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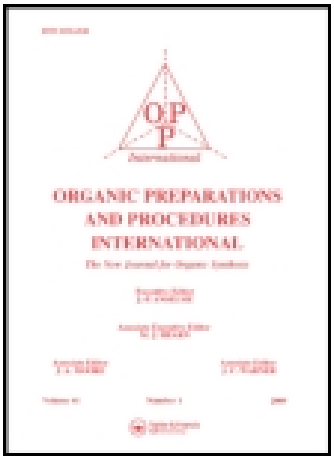

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Preparation of Aryl Azides from Aromatic Amines in *N*-Methyl-2-Pyrrolidonium Bisulfate

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Azides are useful intermediates for the synthesis of organic and bioorganic compounds.[1–6] Azidonucleosides have attracted tremendous interest for the treatment of AIDS.[7] In addition, due to their relatively high stability, aromatic azides have found biological[8,9] and industrial use as photoaffinity labels,[10,11] as cross-linkers in photoresistors,[12] for conducting polymer films,[13] and for light-induced activation of polymer surfaces.[14] Aromatic azides are generally prepared by treatment of diazonium salts with sodium azide, the most commonly used azide source. Aromatic diazonium salts are important intermediates not only in classical organic synthesis but also in the preparation of organic compounds such as organic nano-compounds and in the grafting of organic molecules onto metallic or non-metallic surfaces.[15–18] Therefore, the devel-opment of safe and mild conditions for the preparation of azides is a useful area of investigation.

The most commonly used procedure for the process of diazotization–azidation is usually carried out in two steps; diazotization of the amine with sodium nitrite at low temperatures in hydrochloric or sulfuric acid, and subsequent treatment with azide ion.[19] Usually this method must be carried out below 10°C to prevent phenol formation as a by-product in aqueous media. In continuation of our effort to develop efficient methods in organic synthesis,[20–24] we recently reported one-pot methods for azidation of aromatic compounds[25] by a diazotization-azidation sequence. In the present work, we have developed an efficient and simple method for the diazotization and azidation of aromatic amines using the acidic ionic liquid *N*-methyl-2-pyrrolidonium bisulfate ([H-NMP]HSO_4) as solvent and a novel proton source for the diazotization process at room temperature.

The diazotization of various aryl amines was easily carried out by grinding of the appropriate aromatic amine, $NaNO_2$ and acidic ionic liquid in the presence of a little water at room temperature. The mild reaction conditions, simple work-up and high yields led us to choose this method for the preparation of numerous aromatic azides (*Scheme* 1).

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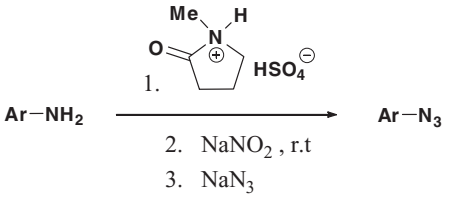

Scheme 1

The ionic liquid [H-NMP]HSO_4, was synthesized by reaction of 1-methylpyrrolidin-2-one with H_2SO_4 in a 1:1 molar ratio. Although the Brönsted acidity is one of the key properties of Brönsted acidic ILs, very little research has been conducted into this field.[26] Different techniques have been employed to measure the acidity of these ionic liquids.[27–29] The pKa value of [H-NMP]HSO_4 was determined by titration with NaOH. Despite the presence of two acidic protons in the structure of the ionic liquid, only one deprotonation step appeared on the pH-metric titration diagram and a pKa value of 1.65 was obtained. The acidic protons appears as a single signal in the ^{1}H NMR (500 MHz, DMSO) spectrum of the ionic liquid. Based on these results, it seems that there is a very rapid exchange between these protons.

This acidic ionic liquid was employed successfully for the synthesis of various aryl diazonium salts starting from the corresponding aryl amines. The prepared aryl diazonium salts were transformed in high yields to aryl azides in the presence of azide ion (*Table 1*).

Table 1
Synthesis of Aryl Azides from Aromatic Amines using [H-NMP]HSO_4[a,b]

Entry	Substrate	Product	Yield (%)	bp./mp (lit.) (°C)
1	4-$HO_2CC_6H_4NH_2$	4-$HO_2CC_6H_4N_3$	97	188–190 (190)[30]
2	4-$O_2NC_6H_4NH_2$	4-$O_2NC_6H_4N_3$	91	70–72 (70-71)[31]
3	2-$O_2NC_6H_4NH_2$	2-$O_2NC_6H_4N_3$	90	52–53 (51-53)[32]
4	4-$NCC_6H_4NH_2$	4-$NCC_6H_4N_3$	85	60–62 (56-59)[33]
5	3-$O_2NC_6H_4NH_2$	3-$O_2NC_6H_4N_3$	84	59–60 (55-56) [34]
6	4-$IC_6H_4NH_2$	4-$IC_6H_4N_3$	86	oil[33]
7	4-$BrC_6H_4NH_2$	4-$BrC_6H_4N_3$	78	Oil (20)[35]
8	4-$MeCOC_6H_4NH_2$	4-$MeCOC_6H_4N_3$	80	40–41 (40-45)[33]
9	4-$PhCOC_6H_4NH_2$	4-$PhCOC_6H_4N_3$	95	70–72 (70-71)[31]
10	2,3-$(Me)_2C_6H_4NH_2$	2,3-$(Me)_2C_6H_4N_3$	64	Oil[35]
11	2-$HO_2CC_6H_4NH_2$	2-$HO_2CC_6H_4N_3$	60	145–147 (147–148)[36]
12	$H_2NC_6H_4SO_2C_6H_4NH_2$	$N_3C_6H_4SO_2C_6H_4N_3$	96	153–154 (154–155)[37]
13	$H_2NC_6H_4OC_6H_4NH_2$	$N_3C_6H_4OC_6H_4N_3$	94	70–72 (67–68)[37]
14	$C_6H_5NH_2$	$C_6H_5N_3$	92	53–54 (53–54.5)[38]

[a]The yields refer to the isolated pure products.
[b]The products were characterized from their spectral (IR, ^{1}H NMR).

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The reactions were accomplished at room temperature in an aqueous medium and in the air without phenol formation as a by-product. Attempts to prepare the diazide from 4-aminoaniline were unsuccessful; however in the cases of *bis*-(*p*-aminophenyl)sulfone and *bis*-(*p*-aminopheny)ether, it was possible to produce the *bis* azides (*Table 1, Entries* ***12*** and ***13***) in high yields. The optimal molar ratio for amine/sodium nitrite/[H-NMP]HSO_4 and NaN_3 was found to be 1:2.5:4:2.5 and for the diamines the ratio was 1:5:8:5. The most important advantages of this diazotization-azidation method are simplicity, short reaction times, straightforward work-up, high yields and production of pure azide without further purification.

The stability of the intermediate aryldiazonium salts prepared using [H-NMP]HSO_4 was studied and it was found that keeping the aryldiazonium salts at room temperature for more than 1 hr, led to lower yields of aryl azides; however, storage of these compounds at 0°C temperature for longer period (up to 7 days) did not lower the overall yields.

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-azidation 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-azidation reaction rate increases using this procedure because these aryldiazonium salts are more stable, however, we recommend carrying the reaction under hood. To evaluate the method and its safety, we scaled up the preparation of phenyl azide from aniline to 100 mmol without any explosion or decreased yield.

In conclusion, we have developed an efficient and simple method for the diazotization and azidation of aromatic amines using the acidic ionic liquid [H-NMP]HSO_4 as a novel proton source for the diazotization process at room temperature. The resulting diazonium salts are relatively stable and react rapidly with sodium azide to produce aryl azides in high yields. The diazonium salts prepared may be kept at 0°C for several days without decomposition.

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Experimental Section

All chemical reagents were purchased from Merck and were used without purification. ^{1}H-NMR spectra were recorded on a Bruker 500 spectrometer using TMS as an internal standard in $CDCl_3$ and FT-IR spectra were obtained as KBr pellets on a JASCO 680-PLUS spectrophotometer. UV spectra were obtained by a JASCO V-570 UV spectrophotometer. Melting points were determined with a Gallenkamp melting apparatus and are uncorrected.

Preparation of Acidic ([H-NMP]HSO_4)

In a 25-mL round bottom flask a mixture containing 0.97 ml (10 mmol) of 1-methyl-2-pyrrolidone in dichloromethane (15 ml) was cooled in ice with stirring. Then 0.53 ml of sulfuric acid (10 mmol) was added dropwise to the reaction mixture within 10 min and the mixture was stirred for 4 h at room temperature. The dichloromethane was removed under reduced pressure using a rotary evaporator and the product was dried at 70°C under vacuum for 1 h to afford the product as an oil in quantitative yields. ^{1}H NMR (500 MHz,

DMSO): δ 1.86 (m, 2H, CH_2), 2.16 (t, 2H, CH_2), 2.65 (s, 3H, CH_3), 3.27 (t, 2H, CH_2), 9.15 (s, H). ^{13}C NMR (500 MHz, D_2O): δ 22.22 (CH_2), 35.09 (CH_2), 42.10–43.51 (CH_2, CH_3), 180 (C=O) ppm. FT-IR: 2300–3600, 1660, 1509, 1302, 1114, 962, 610 cm^{-1}.

Determination of pKa of the Acidic Ionic Liquid

A 0.1 mol L^{-1} solution of *N*-methyl-2-pyrrolidonium bisulfate [H-NMP]HSO_4 was prepared in a volumetric flask, then was titrated with aqueous NaOH solution (0.05 mol L^{-1}). The pH of the solution was measured using a calibrated glass electrode on pH meter at 25°C. The pKa value was calculated from the pH/ V graph.

General Procedure for the Preparation of Aryl Azides

An aromatic amine (1 mmol) was ground in a mortar with 2 ml of water and the acidic ionic liquid (4 mmol, 0.79 g) for 1 min. Then $NaNO_2$ (2.5 mmol, 0.175 g), was added and the mixture was ground for 15–20 min with periodic grinding using a pestle. Then, NaN_3 (2.5 mmol, 0.163 g) was added to the diazonium salt, and grinding continued for 5–10 min until gas evolution was completely stopped. The azidation reaction began immediately after NaN_3 addition, and the reaction mixture volume increased due to the evolution of nitrogen gas. The product paste was treated with water and the precipitated aryl azide products were collected and dried. The liquid azides were extracted with petroleum ether (3 × 20 mL). The solid aryl azides were washed with 10% HCl solution to produce the pure azides without further purification. The grinding of aryl azides using this procedure is safe and all of the reactions were carried out under fume hood.

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