) is collected, giving 89 g. (68%) (Note 14). The fraction above is crystallized from dry pentane (Note 15), yielding 79 g. (60%) of diethyl 2-(cyclohexylamino)vinylphosphonate, m.p. 58–61° (Note 16).

2. Notes

1. This procedure is essentially the same as that described by Dawson and Burger.[3]
2. Bromoacetaldehyde diethyl acetal was distilled; b.p. 74–76° (25 mm.). Its preparation is described in *Org. Synth.*, **Coll. Vol. 3**, 123 (1955).
3. Triethyl phosphite was distilled; b.p. 43–44° (10 mm.). Its preparation is described in *Org. Synth.*, **Coll. Vol. 4**, 955 (1963).
4. The reported[3] boiling point is 128–130° (2 mm.). The checkers found the product to be pure by GC (UCW-98 at 150°). The ^{1}H NMR spectrum had the following characteristic peaks ($CDCl_3$): δ 1.22, 1.34 (2t, J = 7Hz., 12H, 4CH_3), 2.17 (d of d, J = 19 and 6Hz., 2H, CH_2CH), 3.6 [2q, J = 7Hz., 4H, CH(OCH_2CH$_3$)$_2$], 4.1 [2q, J = 7Hz., 4H, ($CH_3CH_2O)_2PO$], 4.90 [d of t, J = 6 and ~6Hz., 1H, $CH_2CH(OC_2H_5)_2$].
5. This procedure is essentially the same as that described by Dawson and Burger.[3]
6. It is necessary to saturate the aqueous layer with sodium chloride in order to extract the product effectively.
7. The checkers found that it was necessary to neutralize any excess acid to prevent polymerization of the product during the distillation.
8. There is no report of the boiling point of the product in the literature.[3] The product has an IR absorption (CCl_4 solution) at 1732 cm.$^{-1}$ (aldehyde C=O).
9. The checkers found that the product contained a 5–6% contamination of starting material [GC (UCW-98, 120°) and ^{1}H NMR]. The ^{1}H NMR spectrum ($CDCl_3$): δ 1.35 (t, J = 7 Hz., 6H, 2CH_3), 3.11 [d of d, J = 22 and 3.5 Hz., 2h, P(O)CH_2CH], 4.2 [2q, J = 7 Hz., 4H, ($CH_3CH_2O)_2PO$], 9.70 (d of t, J = 3 and 1 Hz., 1H, C*H*O).
10. Reagent grade cyclohexylamine was redistilled before use.
11. Dry ether was used to minimize the water content of the solution.
12. To avoid acid-induced dimerization[4] of diethyl 2-(cyclohexylamino)vinylphosphonate, the solution was dried thoroughly, usually overnight, with anhydrous potassium carbonate.
13. The distillation was carried out in the presence of powdered anhydrous potassium carbonate to prevent dimerization[4] of diethyl 2-(cyclohexylamino)vinylphosphonate.
14. The yields were 65–75% in several runs. The distilled oil was sufficiently pure for further use.
15. Reagent grade pentane passed through Merck anhydrous neutral alumina was used. Crystallization was carried out at 0° using 50 ml. of dry pentane. Filtration of the crystals was carried out under dry nitrogen. The submitters succeeded in crystallizing diethyl 2-(cyclohexylamino)vinylphosphonate only after the publication of its preparation.[4] The crystalline product is stable for several months, if stored at 0° under anhydrous conditions.
16. The checkers were not able to obtain the product in crystalline form. The ^{1}H NMR spectrum ($CDCl_3$): δ 1,3 (t, J = 7 Hz., CH_3CH$_2$O), 1.0–2.1 (m, cyclohexyl *H*), 4.0 (quintet, J = 7 Hz., 2 CH_3CH_2O), 4.3–5.0 (broad, N*H*), 5.9–7.7 (m, -CH=CH-). The number of olefinic protons was estimated to be 1.7–1.8 by comparison of the area in the region δ 5.9–7.7 with the total area in the spectrum. Although this value is slightly low, it was found that the sample was sufficiently pure to carry out further transformations. The IR spectrum has the following absorptions (neat): 3300 (N-H str.), 1620, 1210, 1058, 1035, and 955 cm.$^{-1}$.

3. Discussion

Diethyl 2-(cyclohexylamino)vinylphosphonate has proved to be an excellent reagent for conversion of aldehydes and ketones into the corresponding α,β-unsaturated aldehydes.[4,5] Formylmethylenetriphenylphosphorane[6] and diethyl 2,2-(diethoxy)ethylphosphonate[7] have been prepared and used for the conversion of aldehydes, but not ketones and hindered aldehydes, into α,β-unsaturated aldehydes. When ethyl diethylphosphonoacetate[8] or diethyl cyanomethylphosphonate[9] is used to obtain an α,β unsaturated aldehyde, the conversion requires several stages.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 358

References and Notes

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

alumina

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

cyclohexylamine (108-91-8)

Diethyl 2-(cyclohexylamino)vinylphosphonate,
Phosphonic acid, [2-(cyclohexylamino)ethenyl]-, diethyl ester (20061-84-1)

Triethyl phosphite (122-52-1)

ethyl diethylphosphonoacetate (867-13-0)

bromoacetaldehyde diethyl acetal (2032-35-1)

Diethyl 2,2-diethoxyethylphosphonate,
diethyl 2,2-(diethoxy)ethylphosphonate (7598-61-0)

Diethyl formylmethylphosphonate (1606-75-3)

Formylmethylenetriphenylphosphorane

diethyl cyanomethylphosphonate (2537-48-6)