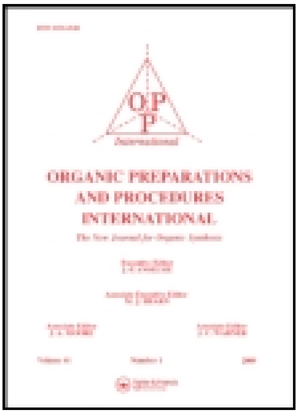

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

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To cite this article: Abdol Reza Hajipour & Mohadeseh Seddighi (2011): Application of $[Hcpy]HSO_4$ Brönsted Acidic Ionic Liquid for the Synthesis of Aryl Iodides from Aromatic Amines, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 43:3, 292-296

To link to this article: http://dx.doi.org/10.1080/00304948.2011.582384

Organic Preparations and Procedures International, 43:292–296, 2011

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2011.582384

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Application of [Hcpy]HSO$_4$ Brönsted Acidic Ionic Liquid for the Synthesis of Aryl Iodides from Aromatic Amines

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Aryl iodide are versatile and useful compounds in organic synthesis, mainly for C–C and C–N bonds formation in metal-catalyzed cross-coupling reactions such as the Suzuki,[1,2] Heck, Stille and Negishi reactions.[3–5] Some aryl iodides can be employed for the synthesis of pharmaceutical and bioactive compounds, X-ray contrast agents or radioactive labeled markers in radioimmunoassay.[6] The general procedure for their preparation involves preparation of aryldiazonium salts by the reaction of aryl amines with sodium nitrite at low temperature in aqueous hydrochloric or sulfuric acid, following treatment with iodine or iodide ion;[7] several other procedures have been used recently.[8–12] Aryl iodides have been prepared in one-pot reaction of diazotization-iodination of amines with HI/KNO$_2$ in DMSO,[13] NaNO$_2$/PTSA/KI in acetonitrile,[14] NaNO$_2$/sulfonated-resin/KI in water,[15] *p*-TsOH/NaNO$_2$/KI in water-paste form[16] and NaNO$_2$/wet silica sulfuric acid/KI.[17] However, some of these methods suffer from disadvantages such as the use of expensive reagents, long reaction times, necessity for temperature control, instability of diazonium salts and the use of organic solvents as a reaction medium.

Over the last years, ionic liquids have been used as solvent or catalyst in organic synthesis due to their remarkable properties such as non-flammability, negligible vapor pressure, high thermal, chemical and electrochemical stability, easy recyclability and high solvating ability. The use of Brönsted acidic ionic liquids has also brought major improvements both as catalyst or in the dual role of catalyst and solvent in many reactions such as the Pechmann reaction,[18] the chemoselective synthesis of 1,1-diacetates,[19] the Prins reaction,[20] the Fischer indole synthesis,[21] the thioacetalization of aldehydes,[22] the synthesis of 1-amidoalkyl-2-naphthols,[23] the biodiesel synthesis[24] and the azidation of alcohols.[25] In

Submitted May 21, 2010.
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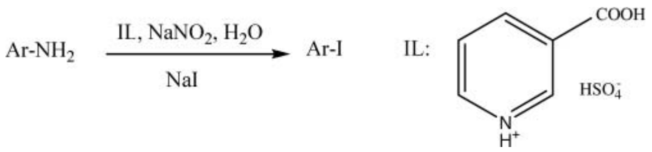
continuation of our effort to develop efficient and green method in organic synthesis,[26–29] herein we report the application of 3-carboxypyridinium hydrogen sulfate [Hcpy]HSO_4 as a novel, inexpensive, green and efficient acidic ionic liquid for the synthesis of aryl iodides from aromatic amines *via* diazonium salt carried out at room temperature and under mild condition with good to high yields with grinding under safe conditions.



To optimize the reaction conditions for preparation of aryl iodides from corresponding amines, 4-aminobenzoic acid was used as a model reaction and we observed that the iodination of 4-aminobenzoic acid with sodium iodide and [Hcpy]HSO_4 in H_2O as solvent in an ice bath gave only 25% yields after 2 h while using the grinding conditions led to higher yields and very shorter reaction times. The best results were obtained using 3 mmol of ionic liquid, 1 mmol of amine, 2 mmol $NaNO_2$, 1.5 mmol NaI and 1 ml water at room temperature; increasing the amount of [Hcpy]HSO_4 did not improve the yield of the yield. In addition, without the use of water the majority of starting material was not converted to the corresponding diazonium salt even after longer reaction time (*Table 1*).

Table 1

Synthesis of Iodoarenes in the Presence of [Hcpy]HSO_4[a]

Cmpd	Time (min)	Yield (%)	mp. (*lit.* mp.)
4-$HO_2CC_6H_4I$	20	85	272–273 (270–273)[15]
4-CNC_6H_4I	25	83	123–125 (124–128)[15]
2-$O_2NC_6H_4I$	20	88	49–51 (49–51)[15]
3-$O_2NC_6H_4I$	20	80	Oil
4-$O_2NC_6H_4I$	20	91	171–173 (172–173)[14]
4-$PhCOC_6H_4I$	20	75	98–100 (101–102)[17]
4-$MeCOC_6H_4I$	20	71	83v84 (84–85)[17]
4-IC_6H_4I	25	68	129–131 (130–131)[14]
4-BrC_6H_4I	25	51	39–41 (40–42)[17]
2-$HO_2CC_6H_4I$	30	47	161–162 (160v161)[17]
2,4-$(NO_2)_2C_6H_3I$	45	38	99–101 (99–101)[17]
3.5-$(NO_2)_2C_6H_3I$	45	40	99–101 (97–99)[17]
4-$PhCOC_6H_4I$	25	89	102–103 (97–99)[17]
3-$PhCOC_6H_4I$	30	88	40v42(40–41)[17]
4-PhC_6H_4I	20	80	111–114 (110–112)[17]
4-$MeOC_6H_4I$	20	84	51v52 (49–50)[17]
4-MeC_6H_4I	20	86	35–38 (35–37)[17]
C_6H_5I	20	85	Oil (oil)[17]

[a]All products were characterized by IR, ^1H NMR and melting points

Table 2

Comparison of Results using [Hcpy]HSO_4 with by Methods for 2-Nitroiodobenzene

Entry	Reagent	Conditions	Time (min)	Yield (%)	Ref.
1	NO_2, NaI	CH_3CN/85°C	15	92	[12]
2	$NaNO_2$, KI, *p*-TsOH	CH_3CN/H_2O/10°C	50	81	[15]
3	Sulfonated-resin, KI, $NaNO_2$	H_2O/ r.t	90	71	[16]
4	*p*-TsOH, $NaNO_2$, KI	H_2O, grinding/r.t	20–30	72	[17]
5	Wet-SSA, $NaNO_2$	H_2O, grinding/r.t	30	83	[18]
6	[Hcpy]HSO_4, $NaNO_2$, KI	H_2O, grinding/r.t	20	88	This work

Various aromatic amines bearing either electron-withdrawing or electron-donating groups were converted rapidly to the corresponding aryl iodides. However, weakly basic aromatic amines such as 2,4-dinitroaniline and 3,5-dinitroaniline were converted to the corresponding aryl iodides only in moderate yields (*Table 1*). Steric hindrance did not has any significant effect on the yields, For example, more hindered *ortho*-substituted aromatic amines such as 2-nitroaniline gave 88% yield in comparison to 91% yield of 4-nitroaniline.

The stability of the generated diazonium salts was studied. When the diazonium salt of 4-nitroaniline was kept at room temperature in air and 0.5 ml of water and sodium iodide were added to the reaction mixture after different periods of time, the results showed that the yield did not change significantly even after keeping the diazonium salt for 10 days under ambient conditions in comparison to the yields of using freshly prepared diazonium salt.

We observed that all the aryldiazonium obtained employing this procedure were safe and non-explosive, this may be because the reactivity of these aryldiazonium salts decreases when they are generate in ionic liquids. Therefore, our diazotization–iodination method is safe and grinding of these aryldiazonium salts in a mortar is not hazardous under our laboratory conditions. In contrast to traditional methods, the diazotization–iodination reaction rate increases using this procedure because these aryldiazonium salts are more stable, however, we recommend carring the reaction under hood. To evaluate the method and its safety, we scale up the iodination of aniline to 100 mmol without any explosion and decrease the yield.

The efficiency of [Hcpy]HSO_4 were compared with those of reported procedures. As illustrated in *Table 2*, the present method in most cases is superior to the other methods.

The present study describes a novel procedure for the synthesis of aryl iodides from corresponding aryl amines by the use of [Hcpy]HSO_4 under mild and green conditions. In this method, the as intermediate diazonium salts are stable for long time at room temperature without decomposition. The use of Brönsted ionic liquid as a green acid is another advantages of this method. As the diazonium salts in this acidic ionic liquid are stable, the reaction is safe and the procedure may be scaled up.

Experimental Section

All yields refer to isolated products after purification. All of the products were characterized by comparison of their spectral (IR, ^{1}H-NMR, TLC and GC) and physical data (combustion analysis, melting and boiling points) All ^{1}H-NMR and ^{13}C-NMR spectra were obtained at 300 and 75 MHz in $CDCl_3$ relative to TMS as an internal standard.

Synthesis of 3-Carboxypyridinium Hydrogen Sulfate ([Hcpy]HSO$_4$)

In a round-bottomed flask, 5.3 ml conc. sulfuric acid (98%, d 1.84) was added dropwise to a mixture of nicotinic acid (12.3 g, 100 mmol) in dichloromethane (40 ml) in an ice bath. The reaction mixture was stirred at room temperature for 30 min and then the solvent was evaporated under reduced pressure to obtain 3-carboxypyridinium hydrogen sulfate as colorless liquid in quantitative yield. ^{1}H NMR (300MHz, D_2O): δ 7.89 (m, 1H), 8.68 (m, 1H), 8.72 (m, 1H), 8.99 (m, 1H) ppm.^{13}C NMR (75MHz, D_2O): δ 127.67, 130.41, 127.24, 144.35, 147.17, 164.59 ppm. IR (KBr): 2465–3270, 1733, 1603, 1397, 1271, 1033, 735, 665 cm^{-1}.

Anal. Calcd for $C_6H_7NO_6S$: C, 32.58; H, 3.19; N, 6.33; S 14.50. Found: C, 32.70; H, 3.30; N, 6.80; S 14.30

General Procedure for the Synthesis of Iodoaromatic compounds

An aromatic amine (1 mmol), sodium nitrite (0.14 g, 2 mmol) and [Hcpy]HSO$_4$ (3 mmol, 0.66 g) were ground in a mortar with a pestle for 2–3 min to afford a homogeneous mixture. Then, 1 ml water was added and the reaction mixture was ground with pestle for 15–20 min until gas evolution ceased to give the corresponding aryldiazonium salt. Finally, sodium iodide (0.23 g, 1.5 mmol) was added to the paste-like diazonium salt. The iodination started immediately after the NaI was added, the volume of the paste increased due to the evolution of nitrogen gas. Then 20 ml of $Na_2S_2O_3$ (5%) was added to the reaction mixture and the precipitated were collected. The pure products were isolated by column chromatography with ethyl acetate: *n*-hexane (1:5) as eluent.

Acknowledgements

We gratefully acknowledge the funding support of this project by the Isfahan University of Technology (IUT), IR Iran (A.R.H.). Further financial support from Center of Sensor and Green Chemistry Research (IUT) is gratefully acknowledged.

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