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HIO_4/Al_2O_3 as a new system for iodination of activated aromatics and 1,3-dicarbonyl compounds

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Abstract—The use of a periodic acid/alumina system for the iodination of activated aromatics and 1,3-dicarbonyl compounds is described.

Iodobenzene derivatives are valuable intermediates in organic synthesis, medicine, and biochemistry.[1] They are widely used in synthesis to form carbon–carbon and carbon–heteroatom bonds in transition metal catalyzed processes such as the Heck, Still, Suzuki, and Ullmann-type coupling reactions.[2–4]

Due to the poor electrophilic strength of iodine, direct iodination of aromatic rings with iodine is difficult and requires the presence of an activating agent in order to produce a strongly electrophilic I^+ species. In recent years, direct iodination methods have been developed using iodonium-donating reagents. However, most of these methods require toxic reagents, harsh conditions, the use of expensive, complicated or sensitive reagents, and the generation of hazardous waste.[5]

On the other hand, 1,3-dicarbonyl compounds are versatile intermediates in organic chemistry.[6] Most methods to transform 1,3-dicarbonyl compounds to their related α-iodo-derivatives rely on modification of *N*-iodosuccinimide[7] whilst the use of other reagents have been less investigated.[8] Therefore, we report a milder, efficient, and environmentally benign procedure for the iodination of activated aromatics and 1,3-dicarbonyl compounds involving periodic acid adsorbed on alumina (HIO_4/Al_2O_3). Periodic acid has been widely used in organic synthesis,[9] however, it can be unreactive and this disadvantage can be overcome by absorption of the reagent onto alumina. Such a supported reagent is more reactive and has the advantage of being easy to remove from the organic product by filtration. Other advantages of HIO_4/Al_2O_3 in comparison to other reagents are mild reaction conditions, enhanced selectivity, and increased yields.[10]

The use of periodic acid as an iodinating agent was first reported by Japanese investigators who used it in the presence of iodine for iodination of activated aromatic compounds.[11]

We have found that periodic acid can be readily decomposed on alumina in aqueous media to produce iodine, as a change of color was evident. This evidence prompted us to investigate HIO_4/Al_2O_3 for the direct iodination of aromatic compounds. As a model we studied the iodination of mesitylene in different solvents (Table 1).

Our observation revealed that, amongst the various solvents, 1,4-dioxane was the most effective, giving a short reaction time, and high yield. To our surprise, in a blank reaction performed without supporting the HIO_4 on

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Keywords: Iodination; Periodic acid; Solid phase; 1,3-Dicarbonyl compounds; Alumina; Activated aromatic compounds.

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Table 1. Effect of solvent on the reaction yield at reflux using HIO_4/Al_2O_3 in the introduction of mesitylene

Solvent[a]	$H_2O/CHCl_3$	H_2O/CH_3CN	H_2O/acetone[b]	H_2O/CH_2Cl_2	H_2O/1,4-dioxane
Time (h)	4	5	3	4	1.5
Yield (%)	55	30	40	50	80

[a] HIO_4 is decomposed in aqueous media and an organic solvent is used to dissolve organic compounds. Typically, we dissolved 2.5 g of periodic acid in a minimum amount of water (2 ml) and then added 5 g of alumina and 10 ml of organic solvent.[12]

[b] Iodoacetone was detected.

alumina, mesitylene was found to remain unconsumed even after 5 h. Thus the role played by the alumina is justified.

With a better understanding of the reaction variables, a series of arenes were subjected to iodination with periodic acid on alumina in dioxane. In all the reactions, we observed regioselective iodination occurring at the more active and less sterically hindered position (Table 2).

This system was very mild and mono-iodination was observed in all cases. Alkyl benzenes were the most active substrates in the iodination by HIO_4/Al_2O_3. Surprisingly, methoxy and hydroxy benzene derivatives, despite their marked activity in electrophilic reactions, gave lower yields. Although, iodination of aniline, *N*,*N*-dialkylanilines, and phenol led to decomposition of these substrates, it was thought that perhaps complexation of the oxygen and nitrogen atoms with the oxidant was responsible for inhibiting the iodination process.

However, when the reaction of phenol and anilines (entries 8, 16, and 17) were performed at reflux, trace amounts of iodinated products along with unidentified by-products, which did not contain iodine and other oxidized products were obtained.[9] This problem could be overcome using phenols possessing two substituents in the *ortho* positions. We have extended our reaction to a series of unactivated aromatic compounds as depicted in Table 2, these compounds were recovered unreacted even after 10 h (entries 7 and 18).

We have also employed our reagent system for the iodination of compounds containing an acidic hydrogen. Fatiadi reported the iodination of 1,3-dicarbonyl compounds with periodic acid in AcOH,[8] however, our reagent system showed a greater yield for the diiodination. It was found that β-dicarbonyl compounds **1**, which are unsubstituted at the α-position undergo diiodination to afford high yields of **2** upon treatment with HIO_4/Al_2O_3 (Table 3). We were not able to achieve mono-iodination, only diiodinated products were obtained. As expected, exposure of α-mono-substituted compounds **3** to HIO_4/Al_2O_3 under the same reaction conditions afforded mono-iodinated products **4**. Table 3 shows some representative examples of this transformation. β-Dicarbonyl compounds were iodinated in good to excellent yields using the HIO_4/Al_2O_3 system in dioxane (Table 3, entries 1–5). Ethyl cyanoacetate showed good reactivity and was iodinated in high yield (entry 6). To extend our investigation, we employed our system for the iodination of less active carbonyl compounds. Treatment of acetophenone and 2-nitropropane with HIO_4/Al_2O_3 afforded iodinated product in high yields (entries 8 and 9). 1,1-Dimethoxyethane was also iodinated in high yield (Table 3, entry 7). Surprisingly, high selectivity was obtained with acetophenone compared with acetone, which produced a mixture of mono and diiodo products.

Table 2. Iodination of activated arenes using HIO_4/Al_2O_3

Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	1,3,5-Trimethylbenzene	2-Iodo-1,3,5-trimethylbenzene	1.5	90
2	1,2-Dimethylbenzene	1,2-Dimethyl-4-iodobenzene	2.5	79
3	1,3-Dimethylbenzene	1,3-Dimethyl-4-iodobenzene	2	81
4	1,4-Dimethylbenzene	1,4-Dimethyl-2-iodobenzene	2.5	80
5	Methoxybenzene	1-Iodo-4-methoxybenzene	2.5	70
6	Benzylphenylether	4-Iodo-benzylphenylether	5	40
7	Diphenylether	No reaction	12	—
8	Phenol	Decomposed	—	—
9	2,6-Dimethylphenol	2,6-Dimethyl-4-iodophenol	3	75
10	2,6-Di-*tert*-butylphenol	2,6-Di-*tert*-butyl-4-iodophenol	3	78
11	2,3-Dimethylphenol	2,3-Dimethyl-4-iodophenol	8	70
12	3-Methoxyphenol	4-Iodo-3-methoxyphenol	4.5	72
13	3,5-Dimethoxyphenol	3,5-Dimethoxy-4-iodophenol	3.5	80
14	2,3-Dimethoxyphenol	2,3-Dimethoxy-4-iodophenol	3.5	75
15	4-Hydroxybenzaldehyde	No reaction	12	—
16	*N*,*N*-Dimethylaniline	Decomposed	—	—
17	*N*,*N*-Diethylaniline	Decomposed	—	—
18	Chlorobenzene	No reaction	12	—

[a] Yields refer to isolated products.

Table 3. Iodination of various carbonyl compounds and alkenes with HIO_4/Al_2O_3

Entry	Carbonyl compound	Iodinated product	Time (h)	Yield[a] (%)
1	$CH_3COCH_2CO_2Et$	$CH_3COCI_2CO_2Et$	1.5	93
2	$CH_3COCH_2COCH_3$	$CH_3COCI_2COCH_3$	1	95
3	$CH_2(COOEt)_2$	$CI_2(COOEt)_2$	2.5	80
4	$CHPh(COOEt)_2$	$CIPh(COOEt)_2$	1.5	90
5	$PhCOCH_2COPh$	$PhCOCI_2COPh$	2	90
6	$NCCH_2CO_2Et$	$NCCI_2CO_2Et$	2	80
7	$CHCH_3(OEt)_2$	$CICH_3(OEt)_2$	1.5	87
8	$CHNO_2(CH_3)_2$	$CINO_2(CH_3)_2$	2	75
9	$PhCOCH_3$	$PhCOCH_2I$	2	92
10	Stilbene[b]	Benzyl phenyl ketone	1	90[c]
11	Styrene	2-Iodophenyl ethanol	3	50[c,d]
		Acetophenone		<10
12	Styrene[e]	Acetophenone	2	92

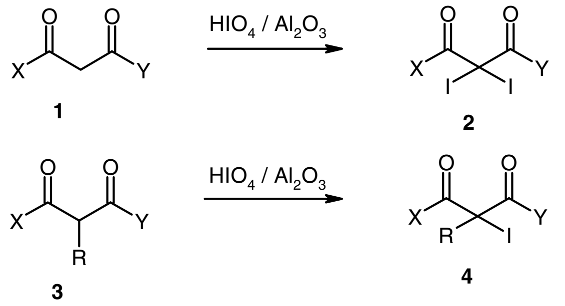
[a] Isolated and unoptimized yields.

[b] Reaction conducted at room temperature.

[c] Reaction yield based on GC analysis.

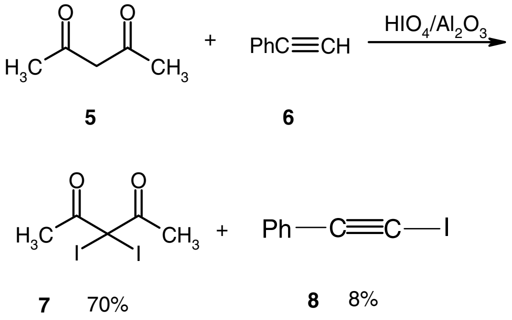
[d] 2-Iodophenylethanol was characterized by comparison with an authentic sample prepared either by reduction of α-iodoacetophenone or according to the literature procedure.[13]

[e] Reaction conducted at reflux.



Attempts to iodinate stilbene using HIO_4/Al_2O_3 led to formation of the oxidized product, benzyl phenyl ketone in excellent yield. Similarly, styrene underwent oxidation at reflux and gave not only acetophenone in 92% yield but also gave a mixture of acetophenone and 2-iodophenyl ethanol at room temperature (Table 3, entries 11 and 12).

In order to probe selectivity issues with regard to this chemistry, pentan-2,4-dione **5** and phenyl acetylene **6** were exposed to HIO_4/Al_2O_3 under standard conditions, leading to the chemoselective diiodination product **7** as the major product accompanied by phenyl iodoethyne **8** in very low yield.



In conclusion, we have developed a simple method using commercially available reagents for the direct iodination of activated aromatics and dicarbonyl compounds under mild conditions.

Typical procedure: Periodic acid (2.5 g) was dissolved in water (2.5 ml) and added to a mixture of alumina (5 g) and dioxane (10 ml) and stirred for 2 h at reflux or at room temperature (a brown color was observed). Then, the arene or β-dicarbonyl compound (5 mmol) was dissolved in dioxane (3 ml) and added to the above mixture. After the appropriate time (reaction was monitored by TLC and GC) the reaction mixture was filtered and the resulting filtrate extracted with diethyl ether. The ether layer was successively washed with aqueous sodium bisulfite (5%) and water (2 × 15 ml) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude product was crystallized or subjected to column chromatography. The products were characterized from their physical constants and NMR, IR, and GC–MS spectra.

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