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Hexabromoacetone and ethyl tribromoacetate: a highly efficient reagent for bromination of alcohol

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Abstract

A new and efficient method for the bromination of alcohols utilizing $Br_3CCOCBr_3/PPh_3$ and Br_3CCO_2Et/PPh_3 is described. Various alcohols can be converted smoothly into their corresponding alkyl bromides in high yields under mild conditions with short reaction times. Based upon ^1H NMR studies using competitive reactions between selected brominating agents and Cl_3CCN, $Br_3CCOCBr_3$ displays the highest reactivity approximately nine times that of CBr_4.

Keywords: Alcohols; Bromination; Hexabromoacetone; Ethyl tribromoacetate; Triphenylphosphine

The transformation of alkyl halides into valuable end products is often utilized in organic syntheses.[1] Alkyl chlorides are often used since they are easily prepared using readily available reagents such as $SOCl_2$, PCl_3 or combined systems of PPh_3 with CCl_4, $Cl_3CCOCCl_3$, Cl_3CCN or Cl_3CCONH_2.[2] However, alkyl chlorides are less reactive than alkyl bromides or iodides.[3] Thus, an efficient and practical protocol for the preparation of alkyl bromides would be valuable. There are relatively few conditions for the conversion of alcohols into bromides. Previous examples include highly toxic reagents such as HBr gas and Br_2 or coupling reagents like CBr_4/PPh_3, Br_2/PPh_3 and Br_2PPh_3 but HBr is always a by-product and high temperatures are often required.[4]

Recently, we have examined the reactivity of various reagents for the chlorination of alcohols and carboxylic acids to give the corresponding alkyl and acyl chlorides.[5] The results clearly showed that the reagents possessing strong electron-withdrawing groups such as $Cl_3CCOCCl_3$ and Cl_3CCN showed the highest reactivity. We have now extended this idea for bromination and have examined $Br_3CCOCBr_3$ and Br_3CCO_2Et. Although $Br_3CCOCBr_3$ was prepared in 1969, only two reports involving the synthesis of bioactive compounds have been addressed.[6] The preparation and the use of Br_3CCO_2Et for the preparation of amides has also been described.[7] Nonetheless, these two reagents have never been reported as reagents for bromination of alcohols. Herein, we wish to report the use of $Br_3CCOCBr_3/PPh_3$ and Br_3CCO_2Et/PPh_3 for the efficient and practical conversion of alcohols into the corresponding alkyl bromides and a relative reactivity study.

Conditions were optimized for the conversion of 2-phenylethanol into 2-phenylethyl bromide (Table 1).

Using a ratio of alcohol:brominating agent:PPh_3 of 1:1.5:1.5 equiv, the desired product was obtained in low to moderate yields in the case of $BrCCl_3$ and Br_3CCO_2H (entries 2 and 3). However, CBr_4, Br_3CCO_2Et and $Br_3CCOCBr_3$ afforded the bromide in excellent yields (entries 4, 7 and 10). Interestingly, decreasing the amount of Br_3CCO_2Et and $Br_3CCOCBr_3$ from 1.5 to 1 and 0.3 equiv, respectively, still provided the desired bromide in quantitative yields (entries 8, 9 and 11–14). Moreover, a short reaction time (15 min) also gave the alkyl bromide in excellent yields (entries 8 and 13).

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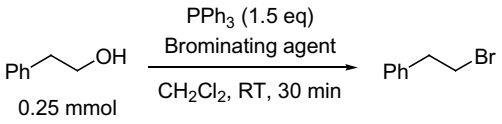
Table 1
Effect of the types of brominating agent, ratio of brominating agent and PPh_3 and reaction time on the conversion of 2-phenylethanol into 2-phenylethyl bromide



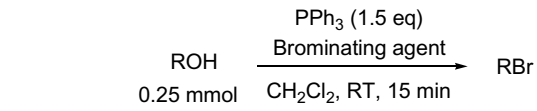
Entry	Brominating agent		Yield[a] (%)
	Type	Amount (equiv)	
1	None	—	0
2	$BrCCl_3$	1.5	21[b]
3	Br_3CCO_2H	1.5	42
4	CBr_4	1.5	96
5		1.0	90
6		0.5	42
7	Br_3CCO_2Et	1.5	95
8		1.0	96, 98[c]
9		0.5	78
10	$Br_3CCOCBr_3$	1.5	98
11		1.0	99
12		0.5	99
13		0.3	99, 98[c]
14		0.25	74

[a] Determined by ^1H NMR.
[b] 2-Phenylethyl chloride was also obtained in 40% yield.
[c] Reaction time was 15 min.

This optimized reaction conditions were utilized in a study on the scope of bromination of various primary, secondary and tertiary alcohols (Table 2).

All the primary and secondary, alkyl and cyclic alcohols studied were converted into the corresponding alkyl bromides in high to excellent yields using Br_3CCO_2Et or $Br_3CCOCBr_3$ (entries 1–11). An olefinic by-product was detected as a minor component from 1:5.60 to 1:7.25 (entries 10 and 11). The formation of an olefinic by-product in a ratio of 1:1.40 was previously observed in the chlorination of cyclooctanol using Cl_3CCONH_2/PPh_3.[2e] The present results indicate that bromide is a more reactive nucleophile than chloride to generate the corresponding cyclic halides via S_N2 displacement. Tertiary alcohols gave the corresponding alkyl bromides in poorer yields (entries 12–15). This implies that the reaction may take place via two competing pathways, substitution versus elimination. $Br_3CCOCBr_3$ was a more efficient brominating agent than Br_3CCO_2Et for tertiary alcohols (entries 14 and 15).

Table 2
Bromination of alcohols

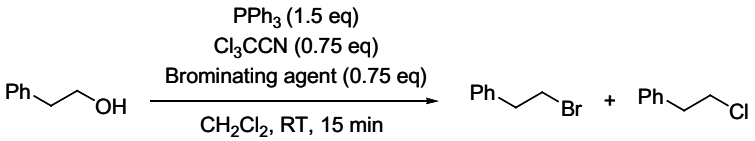


Entry	Alcohol	Brominating agent[a]	Yield[b] (%)	
			RBr	Olefin
1	1-Octanol	$Br_3CCOCBr_3$	97	—
2		Br_3CCO_2Et	Quant	—
3	Phenylmethanol	Br_3CCO_2Et	98	—
4	2-Phenylethanol	$Br_3CCOCBr_3$	98, 83[c,d]	—
5		Br_3CCO_2Et	98, 82[c,d]	—
6	(−)-Nopol	Br_3CCO_2Et	78[c,d]	—
7	(±)-2-Octanol	$Br_3CCOCBr_3$	Quant	—
8		Br_3CCO_2Et	97	—
9	(±)-1-Phenylethanol	Br_3CCO_2Et	98	—
10	Cyclooctanol	$Br_3CCOCBr_3$	84	15
11		Br_3CCO_2Et	87	12
12	1-Adamantanol	$Br_3CCOCBr_3$	42[c,d]	—
13		Br_3CCO_2Et	48[c,d]	—
14	2-Phenyl-2-propanol	$Br_3CCOCBr_3$	67	30
15		Br_3CCO_2Et	42	48

[a] 0.3 equiv $Br_3CCOCBr_3$ was used; 1 equiv Br_3CCO_2Et was used.
[b] Determined by ^1HNMR.
[c] Isolated product.
[d] 3 mmol of ROH was used.

The reactivity of various reagents in the bromination of alcohols to bromides was also investigated using a competitive reaction between Cl_3CCN and various brominating agents towards 2-phenylethanol (Table 3).[8]

Table 3
Comparative reactivity study of brominating agents



Entry	Brominating agent	Yield[a] (%)		Ratio of Br/Cl	Reactivity[b]
		Br	Cl		
1	None	0	76	—	—
2	CBr_4	32	65	0.49	1
3	Br_3CCO_2Et	40	60	0.67	1.37
4	$Br_3CCONEt_2$	47	52	0.90	1.84
5	$Br_3CCOCBr_3$	80	18	4.44	9.06

[a] Determined by ^1H NMR.
[b] Based on CBr_4.

In the absence of brominating agent, 2-phenylethyl chloride was obtained in high yield (entry 1). Br_3CCO_2Et displayed reactivity close to those of CBr_4 and $Br_3CCONEt_2$ (entries 2 and 3). Intriguingly, $Br_3CCOCBr_3$, bearing a strong electron-withdrawing group, significantly displayed the highest reactivity (entry 5). The highest reactivity was associated with the strongest electron-withdrawing groups, just as was observed for chlorination.[5]

In summary, we have disclosed an efficient method for the preparation of alkyl bromides from alcohols using $Br_3CCOCBr_3/PPh_3$ or Br_3CCO_2Et/PPh_3.

A typical procedure for the preparation of an alkyl bromide: To a stirred solution of alcohol (0.25 mmol) and PPh_3 (0.375 mmol) in dry CH_2Cl_2 (0.5 mL) was added Br_3CCO_2Et (0.25 mmol) or $Br_3CCOCBr_3$ (0.075 mmol) at rt (30 °C) under a N_2 atmosphere. After 15 min, the reaction was quenched with cold water and the presence of the corresponding product in the crude mixture was determined by ^1H NMR analysis utilizing toluene as an internal standard or alternatively was isolated by purification through silica gel column chromatography.

A reactivity study: To a stirred solution of alcohol (0.25 mmol) and a mixture of brominating agent (0.188 mmol) and Cl_3CCN (0.188 mmol) in dry CH_2Cl_2 (0.5 mL) was added PPh_3 (0.375 mmol) at rt (30 °C) under a N_2 atmosphere. After 15 min, the amount of the corresponding products in the crude mixture was determined by ^1H NMR analysis using toluene as an internal standard.

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8. The reactivity of the brominating agents was assessed by the ratio of the yields of 2-phenylethyl bromide and 2-phenylethyl chloride obtained.