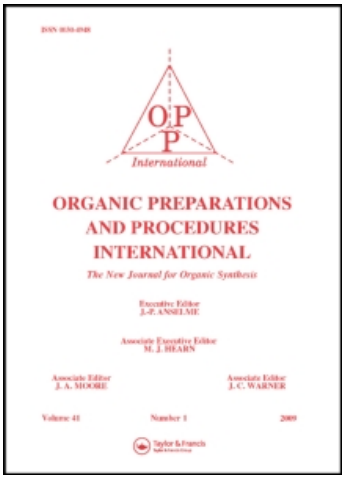

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IODINATION OF AROMATIC COMPOUNDS UNDER MILD AND SOLVENT-FREE CONDITIONS

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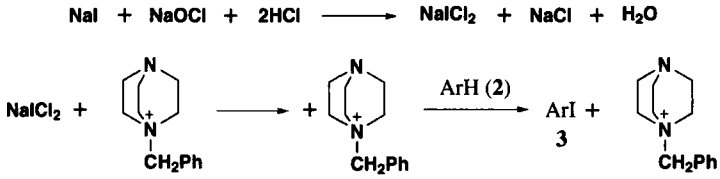
Iodobenzene derivatives are valuable and versatile intermediates which have found wide applications in medicine and biochemistry.[1] However, iodine is a weaker electrophile compared to bromine and chlorine. For this and other reasons (*e. g.*, electrophilic iodination generates hydrogen iodide, which is both a strong reducer and a strong acid and can cause protolytic cleavage of Ar-I), there are only a few known methods available for direct iodination of aromatic compounds[1-6] in which the hydrogen iodide generated is scavenged with mercuric oxides, alkalis, or pyridine,[7] or destroyed by the addition of various oxidants.[8]

Reaction under solvent-free conditions have received increasing attention in recent years. The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulation.[9-11] In connection with our ongoing program to develop environmentally benign methods using solvent-free conditions,[12] we herein report an extremely convenient method for the iodination of activated and deactivated aromatic compounds with 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane dichloroidate (BAABOD, **1**) under solvent-free conditions. The readily prepared reagent (see Experimental Section) is a yellow powder, which is stable and can be stored at room temperature in a dark bottle for months without loss of activity; it is soluble in polar solvents such as methanol, THF, acetonitrile, acetone, DMF, chloroform, ethyl acetate, and dichloromethane, but insoluble in solvents such as carbon tetrachloride, *n*-hexane, and diethyl ether.

The process involves simple mixing of the aromatic compound and reagent **1** in a mortar and grinding the mixture with a pestle to produce a homogenous powder, then allowing the mixture to stand for the specified time (*Table*) at room temperature. This reaction proceeds rapidly and purification of products is very simple. The iodination of activated aromatic compounds **2** proceeded readily (10-25 min) in excellent yields, while deactivated aromatic compounds required 35-45 min at room temperature (*Table*). The reagent does not affect oxidizable groups, such as hydroxy, aldehyde, or amino. The iodination was successfully scaled-up to afford multigram quantities of 4-iodoaniline, 4-iodoanisole and 3-(3-iodo-4-aminophenyl)propionic acid.



Scheme 1

After extraction of the iodoaromatic compounds, the aqueous layer was acidified with 10% HCl and treated with a fresh bath of the aqueous dichloroiodate to regenerate the reagent **1** in quantitave yield. Since as mentioned earlier, acidic conditions are not suitable for electrophilic iodination. Therefore the unique property of this reagent is pehaps due to the fact that the HCl generated during the reaction is intercepted by the second nitrogen of this reagent, thus allowing the reaction to proceed under neutral conditions.

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

Entry	Ar-H	Ar-I	Time (Min)	Yield (%)[c]	mp/°C or bp/°C /torr (*lit.*)
1	C_6H_5OMe	$4\text{-}IC_6H_4OMe$	10	98	50-53 (51-52)[5]
2	$C_6H_5NH_2$	$4\text{-}IC_6H_4NH_2$	10	87	63-65 (62.5-63)[13]
3	$4\text{-}MeC_6H_4NH_2$	$2\text{-}I\text{-}4\text{-}MeC_6H_3NH_2$	12	94	45-47 (40)[14]
4	$3\text{-}ClC_6H_4NH_2$	$4\text{-}I\text{-}3\text{-}ClC_6H_3NH_2$	12	92	64-66 (64-66)[3]
5	$1,2\text{-}(MeO)_2C_6H_4$	$4\text{-}I\text{-}1,2\text{-}(MeO)_2C_6H_3$	10	100	77-78 (75-76)[5]
6	$C_6H_5NH_2COMe$	$4\text{-}IC_6H_4NH_2COMe$	15	98	184-186 (188-189)[13]
7	ClC_6H_5	$4\text{-}I\text{-}ClC_6H_4$	25	90	58-60 (56-57)[15]
8	$4\text{-}MeOC_6H_4CH_2OH$	$3\text{-}I\text{-}4\text{-}MeOC_6H_4CH_2OH$	10	91	142-144
9	$4\text{-}CHOC_6H_4OH$	$2\text{-}I\text{-}4\text{-}CHOC_6H_3OH$	18	98	113-115 (113-115)[16]
10	$1,3,5\text{-}C_6H_5(CH_3)_3$	$2\text{-}I\text{-}1,3,5\text{-}C_6H_2(CH_3)_3$	25	89	30-32 (29-30)[3]
11	PhC_6H_5	$4\text{-}I\text{-}PhC_6H_4$	25	87	114-115 (113-114)[17]
12	$C_6H_5NO_2$	$3\text{-}IC_6H_4NO_2$	45	50	35-37 (34-36)[1]
13	$4\text{-}MeC_6H_4NO_2$	$3\text{-}I\text{-}4\text{-}MeC_6H_3NO_2$	35	68	54-56 (54-56)[1]
14	C_6H_5CHO	$3\text{-}IC_6H_4CHO$	40	83	55-57 (54-56)[1]
15	$C_6H_5CO_2H$	$3\text{-}IC_6H_4COOH$	45	75	186-188 (188-189)[1]
16	C_6H_5COPh	$3\text{-}IC_6H_4COPh$	35	80	40-42 (41-42)[18]
17	$4\text{-}NH_2C_6H_4CO_2H$	$3\text{-}I\text{-}4\text{-}NH_2C_6H_3CO_2H$	25	86	203-205 (203-204)[19]
18	$4\text{-}NH_2C_6H_4(CH_2)_2CO_2H$	$3\text{-}I\text{-}4\text{-}NH_2C_6H_3(CH_2)_2CO_2H$	10	100	242-243

a) Confirmed by comparison with authentic samples (IR, TLC and NMR).[1-8, 13-19] b) Molar ratio of **1:2** (1:1). c) Yield of isolated pure product after purification

To compare the efficiency of this reagent under solid-state conditions and in solution, the reaction of 3-(4-aminophenyl)propionic acid was performed in several solvents, such as methanol, acetone, ether, dichloromethane, and acetonitrile. Although it was determined that acetonitrile was the best solvent for this reaction, 3-(4-aminophenyl)propionic acid with an equimolar amount of this reagent, gave only a 15% yield and several by-products after 24 h reflux. Increasing the amount of the iodination agent to a two molar ratio, failed to increase the yield of the reaction. It was thought that the low yield of the reaction might be increased under non-acidic conditions; however, when 3-(4-aminophenyl)propionic acid was treated with a 1.5 molar ratio of the iodination agent in the presence of a one molar ratio of $NaHCO_3$, 3-(4-amino-3-iodophenyl)propionic acid was produced in only 40% yield after 14 hour refluxing in a mixture of acetonitrile/methanol (1:1).

EXPERIMENTAL SECTION

All yields refer to isolated products after purification by column chromatography. Products were characterized by comparison with authentic samples (IR and ^{1}H-NMR spectra, TLC, melting and boiling points).[1-8, 13-19] All ^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$ and CD_3CN relative to TMS. The IR (KBr) spectra were recorded on a Shimadzu 435 IR spectrophotometer. All reactions were carried out under solid-state conditions at room temperature.

Preparation of 1-Benzyl-4-Aza-1-Azoniabicyclo[2.2.2]Octane Dichloroiodate (1, BAABOD).- To a stirred solution of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride[12i] (26.2 g, 110 mmol) in 100 of water was added to an orange solution of $NaICl_2$ (110 mmol) [prepared from 6% NaOCl (136 mL) or 5.25% NaOCl (156 mL), NaI (110 mmol, 16.5 g), 37% HCl (220 mmol, 22 mL) at 0° and stirred for 20 min at room temperature]. The resulting yellow precipitate was collected and washed with cooled distilled water (2 x 50 mL), and ether 2 x 50 mL) and dried in a desiccator under vacuum over calcium chloride to afford a yellow powder (41.9 g, 104.5 mmol, 95% yield), which decomposed at 210-212° to a dark-brown material. ^{1}HNMR ($CDCl_3$, TMS): δ 7.68 (s, 5H); 4.62 (s, 2H); 3.6-2.9 (two overlapping triplets, 12H).

Anal. Calcd for $C_{13}H_{19}Cl_2IN_2$: C, 38.90; H, 4.74; N, 6.98. Found: C, 38.98; H, 4.81; N, 6.91

Iodination of Aromatic Compounds (2) to the Corresponding Iodoaromatic Derivatives (3). General Procedure.- The aromatic compounds **(2)** (5.0 mmol) were added to the iodination reagent **1** (1.9 g, 5.0 mmol) in a mortar. The reaction mixture was ground with a pestle to produce a homogenous powder and left for the time specified in the Table at room temperature. When TLC (n-hexane:EtOAc, 80:20) showed complete disappearance of starting aromatic compounds **(2)**, to the brown solid was added 5 mL sodium bisulfate (5%) and the reaction mixture was extracted with ether (3 x 5 mL). The combined extracts were dried with $MgSO_4$. Evaporation of the solvent gave corresponding iodoaromatic derivatives (**3**). The product was purified by column chromatography on silica gel using a mixture of *n*-hexane:EtOAc (80:20).

Iodination of Anisole.- Anisole (50.0 mmol, 5.4 g) was added to the iodination reagent **1** (19.0 g, 50.0 mmol) in a mortar. The reaction mixture ground with a pestle until a homogenous powder was

obtained the mixture was allowed to stand at RT for 10 min. When TLC (*n*-hexane:EtOAc, 80:20) showed complete disappearance of anisole, 50 mL of sodium bisulfate (5%) was added to the brown solid. The reaction mixture was then extracted with ether (3 x 5 mL). The combined extracts were dried with $MgSO_4$. Evaporation of the solvent afforded the iodo compound, which was purified by column chromatography on silica gel using a mixture of *n*-hexane:EtOAc (80:20) to give 11.5 g (98%) of colorless solid, mp. 50-53°. ^{1}H NMR: δ 7.35 (d, 2H), 6.45 (d, 2H), 3.85 (s, 3H). ^{13}C: 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, 3.2

4-Iodo-4-methoxybenzyl alcohol, colorless solid, mp. 142-144°. ^{1}H NMR: δ 6.9-7.4 (m, 3H), 4.5 (s, 2H), 3.6 (s, 3H). ^{13}C: δ 140.91, 137.32, 128.38, 126.95, 113.96, 94.37, 64.70, 55.06. MS: m/z, 264.42 (100% • M^+), 108 (100%), 93 (60%), 91(100%), 77 (85%), 65 (50%), 39 (25%).

Anal. Calcd for $C_8H_9IO_2$: C, 36.64; H, 3.4. Found: C, 36.71; H, 3.56

3-(3-iodo-4-aminophenyl)propionic acid, colorless solid, mp. 242-243°. ^{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: δ 179.61, 146.51, 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

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