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Bromination of Alcohols by Boron Tribromide

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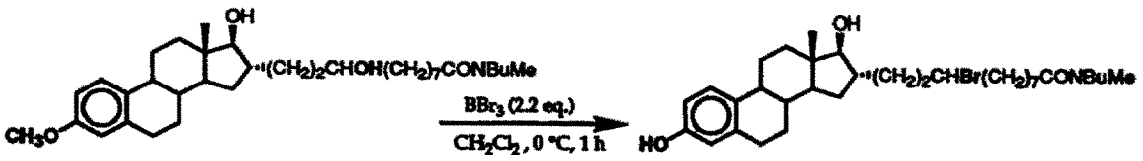
Abstract: Boron tribromide was used as a brominating agent for the conversion of alcohols to bromides. Tertiary alcohols were more reactive than secondary alcohols which were more reactive than primary alcohols.

Boron tribromide (BBr_3) is a useful reagent for the cleavage of ethers.[1,2] During recent years, we have used successfully this reagent for mild demethylation of aryl methyl ether of estradiol derivatives.[3] Moreover, we recently observed that 16α-(hydroxyalkylamide) 3-methyl estradiol 1 was transformed to 16α-(bromoalkylamide) estradiol 2 by this reagent (Scheme 1).[4,5] In this case, two transformations were performed: the cleavage of methoxy aryl group to lead the phenol and the substitution of hydroxyl group on side-chain to give the secondary bromide. Interestingly, the hindered steroidal 17β-hydroxy group was not brominated. To understand more fully and to rationalize these results, we investigated the use of BBr_3 for the bromination of different kinds of alcohols (Table 1).



1 2

Scheme 1

Table 1 shows the different alcohols (tertiary, secondary and primary) used for this study. In the first part (entries 1 to 5), BBr_3 (1.2 eq.) was added at 0 °C to a solution of alcohol in dry CH_2Cl_2 and the progression of reaction was evaluated several times by NMR spectroscopy. Complete bromination of tertiary alcohol (entries 1 and 2) was obtained after 0.25 h. At the same time, 75

and 92% bromides were obtained from the secondary alcohols (entries 3 and 4) but no reaction was observed for the primary alcohol (entry 5). Bromination was completed after 4 h for cyclohexanol (entry 3) and after 1 h for 3-heptanol (entry 4). Under similar conditions, primary alcohol gives only 12% of bromide after 24 h. Using more reagent (2.2 and 3.2 eq.) did not improve the bromide yield. Thus, the reactivity of alcohols follow the order of substitution and tertiary alcohols were more reactive than secondary alcohols, which were more reactive than primary alcohols. This order of reactivity was also observed with the 1,5-hexanediol (entry 6). In this case, only secondary alcohol was brominated. We also used a steroidal substrate with two secondary alcohols of different reactivities (entry 7). For this substrate, we reported the yields of isolated materials after work up and purification by flash chromatography. As expected the hydroxyl group at position 3 is more reactive to bromination than the hindered hydroxyl group at position 17. With 1.2 equivalent of BBr_3, a mixture of starting material (11%) and 3-bromo steroidal compound (51%) was obtained. Moreover, when 2.2 and 3.2 equivalents of reagent were used, we also observed the bromination of less hindered alcohol to give the 3-bromo steroidal compound (61 and 79%) and a small amount of starting material (8 and 5%, respectively). At all concentrations of BBr_3 we always observed a trace (~3%) of unknow material of low polarity (TLC-silica gel). The global yields of isolated compounds were good, ranging from 51 to 79% of mono 3-bromo steroidal compound and 11 to 5% of starting steroidal diol.

After establishing the order of reactivity of alcohols (tertiary > secondary >> primary), we studied the nature of bromide formed. Obviously, tertiary alcohols (entries 1 and 2) and primary alcohol (entry 5) give the corresponding bromides. However, several bromides were obtained from secondary alcohols, except symetrical cyclohexanol (entry 3). Three bromides were obtained in different proportions for 3-heptanol and 1,5-hexanediol (entries 4 and 6). In both cases, the bromine atom of major compound was located at the same position than the OH-group of starting alcohols while the bromine atom was each side of alcohol position for minor compounds. On other hand, secondary steroidal alcohol, 5α-androstane 3β,17β-diol (entry 7), shows a different pattern since we observed only the formation of two diastereoisomeric bromides in proportion 4 : 1 (3β and 3α, respectively). Thus, these results can not be explained by a true Sn1 or Sn2 mechanism and the mechanism is probably a complex one.

In conclusion, boron tribromide (BBr_3) was used successfully for the bromination of tertiary and secondary alcohols. However, hindered secondary alcohols, represented by a 17β-steroidal alcohol, and primary alcohols showed a very low reactivity. The reactivity of this reagent was found similar to that observed for the Lucas reagent (HX + ZnX_2; X= Br, Cl)[6] except for the former proceeding in aprotic solvent. Another important aspect of BBr3-reagent is that, when judiciously used, it can be a useful reagent to perform a double transformation, namely, the cleavage of an aryl alkyl ether and the bromination of alcohol.

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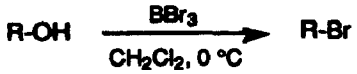
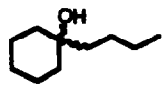
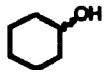
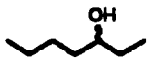
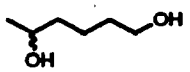
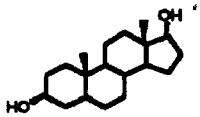
Table 1. Bromination of different alcohols by boron tribromide (BBr_3).[a]



Entry	Substrate	BBr_3 (eq.)	Time (h)	alcohol : bromides (%)[b]	Bromides formed (% of total bromides)[b]
1		1.2	0.25	0 : 100	1-bromo-1-butyl-cyclohexane
2		1.2	0.25	0 : 100	t-butyl-bromide
3		1.2 1.2 1.2 1.2	0.25 0.50 1.0 4.0	25 : 75 17 : 83 15 : 85 0 : 100	bromo-cyclohexane
4		1.2 1.2 1.2	0.25 0.50 1.0	8 : 92 5 : 95 0 : 100	n-bromo-heptane n=2 n=3 n=4 20 61 11 22 61 12 20 67 13
5		1.2 1.2 1.2 1.2 1.2 2.2 3.2	0.25 0.50 1.0 4.0 24 24 24	100 : 0 100 : 0 99 : 1 96 : 4 88 : 12 91 : 9 91 : 9	bromo-octane
6		1.2 2.2 3.2	0.5 0.5 0.5	29 : 71 14 : 86 5 : 95	n-bromo-hexanol n=4 n=5 n=6 16 47 8 22 57 6 21 68 6
7		1.2 2.2 3.2	4.0 4.0 4.0	11 : 51 8 : 61 5 : 79	n-bromo-5α-androstan-17β-ol n=3β n=3α 41 10 49 12 63 16

(a) See note 7 for experimental procedure. (b) For entries 1 to 6, the proportions of alcohol and bromides were determined by NMR spectroscopy (see note 8). For entry 7, the values refer to yields of isolated alcohol and total bromides after purification by flash chromatography while proportions of bromides were determined by NMR spectroscopy (see notes 8 and 9).

References and Notes

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5. Pelletier, J.D.; Labrie, F.; Poirier, D. Steroids **1993**, submitted.
6. March, J. Advanced Organic Chemistry, reactions, mechanisms and structure (2nd Ed.); McGraw-Hill, **1977**; p. 393.
7. **Experimental procedure**: alcohol (2 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and BBr_3 (1.0 M solution in CH_2Cl_2) was added at 0 °C. At appropriate time, 2.0 mL of reactional mixture was poured in water (8 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated to dryness before NMR analysis (Bruker AC/F 300). For entry 2, t-butyl alcohol (27 mmol) was dissolved in 30 mL of dry CH_2Cl_2 and BBr_3 was added at 0 °C. After 0.25 h, reactional mixture was quenched by water (15 mL), extracted with CH_2Cl_2 (2 x 15 mL), dried ($MgSO_4$) and evaporated to dryness before NMR analysis. For entry 6, steroidal alcohol (0.5 mmol) was dissolved in 30 mL of dry CH_2Cl_2 and BBr_3 was added at 0 °C. After 4 h, reactional mixture was quenched by water, extracted with CH_2Cl_2 and the crude compound purified by flash chromatography (silica gel and hexane/EtOAc, 85:15 as eluant).
8. Integration of characteristic NMR signals was used to estimate the proportion of alcohol and bromides. The chemical shifts (δ in ppm) were referenced to acetone-d_6 for entries 1 and 2 (^{13}C NMR), $CDCl_3$ for entries 3 to 6 (^1H NMR) and acetone-d_6 for entry 7 (^1H NMR). Entry 1, CX signals at 70.78 (X = OH) and 78.52 (X = Br); Entry 2, CX signals at 68.40 (X = OH) and 63.58 (X = Br); Entry 3, CHX signals (multiplets) at 3.63 (X = OH) and 4.20 (X = Br), Entry 4, CHX signals (multiplets) at 3.50 (X = OH), 4.13 (X = 2-Br), 3.99 (X = 3-Br or 4-Br) and in complement the CH_3 signals; Entry 5, CH_2 X signals (triplets) at 3.63 (X = OH) and 3.40 (X = Br); Entry 6, CH X signals (multiplets) at 3.79 (X = OH), 4.01 (X = 4-Br), 4.13 (X = 5-Br) and 3.42 (X = 6-Br). Note: in the conditions used the amount of 1-bromo derivatives is considered unimportant; Entry 7, CH X signals (multiplets) at 3.51 (X = OH), 4.12 (X = 3β-Br), 4.80 (X = 3α-Br).
9. Analysis of ^1H and ^{13}C NMR-stectra and HETCOR experiment permit to determine the position and orientation of bromine atom.

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