JOC Article

Tetramethylammonium Dichloroiodate: An Efficient and Environmentally Friendly Iodination Reagent for Iodination of Aromatic Compounds under Mild and Solvent-Free Conditions

Abdol R. Hajipour,[*,†,‡] Marty Arbabian,[†] and Arnold E. Ruoho[†]

Department of Pharmacology, University of Wisconsin, Medical School, 1300 University Avenue, Madison, Wisconsin 53706-1532, and Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran

arhajipour@facstaff.wisc.edu; haji@cc.iut.ac.ir

Received September 19, 2002

Tetramethylammonium dichloroiodate (**1**, TMADCI) as a mild and efficient iodination reagent was prepared. Iodination of different aromatic compounds with this reagent takes place fast and with high yields under solvent-free conditions.

Introduction

Iodobenzene derivatives are valuable, versatile synthetic 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 few known methods available for direct iodination of aromatic compounds,[1−6] and the hydrogen iodide generated may be scavenged with alkalis or pyridine[7] or destroyed by the addition of various oxidants such as mercuric oxides.[8]

Reactions under solvent-free conditions have received increasing attention in recent years. The advantage of these methods over conventional homogeneous reactions is that they provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulation.[9−11]

Results and Discussion

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 TMADCI (**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 its 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, hexane, and diethyl ether (Scheme 1).

SCHEME 1

$$\mathrm{NaI} + \mathrm{NaClO} + 2\mathrm{HCl} \xrightarrow{0\ ^\circ\mathrm{C}} \mathrm{NaICl_2} + \mathrm{NaCl} + \mathrm{H_2O}$$

$$\mathrm{Me_4N^+Cl^-} + \mathrm{NaICl_2} \xrightarrow[\substack{\text{room temperature}\\ 98\%}]{\mathrm{H_2O}/20\ \text{min}} \mathrm{Me_4N^+Cl_2^-} + \mathrm{NaCl}$$

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 homogeneous powder, then allowing the mixture to stand for the specified time (Table 1) at room temperature. This reaction proceeds rapidly, and purification of products is very simple.

Activated aromatic compounds **2** were converted to the corresponding iodo-aromatic compounds **3** under solvent-free conditions at room temperature in excellent yields in 5−20 min; deactivated aromatic compounds were

---

[*] To whom correspondence should be addressed. Fax: 001-608-262-1257.

[†] University of Wisconsin.

[‡] Isfahan University of Technology.

(1) Chaikovski, V. K.; Kharlova, T. S.; Filimonov, V. D.; Saryucheva, T. A. *Synthesis* **1999**, 748.

(2) Krassovska-Swiebocka, B.; Lulinski, P.; Skulski, L. *Synthesis* **1995**, 926.

(3) Dolenc, D. *Synlet.* **2000**, 544.

(4) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. *Synthesis* **1995**, 1273.

(5) Kosynkin, D. V.; Tour, J. M. *Org. Lett.* **2001**, *3*, 991.

(6) Merkushev, E. B. *Synthesis* **1952**, 150.

(7) Kajiagaeshi, S.; Kakinami, T.; Morrivaki, M.; Tanaka, T.; Fufi-Saki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 439.

(8) Serguchev, Yu. A.; Davydova, V. G.; Makhon'kov, D. I.; Cheprakov, A. V.; Beletskaya, I. P. *Zh. Org. Khim.* **1985**, *21*, 2010.

(9) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Michael, D.; Mingos P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (c) Gedye, R. J.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279. (d) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

(10) Abramovitch, A. *Org. Prep. Proc. Int.* **1991**, *23*, 685. (b) Migos, D. M. P.; Baghurst, D. R. I. *Chem. Soc. Rev.* **1991**, *20*, 1. (c) Caddick, S. *Tetrahedron* **1995**, *51*, 10403.

(11) Loupy, A.; Petit, A.; Ramdiani, M.; Yvanaeff, C.; Majdoud, M.; Labiad, B.; Villemin, D. *Can. J. Chem.* **1993**, *71*, 90. (b) Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 3207.

(12) Hajipour, A. R.; Mallakpour, S. E. Imanzadeh, G. *J. Chem. Res.* **1999**, 228. (b) Hajipour, A. R.; Mallakpour, S. E. Adibi, H. *Chem. Lett.* **2000**, 460. (c) Hajipour, A. R.; Mallakpour, S. E. Afrousheh, A. *Tetrahedron* **1999**, *55*, 2311. (d) Hajipour, A. R.; Islami, F. *Ind. J. Chem.* **1999**, *38B*, 461. (e) Hajipour, A. R.; Mallakpour, S. E. Imanzadeh, G. *Chem. Lett.* **1999**, 99. (f) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475. (g) Hajipour, A. R.; Mallakpour, S. E. Backnejad, H. *Synth. Commun.* **2000**, *30*, 3855. (h) Hajipour, A. R.; Mallakpour, S. E.; Afrousheh, A. *Phosphorus, Sulfur Silicon* **2000**, *160*, 67. (i) Hajipour, A. R.; Mallakpour, S. E.; Khoee, S. *Synlett* **2000**, 740. (j) Hajipour, A. R.; Mallakpour, S. E.; Khoee, S. *Chem. Lett.* **2000**, 120.

10.1021/jo0264628 CCC: $22.00

TABLE 1. Iodination of Aromatic Compounds 2 with Reagent 1 to Iodoarenes 3 Under Solvent-Free Conditions at Room Temperature[a,b]

entry	Ar-H **2**	Ar-I **3**	time (min)	yield[c] (%)	mp/°C or bp/°C/Torr (lit.)
1	C_6H_5OMe	$4\text{-}IC_6H_4OMe$	5	100	50−53 (51−52)5
2	$C_6H_5NH_2$	$4\text{-}IC_6H_4NH_2$	5	99	63−65 (62.5−63) 13
3	$3\text{-}MeC_6H_4NH_2$	$4\text{-}I\text{-}3\text{-}MeC_6H_3NH_2$	5	99	45−47 (40) 14
4	$3\text{-}ClC_6H_4NH_2$	$4\text{-}I\text{-}3\text{-}ClC_6H_3NH_2$	7	97	64−66 (64−66)3
5	$1,2\text{-}(MeO)_2C_6H_4$	$4\text{-}I\text{-}1,2\text{-}(MeO)_2C_6H_3$	5	100	77−78 (75−76) 5
6	$C_6H_5NHCOMe$	$4\text{-}IC_6H_4NHCOMe$	10	98	184−186 (188−189)13
7	ClC_6H_5	$3\text{-}I{-}ClC_6H_4$	15	91	58−60 (56−57)15
8	$4\text{-}MeOC_6H_4CH_2OH$	$3\text{-}I\text{-}4\text{-}MeOC_6H_3CH_2OH$	10	100	142−144
9	$4\text{-}CHOC_6H_4OH$	$2\text{-}I\text{-}4\text{-}CHOC_6H_3OH$	5	93	113−115 (113−115)16
10	$1,3,5\text{-}C_6H_3(CH_2)_3$	$2\text{-}I\text{-}1,3,5\text{-}C_6H_2(CH_2)_3$	20	87	30−32 (29−30)3
11	PhC_6H_5	$4\text{-}I\text{-}PhC_6H_4$	20	90	114−115 (113−114)17
12	$C_6H_5NO_2$	$3\text{-}I\ C_6H_4NO_2$	45	75	35−37 (34−36) 1
13	$4\text{-}MeC_6H_4NO_2$	$2\text{-}I\text{-}4\text{-}MeC_6H_3NO_2$	35	82	54−56 (54−56) 1
14	C_6H_5CHO	$3\text{-}IC_6H_4CHO$	30	92	55−57 (54−56) 1
15	C_6H_5COOH	$3\text{-}IC_6H_4COOH$	35	90	186−188 (188−189) 1
16	C_6H_5COPh	$3\text{-}IC_6H_4COPh$	35	80	40−42 (41−42)18
17	$4\text{-}NH_2C_6H_4COOH$	$3\text{-}I\text{-}4\text{-}NH_2C_6H_3COOH$	25	86	203−205 (203−204)19
18	$4\text{-}NH_2C_6H_4(CH_2)_2COOH$	$3\text{-}I\text{-}4\text{-}NH_2C_6H_3(CH_2)_2COOH$	10	100	242−243
19	cocaine	3-iodo-4-cocaine	40	83	gummy oil
20	4-aminococaine	4-amino-3-iodococaine	20	92	195−198

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

TABLE 2. Comparison of Iodination of Some Aromatic Compounds with TMADCI, ICl/Ag_2SO_4,[1] *N*-Iodosaccharin,[20] and $I_2/Pb(OAc)_4$[2]

		yield % (min)			
entry	substrate	TMADCI	ICl/Ag_2SO_4	*N*-iodosacchari	$I_2/Pb(OAc)_4$
1	C_6H_5OMe	100 (5)	85 (60)	81 (120)	85 (60)
2	$C_6H_5NH_2$	99 (5)			
3	$C_6H_5NHCOMe$	98 (10)	55 (60)	80 (360)	55 (60)
4	ClC_6H_5	91 (15)	67 (50)		
5	$4\text{-}MeOC_6H_4CH_2OH$	100 (10)		91 (720)	
6	$C_6H_5NO_2$	74 (45)	53 (120)		
7	C_6H_5COOH	90 (35)	57 (60)		
8	C_6H_5COPh	80 (35)	77 (60)		
9	C_6H_5CHO	92 (30)	61 (40)		
10	$4\text{-}NH_2C_6H_4(CH_2)_2COOH$	100 (10)			
11	cocaine	83 (40)			
12	4-aminococaine	92 (20)			

converted to iodobenzene derivatives after 30−45 min at room temperature in good yield (Scheme 2 and Table 1). Iodination of aromatic compounds with this reagent occurred rapidly under solvent-free and very mild conditions, without using base, toxic heavy metal, or oxidizing reagent. The reagent does not affect oxidizable groups, such as hydroxyl, aldehyde, or amine. The iodination was successfully scaled-up to afford multigram quantities of 4-iodoaniline, 4-iodoanisole, and 3-(3-iodo-4-aminophenyl)propionic acid. Even for the scaled-up reaction, this reaction is mild and is not extremely exothermic. The tetramethylammonium cation could be recovered in quantitative yield. After extraction of the iodoaromatic compounds, the aqueous layer was acidified with 5% HCl and treated with a fresh bath of the aqueous dichloroiodate to produce the reagent **1** in quantitave yield.

To evaluate the efficiency of this reaction under solid-state conditions in comparison to the reaction in solution, several experiments were performed. We performed the reaction of 3-(4-aminophenyl)propionic acid in several solvents, such as methanol, acetone, ether, dichloromethane, and acetonitrile. We determined that acetonitrile is the best solvent for this reaction. When 3-(4-aminophenyl)propionic acid was treated with 1 molar ratio of this reagent, the yield was about 10% and many byproducts were produced after 24 h refluxing. By increasing the amount of iodination reagent to 2 molar ratios, the yield of the reaction was not increased. When 3-(4-aminophenyl)propionic acid was treated with 1.5 molar ratio of the iodination reagent in the presence of 1 molar ratio of $NaHCO_3$, 3-(4-amino-3-iodophenyl)propionic acid was produced in 40% yield after 14 h refluxing in a mixture of acetonitrile/methanol (1:1).

SCHEME 2

$$\underset{\mathbf{2}}{\text{Ar-H}} + \underset{\mathbf{1}}{Me_4N^+Cl_2^-} \xrightarrow[\text{5-45 min, 65−100\%}]{\text{solvent-free conditions}} \underset{\mathbf{3}}{\text{Ar-I}} + HCl + Me_4N^+Cl^-$$

To show the ability of this reagent to iodinate aromatic compounds, we compared some of our results with those reported for ICl/Ag_2SO_4,[1] *N*-iodosaccharin,[20] and $I_2/Pb(OAc)_4$[2] (Table 2). This reagent is superior to ICl/Ag_2SO_4, *N*-iodosaccharin, and $I_2/Pb(OAc)_4$ in term of selectivity,

---

(13) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1963**, *30,* 1101.

(14) Potts, K. T. *Chem. Commun.* **1953**, 3711.

(15) Citterio, A. *Synth. Commun.* **1981**, *11,* 639.

high yields, short reaction time, purity of products, and ease of workup.

In summary, we report here the preparation of tetramethylammonium dichloroiodate (**1**) as a mild, inexpensive, and selective iodination reagent. This iodination reagent is easily prepared from cheap and commercially available starting materials and could be stored for months without losing its activity. The reagent is soluble in polar solvents and slightly soluble in nonpolar solvents. This reagent is an efficient and novel reagent for iodination of activated and deactivated aromatic compounds to the corresponding iodobenzene derivatives in the presence of other oxidizable functional groups under solvent-free conditions. The reaction does not need any base, toxic heavy metals, or oxidizing agent. The reagent can be recovered easily in quantitative yield.

Experimental Section

General Methods. All yields refer to isolated products after purification by column chromatography. Products were characterized by comparison with authentic samples (IR and ^1H NMR spectra, TLC, melting and boiling points).[1−14] All ^1H 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 Tetramethylammonium Dichloroiodate (1, TMADCI). A solution of tetramethylammonium chloride (10.95 g, 100 mmol) in 100 mL of water was added to an orange solution of $NaICl_2$ (110 mmol) [prepared from 6% NaClO (136 mL) or 5.25% NaClO (156 mL), NaI (110 mmol, 16.5 g), and 37% HCl (220 mmol, 22 mL) at 0 °C and stirred for 30 min at room temperature]. The resulting yellow precipitate was collected and washed with cooled distilled water (2 × 50 mL) and ether (2 × 30 mL) and dried in a desiccator under vacuum over calcium chloride to afford a yellow powder (26.66 g, 98 mmol, 98% yield), which decomposed at 198−200 °C to a dark-brown material. ^1H NMR: δ 4.7(s). ^{13}C NMR: δ 29.68 (s). Anal. Calcd for $C_4H_{12}ICl_2N$: C, 17.64; H 4.41. Found: 17.45; H, 4.68.

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** (1.4 g, 5.0 mmol) in a mortar. The reaction mixture was ground with a pestle to produce a homogeneous powder, and the mixture was left for the time specified in Table 1 at room temperature. When TLC (hexane/EtOAc, 80:20) showed complete disappearance of starting aromatic compounds **2**, to the brown solid was added 5 mL of sodium bisulfate (5%) and the reaction mixture was extracted with ether (3 × 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 hexane/EtOAc (80:20).

Iodination of Anisole. Anisole (50.0 mmol, 5.4 g) was added to the iodination reagent **1** (14.0 g, 50.0 mmol) in a mortar. The reaction mixture was ground with a pestle until a homogeneous powder was obtained, and the mixture was allowed to stand at RT for 10 min. When TLC (hexane/EtOAc, 80:20) showed complete disappearance of anisole, 50 mL of a sodium bisulfate (5%) was added to the brown solid. The reaction mixture was then extracted with ether (3 × 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 hexane/EtOAc (80:20), to give 11.5 g (98%) of colorless solid, mp 50−53 °C. ^1H 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.

4-Iodo-4-methoxybenzyl alcohol: colorless solid, mp 142−144 °C. ^1H NMR: δ 6.9−7.4 (m, 3H), 4.5 (s, 2H), 3.6 (s, 3H). ^{13}C NMR: 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 °C. ^1H 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, 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.

3-Iodobenzoyl ecgonine methyl ester: yellow gummy oil. ^1H NMR: δ 8.33 (d, $J = 1.8$, 1H), 7.98 (m, 1H), 7.86 (d, $J = 8.4$, 1H), 7.16 (m, 1H), 5.20 (m, 1H), 3.73 (s, 3H, OMe), 3.29 (m, 1H), 3.01 (m, 1H), 2.42 (m, 1H), 2.23 (s, 3H, NMe), 2.20−1.70 (m, 5H). ^{13}C NMR: δ 180, 170. 149, 138, 135, 120, 118, 117, 65.2, 65.13, 60.78, 50.92, 50.22, 41.31, 35.68, 25.79, 25.50. MS: *m*/*z*, 430 (100%, $M^+ + 1$), 182 (100%), 96 (90%), 94 (80%), 82 (100%), 77 (65%), 66 (30%), 51 (25%), 39 (15%). Anal. Calcd for $C_{17}H_{20}INO_4$: C, 47.55; H, 4.66; N, 3.26. Found: C, 47.72; H, 4.80; N, 3.18.

4-Amino-3-iodobenzoyl ecgonine methyl ester: yellow solid, mp 195−198 °C. ^1H NMR: δ 8.32 (d, $J = 1.8$, 1H), 7.80 (dd, $J = 1.8$, 8.4 1H), 6.69 (d, $J = 8.4$, 1H), 5.25 (m, 1H), 4.50 (br, 2H, NH2), 3.74 (s, 3H, OMe), 3.60 (m, 1H), 3.32 (m, 1H), 3.07 (m, 1H), 2.24 (s, 3H, NMe), 2.46−1.2 (m, 7H). ^{13}C 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.

Acknowledgment. We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran (A.R.H.), and Grant GM 33138 (A.E.R.) from the National Institutes of Health.

JO0264628

---

(16) Barnes, J. H.; Borrows, E. T.; Elks, J.; Hens, B. A.; Long, A. G. *J. Chem. Soc.* **1950,** 2824.

(17) Ibuki, E.; Ozasa, S.; Murai, K. *Bull. Chem. Soc. Jpn.***1975**, *48*, 1868.

(18) Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194.

(19) Klemme, C. J.; Hunter, J. H. *J. Org. Chem.* **1940**, *5*, 227.

(20) Darko, D. *Synlett* **2000**, 544.