Improved Methods for Dehydration and Hydroxy/Halogen Exchange using Novel Combinations of Triphenylphosphine and Halogenated Ethanes

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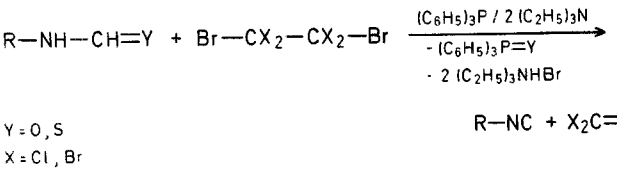
Carbon tetrachloride in combination with triphenylphosphine is a mild and convenient reagent for the chlorination of *O*- and *S*-functional groups, as well as for intra- and intermolecular dehydration reactions[1]. Due to the neutral reaction conditions required, this reagent system has proved to be applicable in the field of sensitive polyfunctional natural products, including carbohydrates, nucleosides, and terpenes[2]. A significant improvement of this system was recently brought about by using hexachloroethane[3] instead of carbon tetrachloride, which was demonstrated in the syntheses of peptides[4] and various heterocycles[5].

We now report further enhanced reactivity of this reagent system by introducing hexabromoethane and 1,2-dibromotetrachloroethane as halogen sources. The required hexabromoethane can easily be prepared from hexachloroethane[6], whereas 1,2-dibromotetrachloroethane is a cheap commercial substance, which nonetheless has been used as a reagent only twice[7,8]. Thus, these halogenated ethanes, in combination with triphenylphosphine easily convert formamides and thionoformamides to the corresponding isonitriles.



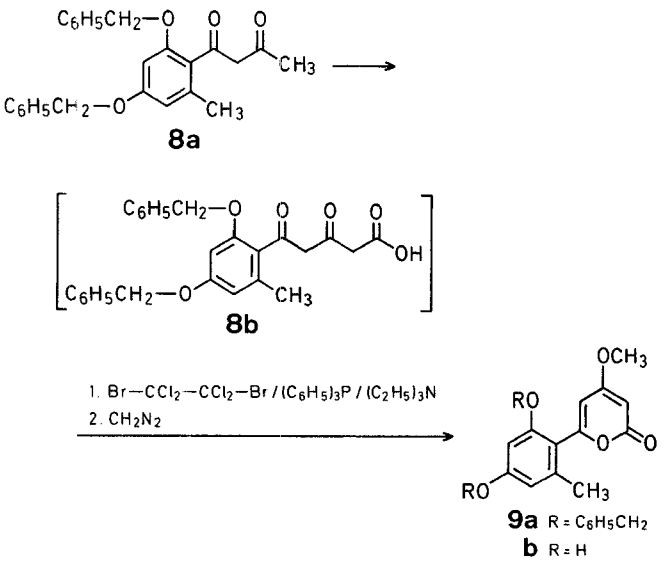
Similarly, we have smoothly dehydrated the amide **3a** and the aldoxime **4a** to the nitriles **3b** and **4b**, and the *N,N'*-dialkylurea **5a** to the carbodiimide **5b**. As seen from Table 1, reactions with 1,2-dibromotetrachloroethane and hexabromoethane proceed at lower temperatures, requiring shorter reaction times, compared with the conventional halogen sources carbon tetrachloride or hexachloroethane.

The strongly enhanced reactivity of the new reagent combinations can apparently be attributed to two effects: the greater polarizability of bromine versus chlorine, and the more facile formation of the product pair $CX_2{=}CX_2/Br^{\ominus}$ from haloethanes compared with the worse formal leaving group $CX_3^{\ominus}$, when using methane derivatives, instead. In the series of perhalogenated alkanes, bromo compounds obviously constitute an optimum as use of carbon tetraiodide causes extensive side reactions.

In the series of the far less reactive 1,2-dihaloalkanes, however, 1,2-diiodoethane is the most attractive due to its acceptable reactivity, combined with the great volatility of the unsubstituted ethene produced, which may be quite advantageous in certain cases.

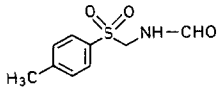
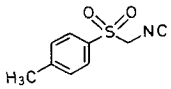
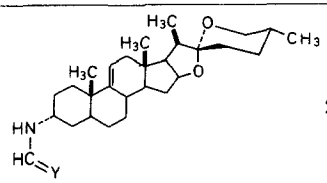
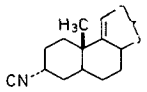
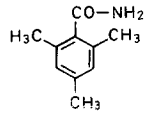
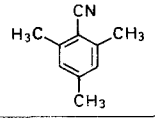
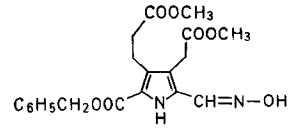
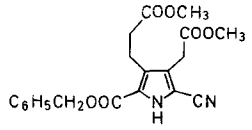
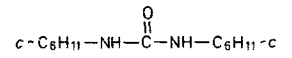
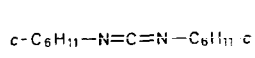
The presented new reagent combinations also smoothly effect S_N2-type replacement of secondary and primary hydroxy groups by halogen, as shown in Table 2.

The utility of the new reagent 1,2-dibromotetrachloroethane/triphenylphosphine could also be demonstrated in the course of the biomimetic synthesis of the aglycon **9b** of the biologically active bitter glucoside aloenin[9]. The key step in this synthesis – lactonization of the crude labile 3,5-dioxopentanoic acid **8b**, obtained by carboxylation of the diketone **8a** had been shown by us[10] to proceed in traces only (<0.5%), with the conventional[11] use of acetic anhydride. Now we have found that use of the system 1,2-dibromotetrachloroethane/triphenylphosphine enables us to run the reaction sequence **8a** → **9b** in 31% yield. Considering the extensive side reaction of migration of the benzyl group during the preceding carboxylation reaction, which leads to the chromone **10** (28%)[10], this overall yield is very satisfactory.



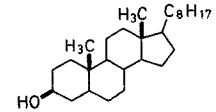
0039-7881/83/0232-0139-03 $ 03.00

Table 1. Dehydration Reactions with Triphenylphosphine and Haloalkanes

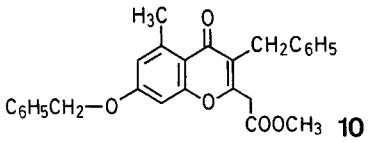
Substrate	Product	Halo-alkane	Reaction Conditions temperature/time[a]	Yield[b] [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Lit. m.p. [°C] or b.p. [°C]/torr	Work-up
1a 	**1b** 	$Br_3C—CBr_3$	−10 °C/<1 min[c]	61	116° (toluene/PE)	116–117°[12]	Column filtration (SiO_2, CH_2Cl_2), crystallization
		$BrCCl_2—CCl_2Br$	−10 °C/<1 min[c]	60			
		$Cl_3C—CCl_3$	25 °C/10 min	29[d]			
		CBr_4	−10 °C/5 min	43[d]			
		CCl_4	85 °C/3000 min[e]	—[d]			
		CJ_4	−10 °C/<1 min[c]	—[d]			
2a 	**2b** 	$BrCCl_2—CCl_2Br$	0 °C/<1 min[c]	85 (Y = O)	232–233° (subl.) (acetone)	232–233° (subl.)[13]	Column chromatography (SiO_2, $CHCl_3$), crystallization
		$BrCCl_2—CCl_2Br$	0 °C/<1 min	71 (Y = S)			
3a 	**3b** 	$BrCCl_2—CCl_2Br$	0 °C/<1 min[c]	90	54–55°	55°[14]	Column filtration, (SiO_2, $CHCl_3$), sublimation
4a 	**4b** 	$BrCCl_2—CCl_2Br$	−10 °C/<1 min[c]	82	see procedure		
		$Br_3C—CBr_3$	−10 °C/<1 min[c]	80			
		CCl_4	85 °C/60 min	77			
		$Cl_3C—CCl_3$	25 °C/90 min	76			
		$JCH_2—CH_2J$	0 °C/60 min	67			
		$BrCH_2—CH_2Br$	85 °C/300 min[e]	1.2			
		$ClCH_2—CH_2Cl$	85 °C/300 min	—			
5a 	**5b** 	$BrCCl_2—CCl_2Br$	0 °C/<1 min[c]	78	155°/12	158–160°/12[15]	After solvent evaporation hexane extraction, distillation

[a] Minimum time for complete reaction, as monitored by T.L.C. and I.R.
[b] Yield of isolated, pure product.
[c] Immediate, exothermic reaction.
[d] Complex reaction mixture.
[e] Incomplete reaction.

Table 2. Hydroxy/Halogen Exchange with Halogenated Ethanes and Triphenylphosphine

Substrate	Product[a]	Haloalkane	Reaction Conditions temperature/time[b]	Yield [%][c]	m.p. [°C]	Lit. m.p. [°C]	$[\alpha]_D$	Lit. $[\alpha]$
6a 	**6b** X = Cl	$Cl_3C—CCl_3$	25 °C/60 min	90	103–104°	103–105°[16]	+31.0° (*c* 1.4, $CHCl_3$)	+30.5°[16]
	6c X = Br	$Br—CCl_2—CCl_2—Br$	25 °C/<1 min	94	103–104°	103–104°[17]	+29.8° (*c* 10.0, $CHCl_3$)	+28.7°[17]
		$Br_3C—CBr_3$	25 °C/<1 min	93				
	6d X = J	$J—CH_2—CH_2—J$	85 °C/60 min	93	108°	111.5–112.5°[18]	+33.4° (*c* 1.4, $CHCl_3$)	+32.3°[18]
7a $H_3C—(CH_2)_{17}—OH$	$H_3C—(CH_2)_{17}—Br$ **7b**	$Br—CCl_2—CCl_2—Br$	−10 °C/<1 min	94	28–28.5°	28.5°[19]	—	—
	$H_3C—(CH_2)_{17}—J$ **7c**	$J—CH_2—CH_2—J$	25 °C/60 min	96	33.5–34°	33.5–34.5°[20]	—	

[a] Products **6b, c, d** worked-up by column chromatography [SiO_2, 1:1 petroleum ether (b.p. 40–60 °C)/ether] and crystallization from methanol; **7b, c** by column filtration [SiO_2, petroleum ether (b.p. 40–60 °C)] and crystallization from dichloromethane/methanol.
[b] Minimum time for complete reaction as monitored by T.L.C.
[c] Yield of isolated, pure product.



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The facile handling of the reagents, also on a small scale, compared with other, moisture-sensitive dehydrating agents, and the mild reaction conditions required should lead to further applications in preparative organic chemistry.

5-Benzoxycarbonyl-2-cyano-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole (4b); Typical Procedure:

To a mixture of **4a** (402 mg, 1.0 mmol) and triphenylphosphine (524 mg, 2.0 mmol) in dry 1,2-dichloroethane (20 ml), a solution of 1,2-dibromotetrachloroethane (652 mg, 2 mmol) and triethylamine (0.560 ml, 4.0 mmol) in dichloroethane (10 ml) is added at −10 °C. Removal of the precipitate by filtration, and evaporation of the solvent under reduced pressure gives an oily residue, which is passed through a short silica gel column and eluted with 1:2 petroleum ether (b.p. 40–60 °C)/ether. Crystallization from ligroin affords the title compound; yield: 316 mg (82%); m.p. 116 °C.

$C_{20}H_{20}N_2O_6$	calc.	C 62.49	H 5.24	N 7.29
(384.4)	found	62.38	5.29	7.38

I.R. (KBr): $\nu = 2215\ cm^{-1}$ (C≡N).

Work-up Procedure for Aglycon 9a, b:

After evaporation of the solvent, methylation with diazomethane (0.15 molar solution in ether, −20 °C); column chromatography [SiO_2 3:1 ether/petroleum ether (b.p. 40–60 °C)]; oil; further characterized by quantitative hydrogenation[10] to the aglycon **9b**; m.p. 212–213 °C (Lit.[9], m.p. 213–214 °C).

The authors wish to thank the Deutsche Forschungsgemeinschaft for financial support.

Received: August 16, 1982
(Revised form: October 4, 1982)

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