

Ionic liquid 1-(4-nitritobutyl)-3-methylimidazolium chloride as a new reagent for the efficient *N*-nitrosation of secondary amines under mild conditions

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Abstract 1-(4-Nitritobutyl)-3-methylimidazolium chloride has been developed as a new reagent for efficient nitrosation of secondary amines at 0 °C to room temperature. A variety of *N*-nitrosamines were prepared in excellent yields by use of this task-specific ionic liquid under mild and heterogeneous conditions.

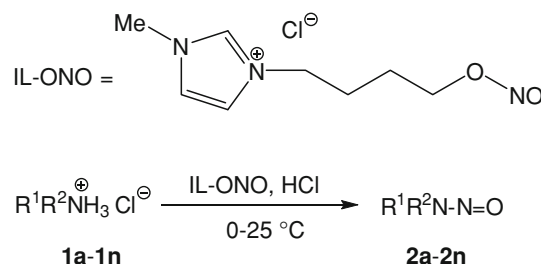
Keywords *N*-Nitrosation · Secondary amines · *N*-Nitrosoamines · Task-specific ionic liquid

Introduction

Room-temperature ionic liquids (RTILs) are a powerful alternative to conventional molecular organic solvents or catalysts because of specific properties such as undetectable vapor pressure, wide liquid range, and ease of recovery and reuse [1–5]. Incorporation of additional functional groups as a part of the cation and/or anion of ionic liquids has led to functionalized ionic liquids, so-called task-specific ionic liquids (TSILs), which have recently attracted chemists' interest. TSILs have been used not only as alternative green solvents, but also as reagents and/or catalysts in synthetic organic chemistry. Wang and Li used TSIL as Lewis base, ligand, and reaction medium for the palladium-catalyzed Heck reaction [4]. Paun and Barklie reported the basic ionic liquid-catalyzed Knoevenagel condensation reaction [6]. Tajik and co-workers reported the nitration of phenols using an acidic ionic liquid under mild conditions [7]. Pawar et al. [8]

synthesized flavones in [bmim]BF₄ ionic liquid. Hajipour and co-workers reported a convenient method for preparation of aldoximes in the presence of in-situ-prepared ionic liquids [9]. Very recently we used an imidazolium-based phosphinite ionic liquid (TSIL-OPPh₂) as a weak Lewis base catalyst and reaction medium for the Biginelli and Knoevenagel reactions and also in the synthesis of nitrones [10–12]. We also used a task-specific phosphinite ionic liquid as reagent and reaction medium for one-pot Horner–Wadsworth–Emmons-type reactions under microwave irradiation [13].



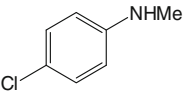
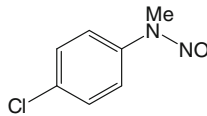
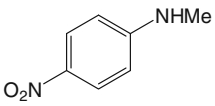
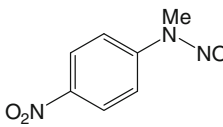
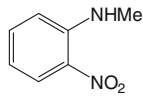
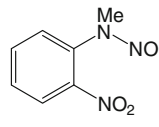
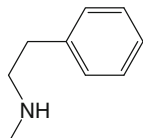
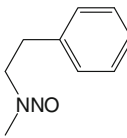
N-Nitrosation of amines is an important reaction in organic synthesis. *N*-Nitrosoamines, which are important organic compounds because of their strong mutagenic and carcinogenic properties [14], have attracted much interest in recent years. These compounds have vasorelaxant activity and have been used as pesticides [15]. A variety of *N,N*-bonded functionality has been synthesized from these useful synthetic intermediates. A variety of nitrosating agents have been reported for nitrosation of amines. The most general reagent, nitrous acid, is generated from sodium nitrite and mineral acid in water or in mixed alcohol–water solvents [16]. Other nitrosating reagents



Scheme 1

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Table 1 1-(4-Nitritobutyl)-3-methylimidazolium chloride as a new reagent for efficient *N*-nitrosation of secondary amines

Entry	Substrate	Product		Time/min	Yield ^a /%
1	Me ₂ NH	Me ₂ NNO	2a	70	92
2	Et ₂ NH	Et ₂ NNO	2b	70	92
3	Bu ₂ NH	Bu ₂ NNO	2c	60	94
4	<i>i</i> -Pr ₂ NH	<i>i</i> -Pr ₂ NNO	2d	60	94
5	Ph ₂ NH	Ph ₂ NNO	2e	70	95
6	(PhCH ₂) ₂ NH	(PhCH ₂) ₂ NNO	2f	65	97
7	PhNHMe	PhN(NO)Me	2g	65	95
8			2h	70	89
9	PhCH ₂ NHEt	PhCH ₂ N(NO)Et	2i	65	90
10	PhCH ₂ NHMe	PhCH ₂ N(NO)Me	2j	70	92
11			2k	85	85
12			2l	90	90
13			2m	90	89
14			2n	70	93

^a Isolated yield

include nitrosyl salts [17], alkyl nitrites [18], dinitrogen tetroxide [19], oxyhyponitrite [20], Fremy's salt [21], *N*-haloamides and sodium nitrite under phase-transfer conditions [22], bis(triphenylphosphine) ammonium nitrite [23], solid acids [24–26], and sodium nitrite (NO⁺·crown·H(NO₃)₂) [27], silica chloride/NaNO₂ [28], and polymeric nitrosation reagents [29, 30].

We wished to develop a new nitrosating agent. In a continuation of our study of organic reactions under green conditions [10–13], we wish to report here the synthesis of

N-nitrosamines by reaction of secondary amines with a task-specific nitrite ionic liquid as reagent in a solventless system (Scheme 1).

Results and discussions

The ionic liquid 1-(4-nitritobutyl)-3-methylimidazolium nitrite (IL-ONO) was synthesized in accordance with our very recent publication [31].

IL-ONO was then evaluated as nitrosonium source for the nitrosation of secondary amines. Nitrosation of dibenzylamine was chosen as a model study. A solution of 4.94 g IL-ONO (22.5 mmol) and 0.92 cm³ HCl (37%, 30 mmol) in 5 cm³ water was added dropwise to a flask containing a stirred aqueous solution of 2.95 g dibenzylamine (15 mmol) and 1.23 cm³ HCl (37%, 40 mmol) at 0 °C. TLC monitoring showed completion of the reaction in 1 h. The stable *N*-nitroso product was characterized by ¹H NMR spectroscopy and comparison of its melting point with the reported value. Different types of secondary amine were subjected to nitrosation in the presence of IL-ONO. The nitrosation reactions were performed at 0–25 °C and took place with good to excellent yields (Table 1). A competitive reaction performed between diphenylamine and anisole showed the chemoselectivity of this method. It was observed that amine nitrosation occurred whereas anisole remained intact in the reaction mixture after 1 h. Melting/boiling points of the products are listed in Table 2. The results showed that *N*-nitrosation occurred faster than electrophilic aromatic nitrosation. Water-insoluble amines were reacted effectively under heterogeneous conditions. NMR spectra showed that products of asymmetrically substituted

secondary amines, for example **2i**, exist as two rotational isomers because of restricted rotation of the N–N bond.

Conclusion

In summary, the task-specific nitrite ionic liquid 1-(4-nitrobutyl)-3-methylimidazolium chloride has been used as an effective reagent for nitrosation of secondary amines under mild heterogeneous conditions. The advantages of this procedure are mild reaction conditions, short reaction times, simple work-up procedure, free of organic solvent, and good yields. Therefore, we believe that the new synthetic method reported here would greatly contribute to environmentally greener and safer processes.

Experimental

All reagents were purchased from Merck and used without further purification. Infrared spectra were recorded in KBr and were determined on a Perkin–Elmer FT-IR spectrometer. ¹H NMR spectra were obtained in CDCl₃ solution from a Bruker Avance AC-400 MHz and ¹³C NMR spectra at 100 MHz on the aforementioned instrument. Elemental analysis was carried out on a Perkin–Elmer 240C elemental analyzer and is reported in percentage atomic abundance. All melting points were measured in open glass-capillaries using a Stuart melting-point apparatus.

General procedure for nitrosation of secondary amines using IL-ONO

Secondary amine (15 mmol) and concentrated hydrochloric acid (40 mmol) were added to water or mixed alcohol–water (5 cm³) and mixed vigorously at 0 °C. While stirring the mixture, a solution of 4.94 g IL-ONO (22.5 mmol) in 3 cm³ water was added slowly. The reaction mixture was left stirring at room temperature for the time shown in Table 1. The products were isolated by filtration and washed three times with cold water to afford the crude *N*-nitrosamines. The crude products were purified by recrystallization from ethyl acetate–*n*-hexane. Products **2h** and **2n** were purified by flash chromatography on silica gel.

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References

- Gong K, Fang D, Wang H-L, Zhou X-L, Liu Z-L (2009) Dyes Pigm 80:30

Table 2 Physical data for products **2a–2n**

Product	Melting point/°C		Boiling point/°C/mbar	
	Found	Reported	Found	Reported
2a	–	–	154 (1,013)	152.5 (1,013) [32]
2b	–	–	175–177 (1,013)	177 (1,013) [32]
2c	–	–	102–104 (11)	103–104 (11) [32]
2d	44–46	47–48 [32]	–	–
2e	64–66	65–66.5 [16]	–	–
2f	57.5–59	57–59 [33]	–	–
2g^a	–	–	129–131 (25)	129 (25) [32]
2h	–	–	215 (1,013)	213–214 (1,013) [32]
2i	–	–	312 (1,013)	[34] ^g
2j^b	–	–	299 (1,013)	298–299.2 (1,013) [35]
2k^c	–	–	309 (1,013)	[36] ^g
2l^d	99–102	103 [37]	–	–
2m^e	–	–	349 (1,013)	[38] ^g
2n^f	–	–	316 (1,013)	[39] ^g

^a The ratio of the two isomers is 3.02:1

^b The ratio of the two isomers is 2.89:1

^c The ratio of the two isomers is 2.29:1

^d The ratio of the two isomers is 2.9:1

^e The ratio of the two isomers is 3:1

^f The ratio of the two isomers is 2.45:1

^g Reference to NMR data

2. Le Z-G, Chen Z-C, Hu Y, Zheng Q-G (2004) *Synthesis* 2809
3. Yue C, Mao A, Wei Y, Lü M (2008) *Catal Commun* 9:1571
4. Wang L, Li H, Li P (2009) *Tetrahedron* 65:364
5. Macfarlane DR, Pringle JM, Johansson KM, Forsyth SA, Forsyth M (2006) *Chem Commun* 1905
6. Paun C, Barklie J, Goodrich P, Gunaratne HQN, McKeown A, Pârvulescu VI, Hardacre C (2007) *J Mol Catal A Chem* 269:64
7. Tajik H, Niknam K, Parsa F (2009) *J Iran Chem Soc* 6:159
8. Bhosale RS, Sarda SR, Giram RP, Raut DS, Parwe SP, Ardhapure SS, Pawar RP (2009) *J Iran Chem Soc* 6:519
9. Hajipour AR, Rafiee F, Ruoho AE (2010) *J Iran Chem Soc* 7:114
10. Valizadeh H, Shockravi A (2009) *Heteroatom Chem* 20:284
11. Valizadeh H, Gholipour H (2010) *Synth Commun* 40:1477
12. Valizadeh H (2010) *Heteroatom Chem* 21:78
13. Valizadeh H, Shockravi A (2009) *Synth Commun* 39:4341
14. Garcia-Rio L, Leis JR, Issglesias E (1997) *J Org Chem* 62:4712
15. Nudelman NS, Bonatti AE (2000) *Synlett* 1825 (references cited therein)
16. Vogel AI, Tatchell AR, Furnis BS, Hannaford AJ, Smith PWG (1986) *Vogels text book of practical organic chemistry*, 4th edn. Longman, London
17. Olah GA (1979) *Aldrichimica Acta* 12:43
18. Lecher H, Siefhen W (1926) *Chem Ber* 59:2594
19. Makhora NN, Karpov GA, Mikhailyuk AN, Bova AE, Khmel'nitskii LI, Novikov SS (1978) *Izv Akad Nauk SSSR Ser Khim* 1:226
20. Chang SK, Harrington GW, Rothstein M, Shergalis WA, Swern D, Vohra SK (1979) *Cancer Res* 39:3871
21. Castedo L, Riguera R, Vázquez MP (1983) *J Chem Soc Chem Commun* 301
22. Nakajima M, Warner JC, Anselme JP (1984) *Tetrahedron Lett* 25:2619
23. Fanning JC, Keefer LK, Larry K (1987) *J Chem Soc Chem Commun* 955
24. Zolfigol MA (1999) *Synth Commun* 29:905
25. Zolfigol MA, Ghaemi E, Madrakian E, Kiany-Borazjani M (2000) *Synth Commun* 30:2057
26. Zolfigol MA, Shirini F, Ghorbani Choghamarani A, Taqiannasab A, Keypour H, Salehzadeh S (2000) *J Chem Res (S)* 420
27. Zolfigol MA, Zebarjadian MH, Chehardoli G, Keypour H, Salehzadeh S, Shamsipur M (2001) *J Org Chem* 66:3619
28. Zolfigol MA, Shirini F, Choghamarani AG (2002) *Synth Commun* 32:1809
29. Zarchi MAK, Noei J (2009) *J Appl Polym Sci* 114:2134
30. Roche D, Lardy C, Tournier L, Prunier M, Valeur E (2010) *Tetrahedron Lett* 51:2277
31. Valizadeh H, Shomali A (2010) *Dyes Pigm.* doi:10.1016/j.dyepig.2010.11.010
32. Hou J-Y, Wang Y-L, Wang J-Y (2003) *J Chem Res (S)* 626
33. Smith JRL, Nee MW, Noar JB, Bruce TC (1984) *J Chem Soc Perkin Trans 2* 255
34. Iranpoor N, Firouzabadi H, Nowrouzi N (2008) *Tetrahedron Lett* 49:4242
35. Seebach D, Enders D (1975) *Chem Ber* 108:1293
36. Loepky RN, Elomari S (2000) *J Org Chem* 65:96
37. Gowenlock BG, Pfab J, Young VM (1997) *J Chem Soc Perkin Trans 2* 915
38. Giumanini AG, Verardo G (1997) *Can J Chem* 75:469
39. Yu Y, Ostresh JM, Houghten RA (2003) *J Org Chem* 68:183