Organic Syntheses

A Publication
of Reliable Methods
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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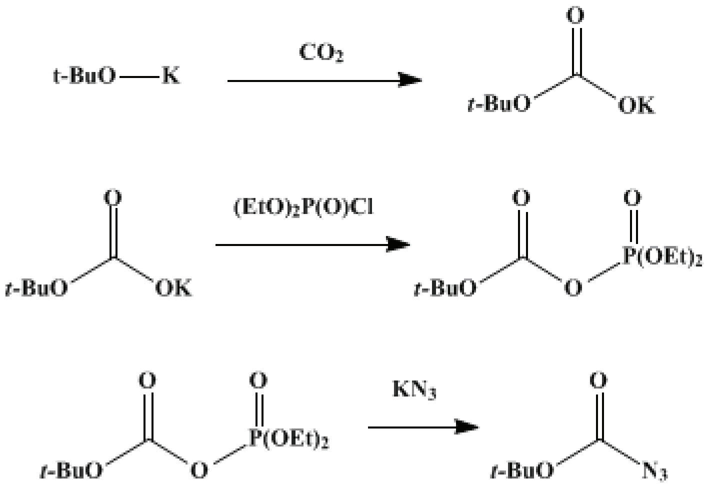
tert-BUTYL AZIDOFORMATE

[Carbonazidic acid, 1,1-dimethylethyl ester]



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Checked by Frederick J. Sauter, Walter J. Campbell, and Herbert O. House.

1. Procedure

Caution! Tests conducted by the Eastman Kodak Company have shown that tert-butyl azidoformate, also known as tert-butoxy carbonyl azide and t-BOC azide, is a thermally unstable, shock-sensitive compound (TNT equivalence: 45%).

A number of less-hazardous reagents that can be substituted for tert-butyl azidoformate in tert-butoxycarbonylation reactions are available, including 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Aldrich Chemical Company), O-tert-butyl S-phenylthiocarbonate (Eastman Organic Chemicals), di-tert-butyl dicarbonate[2] and tert-butyl phenyl carbonate.[3]

A. tert-*Butylcarbonic diethylphosphoric anhydride*. A 500-ml., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas-inlet tube is dried in an oven, flushed with nitrogen, and allowed to cool while an atmosphere of nitrogen is maintained in the reaction vessel. To the flask are added successively 250 ml. of anhydrous tetrahydrofuran (Note 1) and 13.9 g. (0.124 mole) of alcohol-free potassium *tert*-butoxide (Note 2). After the mixture has been stirred for 10 min. under a nitrogen atmosphere to complete dissolution of the salt, the solution is cooled in an ice bath, and a slow stream of anhydrous carbon dioxide (Note 3) is bubbled through the cold solution for 1.5 hours with continuous stirring. While cooling, stirring, and the flow of carbon dioxide are maintained, a solution of 20.6 g. (0.120 mole) of pure diethyl phosphorochloridate (Note 4) in 50 ml. of anhydrous tetrahydrofuran (Note 1) is added dropwise to the reaction mixture, and the cold reaction mixture is stirred for an additional 30 minutes under a carbon dioxide atmosphere. After the solvent has been removed from the reaction mixture by concentration with a rotary evaporator at room temperature, the residual mixture of anhydride and potassium chloride is diluted with 300 ml. of anhydrous diethyl ether and centrifuged, separating the insoluble salt. The salt is successively suspended in two 150-ml. portions of anhydrous ether and centrifuged to remove any remaining ether soluble product. The combined ether solutions are concentrated at room temperature with a rotary evaporator, leaving 25–28 g. (84–91%) of the crude anhydride, as a colorless to pale yellow liquid (Note 5), sufficiently pure for use in the next step.

B. tert-*Butyl azidoformate.* A 300-ml., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas-inlet tube is dried in an oven, flushed with nitrogen, and allowed to cool while a nitrogen atmosphere is maintained in the reaction vessel. To the flask are added 120 ml. of anhydrous dimethyl sulfoxide (Note 6) and 8.1 g (0.10 mole) of powdered potassium azide (Note 7). While a nitrogen atmosphere is maintained in the reaction vessel, the mixture is stirred for 30 minutes to dissolve the bulk of the potassium azide before 25.4 g. (0.100 mole) of *tert*-butylcarbonic diethylphosphoric anhydride is added dropwise with stirring. During this addition the temperature of the reaction mixture is maintained at approximately 25° with a water bath. The resulting solution is stirred at 20–25° for 1 hour; 120 ml. of water is then added dropwise while stirring and external cooling are maintained. The resulting mixture is extracted with three 120-ml. portions of pentane, and the combined pentane extracts are washed successively with 20 ml. of water and 20 ml. of saturated aqueous sodium chloride. After the pentane solution has been dried over magnesium sulfate, the pentane is removed at room temperature with a rotary evaporator. The residual crude product, 11–14 g. of a pale yellow liquid, is distilled under reduced pressure from a distilling flask heated in a water bath. *Caution! This distillation should be conducted in a hood behind a safety shield.* (Note 8). The product is collected as 7.2–9.3 g. (50–65%) of colorless liquid, b.p. 57–61° (40 mm.), n_D^{24} 1.4224–1.4230 (Note 9).

2. Notes

1. A reagent grade of tetrahydrofuran should be redistilled from lithium aluminum hydride immediately before use. In this distillation discontinue heating when the residue in the stillpot has reached a volume of 50–100 ml.
2. Alcohol-free potassium *tert*-butoxide, obtained from the MSA Research Corporation, Callery, Pennsylvania, should be weighed and transferred under anhydrous conditions.
3. The carbon dioxide, obtained from a cylinder or from a container packed with dry ice, should be passed through a drying tube packed with silica gel or anhydrous calcium sulfate.
4. The diethyl phosphorochloridate, available from Stauffer Chemical Company, New York, should be redistilled before use: b.p. 60° (2 mm.), n_D^{25} 1.4153.
5. IR (CCl_4), 1770 (C=O), 1255 and 1292 cm.$^{-1}$ (P=O); ^1H NMR (CCl_4), δ 1.38 (pair of t, $J_{H\text{-}H}$ = 6.6Hz., $J_{P\text{-}H}$ = 2.5 Hz., 6H, $2CH_2CH_3$), 1.53 [s, 9H, $C(CH_3)_3$], and 4.17 (pair of quadruplets, $J_{H\text{-}H}$ = 6.6 Hz., $J_{P\text{-}H}$ = 8.5 Hz., 4H, $2CH_2CH_3$).
6. An analytical grade of dimethyl sulfoxide obtained from J. T. Baker Co. or Matheson, Coleman and Bell was used. The checkers redistilled this solvent from calcium hydride before use; b.p. 83–85° (17 mm.).
7. A commercial grade of potassium azide, obtained from either Eastman Organic Chemicals or Alfa Inorganics, Inc., was purified by recrystallization from aqueous ethanol (1:2, v/v) as previously described.[4] The pure azide, obtained as white solid, m.p. 343° (dec.), was dried in an oven at 110° for 2 hours before use. In this preparation it is preferable to use the more soluble potassium azide rather than sodium azide.
8. Although this distillation has been conducted repeatedly without incident, azides are potentially explosive.[5] Consequently, the distillation should be conducted behind a safety shield and the operator should wear protective equipment. The distilling flask should be heated with a water bath to avoid the possibility of overheating the distillation residue.
9. IR (CCl_4), 2170, 2120 (azide), 1760, and 1735 cm.$^{-1}$ (C=O); ^1H NMR (CCl_4), δ 1.51, singlet, $(CH_3)_3C$; mass spectrum, m/e (rel.int.), 115 (17), 100 (16), 59 (85), 57 (20), 56 (41), 44 (18), 43 (84), 41 (21), 39 (19), 29 (30), 28 (100), 27 (21).

3. Discussion

Although *tert*-butyl azidoformate, a useful reagent for the protection of primary and secondary amino groups[6,7,8,9] has been prepared previously from *tert*-butyl carbazate,[5] the present procedure[10] is more convenient. The intermediate carbonic phosphoric anhydride reacts with nucleophiles other than the azide ion; for example, reaction of this anhydride with amines yields the *tert*-butoxycarbonyl derivatives of amines.[10] Other carbonic phosphoric anhydrides have been prepared by procedures analogous to the method described here.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 157
- Org. Syn. Coll. Vol. 5, 160
- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 418
- Org. Syn. Coll. Vol. 7, 70

References and Notes

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3. U. Ragnarsson, S. M. Karlsson, B. E. Sandberg. and L. E. Larsson, *Org. Synth.*, **Coll. Vol. 6**, 205 (1988).

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

tert-Butylcarbonic diethylphosphoric anhydride

alcohol-free potassium tert-butoxide

ethanol (64-17-5)

ether,
diethyl ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

Pentane (109-66-0)

sodium azide (26628-22-8)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

diethyl phosphorochloridate (814-49-3)

Carbonazidic acid, 1,1-dimethylethyl ester,
tert-Butyl azidoformate,
tert-butoxy carbonyl azide,
t-BOC azide (1070-19-5)

2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (58632-95-4)

O-tert-butyl S-phenylthiocarbonate (36760-43-7)

tert-Butyl phenyl carbonate (6627-89-0)

potassium azide

tert-Butyl carbazate (870-46-2)

Di-tert-butyl dicarbonate (24424-99-5)