Alkylation of Phenols by Oxidation-Reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone and Alkoxydiphenylphosphine

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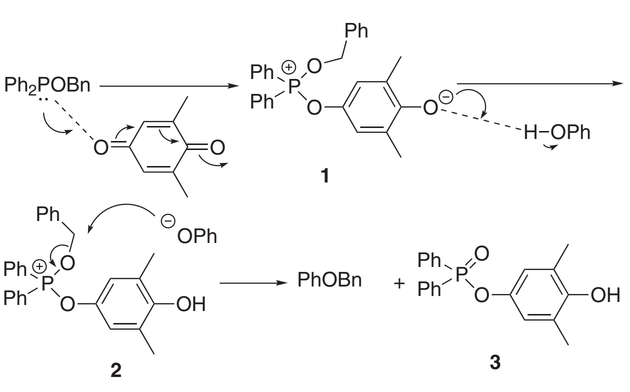
Various alkyl phenyl ethers were obtained in high yields by way of oxidation-reduction condensation where alkoxydiphenylphosphine, prepared easily from chlorodiphenylphosphine and corresponding alcohols, was treated with various phenols in the co-existence of 2,6-dimethyl-1,4-benzoquinone(DMBQ) under mild conditions.

The fundamental concept of oxidation-reduction condensation is to perform dehydration condensation by removing H_2O in elements of 2[H] and [O] with the use of weak reductant-oxidant combination.[1] The strong point of this concept is that the reaction is carried out under mild and neutral conditions without having any assistance of acids or bases. In our previous communication, the high-yielding preparation of various carboxylic benzyl esters was performed by way of a new-type oxidation-reduction condensation that used benzyloxydiphenylphosphine (Ph_2POBn),[2] carboxylic acids and 2,6-dimethyl-1,4-benzoquinone under mild conditions.[3] In the above reaction, Ph_2POBn was assumed to initially react with DMBQ to form an adduct, which then transformed to the phosphonium carboxylate by the interaction with carboxylic acid. Intramolecular attack of the carboxylate anion to the benzylic carbon of the salt afforded the corresponding carboxylic acid ester along with diphenylphosphiric acid 4-hydroxy-3,5-dimethylphenyl ester. Since benzyloxydiphenylphosphine was used in the above reaction, only carboxylic acid benzyl esters resulted.

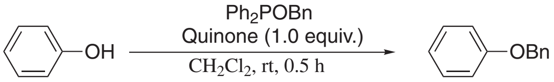
In this new-type oxidation-reduction condensation, alkoxyl group was introduced to the phosphorus in advance, and the reaction completed through the steps in which tetra-valent phosphorus of the intermediate phosphonium salt was converted to so-called penta-valent phosphorus while negatively charged oxygen of adduct 1 (Scheme 1) captured one hydrogen atom synchronously. In order to extend the scope of this type of condensation reaction, a similar oxidation-reduction condensation using several alkoxydiphenylphosphines, phenols and 2,6-dimethyl-1,4-benzoquinone was studied and the corresponding phenyl alkyl ethers were obtained in good yields under mild conditions.



Scheme 1.

In the first place, benzylation of phenol with 1.1 equivalent of Ph_2POBn was tried by using 1.0 equivalent of 1,4-benzoquinone in dichloromethane, and the desired product was obtained in 49% yield within 0.5 h (Table 1, entry 1). When DMBQ was used under the above conditions, the benzyl phenyl ether was obtained in 85% yield (entry 2). On the other hand, the yield lowered to 75% when phenol, 1.1 equivalent of DMBQ and 1.1 equivalent of Ph_2POBn were allowed to react in dichloromethane at 0 °C and stirred for additional 0.5 h at room temperature (entry 3). After screening the reaction conditions, it was found that the desired product was obtained in 92% yield under the above conditions when 1.5 equivalent of Ph_2POBn was used (entries 3–5).

Table 1. Benzylation of phenol with Ph_2POBn and quinones



Entry	Ph_2POBn/equiv.	Quinone	Yield/%
1	1.1	1,4-benzoquinone	49
2	1.1	DMBQ[a]	85
3	1.1	DMBQ	72[b]
4	1.2	DMBQ	85
5	1.5	DMBQ	92

[a]DMBQ(2,6-dimethyl-1,4-benzoquinone). [b]To a mixture of phenol and 2,6-dimethyl-1,4-benzoquinone was added a Ph_2POBn in CH_2Cl_2 at 0 °C and then reacted for 0.5 h at room temperature.

Next, benzylation of various phenols with Ph_2POBn and DMBQ was tried (Table 2). As a result, the corresponding benzyl phenols were obtained in good yields under mild conditions.

A proposed reaction mechanism is shown in Scheme 1: Ph_2POBn initially reacted with DMBQ to form adduct **1**, which then transformed to the phosphonium phenolate **2** by the interaction with phenol. Intramolecular attack of the phenolate anion to the benzylic carbon of the salt **2** afforded the corresponding benzyl ether along with diphenylphosphinic acid 4-hydroxy-3,5-dimethylphenyl ester **3**.

In the present reaction of using phenols, the corresponding benzyl phenols were obtained in good yields under mild conditions which accompanied the by-product **4** formed probably by the competitive reaction between the two moles of initially formed **1** having phenolic nature (Scheme 2).

Alkylations of phenol and p-nitrophenol with several alkoxydiphenylphosphine and DMBQ were tried (Table 3) and the corresponding alkyl phenyl ethers were obtained in good

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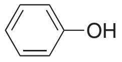
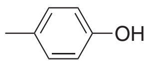
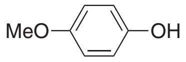
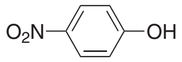
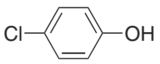
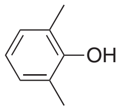
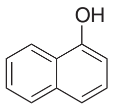
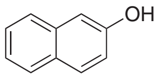
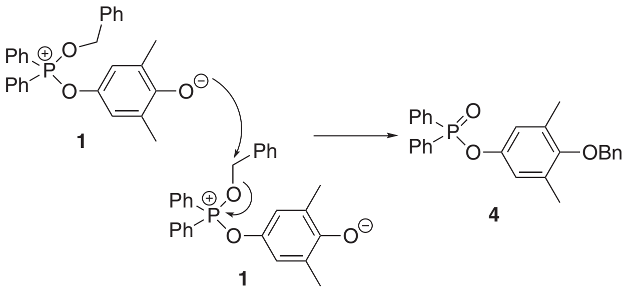
Table 2. Benzylation of various phenol with Ph_2POBn and DMBQ

$$\mathrm{ArOH} \xrightarrow[\mathrm{CH_2Cl_2,\ rt,\ 0.5\ h}]{\mathrm{Ph_2POBn\ (1.5\ equiv.)},\ \mathrm{DMBQ\ (1.0\ equiv.)}} \mathrm{ArOBn}$$

Entry	ArOH	Yield /%
1		92
2		82
3		78
4		88
5		84
6		70
7		81
8		84



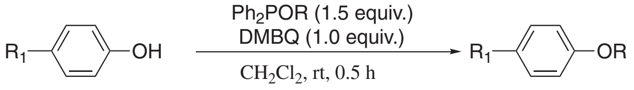
Scheme 2.

yields.

Typical experimental procedure is as follows: to a stirred solution of phenol (0.60 mmol) and DMBQ (0.60 mmol) in dichloromethane (0.25 ml) under argon atmosphere was added a solution of Ph_2POBn (0.90 mmol) in dichloromethane (0.25 ml) at room temperature. The reaction mixture was stirred for 0.5 h at room temperature and was quenched with water after completion of the reaction (detected by TLC). The mixture was extracted with dichloromethane and the organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC to afford the corresponding ethers in high yields.

Thus, a new and efficient method for the alkylation of phenols was established by way of new-type oxidation-reduction condensation using several alkoxydiphenylphosphines having primary or secondary alkoxyl group, milder oxidizing agent such as DMBQ, and phenols. The corresponding alkyl phenyl ethers were obtained in good yields under mild conditions. In addition, it was found that the desired phenyl ether was obtained in 62% yield when alkoxydiphenylphosphine having bulky tertiary butyloxyl group and p-nitrophenol were allowed to react under the above condition. Further study on this type of condensation reaction is now in progress.

Table 3. Alkylation of phenol or p-nitorophenol with several alkoxydiphenylphosphines and DMBQ



Entry	R_1	Ph_2POR	Yield/%
1	H	Ph_2POMe	88
2	H	Ph_2POEt	84
3	H	Ph_2PO^nBu	87
4	H	Ph_2PO^iPr	81
5	NO_2	Ph_2PO^tBu	62[a]

[a] The reaction mixture was refluxed for 10 h.

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References and Notes

1 For example; a) T. Mukaiyama, I. Kuwajima, and Z. Suzuki, *J. Org. Chem.*, **28**, 2024 (1963). b) I. Kuwajima and T. Mukaiyama, *J. Org. Chem.*, **29**, 1385 (1964). c) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, **22**, 1901 (1970).
2 Equimolar amounts of chlorodiphenylphosphine and benzylalcohol were mixed with pyridine in diethyl ether at room temperature under argon atmosphere. Distillation gave colorless oil, Yield 55% (b.p. 155–157 °C/0.2 mmHg). See: B. A. Arbouzov and N. P. Grechkin, *Zh. Obshch. Khim.*, **20**, 107 (1950).
3 T. Mukaiyama, T. Shintou, and W. Kikuchi, *Chem. Lett.*, **2002**, 1126.
4 a) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967). b) D. L. Hughs, in "Organic Reactions," ed. by P. Beak, et al., John Wiley & Sons, New York (1992), Vol. 42, p 335. c) O. Mitsunobu, *Synthesis*, **1981**, 1. d) R. A. Amos, R. W. Emblidge, and N. Havens, *J. Org. Chem.*, **48**, 3598 (1983). e) L. D. Arnold, H. I. Assil, and J. C. Vederas, *J. Am. Chem. Soc.*, **111**, 3973 (1989). f) T. Tsunoda, Y. Yamamiya, and S. Ito, *Tetrahedron Lett.*, **34**, 1639 (1993). g) T. Tsunoda, F. Ozaki, and S. Ito, *Tetrahedron Lett.*, **35**, 5081 (1994). h) A. R. Tunoori, D. Dutta, and G. I. Georg, *Tetrahedron Lett.*, **39**, 8751 (1998).