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Effect of an Ionic liquid [Bmim][Tf_2N] on the rate of reaction in the synthesis of some azole compounds as antifungal agents

Soghra Khabnadideh[1, *], Jason B. Harper[2]

[1]School of Pharmacy and Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]School of Chemistry, University of New South Wales, Sydney NSW 2052, Australia

Email address:
khabns@sums.ac.ir (S. Khabnadideh)

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Abstract: 3-Butyl-1-methyl-1*H*-imidazol-3-iumbis((trifluoromethyl)sulfonyl)amide [Bmim][Tf_2N] as an environmental-friendly solvent was added to the reaction media for synthesis of some new azole compounds as antifungal agents. The effect of [Bmim][Tf_2N] on the rate of reactions was studied using NMR analysis. The results show remarkable increasing in the progress of the reactions. As in recent years the developments of resistance to currently available antifungal azoles in *Candida spp.*, as well as clinical failures in the treatment of fungal infections have been reported therefore intense efforts in antifungal drug discovery are still needed to develop more promising and effective antifungal agents for use in the clinical arena. We present a synthetic route for producing antifungal that is improved by using an ionic liquid.

Keywords: Synthesis, Ionic Liquid, NMR, Antifungal

1. Introduction

Ionic liquids have received considerable attention due to their interesting chemical and physical properties, such as wide liquid range with melting point around room temperature, good stability in air and moisture and high solubility. They are noncorrosive and immiscible with many organic solvents(1). Ionic liquids are alternative reaction media of increasing interest and are regarded as an eco-friendly alternatives, of potential use in place of the volatile organic solvents(2). Some of the reactions in organic solvents have limitations such as longer reaction time, harsher reaction conditions, expensive catalysts, and generation of large amounts of side products(3). The possibility to change solvent nature as a function of the studied reaction is very important. This justifies the growing interest in ionic liquids (ILs) over the past decade(4). Numerous chemical reactions, such as esterification reaction, aldol condensation, Koch carbonylation, polymerization, hydrogenation, Friedel-Crafts reactions, dimerization, Diels-Alder reactions, Mannich reaction, heterocyclic synthesis, cross-coupling reactions, nucleophilic substitution reactions and some enzyme reactions can be carried out in ionic liquids(1, 5-8). Ionic liquids show significant rate enhancements, high yields and selectivities comparable with the best results obtained in conventional solvents(9).

On the other hand invasive fungal infections will continue to cause major complications in immunocompromized patients(10). The recent expansion of antifungal drug research has occurred because there is a critical need for new antifungal agents to treat these life-threatening invasive infections(11). Benzimidazoles are considered as a promising class of bioactive heterocyclic compounds surrounding a diverse range of biological activities such as antihypertensive, anticoagulant, anti-inflammatory and antimicrobial(12). Our previous studies also have been showed benzimidazole derivatives had significant potential for antifungal activity(13, 14). In view of our interest in the development of new syntheses of various antifungal compounds, we investigated the synthesis of benzimidazole derivatives.

In this study some new derivatives of 2-methylbenzimidazole *(series a)*, 5,6-dimethylbenzimidazole *(series b)* and 2-methylimidazole *(series c)* were synthesized and the effect of an ionic liquid, 3-butyl-1-methyl-1*H*-imidazol-3-ium bis-((trifluoromethyl) sulfonyl)amide ([Bmim][Tf_2N]) *(2)*, on the rate of some reactions were investigated.

2. Experimental

2.1. Materials

All chemicals and solvents were purchased from Merck, Germany. ^{1}HNMR spectra were obtained on a Bruker Avance DPX 500 MHZ instrument, USA. Thin-layer chromatography (TLC) was performed using 250 μm silica gel GF plates, Merck, Germany. All reactions were carried out under nitrogen gas.

2.2. Synthesis of Azole Compounds

To a round-bottom flask filled with dry nitrogen, the azole rings reacted with appropriate aryl or alkyl halide (as chloride) in the presence of triethylamine in toluene at reflux for 24 hr unless otherwise specified (this length of time is consistent with literature and allows the product to be isolated; no optimizationwas attempted). Quantities of reagents were chosen for ease of work-up (13, 15). The solvent was evaporated *in vacuo* and the crude product purified by column chromatography using methanol/dichloromethane (1/9) to give the final product. Chemical structures of the final compounds were confirmed using spectroscopic methods (see Table 1).

Series a:

2-Methyl-N,N-diphenyl-1H-benzo[d]imidazole-1-carboxamide (1a)

2-Methyl-1*H*-benzo[*d*]imidazole (2.5mmol, 330 mg), diphenylcarbamic chloride (2mmol, 463 mg) and triethylamine (2.5 mmol, 253 mg, 0.35 ml) were reacted in toluene (15 ml) to give 1a as a white solid (395 mg, 60%, R_f= 0.5).

N,N-Diethyl-2-methyl-1H-benzo[d]imidazole-1-carboxamide (2a)

2-Methyl-1*H*-benzo[*d*]imidazole (6mmol, 793 mg), diethylcarbamic chloride (6mmol, 814 mg, 0.76 ml) and triethylamine (6mmol, 608 mg, 0.83 ml) were reacted in toluene (20 ml) to give 2a as a brown liquid (1.11g, 80%, R_f = 0.7).

2-Methyl-1-trityl-1H-benzo[d]imidazole (3a)

2-Methyl-1*H*-benzo[*d*]imidazole (2 mmol, 265 mg), *chloro(triphenyl)methane (2 mmol, 558 mg) and triethylamine (2 mmol, 202 mg, 0.28 ml) were reacted in toluene (15 ml) to give 3a as a white solid (525 mg, 70%, R_f = 0.6).*

2-Methyl-1-(3-methylbenzyl)-1H-benzo[d]imidazole (4a)

2-Methyl-1H-benzo[d]imidazole (2.5 mmol, 330 mg), 1-(chloromethyl)-3-methylbenzene (2.5 mmol, 352 mg, 0.33 ml) and triethylamine (2.5 mmol, 253 mg, 0.35 ml) were reacted in toluene (15 ml) to give 4a as a brown liquid (500 mg, 85%, R_f = 0.6).

Series b:

N,N-Diethyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1b)

5,6-Dimethyl-1H-benzo[d]imidazole (3 mmol, 440 mg), diethylcarbamic chloride (3 mmol, 407 mg, 0.38 ml) and triethylamine (3 mmol, 304 mg, 0.4 ml) were reacted in toluene (15 ml) to give 1b as a brown liquid (680 mg, 92%, R_f = 0.4).

5,6-Dimethyl-1-trityl-1H-benzo[d]imidazole (2b)

5,6-Dimethyl-1H-benzo[d]imidazole (3 mmol, 440 mg), chloro(triphenyl)methane (3 mmol, 836 mg) and triethylamine (3 mmol, 304 mg, 0.4 ml) were reacted in toluene (15 ml) to give 2b as a white solid (760 mg, 65%, R_f = 0.7).

5,6-Dimethyl-1-(3-methylbenzyl)-1H-benzo[d]imidazole (3b)

5,6-Dimethyl-1H-benzo[d]imidazole (2.5 mmol, 365 mg), 1-(chloromethyl)-3-methylbenzene (2.5mmol, 352 mg, 0.33 ml) and triethylamine (2.5 mmol, 253 mg, 0.35 ml) were reacted in toluene (15 ml) to give 3b as a white solid (457 mg, 73%, R_f= 0.6).

2-Chloro-1-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)ethanone 4b)

5,6-Dimethyl-1H-benzo[d]imidazole (1 mmol, 146 mg), chloroacetyl chloride (1 mmol, 113mg, 0.08 ml) and triethylamine (1 mmol, 101 mg, 0.14 ml) were stirred in toluene (10 ml) at room temperature for 4 hr. The solvent was evaporated in vacuo, the residue was quenched with aqueous sodium hydroxide (5 ml, 1M) and the mixture extracted with dichloromethane. The organic layer was dried using magnesium sulfate and the solvent removed in vacuo to give 4b as a brown powder (130 mg, 58%, R_f =0.5).

Series c:

1-(2-Methyl-1H-imidazol-1-yl)-2-phenylethanone (1c)

2-Methyl-1H-imidazole (2mmol, 165 mg), 2-phenylacetyl chloride (2mmol, 310 mg, 0.26 ml) and triethylamine (2mmol, 202 mg, 0.28 ml) were reacted in toluene (15 ml) to give 1c as brown solid (160mg, 40%, R_f =0.3).

2-Methyl-N,N-diphenyl-1H-imidazole-1-carboxamide (2c)

2-Methyl-1H-imidazole (1mmol, 82 mg), diphenylcarbamicchloride (1mmol, 231 mg) and triethylamine (1mmol, 101 mg, 0.14 ml) were reacted in toluene (10 ml) to give 2c as a solid white powder (170 mg, %61, R_f =0.3).

2.3. Synthesis of Ionic Liquid

3-Butyl-1-methyl-1H-imidazol-3-ium bis((trifluoromethyl) sulfonyl)amide (2)

To a round-bottom flask filled with dry nitrogen, 1-methyl-1 *H*-imidazole (100 mmol, 8.21 g, 7.93 ml) and 1-chlorobutane (120 mmol, 1.11 g, 12.5 ml) were heated at reflux for 5 days. The upper phase was unreacted starting material, the lower phase was collected and washed with ethyl acetate (3×20ml) and dried *in vacuo* to give 3-butyl-1-methyl-1*H*-imidazol-3-ium chloride *(1)* as a pale solid (16.6 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.831 (t, 3H, CH_2-C$\underline{H}_3$, 1.25 (m, 2H, C$\underline{H}_2$CH$_3$), 1.78 (m, 2H, C$\underline{H}_2$CH$_2$CH$_3$), 4.00 (s, 3H NC$\underline{H}_3$); 4.22 (m, 2H, N-C$\underline{H}_2$), 7.46 (s, 1H-Imidazole), 7.62 (s, 1H-Imidazole), 10.35 (s, 1H-Imidazole).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ13.33 ($CH_2\underline{C}H_3$), 19.33 ($\underline{C}H_2CH_3$), 32.05 ($\underline{C}H_2CH_2CH_3$), 36.42 (N$\underline{C}H_3$), 49.61 (N$\underline{C}H_2$), 122.03 ($\underline{C}$=C). 123.72 (C=$\underline{C}$), 137.53 (N-$\underline{C}$=N).

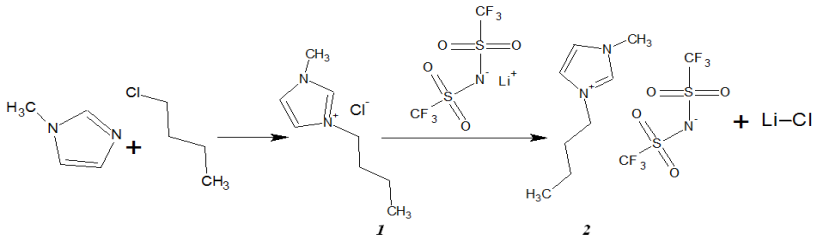
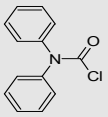
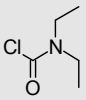
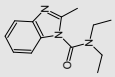
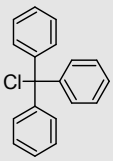
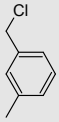
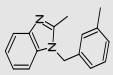
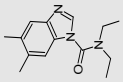
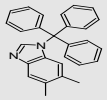
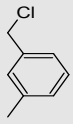
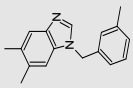
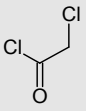
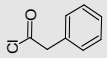
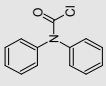
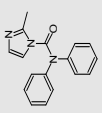


Figure 1. *Synthesis of ionic liquid.*

Table 1. *Synthesis of new azole compounds.*

Compds.	Azole ring	R	Product	Spectroscopic data	Formula, M.W.
1a	2-methyl-benzimidazole			^{1}H NMR: δ 2.75 (s, 3H, C<u>H</u>$_3$), 7.15-7.60 (m, 14H, Aromatic). ^{13}C NMR: δ 15.60, 111.70, 119.24, 123.33, 123.37, 125.94, 127.22, 129.51, 132.56, 142.09, 151.11, 151.89. MS: (m/z, %), 328 (M+, 100), 196 (7).	$C_{21}H_{17}N_3O$, 327.38
2a	2-methyl-benzimidazole			^{1}H NMR: δ 1.15-1.16 (m, 6H, (C<u>H</u>$_3$)$_2$), 2.60 (s, 3H, CH$_3$), 3.35-3.37 (m, 4H, (CH$_2$)$_2$), 7.19-7.67 (m, 4H, Aromatic). ^{13}C NMR: δ 14.70, 22.22, 42.34, 112.89, 121.81, 131.08, 132.13, 140.54, 153.63. MS: (m/z, %), 232 (M+, 100).	$C_{13}H_{17}N_3O$, 231.29
3a	2-methyl-benzimidazole			^{1}H NMR: δ 2.00 (s, 3H, C<u>H</u>$_3$), 5.73-7.72 (m, 19H, Aromatic). ^{13}C NMR: δ 19.41, 114.80, 118.74, 121.54, 121.58, 128.01, 130.42, 136.52, 142.46, 154.60. MS: (m/z, %), 375 (M+, 55), 243 (100), 133 (12).	$C_{27}H_{22}N_2$, 374.48
4a	2-methyl-benzimidazole			^{1}H NMR: δ 2.30 (s, 3H, Benzene-C<u>H</u>$_3$), 2.58 (s, 3H, Imidazole-C<u>H</u>$_3$), 5.28 (s, 2H, C<u>H</u>$_2$), 6.89-7.77 (m, 8H, Aromatic). ^{13}C NMR: δ 14.61, 23.20, 114.87, 123.37, 132.08, 148.63, 157.39. MS: (m/z, %), 237 (M+, 100), 133 (3).	$C_{16}H_{16}N_2$, 236.31
1b	5,6-dimethyl-benzimidazole			^{1}H NMR: δ 1.18 (m, 6H, (C<u>H</u>$_3$)$_2$), 2.33 (s, 3H, CH$_3$), 2.34 (s, 3H, CH$_3$), 3.42-3.44 (m, 4H, (CH$_2$)$_2$), 7.34 (s, 1H, Benzene), 7.52 (s, 1H, Benzene) 8.36 (s, 1H, Imidazole). ^{13}C NMR: δ 13.71, 20.22, 42.84, 112.80, 120.31, 131.08, 132.13, 133.42, 141.64, 141.75, 151.35. MS: (m/z, %), 246 (M+, 100).	$C_{14}H_{19}N_3O$, 245.32
2b	5,6-dimethyl-benzimidazole			^{1}H NMR: δ 2.06 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 6.27 (s, 1H, Benzene), 7.32-7.33 (m, 15H, Trityl). 7.59 (s, 1H, Benzene), 7.84 (s, 1H, Imidazole). ^{13}C NMR: δ 20.19, 20.52, 75.25, 115.44, 120.16, 127.96, 128.12, 130.08, 130.99, 131.38, 133.41, 141.55, 143.24, 143.47. MS: (m/z, %), 389 (M+, 45), 243 (100).	$C_{28}H_{24}N_2$, 388.50
3b	5,6-dimethyl-benzimidazole			^{1}H NMR: δ 2.34-2.40 (m, 9H, CH$_3$), 5.31 (s, 1H, CH$_2$), 5.79 (s, 1H, CH$_2$), 7.02 (s, 1H, Benzene), 7.03-7.29 (m, 4H, Phenyl), 7.65 (s, 1H, Benzene), 7.94 (s, 1H, Imidazole). ^{13}C NMR: δ 20.27, 20.60, 21.39, 48.67, 110.14, 120.32, 124.10, 127.66, 128.88, 128.92, 131.18, 132.27, 135.75, 138.81, 142.52. MS: (m/z, %), 251 (M+, 100), 145 (2).	$C_{17}H_{18}N_2$, 250.34
4b	5,6-dimethyl-benzimidazole			^{1}H NMR: δ 2.39 (s, 6H, CH$_3$), 5.23 (s, 2H, CH$_2$), 7.29 (s, 1H, Benzene), 7.44 (s, 1H, Benzene), 8.01 (s, 1H, Imidazole). ^{13}C NMR: δ 16.77, 24.20, 125.30, 139.16, 141.23, 148.75, 157.34. MS: (m/z, %), 223 (M+, 9), 147 (100).	$C_{11}H_{11}ClN_2O$, 222.67
1c	2-methyl-imidazole			^{1}H NMR: δ 1.28 (s, 3H, C<u>H</u>$_3$), 2.31 (s, 2H-CH$_2$), 6.73-7.37 (m, 7H, Aromatic). ^{13}C NMR: δ 12.80, 121.88, 132.08, 144.60. MS: (m/z, %), 201 (M+, 100), 120 (56), 82 (4).	$C_{12}H_{12}N_2O$, 200.24
2c	2-methyl-imidazole			^{1}H NMR: δ 2.64 (s, 3H, C<u>H</u>$_3$), 6.68 (s, 1H-Iimidazole), 6.72 (s, 1H-Imidazole), 7.13-7.38 (m, 10H, Phenyl). ^{13}C NMR: δ 16.81, 119.88, 130.08, 139.13, 147.60, 151.35. MS: (m/z, %), 278 (M+, 100), 196 (10), 169 (4).	$C_{17}H_{15}N_3O$, 277.32

Lithium bis((trifluoromethyl)sulfonyl)amide (110mmol, 31.6 g), distilled water (50 ml) was added to 3-butyl-1-methyl-1*H*-imidazol-3-ium chloride (95 mmol, 16.6 g) and the reaction mixture was stirred for 3 hours at room temperature. The upper phase was aqueous, the lower phase was collected and dried *in vacuo* to give the desired ionic liquid *(2)* as a colorless liquid (35.9 g, 90 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_2-C$\underline{H}_3$), 1.37 (m, 2H, C$\underline{H}_2CH_3$), 1.87 (m, 2H, C$\underline{H}_2CH_2CH_3$), 3.96 (s, 3H NC$\underline{H}_3$); 4.19 (m, 2H, N-C$\underline{H}_2$), 7.29 (s, 1H-Imidazole), 7.33 (s, 1H-Imidazole), 8.75 (s, 1H-Imidazole).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ13.18 ($CH_2\underline{C}H_3$), 19.31 ($\underline{C}H_2CH_3$), 31.90($\underline{C}H_2CH_2CH_3$), 36.31 (N$\underline{C}H_3$), 49.94(N$\underline{C}H_2$), 117.66 ($\underline{C}F_3$), 121.92 ($\underline{C}F_3$), 122.25 ($\underline{C}$=C). 123.68 (C=$\underline{C}$), 136.05 (N-$\underline{C}$=N).

3. Results

3.1. Effect of [Bmim][Tf_2N] on the Progress of the Reaction

In order to determine the effect of [Bmim][Tf_2N] on progress of the reactions, first compound *2a* was selected and prepared under the following four conditions *(A-D)*. For this purpose 2-methyl-1*H*-benzo[*d*]imidazole (3mmol, 396 mg) and diethylcarbamic chloride (3mmol, 407mg, 0.32 ml) were reacted at 120˚C in either:

1. Toluene (12 ml),
2. Toluene (12 ml) containing triethylamine (3 mmol, 304 mg, 0.4 ml),
3. [Bmim][Tf_2N] (8.8ml) and toluene (3.2 ml), containing triethylamine (3 mmol, 304 mg, 0.4 ml), or
4. [Bmim][Tf_2N] (8.8 ml) and toluene (3.2 ml).

The yields for the reactions under these conditions are shown in Table 2.

Table 2. *Synthesis of compound 2a under different conditions (A-D).*

Entry	Solvent	Base	Yield (%)
A	Toluene	None	20
B	Toluene	triethylamine	70
C	Toluene/[Bmim][Tf_2N] (50/50 by mole)	Triethylamine	60
D	Toluene/[Bmim][Tf_2N] (50/50 by mole)	None	50

Comparison between the yields for the entries *A* and *B* shows an important role for triethylamine because it increases the yield of the reaction by 50%. But comparison between the yields for the entries *C* and *D* which took placed in the presence of [Bmim][Tf_2N], shows only a slight increase in the yield in the presence of triethylamine. It means ionic liquid has a significant solvent effect on the reaction outcome. This conclusion is supported by similar result which is obtained from the comparison between the yields of the conditions *A* and *D*.

3.2. Effect of the [Bmim][Tf_2N] on the Rate of the Reactions

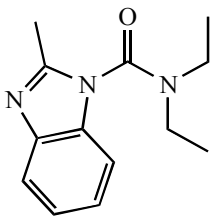


Figure 2. *Chemical structure of compound 2a*

In order to determine the effect of [Bmim][Tf_2N] on the rate of the reaction, two options of the above 4 entries *(A-D)* which had the greatest isolated yields (conditions *B* and *C*) were selected. The reaction to form compound *2a* was repeated and analyzed using ^{1}H NMR spectroscopy to follow formation of the product. For this purpose 2-methyl benzimidazole (132.7 mg, 1 mmol), diethyl carbamyl chloride (0.15 ml, 1.2 mmol, 162.6 mg) and triethylamine (0.13 mL, 1 mmol) were refluxed at 120˚C in either:

A. Toluene (2.5 ml), or

B. Toluene (0.7 ml and [Bmim][Tf_2N] (1.8 ml).

One drop of the reaction mixture was concentrated *in vacuo* and analyzed using ^{1}H NMR spectroscopy after 1, 1.5,2, 3, 4, 6, 8, 12 and 24 hr. The integrals of the signal due to the two CH_2 groups in the side chain were compared to the integral of the signal due to the methyl group of benzimidazole calculate the percent of conversion using the Equation 1.

Equation 1: % of Conversion=(X/3)(3/4)(100)

X=Integral of the signal due to the two CH_2 groups.

The results showed the reaction in the presence of [Bmim][Tf_2N] was complete in 1 hr whereas at this time the reaction in the absence of [Bmim][Tf_2N] had only proceeded to 53% (Table 3 and Figure 1). As such, the process was repeated over a much shorter time frame and at a lower temperature.

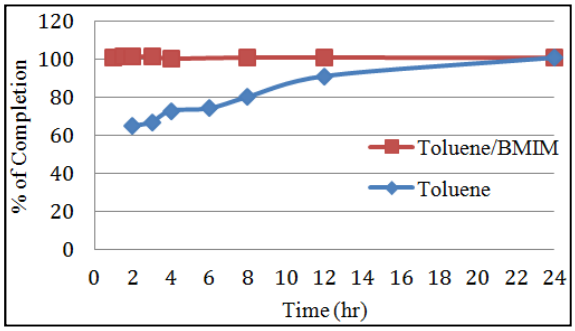


Figure 3. *Effect of [Bmim][Tf_2N]on the extent of conversion for synthesis of compound 2a in 24 hr.*

Table 3. *Effect of [Bmim][Tf_2N] on the extent of conversion for synthesis of compound 2a in 24 hr.*

time (hr)	integral of $(CH_2)_2$ in toluene	integral of $(CH_2)_2$ in [Bmim][Tf_2N]	% of conversion in toluene	% of conversion in [Bmim][Tf_2N]
1	-	4.04	-	101
1.5	-	4.06	-	101.5
2	2.6	4.07	65	101.75
3	2.68	4.07	67	101.75
4	2.92	4.02	73	100.5
6	2.97	-	74.25	-
8	3.21	4.05	80.25	101.25
12	3.65	4.05	91.25	101.25
24	4.04	4.04	101	101

Table 4. *Effect of [Bmim][Tf_2N]on the extent of conversion of compound 2a in 180 min.*

time (min)	integral of $(CH_2)_2$ in toluene	integral of$(CH_2)_2$ in [Bmim][Tf_2N]	% of conversion in toluene	% of conversion in [Bmim][Tf_2N]
2	-	2.34	-	58.5
5	0.11	2.4	2.75	60
10	0.95	2.47	23.75	61.75
15	1.42	2.72	35.5	68
20	1.84	3.27	46	81.75
30	1.94	3.8	48.5	95
60	2.144	4.04	53.6	101
90	2.489	4.06	62.225	101.5
120	2.6	4.2	65	105
180	2.68	4.26	67	106.5

Table 5. *Effect of [Bmim][Tf_2N] on the extent of conversion and isolation of compounds 3a, 4a and 1b-3b.*

Compds.	Azole (1 mmol)	Halide (1 mmol)	Base (1 mmol)	Temperature (°C)	Time (hr)	Eluent for column chromatography
3a	2-methyl-1H-benzo[d]imidazole	(chloromethanetriyl)tribenzene	TEA	80	2	MeOH/DCM
4a	2-methyl-1H-benzo[d]imidazole	1-(chloromethyl)-3-methylbenzene	TEA	90	3	MeOH/DCM
1b	5,6-dimethyl-1H-benzo[d]imidazole	diethylcarbamic chloride	TEA	90	3	MeOH/DCM
2b	5,6-dimethyl-1H-benzo[d]imidazole	(chloromethanetriyl)tribenzene	TEA	80	3	MeOH/ $CDCl_3$
3b	5,6-dimethyl-1H-benzo[d]imidazole	1-(chloromethyl)-3-methylbenzene	TEA	90	3	MeOH/$CDCl_3$

Table 6. *Extent of conversions and yields for synthesis of compounds 2a-4a, 1b-3b in the presence and absence of [Bmim][Tf_2N].*

Compds.	Extent of conversion in toluene (%)	Extent of conversion in toluene and [Bmim][Tf_2N] (%)	Yield in toluene (%)	Yield in toluene and [Bmim][Tf_2N] (%)
2a	53.6	100	40	70
3a	61.75	100	50	75
4a	27.8	44.8	20	28
1b	58.5	84.5	40	50
2b	13	36.5	10	22
3b	27.5	33	18	35

The reaction was repeated at 90°C and analyzed as described above. Results after the first hour were comparable to previously and the extent of conversion at a given time was much greater when the ionic liquid was present.

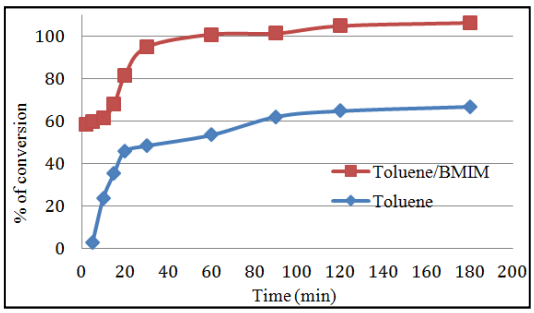


Figure 4. *Effect of [Bmim][Tf_2N]on the extent of conversion for synthesis of compound 2a in 180 min.*

Similar analyses were carried out for compounds *3a, 4a* and *1b-3b*. The extent of conversion after a fixed time was analysed in both toluene and toluene/ionic liquid mixtures. Subsequently the efficacy of separation was tested by isolating the compounds using flash column chromatography. The conditions used are described in Table 5 and the outcomes in Table 6.

For compound *3a* the integrals of the signal due to the aromatic protons were compared to the integral of the signal due to the methyl group to calculate the percent of conversion using Equation 2.

Equation 2: % of Conversion=(X/3)(3/19)(100)

X=Integral of the signal due to the aromatic protons

For compound *4a* the integrals of the signal due to the methylene group compared to the integral of the signal due to the two methyl groups to calculate the percent of conversion using Equation 3.

Equation 3: % of Conversion=(X/6)(6/2)(100)

X=Integral of the signal due to the methylene group

For compound *1b* the integrals of the signal due to the two methylene groups compared to the integral of the signal due to the two methyl groups of benzimidazole ring to calculate the percent of conversion using Equation 4.

Equation 4: % of Conversion=(X/6)(6/2)(100)

X=Integral of the signal due to the two methylene groups

For compound *2b* the integrals of the signal due to the aromatic protons compared to the integral of the signal due to the two methyl groups to calculate the percent of conversion using Equation 5.

Equation 5: % of Conversion=(X/6)(6/18)(100)

X=Integral of the signal due to the aromatic protons

For compound *3b* the integrals of the signal due to the methylene group compared to the integral of the signal due to the three methyl groups to calculate the percent of conversion using Equation 6.

Equation 6: % of Conversion=(X/9)(9/2)(100)

X=Integral of the signal due to the methylene group

Immediately apparent from Table 6 is that for all the compounds consider, the extent of conversion is greater in the presence of an ionic liquid. This demonstrates a significant solvent effect and that the ionic liquid is increasing the rate of formation of the desired products.

Also of note is the fact that the isolated yields of the compounds from the ionic liquid mixture do not always parallel the increase in the extent of conversion. This demonstrates the difficulty in isolating compounds from ionic liquid mixtures and must be taken into account when considering the use of ionic liquids in organic synthesis.

4. Conclusion

Using the traditional bases generally suffered from disadvantages such as waste production, corrosion and environmental problems. Ionic liquids offer a potential way to increase the extent of conversion, in both the presence and absence of bases (1). There has been increasing concern for the development of new greener synthetic pathways which avoid the use of volatile organic solvents and replace them with non-flammable, nonvolatile, non-toxic, and inexpensive green solvents(3). However, many processes carried out in ionic liquids proceed very differently when compared to those in traditional organic solvents. Examples include changes in the rates and selectivity(16).

Our results showed that rate of the reaction for the synthesis of azole compounds is increased dramatically by [Bmim][Tf_2N]. The only disadvantage of this method was in the purification step with difficulty in isolating the material from the ionic liquid.

Acknowledgement

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