Investigation of the Appel reaction with bromotrichloromethane-triphenylphosphine ($BrCCl_3/PPh_3$)

Abdullah Al-Hemyari, Muna Bufaroosha, Thies Thiemann*

Department of Chemistry, United Arab Emirates University, Al Ain, United Arab Emirates. E-mail: thies@uaeu.ac.ae; thiesthiemann@yahoo.de

Abstract: The Appel reaction of an alcohol with CCl_4/PPh_3 and with CBr_4/PPh_3 produce alkyl chlorides and alkyl bromides, respectively. It was found that in the case of using $BrCCl_3$-PPh_3, a mixture of alkyl chlorides and alkyl bromides are formed. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were used as solvents, where the reaction was found to be solvent-dependent.

Keywords: Appel reaction, bromotrichloromethane, alkyl halide

Introduction

The original Appel reaction is a transformation that converts alcohols to alkyl halides, using triphenylphosphine – tetrachlorocarbon (PPh_3-CCl_4) [1] to obtain alkyl chlorides or, more rarely, triphenylphosphine - tetrabromomethane (PPh_3-CBr_4) [2]. In recent times, the combination triphenylphosphine – bromotrichloromethane (PPh_3-$BrCCl_3$) has also been used as a reagent in reactions such as the preparation of benzonitriles from benzaldoximes and benzamides [3], the esterification and amidation of carboxylic acids, the preparation of acid anhydrides and *O*-acyloximes from carboxylic acids [4] and the preparation of 1,1-haloethenes from carbaldehydes in a Corey-Fuchs type transformation [5], all reactions which had been carried out previously with PPh_3-CCl_4 [1]. There is one report on an Appel type conversion of benzyl alcohols to benzyl chlorides using $BrCCl_3$ with an excess of PPh_3. The reason of replacing CCl_4 with $CBrCl_3$ is that CCl_4 is an ozone class 1 depletor with an ozone depletion capacity of 1.08 (WMO 1991) to 1.1 (UNEP 1996) vs. chlorofluorocarbon CFC-11 [6] and thus is banned for most industrial uses. Although a bromo radical has a greater ozone scavenger potential than a chloro radical, bromotrichloromethane has a small but appreciable dipole moment (0.40 D), and this decreases its residency time in the atmosphere in comparison to CCl_4 significantly [7]. In the following, the authors re-evaluate the use of $BrCCl_3$-PPh_3 in the reaction of alcohols to alkyl halides in the original Appel transformation to understand the selectivity of the halide transfer bromide vs. chloride.

Experimental

Melting points were measured with a Stuart SMP10 melting point apparatus and are uncorrected. ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100.5 MHz) spectra were taken on a Varian 400 MHz spectrometer. IR measurements were performed on a Thermo Nicolet FT-IR spectrometer, model Nexus 470. Column chromatography was carried out on ***recycled*** silica gel Merck grade 9385 (pore size 60Å, 230 – 400 mesh, Aldrich). 11-Bromoundecanol (**5**, Sigma-Aldrich), triphenylphosphine (Aldrich), bromotrichloromethane (Aldrich), tetrachlorocarbon (Riedel de Haen), cholesterol (**11**, Fluka), sitosterol (**13**, Merck), 2-phenylethanol (**1**, Merck), 2-octanol (**3**, Sigma-Aldrich), 4-bromobenzyl bromide (**15-Br**, Aldrich), 4-bromobenzyl alcohol (Fluka), and citronellol (**9**, Merck Schuchardt) were acquired commercially. 4-Phenylbutan-2-ol (**7**) was

prepared from 4-phenylbutan-2-one (benzylacetone, Fluka) ($NaBH_4$, MeOH) and 4-bromobenzyl chloride (**15-Cl**) from 4-bromobenzyl alcohol (CCl_4, PPh_3).

General procedure: To PPh_3 (960 mg, 3.66 mmol) in dry CH_2Cl_2 (10 mL) is added dropwise $BrCCl_3$ (760 mg, 3.83 mmol) and the resulting solution is stirred at rt for 25 min., during which time it turns from colorless to yellow to orange-yellow. Thereafter, the alcohol (2.55 mmol) is added by syringe. The reaction is stirred for 14h at rt. Then, the solution is submitted directly to rapid chromatography on silica gel (eluent: CH_2Cl_2).

Competitive reaction of 4-bromobenzyl bromide (xx) and 4-bromobenzyl chloride with PPh₃: To a mixture of 4-bromobenzyl chloride (**15-Cl**, 780 mg, 3.8 mmol) and 4-bromobenzyl bromide (**15-Br**, 950 mg, 3.8 mmol) in dry chloroform (5 mL) was given triphenylphosphine (PPh_3, 980 mg, 3.8 mmol). Reaction aliquots were taken at 30 min., 1h, and 2 h and analyzed directly by ^{1}H NMR (400 MHz, $CDCl_3$).

Selected spectroscopic data:

1-Bromo-11-chloroundecane (**6-Cl**) [8]. – δ_H (400 MHz, $CDCl_3$) 1.27 (m, 10H), 3.40 (2H, t, CH_2, ^3J = 7.2 Hz), 3.53 (2H, t, CH_2, ^3J = Hz). δ_C (100.5 MHz, $CDCl_3$) 26.9, 28.2, 28.7, 28.9, 29.4, 29.4(5), 32.6, 32.8, 34.1 ($\underline{C}H_2Br$), 45.2 ($C\underline{H}_2Cl$).

1,11-Dibromoundecane (**6-Br**) [9]. – δ_H (400 MHz, $CDCl_3$) 1.28 – 1.31 (10H, m), 1.41 – 1.43 (4H, m), 1.81 – 1.88 (4H, m), 3.40 (4H, t, $2CH_2$, ^3J = 7.2 Hz); δ_C (100.5 MHz, $CDCl_3$) 28.2 (2C), 28.7 (2C), 29.4 (3C), 32.8 (2C), 34.1 (2C).

3-Hydroxybutylbenzene (4-phenylbutan-2-ol) (**7**) [9]. – δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, ^3J = 6.4 Hz, CH_3), 1.75 – 1.83 (2H, m), 2.15 (1H, bs, OH), 2.65 – 2.82 (2H, m), 3.82 - 3.87 (1H, m, CHOH), 7.19 – 7.23 (3H, m), 7.29 – 7.32 (2H, m); δ_C (100.5 MHz, $CDCl_3$) 23.6 (CH_3), 32.2 (CH_2), 40.8 (CH_2), 67.5 (CHCl), 125.8 (CH), 128.4 (4C, CH), 142.1 (C_{quat}).

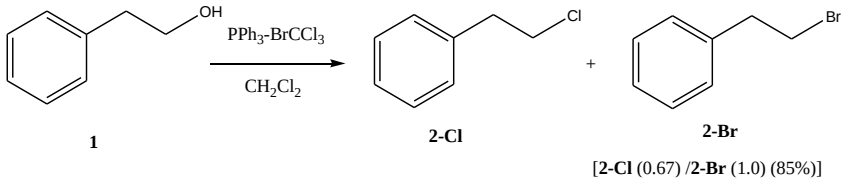
3-Chlorobutylbenzene (**8-Cl**) [10]. – δ_H (400 MHz, $CDCl_3$) 1.57 (3H, d, ^3J = 6.4 Hz, CH_3), 2.03 – 2.09 (1H, m), 2.75 – 2.94 (2H, m), 4.01 – 4.06 (1H, m, CHCl), 7.23 – 7.26 (3H, m), 7.32 – 7.36 (2H, m); δ_H (400 MHz, $CDCl_3$) δ_C (100.5 MHz, $CDCl_3$) 25.5 (CH_3), 32 .9 (CH_2), 42.0 (CH_2), 58.0 (CHCl), 126.1 (CH), 128.5 (2C, CH), 128.6 (2C, CH), 141.1 (C_{quat}).

3-Bromobutylbenzene (**8-Br**) [11]. - δ_H (400 MHz, $CDCl_3$) 1.75 (3H, CH_3, ^3J = 6.8 Hz, CH_3), 2.14 – 2.18 (2H, m), 2.72 – 2.91 (2H, m), 4.07 – 4.12 (m, 1H, CHBr), 7.21 – 7.24 (3H, m), 7.29 – 7.31 (2H, m); δ_H (400 MHz, $CDCl_3$) 26.6 (CH_3), 34.0 (CH_2), 42.7 (CH_2), 51.0 (CHBr), 126.1 (CH), 128.5 (4C, CH), 141.0 (C_{quat}).

Cholesteryl chloride (3β-chlorocholest-5-ene, **12-Cl**) [12]. - δ_H (400 MHz, $CDCl_3$) 0.68 (3H, s, CH_3), 0.87 (dd, ^3J = 6.4 Hz, 1.8 Hz, 6H), 0.90 (d, ^3J = 6.4 Hz, 3H), 0.95 – 1.05 (m, 3H), 1.04 (3H, s, CH_3), 1.07 - 1.22 (m, 7H), 1.22 – 1.73 (m, 10H), 1.79 – 1.93 (m, 2H), 1.95 – 2.12 (m, 3H), 2.14 – 2.25 (m, 1H), 2.59 (m, 1H), 2.73 (m, 1H), 3.78 (tt, J = 12.4, 4.3 Hz, 1H), 5.38 (dt, J = 5.3 Hz, 1.9 Hz, 1H), δ_C (100.5 MHz, $CDCl_3$) δ 11.9, 18.8, 19.4, 21.2, 22.7, 22.8, 23.9, 24.5, 28.2, 28.3, 31.3, 31.9 (2C), 35.9, 36.3, 36.4, 39.3, 39.6, 39.8, 42.5, 43.6, 50.1, 56.2, 56.9, 60.4, 122.6, 141.0.

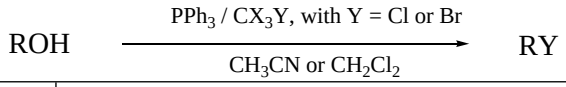
Cholesteryl bromide (3β-bromocholest-5-ene, **12-Br**) [13]. – δ_H (400 MHz, $CDCl_3$) 0.67 (s, 3H), 0.86 (dd, ^3J = 6.4 Hz, 1.8 Hz, 6H), 0.91 (d, ^3J = 6.6 Hz, 3H), 0.93 - 1.02 (m, 3H), 1.04 (s, 3H), 1.05 – 1.20 (m, 7H), 1.21 – 1.70 (m, 10H), 1.77 – 1.91 (m, 2H), 1.93 – 2.09 (m, 3H), 2.13 – 2.23 (m, 1H), 2.58 (ddd, J = 13.6 Hz, 4.7 Hz, 2.3 Hz, 1H), 2.68 – 2.79 (m, 1H), 3.92 (tt, J = 12.3 Hz, 4.5 Hz, 1H), 5.36 (dt, J = 5.3 Hz, 1.9 Hz, 1H), δ_C (100.5 MHz, $CDCl_3$) δ 11.8, 18.7, 19.2, 20.9, 22.6, 22.8, 23.8, 24.3, 28.0, 28.2, 31.7 (2C), 31.8, 34.4, 35.8, 36.2, 36.4, 39.1, 39.6, 39.7, 42.3, 44.3, 52.7, 56.1, 56.7, 122.4, 141.5.

Results and Discussion



Scheme 1. Appel reaction of 2-phenylethanol (1) with $BrCCl_3$-PPh_3.

Earlier we had already reported that in our hands the reaction of 2-phenylethanol (**1**) with PPh_3-$BrCCl_3$ in CH_2Cl_2 at rt led to a mixture of 2-phenylethyl bromide (**2-Br**) and 2-phenylethyl chloride (**2-Cl**) in a 6:4 ratio (Scheme 1) [14]. Thereafter, the authors investigated whether this trend holds true with other substrates (Table 1). As can be seen, in all reactions of alkanols with PPh_3-$BrCCl_3$ in CH_2Cl_2 at rt mixtures of alkyl bromides and alkyl chlorides are produced, where the alkyl bromides are often but not exclusively formed in slight excess.



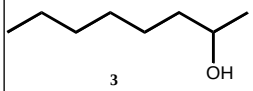
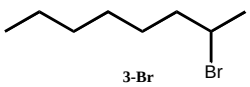
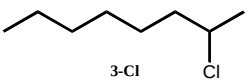
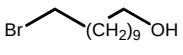
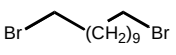
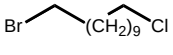
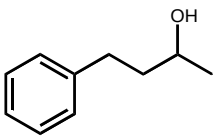
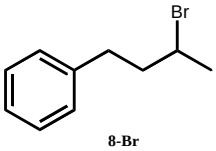
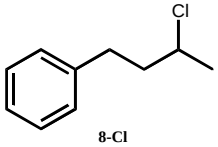
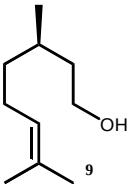
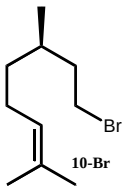
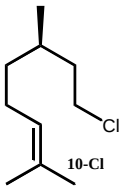
Substrates	Products	Yield
 3	 **3-Br**  **3-Cl**	$BrCCl_3$ CH_2Cl_2: **3-Br** (0.85) / **3-Cl** (1.0) Yield: 76% $BrCCl_3$ CH_3CN: **3-Br** (8.6)/ **3-Cl** (1.0) Yield: 74% CCl_4: **3-Cl** Yield:68%
 5	 **6-Br**  **6-Cl**	$BrCCl_3$ CH_2Cl_2: **6-Br** (1.0) / **6-Cl** (0.43) Yield: 81% $BrCCl_3$ CH_3CN: **6-Br** (4.5)/ **6-Cl** (1.0) Yield: 78% CCl_4: **6-Cl** Yield:72%
 7	 **8-Br**  **8-Cl**	$BrCCl_3$ CH_2Cl_2: **8-Br** (1.0) / **8-Cl** (0.73) Yield: 83% $BrCCl_3$ CH_3CN: **8-Br** (6.8)/ **8-Cl** (1.0) Yield: 79% CCl_4: **8-Cl** Yield:72%
 9	 **10-Br**  **10-Cl**	$BrCCl_3$ CH_2Cl_2: **10-Br** (1.0) / **10-Cl** (0.77) Yield: 87% $BrCCl_3$ CH_3CN: **10-Br** (5.1)/ **10-Cl** (1.0) Yield: 80% CCl_4: **10-Cl** Yield:75%

Table 1. Appel reaction of primary and secondary alcohols with $BrCCl_3$-PPh_3.

In all instances and for comparison, the substrates used were also reacted with the system PPh_3-CCl_4 in CH_2Cl_2 to obtain the alkyl chlorides. Also, steroidal alcohols cholesterol (**11**) and sitosterol (**13**) have been submitted to PPh_3-$BrCCl_3$ in CH_2Cl_2 to again show mixtures of steroidal chlorides and bromides (Table 2). Aliquots were drawn from the selected reaction mixtures. It could be shown that after the alcohol was consumed no detectable change in the ratio of alkyl chloride to alkyl bromide occurred. Although the reactions were found to be nearly complete after 90 min., the reaction mixtures were stirred for 14h (at rt) for convenience and to ensure complete reaction.

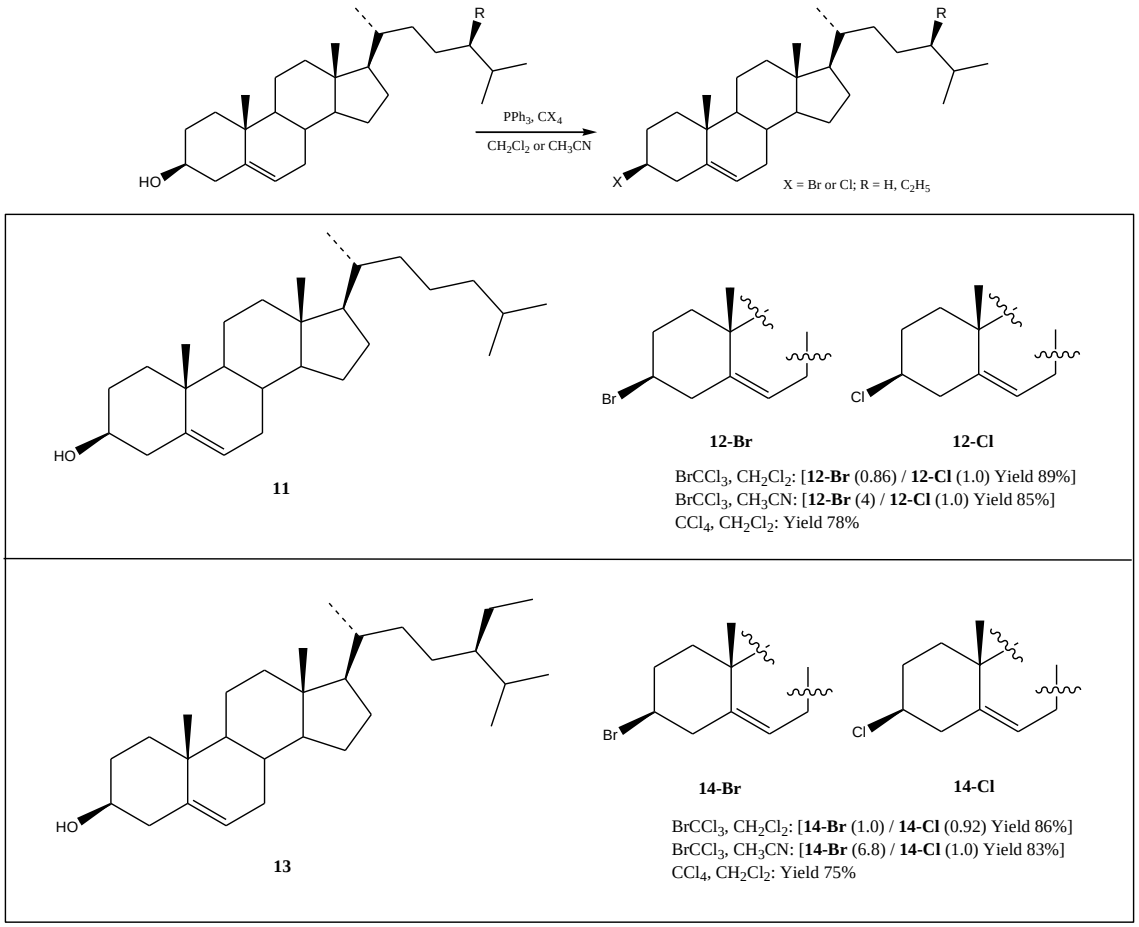


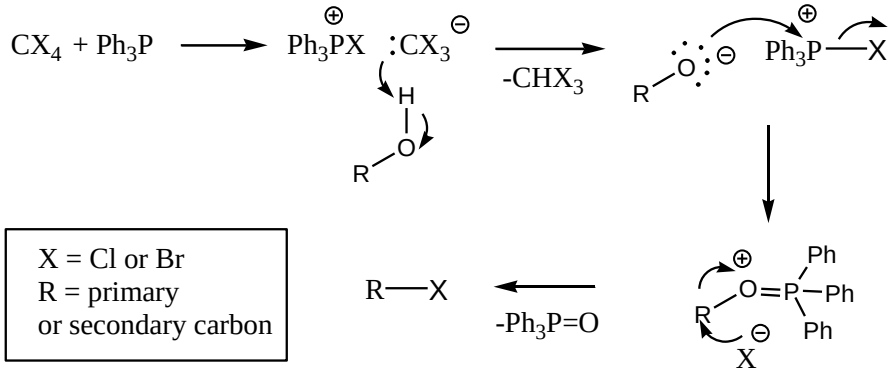
Table 2. Appel reaction of steroidal alcohols with $BrCCl_3$-PPh_3.

The reported exclusive isolation of benzyl chlorides from the reaction of benzyl alcohols with $BrCCl_3$-PPh_3, but with an excess of PPh_3 can most likely be explained by the higher reactivity of the benzyl bromide towards PPh_3 as compared to the benzyl chloride. In order to investigate the comparative reactivities of benzyl chlorides and benzyl bromides towards PPh_3, a 1:1 mixture of 4-bromobenzyl bromide (**15-Br**) and 4-bromobenzyl chloride (**15-Cl**) was reacted with 1 mol eq. of PPh_3 at rt, albeit in $CHCl_3$ (Scheme 2). After 30 min., 1h and 2h, ^1H NMR samples were taken, which showed a higher reactivity of the 4-bromobenzyl bromide (**15-Br**) in this competitive experiment, where mainly 4-bromobenzyl chloride remained unreacted (**15-Cl**/**15-Br**: 4.46/1.70

[30 min.], 3.18/0.76 [1h], 3.24/0.53 [2h]). After 2h, excess PPh_3 was added, which resulted in further increase in the ratio of the remaining substrates (**15-Cl**/**15-Br**: 2.94/0.25 [2h + 0.5 h]).

Scheme 2. Competitive reaction of 4-bromobenzyl bromide (**15-Br**) and 4-bromobenzyl chloride (**15-Cl**) with triphenylphosphine

When changing the solvent from dichloromethane (CH_2Cl_2) to acetonitrile (CH_3CN), the reaction became more selective, producing mainly alkyl bromides. This trend was noted for both secondary alcohols and primary alcohols. The accepted mechanism of the Appel reaction is provided in Scheme 3. Currently, the authors investigate, if the observed solvent effect leads to further details regarding the mechanism.



Scheme 3. General reaction mechanism of the Appel reaction.

Conclusions

The reaction of alkanols with $BrCCl_3$-PPh_3 in CH_2Cl_2 gives a mixture of alkyl bromides and alkyl chlorides. Most likely, the predominant isolation of benzyl chlorides from the reaction of benzyl alcohols with $BrCCl_3$ and an excess of PPh_3 can be explained with the higher reactivity of benzyl bromides as compared to benzyl chlorides in regard to PPh_3 to form the corresponding phosphonium bromides. A change of solvent to CH_3CN leads to predominately the alkyl bromides with $BrCCl_3$-PPh_3.

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