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Iodination of alcohols using triphenylphosphine/iodine under solvent-free conditions using microwave irradiation

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Abstract—A straightforward and effective procedure for the conversion of benzylic, allylic and aliphatic alcohols to the corresponding iodides using Ph_3P/I_2 under solvent-free conditions using microwave irradiation is reported.

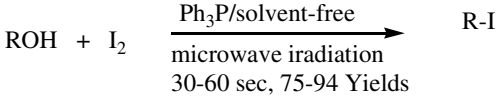
1. Introduction

Organic halides are very useful intermediates in organic synthesis.[1] They react with nucleophiles, such as amines or alkoxides, to give the corresponding substituted products and can be lithiated to introduce electrophiles via a halogen–lithium exchange reaction.[2] Alkyl iodides or bromides are widely used for carbon–carbon coupling reactions, and also act as intermediates in substitution, elimination and rearrangement reactions. Alkyl iodides are less stable than the corresponding chloride or bromide and more reactive than the other halides, and in some cases iodides are the only reactive halides.[3] The most common precursors to alkyl halides are alcohols, and their conversion into iodides is one of the most frequently used functional group transformation reactions.[4]

To perform iodination of hydroxyl groups, several methods have been described using a variety of reagent systems, such as BF_3–Et_2O/NaI,[5] P_2I_4,[6] P_4/I_2,[7] Cl_2SO–DMF/KI,[8] MgI_2,[9] HI,[10] $ClSiMe_3$/NaI,[11] R_3PI_2–Et_2O, or C_6H_6/HMPA,[12] $CeCl_3{\cdot}7H_2O$/NaI,[13] PPh_3/DDQ/$R_4N^+X^-$,[14] KI/$BF_3{\cdot}Et_2O$,[15] $ZrCl_4$/NaI,[16] I_2/petroleum ether,[17] and NaI/Amberlyst 15.[18] Polymer-supported triphenylphosphine/I_2/ImH has also been used for the iodination of benzylic alcohols.[19] Although some of these methods have convenient protocols with good to high yields, the majority of these methods suffer from drawbacks such as the presence of hazardous vapor, high temperature, long reaction times, moisture sensitivity of the using reagents, low yields, harsh reaction conditions, non-commercially available materials and tedious work-up procedures. Thus introducing new methods with higher efficiency and selectivity, less toxicity, easy handling and also using inexpensive and commercially available materials are important.

2. Results and discussion

In recent years, there has been a growing interest in the application of microwave irradiation in chemical reaction enhancement,[20] because of its cleaner reactions, decreased reaction time and easier work-up. In continuation of our ongoing efforts in this area and developing new methods in organic synthesis,[20–23] herein we wish to report an efficient and mild procedure for the iodination



R = Aliphatic, Benzylic and Allylic

Scheme 1.

Keywords: Iodination; Alcohols; Ph_3P; Solvent-free; Microwave.
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of alcohols using a combination of triphenylphosphine and iodine under solvent-free conditions using microwave irradiation (Scheme 1).

The iodination of benzyl alcohol was selected for optimization of the reaction conditions. Initially, we studied the conversion of benzyl alcohol (1 mmol, 0.1 mL) to benzyl iodide with triphenylphosphine (1.0 mmol, 0.26 g) and iodine (1.0 mmol, 0.25 g) in the presence of various solvents and also under solvent-free conditions (grinding) with or without microwave irradiation. As shown in Table 1 in comparison to other conditions the reaction proceeds rapidly under solvent-free condition with microwave irradiation and gives an optimal yield. Therefore, we investigated the iodination of various benzylic, allylic and aliphatic alcohols in the presence Ph_3P and iodine (Table 2).

A variety of alcohols were smoothly converted to the corresponding iodides using I_2/Ph_3P system under microwave irradiation using a domestic microwave. The reaction is highly selective for the conversion of benzylic and allylic alcohols in the presence of aliphatic alcohols (Table 2). In the case of phenol, the conversion into the corresponding iodides was not carried out even after prolonged stirring in acetonitrile. The generality of the method was examined using alkyl aryl, allyl, alkyl and also cyclic alcohols. To test the safety of the method, the iodination of 4-methoxy benzyl alcohol was successfully scaled-up to 5 mmol without any risks and decreasing the yield of 4-methoxy benzyl iodide.

In order to evaluate the chemoselectivity of this method, we studied competitive reactions for the iodination of benzylic alcohols in the presence of phenol and saturated alcohols. The remarkable selectivity of these reactions allowed only benzylic hydroxyl groups to be iodinated without affecting other OH groups (Table 3, entries 1–3). We also studied the iodination of benzyl alcohol versus 4-methoxybenzyl alcohol and 4-nitrobenzyl alcohol in the presence of benzyl alcohol. These reactions proceeded with high selectivity showing the importance of electronic effects upon these reactions using this technique (Table 3, entries 4 and 5).

In conclusion, we have developed a simple, direct and high chemoselective process for the iodination of benzylic, allylic and aliphatic alcohols using Ph_3P/I_2 under solvent-free conditions using microwave irradiation. The mild reaction conditions, short reaction times, good to high yields, low cost, easy preparation and handling of silica sulfuric acid are the advantages of this method.

Table 1. Conversion of benzyl alcohol to benzyl iodide under different conditions using I_2/Ph_3P

Solvent	Time	Benzyl iodide (%)[c]
Acetonitrile[a]	1.5 h	35
Ethyl acetate[a]	5 h	20
Diethyl ether[a]	5 h	10
THF[a]	5 h	10
Dichloromethane[a]	1.5 h	30
Solvent-free[b]	10 min	55
Microwave irradiation	40 s	82

[a] Stirring at room temperature in 5 mL of solvents.
[b] Grinding at room temperature.
[c] Yields refer to isolated pure products.

3. Experimental

3.1. General

All reagents were purchased from Merck and Aldrich, and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopic data (IR, ^1H NMR and MS analysis). ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$, unless otherwise stated, relative to TMS (0.00 ppm). GC analysis was run with Shimadzu GC-14A. All of the reaction was carried out under hood with strong ventilation using a domestic Samsung microwave (South Korea) oven (2450 MHz, 900 W) without any modification.

3.2. Iodination of 4-bromobenzyl alcohol (typical procedure)

In a mortar a mixture of 4-bromobenzyl alcohol (1 mmol, 0.19 g), I_2 (1.0 mmol, 0.25 g) and triphenylphosphine (1.0 mmol, 0.26 g) was ground with a pistol (30 s) to a homogeneous mixture. The mixture was transferred to a sealed Teflon vessel, and the reaction mixture was irradiated for the time specified in Table 2. The progress of the reaction was monitored by TLC or GC. After disappearing the alcohol TLC (*n*-hexane–EtOAc, 3:1) the reaction mixture was diluted with ether (25 mL) and filtered to removed the solids. The organic layer was washed with an aqueous solution of $Na_2S_2O_3$ (10%, 10 mL), then H_2O (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the mixture of the products was purified by short column chromatography (*n*-hexane–EtOAc, 3:1). 4-Bromobenzyl iodide was obtained in 80% (0.237 g) yield as a crystalline white solid. Mp 57–59 °C; ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.43$ (d, $J = 8.5$ Hz, 2H), 7.26 (d, $J = 8.5$ Hz, 2H), 4.42 (s, 2H); IR (KBr) cm^{-1}: 3020, 2900, 2850, 1590, 1490, 1420, 1200, 1150, 1030, 850, 670; MS (EI), *m/e* (relative intensity): 298 (M^++2, 3), 296 (M^+, 3), 171 (100), 169 (100), 127 (25), 91 (42), 90 (100), 89 (95), 77 (12), 76 (10), 63 (60), 39 (25).

3.3. Iodination of 4-methoxybenzyl alcohol in the presence of benzyl alcohol (typical procedure)

In a mortar a mixture 4-methoxybenzyl alcohol (1 mmol, 0.138 g), benzyl alcohol (1 mmol, 0.1 mL), I_2 (1.0 mmol, 0.25 g) and triphenylphosphine (1.0 mmol, 0.26 g) was ground with a pistol to a homogeneous mixture. The mixture was transferred to a sealed Teflon vessel and the reaction mixture was irradiated for 60 s. The progress of the reaction was monitored by TLC or GC. 4-Methylbenzyl iodide was obtained in 90% yield and benzyl alcohol was intact (Table 3, entry 4).

Table 2. Conversion of alcohols to the corresponding Iodides using Ph_3P/I_2 with microwave irradiation[a,b]

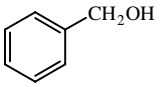
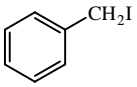
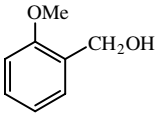
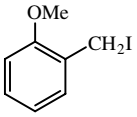
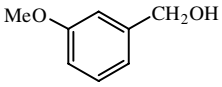
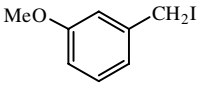
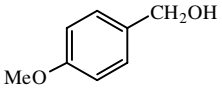
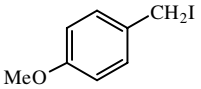
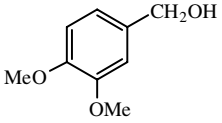
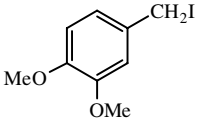
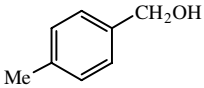
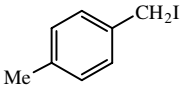
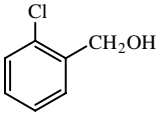
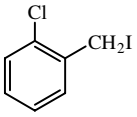
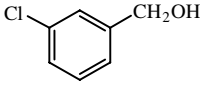
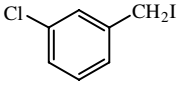
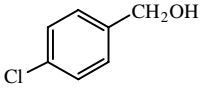
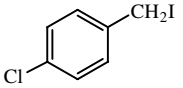
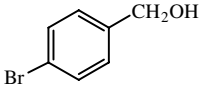
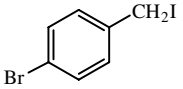
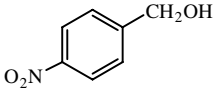
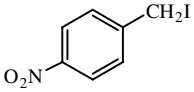
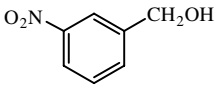
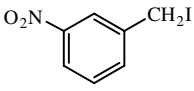
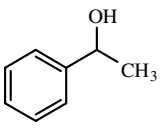
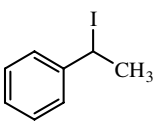
Entry	Substrate	Product	Time (sec)	Yield (%)
1			40	80
2			30	90
3			50	88
4			50	95
5			30	90.
6			30	87
7			40	78
8			40	80
9			30	92
10			30	80
11			50	80
12			50	78
13			30	90

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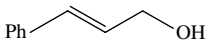
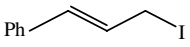
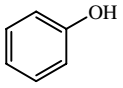
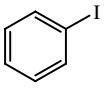
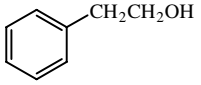
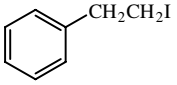
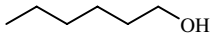
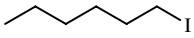
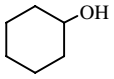
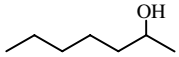
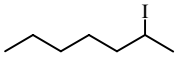
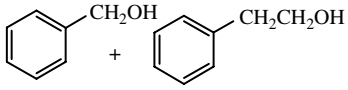
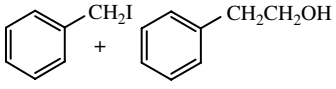
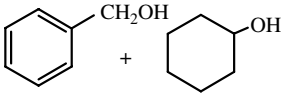
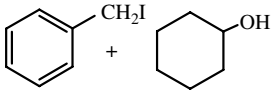
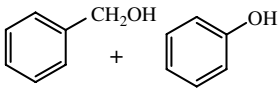
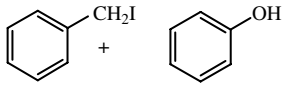
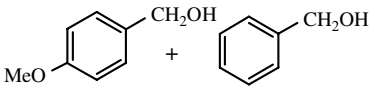
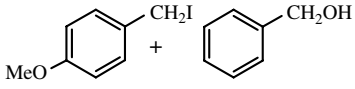
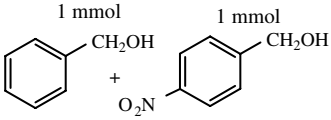
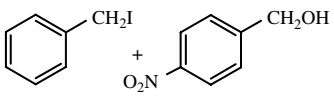
Table 2 (*continued*)

Entry	Substrate	Product	Time (sec)	Yield (%)
14			60	85
15			5	0
16			50	78
17			50	75
18			40	90
19			50	84
20	Cyclododecane	Cyclododecyl iodide	60	75

[a] The molar ratio of alcohol/KI/SSA is 1:1.2:1.2.
[b] Yields refer to pure isolated products and were characterized by comparison of their physical and spectral data (IR, ^{1}H NMR, MS) with authentic samples.

Table 3. Competitive reaction for selective iodination of different alcohols[a]

1		Ph_3P/solvent-free microwave iradiation 60 sec		80% 100%
	1 mmol 1 mmol			
2		Ph_3P/solvent-free microwave iradiation 60 sec		90% 100%
	1 mmol 1 mmol			
3		Ph_3P/solvent-free microwave iradiation 60 sec		90% 100%
	1 mmol 1mmol			
4		Ph_3P/solvent-free microwave iradiation 60 sec		90% 100%
	1 mmol 1 mmol			
5		Ph_3P/solvent-free microwave iradiation 60 sec		80% 100%
	1 mmol 1 mmol			

[a] The progress of the reaction was determined by GC and TLC analysis.

3.4. Benzyl iodide

IR (neat) cm^{-1}: 3010, 2930, 1595, 1485, 1430, 1070, 835, 750, 660. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.3–7.0$ (m, 5H), 3.95 (s, 2H).

3.5. 4-Methoxybenzyl iodide

IR (neat) cm^{-1}: 3015, 2920, 1600, 1480, 1255, 1200, 1100, 815, 690. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.1$ (d, $J = 7.3$ Hz, 2H), 6.8 (d, $J = 7.3$ Hz, 2H), 3.85 (s, 2H), 3.75 (s, 3H).

3.6. 2-Chlorobenzyl iodide

IR (neat) cm^{-1}: 3010, 2910, 1595, 1500, 1420, 1400, 1210, 1150, 1035, 830, 750, 660. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.43$ (d, $J = 9.3$ Hz, 1H), 7.36 (d, $J = 9.3$ Hz, 1H), 7.23 (m, 2H), 4.54 (s, 2H).

3.7. 4-Chlorobenzyl iodide

IR (KBr) cm^{-1}: 3010, 2915, 1605, 1505, 1490, 1410, 1205, 1150, 1080, 825, 665. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.37$ (d, $J = 9.5$ Hz, 2H), 7.3 (d, $J = 9.5$ Hz, 2H), 4.45 (s, 2H).

3.8. 4-Nitrobenzyl iodide

IR (KBr) cm^{-1}: 3060, 2980, 1600, 1525, 1400, 1350, 1220, 1100, 835, 800, 670. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 8.17$ (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 2H), 4.5 (s, 2H).

3.9. 3-Nitrobenzyl iodide

IR (KBr) cm^{-1}: 3075, 2980, 1595, 1530, 1410, 1345, 1205, 1160, 1010, 875, 790, 700, 670. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 8.25$ (s, 1H), 8.13 (d, $J = 7$ Hz, 1H), 7.72 (d, $J = 7.7$ Hz, 1H), 7.51 (t, $J = 8$ Hz, 1H), 4.51 (s, 2H).

3.10. Cinnamyl iodide

IR (neat) cm^{-1}: 3030, 2925, 2850, 1650, 1600, 1495, 1450, 1135, 1035, 760, 665. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.20$ (s, 5H), 6.75 (d, $J = 16.3$ Hz, 1H), 6.55 (m, 1H), 3.45 (d, $J = 6.8$, 2H).

3.11. 1-Iodo-1-phenyl ethane

IR (neat) cm^{-1}: 3125, 2970, 2860, 1600, 1495, 1445, 1360, 1200, 1025, 965, 845, 760, 675. ^1H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.12$ (s, 5H), 4.74 (q, $J = 7$ Hz, 1H), 2.46 (d, $J = 7$ Hz, 3H).

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