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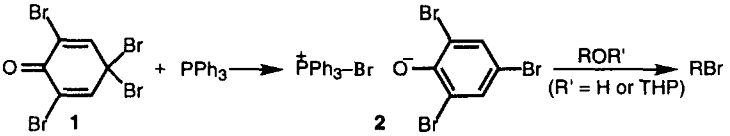
A Mild and Efficient Method for Converting Alcohols and Tetrahydropyranyl Ethers to Bromides with Inversion of Configuration

Akira Tanaka[a]*and Takayuki Oritani[b]

[a] Division of Environmental Bioremediation, Graduate School of Agriculture and [b] Department of Applied Biological Chemistry, Faculty of Agriculture, Tohoku University, 1-1 Tsutsumidori-amamiyamachi, Aoba-ku, Sendai 981, Japan

***Abstract*:**Bromotriphenylphosphonium salt **2**, generated by adding 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**1**) to triphenylphosphine in CH_2Cl_2 or CH_3CN converted alcohols and tetrahydropyranyl ethers to the corresponding bromides in high yields. © 1997 Elsevier Science Ltd. All rights reserved.

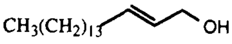
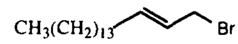
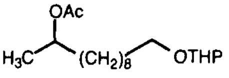
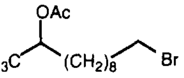
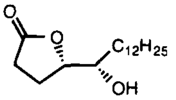
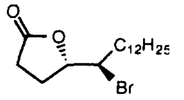
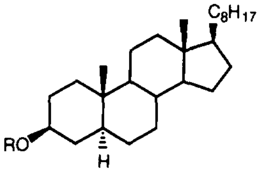
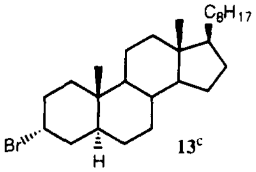
Alkyl bromides are important and versatile intermediates for alkylation and preparation of alkylmetal salts such as Grignard reagents. There are numerous methods for accessing bromides from the corresponding alcohols, while direct transformation of ethers to alkyl bromides has been also reported, but to a lesser extent.[1,2] In particular, the methods for delivering bromides under mild and neutral conditions are frequently employed in view of their clean product forming and high-yielding results, *e.g.*, PPh_3/CBr_4, PPh_3/diethyl azodicarboxylate/ RBr or LiBr.[3] However, the most popular reagent, PPh_3/CBr_4 can not generally lead to satisfactory results for secondary alcohols.[4] In this communication, we report a new reagent system converting primary and secondary alcohols and tetrahydropyranyl ethers to the corresponding bromides under mild and neutral conditions.



2,4,4,6-Tetrabromo-2,5-cyclohexadienone (**1**)[5] is a brominating agent which is often employed for the brominative cyclization of polyenes. When **1** was treated with an equimolar amount of PPh_3 in dry dichloromethane, an exothermic reaction took place to produce bromotriphenylphosphonium salt **2**. As shown in Table 1,[6] we found that this salt was able to transform various alcohols and tetrahydropyranyl ethers to the corresponding bromides in high yields. Dichloromethane was the solvent of choice in view of its high ability to solubilize salt **2** and the simple work-up procedure comprising only evaporation of the solvent. Acetonitrile can also be used, although the reaction is a little slower than that in dichloromethane. Tetrahydrofuran, 1,2-dimethoxyethane and nitromethane were ineffective, because the reaction did not proceed at all and, in particular, salt **2** was sparingly soluble in the former two solvents. Since the bromide formation in the secondary alcohols was slower relative to that in the primary alcohols, particularly in the case of the corresponding THP ethers, a large excess of the reagents was necessitated. As shown in Scheme 1, the mechanism of this reaction appears to be similar to that of other related reactions consisting of triphenylphosphine and co-reagents such as molecular bromine and carbon tetrabromide. That the S_N2 process leading to inversion of configuration is involved in this developed reagent system is evident from the results in entries 6 and 7.

In conclusion, we found that the salt **2**, generated from 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**1**) and triphenylphosphine, was a quite effective species converting alcohols and tetrahydropyranyl ethers to the corresponding bromides in high yields. This method offers an efficient alternative to the existing methods for accessing alkylbromides. Since the intervention of alkoxytriphenylphosphonium intermediate **3**, that is also proposed for the Mitsunobu type reactions,[3,8] would permit other useful chemical transformations, we are now investigating applications of this newly developed reagent system.

Table 1

Entry	Substrate		Equiv.of Reagent 2	Time(h)	Yield (%)	Product
1	$CH_3(CH_2)_{17}OR$	**4a** R = H	1.4	4	99	$CH_3(CH_2)_{17}Br$ **5**
2		**4b** R = THP	2.5	2	98	
3	 **6**		1.8	10	98[b]	 **7**
4	 **8**		2.5	3	78	 **9**
5	 **10** (+)-muricatacin[a]		3.0	8	88[b]	 **11**[c]
6		**12a** R = H	2.2	5	86	 **13**[c]
7		**12b** R = THP	3.0	5	91	

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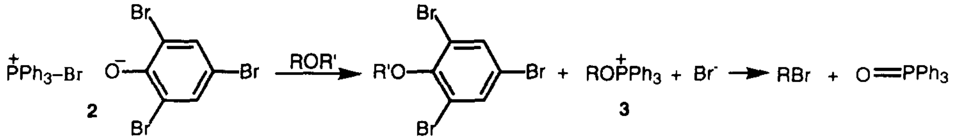
a) See ref. 9. b) The reaction was performed in CH_3CN. c) The product was identical with an authentic sample obtained by treating with PPh_3/CBr_4, which was known as an SN2 process.



Scheme 1

REFERENCES AND NOTES

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2. Larock, R. C.; *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989.
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5. This reagent was prepared by the method of ref. 7. Recrystallization from $CHCl_3$ afforded pure **1** as golden yellow crystals, which could be stored at -10° C for several months.
6. A typical experimental procedure is as follows: To a solution of PPh_3 (576 mg, 2.2 mmol) in CH_2Cl_2 (4 ml) was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**1**)(902 mg, 2.2 mmol) below 5° C under N_2. After complete disappearance of the yellow color, 3*b*-cholestanol (**12a**)(389 mg, 1 mmol) was added and the mixture was stirred for 5 h at room temperature. Evaporation of the solvent left a viscous residue, which was washed thoroughly with hexane. Concentration and SiO_2 column chromatography using hexane led to 3a-bromocholestane (**1 3**)(388 mg, 86% yield), together with 2,4,6-tribromophenol (320 mg, 97%).
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