

## 1-Butyl-3-methylimidazolium Nitrite as a Reagent for the Efficient *N*-Nitrosation of Secondary Amines

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1-Butyl-3-methylimidazolium nitrite, [bmim]NO<sub>2</sub> was used as a new effective reagent for the preparation of *N*-nitrosamines from the corresponding secondary amines at 0 °C to room temperature, under mild conditions in good to excellent yields.

**Keywords:** *N*-Nitrosation, Secondary amines, *N*-Nitrosoamines, Task-specific ionic liquid

### INTRODUCTION

*N*-Nitrosoamines as important organic compounds have attracted considerable interest in recent years due to their strong mutagenic and carcinogenic properties [1] and are prepared *via* the *N*-nitrosation of amines. These compounds are involved in vasorelaxant activity and have been used as pesticides [2]. These useful synthetic intermediates have been used for the synthesis of various *N,N*-bonded functionalities. From among a variety of reported nitrosating agents, nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol-water solvents, is mostly used for the nitrosation of amines [3]. Nitrosyl salts [4], alkyl nitrites [5], dinitrogen tetroxide [6], oxyhyponitrite [7], Fremy's salt [8], *N*-haloamides and sodium nitrite under phase-transfer conditions [9], bis(triphenylphosphine) ammonium nitrite [10], solid acids [11-13], [NO<sup>+</sup>. Crown. H (NO<sub>3</sub>)<sub>2</sub>] [14], and silica chloride/NaNO<sub>2</sub> [15] are also reported as nitrosating reagents in literature. The application of N<sub>2</sub>O<sub>4</sub>/NO<sub>2</sub> in organic reactions was recently reported by Shiri *et al.* [16].

On the other hand, room temperature ionic liquids are very attractive alternatives to volatile solvents due to their very low vapor pressure and being thermally stable. Ionic liquids have

been successfully used as solvents and/or catalysts in several classical organic processes [17-19]. Ionic liquids containing specific functional groups, known as task-specific ionic liquids (TSILs), can be used as reagent and/or catalyst and as reaction medium, which further enhances the versatility of ionic liquids [20-22]. Haihong and co-workers used task-specific basic ionic liquid immobilized on mesoporous silicas as an efficient and reusable catalyst for Knoevenagel condensation in aqueous media [23]. Hajipour *et al.* prepared aldoximes using *in situ* prepared ionic liquids under convenient conditions [24].

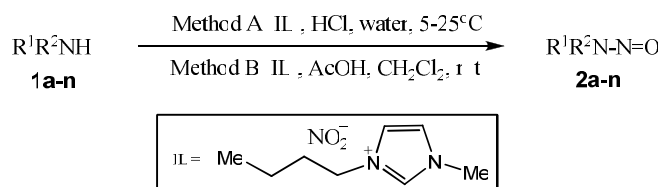
Recently we used the TSIL-OPPh<sub>2</sub> as a weak Lewis base catalyst and reaction medium for the Biginelli and Knoevenagel reactions as well as in the synthesis of nitrones [25-27]. We also reported the diazotization of anilines using a new nitrite ionic liquid (IL-ONO) and the subsequent azo-coupling for the efficient preparation of azo dyes [28]. We wish to report here the efficient *N*-nitrosation of secondary amines **1a-n** using task-specific nitrite ionic liquid, [bmim]NO<sub>2</sub> under mild conditions. (Scheme 1).

### EXPERIMENTAL

#### General

All reagents were purchased from Merck Company and used without further purification. Infrared spectra were

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Scheme 1. 1-Butyl-3-methylimidazolium nitrite as a new reagent for the nitrosation of secondary amines

recorded in KBr and were determined on a Perkin Elmer FT-IR spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance AC-400 MHz using  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  as the deuterated solvent and TMS as the internal standard. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. All melting points were measured in open glass-capillaries using Stuart melting point apparatus.

### Preparation of 1-Butyl-3-methylimidazolium Nitrite, [bmim] $\text{NO}_2$

1-Butyl-3-methylimidazolium chloride was prepared from the reaction of *N*-methylimidazole with *n*-butylchloride at  $80^\circ\text{C}$  under neat conditions. Sodium nitrite (23 mmol) was added to a solution of this freshly prepared ionic liquid (20 mmol) in dichloromethane (10 ml) and stirred for 24 h at room temperature. The suspension was filtered to remove the precipitated sodium chloride salt and the organic layer was washed with water ( $3 \times 8$  ml) to the extent that no precipitation of  $\text{AgCl}$  occurred in aqueous phase on addition of a concentrated  $\text{AgNO}_3$  solution. The solvent and other volatile materials were removed from organic layer under vacuum and the resulting ionic liquid was stirred with activated charcoal for 12 h, after which the ionic liquid was passed through a short alumina column(s) (acidic and/or neutral) to give a colorless ionic liquid, which was dried at  $100^\circ\text{C}$  under vacuum for 24 h or until there was no visible signs of water in the IR spectrum. Yields 80%. IR (KBr): 1652, 1617, 1532, 1350, 1190  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.05 (3H, t,  $-\text{CH}_3$ ), 1.41 (2H, m,  $\text{CH}_2$ ), 1.76 (2H, m,  $\text{CH}_2$ ), 3.83 (3H, s,  $\text{N-CH}_3$ ), 3.97 (2H, t,  $-\text{N-CH}_2$ ), 7.21 (1H, d, Ar-H), 7.40 (1H, d, Ar-H), 9.12 (1H, broad, Ar-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ ) 11.7, 18.3, 25.6, 36.4, 37.8, 124.7, 126.8, 140.0. Anal. Calcd. (%) for  $\text{C}_8\text{H}_{15}\text{N}_3\text{O}_2$ : C, 51.88; H, 8.16; N, 22.69.

Found (%): C, 52.12; H, 8.21; N, 22.58.

### General Procedure for *N*-Nitrosation Using New Nitrite Ionic Liquid

**Method A.** Secondary amine (10 mmol) and concentrated hydrochloric acid (12.5 mmol) were mixed in water or alcohol-water solvent and stirred vigorously at  $5^\circ\text{C}$ . While stirring the mixture, a solution of [bmim] $\text{NO}_2$  (11 mmol) in water (3 ml) was added gently and stirring was continued for 30 min at  $5\text{--}25^\circ\text{C}$ . The precipitate, *N*-nitrosamine, was filtered and washed with cold water. For the soluble nitrosamines in water, NaCl was added for precipitation of the products. The crude product was recrystallized from EtOH/AcOEt to obtain pure nitrosamine. If required, this product is further purified by flash chromatography on silica gel using ethylacetate/petroleum ether (1:7) as eluent.

**Method B.** A mixture of secondary amine (10 mmol), [bmim] $\text{NO}_2$  (11 mmol) and acetic acid (12.5 mmol) in dichloromethane (5 ml) was stirred vigorously at room temperature till the completion of the reaction as indicated by TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by recrystallization from EtOH/EtOAc to obtain the related *N*-nitroso product **2a-n** (Table 1). If required, this product was further purified by flash chromatography on silica gel using ethylacetate/petroleum ether (1:7) as eluent.

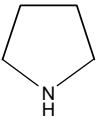
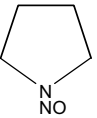
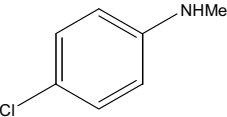
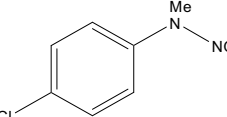
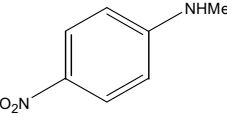
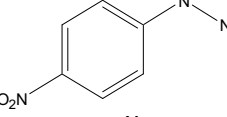
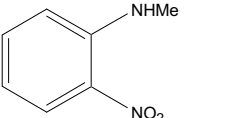
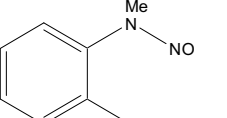
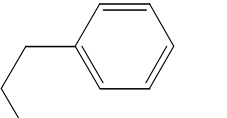
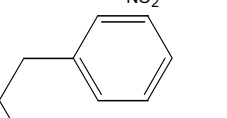
## RESULTS AND DISCUSSION

The ionic liquid, 1-butyl-3-methylimidazolium nitrite was prepared from 1-butyl-3-methylimidazolium chloride by the exchange of chloride anion with nitrite anion in contact with sodium nitrite solution at room temperature in 80% yield. The [bmim] $\text{NO}_2$  was then evaluated as the nitrosation source for the nitrosation of secondary amines in the presence of an acid.

As a typical experiment, dibenzylamine was chosen as a model secondary amine. While stirring the mixture of an equimolar amount of dibenzylamine and HCl 37% in water, [bmim] $\text{NO}_2$  was added at  $5\text{--}25^\circ\text{C}$ . TLC monitoring showed the completion of the reaction after 25 min and the related *N*-nitrosamine product, *N*-nitrosodibenzylamine **2f**, was isolated in 85% yield. The stable *N*-nitroso product was characterized by FT-IR and  $^1\text{H}$  NMR spectroscopy and elemental analysis.

## 1-Butyl-3-methylimidazolium Nitrite as a Reagent

**Table 1.** 1-Butyl-3-Methylimidazolium Nitrite as a New Reagent for the Efficient N-Nitrosation of Secondary Amines

Entry	Substrate	Nitrosamine	Product number	Time(min)		Yield (%) <sup>a</sup>	
				Method A	Method B	Method A	Method B
1	Me <sub>2</sub> NH	Me <sub>2</sub> NNO	<b>2a</b>	30	35	89	86
2	Et <sub>2</sub> NH	Et <sub>2</sub> NNO	<b>2b</b>	30	35	85	86
3	Bu <sub>2</sub> NH	Bu <sub>2</sub> NNO	<b>2c</b>	35	45	88	88
4	(i-propyl) <sub>2</sub> NH	(i-propyl) <sub>2</sub> NNO	<b>2d</b>	30	40	82	84
5	Ph <sub>2</sub> NH	Ph <sub>2</sub> NNO	<b>2e</b>	25	30	91	88
6	(PhCH <sub>2</sub> ) <sub>2</sub> NH	(PhCH <sub>2</sub> ) <sub>2</sub> NNO	<b>2f</b>	30	40	90	88
7	PhNHMe	PhN(NO)Me	<b>2g</b>	32	40	92	90
8			<b>2h</b>	40	50	83	80
9	PhCH <sub>2</sub> NHEt	PhCH <sub>2</sub> N(NO)Et	<b>2i</b>	30	35	85	82
10	PhCH <sub>2</sub> NHMe	PhCH <sub>2</sub> N(NO)Me	<b>2j</b>	35	45	83	80
11			<b>2k</b>	30	35	88	87
12			<b>2l</b>	32	40	92	91
13			<b>2m</b>	30	35	90	85
14			<b>2n</b>	35	35	87	87

<sup>a</sup>Isolated yield.

Optimization of the reaction conditions was studied with different molar ratios of the HCl, ionic liquid and dibenzylamine. The best ratio was found to be 1.25:1.10:1. Under optimized conditions, the product **2f** was prepared in 90% yield (Method A, Table 1). We examined this procedure in various organic solvents using several organic acids such as AcOH, benzenesulfonic acid and benzoic acid as catalysts. From the results obtained, it was clear that the reaction in dichloromethane using AcOH should be the one for the

nitrosation of secondary amines, since a comparatively higher yield was produced in a shorter reaction time (Method B, Table 1). This ionic liquid was then used for the nitrosation of different secondary amines under optimized conditions *via* the two methods. For comparison, the results from the two methods are presented in Tables 1 and 2.

Chemoselectivity of these methods was determined *via* the competitive reaction which took place between diphenylamine and anisole. It was observed that *N*-nitrosation versus

**Table 2.** Melting/Boiling Points of the Products

Product number	Melting point (°C)		Boiling point (°C mmHg <sup>-1</sup> )	
	Found	Reported [Lit.]	Found	Reported [Lit.]
<b>2a</b>	-	-	154/774	152.5/774 [29]
<b>2b</b>	-	-	175-177	177 [29]
<b>2c</b>	-	-	115/14	116-117.5/14 [30]
<b>2d</b>	44-46	46-48 [29]	-	-
<b>2e</b>	64-66	65-66.5 [3]	-	-
<b>2f</b>	57.5-59	57-59 [31]	-	-
<b>2g<sup>a</sup></b>	-	-	129/19	127-128/19 [29]
<b>2h</b>	-	-	215	213-214 [29]
<b>2i</b>	-	-	312	309-310.5 [32]
<b>2j<sup>b</sup></b>	-	-	299	298-299.2 [33]
<b>2k<sup>c</sup></b>	-	-	Colorless oil	Colorless oil ([34])
<b>2l<sup>d</sup></b>	100-101	103 [35]	-	-
<b>2m<sup>e</sup></b>	-	-	Pale yellow oil	Pale yellow oil ([36])
<b>2n<sup>f</sup></b>	-	-	Colorless oil	Colorless oil ([37])

<sup>a</sup>The ratio of two isomers is 3.02:1. <sup>b</sup>The ratio of two isomers is 2.89:1. <sup>c</sup>The ratio of two isomers is 2.29:1. <sup>d</sup>The ratio of two isomers is 2.9:1. <sup>e</sup>The ratio of two isomers is 3:1. <sup>f</sup>The ratio of two isomers is 2.45:1.

electrophilic aromatic nitrosation occurred selectively and anisole remained intact in the reaction mixture after 1 h.

In summary, task-specific ionic liquid, 1-butyl-3-methylimidazolium nitrite was used as an effective nitrosonium source for the nitrosation of secondary amines under convenient conditions. The advantages of this protocol are mild reaction conditions, short reaction times, simple work-up procedure and good to excellent yields.

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