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Graphical Abstract

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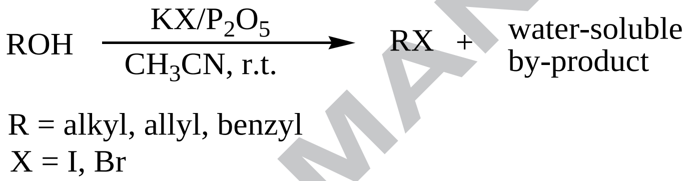

$$\mathrm{ROH} \xrightarrow[\mathrm{CH_3CN,\ r.t.}]{\mathrm{KX/P_2O_5}} \mathrm{RX} + \text{water-soluble by-product}$$

R = alkyl, allyl, benzyl
X = I, Br

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LETTERS

An efficient and selective method for the iodination and bromination of alcohols under mild conditions

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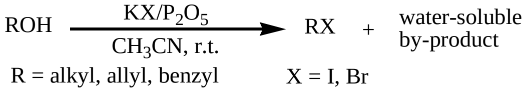
Abstract— A straightforward and effective procedure for the conversion of a variety of alcohols into the corresponding alkyl iodides and bromides is described using KX/P_2O_5 (X=I, Br). The reactions were easily carried out in acetonitrile under mild conditions. Using this method, the selective conversion of benzylic alcohols in the presence of aliphatic alcohols was achieved.

Keywords: Iodination, bromination, alcohols, phosphorus pentoxide, alkyl halides.

Alkyl halides, especially iodides and bromides, are important intermediates in organic and medicinal chemistry so much so that almost 22% of functional group interconversions in drug manufacturing involve the halogenation of alcohols.[1] These compounds can react with a number of nucleophiles such as amines, alkoxides or thiols to give the corresponding substituted products.[2] Alkyl iodides or bromides are widely used for carbon-carbon coupling reactions and also act as intermediates in substitution, elimination and rearrangement reactions. It should be mentioned that, by metal-halogen exchange, alkyl halides can be converted into nucleophilic organometallic species that can be used in subsequent reactions.[3] The most common precursors to alkyl halides are alcohols and this reaction is one of the most significant transformations in organic synthesis. This transformation can traditionally be carried out by a two-step procedure involving the conversion of an alcohol into the corresponding tosylate followed by halide ion displacement.[4] However, this often suffers from low yields in the tosylation step, especially in the cases of sterically hindered alcohols, where large amounts of metal halides, long reaction times and harsh reaction conditions must be used. A number of methods have been reported for the direct halogenation of alcohols, mostly based on phosphorus chemistry. Examples include PPh_3/X_2,[5] PPh_3/CX_4,[6] PPh_3/I_2/imidazole,[7] PPh_3/*N*-haloimides,[8] PPh_3/DEAD/MeI,[9] PPh_3/DEAD/LiI,[10] $P(OPh)_3$/MeI,[11] BINOL-PCl/I_2[12] and PPh_3/DDQ/R'_4NX.[13] A major drawback of these procedures is the formation of a stoichiometric amount of triphenylphosphine oxide or organic phosphonate derivatives as by-products, which can make product purification difficult and time-consuming. In order to solve this problem, a few special reagents such as tris[4-(1*H*,1*H*-perfluorooctyloxyphenyl)] phosphine,[14] polymer-supported PPh_3,[15] silicaphosphine[16] thioiminium salt[17] and $[Et_2NSF_2]BF_4$(XtalFluor-E)[18] have been reported. However, these materials are expensive and not easily available. Recently, the development of phosphorus (V) and cyclopropenone-based catalytic S_N2 reactions have been reported for the chlorination and bromination of alcohols.[19] Herein, in continuation of our studies on the application of P_2O_5 in organic synthesis,[20] we report an efficient and convenient procedure for the conversion of alcohols into the corresponding alkyl iodides and bromides using phosphorus pentoxide in the presence of potassium iodide or potassium bromide (Scheme 1). These reactions are easily carried out at room temperature under mild conditions. In contrast to the previously cited reagents, phosphorus pentoxide is inexpensive, non-toxic and commercially available. One of the most important advantages of the present procedure is the formation of a water-soluble by-product (phosphorus oxoacid) that makes the work-up procedure easy and convenient.



$$\mathrm{ROH} \xrightarrow[\mathrm{CH_3CN,\ r.t.}]{\mathrm{KX/P_2O_5}} \mathrm{RX} + \text{water-soluble by-product}$$

R = alkyl, allyl, benzyl X = I, Br

Scheme1. Direct iodination and bromination of alcohols.

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Alkyl iodides are more reactive than the corresponding bromides or chlorides and in some cases, show unique reactivity. Therefore, the conversion of alcohols to alkyl iodides is a very important transformation in organic synthesis. The reactions of alcohols with alkali metal iodides in the presence of strong Lewis[21] or Brønsted acids[22] have been reported as general protocols for the synthesis of alkyl iodides. Although these methods are useful procedures for the iodination of benzylic alcohols, the majority are not suitable for the iodination of aliphatic alcohols. This may be due to the following reaction (Scheme 2).[23]

$$O_2 + 4I^- + 4H^+ \rightarrow 2I_2 + 2H_2O$$

Scheme 2. Oxidation of iodide ion by oxygen.

As shown in Scheme 2, an iodide ion in the presence of a strong acid can gradually be oxidized by atmospheric oxygen at room temperature. Because the iodination of aliphatic alcohols need longer reaction times than that of benzylic ones, this reaction can compete with the iodination reaction and reduces its activity. Moreover, by increasing the reaction time, the molecular iodine formed can oxidize alcohols to the corresponding carbonyl compounds as by-products.[24] Although P_2O_5 is a strong dehydrating agent, it is not introduced as a strong acid to accelerate the oxidation of iodide. Therefore, by using this procedure, molecular iodine was slowly formed and consequently the by-product of oxidation was obtained in negligible yield. Thus, using the presented method, a variety of benzylic and aliphatic alcohols could easily be converted to the corresponding alkyl iodides in good yields and short reaction times.

First, to find the best conditions for these reactions, the iodination of 4-chloro benzyl alcohol was studied using different ratios of potassium iodide and phosphorus pentoxide in acetonitrile at room temperature (Table 1). This showed that the best molar ratio of ROH/KI/P_2O_5 was 1/1.5/1.5 (Table 1, entry 4). We also studied this reaction without P_2O_5 under the same conditions which demonstrated that no product was obtained after a prolonged reaction time (Table 1, entry 5). Therefore, the existence of phosphorus pentoxide was necessary for the reaction. Moreover, the solvent effect was examined using various solvents and also under solvent-free conditions (Table 1, entries 6-9). Under the same conditions, the reaction proceeded more rapidly in acetonitrile and the product was obtained in the optimal yield (Table 1, entry 4).

After selecting the best reaction conditions, to study the generality of the present method, the iodination of a number of benzylic, allylic and aliphatic alcohols were studied (Table 2).[25] Various benzylic alcohols with electron-donating or electron-withdrawing groups on the aromatic ring were smoothly converted into the corresponding iodides in good to high yields. It should be mentioned that in comparison with the electron-donating group containing compounds, the substitution of those with electron-withdrawing groups decreased the rate of the reaction (Table 2, entries 8-10). The iodination of (*R*)-(+)-1-phenylethanol was studied however the corresponding product was racemized during the course of the reaction (Table 2, entry 13). In the cases of cinnamyl alcohol and benzhydrol, the by-products of oxidation were observed in 10-20% yields. To prevent this problem, the reactions were carried out under a nitrogen atmosphere and the related products were obtained in good yields (Table 2, entries 14, 15). It is notable that the method was suitable for the iodination of aliphatic alcohols. However, extended reaction times and higher quantities of the reagents were required to progress the reactions. Although the reaction rates of aliphatic alcohols were lower than those of benzylic ones, they were easily converted into their alkyl iodides in good to high yields (Table 2, entries 16-20). In the case of cyclohexanol, 2-octanol and 1-adamantol, the reactions progressed smoothly at 45 °C to give the corresponding products in good yields (Table 2, entries 17-19).

Table 1. Conversion of 4-chloro benzyl alcohol into 4-chloro benzyl iodide using P_2O_5 and KI under different conditions at room temperature [a]

Entry	Solvent	Molar ratio of ROH/KI/P_2O_5	Time (h)	Yield (%) [b]
1	CH_3CN	1/1/1	1	78
2	CH_3CN	1/1.2/1.2	1	87
3	CH_3CN	1/1.4/1.4	1	98
4	CH_3CN	1/1.5/1.5	0.5	100
5	CH_3CN	1/1.5/0	5	0
6	CH_2Cl_2	1/1.5/1.5	1	32
7	THF	1/1.5/1.5	1	15
8	Dioxane	1/1.5/1.5	1	18
9	Solvent-free (grinding)	1/1.5/1.5	0.5	25

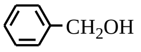
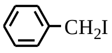
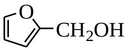
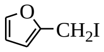
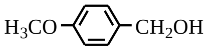
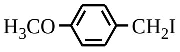
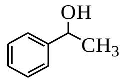
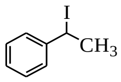
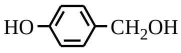
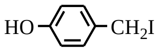
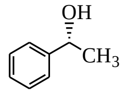
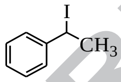
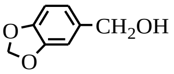
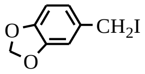
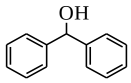
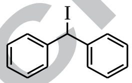
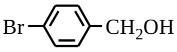
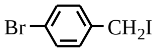
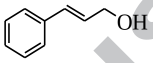
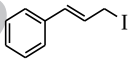
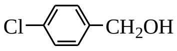
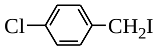
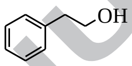
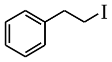
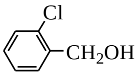
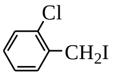
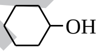
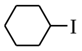
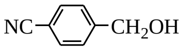
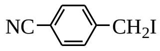
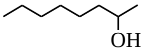
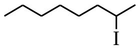
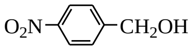
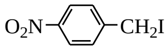
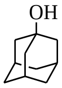
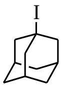
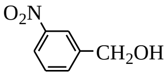
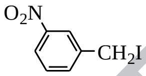
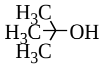
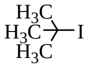
[a] The reaction was carried out in 5 mL of solvent.

[b] Based on GC analysis.

After exploring the iodination reactions, the possibility of direct bromination of alcohols was studied by using KBr/P_2O_5 at room temperature. The optimal conditions used in iodination were selected for the bromination of various alcohols. In all cases the corresponding alkyl bromides were obtained in good to high yields (Table 3).[26] As expected, in comparison with the benzylic or allylic alcohols, the reaction progress of the aliphatic ones needed longer reaction times, higher quantities of the reagents and higher temperatures to give the corresponding products in good yields (Table 3, entries 15-18).

It was noteworthy that sensitive alcohols such as 4-hydroxybenzyl alcohol (Table 2, entry 3), piperonyl alcohol (Table 2, entry 4), furfuryl alcohol (Table 2, entry 11 and Table 3, entry 10) and cinnamyl alcohol (Table 2, entry 15 and Table 3, entry 14) were found to be well-matched to the iodination or bromination reaction conditions.

Table 2. Conversion of alcohols into iodides using KI/P_2O_5.[a,b]

Entry	Alcohol	Product	Time (min)	Yield (%)[b]	Entry	Alcohol	Product	Time (min)	Yield (%)[c]
1			25	90	11			15	100[e]
2			25	89	12			30	86
3			25	87	13			30	85
4			15	85	14[d]			60	84
5			25	89	15[d]			60	80
6			25	93	16[d]			120	90
7			30	87	17[d]			120	87[e]
8[d]			120	81	18[d]			120	83[e]
9[d]			120	80	19[d]			120	88[e]
10[d]			120	83	20[d]	 $(H_3C)_3C{-}OH$	 $(H_3C)_3C{-}I$	120	100[e]

[a] The products were characterized from their spectral data and compared with authentic samples.

[b] All reactions were conducted at room temperature except for entries 17-19, which were at 45 °C.

[c] Isolated product.

[d] Molar ratio of alcohol/KI/P_2O_5 was 1/ 1.5/2.

[e] Yields refer to GC-Mass analysis.

Finally, to show the chemoselectivity of the present method, a number of competitive reactions were performed using stoichiometric amounts of alcohols and reagents in a binary system (Table 4). The results showed good selectivity between benzylic and aliphatic alcohols and also between benzyl alcohol and 4-nitrobenzyl alcohol.

In summary, an efficient and selective method for the iodination and bromination of alcohols to give their corresponding alkyl iodides and bromides was introduced using KX/P_2O_5 (X=I, Br). The use of non-toxic and inexpensive materials, simple and clean work-up procedure, short reaction times, good yields of the products and mild reaction conditions are the advantages of the described method.

Acknowledgments

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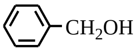
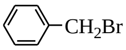
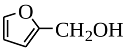
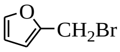
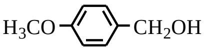
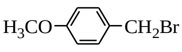
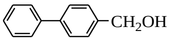
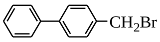
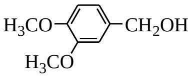
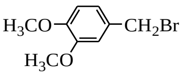
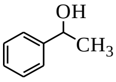
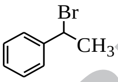
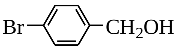
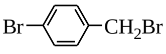
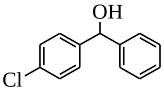
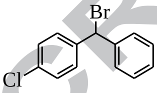
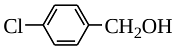
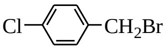
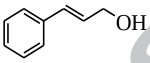
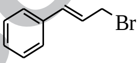
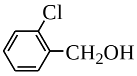
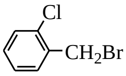
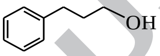
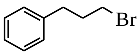
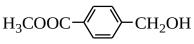
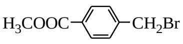
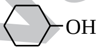
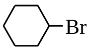
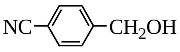
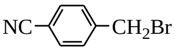
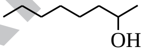
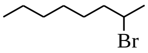
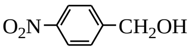
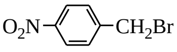
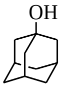
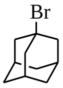
References and notes

1. (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Härtinger, S. *In Science of Synthesis*. Georg Thieme Verlag, New York, 2007.
2. Nelson, J. D. *Practical synthetic organic chemistry: reactions, principles, and techniques*. Caron, S. (Ed.), John Wiley & Sons, Inc., Hoboken, 2011.
3. (a) Rappoport, Z.; Marek, I. *The Chemistry of Organolithium Compounds*; John Wiley & Sons Ltd.: Chichester, 2004. (b) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1988.

Table 3. Conversion of alcohols into bromides using KBr/P_2O_5.[a,b]

Entry	Alcohol	Product	Time (min)	Yield (%)[b]	Entry	Alcohol	Product	Time (min)	Yield (%)[c]
1			25	89	10			15	100[e]
2			25	90	11			60	91
3			25	92	12			30	90
4			25	91	13[d]			60	89
5			25	92	14			60	88
6			30	89	15[d]			120	82
7			30	87	16[d]			150	85[e]
8[d]			60	89	17[d]			150	81[e]
9[d]			60	90	18[d]			150	83[e]

[a] The products were characterized from their spectral data and compared with authentic samples.

[b] All reactions were conducted at room temperature except for entries 15-18, which were at 45 °C.

[c] Isolated products.

[d] Molar ratio of alcohol/KBr/P_2O_5 was 1/ 1.5/ 2.

[e] Yields refer to GC-Mass analysis.

Table 4. Competitive reactions of different alcohols in a binary system.[a]

Entry	Binary mixture of alcohols	Reagent	Time (min)	Yield [b]
1	$4\text{-}ClC_6H_4CH_2OH + PhCH_2CH_2OH$	KI/P_2O_5	25	85:15
2	$PhCH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	KI/P_2O_5	25	90:10
3	$PhCH_2OH + 4\text{-}NO_2C_6H_4CH_2OH$	KI/P_2O_5	25	92:8
4	$PhCH_2OH + PhCH_2CH_2CH_2OH$	KBr/P_2O_5	25	88:12
5	$PhCH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	KBr/P_2O_5	25	93:7
6	$PhCH(OH)CH_3 + CH_3(CH_2)_5CH(OH)CH_3$	KBr/P_2O_5	30	90:10

[a] Reaction carried out in MeCN (5 mL) at r.t..

[b] Based on GC analysis.

4. (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*. John Wiley & Sons, INC. 5th ed. 2001. (b) Liu, Y.; Xu, Y.; Jung, S. H.; Chae, J. *Synlett* **2012**, 2692.
5. (a) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc*. **1964**, *86*, 964. (b) Hajipour, A. R.; Falahati, A. R.; Ruoho, A. *Tetrahedron Lett*. **2006**, *47*, 4191.
6. (a) Lee, J. B.; Downie, I. W. *Tetrahedron* **1967**, *23*, 359. (b) Calzada, J. G. Hooz, J. *Org. Synth*. **1974**, *54*, 63.
7. (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun*. **1979**, 978. (b) Classon, B.; Liu, Z. *J.Org. Chem*. **1988**, *53*, 6126.
8. (a) Bose, A. K.; Lal, B. *Tetrahedron Lett*. **1973**, *14*, 3937. (b) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohydr. Res*. **1972**, *24*, 45. (c) Iranpoor, N.; Firouzabadi, H.; Aghapour, Gh. *Synlett* **2001**, 1176.
9. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
10. Falck, J. R.; Manna, S. *Synth. Commun*. **1985**, *15*, 663.
11. (a) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc*. **1953**, 2224. (b) Rydon, H. N. *Org. Synth. Coll*. **1988**, *6*, 830.
12. Noroozi Pesyan, N.; Khalafy, J.; Khani-Meinagh, H. *Turk. J. Chem*. **2009**, *33*, 527.

13. Iranpoor, N.; Firouzabadi, H.; Aghapour, Gh.; Vaezzadeh, A. R. *Tetrahedron* **2002**, *58*, 8689.
14. Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett*. **2003**, *44*, 7589.
15. (a) Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. *J. Org. Chem*. **1983**, *48*, 3721. (b) Anilkumar, G.; Nambu, H.; Kita, Y. *Org. Proc. Res. Dev*. **2002**, *6*, 190. (c) Arsted, E.; Barrett, A. G. M.; Hopkins, B. T.; Kobberling, J. *Org. Lett*. **2002**, *4*, 1975. (d) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107.
16. Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. *Tetrahedron* **2005**, *61*, 5699.
17. Ellwood, A. R.; Porter, M. J. *J.Org. Chem*. **2009**, *74*, 7982.
18. Pouliot, M. F.; Mahe', O.; Hamel, J. D.; Desroches, J.; Paquin, J. F. *Org. Lett*. **2012**, *14*, 5428.
19. (a) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. *J. Org. Chem.* **2011**, *76*, 6449. (b) Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed*. **2011**, *50*, 12222. (c) An, J.; Denton, R. M.; Lambert, T. H.; Nacsa, E. D. *Org. Biomol. Chem*. **2014**, *12*, 2993.
20. (a) Hajipour, A. R.; Zarei, A.; Ruoho, A. E. *Tetrahedron Lett*. **2007**, *48*, 2881. (b) Zarei, A.; Hajipour, A. R.; Khazdooz, L. *Tetrahedron Lett*. **2008**, *49*, 6715. (c) Zarei, A.; Hajipour, A. R.; Khazdooz, L.; Mirjalili, B. B. F.; Zahmatkesh, S. *J. Mol. Catal. A: Chem.* **2009**, *301*, 39. (d) Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Ruoho, A. E. *Synth. Commun*. **2009**, *39*, 2702. (e) Zarei, A.; Hajipour, A. R.; Khazdooz, L. *Dyes Pigments* **2010**, *85*, 133. (f) Zarei, A.; Hajipour, A. R.; Khazdooz, L. *Synth. Commun*. **2011**, *41*, 1772. (g) Zarei, A. *Iranian Journal of Catalysis* **2012**, *2*, 7.
21. (a) Deo, M. D.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **2000**, *65*, 2830. (b) Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Tetrahedron Lett*. **2001**, *42*, 951. (c) Hayat, S.; Rahman, A. U.; Khan, K. M.; Choudhary, M. I.; Mahravi, G. M.; Ullah, Z.; Bayer, E. *Synth. Commun*. **2003**, *33*, 2531. (d) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett*. **2004**, *45*, 7451. (e) Satam, J. R.; Jayaram, R. V. *Catal. Commun*. **2008**, *9*, 1033.
22. (a) Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* **2001**, *31*, 827. (b) Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, 635. (c) Lee, J. C.; Park, J. Y.; Yoo, E. S. *Synth. Commun*. **2004**, *34*, 2059. (d) . Khan, K. M.; Ullah, Z.; Perveenb, S.; Maharvia, G. M.; Shah, S. T. A.; Ambreen, N.; Choudhary, M. I.; Rahman, A. U.; Voelter, W. *Letters in Org. Chem*. **2005**, *2*, 644. (e) Hajipour, A. R.; Zarei, A.; Ruoho, A. E. *Synth. Commun*. **2006**, *36*, 1039. (f) Khan, K. M.; Ullah, Z.; Perveen, S.; Hayat, S.; Ali, M.; Voelter, W. *Nat. Prod. Res*. **2008**, *22*, 1264. (g) Gupta, N.; Kad, G. L.; Singh, J. *J. Mol. Catal. A: Chem*. **2009**, *302*, 11. (h) Hajipour, A. R.; Rafiee, F.; Ruoho, A. *Synth. Commun*. **2011**, *41*, 603.
23. Vogel, A.; I. *Vogel's Qualitative Inorganic Analysis*. John Wiley & Sons, 6th ed. 1990.
24. Farhadi, S.; Zabardasti, A.; Babazadeh, Z. *Tetrahedron Lett*. **2006**, *47*, 8953.
25. *General procedure for the iodination of alcohols using KI/P_2O_5:* To a mixture of alcohol (1.0 mmol) and KI (1.5 mmol, 0.25 g) in acetonitrile (5 mL), P_2O_5 (1.5 mmol, 0.23 g) was added and the reaction stirred at room temperature for the time specified in Table 2. After reaction completion (TLC or GC), the reaction mixture was filtered and the residue washed with ethyl acetate (3 × 8 mL). The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$ (10%, 10 mL), water (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the corresponding product. If necessary, further purification was performed by column chromatography.
26. *General procedure for the bromination of alcohols using KBr/P_2O_5:* To a mixture of alcohol (1 mmol) and KBr (1.5 mmol, 0.18 g) in acetonitrile (5 mL), P_2O_5 (1.5 mmol, 0.23 g) was added and the reaction was stirred at room temperature for the time specified in Table 3. After reaction completion (TLC or GC), the reaction mixture was filtered and the residue washed with ethyl acetate (3 × 8 mL). The combined organic layers were washed with water (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the corresponding product. If necessary, further purification was performed by column chromatography.