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Triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone as a new, selective and neutral system for the facile conversion of alcohols, thiols and selenols to alkyl halides in the presence of halide ions

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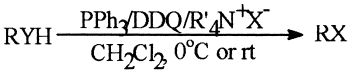
Abstract—A mixture of triphenylphosphine (Ph_3P) and 2,3-dichloro-5,6-dicyanobenzoquinone in CH_2Cl_2 affords a complex which in the presence of R_4NX (X=Cl, Br, I) converts alcohols, thiols and selenols into their corresponding alkyl halides in high yields at room temperature. The method is highly selective for the conversion of 1° alcohols in the presence of 2° ones and also 1° and 2° alcohols in the presence of 3° alcohols, thiols, epoxides, trimethylsilyl- and tetrahydropyranyl ethers, 1,3 dithianes, disulfides, and amides.

1. Introduction

The interaction of quinones as electron-acceptors with derivatives of group VB elements in their trivalent state as electron–donors has been extensively investigated.[1] A number of investigations have dealt more specifically with the structure of the products formed between quinones and tertiary amines, phosphites and phosphines.[2,3] Although some investigations have been carried out on the reaction of tertiary phosphines with quinones and on their product structures,[1–3] the application of these mixed materials as reagents in organic synthesis have not been extended yet. The conversion of alcohols into their corresponding halides is frequently a useful and necessary synthetic operation especially under neutral conditions. This conversion can be accomplished in different ways. A two-step procedure involved the transformation of an alcohol into the tosylate followed by an S_N2 halide ion displacement and the reaction of an alcohol with phosphorus trihalides are considered as classical methods for this purpose.[4] However, the classical sulfonate method usually suffers from the low yield of tosylation reaction especially in the case of sterically hindered alcohols,[5] and the drastic reaction conditions.[6] Some more recent methods have also been appeared such as the use of Ph_3P/X_2,[7a] Ph_3P/CCl_4,[7b] Ph_3P/*N*-haloimides,[8] and the combination of trimethylsilyl chloride and sodium iodide.[9] The conversion of 3β-cholestanol into 3α-iodocholestane using Mitsunobu's reagent in the presence of methyl iodide has also been reported.[10] It seems that the above reported procedures encountered some limitations regarding the selection of nucleophiles or poor yields and undesired products.[11] Although the conversion of alcohols into alkyl halides is widely studied, reports on the formation of alkyl halides from thiols are rare[12] and to the best of our knowledge, direct preparation of alkyl halides from selenols has not been reported in the literature yet.

2. Results and discussion

Very recently, we reported on the application of Ph_3P/*N*-halosuccinimides (NXS, X=Cl, Br, I) for the conversion of thiols into alkyl halides.[13] In continuation of our work on the new applications of Ph_3P in organic synthesis, we here report a new, neutral, simple and highly selective method for the efficient conversion of alcohols, thiols and selenols into their corresponding alkyl halides. We believe that in addition to the high selectivity of this method, the use of halides as their ammonium or quaternary ammonium salts with safe and convenient handling instead of molecular halogens[7a] could be considered as a strong advantage of this method (Scheme 1).



Scheme 1. Y=O, S, Se; X=Cl, Br, I; and R′=H, *n*-butyl, *n*-hexyl.

Keywords: quinones; triphenylphosphine; 2,3-dichloro-5,6-dicyanobenzoquinone.

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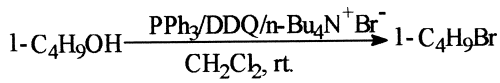


Scheme 2.

Table 1. Reaction of 1-butanol with Ph_3P/DDQ/n-Bu_4NBr in CH_2Cl_2 at room temperature

Entry	Molar ratio of ROH/PPh_3/DDQ/$Bu_4N^+Br^-$	Time (h)	Yield (%)[a]
1	1/1.1/1.1/1.1	Immediately	96
2	1/0.7/1.1/1.1	Immediately	75
3	1/1.1/0.7/1.1	Immediately	67
4	1/1.1/1.1/1.1	Immediately	91[b]
5	1/1.2/1.2/2[c]	8.0	81[b]
6	1/0/1.1/1.1	1.0	7
7	1/1.1/1.1/1.1	3.0	0[d]
8	1/1.1/1.1[e]	1.0	76
9	1/1.1/1.1[f]	1.0	54

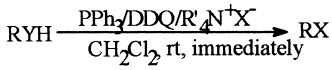
[a] GC analysis using *n*-octane as internal standard.
[b] Acetonitrile was used as solvent.
[c] NH_4Br was used as the source of nucleophile.
[d] THF was used as a solvent.
[e] Molar ratio relates to ROH/PPh_3/NBS.
[f] Molar ratio relates to ROH/PPh_3/TABCO.

In order to optimize the reaction conditions, we first examined the effect of different ratios of Ph_3P/2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and tetrabutylammonium bromide as a brominating agent and also the solvent for the conversion of 1-butanol to 1-bromobutane (Scheme 2, Table 1). As shown in Table 1, the reaction of 1-butanol with Ph_3P/DDQ/tetrabutylammonium bromide with the ratio of 1/1.1/1.1/1.1 in CH_2Cl_2 (entry 1) or CH_3CN (entry 4) produced immediately 1-bromobutane in 96 and 91% yields respectively. We have also used finely powdered ammonium bromide in acetonitrile which was more soluble for this purpose. A mixture of PPh_3/DDQ/NH_4Br (1.2/1.2/2) in CH_3CN was well stirred for 1.5 h at room temperature. Addition of 1-butanol to this mixture produced 1-bromobutane in 81% yield after 8 h (Table 1, entry 5). This result shows that the reaction with more soluble tetrabutyl ammonium bromide is much faster than the reaction using ammonium bromide. In the absence of Ph_3P, using DDQ/tetrabutylammonium bromide, 1-bromobutane was obtained in only 7% yield after 1 h (Table 1, entry 6). We found that the similar reaction in THF with Ph_3P/DDQ/tetrabutylammonium bromide did not occur and unreacted starting material was isolated intact after 3 h (Table 1, entry 7). In order to show the efficiency of the presented method with respect to the previously reported procedure using PPh_3/NBS, we tried the conversion of 1-butanol by this reagent. We found that 1-bromobutane was produced in 76% after 1 h (Table 1, entry 8). The use of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) as another source of electrophilic bromine instead of NBS was also studied for this conversion. Using this reagent system produced 1-bromobutane in only 54% after 1 h.

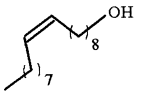
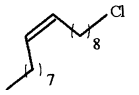
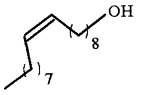
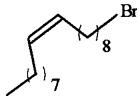
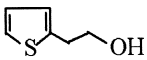
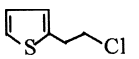
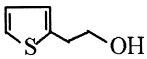
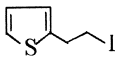
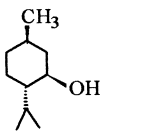
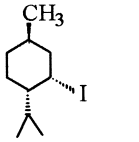
These results show the higher efficiency of using Ph_3P/DDQ/tetrabutylammonium bromide for this conversion.

We therefore chose CH_2Cl_2 as a suitable solvent for this reaction and used the optimized stoichiometric ratio of the mixed reagents for the conversion of structurally different

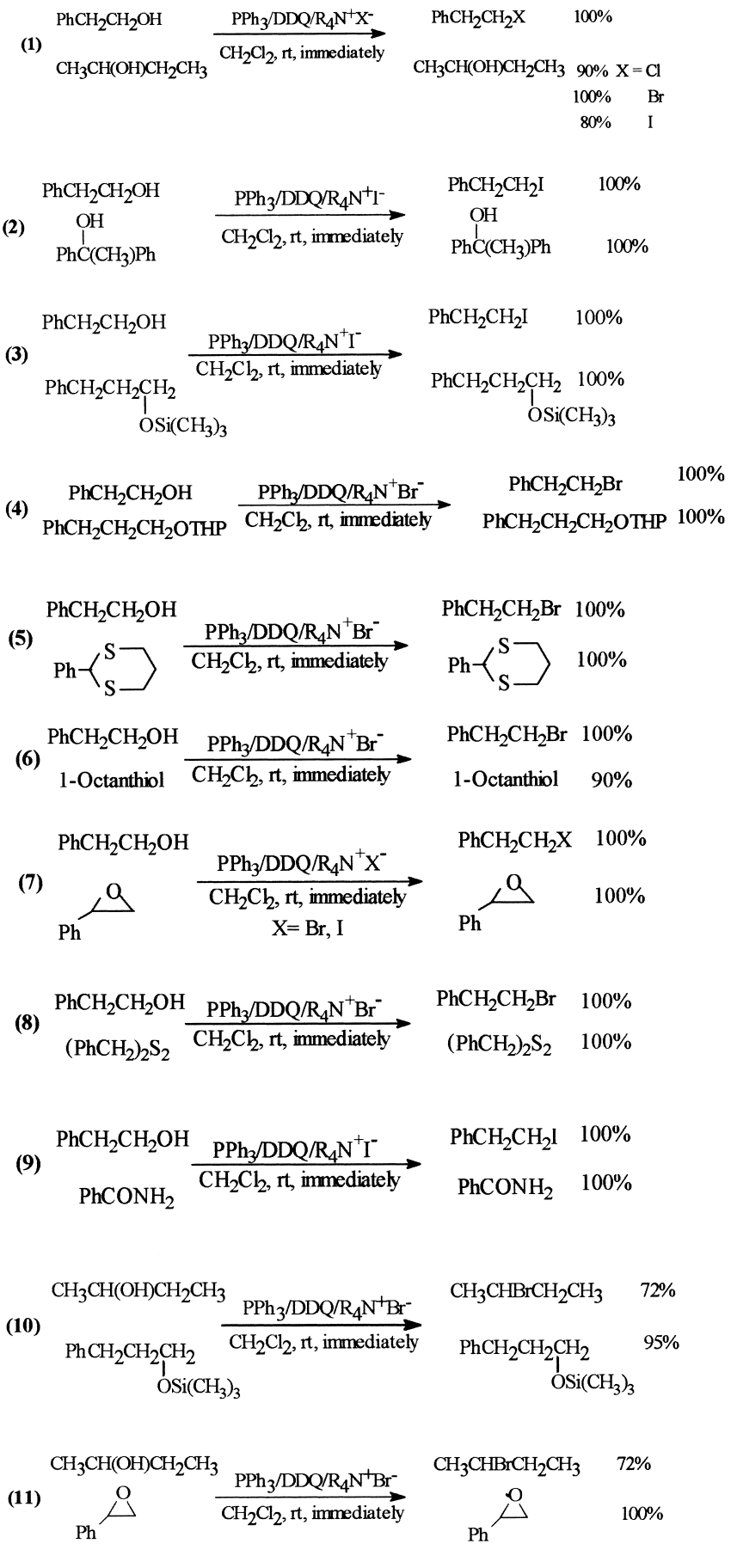
Table 2. Conversion of alcohols, thiols and selenols into alkyl halides



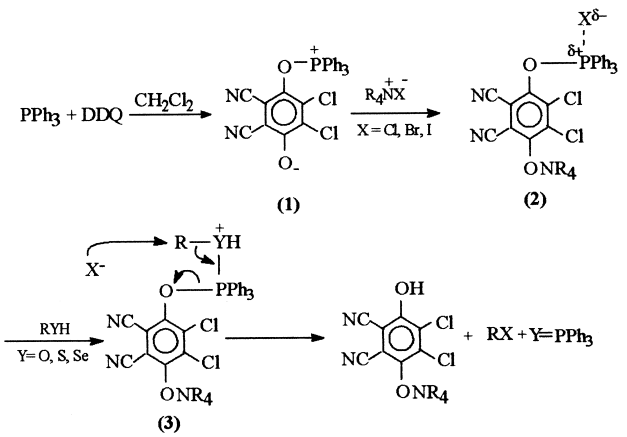
Y= O, S, Se
X= Cl, Br, I

Entry	RYH	RX[a]	Yield (%)
1	1-C_4H_9OH	1-C_4H_9Cl	85[b]
2	1-C_4H_9OH	1-C_4H_9Br	96[b]
3	1-C_4H_9OH	1-C_4H_9I	90[b]
4	1-Dodecanol	1-Bromododecane	85[c]
5	1-Dodecanol	1-Iododecane	86[c]
6	$PhCH_2CH_2OH$	$PhCH_2CH_2Cl$	82[c]
7	$PhCH_2CH_2OH$	$PhCH_2CH_2Br$	70[c]
8	$PhCH_2CH_2OH$	$PhCH_2CH_2I$	87[c]
9	1-Octanol	1-Bromooctane	76[b]
10	1-Octanol	1-Iodooctane	75[c]
11	$CH_3CHOHCH_2CH_3$	$CH_3CHBrCH_2CH_3$	72[b]
12	$CH_3CHOHCH_2CH_3$	$CH_3CHICH_2CH_3$	86[b]
13	$CH_3CHOHCH_3$	$CH_3CHBrCH_3$	73[b]
14	$CH_3CHOHCH_3$	CH_3CHICH_3	85[b]
15	$PhCH_2OH$	$PhCH_2Cl$	90[b]
16	$PhCH_2OH$	$PhCH_2Br$	70[c]
17	$PhCH_2OH$	$PhCH_2I$	65[c]
18	$HOCH_2CH_2OH$	$BrCH_2CH_2Br$	78[b,d]
19	$CH_2{=}CHCH_2OH$	$CH_2{=}CHCH_2Br$	95[b]
20			83[c]
21			78[c]
22	PhCHOHCOPh	PhCHBrCOPh	73[c,e]
23	$PhNHCH_2CH_2OH$	$PhNHCH_2CH_2Br$	94[c]
24	$PhNHCH_2CH_2OH$	$PhNHCH_2CH_2I$	92[c,f]
25			70[c]
26			75[c]
27			35[c]
28	$CH_3CH_2OCH_2CH_2OH$	$CH_3CH_2OCH_2CH_2Br$	98[g,h]
29	$CH_3CH_2OCH_2CH_2OH$	$CH_3CH_2OCH_2CH_2I$	99[g,h]
30	$CH_3CH_2CH_2CH_2SH$	$CH_3CH_2CH_2CH_2I$	85[b,i]
31	$CH_3CH_2CH_2CH_2SH$	$CH_3CH_2CH_2CH_2Br$	71[b,i]
32	$CH_3(CH_2)_{10}CH_2SH$	$CH_3(CH_2)_{10}CH_2I$	70[f,h]
33	$CH_3CH_2CH_2CH_2SeH$[j]	$CH_3CH_2CH_2CH_2Br$	70[b,i]
34	$PhCH_2SeH$[j]	$PhCH_2Cl$	65[b,i]

[a] The molar ratio for alcohol/PPh_3/DDQ/(*n*-butyl)$_4$NX (X=Br, I) is 1/1.2/1.2/1.2 and for alcohol/PPh_3/DDQ/(*n*-hexyl)$_4$NCl is 1:1.4:1.4:1.4.
[b] GC analysis using *n*-octane or *n*-nonane as internal standard.
[c] Isolated yield.
[d] In this case, the molar ratio of alcohol/PPh_3/DDQ/(*n*-butyl)$_4$NBr is 1/2.2/2.2/2.2.
[e] In this case, alcohol was added to the stirring mixture of PPh_3/DDQ/(*n*-butyl)$_4$NBr using the molar ratio 1/1.1/1.1/1.1. After 1 h, 0.4 molar equivalents of PPh_3, DDQ and (*n*-butyl)$_4$NBr were added and the reaction mixture was stirred for another hour.
[f] This reaction with Ph_3PI_2 produced only 15% of the same product together with an unidentified product.
[g] Yield is based on the NMR analysis.
[h] $CDCl_3$ was used as solvent.
[i] Molar ratio of thiol/PPh_3/DDQ/(*n*-butyl)$_4$NX (X=Br, I) was 1/1.4/1.1/1.4 and the reaction mixture was stirred for 1–4 h in the ice bath.
[j] Selenols were prepared according to the literature.[15]


(1)
PhCH2CH2OH
CH3CH(OH)CH2CH3
PPh3/DDQ/R4N+X-
CH2Cl2, rt, immediately
PhCH2CH2X 100%
CH3CH(OH)CH2CH3 90% X = Cl
100% Br
80% I
(2)
PhCH2CH2OH
OH
PhC(CH3)Ph
PPh3/DDQ/R4N+I-
CH2Cl2, rt, immediately
PhCH2CH2I 100%
OH
PhC(CH3)Ph 100%
(3)
PhCH2CH2OH
PhCH2CH2CH2
OSi(CH3)3
PPh3/DDQ/R4N+I-
CH2Cl2, rt, immediately
PhCH2CH2I 100%
PhCH2CH2CH2 100%
OSi(CH3)3
(4)
PhCH2CH2OH
PhCH2CH2CH2OTHP
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
PhCH2CH2Br 100%
PhCH2CH2CH2OTHP 100%
(5)
PhCH2CH2OH
Ph
S
S
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
PhCH2CH2Br 100%
Ph
S
S
100%
(6)
PhCH2CH2OH
1-Octanthiol
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
PhCH2CH2Br 100%
1-Octanthiol 90%
(7)
PhCH2CH2OH
O
Ph
PPh3/DDQ/R4N+X-
CH2Cl2, rt, immediately
X= Br, I
PhCH2CH2X 100%
O
Ph
100%
(8)
PhCH2CH2OH
(PhCH2)2S2
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
PhCH2CH2Br 100%
(PhCH2)2S2 100%
(9)
PhCH2CH2OH
PhCONH2
PPh3/DDQ/R4N+I-
CH2Cl2, rt, immediately
PhCH2CH2I 100%
PhCONH2 100%
(10)
CH3CH(OH)CH2CH3
PhCH2CH2CH2
OSi(CH3)3
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
CH3CHBrCH2CH3 72%
PhCH2CH2CH2 95%
OSi(CH3)3
(11)
CH3CH(OH)CH2CH3
O
Ph
PPh3/DDQ/R4N+Br-
CH2Cl2, rt, immediately
CH3CHBrCH2CH3 72%
O
Ph
100%

Scheme 3.



Scheme 4.

alcohols into their corresponding alkyl halides. The results of this study are shown in Table 2. As shown in Table 2, this method is very suitable for the conversion of primary, secondary, benzylic and allylic alcohols as well as diols into alkyl halides (Table 2, entries 1–19). Although the capability of DDQ for oxidation of benzylic alcohols has been demonstrated,[14] but in our reactions, no oxidative product was observed. The present method can be applied for the preparation of alkyl halides from alcohols having sensitive functional groups such as carbon–carbon double bonds (Table 2, entries 20 and 21), carbonyl groups (Table 2, entry 22), amino groups (Table 2, entries 23 and 24), sulfur atom (Table 2, entries 25 and 26), and ethereal bond (Table 2, entries 28 and 29). In the conversion of (−)-menthol to its iodide, the reaction proceeded through a SN_2 reaction with the clean inversion of configuration (Table 2, entry 27).[16] We then applied this method for the conversion of thiols to their corresponding alkyl halides (Table 2, entries 30–32). In these reactions, due to the ready dimerization of thiols into disulfides by DDQ,[17] the amount of triphenylphosphine was slightly increased in comparison with the reaction of alcohols and the reactions were performed in ice bath.

The optimized ratio of RSH/Ph_3P/DDQ/R_4NX was found to be 1/1.4/1.1/1.4. When we reacted selenols under the same reaction conditions as thiols, the reactions furnished the corresponding alkyl halides in good yield (Table 2, entries 33 and 34). In order to have more insight into the applicability, selectivity and limitation of this new method, we studied the possibility of the conversion of alcohols in the presence of some other functional groups in binary mixtures. The most important point about the selectivity of this reaction is that primary alcohols can be converted to their corresponding halides (X=Cl, Br, I) in the presence of secondary ones with excellent selectivity. This reagent also converted both primary and secondary alcohols into alkyl halides with excellent selectivity in the presence of tertiary alcohols, thiols, epoxides, silyl ether, tetrahydropyranyl ethers, 1,3-dithianes, disulfides and amides. The conversion yields obtained for the selective reactions of different binary mixtures are shown in Scheme 3. However, the conversion of phenol or 2,4-dinitrophenol as aryl alcohols into their corresponding halides was unsuccessful with the present method and starting materials remained completely intact. Also, in treatment of cyclohexanol and (−)-menthol as example of monocyclic alcohols with the mixture of PPh_3/DDQ/(*n*-butyl)$_4$NBr (1/1.1/1.1/1.1), at room temperature, the corresponding halides were obtained in low yields together with the formation of eliminated products as the major products.

We compared the selectivity of our method with some of the reactions of Scheme 3 using Ph_3PBr_2 as the reagent. The reaction of binary mixture of entry 1 with Ph_3PBr_2 gave 100% conversion for primary alcohol and 40% conversion for the secondary one. In the case of binary mixture of entry 2, in addition to the complete conversion of primary alcohol into its alkyl bromide, dehydration reaction of 3° alcohol to its corresponding alkene (50%) also occurred. Reaction of the binary mixture of entry 3 with Ph_3PBr_2, showed a reverse selectivity and trimethylsilyl ether was converted into its alkyl bromide while the alcohol remained unchanged. The binary mixtures of entries 5 and 7 were also subjected to the reaction with Ph_3PBr_2. In the case of entry 5, 60% of the 1,3-dithiane and in the case of entry 7, 80% of the epoxide were also consumed. This comparison shows the high selectivity of the presented method.

Although the mechanism of the reaction is not clear, on the basis of the reports on the reaction of Ph_3P and DDQ, the formation of complex (**1**) can be assumed.[3a] Treatment of R_4NX (X=Cl, Br, I) with (**1**) could produce (**2**) which later reacts with RYH (Y=O, S, Se) to give the intermediate (**3**). Subsequently, an S_N2-type displacement on the intermediate (**3**) by halide anion led to the formation of the desired alkyl halide (Scheme 4). The major deriving force for this reaction could well be due to the aromatization of DDQ ring and the formation of Ph_3PY (Y=O, S, Se). The order of addition of the reagents in this reaction is very important. We observed that if alcohol is added to the mixture of Ph_3P and DDQ (**1**) before the addition of R_4NX, instead of the formation of alkyl halide, the mono- and dialkyl ethers of dihydro-DDQ are produced. This reaction could be some how similar to the reaction of chloranil and trialkyl phosphites which is reported to produce tetrachlorohydroquinone alkyl ethers.[3]

3. Conclusion

In conclusion, the present investigation has demonstrated that the use of PPh_3/DDQ/R_4NX offers a simple, novel and convenient method for the conversion of a wide varieties of alcohols, thiols and selenols to their corresponding alkyl halides. The method not only shows excellent selectivity between different types of alcohols, but also between alcohols and many other reactive functional groups. Availability and ease of handling of the reagents, easy work up, high yields, operation at room temperature and especially the possibility of using the desired halide anion as nucleophile can be considered as strong points of this method.

4. Experimental

Chemicals were obtained from Merck and Fluka chemical

companies. Infrared spectra were recorded on a Perkin–Elmer 781 spectrophotometer. All the products obtained in this research are known compounds. Nuclear magnetic resonance spectra were recorded on a Brucker Advanced DPX-250 MHz spectrometer using tetramethylsilane as internal standard. GC spectra were recorded on a shimadzu GC-14A. Thin-layer chromatography was carried out on silica-gel 254 analytical sheets obtained from Fluka.

4.1. Typical procedure for the conversion of 1-dodecanol to 1-bromododecane

To a flask containing a stirring mixture of DDQ (1.2 mmol) and PPh_3 (1.2 mmol) in dry CH_2Cl_2 (10 ml), was added (*n*-butyl)$_4$NBr (1.2 mmol) at room temperature. 1-dodecanol (1 mmol) was then added to this mixture. The yellow color of the reaction mixture was immediately changed to deep red. GC analysis showed the immediate completion of the reaction. The solvent was evaporated. Column chromatography of the crude mixture on silica-gel using *n*-pentane as eluent gave 1-bromododecane in 85% yield. The product was identified by its comparison with an authentic sample.

Acknowledgements

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