

An Efficient, Catalytic, Aerobic, Oxidative Iodination of Arenes Using the $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ Polyoxometalate as Catalyst

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Abstract: Iodination of arenes was carried out by reacting 1 equiv of arene substrate with 0.5 equiv of iodine under an oxygen atmosphere with $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ as oxidation catalyst. The synthesis is an inherently waste-free method for the preparation of iodoarenes.

Iodine-substituted aromatic compounds are important and the most reactive intermediates for various cross-coupling reactions and especially useful for formation of carbon-carbon and carbon-heteroatom bonds.¹ Iodoarenes can be synthesized from bromo- or chloroarenes using BuLi and then iodine or via the Sandmeyer reaction from aromatic amines. However, direct iodination of arenes is logically and therefore a priori more attractive, but such preparations are not straightforward since iodination reactions of arenes with molecular iodine are only weakly catalyzed by Lewis acids as opposed to the analogous chlorination and bromination reactions. Thus, direct iodination of arenes requires the oxidation of iodine to the more reactive species with a pronounced I^+ character. Broadly speaking, many oxidizing reagents for iodine have been considered for formation of I^+ like species either in situ or as stable isolable intermediates.² Some examples, mostly postdating a comprehensive review,² include nitric acid/sulfuric acid,² iodic or periodic acid,³ diiodine pentaoxide,⁴ silver salts such as silver trifluoroacetate,⁵ alumina,⁶ bis(pyridine)iodonium(I) tetrafluoroborate,⁷ lead(IV) acetate,⁸ bis(trifluoroacetoxy)-iodobenzene,⁹ cerium ammonium nitrate,¹⁰ and fluorine and xenon difluoride.¹¹ All these methods, while synthetically effective, have the obvious disadvantage that

at least stoichiometric amounts of oxidizing agent are needed leading to formation of significant amounts of waste. A slightly less problematic solution is to use sodium hypochlorite as oxidant to form quaternary ammonium ICl_2^- salts that are effective electrophilic iodination reagents.¹² Here, the byproducts are sodium chloride formed both in the preparation of the ICl_2^- salts and the iodination reaction and quaternary ammonium chlorides that in principle could be recycled.

A preferred iodination technique would espouse the use of molecular oxygen as the oxidant for formation of the active iodination species. Such a procedure is possible by use of a pertinent polyoxometalate, $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$, as catalyst for the aerobic oxidative iodination as presented in Scheme 1. As is observable from Scheme 1, such a synthetic method is inherently waste-free. It is notable that in the past the $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ polyoxometalate has often been similarly used for aerobic oxidation whereby the oxidation of the substrate occurs by electron transfer and the reduced polyoxometalate is reoxidized by oxygen.¹³

The typical procedure for the catalytic aerobic iodination of relatively activated arenes involves the reaction of 1 equiv of the arene substrate with 0.5 equiv of iodine and a catalytic amount, 1 mol %, of $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$ in acetonitrile under O_2 . The results are presented in Table 1. First, concerning reactivity one may observe that the reaction conversions were high with very good to excellent selectivity to the monoiodination product. Second, the yields in iodine were nearly quantitative in all cases; therefore, there is very little waste product produced in these reactions. Third, there was relatively high regioselectivity observed in the iodination reactions. Thus, anisole, 1,2-dimethoxybenzene, 1-methoxynaphthalene, and phenol gave almost exclusive iodination at the para position; aniline also showed relatively high para selectivity. Thiophene and benzothiophene were iodinated mostly at the 2-position. Notable also is the observation that $\text{V}(\text{O})(\text{acac})_2$ was not an active catalyst; only traces of product were found in the iodination of anisole.

It would appear from the results above that the iodination procedure is limited to the more activated arenes. However, by using nitrobenzene as solvent instead of acetonitrile, higher temperatures, and somewhat longer reaction times, reactivity for less reactive arenes significantly increased, Table 2, thus extending

(1) *Metal-Catalyzed Cross-coupling Reactions*, Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1997.

(2) Merkushev, E. B. *Synthesis* **1988**, *10*, 923–937.

(3) (a) Mattern, D. L. *J. Org. Chem.* **1984**, *49*, 3051–3053. (b) Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 951–956. (c) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128–131.

(4) Brazdil, L. C.; Cutler, C. J. *J. Org. Chem.* **1996**, *61*, 9621–9622.

(5) (a) Barnett, J. R.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 6129–6134. (b) Wing-Wah, S.; Lodge, B. A. *Tetrahedron Lett.* **1989**, *30*, 3769–3772.

(6) Pagni, R. M.; Kabalka, G. W.; Boothe, R.; Gaetano, K.; Stewart, L. J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhardt, T. *J. Org. Chem.* **1988**, *53*, 4477–4482.

(7) Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058–2060.

(8) Krassowska-Swiebocka, B.; Lulinski, P.; Skulski, L. *Synthesis* **1995**, *8*, 926–928.

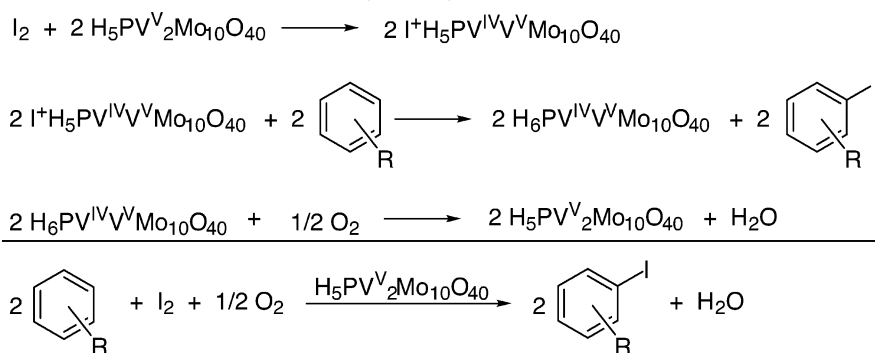
(9) Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis* **1980**, *6*, 486–487.

(10) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928–4933.

(11) (a) Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552–3555. (b) Shellhamer, D. F.; Jones, B. C.; Pettus, B. J.; Petts, T. L.; Stringer, J. M.; Heasley, V. L. *J. Fluorine Chem.* **1998**, *88*, 37–39.

(12) (a) Kosynkin, D. V.; Tour, J. M. *Org. Lett.* **2001**, *3*, 991–992. (b) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600–602. (c) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. *Chem. Lett.* **1987**, 2109–2122. (d) Custelceanu, R.; Vlassa, M.; Silberg, I. A. *Monatsh. Chem.* **1997**, *128*, 919–925. (e) Hajipour, A. R.; Arabian, M.; Ruoho, A. E. *J. Org. Chem.* **2002**, *67*, 8622–8624. (f) Wariishi, K.; Morishima, S.-I.; Inagaki, Y. *Org. Process Res. Dev.* **2003**, *7*, 98–100.

(13) (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171–198. (b) Kozhevnikov, I. V. *Catalysis by Polyoxometalates*; Wiley: Chichester, England, 2002. (c) Neumann, R. *Prog. Inorg. Chem.* **1998**, *47*, 317–370. (d) Hill, C. L.; Prosser-McCartha, C. M. *Coord. Chem. Rev.* **1995**, *143*, 407–455. (e) Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113–252.

SCHEME 1. Aerobic Iodination of Arenes Catalyzed by H₅PV₂Mo₁₀O₄₀**TABLE 1. Iodination of Activated Arenes Catalyzed by H₅PV₂Mo₁₀O₄₀^a**

substrate	product	conversion, ^b mol %	selectivity, ^c mol %
anisole	4-iodoanisole	98	99.5
1,2-dimethoxybenzene	4-iodo-1,2-dimethoxybenzene	96	98
1,3-dimethoxybenzene	4-iodo-1,2-dimethoxybenzene, 2-iodo-1,3-dimethoxybenzene	86	87, 9
1,4-dimethoxybenzene	2-iodo-1,4-dimethoxybenzene	97	92
4-methylanisole	2-iodo-4-methylanisole	96	100
aniline	4-iodoaniline, 2-iodoaniline	89	83, 12
phenol	4-iodophenol, 2-iodophenol	100	98, 2
1,3,5-trimethylbenzene	2-iodo-1,3,5-trimethylbenzene	91	100
1,4-dimethylbenzene	2-iodo-1,4-dimethylbenzene	11, 99 ^d	100
thiophene	2-iodothiophene	80	66 ^e
benzothiophene	2-iodo-benzothiophene, 3-iodo-benzothiophene	94	85, 3
1-methoxynaphthalene	4-iodo-1-methoxynaphthalene	99	98
2-methoxynaphthalene	1-iodo-2-methoxynaphthalene	92	100

^a Reaction conditions: 1 mmol of substrate, 0.01 mmol of H₅PV₂Mo₁₀O₄₀, 0.5 mmol of I₂ 2 atm of O₂, 1 mL of acetonitrile in a 15 mL glass pressure tube, 80 °C, 8 h. Analysis by GC and GC-MS on a Restek Rtx-5MS column (30 m × 0.32 mm with a 0.25 μm 5% phenyl, 95% methysilicone coating) and by ¹H NMR carrying out the reactions in CD₃CN. ^b mol % of substrate reacted. ^c mol % of product of all products; the remaining products were diiodinated arenes. ^d Reaction was carried out in nitrobenzene instead of acetonitrile. ^e 2,5-Diiodothiophene was the other product.

TABLE 2. Iodination of Nonactivated Arenes Catalyzed by H₅PV₂Mo₁₀O₄₀^a

substrate	product	conversion, ^b mol %	selectivity, ^c mol %
toluene	4-iodotoluene, 2-iodotoluene	>99	85, 15
biphenyl	4-iodobiphenyl, 4,4'-diiodobiphenyl	85	80, 20
naphthalene	1-iodonaphthalene	72	100
bromobenzene	1-bromo-4-iodobenzene, 1-bromo-2-iodobenzene	91	81, 19
chlorobenzene	1-chloro-4-iodobenzene, 1-chloro-2-iodobenzene	92	80, 20

^a 1 mmol of substrate, 0.01 mmol of H₅PV₂Mo₁₀O₄₀, 0.5 mmol of I₂ 2 atm of O₂, 1 mL of nitrobenzene in a 15 mL glass pressure tube, 120 °C, 36 h. Analysis by GC and GC-MS on a Restek Rtx-5MS column (30 m × 0.32 mm with a 0.25 μm 5% phenyl, 95% methysilicone coating) and by ¹H NMR carrying out the reactions in C₆D₅NO₂. ^b mol % of substrate reacted. ^c mol % of product of all products; the remaining products were diiodinated arenes.

the synthetic utility of the technique. As for the more activated arenes, also in this case high yields, selectivity to monoiodoarenes and high regioselectivity were attained.

Since the H₅PV₂Mo₁₀O₄₀ polyoxometalate is both a strong Brønsted acid and an oxidizing agent, there are two possible general explanations for the catalytic activity of H₅PV₂Mo₁₀O₄₀. The first explanation is based on the possible polarizing effect of H₅PV₂Mo₁₀O₄₀ on molecular iodine leading to a I^{δ+}-I^{δ-}-type intermediate, which after reaction with the arene substrate would yield the

iodinated arene and HI. Conceivably, the HI species could then be oxidized by H₅PV₂Mo₁₀O₄₀ in a catalytic manner so as to yield more I₂. Alternatively, as presented in Scheme 1, the molecular iodine is directly oxidized to two I⁺-type species that react with the arene substrate. To differentiate between these two possible generalized mechanistic pathways, comparative reactions were performed with anisole as model substrate as summarized in Figure 1. Comparison of the results of the iodination reaction without catalyst with those using the non-oxidizing acids, H₂SO₄ and H₃PW₁₂O₄₀ clearly shows that

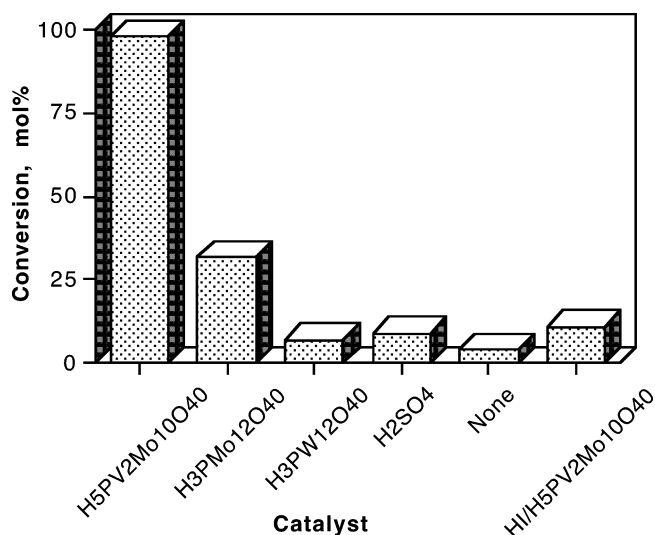


FIGURE 1. Iodination of anisole under different reactions conditions: 1 mmol of anisole, 0.01 mmol of catalyst, 0.5 mmol of I₂, 2 atm of O₂, 1 mL of acetonitrile, 80 °C, 8 h. For entry HI/ H₅PV₂Mo₁₀O₄₀, 1 mmol of HI was used instead of I₂.

there is no significant acid catalysis for the iodination with I₂. Furthermore, the finding that the use of HI in

place of I₂ with H₅PV₂Mo₁₀O₄₀ as catalyst did not yield significant iodination also argues strongly against the formation and then oxidation of I⁻. This indicates that the formation of an active electrophilic iodine species is very sluggish from HI and H₅PV₂Mo₁₀O₄₀. In fact, the limited activity of HI is somewhat surprising since more difficult to oxidize HBr has been used as a brominating agent in the presence of H₅PV₂Mo₁₀O₄₀ and oxygen.¹⁴ Clearly, strongly oxidizing H₅PV₂Mo₁₀O₄₀ is the most active catalyst; H₃PMo₁₂O₄₀ is also oxidizing but the well-known slower reoxidation of the reduced species limits the reaction.¹³

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Supporting Information Available: A detailed Experimental Section. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Neumann, R.; Assael, I. *J. Chem. Soc., Chem. Commun.* **1988**, 1285–1287.