



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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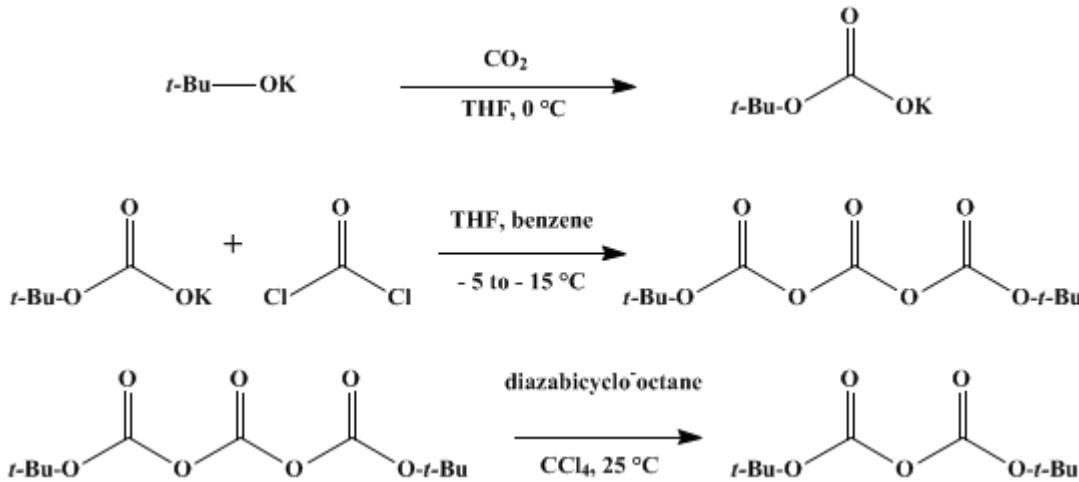
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.418 (1988); Vol. 57, p.45 (1977).

DI-*tert*-BUTYL DICARBONATE

[Dicarboxylic acid, bis(1,1-dimethylethyl) ester]



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Checked by John C. DuBose and Herbert O. House.

1. Procedure

Caution! Since the toxic gas phosgene is employed in this preparation, the reaction should be performed in an efficient hood. The glassware, which may be coated with a solution of phosgene, should be washed before it is removed from the hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Di-tert-butyl tricarbonate*. A 1-l., three-necked flask, fitted with a mechanical stirrer, a 200-ml. pressure-equalizing dropping funnel, a calcium chloride-filled drying tube, and gas-inlet tube with a minimum internal diameter of 6 mm. (Note 1) extending nearly to the bottom of the flask, is dried either by heating with a free flame while passing anhydrous nitrogen through the apparatus, or by heating to 120° for several hours in an oven. Before use, the dropping funnel should be calibrated to indicate levels corresponding to 85 ml. and 105 ml. of liquid. While an atmosphere of anhydrous nitrogen (Note 2) is maintained inside the apparatus, it is allowed to cool before a mixture of 44.8 g. (0.400 mole) of alcohol-free potassium *tert*-butoxide (Note 3) and 550 ml. of anhydrous tetrahydrofuran (Note 4) is added to the reaction flask. The mixture is stirred under an atmosphere of anhydrous nitrogen for 5–10 minutes to obtain a solution. (Note 3), (Note 5). The reaction flask is immersed in an ice–salt bath maintained at –5° to –20°, and all subsequent steps, including solvent removal, are performed with this cooling bath in place. A stream of anhydrous carbon dioxide (Note 2) is passed through the cold reaction solution for 30 minutes with vigorous stirring, resulting in the formation of a thick, creamy slurry in the reaction flask. While the reaction mixture is being saturated with carbon dioxide, 85 ml. of anhydrous benzene is added to the dropping funnel. A stream of phosgene is bubbled through the benzene until the total volume of the solution is 105 ml., corresponding to the addition of approximately 24 g. (0.24 mole) of phosgene (Note 6). When the addition of carbon dioxide is complete, the phosgene solution is added to the cold reaction slurry, dropwise and with vigorous stirring, over 1 hour, maintaining the temperature of the cooling bath at –5° to –15°. During this addition the reaction mixture

becomes less viscous but remains a white slurry. When the addition of the **phosgene** solution is complete, the cold reaction mixture is stirred for an additional 45 minutes while a stream of anhydrous **nitrogen** is passed through the reaction solution to sweep out most of the excess **phosgene**. The fittings are removed from the reaction flask, two of the three necks are stoppered, and the volume of solvents in the reaction flask is reduced from about 650 ml. to 100 ml. with a rotary evaporator. During evaporation the flask should be continuously cooled in an ice–salt bath maintained at -5° to 0° . This evaporation should be performed with either a very efficient aspirator or with a mechanical vacuum pump fitted with an efficient cold trap. Since some **phosgene** is still present in the reaction mixture, the exhaust from the aspirator or the vacuum pump should be discharged in the hood and any material collected in a cold trap should be emptied in the hood. The residual slurry of finely divided **potassium chloride** is filtered with suction in a large-diameter, fritted-glass funnel, precooled with 50 ml. of ice-cold **pentane**. During filtration the filter funnel may be loosely covered with an inverted large-diameter funnel through which a stream of **nitrogen** is passed to protect the contents of the funnel from atmospheric moisture. The residue in the reaction flask is washed into the filter funnel with 350 ml. of ice-cold **pentane** and washed with two additional 100-ml. portions of ice-cold **pentane**, leaving white **potassium chloride** as a residue. The combined filtrate and **pentane** washings are concentrated to dryness at 0° with a rotary evaporator, under reduced pressure supplied by a vacuum pump equipped with an efficient cold trap, yielding 33.7–39.6 g. (64–75%, (Note 7)) of di-*tert*-butyl tricarbonate as a colorless solid. This crude product is recrystallized by dissolving it in 1250 ml. of **pentane** at room temperature, and cooling the solution to -15° . The **pentane** mother liquors are concentrated with a rotary evaporator, giving two additional crops of crystalline product. The total yield is 31.2–32.8 g. (59–62%) of the pure di-*tert*-butyl tricarbonate as colorless prisms, m.p. $62\text{--}63^{\circ}$ (dec.) (Note 8).

B. *Di-tert-butyl dicarbonate*. A solution of 20.0 g. (0.0763 mole) of di-*tert*-butyl tricarbonate in 75 ml. of **carbon tetrachloride** is placed in a 600-ml. beaker fitted with a magnetic stirrer, and 0.10 g. (0.89 mmole) of freshly sublimed **1,4-diazabicyclo[2.2.2]octane** (Dabco) is added (Note 9), resulting in the rapid evolution of **carbon dioxide**. The reaction mixture is stirred at 25° for 45 minutes, to complete the loss of **carbon dioxide** (Note 10), before 35 ml. of water, containing **citric acid** sufficient to make the aqueous layer slightly acidic, is added. The organic layer is separated, dried over anhydrous **magnesium sulfate**, and concentrated at 25° with a rotary evaporator. The residual liquid is distilled under reduced pressure, yielding 13.3–15.1 g. (80–91%) of **di-tert-butyl dicarbonate** as a colorless liquid, b.p. $55\text{--}56^{\circ}$ (0.15 mm.) or $62\text{--}65^{\circ}$ (0.4 mm.) n_D^{25} 1.4071–1.4072 (Note 11).

2. Notes

1. A gas-inlet tube of smaller diameter or a tube fitted with a fritted-glass outlet tends to become clogged during this preparation and is not recommended.
2. The submitters dried this gas by passing it successively through an empty trap, through a trap containing concentrated **sulfuric acid**, and through another empty trap. The checkers used this drying procedure for **carbon dioxide** but dried the **nitrogen** by passing it through a column of molecular sieves.
3. The submitters employed alcohol-free potassium *tert*-butoxide, purchased from K & K Laboratories, without further purification; the checkers employed comparable material taken from a freshly opened bottle purchased from MSA Research Corporation. The submitters report that among approximately ten different bottles of commercial **potassium *tert*-butoxide** used, only material from one bottle failed to form the tricarbonate. The defective material was an extremely fine powder that failed to dissolve when stirred with **tetrahydrofuran**. Solubility in **tetrahydrofuran** appears to be a good criterion for the purity of alcohol-free potassium *tert*-butoxide. The checkers have observed that a 1:1 complex of **potassium *tert*-butoxide** and ***tert*-butyl alcohol** is much less soluble in ethereal solvents than is alcohol-free potassium *tert*-butoxide.
4. A reagent grade of **tetrahydrofuran** (b.p. $65\text{--}66^{\circ}$) was distilled from **lithium aluminum hydride** before use.
5. The submitters reported that their solution had a faint blue color at this point.
6. If desired, the dropping funnel may be removed from the reaction flask and replaced with a calcium chloride drying tube during the preparation of the **phosgene** solution. When preparation of the **phosgene** solution is complete, the drying tube should be removed and quickly replaced with the dropping funnel containing the **phosgene** solution.
7. Although the submitters report that this crude product is suitable for use in the next step of this

preparation, the checkers found that once, when using the crude product, the subsequent reaction did not go to completion unless an extra quantity of the diamine base was added. This suggests that some potentially acidic impurity such as *tert*-butyl chloroformate may be present in the crude product and could interfere with the subsequent reaction. The checkers therefore recommend that the product be purified before use in the next step of this preparation.

8. Although this tricarbonate undergoes thermal decomposition when heated above its melting point (63°), forming *tert*-butyl alcohol, isobutylene, and carbon dioxide, the product appears to be stable to storage at temperatures of 25° or less. The product exhibits IR bands (CCl₄) attributable to C=O stretching at 1845, 1810, and 1780 cm.⁻¹; the ¹H NMR spectrum (CCl₄) exhibits a singlet at δ 1.55.

9. The submitters report that both 1,4-diazabicyclo[2.2.2]octane and triethylamine have been used to catalyze this decomposition. Triethylamine was less satisfactory as a catalyst because of its relatively rapid reaction with the solvent, carbon tetrachloride, to form triethylamine hydrochloride, and because of difficulty encountered in separating triethylamine from the dicarbonate product. The 1,4-diazabicyclo[2.2.2]octane was efficiently separated from the dicarbonate product by the procedure described in which the crude product was washed with very dilute acid.

10. The progress of this reaction may be monitored either by IR, observing the disappearance of the band at 1845 cm.⁻¹, or by ¹H NMR (CCl₄), following the replacement of the reactant peak (CCl₄) at δ 1.55 by the product peak at δ 1.50.

11. The submitters report that this product solidifies when cooled and melts at 21–22° and that the product is stable when stored in a refrigerator. The product exhibits IR absorption (CCl₄) attributable to C=O stretching at 1810 and 1765 cm.⁻¹ and a ¹H NMR (CCl₄) singlet at δ 1.50. The mass spectrum of the product exhibits the following relatively abundant fragment peaks: *m/e* (relative intensity), 60(10), 59(99), 57(34), 56(86), 55(47), 50(21), 44(100), 43(30), 41(91), 40(27), and 39(61).

3. Discussion

Di-*tert*-butyl tricarbonate, an example of hitherto unknown class of compounds, has been prepared only by the present procedure.^{2,3,4} The corresponding sulfur compound, *tert*-C₄H₉SCO₂CO₂COS-*tert*-C₄H₉, also belongs to a new class of compounds and has been prepared by a similar procedure in comparable yields.^{4,5} Both tricarbonates are smoothly converted by basic catalysts into the corresponding dicarbonates (sometimes called pyrocarbonates); kinetic studies and differences in thermal decomposition of both tricarbonates have been reported, as well as other reactions of these materials.^{4,6} The amine-catalyzed decomposition of the tricarbonates to dicarbonates is believed to involve initial nucleophilic attack by the amine at the center carbonyl group of the tricarbonate.^{4,6} Di-*tert*-butyl dicarbonate had been obtained previously⁷ in 5% yield; no study of its properties was reported.⁷ The di-*tert*-butyl dicarbonate and its sulfur analog have been shown to react with amino acids and their derivatives to form the corresponding *N*-*tert*-butoxycarbonyl (*t*-BOC) and *N*-*tert*-butylthiocarbonyl derivatives,³ which are valuable protecting groups for amino functions. The dicarbonates described in the present synthesis are very mild reagents for the preparation of *t*-BOC and *N*-*tert*-butylthiocarbonyl derivatives, and may have application in selective reactions with enzymes, nucleic acids and their component nucleotides and nucleosides. Diethyl dicarbonate has been extensively studied in reactions of this type.^{8,9}

Other reagents which have been found useful for the synthesis of *t*-BOC derivatives include the hazardous *tert*-butoxycarbonyl azide¹⁰ (see warning, p. 207), *tert*-butyl phenyl carbonate,¹¹ and 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile.¹²

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 207
- Org. Syn. Coll. Vol. 7, 70
- Org. Syn. Coll. Vol. 9, 268

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

Di-tert-butyl tricarbonate

alcohol-free potassium tert-butoxide

Diethyl dicarbonate

sulfuric acid (7664-93-9)

Benzene (71-43-2)

citric acid (77-92-9)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

phosgene (75-44-5)

Triethylamine hydrochloride (554-68-7)

Pentane (109-66-0)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

isobutylene (9003-27-4)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

tert-butoxycarbonyl azide (1070-19-5)

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

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

1,4-diazabicyclo[2.2.2]octane (280-57-9)

tert-butyl chloroformate

Di-tert-butyl dicarbonate,
Dicarboxylic acid, bis(1,1-dimethylethyl) ester (24424-99-5)

potassium tert-butoxide (865-47-4)