Synlett J. Long et al. Letter

Ph_3P/I^--Promoted Dichlorination or Dibromination of Epoxides with XCH_2CH_2X (X = Cl or Br)

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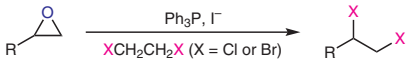


Received: 03.09.2018
Accepted after revision: 30.09.2018
Published online: 19.12.2018
DOI: 10.1055/s-0037-1610308; Art ID: st-2018-d0570-l

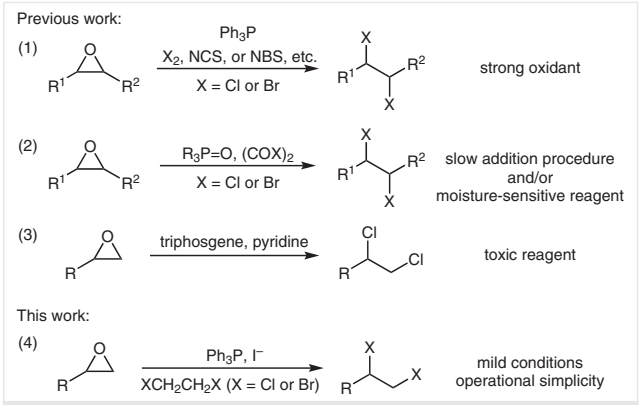
Abstract Ph_3P/I^--promoted dichlorination and dibromination of epoxides by using XCH_2CH_2X (X = Cl or Br) as the halogen source and reaction solvent is described. All reagents are widely available and easy to handle, and mild conditions and operational simplicity make this protocol attractive.

Key words epoxide, dichlorination, dibromination, 1,2-dihalides, triphenylphosphine

Organohalogenated compounds have found widespread application in various research areas, such as organic synthesis, pharmaceuticals, agrochemicals, and functional materials.[1] 1,2-Dihalides, particularly organohalogen structural motifs found in various families of natural products such as chlorosulfolipids isolated from fresh-water microalgae and polyhalogenated monoterpenoids isolated from red algae,[1c] have received increasing attention from the synthetic community. Many approaches have been developed for the synthesis of 1,2-dihalides, such as dihalogenation of alkenes[2] and dihalogenation of epoxides. Dihalogenation of epoxides has become an efficient and straightforward strategy as epoxides are widely available starting materials.

The dihalogenation of epoxides[3] could occur well under the Appel conditions[4] (Scheme 1, eq. 1). This method is quite effective and has been applied to the total synthesis of natural products,[5] but a strong oxidant is required in the reaction, which would result in a poor functional group compatibility. The group of Denton developed a $Ph_3P{=}O$-catalyzed halogenation[6] and found that dichlorination of epoxides could be achieved by this catalytic approach[6b] (Scheme 1, eq. 2). The usual stoichiometric triphenylphosphine oxide waste was avoided compared with traditional Appel reaction, but this method suffers from the need for simultaneous slow addition of the chlorine source, oxalyl chloride, and the substrate. On the basis of Denton's approach, Toy used heterogeneous polymer-supported triphenylphosphine oxides to realize dihalogenation (Scheme 1, eq. 2).[7] The polymer-supported triphenylphosphine oxides could be recovered and reused with no appreciable decrease in reactivity, but the use of moisture-sensitive reagents, oxalyl chloride, or oxalyl bromide is required in the dihalogenation reaction. Recently, Kartika reported a dichlorination promoted by a reagent system consisting of triphosgene and pyridine (Scheme 1, eq. 3).[8] In contrast to previous methods, no triphenylphosphine oxide was generated, and clean crude products could be obtained simply upon aqueous workup. However, the use of the hazardous reagent, triphosgene, may limit the synthetic utility of this method. Apparently, the development of mild protocols for dihalogenation of epoxides would be highly desirable.

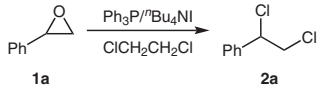
The chemistry of phosphonium salts has evolved dramatically in that phosphonium salts could serve as versatile reagents, catalysts, or intermediates.[9] We have found unexpectedly that the phosphonium salts could act as valuable nucleophilic reagents under suitable conditions.[10] Further studies into this interesting chemistry led us to discover that active iodophosphonium salts could be produced from the $Ph_3P/I^-/XCH_2CH_2X$ (X = Cl or Br) system or the Ph_3P/ICH_2CH_2I system. Since iodophosphonium salts are quite reactive towards *O*-nucleophiles, these two reagent



Scheme 1 Dihalogenation of epoxides

systems could be applied to deoxy functionalization of alcohols and aldehydes.[11] Herein, we disclosed that the Ph_3P/I^-system can promote dichlorination and dibromination of epoxides by using XCH_2CH_2X (X = Cl or Br) as the halogen source and reaction solvent (Scheme 1, eq. 4). All reagents are widely available and easy to handle, and mild conditions and operational simplicity make this protocol attractive.

Table 1 Optimization of the Reaction Conditions for Dichlorination[a]

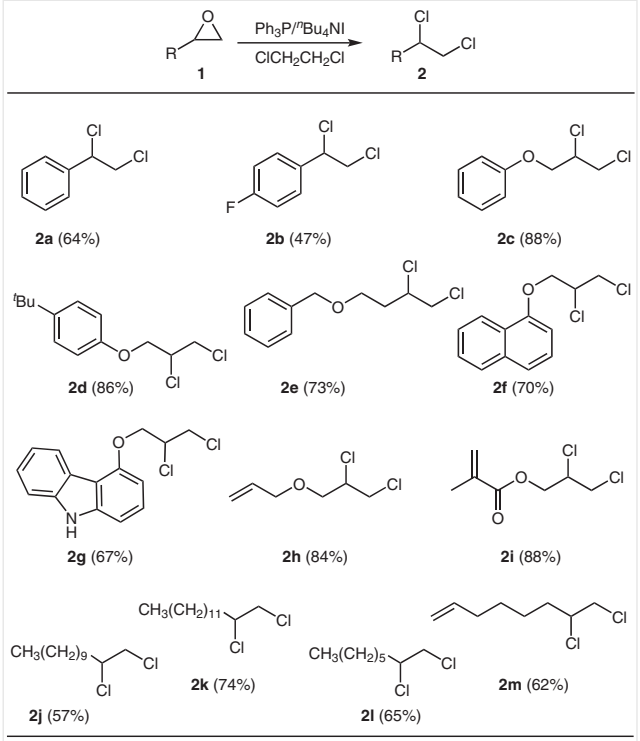


Entry	Ratio[b]	Temp (°C)	Time (h)	Yield (%)[c]
1	1:1.2:1.2	40	9.5	ND
2	1:1.2:1.2	60	9.5	43
3	1:1.2:1.2	80	9.5	80
4	1:1.2:1.2	100	9.5	70
5	1:1.2:1.2	120	9.5	54
6	1:1.2:1.2	80	4	74
7	1:1.2:1.2	80	8	76
8	1:1.4:1.2	80	4	75
9	1:1.8:1.2	80	4	71
10	1:2.0:1.2	80	4	75
11	1:1.2:1.4	80	4	80
12	1:1.2:1.6	80	4	75
13	1:1.2:1.8	80	4	71
14	1:1.2:2.0	80	4	72

[a]Reaction conditions: substrate **1a** (0.2 mmol), Ph_3P, $^nBu_4NI$, and $ClCH_2CH_2Cl$ (2 mL) at the indicated temperature for the indicated time; ND = not detected.
[b]Molar ratio of **1a**/Ph_3P/$^nBu_4NI$.
[c]The yield was determined by ^1H NMR spectroscopy with the use of $PhCH_3$ as an internal standard.

Our initial attempts at the $Ph_3P/^nBu_4NI$-promoted dichlorination of epoxide **1a** with the use of $ClCH_2CH_2Cl$ as the chlorine source and reaction solvent revealed that the reaction temperature played an important role (Table 1, entries 1–5). No desired product was detected at 40 °C (Table 1, entry 1), a good yield was obtained at 80 °C (Table 1, entry 3), and the yield was decreased at a higher temperature (Table 1, entries 4 and 5). The decreased yield at high temperatures should be because benzyl chloride would be converted into benzyl cation intermediate. The reaction process was monitored by ^1H NMR spectroscopy (Table 1, entries 6 and 7), and it was found that a reaction time of 4 h could give 74% yield (Table 1, entry 6). Increasing the loading of Ph_3P did not increase the yield (Table 1, entries 8–10). The yield was not increased significantly either by increasing the loading of iodide anion source, $^nBu_4NI$ (Table 1, entries 11–14). The desired product was obtained in 80% yield by using slight excess of Ph_3P and $^nBu_4NI$ (Table 1, entry 11).

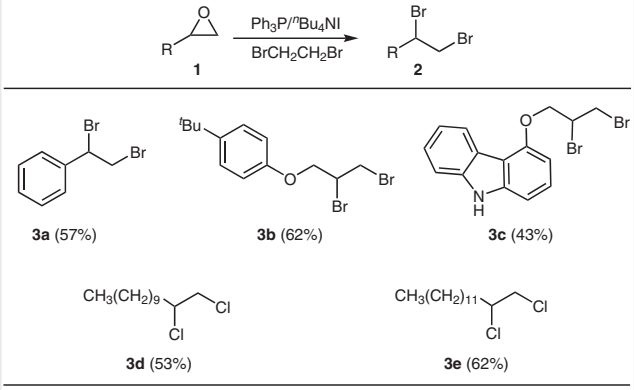
With the optimal conditions in hand (Table 1, entry 11), we then investigated the substrate scope of the Ph_3P/I^--promoted dichlorination of epoxides. As shown in Scheme 2, various epoxides were converted well into the desired products in moderate to good yields. Since secondary benzyl chlorides might readily undergo dechlorination to generate benzyl cation, the desired products were isolated in



Scheme 2 Dichlorination of epoxides. Isolated yields are given. *Reagents and conditions*: substrate **1** (0.5 mmol), Ph_3P (0.6 mmol), and $^nBu_4NI$ (0.7 mmol) in $ClCH_2CH_2Cl$ (5 mL) at 80 °C for 4 h.

lower yields (**2a**,**b**). Interestingly, the epoxides, cyclic ethers, smoothly underwent deoxychlorination, but the acyclic ethers remained intact. This is apparently because of the strong strain energy present in the cyclic substrates. A wide range of functional groups could be tolerated, such as ether, ester, alkene, and heterocycle.

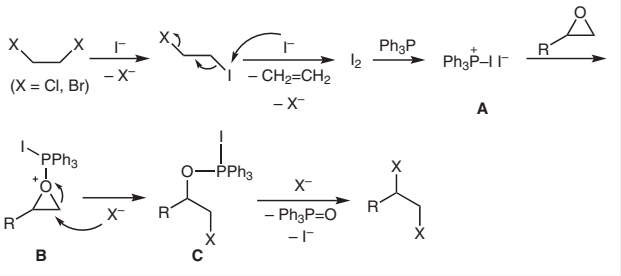
The successful dichlorination prompted us to investigate the dibromination of epoxides by using $BrCH_2CH_2Br$ as the reaction solvent (Scheme 3). A brief survey of the reaction conditions revealed that 82% yield (**3a**) could be obtained at a lower reaction temperature (40 °C) compared with dichlorination (see Supporting Information). In contrast to dichlorides, dibromides were isolated in lower yields. This is because secondary bromides showed lower stability due to the debromination process to generate secondary cation.



Scheme 3 Dibromination of epoxides. Isolated yields are given. *Reagents and conditions*: substrate **1** (0.5 mmol), Ph_3P (0.6 mmol), and $^nBu_4NI$ (0.7 mmol) in $BrCH_2CH_2Br$ (5 mL) at 40 °C for 2 h.

Although iodide anion was present in the reaction systems, no iodination product was detected, probably because the attack of chloride or bromide anion was more rapidly due to the stronger C–X bond (X = Cl or Br) than C–I bond.

On the basis of their mechanistic investigations, Hine and co-workers proposed that $BrCH_2CH_2Br$ would readily react with I^- via an S_N2 process to generate ICH_2CH_2Br, which further reacts with I^- to give I_2, $CH_2{=}CH_2$ and Br^-.[12] Deuterated experimental evidence collected by Rabinovitch and co-workers revealed that the overall elimination of 1,2-dibromoethane promoted by I^- is a *cis*-elimination process,[13] further supporting the mechanism proposed by Hine. Taking into account of the above results and our previous observation,[11a] the plausible mechanism is proposed as shown in Scheme 4. The solvent XCH_2CH_2X reacts with I^- via a substitution process followed by elimination to provide molecular iodine I_2, which would readily oxidize Ph_3P to form iodophosphonium salt **A**.[14] The active salt **A** can act as a Lewis acid and its coordination with epoxide gives intermediate **B**. The coordination actives the terminal C–O bond, and the attack of X^- at this bond generates halogenation intermediate **B**. The C–O bond in this intermediate is also quite active and a second attack of X^- affords the final product.



Scheme 4 The proposed reaction mechanism

As shown in the proposed mechanism, iodophosphonium salt **A** could be directly formed from the Ph_3P/I_2 system. It has been reported that the Ph_3P/I_2 system could be applied to esterification[14b,15] and iodination.[16] However, the high toxicity of I_2 would lead to operationally inconvenience. In sharp contrast, the operational simplicity and the wide availability of XCH_2CH_2X (X = Cl or Br) make our protocol attractive.

In summary, we have described the Ph_3P/I^--promoted dichlorination and dibromination of epoxides by using XCH_2CH_2X (X = Cl or Br) as the halogen source and reaction solvent. XCH_2CH_2X (X = Cl or Br) are widely available chemicals, and the dichlorination and dibromination occurred smoothly under mild conditions. The operational simplicity makes this protocol attractive, and therefore it may find application in the synthesis of 1,2-dihalogenated pharmaceuticals or organic intermediates.

Funding Information

We thank the National Basic Research Program of China (2015CB931903), the National Natural Science Foundation (21421002, 21472222, 21502214, 21672242, 81273537), the Chinese Academy of Sciences (XDA02020105, XDA02020106), the Key Research Program of Frontier Sciences (CAS) (QYZDJSSW-SLH049), the Key Project of Hunan Province Science and Technology Department (2016DK2001), the Key Project of Hunan Provincial Education Department (No. 17A190), the Zhengxiang Scholar Program of the University of South China, Hunan Provincial Hengyang City Joint Fund (2017JJ4050), and the Key Project of Hengyang Science and Technology Department(2017KJ166) for financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610308.

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