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Acetonyltriphenylphosphonium Bromide in Organic Synthesis: An Extremely Efficient Catalyst for the Protection and Deprotection of Alcohols as Alkyl Vinyl Ethers

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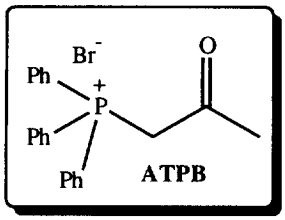
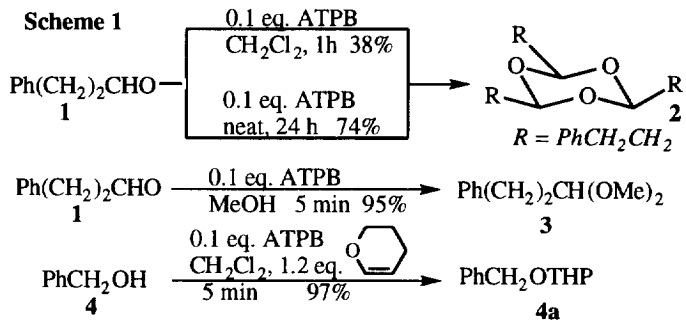
Abstract: Acetonyltriphenylphosphonium bromide (ATPB) was an extremely effective catalyst in the preparation of THP, THF, and EE ethers as well as cleavage of THP, THF, and EE ethers to the corresponding alcohols. It could be applied to 1°, 2° and 3° alcohols and phenol.

Acetonyltriphenylphosphonium bromide (ATPB) is a precursor in the preparation of 1-(triphenylphosphoranylidene)-2-propanone used in a Wittig reaction. There are no reports on the use of ATPB in organic synthesis other than in ylide formation.[1] In the course of studying the counteranion effect on the reactivity of the phosphonium salt in the Wittig reaction, ATPB was found to be a catalyst in the trimerization of the aldehyde.[2] The trimerization occurred under neat conditions rather than in the solution (Scheme 1). We tried



Scheme 1



to improve the chemical yield of the trimer by changing the solvent system. In the presence of ATPB, aldehyde **1** was dissolved in a mixture of MeOH and CH_2Cl_2. The dimethylacetal **3** was formed in excellent yield in 5 min. Intrigued by the peculiar catalytic activity of ATPB, we tried to react the benzyl alcohol (**4**) with 3,4-dihydro-2*H*-pyran to give the corresponding OTHP derivative **4a** and the result was extremely encouraging (Scheme 1). The 2-tetrahydropyranyl ether (OTHP) and 1-ethoxyethyl ether (OEE) are two of the most versatile protecting groups for the alcohols in organic syntheses because of their low cost, the ease of their installation,

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Scheme 2

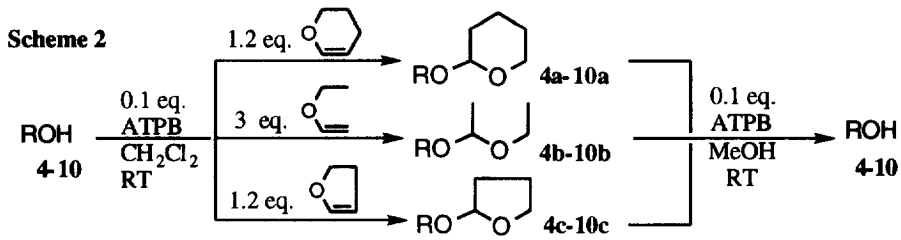
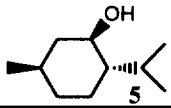
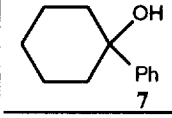
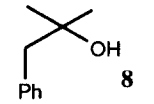
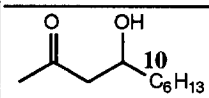


Table 1: Protection of alcohols with alkyl vinyl ether and its deprotection catalyzed by ATPB.

Entry	Alcohol	Time (min)	Isolated Yield (%)	Protected Alcohol	Time (min)	Isolated Yield of the Deprotection (%)
1	$PhCH_2OH$ **4**	<5	97	-OTHP **4a**	60	90 **4**
2	$PhCH_2OH$ **4**	<5	94	-OEE **4b**	15	92 **4**
3	$PhCH_2OH$ **4**	<5	95	-OTHF **4c**	10	90 **4**
4	 **5**	<5	98	-OTHP **5a**	70	90 **5**
5		<5	92	-OEE **5b**	10	94 **5**
6		<5	99	-OTHF **5c**	15	93 **5**
7	Cholesterol **6**	<5	90	-OTHP **6a**	50	99[a] **6**
8	Cholesterol **6**	<5	97	-OEE **6b**	30	96[a] **6**
9	Cholesterol **6**	<5	97	-OTHF **6c**	30	95[a] **6**
10	 **7**	20	86	-OTHP **7a**	10	98 **7**
11		10	83	-OEE **7b**	10	97 **7**
12		10	80	-OTHF **7c**	10	97 **7**
13	 **8**	30	88	-OTHP **8a**	30	96 **8**
14		20	83	-OEE **8b**	20	92 **8**
15		30	84	-OTHF **8c**	20	90 **8**
16	PhOH **9**	<5	92[b]	-OTHP **9a**	10	92 **9**
17	PhOH **9**	<5	88[c]	-OEE **9b**	10	90 **9**
18	PhOH **9**	<5	87[b]	-OTHF **9c**	10	93 **9**
19	 **10**	25	84	-OTHP **10a**	50	92 **10**

[a] Cosolvent of CH_2Cl_2 and MeOH (1:1 by volume) was used in the reaction in order to dissolve cholesterol derivatives. [b] 3.0 Mol equiv of 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran were used. [c] 5.0 Mol equiv of ethyl vinyl ether were used.

their general stability to most nonacidic reagents, and the ease with which they can be removed.[3] The tetrahydrofuranyl ether (ROTHF) has also been used as a protecting group for alcohols. A variety of reagents have been developed for these protections which include mainly protic acids,[4] Lewis acids,[5] basic conditions,[6] neutral conditions,[7] transition metal catalysts,[8] and heterogeneous catalysts.[9] On the other hand, the

deprotection of these ethers were carried out under acidic[3,4d, 9b,10], neutral,[11] and reductive conditions.[12] Encouraged by our discovery, we tried to investigate the applications of ATPB in the protection of alcohols with alkyl vinyl ethers and their deprotection. In this report, we describe the results of our efforts in this direction.

Alcohols of different types (primary, secondary, tertiary, and phenolic) reacted with 3,4-dihydro-2*H*-pyran (1.2 mol equiv) in the presence of 0.1 mol equiv of ATPB in CH_2Cl_2 at RT to give THP ethers in excellent yields. (Entries 1, 4, 7, 10, 13, 16, Table 1 and Scheme 2).[14] These THP ethers could also be deprotected under the catalysis of ATPB in MeOH at RT to afford the corresponding alcohols in excellent yields as shown in Table 1 and Scheme 2.[15] It is noteworthy that all the reactions mentioned above were complete in a short time at RT. In the protection of phenol, the reaction was incomplete and only 65% yield of the THP ether was formed if 1.2 mol equiv of 3,4-dihydro-2*H*-pyran was used in the reaction. It needed 3 mole equiv of the reagents in order to give the product **9a** in excellent yield (Entry 16). Under acidic conditions, tertiary alcohol **7** is known to undergo dehydration[16] and β-hydroxyketone **10** could undergo both retro-aldol reaction and dehydration.[17] ATPB could be applied to catalyze the protection and deprotection of these two compounds perfectly (Entries 10 and 19).

Similar conditions could be applied to the preparation of 1-ethoxyethyl ethers (ROEE, Entries 2, 5, 8, 11, 14 and 17, Table 1) and tetrahydrofuranyl ethers (ROTHF, Entries 3, 6, 9, 12, 15 and 18) in excellent yields from different kinds of alcohols. ATPB could also be used in the deprotection of these two ethers as shown in Table 1 and Scheme 2. In general, in the presence of ATPB, 1.2 mol equiv of 2,3-dihydrofuran or 3 mol equiv of ethyl vinyl ether were needed to react with alcohols. However, in the protection of phenol, it needed 5 mole equiv of the ethyl vinyl ether in order to give the product **9b** in excellent yield (Entry 17). Use of less amounts of the ethyl vinyl ether resulted in an incomplete reaction. In the literature, 2-chlorotetrahydrofuran was used in the protection of alcohols instead of 2,3-dihydrofuran . It was reported that either a laborious workup procedure[18] or low yield[19] occurred when 2,3-dihydrofuran was used as a reagent. Interestingly, by using 0.1 mol equiv of ATPB as a catalyst, alcohols of different types could react with 2,3-dihydrofuran to give THF ethers in excellent yields.

In summary, our protocol provides a useful alternative for the preparation of THP, THF, and EE ethers as well as cleavage of THP, THF, and EE ethers to the corresponding alcohols. ATPB is easily prepared in one step from Ph_3P and bromoacetone.[20] The advantages of this methodology are mild conditions, fast reaction rate, excellent yields and tolerance to acid-sensitive functionalities.

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14. Typical procedure for the protection reaction catalyzed by ATPB. To a solution of cholesterol (**6**) (288.1 mg, 0.74 mmol) and 3,4-dihydro-2*H*-pyran (75.1 mg, 0.87 mmol) in 1.5 mL of CH_2Cl_2 was added ATPB (29.7 mg, 0.07 mmol) and the solution was stirred at RT. The reaction was complete in 5 min. The solution was concentrated and chromatographed on silica gel to give the desired product **6a** (315.8 mg, 0.67 mmol) in 91% yield.
15. Typical procedure for the deprotection reaction catalyzed by ATPB. To a solution of OTHP-protected compound **6a** (66.5 mg, 0.14 mmol) in a mixture of CH_2Cl_2-MeOH (2.8 mL; 1:1 by volume) was added ATPB (56 mg, 0.14 mmol) and the solution was stirred at RT for 50 min. (Note: Compound **6a** was not quite soluble in MeOH so CH_2Cl_2 was used as a cosolvent. Only MeOH was used in the other cases.) The solution was concentrated and chromatographed on silica gel to give the desired product **6** (54 mg, 0.14 mmol) in 99% yield.
16. If *p*-toluenesulfonic acid was used as catalyst in the reaction, the major product is 1-phenylcyclohexene (86% yield) and the THP ether **7a** was formed in 2% yield only.
17. If *p*-toluenesulfonic acid was used as catalyst in the reaction, complex mixtures were formed, as indicated by TLC and the THP ether **10a** was isolated in 40% yield.
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20. PPTS is an excellent reagent for the the preparation and deprotection of THP ethers (see ref. 4d) However, it is quite hydroscopic. ATPB is much less hydroscopic than PPTS.