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Recyclable ionic liquid iodinating reagent for solvent free, regioselective iodination of activated aromatic and heteroaromatic amines

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This article describes a simple, efficient method for iodination of activated aromatic and heteroaromatic amines using recyclable 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI) as an ionic liquid iodinating reagent, in the absence of any solvent. The main advantages are simple efficient procedure, good yields and no need of any base/toxic heavy metals, or oxidizing agent. The ionic liquid was recovered and recycled in five subsequent reactions, without much loss of activity. This method was applied for the synthesis of antiprotozoal drug Iodoquinol and antifungal drug Clioquinol.

Introduction

Aryl iodides are important intermediates in organic synthesis, medicine and biochemistry.[1] They are also valuable and reactive intermediates for various cross-coupling reactions, for example,[2] Heck, Stille and Negishi cross-coupling. Direct iodination using I_2 is a simple method, but is not straight forward and requires the oxidation of iodine to the more reactive species with a pronounced I^+ nature. Iodination of aromatic compounds has been carried out using molecular iodine together with strong oxidising agents such as nitric acid, sulphuric acid, iodic acid, sulphur trioxide and hydrogen peroxide,[3] ceric ammonium nitrate,[4] bismuth (III) nitrate pentahydrate,[5] sodium hypochlorite and urea-hydrogen peroxide.[6] Several reagents reported for iodination of aromatic compounds include iodine and 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate[7], iodine and pyridine/dioxane[8], $AgNO_3/I_2$[9], $I_2/NaBO_3.4H_2O$ in ionic liquid[10], I_2/HIO_3, heat[11], I_2/CrO_3[13], $NaClO_2/NaI/HCl$[14], KI/K_2FeO_4 in water[15], N-iodosuccinimide and catalytic trifluoroacetic acid[16], $pyCl/CH_3OH$[17], $I_2/Pb(OAc)_4$[12], KI/H_2O_2[18], $KI/KIO_3/H^+$[19], $KClO_3/KI/HCl$[20], NCS/NaI[21] and iodine with H_2O_2 and O_2.[22] Strong Lewis acids or Bronsted acids, such as trifluoroacetic acid,[23] trifluoromethanesulfonic acid and $BF_3.OEt_2$-H_2O[24] have been utilised for electron-withdrawing groups on the aromatic ring, which is not suitable for acid-sensitive functional groups. Hence, there is an increasing demand for new greener methods for iodination without catalyst and solvent. Iodination using ICl is usually carried out in polar solvents, such as methanol, water and acids such as acetic acid, trifluoroacetic acid, aq. hydrochloric acid, sulphuric acid, etc., in which the heterolytic dissociation facilitates electrophilic attack of iodine.[25] Iodination using ICl is carried out in Lewis acids[26] such as $Hg(OTf)_2$ and AgOTf.

Very few ammonium ICl_2^- salts have been reported for the iodination of aromatic compounds. Hexamethylene bis(N-methylimidazolium) bis(dichloroiodate)[27] an ionic liquid iodinating reagent has been used for iodination of aromatic amines. The drawback was that the reaction requires $CaCO_3$ as a base and the recycle yields are less (82%). Benzyltrimethylammonium dichlroiodate,[28] was used for iodination. The drawback was the use of MeOH as solvent and the requirement of $CaCO_3$ as a base. A variety of 1,3-dialkylimidazolium trihalide-based ionic liquids were used for iodochlorination for alkenes and alkynes and not for iodination.[29]

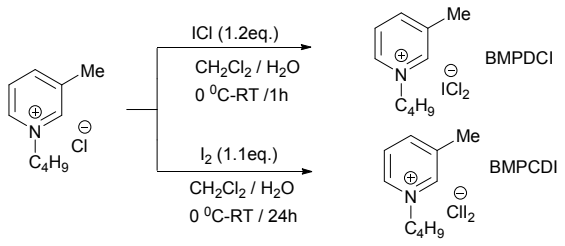
Polymer based ionic iodinating reagent, poly[*N*-(2-aminoethyl)-acrylamido]triethylammonium dichloroiodate[30] was used for iodination, which required two-fold molar excess of reagent, $CHCl_3$ as solvent and was limited to ketones only. Recently, 1,4-dibenzyl-1,4-diazoniabicyclo[2.2.2]octane dichloroiodate was used for iodination of aryl amines, but the reagent was not recovered or recycled.[31] Hence, there was a need to develop new recyclable reagent for iodination in the absence of solvent/base/catalyst and with better recycle yields.

Ionic liquids are intersting media for greener reaction protocols.[32] Reaction under solvent-free conditions have received increasing attention in recent years. But there are only few examples of iodinating ionic liquid reagent.[33] To the best of our knowledge, this procedure represents the application of recyclable novel ionic liquid for iodination in the absence of any solvent/catalyst/base, with better recovery and recycle yields.

Results and discussion

The reaction of 1-butyl-3-methylpyridinium chloride[34] with 1.2 eq. of ICl or 1.1 eq. I_2 at 0^0 C, afforded the water soluble dark reddish brown ionic liquid 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI) or 1-butyl-3-methylpyridinium chlorodiiodide (BMPCDI) in quantitative yields (Scheme 1). Both these ionic liquids were stable and stored in dark at 10^0 C for several months without any change in color, loss of reactivity and degradation (checked by NMR).

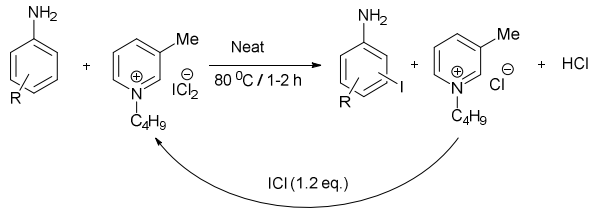
Scheme 1 Synthesis of ionic liquid 1-butyl-3-methyl-pyridinium dichloroiodate (BMPDCI) and 1-butyl-3-methyl-pyridinium dichloroiodide (BMPCDI)



We have been previously engaged in the synthesis of 1-butyl-3-methylpyridinium tribromide for regioselective

bromination of anilines and phenols.[35] Coupled with our previous experience, we considered the application of iodine monochloride ionic liquid (BMPDCI) for iodination of amines in an attempt to afford an improved new recyclable iodination protocol (Scheme 2).

Scheme 2 Iodination of aromatic amines using 1-butyl-3- methyl-pyridinium dichloroiodate (BMPDCI)



After screening different DCI for iodination (Table 1), it was found that BMPDCI was the best iodinating reagent. For BMPDCI (entry 4), at room temperature, only 33 % of the product was isolated, but at 80 ^{0}C, the yield was 90%. At R.T., dichloroiodates (Entry 1, 2 & 3) afforded the iodinated products,

Table 1 Optimisation of dichloroiodate for iodination of 2,6-dimethylaniline (1.0 eq.) using DCI (1.2 eq.).

Entry	Product	Temperature	Time (h)	Isolated yield (%)
1	1-Butylpyridinium	R.T	1	33
	Dichloroiodate	80 ^{0}C	1	69
2	Tetrabutylammonium	R.T.	1	70
	Dichloroiodate	80 ^{0}C	1	77
3	1,3-Dibutylimidazolium	R.T.	1	54
	Dichloroiodate	80 ^{0}C	1	34
4	**BMPDCI**	R.T.	1	33
		80 ^{0}C	**1**	**90**

but in low yields.

At the initiation of this work, we studied the reaction of *N,N*-dimethylaniline as a model with BMPDCI in different solvents (Table 2). Initially, when the reaction was performed at room temperature in methanol, there was no formation of product. Hence, the reaction mixture was refluxed for one hour to obtain the desired product in 96% (entry1). The same reaction in

Table 2 Comparison of various solvents for iodination of N,N-dimethylaniline (1.0 mmol) using BMPDCI (1.2 mmol) under reflux conditions.

Entry	Solvent	Time(h)	GC Yield (%)
1	MeOH	1, 2	96, 92
2	Ethylene dichloride (EDC)	1, 2	39, 28
3	EDC+ MeOH (10ml + 4ml)	1, 2	98, 98
4	Hexane	1, 2	96, 86
5	$CHCl_3$	1	96
6	**No solvent (at 80 ^{0}C)**	**1**	**98**

ethylene dichloride under reflux conditions afforded only 39% yield after 1 hour and 28% yield after two hours. It was observed that when a mixture of 1,2-dichloroethane and MeOH were used, the yields were better (98% yield) as compared with other solvents. In hexane the yields was 96% after one hour and after two hours the yield was 86%. Similarly, in chloroform the yield was 96% after one hour reflux. But, when the same reaction was carried out without any solvent, quantitative yields of the product was formed in one hour at 80 ^{0}C (entry 6). Hence, all further reactions were carried out in the absence of any solvent.

The reaction of 2,6-diethylaniline with 1-butyl-3-methyl-pyridinium dichloroiodate (1.2 eq.) was carried out at different temperatures (50 ^{0}C, 80 ^{0}C, 100 ^{0}C and 120 ^{0}C) in the absence of any organic solvent. (Table 3) At room temperature there was no formation of product and starting material was completely recovered. It was observed with an increase in temperature from 50 ^{0}C to 80 ^{0}C, the formation of product increased from 91% to 97%. (entries 2 & 3). But surprisingly, at 100 ^{0}C after one hour, a mixture of 4-iodo-2,6-diethyl aniline and 4-chloro-2,6-diethyl aniline were obtained in 4% and 17 % respectively. Similarly, the reaction at 120 ^{0}C afforded a mixture of 4-iodo- and 4-chloro-2,6-diethyl aniline in 2% and 22 % respectively. This

Table 3 Optimisation of reaction temperature for iodination of 2,6-diethylaniline (1.0 eq.) using BMPDCI (1.2 eq.).

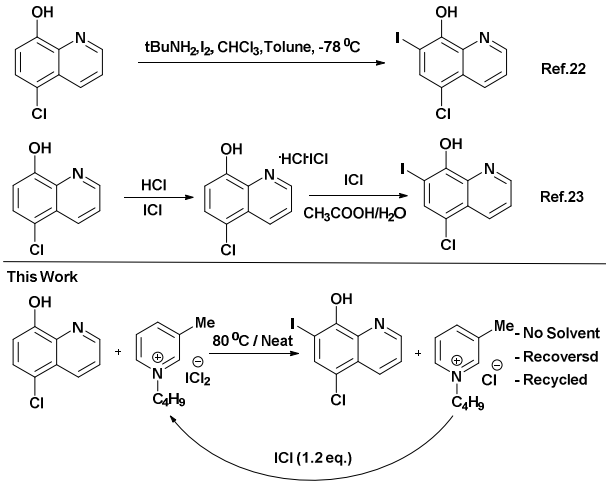
Entry	Product	Temperature	Time (h)	G.C yied (%)	
				A	B
1	4-iodo-2,6-diethyl	R.T.	1	97	0
	aniline (A)		2	98	0
2	4-iodo-2,6-diethyl	50 ^{0}C	1	91	0
	aniline (A)		2	91	0
3	**4-iodo-2,6-diethyl**	**80 ^{0}C**	**1**	**97**	**0**
	aniline (A)		2	97	0
4	A + 4-chloro-	100 ^{0}C	1	4	17
	2,6-diethyl aniline(B)		2	5	18
5	A + 4-chloro-	120 ^{0}C	1	2	22
	2,6-diethyl aniline		2	4	9

A* = 4-iodo-2,6-diethyl aniline, B* = 4-chloro-2,6-diethyl aniline

indicated that BMPDCI is not stable at high temperature. Hence, it was concluded to perform all further reactions at 80 ^{0}C for 1 hour.

To evaluate the application of this new reagent for iodination, a variety of aromatic amines were reacted with 1-butyl-3-methyl-pyridinium dichloroiodate (1.2 eq.) at 80 ^{0}C in the

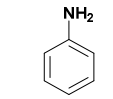
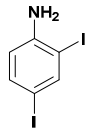
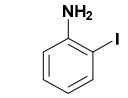
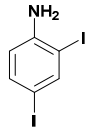
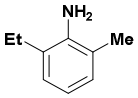
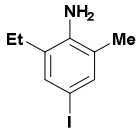
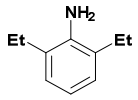
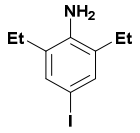
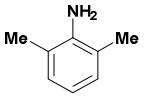
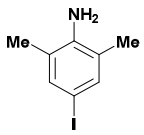
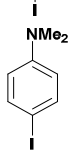
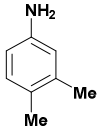
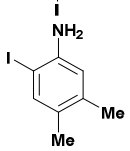
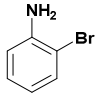
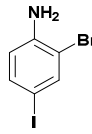
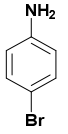
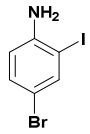
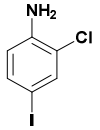
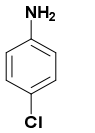
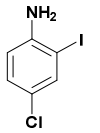
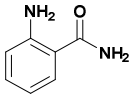
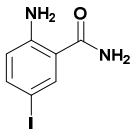
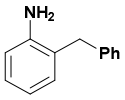
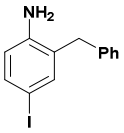
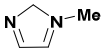
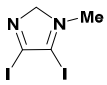
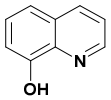
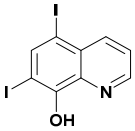
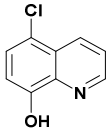
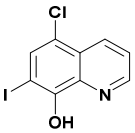
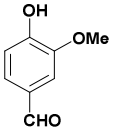
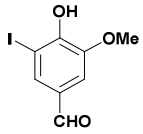
Scheme 3 Synthesis of Clioquinol



absence of any solvent. The results are summarized in Table 4. Iodination of aniline with 2.0 eq. of BMPDCI afforded a mixture of 2,4-diodoaniline (90 %) as the major product (entry 1) and 4-diiodoaniline (9%). The same reaction with 1.0 eq. of BMPDCI afforded p-iodoaniline as the major (80%) and 2,4-diodoaniline (19 %)

The iodination of 2,6-dimethylaniline with 1-butyl-3-methyl-pyridinium dichloroiodate (1.2 eq.) preferably takes place at the para postion with a high yield (95%) of the product (entry 5). Iodination of benzene, benzoic acid, nitrobenzene and benzaldehyde did not proceed even when the reaction was continued at 80^{0}C for 24 h. (entry 18). Surprisingly, anisole was not iodinated, even though it is a good electron donating group. This indicates that the present protocol requires the presence of an electron donating group on the aromatic ring to facilitate the electrophilic aromatic iodination reaction. The reaction of aromatic amines with 1-butyl-3-methylpyridinium dichloroiodate at 80 ^{0}C in the absence of any solvent afforded the corresponding iodo compounds with high regioselectivity

Table 4 Iodination of aniline and hetero-aromatic derivatives using 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI)

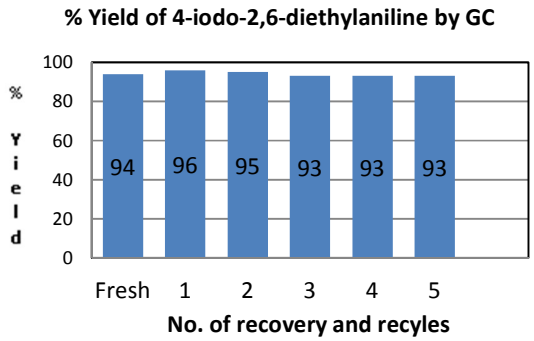
Entry	Amine	Product	Time	Yield A	Yield B
1			2	90	85
2			1	98	95
3			1	80	75
4			1	94	90
5			1 1	67 99	62 95
6			1	92	86
7			1	97	93
8			1	86	80
9			1 2	75 99	69 98
10			1	93	97
11			1	79	73
12			1	77	73
13			1	80	76
14			5	74	69
15			1	-	84
16			1	-	93
17			1	84	80
18		No Reaction	24	0	0

A = GC Yield, B = Isolated yield, c = 2 eq. of BMPDCI used. R = H, CHO, NO_2, OMe, COOH.

and in good to excellent yields. The results also indicate that the aromatic amines are more selective for nuclear iodination and no side-chain iodination was observed in the case of methyl/ethyl substituted amines (Table 4, entries 3, 4, 5 & 7). It was observed that aniline with open *ortho* and *para* positions, were iodinated with high selectivity to yield para-iodinated products exclusively. If the *para*-position is substituted, the iodination were at the *ortho*-position (Entries 7, 9 & 11) and vice-versa. (Entries 2, 8, 10, 12 & 13) BMPCDI on reaction with *N*,*N*-dimethylaniline at 80 ^{0}C afforded the para iodinated product in 45% yield after 4 h, indicating this reagent to be not efficient as BMPDCI. It is important to mention that this protocol was successfully applied to heteroaromatic compounds with better yields than the reported procedure.[29] For example, the reported yield of 4,5-diiodo-1-methylimidazole was 47%, in the presence of calcium carbonate.[29] Using our new protocol, 4,5-diiodo-1-methylimidazole was obtained in 80% yields and did not require any base (Table 4, entry 14). 5,7-diiodo-8-hydroxy quinoline an antiprotozoal drug is used for the treatment of an intestinal infection called amebiasis and is available in the market under the trade named Iodoquinol.[36] This was easily prepared in 84% yield from 8-hydroxyquinoline (entry 15). 5-chloro-7-iodo-8-hydroxy quinoline is an antifungal and antiprotozoal drug available in the market under the trade name Clioquinol.[37,38,39] This was easily prepared in 93% yield from 5-chloro-8-hydroxyquinoline. (entry 16 and Scheme 3). 5-5-

iodovanillin is an important intermediate for the synthesis of psychedelic drug mescaline, escaline and proscaline.[38] Vanillin was reported to be
iodinated in an aq. solution of sodium triiodide (NaI_3.NaI).[40] The drawbacks were the reaction required 1N NaOH and 3.5N aq, H_2SO_4, rendering the procedure to be harsh and environmentally non-friendly. 5-iodovanillin was easily prepared from vanillin using BMPDCI in 80% yield, in the absence of solvent/base/acid, rendering the procedure to be eco-friendly (entry 17). The spectroscopic data for the iodinated compounds matched the reported literature data.

Fig. 1 Recovery and reusability of BMPDCI



A set of experiment were carried out to examine the recovery and reusability of 1-butyl-3-methylpyridinium dichloroiodate(BMPDCI) for iodination reaction. After completion of the reaction, ethylacetatewas added, followed by water. The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layer was evaporated under vacuum, dried using sodium sulfate to afford the crude product, which on further column chromatography using silica gel afforded the pure iodinated product. The water layer was evaporated under vacuum at 60 ^{0}C to recover 1-butyl-3-methylpyridinium chloride (BMPCI). Addition of ICl (1.2 eq.) to 1-butyl-3-methylpyridinium chloride in water and dichloromethane (as reported in Scheme 1), afforded 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI), which was used for further iodination reactions. The 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI) was recovered and reused for up to five runs with >93% yield of the iodinated product and without any loss of activity (Fig.1). To exhibit the recovery and reusability of 1-butyl-3- methylpyridinium dichloroiodate (BMPDCI), 2,6-diethylaniline was chosen as a model example.

Conclusion

1-butyl-3-methyl-pyridinium dichloroiodate which can be easily prepared provides a recyclable iodinating agent for activated aromatic amines in the absence of any solvent. Main advantages are no need of any oxidant/catalyst/base, simple practical procedure, good yields, recyclable iodinating reagent, renders this protocol environmentally benign. The reagent is easliy prepared from commercial materials viz. 3-methylpyridine, which is the main precursor for the synthesis of nicotinic acid. This work successfully realised the dual role of 1-butyl-3-methyl-pyridinium dichloroiodate as an iodinating reagent and solvent.

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Recyclable ionic liquid iodinating reagent for solvent free, regioselective iodination of activated aromatic and heteroaromatic amines

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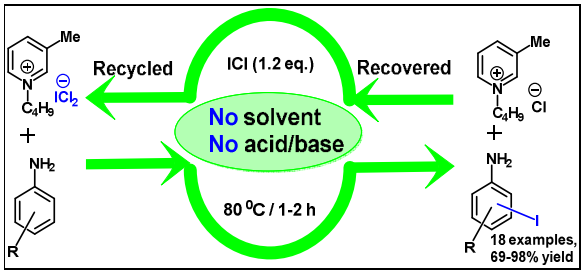

This article describes a simple, efficient method for iodination of activated aromatic and heteroaromatic amines using recyclable 1-butyl-3-methylpyridinium dichloroiodate (BMPDCI) as an ionic liquid iodinating reagent, in the absence of any solvent. The main advantages are simple efficient procedure, good yields and no need of any base/toxic heavy metals, or oxidizing agent. The ionic liquid was recovered and recycled in five subsequent reactions, without much loss of activity. This method was applied for the synthesis of antiprotozoal drug Iodoquinol and antifungal drug Clioquinol.