Effective and regioselective iodination of arenes using iron(III) nitrate in the presence of tungstophosphoric acid

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Abstract: An easy, cheap, and effective method for iodination of various aromatic compounds takes place with molecular iodine and iron nitrate nonahydrate as the oxidant in the presence of a catalytic amount of tungstophosphoric acid in dichloromethane, with good yield and high regioselectivity under very mild conditions.

Key words: iodination, arenes, iodine, iron(III) nitrate, tungstophosphoric acid.

Résumé : On a mis au point une méthode facile, peu coûteuse et efficace de procéder à l'iodation de divers composés aromatiques; elle fait appel à de l'iode moléculaire et du nonahydrate du nitrate de fer qui agit comme agent oxydant en présence de quantités catalytiques d'acide tungstophosphorique dans le dichlorométhane et elle donne de bons rendements et une régiosélectivité élevée dans des conditions très douces.

Mots clés : iodation, arènes, iode, nitrate de fer(III), acide tungstophosphorique.

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Introduction

Heteropoly acids (HPAs) and their salts are useful acid and oxidation catalysts for various reactions and there are already many practical applications (1-3). One of the most interesting aspects may be the fact that they can be used in various kinds of reaction media or fields. Furthermore, they can be active solid acid catalysts and can provide unique reaction fields such as a pseudoliquid that is a "catalytically active solid solvent". HPA catalysts will find more green and sustainable applications in the future (4). Solid HPAs possess purely Brønsted acidity and are stronger than the usual mineral acids such as H₂SO₄, HCl, HNO₃, HClO₄, CF₃SO₃H, etc. (5, 6), and than conventional solid acids such as SiO₂-Al₂O₃, H₃PO₄-SiO₂, HX, HY, and H-ZSM-5 zeolites, Amberlyst-15, and Nafion-H (7). Among HPAs, polytungstic acids are the most widely used catalysts because of their high acid strengths, thermal stabilities, and low reducibility. Tungstophosphoric acid $(H_3PW_{12}O_{40})$ is a inexpensive, reusable, heterogeneous, and easily available catalyst (8, 9).

Iodoaromatic compounds are useful synthetic reagents for fine organic synthesis. They are valuable, versatile synthetic intermediates and have found wide applications in medicine and biochemistry (10, 11). The direct iodination of arenes with molecular iodine under mild conditions requires an oxidizing agent to activate the low reactivity of iodine. The oxidants such as oleum (12*a*), Pb(OAc)₄ (12*b*), diiodine pentoxide (12*c*), CrO₃ (12*d*), sodium perborate (12*e*), hydrogen peroxide (12e), KMnO₄ (12f), MnO₂ (12f), tetrabutylammonium disulfate (12g), sodium periodate (12h), sodium iodate (12h), ceric ammonium nitrate(CAN) (12i), F-TEDA- BF_4 (1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (12j, 12k), urea-H₂O₂ (12l), etc., were reported. Recently, silica-supported $Bi(NO_3)_3 \cdot 5H_2O$ and Fe(NO₃)₃·9H₂O (silfen) were used as mild oxidizing agents for the iodination of active arenes (12m, 12n). However, most of the described reactions in the literature require one or some of the following conditions: an excess of the reagent or strong oxidizing agent, hazardous toxic solvents such as acetonitrile at elevated temperature, the use of expensive catalysts that need to be prepared prior to use, corrosive mineral acids, expensive Lewis acids, the use of corrosive and moisture-sensitive iodine monochloride, iodine vapor irritant in solvent free conditions and mostly waste remains.

Here, we describe an improved, simple, and eco-friendly method for regioselective iodination of arenes with iodine and iron(III) nitrate nonahydrate as the oxidant in the presence of a catalytic amount of tungstophosphoric acid at room temperature with good yields (Scheme 1).

Results and discussion

Effect of catalyst

Iron(III) nitrate nonahydrate, an abundant, inexpensive, nontoxic, and commercially available reagent can be used as an oxidant in the presence of a catalytic amount of dehy-

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Scheme 1. Iodination of arenes with iron nitrate in the presence of tungstophosphoric acid at room temperature.



$$R = OCH_3, CH_3, OH, NH_2, NHCOCH_3$$
$$R' = OCH_3, CH_3, NO_2, Br, H$$

drated heteropoly acids. Primarily, iodination of anisole, as a model compound, was performed in the presence of several HPAs and some other solid acids in dichloromethane at room temperature for 8 h (GC results are presented in Table 1). The result shows that in the absence of the catalyst, the reaction proceeds with low yield, but in the presence of HPAs, this conversion proceeded efficiently under similar reaction conditions. In this reaction, anisole was converted to *p*-iodoanisole in good yield and excellent regioselectivity (100%) without the formation of diiodinated derivatives. To show that tungstophoric acid is more effective than other HPAs and solid acids, we chose $H_3PW_{12}O_{40}$, which is a very efficient and environmentally friendly catalyst (6), for further iodination studies.

Heterogeneous acid-catalyzed systems

Heteropoly acids and solid acids are not dissolved in dichloromethane, thus the iodination reaction takes place in heterogeneous conditions. The acid catalysis of heteropoly compounds in the solid state is classified into "surface-type" and "bulk-type" catalysis. Catalytic reactions involving polar molecules (here, anisole) occur not only at the surface, but also in the bulk solid HPAs. This shows good parallelism between catalytic activity (bulk-type) and acidity (surfacetype) (13). Under bulk-type conditions, all of the acid sites are available to the reactant and therefore high catalytic activity could be expected. Cs and NH₄ salts (scarcely soluble in polar solvents) usually show only surface-type catalysis. However, solid HPAs containing a cation of low ionic radii to charge ratio (H⁺) readily absorb small polar molecules and tend to exhibit pseudoliquid behaviour (bulk-type), and are soluble in polar solvents. The diffusion of reactant molecules in the solid is faster than the reaction; the solid bulk forms a pseudoliquid phase in which the catalytic reaction can proceed (14). Therefore, the heteropoly salts containing Cs, NH₄, and Fe (Table 1, entries 6–9) showed less catalytic activity than HPAs containing W and Mo (Table 1, entries 3-5).

On the other hand, although Keggin-type HPAs $(H_3PM_{12}O_{40}, M = W, Mo)$ are much stronger acids than the Dawson-type HPAs $(H_6P_2Mo_{18}O_{62})$ (6), but Dawson-type heteropoly acids, because of their amorphous shape (ellipsoidal shape of the polyanion), show higher catalytic acivity than Keggin-type HPAs, and this is because of their crystal-line shape (spherical shape) (14). Consequently, we can see a low selectivity in the iodination of anisole in the presence

Table 1. Iodination of anisole with $Fe(NO_3)_3 \cdot 9H_2O$ in the presence of various heteropoly acids and other solid acids in CH_2Cl_2 at room temperature for 8 h.

Entry	Catalyst	Conv. (%)	GC yield (%) ^a
1	None	36	36
2	$H_3PW_{12}O_{40}^{\ b}$	78	77
3	$H_{3}PW_{12}O_{40}$	100	99
4	$H_3PMo_{12}O_{40}$	92	92
5	H ₃ PW ₁₂ O ₄₀ :H ₃ PMo ₁₂ O ₄₀ ^c	97	96
6	Cs _{2.5} H _{0.5} PW ₁₂ O ₄₀	83	82
7	Cs _{2.5} H _{0.5} PMo ₁₂ O ₄₀	75	75
8	$(NH_4)_2 HPW_{12}O_{40}$	72	71
9	Fe _{0.85} H _{0.45} PMo ₁₂ O ₄₀	80	79
10	$H_6P_2Mo_{18}O_{62}$	82	74, 7^d
11	Montmorillonite-K10 ^e	85	85
12	Amberlyst-15H ^{+e}	89	89
13	Silica gel ^e	83	82
14	$H_3PW_{12}O_{40}^{f}$	88	>86

Note: Reaction conditions: anisole (1 mmol), I₂ (0.6 mmol), Fe(NO₃)₃·9H₂O (0.4 mmol), catalyst (0.1 mmol), CH₂Cl₂ (1 mL).

^{*a*}Product: 4-IC₆H₄OMe.

^bCatalyst: 0.05 mmol.

^cHPW and HPMo in equal molar ratio.

^{*d*}By-product: 2-IC₆H₄OMe.

^eOne gram of solid acid was used.

^fCatalyst: after recovery and reuse.

of $H_6P_2Mo_{18}O_{62}$. The formation of the resulting by-product is due to the amorphous shape and high catalytic activity in Dawson-type HPAs (Table 1, entry 10). Also, solid acids show only surface-type activity, so their catalytic activities are less than those of $H_3PM_{12}O_{40}$ (M = W, Mo) (Table 1, entries 11–13). One of the most desirable properties for a catalyst is the ease of its recovery. We have found that $H_3PW_{12}O_{40}$ can be easily recovered and recycled simply by filtering (by diethyl ether) and drying (Table 1, entry 14). The recovery had only slightly decreased their catalytic activity (because of the reduction of tungsten atoms) without structural degradation.

Effect of oxidant

We also investigated other metal nitrates for the iodination of anisole under similar reaction conditions in dichloromethane at room temperature for 8 h (GC results are presented in Table 2). The results revealed that in the absence of the oxidant (Table 2, entry 1), and also with an excess of the catalyst (tungstophosphoric acid) (Table 2, entry 2), the iodination reaction did not proceed after 8 h. Therefore, we have concluded that in the presence of oxidant, most of the metal nitrates were effective oxidants for this reaction, but iron(III) and bismuth(III) nitrates gave better results. These results were expected regarding their reduction potential.

Effect of solvent

The iodination of anisole was also conducted in different solvents at room temperature for 8 h (GC results are presented in Table 3). The results show that in the absence of solvent (Table 3, entry 1) the iodination reaction proceeds with low yield after 1 h at room temperature. The iodination

Metal nitrates Conv. (%) GC yield $(\%)^a$ Entry 0 0 1 None 2 None^b 0 0 3 3 Mn(NO₃)₃·4H₂O 2 4 Fe(NO₃)₃·9H₂O 100 99 5 Bi(NO₃)₃·5H₂O 97 96 6 Ce(NO₃)₃·6H₂O 25 24 7 $(NH_4)_2[Ce(NO_3)_6]$ (CAN) 68 69 8 77 Cu(NO₃)₂·3H₂O 78 9 Ni(NO₃)₂·6H₂O 58 57

Table 2. Iodination of anisole with various metal nitrates in the presence of $H_3PW_{12}O_{40}$ in CH_2Cl_2 at room temperature for 8 h.

Note: Reaction conditions: anisole (1 mmol), I_2 (0.6 mmol), metal nitrate (0.4 mmol), $H_3PW_{12}O_{40}$ (0.1 mmol), CH_2Cl_2 (1 mL).

^{*a*}Product: 4-IC₆H₄OMe.

^bCatalyst: 0.5 mmol.

reaction also proceeds with the use of microwave irradiation (using a common household microwave oven) under solvent-free conditions for 2 min with the power set at 200 W (Table 3, entry 2). The microwave-assisted method has been accepted as a method for dramatically reducing reaction time, and for increasing isolated yields of products compared with the conventional method, but unfortunately this technique is not a selective tool. The results (Table 3, entries 3-6) show that the efficiency and the yield of the reaction in chlorinated solvents is much more than other solvents at room temperature. We chose dichloromethane for further studies.

On the other hand, HPAs do not dissolve in nonpolar solvents (chlorinated solvents), thus the iodination reaction takes place in a heterogeneous system. HPAs have very high solubility in polar solvents such as water, lower alcohols, ketones, ethers, esters, etc. They absorb a large amount of polar solvents not only on the surface, but also in the bulk of crystalline HPA, forming heteropoly acid solvates (14). Consequently, a homogeneous system exists. Therefore, the iodination reaction in ethyl acetate and MeOH takes place in homogeneous conditions (Table 3, entries 11 and 12). The formation of a by-product can result from high catalytic activity in homogeneous conditions. For relatively polar solvents, we can expect heterogeneous bulk-type (pseudoliquid) catalysis conditions (Table 3, entries 7–10).

According to the results obtained from effects of catalyst, metal nitrate, and solvent, our method is suitable for the iodination of arenes. The aromatic compounds were converted to the corresponding monoiodoaromatic compounds at room temperature in good yields with excellent regioselectivities for 8–24 h. The results of this study are shown in Table 4.

The iodination occurred at a less sterically hindered position. As anticipated, *o*-iodination occurred only when the para position was occupied. In the present method, the formation of a nitro derivative was not observed in spite of increasing reaction time. Our investigation showed that the electron-releasing substituents increased the rate of reaction and yield; however, the electron-attracting groups decreased the rate of reaction and yield of iodination. Aromatic compounds, such as acetanilide, aniline, and phenol, were converted to the corresponding monoiodoproducts in good

Table 3. Iodination of anisole with $Fe(NO_3)_3 \cdot 9H_2O$ in the presence of $H_3PW_{12}O_{40}$ in various solvents at room temperature for 8 h.

Entry	Solvent	Conv. (%)	GC yield (%) ^a
1	0^b	35	>33
2	0^c	100	58, 40^d
3	CH_2Cl_2	100	>99
4	ClCH ₂ CH ₂ Cl	99	>97
5	CHCl ₃	94	93
6	CCl_4	94	92
7	Et ₂ O	33	32
8	THF	32	31
9	DMF	13	12
10	DMSO	31	30
11	Ethyl acetate	98	61, 37 ^d
12	MeOH	46	28, 18 ^d

Note: Reaction conditions: anisole (1 mmol), I_2 (0.6 mmol), Fe(NO₃)₃·9H₂O (0.4 mmol), H₃PW₁₂O₄₀ (0.1 mmol), solvent (1 mL).

^aProduct: 4-IC₆H₄OMe.

^bSolventless for 1 h.

^cSolventless for 2 min and microwave irradiation (200 W).

^{*d*}By-product: 2-IC₆H₄OMe.

yields (Table 4, entries 6–9). Xylenes and toluene were converted to iodo derivatives in relatively good yields (Table 4, entries 10–12), but activated naphthalenes were converted to diiodinated derivatives (Table 4, entries 13 and 14). Finally, this method is only suitable and effective for activated aromatic compounds.

Conclusion

The present method is very simple, cheap, effective, and selective for iodination of electron-rich aromatic compounds, which when carried out under mild conditions and ambient temperature by tungstophosphoric acid, is an effective, readily available, recoverable, reusable, and low-cost catalyst.

Experimental

Chemicals were purchased from Fluka and Merck. Organic solvents were purified and dried by the procedures extracted from Vogel's textbook of practical organic chemistry (5th ed. John Wiley and Sons, New York. 1991). $H_{3}PW_{12}O_{40}$, $H_{3}PMo_{12}O_{40}$, Cs_{2.5}H_{0.5}PMo₁₂O₄₀, and (NH₄)₂HPW₁₂O₄₀ were purchased from Merck and were purified by extraction with Et₂O from aqueous solutions of the acids, and dried and dehydrated by evacuating at 150-300 °C for 1 to 2 h. These HPAs can be prepared according to the known procedures (15). Some solid HPAs and their salts, such as $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, $Fe_{0.85}H_{0.45}PMo_{12}O_{40}$, and $H_6P_2Mo_{18}O_{62}$, were prepared according to the reported methods (16) in our laboratory.

General reaction procedure

To iodine (0.6 mmol, 0.152 g) in dichloromethane (1 mL), iron nitrate (0.4 mmol, 0.161 g) and then $H_3PW_{12}O_{40}$ (0.1 mmol, 0.288 g) were added. After 10 min, arene (1 mmol) was added and the reaction mixture was stirred at room temperature for 8–24 h. The completion of the reaction

Entry	Substrate	Time (h)	Product	Yield (%) ^a
1	C ₆ H ₅ OMe	8	4-IC ₆ H ₄ OMe	92
2	$1,3-(MeO)_2C_6H_4$	2	4-I-1,3-(MeO) ₂ C ₆ H ₃	76^{b}
			2-I-1,3-(MeO) ₂ C ₆ H ₃	23^{b}
3	2-MeC ₆ H ₄ OMe	10	4-I-2-MeC ₆ H ₃ OMe 90	
4	4-MeC ₆ H ₄ OMe	13	2-I-4-MeC ₆ H ₃ OMe	75
5	2-BrC ₆ H ₄ OMe	24	4-I-2-BrC ₆ H ₃ OMe	46
6	C ₆ H ₅ NHCOMe	12	4-IC ₆ H ₄ NHCOMe	78
7	C ₆ H ₅ NH ₂	12	$4-IC_6H_4NH_2$	82
8	$2-NO_2C_6H_4NH_2$	24	4-I-2-NO ₂ C ₆ H ₃ NH ₂	9
9	C ₆ H ₅ OH	10	4-IC ₆ H ₄ OH	79
10	$1,2-(Me)_2C_6H_4$	20	4-I-1,2-(Me) ₂ C ₆ H ₃	40
11	$1,4-(Me)_2C_6H_4$	24	2-I-1,4-(Me) ₂ C ₆ H ₃	34
12	C ₆ H ₅ Me	12	4-IC ₆ H ₄ Me	59
13	$1-MeOC_{10}H_7$	6	4-I-1-MeOC ₁₀ H ₆	84^{b}
			2-I-1-MeOC ₁₀ H ₆	16^{b}
14	$2-MeOC_{10}H_7$	6	1-I-2-MeOC ₁₀ H ₆	76^{b}
			$3-I-2-MeOC_{10}H_6$	10^{b}

Table 4. Iodination of various arenes with $Fe(NO_3)_3 \cdot 9H_2O$ catalyzed by $H_3PW_{12}O_{40}$ in CH_2Cl_2 at room temperature.

Note: Reaction conditions: substrate (1 mmol), I_2 (0.6 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (0.4 mmol), $H_3PW_{12}O_{40}$ (0.1 mmol), CH_2CI_2 (1 mL).

^aIsolated yield.

^bGC yield.

was monitored by TLC and GC. After the usual work-up of the reaction mixture with Na_2SO_3 (25 mL, 5%), the crude product was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried over MgSO₄ and filtered, the crude product was purified by column chromatography on silica gel (petroleum ether – ethyl acetate, 5:1). All products are well-known in the literature. The products were identified by the comparison of their mp and IR data with those reported for the authentic samples in the literature.

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