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Deprotonation of Benzylic Ethers Using a Hindered Phosphazene Base. A Synthesis of Benzofurans from *Ortho*-Substituted Benzaldehydes

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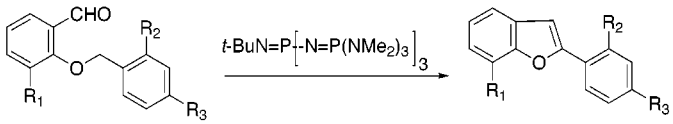
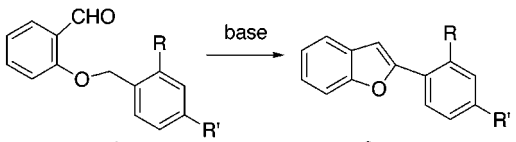
ABSTRACT



The hindered nonionic phosphazene base P_4-*t*-Bu efficiently deprotonates *o*-arylmethoxy benzaldehydes, leading to a direct synthesis of benzofurans. Strong ionic bases such as LDA, LiTMP, and KH failed.

Many natural products and biologically significant synthetic compounds contain either a benzofuran or a dihydrobenzofuran subunit.[1] As a consequence, a number of preparations of benzofurans have been reported.[2] Recently there has been growing interest in developing general and versatile synthetic methods for the synthesis of benzofuran derivatives because of their activity as modulators of androgen biosynthesis (furano steroids),[3] as inhibitors of 5-lipoxygenase, as antagonists of angiotensin II receptors,[4] as blood coagulation factor Xa inhibitors,[5] and as ligands for the adenosine A_1 receptor.[6] Some 2-aryl benzofuran derivatives are potent calcium blockers,[7] and some of them show very good fungicidal activity in vitro and in vivo.[8] As part of a program to develop direct syntheses of natural antiviral agents,[9] we report a novel strategy for the synthesis of benzofurans.

One route to benzofurans from substituted benzaldehydes is illustrated below. This reaction is effective provided that at least one of the substituents R or R′ on the benzyl subunit is an electron-withdrawing group such as a nitro or cyano group. Potassium *tert*-butoxide and sodium ethoxide are typically used to effect this reaction.[10] Another route to benzofurans from substituted benzaldehydes involves a photochemical hydrogen atom abstraction reaction to give a dihydrobenzofuranol which can be converted into a benzofuran by dehydration.[11] This strategy has rarely been employed for the synthesis of highly functionalized benzofurans.



1 2

We had originally planned to prepare **2** from benzaldehyde **1** (R = OMe, R′ = H) by the two-step sequence involving

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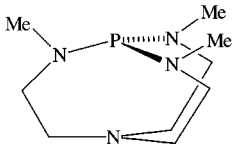
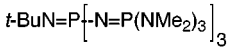
a photochemical hydrogen atom abstraction reaction followed by dehydration using $POCl_3$ and pyridine. Although this reaction sequence worked well on a millimole scale, the photochemical step proved difficult to scale-up.

We next tried the base-mediated reaction. In view of the absence of an electron-withdrawing group on the benzyl moiety, we examined the deprotonation of the benzylic ether of **1** using strong bases in anhydrous media. Treatment of **1** (R = OMe, R′ = H) with lithium diisopropylamide (LDA) in THF from −78 to 25 °C returned recovered starting material. The reaction of **1** with lithium tetramethypiperidide (LiTMP) in THF from 0 to 25 °C afforded mostly recovered starting material with byproducts that were not derived from proton abstraction at the benzylic ether position. Benzaldehyde **1** did not react with sodium hydride or potassium hydride in THF or DMF.

Recently, Verkade reported the use of nonionic phosphorus "superbases" such as **3** to effect selective organic reactions.[12] Schwesinger[13] [who originally synthesized **4**[14] ("P_4-*t*-Bu")] and others[15] have described carbanion chemistry employing this base. In view of the demonstrated utility of these strong nonionic bases for carbanion chemistry, phosphazane **3** and phosphazene **4** were next examined.[16]



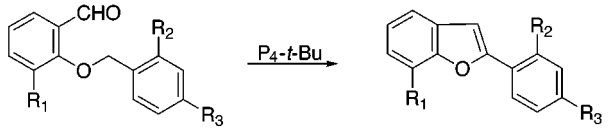
3



4

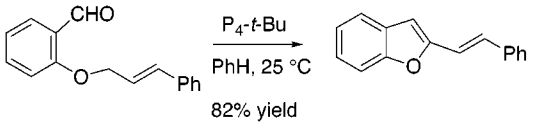
Although **3** did not deprotonate **1**, **4** efficiently converted a series of benzaldehydes directly into benzofurans in good isolated yields.[16] The reaction of **1** with 1.1 equiv of commercially available **4** in pivalonitrile at 90−100 °C afforded 2-(2-methoxyphenyl)benzofuran in 49% isolated yield. When benzene was used as the solvent, the yield was 47%. Results with a series of aldehydes are given in Table 1.

Table 1. Cyclizations Using P_4-*t*-Bu



entry	R_1	R_2	R_3	solvent	time (h)	*T* (°C)	% yield
1	H	OMe	H	benzene	12	reflux	47
2	H	OMe	H	pivalonitrile	8	90	49
3	OMe	OMe	H	benzene	14	reflux	48
4	OMe	OMe	H	pivalonitrile	12	90	51
5	H	H	H	benzene	14	reflux	69
6	H	OCH_2OCH_3	H	benzene	12	reflux	50
7	H	H	NO_2	benzene	1	reflux	78

Additionally, we examined the cyclizations of propenyloxy benzaldehydes. The reaction of *o*-propenyloxybenzaldehyde with **4** afforded a complex mixture of products. However, the reaction of 3-phenylpropenyloxybenzaldehyde (shown below) with **4** produced an 82% yield of the corresponding benzofuran.



The reaction of benzaldehydes with **4** offers a new strategy for the synthesis of benzofurans. Reaction conditions are mild and convenient. Functional groups such as ethers, acetals, and alkenes are compatible with the reaction conditions.

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(16) **General Procedure for making benzofurans:** To a stirred solution of the benzaldehyde (0.42 mmol) in dry benzene under N_2 was added P_4-*t*-Bu (0.46 mmol as a 1 M solution in hexane available from Fluka) at room temperature. The reaction was then carried out at the temperature given in Table 1. When the reaction was complete, as indicated by TLC, the reaction mixture was loaded directly onto a 40−140 mesh silica gel column and eluted with 2% ethyl acetate in hexanes to give pure 2-arylated benzofurans in good to moderate yields. Entry 1 of Table 1: Oishi, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 179. Entry 7 of Table 1: mp 177−179 °C (177−178 °C, Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1999**, 1357).