H_5IO_6/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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A simple method for the *in situ* generation of iodine using H_5IO_6/KI has been developed, and its application in silylation of OH group and iodination of aromatic amines is described.

Introduction. – So far, no report has been found in the literature on the *in situ* generation of the molecular iodine (I_2) by the reaction of iodide salts and orthoperiodic acid (H_5IO_6). Previously, I_2 has been used only as a reagent, but in recent years, I_2-catalyzed reactions have grown in importance in organic synthesis [1–8]. Molecular iodine (I_2) is a versatile catalyst in organic synthesis, but it is highly corrosive, toxic, and sublimable, making its use somewhat unattractive; also there are some environmental hazards with respect to its handling. To overcome these disadvantages with I_2, an attempt to introduce I_2 *in situ* in the reaction mixture seems to be practically useful.

During the last years, several new methods for *in situ* generation of bromine have been developed [9], but the number of protocols that are available to achieve molecular iodine *in situ* in the reaction mixture is limited [10–16]. 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. Therefore, the development of quick, inexpensive, widely applicable, and environmentally benign iodinating agents is still an active area of research.

Orthoperiodic acid (H_2IO_6) has attracted much interest owing to its potential as oxidant in organic reactions and transformations [17–19]. The use of H_5IO_6 has been known for a long time, and it has been widely employed in numerous and different organic reactions such as iodination [20–22] and deprotection [23]. This reagent has several advantages such as cost-effectiveness, non-toxicity, and the simple and clean workup of products.

Results and Discussion. – Against the background presented, we have carried out a detailed investigation aimed at the preparation of *in situ* generation of the I_2 by the reaction of KI and H_5IO_6. We found that this system could play a dual role as a reagent system for iodination of aromatic amines and as a catalyst system in trimethylsilylation of alcohols and phenols. We assume that our method is general, simple, mild, rapid, inexpensive, and new.

At the beginning of this work, we studied iodination of 4-phenylmorpholine as model compound with KI and H_5IO_6 in different solvents (*Scheme 1* and *Table 1*). Our investigation revealed that, amongst the various solvents, a mixture of CH_2Cl_2/H_2O 1:1 was the most effective, as a change of color was evident. Also the effective amount of H_5IO_6 acid on the reaction was studied, as shown in *Table 2*; 1.2 mmol of H_5IO_6 gives a high yield in a short reaction time.

Scheme 1

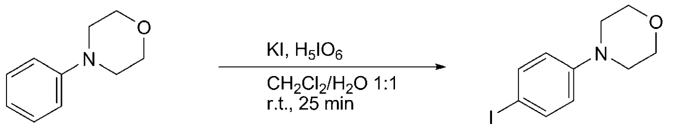


Table 1. *Comparison of Various Solvents for Iodination of 4-Phenylmorpholine Using H_5IO_6 and KI*

Entry	Solvent	Time [min]	Yield [%][a])
1	CH_2Cl_2	120	–
2	CH_2Cl_2/H_2O 1:1	25	95
3	MeCN	120	30
4	$MeCN/H_2O$ 1:1	120	60
5	$MeCH_2OH$	120	68
6	THF/H_2O 1:1	120	80
7	$CHCl_3$	120	–
8	Hexane	120	–

[a]) Refers to yields of isolated iodide on reaction of 1.2 mmol of H_5IO_6 and KI with 4-phenylmorpholine (1.0 mmol) in 10 ml of solvent or solvent mixture at room temperature.

Table 2. *Effect of the Amount of H_5IO_6 on the Iodination Yield of 4-Phenylmorpholine* (1.0 mmol)[a])

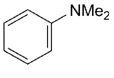
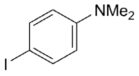
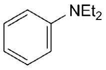
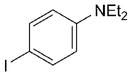
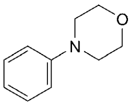
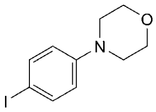
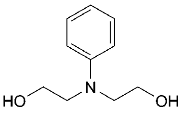
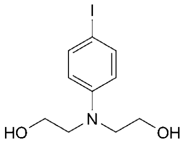
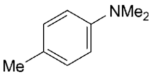
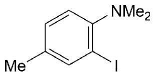
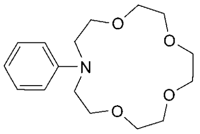
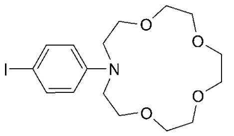
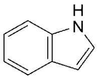
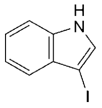
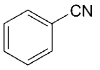
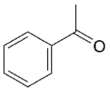
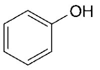
Entry	H_5IO_6 [mmol]	Yield [%][b])
1	0.4	30
2	0.6	45
3	0.8	59
4	1	82
5	1.2	95

[a]) Reaction conditions: KI (1.2 mmol), time: 25 min; solvent: 10 ml of CH_2Cl_2/H_2O 1:1; room temperature. [b]) Yield of the isolated iodide.

With a better understanding of the reaction variables, a series of aromatic amines were subjected to iodination with KI and H_5IO_6 at room temperature in CH_2Cl_2/H_2O 1:1 as a two phase system. In all of the reactions, we observed that mono-iodination took place regioselectively at the more active and less hindered position (*Table 3*). Even though H_5IO_6/KI is capable of oxidizing alcohol [24], it remains intact during the iodination of the aromatic nucleus (*Entry 4*).

Several attempts for mono-iodination of phenols were unsuccessful and led to mixtures. We have extended our reaction to a series of unactivated aromatic

Table 3. *Iodination of Aromatic Amines under Standard Conditions with H_5IO_6/KI in CH_2Cl_2/H_2O 1 : 1 at Room Temperature*[a])

Entry	Substrate	Product	Time [min]	Yield [%][b])
1			40	90
2			70	93
3			25	95
4			80	88
5			60	79
6			60	98
7			15	95
8		No reaction	120	–
9		No reaction	120	–
10		Sluggish	15	

[a]) See procedure in *Exper. Part.* [b]) Yields refer to isolated products which were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures.

compounds as depicted in *Table 3*; these compounds remained unchanged even after 2 h (*Entries 8* and *9*).

To extend the application of this method, we have employed H_5IO_6/KI catalytically for trimethylsilylation of alcohols and phenols. In this context, we have found that a combination of H_5IO_6 and a catalytic amount of KI generate *in situ* I_2 as an efficient catalyst for the trimethylsilylation of alcohols and phenols in the presence of 1,1,1,3,3,3-hexamethyldisilazane (HMDS; *Scheme 2*). To find the best system for the *in situ* generation of I_2, we first studied a number of oxidizing agents in combination of KI for the trimethylsilylation of alcohols and phenols. As can be seen in *Table 4*, the best results were achieved with the H_5IO_6/KI system.

Scheme 2

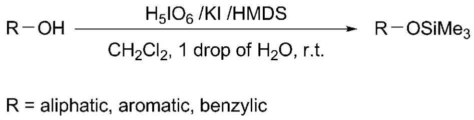


Table 4. *Comparison between Various Oxidizing Agents/KI Systems for the Trimethlsilylation of Benzyl Alcohol*[a])

Entry	Oxidant	Time [h]	Yield [%][b])
1	$Na_2S_2O_8$	2	–
2	$K_2S_2O_8$	2	–
3	Sodium perborate	2	–
4	$NH_4S_2O_8$	2	–
5	H_5IO_6	immediate	100
6	H_5IO_6[c])	8	–
7	–[d])	immediate	100
8	UHP[e])	2	–
9	DABCO/DNODP[f])	2	–
10	PVP/H_2O_2[g])	2	–
11	Sodium percarbonate	2	–

[a]) Reaction conditions: Benzyl alcohol (1.0 mmol); oxidant (0.2 mmol); KI (0.2 mmol); 1 ml of moistened CH_2Cl_2. [b]) GC Yield. [c]) Without KI. [d]) Reaction conditions: Benzyl alcohol (1.0 mmol); I_2 (0.1 mmol); 1 ml of moistened CH_2Cl_2. [e]) UHP = Urea hydrogen peroxide. [f]) DABCO/DNODP: 1,4-Diazabicyclo[2.2.2]octane 1,4-bis(oxide)/bis(hydrogen peroxide). [g]) Polyvinylpyrrolidone/H_2O_2 (PVP/H_2O_2).

In addition to KI, we also used catalytic amounts of KCl and KBr for silylations. The results are collected 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*). Thus, a variety of alcohols and phenols were subjected to silylation reaction with a combination of H_5IO_6 and a catalytic amount of KI in the presence of HMDS. All protection reactions were performed under mild and homogeneous conditions, at room temperature, and with good-to-high yields. These reactions were carried out in CH_2Cl_2 moistened by one drop of H_2O (*Table 7*).

As shown in *Table 7*, in the cases of primary and secondary alcohols, the reactions were completed rapidly, and different types of highly hindered tertiary alcohols were successfully converted to the corresponding trimethylsilyloxy (TMSO) derivatives in

Table 5. *Comparison of Various Types of MX for the Trimethylsilylation of Benzyl Alcohol*[a])

Entry	MX	Time [h]	Yield [%][b])
1	KI	immediate	100
2	KI[c])	1	–
3	KCl	1	–
4	KBr	1	64

[a]) Reaction condition: Benzyl alcohol (1.0 mmol); H_5IO_6 (0.2 mmol); MX (0.2 mmol), 1 ml of moistened CH_2Cl_2. [b]) GC Yield. [c]) Solvent-free.

Table 6. *Comparison of Various Solvents for Trimethylsilylation of Benzyl Alcohol Using I_2 Generated* in situ *from H_5IO_6* (0.2 mmol) *in the Presence of a Catalytic Amount of KI* (0.2 mmol)

Solvent	[ml/drop]	Time [h]	Yield [%][a])
MeCN	2/0	2	33
MeCN/H_2O[b])	2/1	2	75
CH_2Cl_2	2/0	2	-
CH_2Cl_2/H_2O[b])	5/1	2	70
CH_2Cl_2/H_2O[b])	2/1	immediate	100
THF/H_2O[b])	2/1	2	50
$CHCl_3$/H_2O[b])	2/1	2	85
Hexane	2/0	2	–

[a]) GC Yields. [b]) Moistened solvent.

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 TMSO derivatives in short reaction times and in almost quantitative yields. We observed that amines and thiols were not silylated under these conditions even after prolonged reaction times (*Table 8*, *Entries 5* and *6*).

For confirming this claim that I_2 is the actual catalyst, we conducted trimethylsilylation of $PhCH_2OH$ with HMDS in the presence of catalytic amounts of H_5IO_6 (0.2 mmol) instead of the H_5IO_6/KI system, no reaction occurred event after 8 h (*Table 4*, *Entry 6*), while $PhCH_2OH$ was trimethylsilylated with HMDS in the presence of H_5IO_6/KI or I_2, in very short reaction times (*Table 4*, *Entries 5* and *7*).

Conclusions. – A simple method for the *in situ* generation of molecular iodine from nontoxic and commercially available materials has been developed that could be utilized for a dual role: as a reagent system in iodination of aromatic amines, and as a catalyst system in trimethylsilylation of alcohols and phenols.

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Table 7. *Trimethylsilylation of Alcohols* (1 mmol) *Using HMDS* (1 mmol) *Catalyzed with* I_2 *Generated* in situ *from* H_5IO_6 (0.2 mmol) *in the Presence of a Catalytic Amount of KI* (0.2 mmol) *in* CH_2Cl_2 *and One Drop of* H_2O *at Room Temperature*

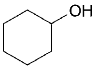
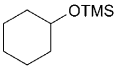
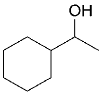
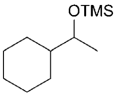
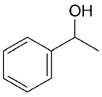
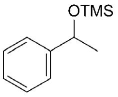
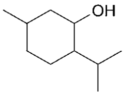
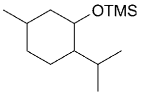
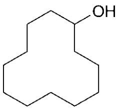
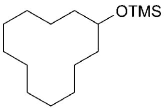
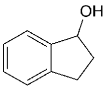
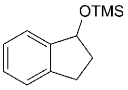
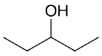
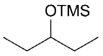
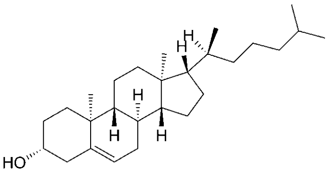
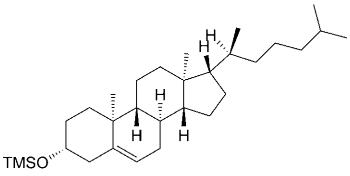
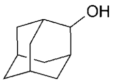
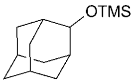
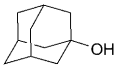
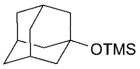
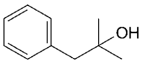
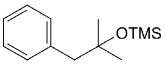
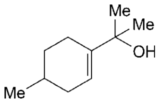
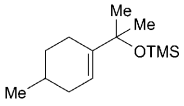
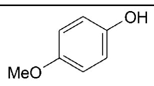
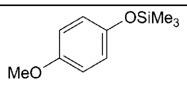
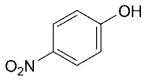
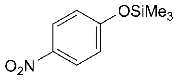
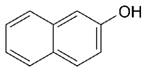
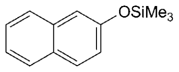
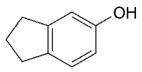
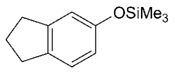
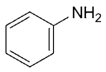
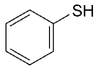
Entry	Substrate	Product	Time [min]	Yield [%]a)
1	$PhCH_2OH$	$PhCH_2OSiMe_3$	immediate	95
2	$4\text{-MeO}-C_6H_4CH_2OH$	$4\text{-MeO}-C_6H_4CH_2OSiMe_3$	immediate	93
3	$4\text{-Cl}-C_6H_4CH_2OH$	$4\text{-Cl}-C_6H_4CH_2OSiMe_3$	immediate	97
4	$2,4\text{-(Cl)}_2C_6H_4CH_2OH$	$2,4\text{-(Cl)}_2C_6H_4CH_2OSiMe_3$	immediate	94
5	$PhCH_2CH_2OH$	$PhCH_2CH_2OSiMe_3$	3	90
6	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OSiMe_3$	immediate	95
7	$PhCH(OH)Ph$	$PhCH(OSiMe_3)Ph$	2	92
8	$Me(CH_2)_6CH_2OH$	$Me(CH_2)_6CH_2OSiMe_3$	immediate	90
9			12	91
10			15	85
11			immediate	83
12			60	95
13			11	98
14			immediate	93
15			immediate	94
16			immediate	94
17			9	91

Table 7 (cont.)

Entry	Substrate	Product	Time [min]	Yield [%][a])
18			10	93
19			50	85
20			30	93

[a]) Yields refer to isolated products which 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 H_5IO_6* (0.2 mmol) *in the Presence of a Catalytic Amount of KI* (0.2 mmol) *in CH_2Cl_2 and One Drop of H_2O at Room Temperature*

Entry	Substrate	Product[a])	Time [min]	Yield [%][b])
1			immediate	96
2			immediate	97
3			25	95
4			immediate	92
5		–	–	no reaction
6		–	–	no reaction

[a]) All products were characterized by comparison of their spectral data (IR, ^{1}H-NMR) with those of authentic samples. [b]) Yields of isolated silyl ethers.

Experimental Part

Typical Procedure for Iodination of 4-Phenylmorpholine. To a soln. of 4-phenylmorpholine (1.0 mmol, 163 mg) in CH_2Cl_2 (5 ml) were added KI (1.2 mmol, 199 mg) and a soln. of H_5IO_6 (1.2 mmol, 273 mg) in H_2O (5 ml), and the mixture was stirred vigorously for 15 min at r.t. After completion of reaction, which was indicated by TLC, the mixture was transferred to a separatory funnel, and a 10% aq.

$Na_2S_2O_3$ soln. (25 ml) was added. The aq. fraction was extracted with CH_2Cl_2 (3 × 15 ml). The org. layer was dried (Na_2SO_4), and 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 the product (274 mg, 95 %). M.p. 128–130°. Satisfactory anal. and spectroscopic properties.

General Procedure for Trimethylsilylation of Alcohols and Phenols. The alcohol or phenol (1.0 mmol) was added to a mixture of H_5IO_6 (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 dropwise to this mixture within 5 min. The mixture was stirred vigorously at r.t. for the specified time (*Tables 7* and *8*). After completion of the reaction (TLC), the mixture was filtered, and the solids were washed with CH_2Cl_2 (5 ml). Powdered $Na_2S_2O_3$ (12.0 mmol) 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 org. layer was separated, and the filtrate was dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the almost pure product.

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