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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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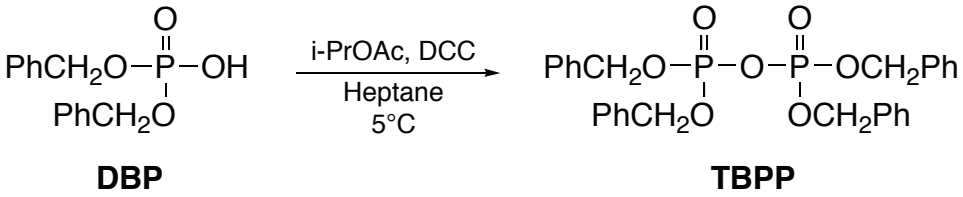
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.080.0219
Organic Syntheses, Vol. 80, p. 219-226 (2003); Coll. Vol. 11, p. 1001-1006 (2009).

TETRABENZYL PYROPHOSPHATE
[[Diphosphoric acid, tetrakis(phenylmethyl) ester]]



DBP **TBPP**

Submitted by Todd D. Nelson,[1] Jonathan D. Rosen,[1] M. Bhupathy,[1] James McNamara[1], Michael J. Sowa,[2] Chad Rush,[2] and Louis S. Crocker.[3]
Checked by Stuart J. Conway and Andrew B. Holmes.

1. Procedure

A flame-dried, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, low-temperature thermometer, and two rubber septa (Note 1). A balloon filled with argon is connected via an inlet needle through the central rubber septum. The vessel is charged with 15.24 g (54.8 mmol) of dibenzyl phosphate (DBP) (Notes 2, 3) and flushed with argon from the balloon, then 60 mL of isopropyl acetate is introduced through the side septum by syringe. The resulting slurry is stirred and cooled to 3 ± 3 °C, and the balloon is temporarily removed from the central inlet needle while 26 mL of a 1.08M solution (28.2 mmol) of 1,3-dicyclohexylcarbodiimide (DCC) in isopropyl acetate (Notes 4, 5) *(Caution!)* is added via cannula from a flame-dried, 100-mL, round-bottomed flask equipped with another argon-inflated balloon. The reaction temperature is maintained at 3 ± 3 °C by controlling the addition through the cannula by simply removing and re-inserting the needle in the flask containing the DCC (Notes 6, 7). The cold slurry is filtered through a sintered glass filter funnel under aspirator vacuum and the 1,3-dicyclohexylurea (DCU) waste cake is rinsed with 4 × 12-mL portions of isopropyl acetate. The filtrate and rinses are combined and concentrated at 25 °C in vacuo on a rotary evaporator to a final volume of 30 mL (Notes 8, 9).

The concentrated solution is transferred to a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, low-temperature

thermometer and two rubber septa (Note 1). A balloon filled with argon is connected via an inlet needle through the central rubber septum. The solution is diluted by adding 10 mL of heptane through the septum using a syringe (Note 10). The resulting slurry is stirred at room temperature for 15 min, then 80 mL of heptane is added via syringe to the stirred slurry over 10 min (Note 11). The slurry is then cooled to 3 ± 3 °C and stirred for 1 h. The solids are collected using a sintered glass filter funnel with aspirator vacuum and the filter cake is washed with 3 × 20-mL portions of 20% (v/v) isopropyl acetate/heptane. The filter cake is dried under reduced pressure, then transferred to a 250-mL, round-bottomed flask and flushed with a blanket of argon four times at room temperature. The product was allowed to stand under an atmosphere of argon at room temperature overnight (Note 12) to afford 13.0-14.15 g (88-96%) of tetrabenzyl pyrophosphate as a white crystalline solid (Note 13).

2. Notes

1. The submitters used a 12-L, round-bottomed flask equipped with an overhead stirrer, thermocouple, N_2 inlet, and addition funnel to process 762 g of DBP.

2. The submitters carried out this preparation on fifty times the scale reported here.

3. Dibenzyl phosphate was purchased from Aldrich Chemical Company, Inc. The submitters purchased dibenzyl phosphate from Digital Specialty Company, Inc.

4. The checkers dissolved 5.8 g of DCC in 26 mL of isopropyl acetate (both purchased from Aldrich Chemical Company, Inc.). The submitters obtained a prepared solution of DCC (1.08M in isopropyl acetate) from Schweizerhall, Inc.

5. DCC, a strong sensitizer, is readily absorbed through the skin and may cause an allergic skin reaction. This compound is extremely destructive to tissue of the mucous membranes, upper respiratory tract, eyes and skin.

6. Although the dibenzyl phosphate is not completely soluble in isopropyl acetate, it is apparently sufficiently soluble to allow formation of tetrabenzyl pyrophosphate which remains in solution while a slurry of 1,3-dicyclohexylurea (DCU) forms as a white precipitate.

7. Typical addition times are between 10-20 min and the reaction is complete within 90 min (HPLC). The submitters found that addition times of 25-35 min (with 762 g of dibenzyl phosphate) were typical and the reaction was complete within 30 min. The checkers used the following HPLC conditions:

Column:	Dynamax C18, 5 × 250 mm, 8 μm particle size
Guard Tube:	Dynamax C18 Guard, 8 μm particle size
Mobile phase:	Acetonitrile:water 70:30 (v/v)
Run time:	20 min
Flow rate:	1.5 mL/min, at room temperature

Detection at 220 nm and 260 nm (diode array detector)
Retention time for tetrabenzyl pyrophosphate = 12.0 min

The checkers found it advantageous to monitor the reaction by detection at 260 nm as well as 220 nm because at the longer wavelength there was no absorption peak due to isopropyl acetate. The final purity of the sample and the absence of isopropyl acetate were then verified by repeating the HPLC analysis using detection at 220 nm. The submitters used the following HPLC conditions:

Column:	Zorbax RX-C8, 4.6 × 250 mm, 5 μm particle size
Mobile phase:	A) Acetonitrile B) 0.1% H_3PO_4 buffered water Step gradient: 40:60 A:B to 70:30 A:B over 10 min, hold for 5 min, 70:30 A:B to 40:60 A:B over 2 min, hold for 3 min.
Flow rate:	1.5 mL/min, at room temperature

Detection at 220 nm
Retention time for tetrabenzyl pyrophosphate = 12.8 min

8. Concentration of the solution on the rotary evaporator must be ended before the solution becomes saturated. The submitters carried out this process by reduced pressure distillation. The solubility of tetrabenzyl pyrophosphate in isopropyl acetate at 25 °C is ca. 676 mg/g.

9. All operating temperatures should be kept at room temperature or below due to the very large exothermic potential exhibited by dibenzyl phosphate and tetrabenzyl pyrophosphate.

10. The submitters seeded the batch with 1 mol% of tetrabenzyl pyrophosphate. The checkers found it unnecessary to use seed crystals.

11. The solvent composition of the system is approximately 4:1 heptane:isopropyl acetate. This was predetermined by using solubility data of tetrabenzyl pyrophosphate under different conditions (listed below) at 5 °C.

Heptane:isopropyl acetate (v/v)	Solubility (mg TBPP/g solvent)[a]
1:4	82
2:3	34
3:2	10.6
4:1	2.8

[a]Measured at 5 °C

12. The submitters dried the product cake in vacuo and under a blanket of argon overnight at room temperature.

13. The submitters obtained 671 g (91%) from 762 g of dibenzyl phosphate. Characterization data for tetrabenzyl pyrophosphate include the following: TLC on Merck kieselgel 60 F_{254}, R_f = 0.42 (1:1 EtOAc:hexane); mp 59-60 °C (lit.[4] 61-62 °C, from cyclohexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.10-5.13 (m, 8 H), 7.33 (s, 20 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.3 (t, 4 C, J = 3), 127.9 (s, 8 C), 128.4 (s, 8 C), 128.6 (s, 4 C), 134.8 (t, 4 C, J = 4); ^{31}P NMR (162 MHz, $CDCl_3$) δ: −12.3 (s, 2 P); IR ($CHCl_3$) cm^{-1}: 3012, 1498, 1456, 1381, 1292, 1021, 956. MS (ES^+) *m/z* (rel intensity) 561 (100, M + Na)$^+$, 539 (50, M + H)+; *m/z* 539.1390 ([M + H]$^+$, calcd for $C_{28}H_{29}O_7P_2$ 539.1389. Anal. Calcd for $C_{28}H_{28}O_7P_2$: C, 62.5; H, 5.2; Found: C, 62.4; H, 5.2.

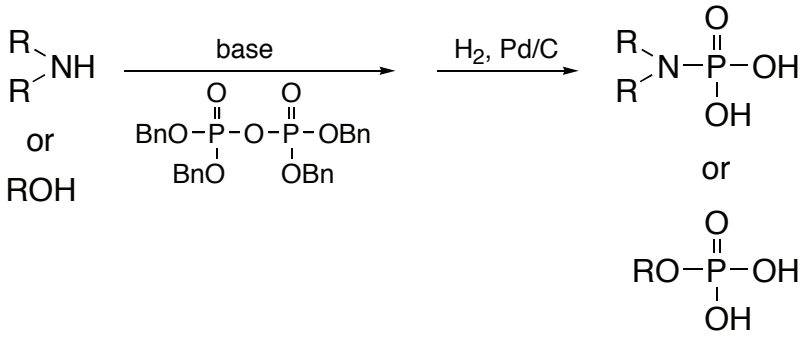
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Recently, tetrabenzyl pyrophosphate (TBPP) has become increasingly utilized for either *O*- or *N*-phosphorylations in complex molecules. A wide variety of substrates have been successfully phosphorylated by the title reagent and this transformation has often been cited as a key step in many syntheses. Debenzylation of the resulting dibenzyl phosphoryl moiety is usually facile and cleanly affords the corresponding phosphate.

In recent years, tetrabenzyl pyrophosphate has been used to synthesize a wide variety of phosphate-containing biologically active molecules,[5] which include prodrugs of tachykinin receptor antagonists,[6] angiotensin II antagonists,[7] 5-phosphatase inhibitors,[8] DHQ synthase inhibitors,[9] EPSP synthase inhibitors,[10] HIV protease inhibitors,[11] SH2 domain inhibitors,[12] antifungal agents[13] and antitumor agents.[14]



With the increasing use of tetrabenzyl pyrophosphate,[15] especially in the pharmaceutical industry, a cost-effective and convenient multi-kilogram preparation of tetrabenzyl pyrophosphate was desirable. The current procedure is a modification of an earlier synthesis by Todd.[4] Tetrabenzyl pyrophosphate has also been synthesized from: 1) *N*-hydroxysuccinimide and *N*-mercaptosuccinimide esters[16] and 2) the corresponding silver phosphate in carbon disulfide.[17]

Tetrabenzyl pyrophosphate should be stored in a freezer as a dry solid. Stability data on TBPP are tabulated below [reported in Liquid Chromatography Area Percent (LCAP)]. The only impurity detected was dibenzyl phosphate. For this study, solid TBPP was sealed in scintillation vials with Parafilm, which were in turn enclosed in desiccators with indicating Drierite.

Table. Stability Data for TBPP

Temperature	0 days	19 days	31 days	62 days
25 °C	99.9	97.1	96.9	95.5
0 °C	99.9	99.5	99.0	98.4
−25 °C	99.9	99.7	99.7	99.3

1. Merck Research Laboratories, Department of Process Research, P.O. Box 2000, Rahway, NJ 07065.

2. Merck Research Laboratories, Department of Chemical Engineering Research and Development, P.O. Box 2000, Rahway, NJ 07065.

3. Merck Research Laboratories, Department of Analytical Research, P.O. Box 2000, Rahway, NJ 07065.

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15. A *Chemical Abstracts* search regarding tetrabenzyl pyrophosphate (on February 1, 2002) revealed a significant increase in the use of this reagent, as indicated by the following data:

Period	Number of Citations
2002-1991	73
1990-1981	10
1980-1971	1

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

Tetrabenzyl pyrophosphate: Diphosphoric acid, tetrakis(phenylmethyl) ester (9); (990-91-0)

Dibenzyl phosphate (8): Phosphoric acid, bis(phenylmethyl) ester (9); (1623-08-1)

Isopropyl acetate (8): Acetic acid, 1-methylethyl ester (9); (108-21-4)

1,3-Dicyclohexylcarbodiimide (8): Cyclohexanamine, *N,N*'-methanetetraylbis- (9); (538-75-0)

1,3-Dicyclohexylurea: Urea, dicyclohexyl- (9); (2387-23-7)