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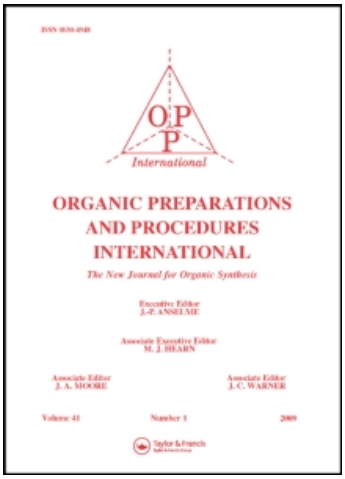

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METHYLTRIPHENYLPHOSPHONIUM PEROXYDISULFATE AND IODINE AS MILD REAGENTS FOR THE IODINATION OF ACTIVATED AROMATIC COMPOUNDS

Abdol R. Hajipour[ab]; A. E. Ruoho[b]
[a] Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan, IRAN [b] Department of Pharmacology, University of Wisconsin Medical School, Madison, WI, USA

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METHYLTRIPHENYLPHOSPHONIUM PEROXYDISULFATE AND IODINE AS MILD REAGENTS FOR THE IODINATION OF ACTIVATED AROMATIC COMPOUNDS

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Submitted by (02/24/05)

Abdol R. Hajipour*[†, ††] and A. E. Ruoho[††]

[†] *Pharmaceutical Research Laboratory, College of Chemistry Isfahan University of Technology, Isfahan 84156, IRAN*

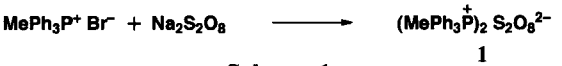
[††] *Department of Pharmacology, University of Wisconsin Medical School 1300 University Avenue, Madison, WI 53706-1532, USA*

e-mail: haji@cc.iut.ac.ir

Aromatic iodides have been widely used in radiolabeling studies, and as synthetic intermediates in the formation of new carbon-carbon or carbon-heteroatom bonds *via* replacement of their iodine atoms with electrophiles.[1] Despite the importance of iodoarenes, there are few good methods in the literature for the iodination of aromatic compounds. Conventional methods for aromatic iodination involve the use of molecular iodine together with highly toxic heavy metal compounds, or mineral acids which are undesirable from the environmental point of view.[2] Other methods for iodination of aromatic compounds[3-12] involve environmental hazards such as handling and storage of molecular iodine, strongly acidic conditions, expensive and complex catalysts, toxic metallic compounds and the use of oxidizing reagents that are difficult to prepare.

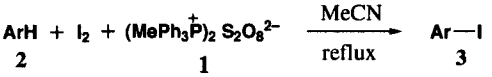
In connection with our ongoing program to develop new reagents for iodination of aromatic compounds,[13] we herein report an efficient method for the iodination of activated

aromatic compounds with methyltriphenylphosphonium peroxydisulfate (**MTPPS**) (**1**). This reagent is readily prepared in high yield by dropwise addition of an aqueous solution of sodium persulfate to an aqueous solution of methyltriphenylphosphonium bromide at room temperature. Filtration and drying of the precipitate produced a white powder which is quite stable and can be stored at room temperature in the absence of light for months without loss of its activity. It is soluble in polar solvents such as methanol, THF, acetonitrile, acetone, DMF and DMSO, but insoluble in solvents such as carbon tetrachloride, hexane, and diethyl ether (*Scheme 1*).



Scheme 1

This paper reports the iodination of various activated aromatic compounds with reagent **1** as oxidizing agent and iodine as iodinating reagent in refluxing acetonitrile in good to excellent yields. Activated aromatic compounds **2** were converted to the corresponding iodoaromatic compounds **3** in excellent yields in 0.5-2.0 hrs (*Scheme 2* and *Table*). Iodination of aromatic



Scheme 2

Table 1. Iodination of Aromatic Compounds **2** with Reagent **1** to Iodoarenes **3** [a, b]

Entry	Ar-H	Ar-I	Time (hr)	Yield[c] (%)	mp/°C (*lit.*)[13]
1	C_6H_5OMe	4-I-C_6H_4OMe	0.4	94	50-53 (51-52)[13a]
2	1,2-$(MeO)_3C_6H_4$	4-I-1,2-$(MeO)_2C_6H_3$	0.4	91	77-78 (75-76)[13b]
3	$C_6H_5NHCOMe$	4-I-$C_6H_4NHCOMe$	2.0	83	184-186 (188-189)[13a]
4	1,3,5-$(Me_3)C_6H_3$	2-I-1,3,5-$(Me_3)C_6H_2$	3.0	80	30-32 (29-30)[14]
5	Biphenyl	4-Iodobiphenyl	3.0	78	114-115 (113-114)[13b]
6	4-$MeC_6H_4NO_2$	2-I-4-$MeC_6H_3NO_2$	12	80	54-56 (54-56)[13a]
7	4-$NH_2C_6H_4(CH_2)_2COOH$	3-I-4-$NH_2C_6H_3(CH_2)_2COOH$	4	82	242-243 (242-243)[13a]
8	(-)-4-Aminobenzoyl-ecgonine methyl ester	(-)-3-Iodo-4-aminobenzoyl-ecgonine methyl ester	4	83	195-198 (195-198)[13a]
9	1-Methoxynaphtalene	4-Iodo-1-methoxynaphtalene	0.4	90	52-53 (52-53)[14]
10	2-Methoxynaphtalene	1-Iodo-2-methoxynaphtalene	0.4	98	85-87 (82-84)[14]
11	Aniline	4-Iodoaniline	0.3	96	62-64 (63-65)[13b]
12	4-(*tert*-Butyl)aniline	2-Iodo-4-(*tert*-butyl)aniline	0.3	80	Oil[14]
13	4-Nitroaniline	2-Iodo-4-nitroaniline	0.5	90	105-106 (98-100)[14]

a) Confirmed by comparison with authentic samples (IR, TLC, and NMR).[13] b) Molar ratio of **1**:**2** (1:1). c) Yield of isolated product after purification

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compounds with this reagent occurred rapidly under refluxing conditions, without the use of base or toxic heavy metal. The procedure was successfully scaled-up to afford multigram quantities of 4-iodoanisole, and 3-(3-iodo-4-aminophenyl)propionic acid.

In summary, methyltriphenylphosphonium peroxydisulfate (**MTPPS, 1**) is a mild and inexpensive oxidation reagent which can be used for the efficient iodination of activated aromatic compounds with molecular iodine.

EXPERIMENTAL SECTION

Mps were determined on a Gallenkamp melting point apparatus and are uncorrected. Products were characterized by comparison with authentic samples (IR and ^{1}H NMR spectra, TLC, melting and boiling points).[15] All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and CD_3CN relative to TMS. The IR spectra were obtained as KBr pellets on a Shimadzu 435 IR spectrophotometer.

Preparation of Methyltriphenylphosphonium Peroxydisulfate.- A solution of sodium persulfate (11.9 g, 50 mmol) in 100 mL of water was added to a solution of methyltriphenylphosphonium bromide (35.6, 100 mmol) and stirred for 30 min at room temperature The resulting white precipitate was collected and washed with cold distilled water (2 x 50 mL) and dried in a desiccator under vacuum over calcium chloride to afford a white powder (35.1, 94% yield), which decomposed at 210-212°C to a dark-brown material. IR (KBr): 3100, 2980, 1600, 1495, 1480, 1260,1190, 1050, 860, 750, 690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.9-7.7 (m, 15 H), 3.19 (d, J = 14.6, P-$\underline{CH_3}$). ^{13}C NMR: δ 134.5, 134.4, 132.5, 132.3, 129.7, 129.3, 116.4.

Anal. Calcd for $C_{38}H_{36}O_8P_2S_2$: C: 61.13; H: 4.83; S: 8.58. Found C: 61.20; H, 4.90. S, 8.40

Iodination of Aromatic Compounds (2) to the Corresponding Iodoaromatic Derivatives (3). General Procedure.- In a round-bottomed flask containing the aromatic compounds **2** (5.0 mmol) in CH_3CN (25 mL) were added reagent **1** (3.73 g, 5.0 mmol) and iodine (1.27 g, 5 mmol). The reaction mixture was heated at reflux for the time specified in *Table 1*. When TLC (hexane/EtOAc, 80:20) showed complete disappearance of the starting aromatic compounds **2**, the solvent was evaporated to give a brown residue. It was dissolved in CH_2Cl_2 (30 mL) and washed with 5% aqueous sodium bisulfate (2 x 10 mL) and the organic layer was dried with $MgSO_4$ and evaporation of the solvent gave the corresponding iodoaromatic derivatives (**3**). The product was purified by column chromatography on silica gel using a mixture of hexane/EtOAc (80:20).

Iodination of Anisole: Colorless solid, mp 50-53°C. ^{1}H NMR: δ 7.35 (d, 2H), 6.45 (d, 2H), 3.85 (s, 3H). ^{13}C NMR: δ 142.81, 136.25, 129.36, 126.65, 112.86, 68.70. MS: *m/z*, 234.22 (100%, M$^+$), 108 (100%), 77 (8%), 65 (65%).

Anal. Calcd for C_7H_7IO: C, 35.90; H, 2.99. Found: C, 35.70; H, 3.20

3-(3-Iodo-4-aminophenyl)propionic Acid: Colorless solid, mp 242-243°C. ^{1}H NMR: δ 10.2 (s, 1H), 6.7-7.3 (m, 3H), 3.18 (s, 2H), 2.98 (t, 2H), 2.58 (t, 2H). ^{13}C NMR: δ 179.61, 146.51,

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140.19, 128.59, 126.41, 119.48, 33.68, 30.59. MS: *m/z*, 301.52 (100%, M^+), 289 (100%), 150 (90%), 104 (80%), 93 (100%), 77 (65%), 66 (30%), 51 (25%), 39 (15%).

Anal. Calcd for $C_9H_{10}INO_2$: C, 35.88; H, 3.32; N, 4.65. Found: C, 35.69; H, 3.44; N, 4.58

4-Amino-3-iodo-benzoylecgonine Methyl Ester: yellow solid, mp 195-198°C. 1 H NMR: δ 8.32 (d, J = 1.8, 1 H), 7.80 (dd, J = 1.8, 8.4 1 H), 6.69 (d, J = 8.4, 1 H), 5.25 (m, 1 H), 4.50 (br, 2 H, NH2), 3.74 (s, 3 H, OMe), 3.60 (m, 1 H), 3.32 (m, 1 H), 3.07 (m, 1 H), 2.24 (s, 3 H, NMe), 2.46-1.2 (m, 7 H). 13C NMR: δ 175, 170, 150, 135, 132, 128, 126.3, 126.0, 68.4, 66.23, 61.78, 50.92, 50.22, 41.31, 35.68, 25.79, 25.50. MS: m/z, 445 (100%, M+ + 1), 182 (92%), 96 (95%), 94 (75%), 82 (80%), 77 (65%), 66 (30%), 51 (25%), 39 (15%).

Anal. Calcd. for $C_{17}H_{21}IN_2O_4$: C, 45.95; H, 4.73; N, 6.31. Found: C, 45.862; H, 4.85; N, 6.24

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A PRACTICAL LARGE-SCALE PREPARATION OF 5'-BROMOSPIRO(CYCLOHEXANE-1,3'-[3H]INDOL)-2'(1'H)-ONE

Submitted by (03/30/05) Bogdan K. Wilk*, Arkadiy Rubezhov, Jean L. Helom, Lisa R. Routel, and John R. Potoski

Wyeth Research, Chemical Development
401 N. Middletown Road, Pearl River, NY 10965
e-mail: wilkb@wyeth.com

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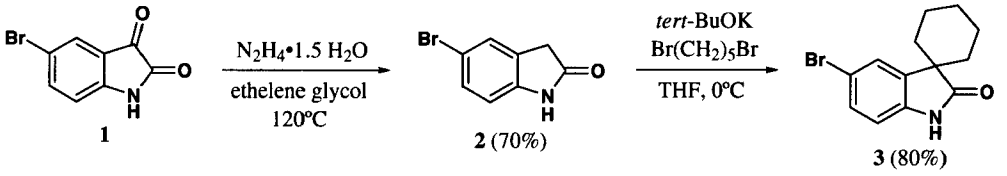
We were interested in a large-scale preparation of 5'-bromospiro(cyclohexane-1,3'-[3H]indol)-2'(1'H)-one (**3**), an intermediate in the synthesis of progesterone receptor modulators.[1] Initially, the compound was prepared from oxindole using the Kende procedure[2a] by alkylation followed by bromination with bromine in acetic acid/chloroform.[3] Unfortunately, this sequence gave multiple impurities in the alkylation product.[1a,4] On large scale, this was a serious problem and we had to resort to chromatography and recrystallization.[5] The subsequent bromination had to be carefully controlled to avoid over-bromination. In addition, brominated impurities were formed from the side-products generated in the alkylation step.



The regioselectivity and purity problems were overcome by simply changing the order of transformations, *i. e.* introduction of bromine in the oxindole core followed by alkylation of 5-bromooxindole (**2**),[3,6] which was prepared from inexpensive, technical grade 5-bromoisatin (**1**).[7] It was found that *n*-butyllithium could be replaced with potassium *tert*-butoxide and 1,5-diiodopentane with the more stable 1,5-dibromopentane at 0°C in tetrahydrofuran (THF) in the alkylation step.[8] In comparison to the initial sequence, the reaction was clean and the product crystallized out upon replacement of THF with acetonitrile.[9]