

1,2-Dibromotetrachloroethane: an efficient reagent for many transformations by modified Appel reaction

Selçuk EŞSİZ^{*}, Arif DAŞTAN

Department of Chemistry, Faculty of Science, Atatürk University, Erzurum, Turkey

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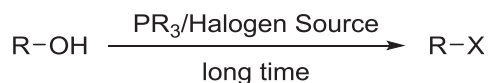
Abstract: An efficient and facile method has been developed for the synthesis of alkyl bromides from various alcohols under mild conditions using a triphenylphosphine (PPh₃)/1,2-dibromotetrachloroethane (DBTCE) complex in excellent yields and very short time (5 min). This method can also be applied for the transformation of chiral alcohols to their corresponding bromides in very high enantiomeric excess. The PPh₃/DBTCE complex is also successfully applied to ring-opening reactions of cyclic ethers in mild conditions. Esterification, amidation, and formation of acid anhydrides under very mild experimental conditions are also successfully accomplished by following a modification of the Appel reaction protocol in this work.

Key words: Alkyl bromides, 1,2-dibromotetrachloroethane, ring-opening reaction, Appel reaction, configuration inversion

1. Introduction

Organic halides and especially organic bromides are very important building blocks in synthetic organic chemistry.¹ Alkyl bromides are often used in synthetic organic chemistry because they can be easily prepared using many reagents. In organic laboratories, organic total syntheses without a halogenated starting compound or intermediate molecule are almost completely absent. For this reason, an efficient and practical protocol for the preparation of alkyl bromides is important. There are several methods to synthesize alkyl bromides by using alcohols^{2–8} and carbonyl compounds, such as aldehydes,^{9–12} ketones,¹² and carboxylic acids.¹³ The Appel reaction is a significant procedure for the synthesis of alkyl bromide and is based on using a combined system of triphenylphosphine (PPh₃) or its derivatives with a source of halogen (Scheme 1).^{14–19} Besides alkyl halide synthesis, recently many modified Appel reactions have been developed for various conversions, such as ring-opening reactions of epoxide,^{20,21} allene synthesis,²² and transformation to esters,^{23,24} amides,²⁴ and acid anhydride.²⁴ 1,2-Dibromotetrachloroethane (DBTCE) is a mild brominating reagent for bromination of olefins. In a previous work, we studied the reaction of DBTCE with various bicyclic strained alkenes and we showed that DBTCE is a very effective reagent for preventing Wagner–Meerwein rearrangements during the bromination of bicyclic alkenes as the reaction takes place via radical intermediates.^{25,26} In this work we aimed to use DBTCE as an agent for the modification of Appel reagent for various transformations.

*Correspondence: sessiz@atauni.edu.tr

**Scheme 1.** General Appel reaction.

2. Results and discussion

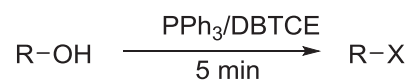
A quick and efficient synthesis of alkyl bromides in mild conditions starting from easily available compounds is very important. In this paper, we develop an effective method for the preparation of alkyl bromides using modified Appel reaction conditions as given in Table 1.

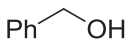
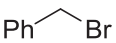
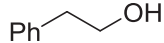
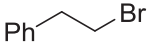
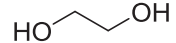

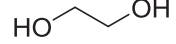
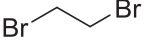
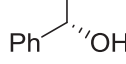
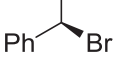
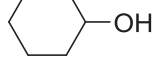
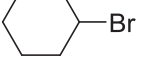
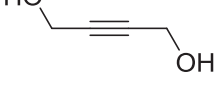
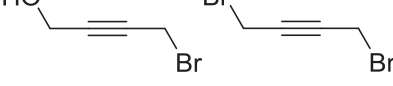
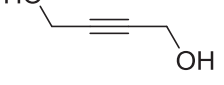
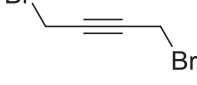
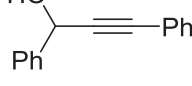
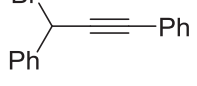
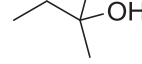
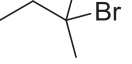
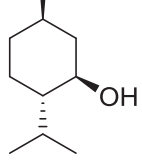
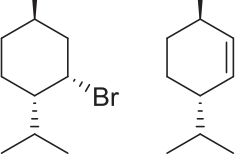
The conversion of various alcohols into their corresponding alkyl bromides with PPh₃ and DBTCE was performed in dichloromethane at room temperature. The reaction was completed in a short time and produced the corresponding bromides in excellent yields (Table 1). We also showed that the reaction takes place with absolute inversion of configuration and no racemization is observed if enantiomerically pure alcohol is used (Table 1, entries 5 and 11).

Regardless of the type of alcohol, conversion to alkyl bromide is easily possible with this method. Although DBTCE contains chlorine atoms and has two times more chlorine atoms than bromine atoms, we did not observe any alkyl chloride in the given reaction conditions. However, Newman et al. reported that aliphatic alcohols formed a mixture of organochlorides and bromides in the case of using PPh₃/CBrCl₃, which consists of the same atoms as DBTCE.²⁷ They showed that, in contrast to aliphatic alcohols, benzylic alcohols produced only chlorides.²⁷ The driving force for chemoselective formation of only bromine compounds instead of also chlorine compounds in the present work is attributed to the easy formation of thermodynamically favored tetrahaloethylene according to the mechanism described in Scheme 2. It is clear that instead of the formation of a more basic carbanion formed after the classical Appel reagent, a Cl⁻ anion is formed in these reaction conditions and it is consumed during the proton abstraction from alcohol. The formation of only a Cl⁻ anion, rather than a Br⁻ anion, is exactly confirmed by the presence of only the bromotrichloroethylene¹¹ structure after the reaction. The chemoselectivity in this reaction is attributed to the favored interaction between bromine atoms and the phosphorus atom in PPh₃ according to the HSAB theory.

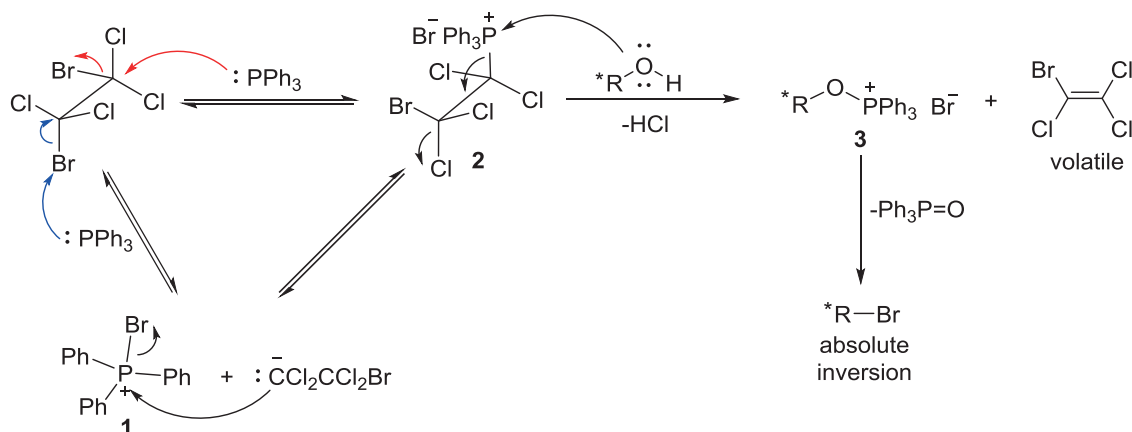
After this assumption, the following reaction mechanism is proposed for the reaction (Scheme 2). Phosphonium ion pair **2**²⁸ is formed by reaction of PPh₃ and DBTCE.²⁸ The first path is that PPh₃ is activated by abstracting one bromine atom, and phosphonium ion pair **1** is formed. Then the degenerative nucleophilic substitution at the phosphonium center in phosphonium ion pair **1** gives phosphonium ion pair **2**.²⁸ The second is like a typical S_N2 reaction; PPh₃ attacks the back side of bromine in DBTCE and phosphonium ion pair **2** is formed. Phosphonium ion pair **2** reacts with alcohol to produce alkyl phosphonium ion **3** and bromotrichloroethylene²⁹ as a byproduct. Further attack of the bromine counterion on the alkyl fragment of the alkoxyphosphonium leads to an alkyl bromide along with triphenylphosphineoxide. When chiral alcohols are used (Table 1, entries 5 and 11), the reaction takes place with absolute inversion of configuration like a typical S_N2 reaction as a bromine ion attacks the back side of the two leaving groups of alkoxyphosphonium (**3**) and alkyl bromides are stereoselectively formed as a single enantiomer. Similar to secondary and primary alcohols, effective transformations were observed in the reactions of tertiary alcohols (Table 1, entry 10).

Having achieved effective conversion of alcohols into alkyl halides, we examined other variations of Appel-type transformations. The cleavage of cyclic ethers is an important and versatile reaction in organic synthesis. The ring-opening reaction of epoxides, strained three-membered cyclic ethers, is comparatively easy;

Table 1. Reaction of alcohols to alkyl bromides.

Entry	Alcohol	Product	Yield / % ^a
1			97
2			97
3			45:50
4 ^b			96
5			96
6			95
7			45:50
8 ^b			92
9			90
10 ^c			85
11			60:35

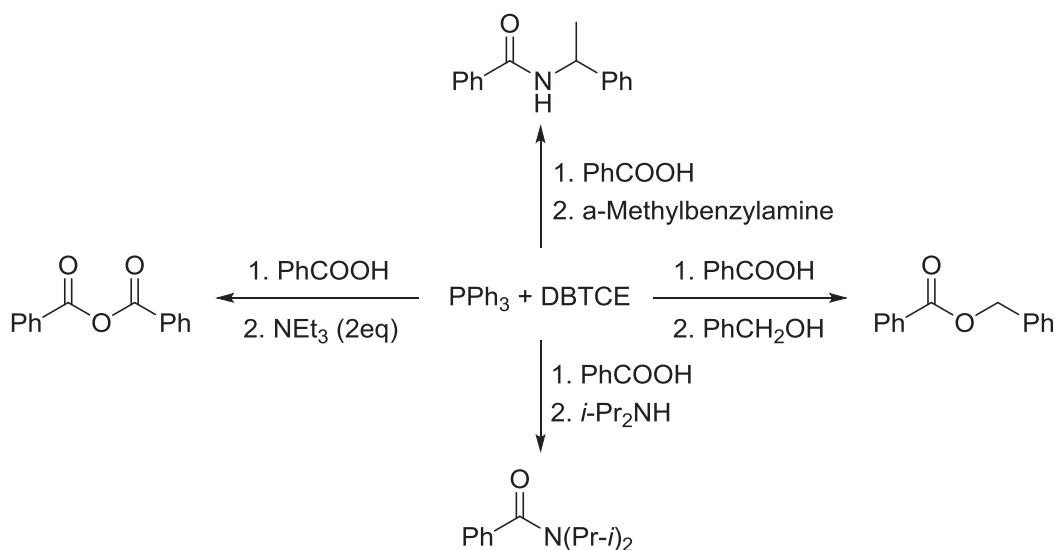
^a Isolated yield^b 2 equivalent DBTCE and PPh₃^c reaction time 2h



Scheme 1. Reaction mechanism for conversion of alcohol to alkyl bromides.

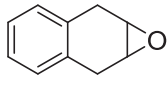
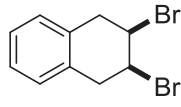

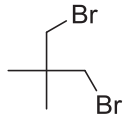

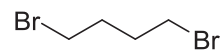

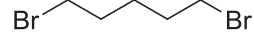
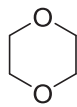
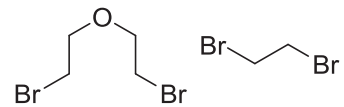
however, cleavage of larger membered cyclic ether in mild conditions is still a challenging problem. Therefore, the development of alternative or better methods is valuable. Herein, we wish to report our results on the stereoselective conversion of epoxides to vicinal *cis*-dibromides, oxetanes to 1,3-dibromides, oxolanes to 1,4-dibromides, and tetrahydropyrans to 1,5-dibromides using the system $\text{PPh}_3/\text{DBTCE}$ under mild and neutral conditions in high yield, up to 96% (Table 2). An Appel-type ring-opening reaction of four or more rings is described in this work and to the best of our knowledge there is no such report in the literature about it. Our results are summarized in Table 2.

Al Azani et al. reported Appel-type transformations of acid to esters, *o*-acyloximes, amides, and acid anhydrides by using a $\text{BrCCl}_3\text{-PPh}_3$ system as halogenation agent instead of using hazardous classical Appel reagents such as $\text{CCl}_4\text{-PPh}_3$.²⁴ In this work, we also studied transformations of carboxylic acid to esters, amides, and acid anhydrides using DBTCE-PPh_3 . For this purpose, benzoic acid was treated with a mixture of $\text{PPh}_3/\text{DBTCE}$ in the presence of acid, amine, or alcohol and acid derivatives were successfully obtained (Scheme 3).



Scheme 3. Functionalization of carboxylic acid by modified Appel reaction.

Table 2. Ring-opening reactions.

Entry	Ether	Product	Yield / % ^a
1			96
2			95
3			95
4			80
5 ^b			nr

^a Isolated yield^b 5 equivalent DBTCE and PPh₃

In conclusion, we have shown that, in a modified Appel-type reaction, the combination of DBTCE and PPh₃ can be used to convert primary, secondary, tertiary, propargylic, and benzylic alcohols into alkyl bromides. It was also shown that cleavage of cyclic ether in mild conditions using these reagents is successfully accomplished. This procedure provides a significant improvement over the classical methods since it has a considerably practical protocol for organic chemistry because of its mild conditions and very short reaction time and easy purification of the products. In contrast to rings with 3-, 4-, and 5-membered cyclic ether, the reaction took a long time for rings with 6 or more members.

3. Experimental

3.1. General

Column chromatography was performed using silica-gel 60 (Merck). Chromatography was carried out using petroleum ether or a combination of petroleum ether and ethyl acetate as an eluent. The products were identified by comparison of their spectral data with those of known compounds.

3.2. Synthesis of DBTCE

A solution of tetrachloroethylene (81.1 g, 50.0 mL, 489.1 mmol) and molecular bromine (46.9 g, 15.0 mL, 293.4 mmol) was irradiated with a 500-W lamp at reflux temperature in a 500-mL flask equipped with a reflux

condenser for 2 h. The resulting reaction mixture was allowed to warm to room temperature. The mixture was diluted with a solution of sodium hydroxide (10%, 100 mL) and the mixture was extracted with dichloromethane (3 × 100 mL). Combined organic layers were washed with water, dried over Na₂SO₄, and concentrated. The crude product was recrystallized from *n*-hexane and 90.0 g (94%) of DBTCE was obtained.

3.3. General procedure for conversion to bromide

PPh₃ (2.2 mmol) was dissolved in freshly distilled dichloromethane (4.0 mL) at 20 °C. A solution of DBTCE (2.2 mmol) in freshly distilled dichloromethane (4.0 mL) was added to the solution dropwise and the white colloidal mixture was stirred for 2 min. A solution of alcohol (2.0 mmol) or cyclic ether (1.0 mmol) in freshly distilled dichloromethane (4.0 mL) was added to the mixture dropwise over 2 min and during adding the reaction mixture became a colorless solution. The resulting solution was stirred for 5 min and the mixture was purified by flash column on 20 g of silica gel using petroleum ether or a mixture of petroleum ether/EtOAc (1:1).

(*R*)-(1-Bromoethyl)benzene^{30–31}: [α]_D + 41° (c = 1.0, CHCl₃). The product should be stored at low temperature because it is not stable for long at room temperature and slowly converted to racemic form.

(1*S*,2*S*,4*R*)-2-Bromo-1-isopropyl-4-methylcyclohexane³²: [α]_D + 62° (c = 1.38, ethanol).

Bromtrichloroethylene²⁹: ¹³C-NMR (100 MHz, CDCl₃): δ = 121.7, 106.0.

cis-2,3-Dibromo-1,2,3,4-tetrahydronaphthalene: mp = 65–66 °C, colorless crystals from methylene chloride/ *n*-hexane (1:4). ¹H NMR (400 MHz, CDCl₃): δ = 7.24–7.20 (AA' part of AA'BB' system, 2H), 7.14–7.10 (BB' part of AA'BB' system, 2H), 4.77–4.74 (m, 2H), 3.99 (dd, A part of AB system, *J* = 3.0 Hz, *J* = 17.8 Hz, 2H), 3.30 (d, B part of AB system, *J* = 17.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 130.7, 129.0, 126.8, 49.2, 34.5. IR (KBr, cm⁻¹): 3025, 2937, 2888, 1582, 1495, 1454, 1419, 1339, 1257, 1210, 1157, 1109, 958, 856, 740.

3.4. General procedure for conversion to acid derivatives

PPh₃ (1.1 mmol) was dissolved in freshly distilled dichloromethane (4.0 mL) at 20 °C. A solution of DBTCE (1.1 mmol) in freshly distilled dichloromethane (4.0 mL) was added to the solution dropwise and the white colloidal mixture was stirred for 2 min. Benzoic acid (1.0 mmol) in freshly distilled dichloromethane (4.0 mL) was added to the mixture dropwise. The resulting solution was stirred for 30 min and amine (1.1 mmol) or alcohol (1.1 mmol) was added to the mixture followed by stirring for 30 min. The mixture was purified by flash column on 20 g of silica gel using a mixture of petroleum ether/EtOAc (1:1).

Acknowledgment

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