HIO_3/KI: A new combination reagent for iodination of aromatic amines and trimethylsilylation of alcohols and phenols through in situ generation of iodine under mild conditions

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Abstract

A combination of iodic acid and potassium iodide has been used for trimethylsilylation of alcohols and phenols in the presence of HMDS and iodination of aromatic amines. The reactions occur very rapidly to provide the products in good to high yields in dichloromethane at room temperature while the use of toxic and corrosive molecular iodine is avoided.

Keywords: Iodic acid, iodination, silylation, aromatic amines, alcohols, phenols

Introduction

Previously, molecular iodine was used only as a reagent but, in recent years, molecular iodine-catalyzed reactions have grown in importance in organic synthesis.[1-20] Although molecular iodine is a versatile catalyst in organic synthesis, it is highly corrosive, toxic and sublimable, making its use somewhat unattractive and also there are some environmental hazards with respect to its handling. In order to overcome these disadvantages with molecular iodine, an attempt to introduce molecular iodine in situ in the reaction mixture seems to be practically useful.

During the last ten years, several new methods for in situ generation of bromine have been developed,[21] but the numbers of protocols that are available to achieve molecular iodine in situ in the reaction mixture is limited.[22-25] In addition, most of these protocols suffer from disadvantages such as complex and strong oxidizing agents, harsh reaction conditions and formation of significant amount of waste.[26-28] Therefore, the development of quick, inexpensive, widely applicable, and environmentally benign iodinating agents is still an active area of research.

Iodic acid (HIO_3) has attracted much interest owing to its potential as an oxidant.[29-34] The use of iodic acid has been known for a long time and has been widely employed in numerous and

different organic reactions such as iodination[29,35] and deprotection,[36] but no report seems to be found in literature on the in situ generation of molecular iodine by the reaction of iodide salts and iodic acid. This reagent has several advantages such as cost-effectiveness, low-toxicity to humans[37] and the exceedingly simple and clean workup of products.

Results and Discussion

Against the background presented above, we have carried out a detailed investigation aimed at the preparation of in situ generation of the molecular iodine by the reaction of potassium iodide and iodic acid and found that this system could play a dual role as a reagent system for the iodination of aromatic amines and as a catalyst system for trimethylsilylation of alcohols and phenols. We believe that the present method is general, simple, mild, rapid, inexpensive, and new to the literature.

At the inception of this work, we studied the reaction of *N*-phenylmorpholine as a model with potassium iodide and iodic acid in different solvents (Table 1). Our observation revealed that, amongst the various solvents, the mixture of CH_2Cl_2/H_2O (1:1) was the most effective, as a change of color was evident. Also the influence of amount of iodic acid on the yield of reaction was studied, as summarized in Table 2, 1.2 mmol of iodic acid gives a short reaction time and high yield.

Table 1. Comparison of various solvents for iodination of *N*-phenylmorpholine (1.0 mmol) using HIO_3 (1.2 mmol) and KI (1.2 mmol)

Entry	Solvent	Time (min)	Yield (%)[a]
1	CH_2Cl_2	180	---
2	CH_2Cl_2/H_2O	15	92
3	CH_3CN	110	20
4	CH_3CN/H_2O	120	60
5	CH_3CH_2OH	100	70
6	THF/H_2O	120	75
7	$CHCl_3$	100	---
9	*n*-Hexane	100	---

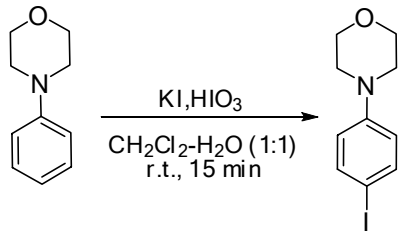
[a] Refers to isolated yield.

Table 2. Amount of HIO_3 on the iodination yield of *N*-phenylmorpholine[a]

Entry	HIO_3 (mmol)	Yield (%)[b]
1	0.4	40
2	0.6	45
3	0.8	67
4	1	80
5	1.2	92
6	1.4	92

[a] Reaction conditions: KI (1.2 mmol), time: 15 min.; Solvent: CH_2Cl_2/H_2O (1:1); room temperature. [b] Isolated yields.

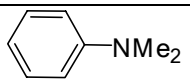
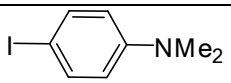
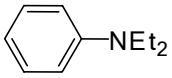
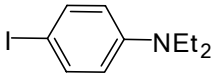
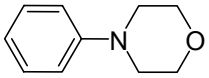
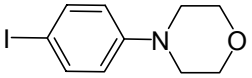
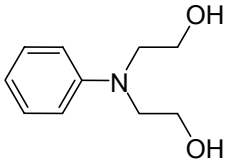
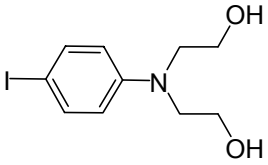
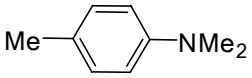
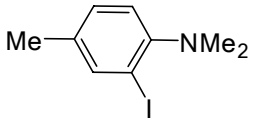
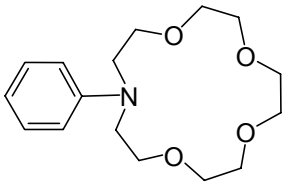
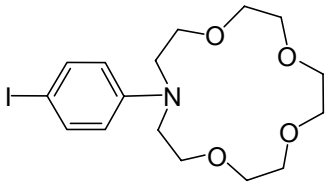
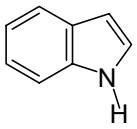
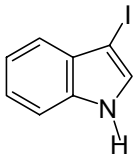
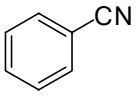
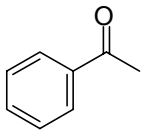
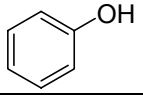
With a better understanding of the reaction variables, a series of aromatic amines were subjected to iodination with potassium iodide and iodic acid at room temperature in CH_2Cl_2/H_2O (1:1) as a two phase system. In all reactions, we observed that mono-iodination took place and regioselective iodination occurred at the more active and less hindered sites (Table 3, Scheme 1). Even though it seems that HIO_3/KI is capable of oxidizing alcohol, [34] it remains intact during the iodination of aromatic nucleus (Entry 4). Several attempts to produce mono iodinated derivative of phenol were unsuccessful and led to a sluggish mixture. We have extended our reaction to a series of unactivated aromatic compounds as depicted in Table 3, these compounds were unreacted even after 2 h (Entries 8, 9).



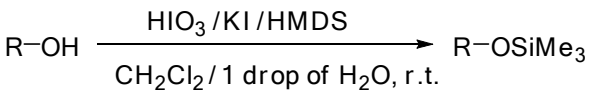
Scheme 1. Iodination of aromatic amines using KI and iodic acid.

To extend application of this method in organic reactions and transformations, we have employed our method as a catalytic system for trimethylsilylation of alcohols and phenols. In this context, we have found that a combination of iodic acid and a catalytic amount of KI in the presence of HMDS generate I_2 in situ as an efficient catalyst for the trimethylsilylation of alcohols and phenols (Scheme 2). To find the best system for in situ generation of I_2, first we studied a number of oxidizing agents in combination of KI for the trimethylsilylation of alcohols and phenols. As it can be seen in Table 4, the best results are related to the HIO_3/KI system.

Table 3. Iodination of aromatic amines to mono iodo derivatives with HIO_3 (1.2 mmol) in the presence of KI (1.2 mmol) in CH_2Cl_2 and H_2O (1:1) at room temperature

Entry	Substrate	Product	Time (h:min)	Yield (%)[a]
1			00:50	95
2			2:00	88
3			00:15	92
4			00:20	85
5			1:00	79
6			1:00	97
7			00:15	90
8		N.R.	2:00	---
9		N.R.	2:00	---
10		Sluggish	00:15	---

[a] Refers to isolated yields (The products were characterized by comparison of their spectroscopic and physical data with those of the samples synthesized by reported procedures).



Scheme 2. Trimethylsilylation of alcohols and phenols using KI and iodic acid.

Table 4. Comparison between various oxidizing agents/KI systems for the trimethylsilylation of benzyl alcohol[a]

Oxidant	Time (h)	Yield (%)[b]
$Na_2S_2O_8$	2	-
$K_2S_2O_8$	2	-
Sodium perborate	3	-
$(NH_4)_2S_2O_8$	1	-
HIO_3	immediate	100
HIO_3[c]	6	60
UHP[d]	2	-
DABCO–DNODP[e]	2	-
PVP–H_2O_2[f]	2	-
Sodium percarbonate	3	-

[a] Reaction condition: Benzyl alcohol (1.0 mmol); oxidant (0.2 mmol); KI (0.2 mmol). [b] GC yield. [c] Without KI. [d] Urea hydrogen peroxide [UHP]. [e] 1,4-Diazabicyclo[2.2.2]octane 1,4-bis(oxide)-bis(hydrogen peroxide) [DABCO– DNODP]. [f] Polyvinylpyrrolidone-hydrogen peroxide [PVP–H_2O_2].

In addition to KI, we used catalytic amount of KCl and KBr for the described system and the obtained results are depicted in Table 5. From these results, it is clear that KI is more efficient than KCl or KBr. Also as a model we studied the trimethylsilylation of benzyl alcohol in different solvents (Table 6).

Table 5. Comparison of different types of MX for the trimethylsilylation of benzyl alcohol[a]

Oxidizer acid	MX	Time (h)	MX	Yield (%)[b]
HIO_3	KI	immediate	KI	100
HIO_3	KI[c]	1	KI[c]	-
HIO_3	KCl	1	KCl	-
HIO_3	KBr	1	KBr	58

[a] Reaction condition: Benzyl alcohol (1.0 mmol); HIO_3 (0.2 mmol); MX (0.2 mmol), 1 mL moistened CH_2Cl_2. [b] GC yield. [c] Solvent-free.

Table 6. Comparison of various solvents for the trimethylsilylation of benzyl alcohol using I_2 generated in situ from HIO_3 (0.2 mmol) in the presence of a catalytic amount of KI (0.2 mmol)

Solvent	The amount of solvent (ml/drop)	Time (h)	Yield (%)[a]
CH_3CN	2	2	30
CH_3CN/H_2O	2/1	2	75
CH_2Cl_2	2	2	-
CH_2Cl_2/H_2O	5/1	2	70
CH_2Cl_2/H_2O	2/1	immediate	100
THF/H_2O	2/1	2	50
$CHCl_3/H_2O$	2/1	2	85
n-Hexane	2	2	-

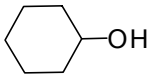
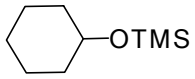
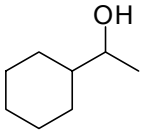
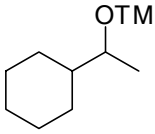
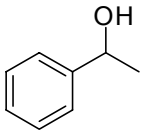
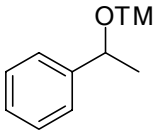
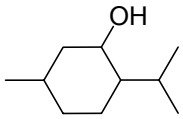
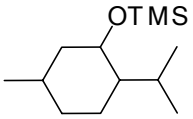
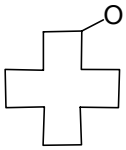
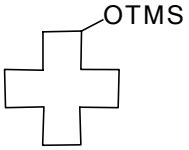
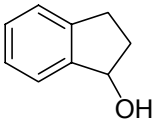
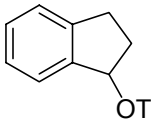
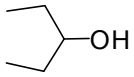
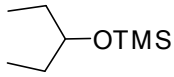
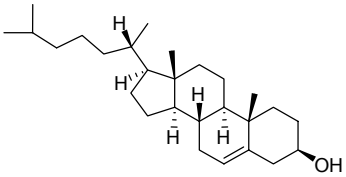
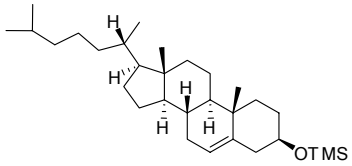
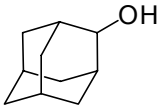
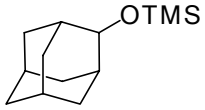
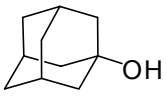
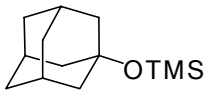
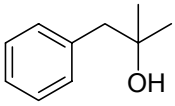
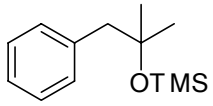
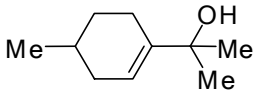
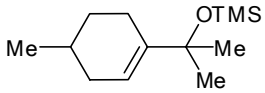
[a] GC yield.

Thus, a variety of alcohols and phenols were subjected to silylation reaction with a combination of iodic acid and a catalytic amount of KI in the presence of HMDS. All protection reactions were performed under mild and homogeneous conditions, at room temperature with good to high yields. These reactions were carried out in wet CH_2Cl_2 (Table 7).

As shown in Table 7, in the cases of primary and secondary alcohols the reactions were completed rapidly. Also, different types of highly hindered tertiary alcohols were successfully converted to the corresponding trimethylsilyl ethers in almost quantitative yields at room temperature (Table 7, Entries 18-20). Moreover, no side products were observed in these reactions. The data in Table 8 clearly show that different types of phenols were successfully converted to the corresponding silyl ethers in short reaction times and in almost quantitative yields. We observed that amines and thiols were not silylated under these reaction conditions even after prolonged times (Table 8, Entries 5,6).

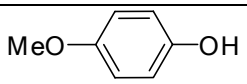
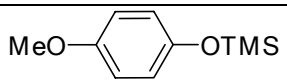
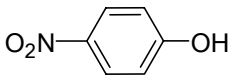
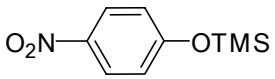
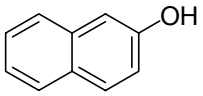
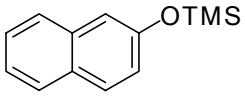
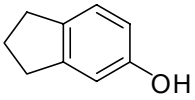
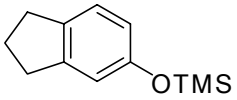
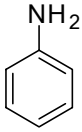
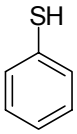
Table 7. Trimethylsilylation of alcohols (1.0 mmol) using HMDS (1.0 mmol) catalyzed with I_2 generated in situ from HIO_3 (0.2 mmol) in the presence of a catalytic amount of KI (0.2) in dichloromethane and one drop of water at room temperature

Entry	Substrate	Product	Time(min)	Yield (%)[a]
1	$PhCH_2OH$	$PhCH_2OTMS$	immediate	92
2	4-MeO-$C_6H_4CH_2OH$	4-MeO-$C_6H_4CH_2OTMS$	immediate	90
3	4-Cl-$C_6H_4CH_2OH$	4-Cl-$C_6H_4CH_2OTMS$	immediate	95
4	2,4-$(Cl)_2C_6H_4CH_2OH$	2,4-$(Cl)_2C_6H_4CH_2OTMS$	immediate	97
5	$PhCH_2CH_2OH$	$PhCH_2CH_2OTMS$	immediate	90
6	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OTMS$	immediate	93
7	PhCH(OH)Ph	PhCH(OTMS)Ph	immediate	91

8	$CH_3(CH_2)_6CH_2OH$	$CH_3(CH_2)_6CH_2OTMS$	immediate	94
9			2	90
10			immediate	88
11			immediate	80
12			45	95
13			8	92
14			immediate	95
15			immediate	96
16			immediate	90
17			10	92
18			15	90
19			45	88
20			35	93

[a] Refers to isolated yields (The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures).

Table 8. Trimethylsilylation of phenols (1.0 mmol) using HMDS (1.0 mmol) catalyzed with I_2 generated in situ from HIO_3 (0.2 mmol) in the presence of a catalytic amount of KI (0.2) in CH_2Cl_2 and one drop of H_2O at room temperature

Entry	Substrate	Product[a]	Time (min)	Yield(%)[b]
1			immediate	95
2			immediate	93
3			15	97
4			immediate	90
5		-	N.R.	-
6		-	N.R.	-

[a] All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic samples. [b] Isolated yields

To prove this claim that molecular iodine is an actual catalyst, we conducted trimethylsilylation of benzyl alcohol with hexamethyldisilazane in the presence of catalytic amounts of iodic acid (0.2 mmol) instead of the system of HIO_3/KI. The reaction was not completed after 6 h (Table 4, Entry 6), while benzyl alcohol was trimethylsilylated with hexamethyldisilazane in the presence of HIO_3/KI, in very short reaction times (Table 7, Entry 1).

Conclusions

In conclusion, we have developed a simple protocol using commercially available materials that could be utilized for a dual role: as a combination reagent for iodination of aromatic amines and as a catalyst system for trimethylsilylation of alcohols and phenols.

Experimental Section

Typical procedure for iodination of *N*-phenylmorpholine

KI (1.2 mmol, 199 mg) and a solution of HIO_3 (1.2 mmol, 211 mg) in H_2O (5 mL) were added to a solution of *N*-phenylmorpholine (1.0 mmol, 163 mg) in CH_2Cl_2 (5 mL) at room temperature and the mixture was stirred vigorously for 15 min. at room temperature. After completion of reaction that was indicated by TLC, the reaction mixture was transferred to a separatory funnel and a 10 % aqueous $Na_2S_2O_3$ solution (25 mL) was added. The aqueous fraction was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried with Na_2SO_4. The solvent was removed by simple distillation to give a crude product (283 mg; 98 %). Further purification was carried out by crystallization from cold hexane to afford a pale yellow crystalline product (265 mg; 92 %), mp 128-130 °C, which showed satisfactory analytical and spectroscopic properties.

General procedure for trimethylsilylation of alcohols and phenols

The alcohol or phenol (1.0 mmol) was added to a mixture of HIO_3 (0.2 mmol) and KI (0.2 mmol) in CH_2Cl_2 (1 mL) and one drop of H_2O. Then HMDS (1.0 mmol in 1 mL CH_2Cl_2) was added drop wise to this mixture within 5 min. The mixture was stirred vigorously at room temperature for the specified time (Table 7,8). After completion of the reaction (TLC), the mixture was filtered and the solids were washed with CH_2Cl_2 (5 mL). Powdered $Na_2S_2O_3$ (2 g) was added, the mixture was stirred for additional 5 min, and the resulting mixture was filtered. Finally, H_2O (10 mL) was added to destroy the extra amount of HMDS, the organic layer was separated and the filtrate was dried with Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure product.

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