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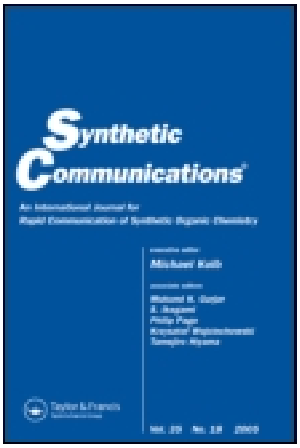

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Efficient Method for Iodination of Alcohols using KI/Silica Sulfuric Acid (SSA)

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Efficient Method for Iodination of Alcohols using KI/Silica Sulfuric Acid (SSA)

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Abstract: A straightforward and effective procedure for the conversion of benzylic and allylic alcohols to the corresponding iodides using KI/SSA in acetonitrile at room temperature.

Keywords: Alcohols, iodination, potassium iodide, silica sulfuric acid

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

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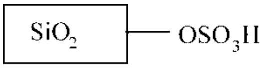
used for ionic and radical carbon–carbon coupling reactions and also act as intermediates in substitution, elimination, and rearrangement reactions. Alkyl iodides are less stable than the corresponding chloride or bromide and more reactive than the other halides, and in some cases iodides are the only 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_3Et_2O/NaI,[5] P_2I_4,[6] P_4/I_2,[7] Cl_2SODMF/KI,[8] MgI_2,[9] HI,[10] $ClSiMe_3/NaI$,[11] $R_3PI_2Et_2O$, 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] 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 reagents, low yields, harsh reaction conditions, noncommercially available materials, and tedious workup procedures. Introducing new methods with higher efficiency and selectivity, less toxicity, and easy handling, and which use inexpensive and commercially available materials, is important.

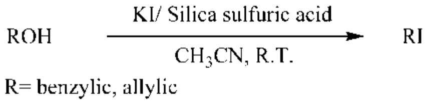
RESULTS AND DISCUSSION

In a continuation of our studies on the application of solid acids, we found that silica sulfuric acid (SSA) (**I**) has many advantages over sulfuric acid. This reagent is safe, easy handled, and environmentally benign, and presents fewer disposal problems. Therefore, SSA can be an excellent candidate for sulfuric acid replacement in organic reactions.[20]



I

In this article we report an efficient and mild procedure for iodination of alcohols using a combination of SSA and potassium iodide under heterogeneous conditions (Scheme 1).



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 SSA (1.2 mmol, 0.35 g) and potassium iodide (1.2 mmol, 0.2 g) in the presence of various solvents and also under solvent-free conditions (grinding). As shown in Table 1, in comparison to other conditions the reaction proceeds rapidly in acetonitrile and gives optimal yield. Therefore, we investigated the iodination of various benzylic and allylic alcohols in the presence of SSA and potassium iodide in acetonitrile at room temperature (Table 2). It was also observed that when benzyl alcohol was treated with KI without SSA, no change took place at all, implying that SSA plays an important role in this reaction.

A variety of benzylic and allylic alcohols were smoothly converted to the corresponding iodides using the KI/SSA system at room temperature. The reactions are highly selective for the conversion of benzylic and allylic alcohols to the corresponding iodides in good to high yields (Table 2). In the case of phenol and saturated alcohols, the conversion into the corresponding iodides was not carried out even after prolonged stirring in acetonitrile (Table 2, entries 19–23). We also studied other solid supports such as SiO_2, Al_2O_3, zeolite HZSM-5, and montmorillonite K10 for this conversion. As shown in Table 2 (entries 2–5), conversions of benzyl alcohol to benzyl iodide with KI/SiO_2, KI/Al_2O_3, KI/montmorillonite K10, and KI/HZSM-5 were carried out in low yields. Furthermore, we investigated various benzylic alcohols with both electron-donating and electron-withdrawing groups on the aryl ring. The reaction is slightly accelerated by an electron-donating group (Table 2, entries 6–10), and the substitution of the electron-withdrawing group on the aromatic ring retards the transformation (Table 2, entries 11–16).

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

Table 1. Conversion of benzyl alcohol to benzyl iodide under different conditions using KI/SSA

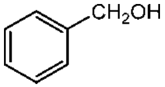
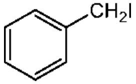
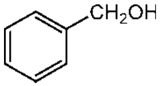
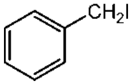
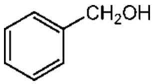
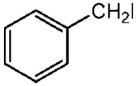
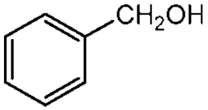
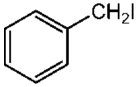
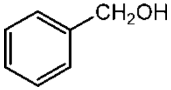
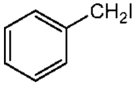
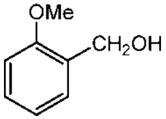
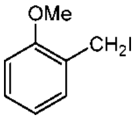
Solvent	Time	Benzyl iodide (%)[c]
Acetonitrile[a]	1.5 h	85
Ethyl acetate[a]	5 h	40
Diethyl ether[a]	5 h	25
THF[a]	5 h	35
Dichloromethane[a]	1.5 h	70
None[b]	10 min	55

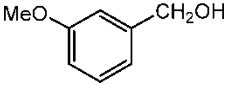
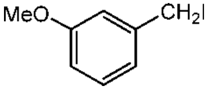
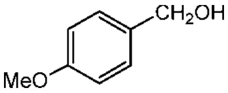
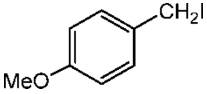
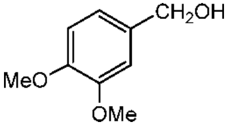
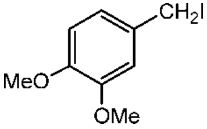
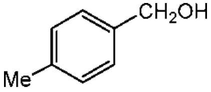
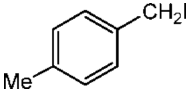
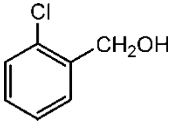
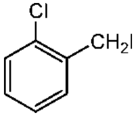
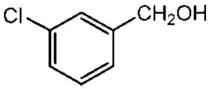
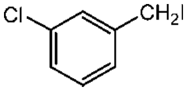
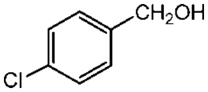
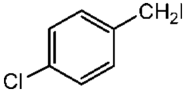
[a] Stirring at room temperature in 5 mL of solvents.

[b] Grinding at room temperature.

[c] Yields refer to isolated pure products.

Table 2. Conversion of alcohols to iodides using KI/ SSA at room temperature[a,b]

Entry	Substrate	Reagent	Product	Time (h)	Yield (%)
1		KI, SSA		1.5	85
2		KI, SiO_2		5	10
3		KI, Al_2O_3		5	5
4		KI, Montmorillonitek10		5	8
5		KI, HZSM-5		5	10
6		KI, SSA		1	90

7		KI, SSA		1	88
8		KI, SSA		0.75	95
9		KI, SSA		0.75	90
10		KI, SSA		1.5	87
11		KI, SSA		2	78
12		KI, SSA		2	80
13		KI, SSA		2	82

(*continued*)

Table 2. Continued

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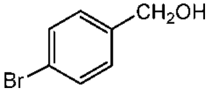
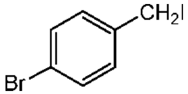
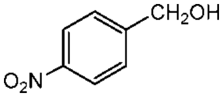
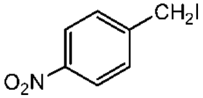
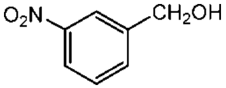
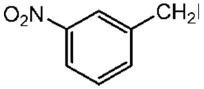
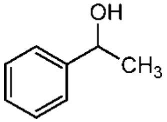
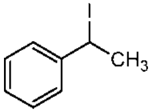
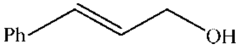
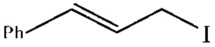
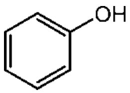
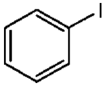
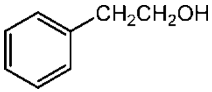
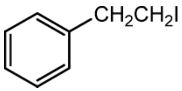
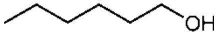
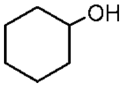
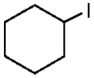
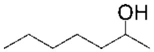
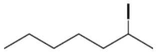
14		KI, SSA		2	80
15		KI, SSA		5	60
16		KI, SSA		5	55
17		KI, SSA		1	85
18		KI, SSA		1.5	80
19		KI, SSA		5	0

20		KI, SSA		5	0
21		KI, SSA		5	0
22		KI, SSA		5	0
23		KI, SSA		5	0

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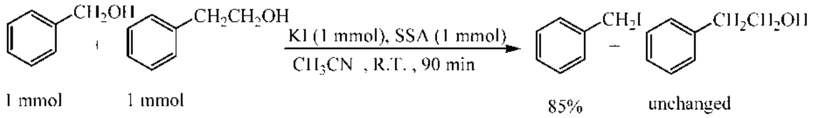
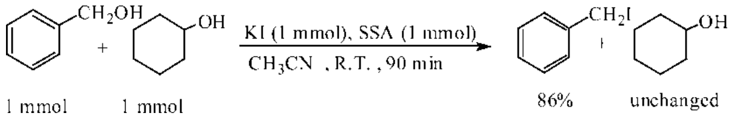
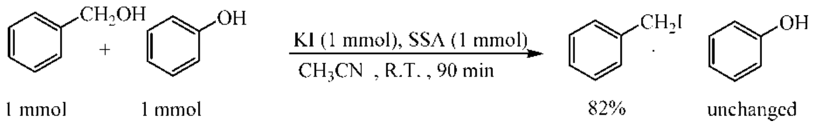
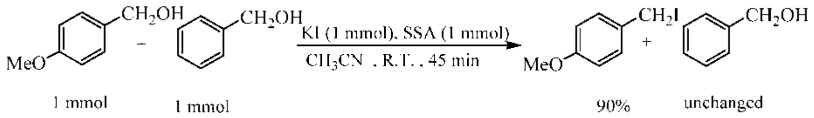
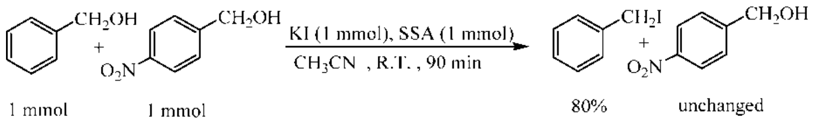
[a]The molar ratio of alcohol/KI/SSA is 1 : 1.2 : 1.2.

[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. KI/SSA used for selective iodination of different alcohols[a]

1	
2	
3	
4	
5	

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

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 in the presence of KI/SSA, showing the importance of electronic effects upon these reactions using this technique (Table 3, entries 4, 5).

In conclusion, we have developed a simple, direct, and highly chemoselective process for the iodination of benzylic and allylic alcohols using KI/SSA. The mild reaction conditions, short reaction times, good to high yields, low cost, and easy preparation and handling of SSA are the advantages of this method.

EXPERIMENTAL

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 spectroscopy data (IR, ^{1}H NMR, and MS analysis). ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise stated, relative to TMS (0.00 ppm). GC analysis was run with a Shimadzu GC-14A.

Preparation of Silica Sulfuric Acid

A 500-mL suction flask was equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (46.6 g, 0.4 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). The reaction vessel was charged with 60.0 g of silica gel; the chlorosulfonic acid was added dropwise over a period of 40 min at rt. The HCl gas was evolved from the reaction vessel immediately after the addition of few drops of chlorosulfonic acid. The mixture was shaken for 30 min at room temperature to obtain 92.0 g of a white solid powder (SSA).

Iodination of 4-Brombenzyl Alcohol (Typical Procedure)

SSA (1.2 mmol, 0.35 g) was added in several portions to a solution of 4-bromobenzyl alcohol (1 mmol, 0.187 g) and KI (1.2 mmol, 0.2 g) in CH_3CN (5 mL). The mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC or GC. After 2 h, the reaction mixture was diluted with ether (25 mL) and filtered. 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 separated and 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% yield (0.237 g) of crystalline white solid, mp 57–59 °C, ^{1}H NMR (FT-300 MHz, $CDCl_3$, TMS) $\delta = 7.43$ (d, $J = 8.5$ Hz, 2 H), 7.26 (d, $J = 8.5$ Hz, 2 H), 4.42 (s, 2 H). 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).

Iodination of 4-Methoxybenzyl Alcohol in the Presence of Benzyl Alcohol (Typical Procedure)

SSA (1 mmol, 0.28 g) was added in several portions to a mixture of 4-methoxybenzyl alcohol (1 mmol, 0.138 g), benzyl alcohol (1 mmol, 0.1 mL), and KI (1 mmol, 0.166 g) in CH_3CN (5 mL). Then the reaction mixture was stirred for 45 min. (The progress of the reaction was followed by TLC/GC.) 4-Methylbenzyl iodide was determined in 90% yield, and benzyl alcohol was intact (Table 3, entry 4).

IR and ^{1}H NMR of Some of the Iodinated Products

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

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

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

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

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

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

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

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

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