The Reduction of Aryl Diethyl Phosphate Esters with Lithium Di-*tert*-butylbiphenylide Radical Anion: Aromatic Hydrocarbons via the Deoxygenation of Phenols

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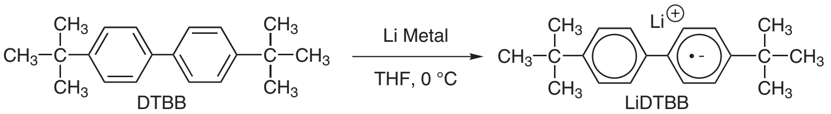
Abstract: The reduction of aryl diethyl phosphate esters by lithium 4,4′-di-*tert*-butylbiphenylide (LiDTBB) in THF at 0 °C is described. The reactions can be carried out either stoichiometrically (3.0 equiv LiDTBB) or with only a catalytic amount of DTBB (0.25 equiv) in the presence of lithium (2.1–3.0 equiv) and the phosphate. Products are separated from DTBB by solubility differences, by acid/base vs. neutral extraction, or by flash chromatography.

Key words: reduction, phosphates, deoxygenation, phenols, arenes

Synthetic organic chemists continually seek innovative chemical transformations that are chemo- and regioselective. Because hydroxyl groups contribute unusual activity and specific directive effects to substitutions in aromatic compounds, their use in regioselective syntheses is attractive. However, their utility is greatly expanded when they can be chemoselectively removed in a later synthetic step. Several natural products or analogs have been synthesized utilizing this type of transformation. The synthesis of 4-demethoxydaunomycinone, the aglycone of the antitumor and antileukemic agent idarubicin (4-demethoxydaunorubicin), has been accomplished by reduction of the triflate ester prepared from natural daunomycinone.[1a] A similar transformation has been applied in the synthesis of the *Gelsemium* alkaloid koumine[1b] and the isoflavonoid phytoalexin (±)-homopterocarpin.[1c] Furthermore, the usefulness of the benzannulation reaction of chromium carbene complexes with alkynes (Dötz reaction) is enhanced by the ability to remove the phenolic hydroxy group introduced as a result of CO insertion during the formation of the aromatic ring. Synthesis of the furanocoumarin angelicin,[1d,e] and model studies for the synthesis of olivin and chromomycinone,[1d] have demonstrated the value of this procedure.

Most known methods for deoxygenating phenols[2] are not carried out on the free hydroxy compound but rather involve conversion into a suitable derivative, followed by reduction via one of three types of reaction: (1) heterogeneous catalytic hydrogenation,[3] (2) homogeneous Pd(0)-catalyzed reduction,[4] or (3) alkali dissolving metals or other zero-valent metal reduction.[5] Dissolving metal reduction, particularly of phosphate esters of phenols, with lithium, sodium, or potassium metal in liquid ammonia solution at –33 °C or colder has been reported as a useful method for this transformation.[5d–h] We have recently been investigating a modification of this reduction of aryl phosphates[6] in which the reducing agent is lithium di-*tert*-butylbiphenylide (LiDTBB), an aromatic radical-anion reagent that can be conveniently generated[7] and used in the organic solvent THF at ice temperature (0–5 °C) (Scheme 1), rather than in corrosive and toxic NH_3 at the less convenient temperatures below –33 °C required to liquefy this gas. Although the use of sodium naphthalenide in THF had been described in a study of the mechanism of the reductive cleavage of aryl diethyl phosphates with electron-donors reductive cleavages with LiDTBB had not been reported[5i] prior to disclosure of our initial results.[6] Subsequently, the generation of organolithium reagents from phosphates with catalytically-generated LiDTBB, and their in situ reaction with various electrophiles (Barbier conditions) was reported.[8] The 4,4′-di-*tert*-butylbiphenyl (DTBB)[9] precursor to the radical-anion is in turn easily prepared by $FeCl_3$-catalyzed Friedel–Crafts bis-alkylation of biphenyl by *tert*-butyl chloride in CH_2Cl_2.[9b] Usually the required diethyl phosphates can be efficiently prepared from the corresponding phenols via phosphorylation with diethyl chlorophosphate generated in situ from the inexpensive diethyl phosphite and CCl_4[5d,10] (Scheme 2), or by other methods.[2a,5e–h,11] In this



Scheme 1 Preparation of lithium 4,4′-di-*tert*-butylbiphenylide (LiDTBB).

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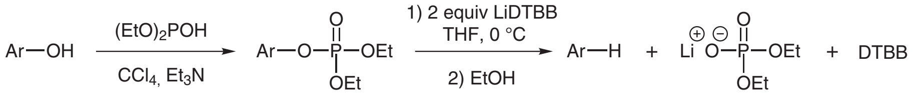


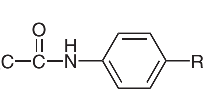
Scheme 2 Preparation and LiDTBB reduction of aryl diethyl phosphates

paper we describe our results with the LiDTBB reduction of the diethyl phosphate esters of a variety of phenols (Scheme 2).

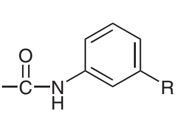
Initially we attempted the stoichiometric reduction (theoretically 2.0 equiv of radical-anion) of the diethyl phosphate **2** of 4-acetamidophenol (**1**, acetaminophen) with LiDTBB. Addition of **2** to a THF solution of 2.3 equivalents of LiDTBB at 0 °C, however, gave only a 10% yield of acetanilide (**3**) product (Table 1, entry 1), but increasing the amount of LiDTBB to 2.9 equivalents resulted in a 74% yield of **3** (entry 2). We also discovered that the reduction could be conducted catalytically with respect to DTBB (entry 3) by adding the phosphate to a THF solution of only 0.25 equivalents of DTBB containing 3.0 equivalents of Li metal, to give an 80% yield of **3** after 3.75 hours of stirring at 0 °C. Time required for the catalytic reaction could be decreased to a more reasonable 2.5 hours by increasing the 0.10 M concentration of the phosphate to 0.50 M (entry 4), yielding 73% of **3**. Other phosphates could be reduced similarly (Table 1).

The product arenes could be isolated and the DTBB recovered by a number of methods. In some cases there was a sufficiently large difference in solubility between DTBB, which is very soluble in hexanes, and the reduction product to permit facile separation. Thus in the reduction of **2** and **5**, addition of hexanes to the crude product

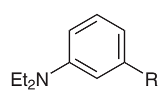
Table 1 Aryl Diethyl Phosphate Ester Preparation and LiDTBB Reduction



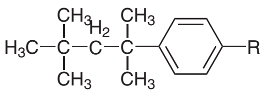
1: R = OH
2: $R = O_2P(OEt)_2$
3: R = H



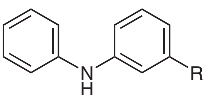
4: R = OH
5: $R = O_2P(OEt)_2$
6: R = H



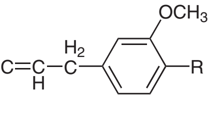
7: R = OH
8: $R = O_2P(OEt)_2$
9: R = H



10: R = OH
11: $R = O_2P(OEt)_2$
12: R = H



13: R = OH
14: $R = O_2P(OEt)_2$
15: R = H



16: R = OH
17: $R = O_2P(OEt)_2$
18: R = H

Entry	ArOH	Aryl diethyl phosphate	Phosphate yield (%)	Moles reduced	Lithium (equiv)	DTBB (equiv)	Concentration	Conditions	Time	ArH product	ArH yield (%)
1	**1**	**2**	85–96	0.01	2.3	2.3	0.10 M	Stoichiometric[a]	5 min	**3**[c]	10
2	**1**	**2**	85–96	0.01	2.9	2.5	0.10 M	Stoichiometric[a]	5 min	**3**[c]	74
3	**1**	**2**	85–96	0.01	3.0	0.25	0.10 M	Catalytic[b]	3.75 h	**3**[c]	80
4	**1**	**2**	85–96	0.01	3.0	0.25	0.50 M	Catalytic[b]	2.5 h	**3**[c]	73
5	**4**	**5**	ca 100	0.01	3.0	3.0	0.10 M	Stoichiometric[a]	5 min	**6** (**3**)[c]	83
6	**7**	**8**	93	0.01	2.1	0.25	0.50 M	Catalytic[b]	2.0 h	**9**[d]	61
7	**10**	**11**	ca 100	0.01	3.0	3.0	0.10 M	Stoichiometric[a]	5 min	**12**[e,12]	65
8	**13**	**14**	76–90	0.01	3.0	3.0	0.10 M	Stoichiometric[a]	20 min	**15**[e]	32
9	**13**	**14**	76–90	0.01	3.0	0.25	0.50 M	Catalytic[b]	5.5 h	**15**[e]	48
10	**16**	**17**	92	0.01	3.0	3.0	0.10 M	Stoichiometric[a]	5 min	**18**[e,2a]	28

[a] Stoichiometric mode of reaction: Solution of phosphate in THF added rapidly to LiDTBB in THF at 0 °C.

[b] Catalytic mode of reaction: Solution of phosphate and DTBB in THF stirred with Li metal at 0 °C.

[c] Separated from DTBB by adding hexanes to the crude product and filtering.

[d] Separated from DTBB by treating the crude product with 5% aq HCl, extracting with CH_2Cl_2 to remove DTBB, making the aq layer basic with NaOH, and extracting the reduction product with CH_2Cl_2.

[e] Separated from DTBB by flash chromatography on silica gel.[13]

dissolved the DTBB, leaving behind nearly pure acetanilide (**3/6**). In cases where the reduction product was sufficiently acidic or basic (e.g., **9**), it could be separated from the neutral DTBB by aqueous base or acid extraction. Whenever these two techniques could not be applied, the DTBB was separated from the reduction product by flash chromatography[13] (e.g., **12**, **15**, **18**), effecting the separation of DTBB from even very similar aromatic hydrocarbons such as **12**. In most cases the recovery of DTBB was 80–100%, allowing it to be reused after simple recrystallization.

General Procedures

Stoichiometric Reduction

A deep green solution of LiDTBB (3.0 equiv) in anhyd THF (100 mL) was prepared[7] by stirring a solution of DTBB (7.99 g, 0.03 mol) and Li metal (cut in small pieces) (0.21 g, 0.03 mol) at 0 °C under an Ar atmosphere[14] for 3–4 h. Rapidly adding to this a solution of the diethyl phosphate (0.01 mol) in THF (5 mL) via syringe discharged the color of the radical-anion by the end of the addition to give a red to brown solution. After stirring for a further 5 min, the reaction was quenched by rapidly adding EtOH (1–5 mL) via syringe and stirring until any remaining small pieces of metallic lithium dissolved. The reaction mixture was then poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solutions were dried over anhyd $MgSO_4$ and the solvents removed in vacuo to leave a mixture of the crude reduction product and DTBB.

Catalytic Reduction

To a solution of DTBB (0.64 g, 2.5 mmol, 0.25 equiv) in anhyd THF (20 mL) at 0 °C under Ar[14] was added Li metal (cut in small pieces) (0.21 g, 0.03 mol, 3.0 equiv). This mixture was stirred until the green color of the LiDTBB filled the solution and then the phosphate (0.01 mol) in THF (5 mL) was added rapidly via syringe, completely discharging the green color. This reaction mixture was stirred at 0 °C for 2–5.5 h until the green color returned. The reaction was then quenched with EtOH (1–5 mL) and worked up as above.

Product Isolation Procedures and Recovery of DTBB

Based on Solubility Differences (Entry 3)

Addition of hexanes to the crude mixture of acetanilide (**3**) and DTBB resulted in the dissolution of the DTBB. Filtration and washing of the insoluble residue gave **3** (1.15 g, 80%); mp 106–108 °C. Evaporation of the hexanes solution gave recovered DTBB.

Based on Acid/Base/Neutral Character (Entry 6)

The EtOH-quenched reaction mixture containing amine **9** and DTBB was stirred with water (25 mL) and 5% aq HCl solution (25 mL), and the mixture was then extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were dried over anhyd $MgSO_4$ and evaporated in vacuo to leave recovered DTBB. The aqueous acid solution was then made strongly basic with 6 N aq NaOH (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). Drying of the organic extracts over anhyd $MgSO_4$ and evaporation in vacuo gave liquid amine **9** (0.90 g, 61%).

Separation by Flash Chromatography

Flash silica gel (40 μm, 60 Å) was purchased from Scientific Absorbants, Inc.

Entry 7: The crude mixture of **12** and DTBB was separated by flash chromatography on a 50 mm × 16.5 cm column of silica gel, eluting with hexanes, to give liquid **12** (1.24 g, 65%).

Entry 8: The crude mixture of **15** and DTBB was separated by flash chromatography on a 50 mm × 16.5 cm column of silica gel, eluting with hexanes–EtOAc (95:5) to give **15** (0.54 g, 32%); R_f 0.21; mp 52–52.8 °C. In addition DTBB was recovered (6.71 g, 84%); R_f 0.55; mp 124.5–127 °C.

Entry 9: In similar fashion the crude mixture of **15** and DTBB was separated by flash chromatography on a 50 mm × 15 cm column of silica gel, eluting with hexanes–EtOAc (95:5), to give **15** (0.82 g, 48%).

Entry 10: The crude mixture of **18** and DTTB was separated by flash chromatography on a 50 mm × 15 cm. column of silica gel, eluting with hexanes–CH_2Cl_2 (60:40), to give liquid **18** (0.41 g, 28%); R_f 0.32. DTBB was recovered (7.21 g, 90%) as well; R_f 0.59; mp 124–26 °C.

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