2,4,4,6-Tetrabromocyclohexa-2,5-dienone in the presence of triphenylphosphine as a regiospecific and stereoselective reagent for the nucleophilic substitution of bromine for hydroxyl

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A highly reactive, regio- and stereo-specific reagent, a 2,4,4,6-tetrabromocyclohexa-2,5-dienone–triphenylphosphine complex, has been used for the first time in the nucleophilic substitution of bromine for hydroxyl in alcohols.

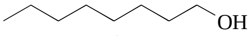
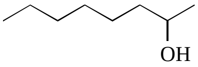
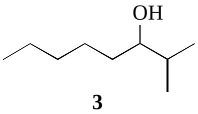
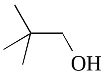
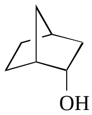
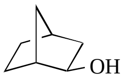
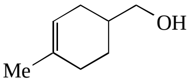
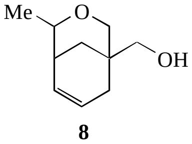
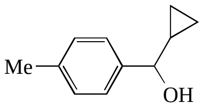
2,4,4,6-Tetrabromocyclohexa-2,5-dienone **I** is known to be a useful reagent for the cation radical bromination of a broad range of organic compounds and for the electrophilic bromination of phenols and dialkylanilines.[1,2] However, no examples of its application as a donor of nucleophilic bromine have been reported to date. We found that tetrabromide **I** can successfully be used in the nucleophilic substitution of bromine for hydroxyl, *i.e.*, serve as a source of nucleophilic halogen.

In our previous work[3,4] we studied complexes of triphenylphosphine with esters of trichloro- and tribromo-acetic acids and with trichloroacetonitrile. When these complexes are used, nucleophilic substitution in alcohols occurs in high yields and highly regio- and stereospecifically. It should be noted that esters of tribromoacetic acid are less readily available synthetically than esters of trichloroacetic acid.

To broaden the range of halophilic compounds that allow one to perform nucleophilic substitution of bromine for the hydroxyl group, we resorted to the readily available tetrabromide **I**.[2]

Based on literature data,[3–5] we assume that the reaction of

Table 1 Optimum conditions for various substrates in the substitution reaction.

Starting compounds	T/°C	t/h	Solvent	Yield (%)	Isomeric purity[a] (%)
 **1**	–10	0.25	MeCN	99	100
 **2**	–5	0.5	MeCN	90	99.9
	0	0.5	MeCN	90	99.9
 **3**	0	1	MeCN	55	63[b]
	0	1	CH_2Cl_2	55	87[c]
 **4**	0	2	$C_6H_3Cl_3$	98	99
 **5**	0	12	CH_2Cl_2	60	99[d]
	0	12	MeCN	40	99[d]
 **6**	0	12	CH_2Cl_2	85	99[d]
	0	12	MeCN	67	99[d]
 **7**	0	2	CH_2Cl_2	80	98[e]
 **8**	0	2	CH_2Cl_2	80	98.9[e]
 **9**	–10	2	CH_2Cl_2	70	99[f]

[a] Determined by GLC. [b] 37% olefin. [c] 13% olefin. [d] *exo*-Bromonorbornane is the only product. [e] Determined by ^{1}H NMR spectroscopy. [f] (*E*)-1-*p*-Tolyl-4-bromobut-1-ene is the only product.

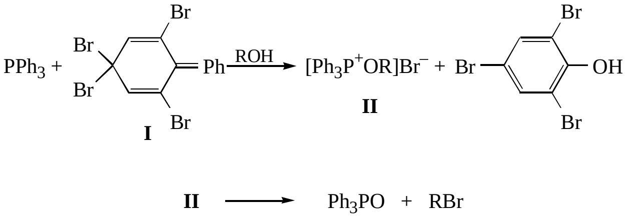
triphenylphosphine with tetrabromide **I** starts with attack of the nucleophilic phosphorus atom on an electrophilic centre, a halogen atom, *i.e.* a halophilic interaction.[6] Unlike the previously studied reactions of CCl_3X (where X = COOR; CN) with triphenylphosphine, the reaction of the latter with tetrabromide **I** occurs exothermically and at a high rate. In the presence of alcohols, oxyphosphonium intermediates **II** are formed. It is obviously in intermediate **II** that nucleophilic substitution occurs to give the corresponding bromides (Scheme 1).

The substitution reaction has general applicability, and this complex reacts with primary, secondary, sterically hindered and cage alcohols under sufficiently mild conditions to give high yields of the corresponding bromides. We found that the optimum conditions of substitution are as follows: a polar solvent (acetonitrile), temperature from –10 °C to 0 °C, reagent ratio alcohol : triphenylphosphine : tetrabromide **I** = 1:1:1 (Table 1).

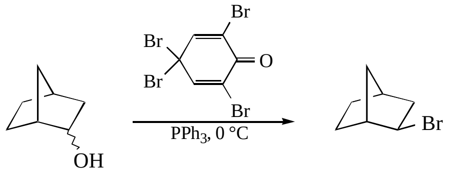
It was shown for octan-1-ol **1** as an example that the replacement of the hydroxyl group in primary alcohols occurs in 15 min in an almost quantitative yield.

This reagent was found to be regiospecific, which was demonstrated for the replacement of the hydroxyl group in secondary and especially in branched secondary alcohols. For example, octan-2-ol **2** is transformed into 2-bromooctane in 90% yield and with an isomeric purity of 99.9%. In spatially hindered alcohols, such as 2-methyloctan-3-ol **3**, substitution occurs in 40% yield, which is the best yield for such alcohols. Usually nucleophilic substitution in such alcohols is accompanied by rearrangements and elimination if classical reagents or even reagents based on triphenylphosphine are used.[5] It should be emphasised that in the case studied, the yield of the olefin is only 13% and no rearrangement products are formed. (Literature data for the $PPh_3{\cdot}CBr_4$ complex for an analogous structure, 3-methylbutan-2-ol:[7] the reaction yield is 30%, 8% of which is an isomerised product). Even the reaction with neopentyl alcohol **4** occurs without isomerisation of the carbon skeleton under very mild conditions (0 °C) in a quantitative yield and with high isomeric purity (99%) (for the $PPh_3{\cdot}CBr_4$ complex, the yield of neopentyl bromide is 42%[8]).

The replacement of hydroxyl in cage alcohols occurs under similar conditions (0 to +5 °C), and the process is strictly regiospecific. For example, the replacement in both *endo*-**5** and *exo*-**6** norborneols results in *exo*-bromonorbornane in high yield (60%), the isomeric purity of the product being over 99%. This is a very high yield for such systems.[9] *Exo*- and *endo*-isomers differ in the chemical shift of the methine proton at the C^2 atom in the ^1H NMR spectra. In both cases the chemical shift of this proton in the product is 3.95 ppm (lit.,[10] 3.9 ppm).



Scheme 1



The high regio- and stereo-specificity of the reagent was also shown for alcohols such as analogues of natural carbinols. For example, alcohols **7** and **8** react with the complex under study to give exclusively regio-substitution products, whose structure was confirmed by ^1H NMR spectroscopy.

The substitution in secondary carbinols containing cyclopropane substituents occurs through stereospecific opening of the cyclopropane ring. The reaction of *p*-tolylcyclopropylcarbinol **9** gives (*E*)-1-*p*-tolyl-4-bromobut-1-ene as the only product.

The data presented above suggest the high reactivity, regiospecificity and stereoselectivity of 2,4,4,6-tetrabromocyclohexa-2,5-dienone in the presence of triphenylphosphine in the nucleophilic substitution of bromine for a hydroxyl group. The proposed method looks extremely promising for fine organic syntheses.

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