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SHORT COMMUNICATION

REGIOSELECTIVE IODINATION OF ARYL AMINES USING 1,4-DIBENZYL-1,4-DIAZONIABICYCLO [2.2.2] OCTANE DICHLOROIODATE IN SOLUTION AND UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT. 1,4-Dibenzyl-1,4-diazoniabicyclo[2.2.2]octane dichloroiodate is an efficient and regioselective reagent for iodination of aryl amines. A wide variety of aryl amines in reaction with this reagent afforded regioselectively iodinated products. The iodination reaction can be carried out in solution or under solvent-free condition at room temperature.

KEY WORDS: Regioselective iodination, Aryl amines, 1,4-Dibenzyl-1,4-diazoniabicyclo [2.2.2] octane dichloroiodate, Solvent-free conditions

INTRODUCTION

Aromatic iodo compounds are versatile building blocks for the preparation of organometallic reagents and some are potential intermediates for the synthesis of pharmaceutical and bioactive molecules [1]. They are also useful in metal-catalyzed (e.g., Heck, Stille and Negishi), cross coupling reactions, which are widely employed in C–C, C–N, etc., bond forming reactions [2]. Because of the low reactivity of molecular iodine, direct iodination of aromatic compounds is difficult. This problem is overcome by activating iodine for effective electrophilic substitution. Hence, synthetic methods involving a source of I^+ as the reactive species seem to be the most convenient procedures for the direct iodination of arenes. Generally, aromatic compounds are iodinated using iodine in the presence of a Lewis acid or an oxidizing agent.

Several reagents reported for iodination of aromatic compounds include iodine and 1,4-bis (triphenylphosphonium)-2-butene peroxodisulfate [3], iodine and pyridine/dioxane [4], $AgNO_3/I_2$ [5], $I_2/NaBO_3.4H_2O$ in ionic liquid [6], I_2/HIO_3, heat [7], $I_2/Pb(OAc)_4$ [8], I_2/CrO_3 [9], $NaClO_2$/NaI/HCl [10], KI/K_2FeO_4 in water [11], *N*-iodosuccinimide and catalytic trifluoroacetic acid [12], pyCl/CH_3OH [13], KI/H_2O_2 [14], $KI/KIO_3/H^+$ [15], $KClO_3$/KI/HCl [16], NCS/NaI [17] and iodine with H_2O_2 and O_2[18]. However, in spite of their potential utility, the practical application of most of these reagents suffers from disadvantages such as harsh reaction conditions, low regioselectivity, the use of expensive or less easily available reagents, long reaction times, low yields and tedious work-up. Therefore, due to importance of aryl iodides, introduction of new methods for the preparation of these compounds in terms of increase of the selectivity and also the yields of the *para*-products, potential simplicity, and short reaction times, is still in demand. Furthermore, the use of inexpensive and environmentally friendly reagents such as dichloroiodate salt was reported by Tour *et al.* [19] and others [20] in solvent or solvent-free conditions for iodination of aromatic compounds. 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 [21-23]. Due to

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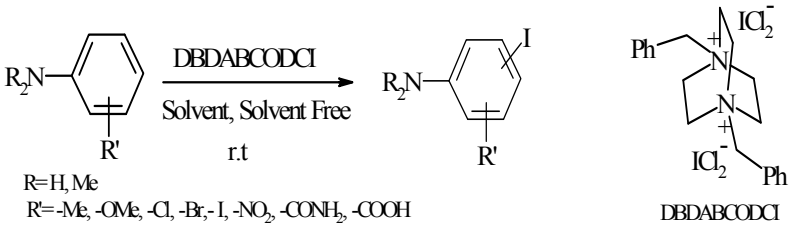
importance of aryl iodo-compounds and solvent-free condition in organic synthesis, in our procedure we have reported a mild, efficient and regioselective method for iodination of aryl amines in the presence of 1,4-dibenzyl-1,4-diazoniabicyclo [2.2.2] octane dichloroiodate (DBDABCODCI) as a reagent in solvent and solvent-free conditions. The protocol proved to be highly selective, as a single isomer was formed exclusively in all of the substrates (Scheme 1).

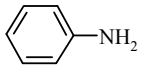
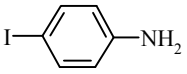
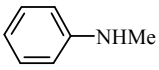
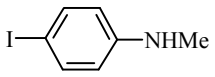
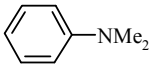
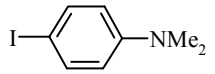
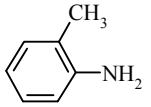
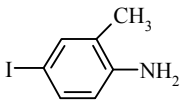


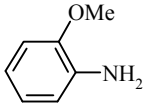
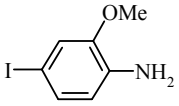
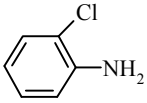
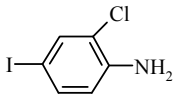
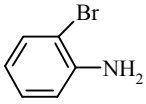
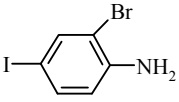
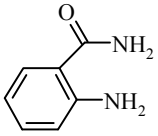
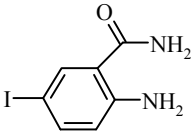
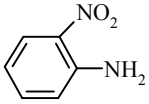
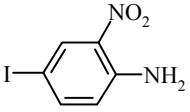
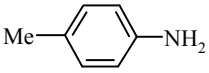
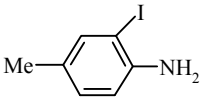
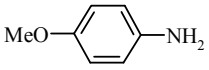
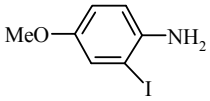
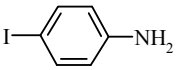
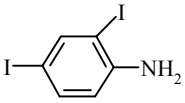
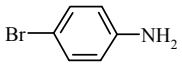
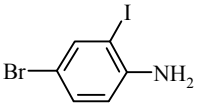
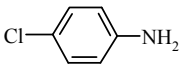
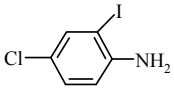
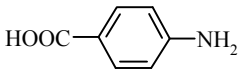
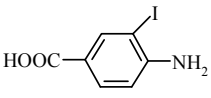
Scheme 1. Iodination of aryl amines in the presences of DBDABCODC.

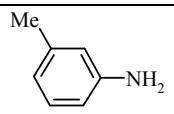
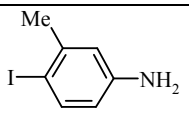
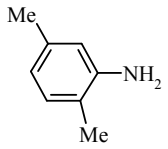
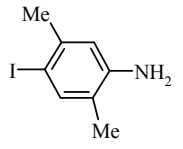
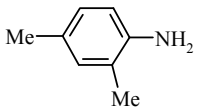
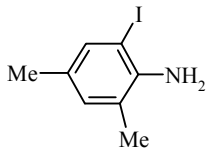
RESULTS AND DISCUSSION

In our first experiment, in order to find the optimum reaction conditions, we have reacted 4-chloroaniline (1 mmol) with DBDABCODCI (1 mmol) in many solvents listed in Table 1, in the presence of different bases at room temperature. As indicated when 4-chloroaniline reacted with DBDABCODCI in mixture of CH_2Cl_2/MeOH (1:1) as a solvent and $NaHCO_3$ (1 mmol) as a base an excellent yield of the 4-chloro-2-iodoaniline was obtained (70%). To test the generality of this procedure, we have examined the iodination of different aryl amines and in more case aryl iodo amines achieved in good to excellent yield (Table 1).

Table 1. Iodination of aryl amines in the presence of DBDABCODCI[a].

Entry	Aryl amine	Product[b]	Time (min)[c]	Yield (%)[d]	Mp/°C	Ref.
1			60(10)	90(95)	61-62	19
2			60(10)	88(91)	-	19
3			60(10)	85(92)	80-82	24
4			60(10)	90(93)	88-90	24

5			60(10)	89(92)	-	25
6			120(20)	80(85)	62-64	24
7			120(20)	85(88)	70-72	24
8			4(45)	70(70)	180-182	26
9			240(45)	45(48)	121-123	13
10			90(10)	84(90)	38-40	27
11			90(10)	81(90)	-	28
12			90(25)	82(86)	94-96	24
13			120(25)	85(89)	70-72	29
14			240(25)	70(70)	37-39	13
15			360(30)	55(50)	200-202	30

16			120(15)	87(90)	50-52	31
17			120(15)	89(90)	69-71	19
18			120(20)	73(80)	62-64	19

[a]Reaction conditions: Aryl amine (1 mmol), DBDABCODCI (1 mmol), $NaHCO_3$ (1 mmol), room temperature, in CH_2Cl_2 : MeOH (1:1) and solvent-free condition (base not required). [b]All of the products were identified by comparing melting point and ^1H NMR with those of authentic samples reported in literature. [c]The numbers in parentheses represent the results obtained in the solvent-free conditions. [d]Yields refer to isolated products.

As shown in Table 1, when aniline, *N*-methylaniline and *N,N*-dimethylaniline examined under optimum conditions an excellent yield of the corresponding products with good selectivity was obtained (entries 1-3). Similarly, aniline derivatives substituted in *ortho* or *meta* position with DBDABCODCI gave the corresponding *para* iodoarylamine in well to excellent yield (entries 4-8 and 16, 17). Furthermore, when *para* substituted aniline derivatives were used, the substitution occurs in *ortho* position with good yield (entries 10-15). On the other hand, when electron-donating groups are present on the aryl amine the reaction was faster and the yield of the iodo product was higher (for example, entries 4,5 vs. entries 9 and 15). Also, this protocol can be successfully applied for the iodination of aryl amines under solvent-free condition.

In conclusion, we have developed a general, regioselective method for the iodination of aryl amines using DBDABCODCI as an environmentally friendly and mild iodinating reagent. The protocol proved to be highly selective, as a single isomer was formed exclusively in all of the substrates. Furthermore, the reaction condition is easy and safe and this reagent is easily prepared by commercial materials.

EXPERIMENTAL

Materials were purchased from Merck and Aldrich companies. Melting points were taken on a Barnstead Electrothermal 9100 melting point apparatus equipped with a microscope and are uncorrected. Reactions in solution were monitored by thin-layer chromatography (TLC) of worked up reaction aliquots. Analytical TLC was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was carried out on silica gel 60 (70–230 mesh). NMR data were recorded on 300 and 500 MHz NMR spectrometers from Bruker. IR spectra were recorded on a Frontier FT-IR (Perkin Elmer) spectrometer using a KBr disk. All yields refer to isolated products.

Preparation of DBDABCODCI. A solution of *N,N'*-dibenzyl-1,4-diazonia bicyclo [2.2.2] octane dichloride (10 mmol, 3.64 g) in 10 ml of water was added to orange solution of $NaICl_2$ (11 mmol) [prepared from 5.25% NaClO (15.6 mL), NaI (11 mmol, 1.65 g)] and 37% HCl (22

mmol, 2.2 mL) at 0 °C and stirred for 30 min at room temperature. The resulting yellow precipitate was collected and washed with cooled water and ether and dried in desiccator to afford a yellow solid (90%), which decomposed at >180 °C to a dark-brown material. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H(ppm): 7.53 (10H, arom, s), 4.78 (4H, CH_2, s), 3.83 (12H, CH_2, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C(ppm): 133.0, 130.7, 129.2, 126.4, 66.5, 50.1. Anal. calcd. for $C_{20}H_{26}N_2Cl_4I_2$: C, 34.81; H, 3.08; N, 4.06. Found: C, 34.61; H, 3.28; N, 4.16. IR (KBr): 3401, 3295, 3176, 1674, 1610, 1543, 1478, 1409, 1388, 1299, 1163, 1066, 893, 820, 765, 725, 698, 632, 536, 506 cm^{-1}.

General procedure for the iodination of aryl amines in solution. DBDABCODCI (0.5 mmol) and $NaHCO_3$ (1 mmol) were added to a solution of aryl amine (1 mmol) in CH_2Cl_2: MeOH (1:1). The reaction mixture was stirred at room temperature for the specified time. After completing reaction which monitored by TLC, the ethyl acetate added to mixture and filtered, the organic layer washed with 5% aqueous sodium thiosulfate, and dried over $MgSO_4$. The solvent was removed in vacuum and the crude mixture was purified by column chromatography using ethyl acetate and hexane mixture and analyzed by m.p. and ^{1}H NMR spectroscopy.

General procedure for the iodination of aryl amines under solvent-free conditions. DBDABCODCI (0.5 mmol) and aryl amine (1 mmol) were triturated together in a porcelain mortar at room temperature. After completing reaction which monitored by TLC, the ethyl acetate added to mixture and filtered, the organic layer washed with 5% aqueous sodium thiosulfate, and dried over $MgSO_4$. The solvent was removed in vacuum and the crude mixture was purified by column chromatography using ethyl acetate and hexane mixture and analyzed by m.p. and ^{1}H NMR spectroscopy.

4-Iodoaniline (Entry 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.41 (2H, arom, d, J = 8.3 Hz), 6.47 (2H, arom, d, J = 8.3 Hz), 3.48 (2H, NH_2, s).

4-Iodo N,N-dimethylaniline (Entry 3). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.50 (2H, arom, d, J = 9.0 Hz), 6.53 (2H, arom, d, J = 9.0 Hz), 2.95 (6H, CH_3, s).

4-Iodo-o-toluidine (Entry 4). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.37 (1H, arom, s), 7.32 (1H, arom, d, J = 8.3 Hz), 6.47 (1H, arom, d, J = 8.3 Hz), 3.57 (2H, NH_2, s), 2.14 (3H, CH_3, s).

4-Iodo-o-anisidine (Entry 5). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.11 (1H, arom, d, J = 8.1 Hz), 7.09 (1H, arom, s), 6.54 (1H, arom, d, J = 8.1 Hz), 3.86 (3H, OCH_3, s).

2-Amino-5-iodobenzamide (Entry 8). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.65 (1H, arom, s), 7.47 (1H, arom, d, J = 8.0 Hz), 6.50 (1H, arom, d, J = 8.0 Hz), 5.74 (4H, NH_2, s).

4-Chloro-2-iodoaniline (Entry 14). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.63 (1H, arom, d, J = 2.2 Hz), 7.13 (1H, arom, d, J = 8.5 Hz), 6.69 (1H, arom, d, J = 8.5 Hz), 4.12 (2H, NH_2, s).

4-Iodo 2,5-dimethylaniline (Entry 17). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H (ppm): 7.47 (1H, arom, s), 6.62 (1H, arom, s), 3.51 (2H, NH_2, s), 2.34 (3H, CH_3, s,), 2.12 (3H, CH_3, s).

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