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Zwitterionic-type molten salt-catalyzed *syn*-selective aza-Henry reaction: solvent-free one-pot synthesis of β-nitroamines

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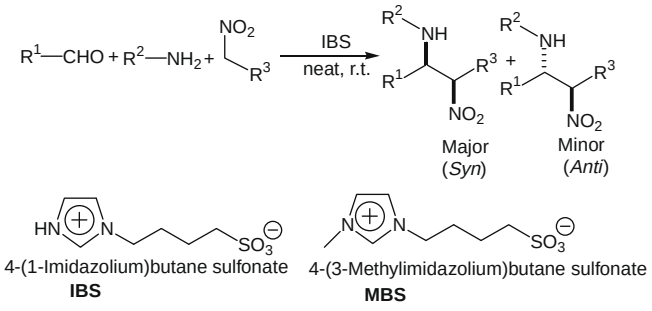
ABSTRACT

Zwitterionic imidazolium sulfonates are excellent catalysts for stereoselective aza-Henry reaction under solvent-free conditions. The major *syn*-β-nitroamine is obtained in high yields. This three-component condensation reaction catalyzed by zwitterionic-type molten salt deserves attention in its own right as a useful method.

The nucleophilic addition of nitroalkanes to imines and related compounds (aza-Henry or nitro-Mannich reaction) is a powerful synthetic transformation that allows creation of a carbon–carbon bond with concomitant generation of two vicinal stereogenic centers bearing nitro and amino functional groups.[1] The resulting β-nitroamines represent rather useful synthetic building blocks because the two nitrogenated functions are present in different oxidation states, thus giving access to further transformations with complete chemoselectivity. Additionally, the nitro moiety can be transformed into other interesting functional groups like carbonyl groups, hydroxylamines, and oximes or nitriles.[2] The 1,2-diamine structural motif is important in biologically active natural products.[3] In recent years, several synthetic diamine derivatives have also been employed as medicinal agents.[4] Besides these, the use of vicinal diamines in organic synthesis in the field of catalytic asymmetric synthesis has also increased considerably during the last few years, due to their use both as ligands[5] and as organocatalysts.[6]

Over the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically feasible, and an important area of green chemistry deals with solvent minimization.[7] In our earlier investigations, we reported various multicomponent reactions under solvent-free conditions.[8] Although nucleophilic additions of nitroalkanes to imines were studied by several groups in the past, all the associated work was devoted to racemic derivatives.[9] The first stereoselective aza-Henry reaction was reported by Anderson and co-workers, who described the addition of the lithium salts of various nitroalkanes to *N*-(*p*-methoxybenzyl) imines.[10] Diastereoselective aza-Henry reaction is in most cases catalyzed or promoted by metal salts, and several drawbacks lie in the cost and the toxicity of the metal species and in the use of organic solvents that are often ecologically harmful. To address these problems, recently a few asymmetric organocatalyzed aza-Henry reactions have been reported.[11] In most cases, the *anti* isomer was predominant. There is only one method for *syn*-selective catalytic asymmetric nitro-Mannich reaction reported by Shibasaki's group.[12] Herein we report a new, significantly simplified, and environmental-friendly approach to the zwitterion-catalyzed aza-Henry reaction using solvent- and metal-free conditions (Scheme 1). The *syn* isomer was obtained predominantly under the present reaction conditions.



Scheme 1.

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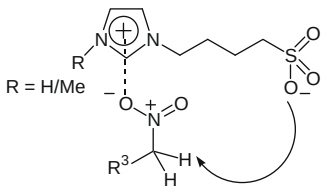

Figure 1.

Table 1
Zwitterion (IBS)-catalyzed synthesis of β-nitroamines

Entry	R^1	R^2	R^3	Time (h)	Yield[a] (%)	*syn*:*anti*[b]
1	C_6H_5	C_6H_5	Me	60	89	95:5
2	C_6H_5	4-MeC_6H_4	Me	55	92	94:6
3	C_6H_5	4-MeC_6H_4	Et	60	85	>98:2
4	C_6H_5	4-OMe–C_6H_4	Et	60	75	98:2
5	C_6H_5	3-ClC_6H_4	Me	65	84	95:5
6	C_6H_5	4-CO_2Et–C_6H_4	Me	65	82	94:6
7	4-OMe–C_6H_4	4-ClC_6H_4	Et	60	85	98:2
8	4-OMe–C_6H_4	3-NO_2–C_6H_4	Me	65	80	77:23
9	4-Me–C_6H_4	C_6H_5	Me	60	80	98:2
10		4-FC_6H_4	Me	65	77	74:26
11	4-FC_6H_4	C_6H_5	Et	55	80	80:20
12	4-BrC_6H_4	C_6H_5	Me	55	80	75:25
13	4-NO_2–C_6H_4	4-MeC_6H_4	Me[c]	70	78	88:12

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy after flash chromatography.
[c] Added 2 equiv nitroethane.

As a part of our ongoing studies on green synthesis, we decided to synthesize task-specific ionic liquid and to test the effectiveness of molten salts as catalyst for various chemical transformations.[13] Reaction of the neutral nucleophiles, *N*-methyl imidazole, or imidazole with 1,4-butane sulfone produces the requisite zwitterionic-type molten salts in excellent yields.[14] The experimental procedure for the synthesis of β-nitroamine is very simple.[15] The coupling reaction of benzaldehyde (2 mmol), aniline (2 mmol), and nitroethane (2 mmol) was carried out in the presence of zwitterionic-type molten salt (10 mol %) at room temperature without added solvent. The reaction afforded predominantly the *syn* isomer with high diastereoselctivity in excellent yields. The 4-(1-imidazolium)butane sulfonate (IBS)-catalyzed reaction showed better selectivity (*syn*:*anti* 95:5) in high yield (89%) compared to 4-(3-methylimidazolium)butane sulfonate (MBS)-catalyzed reaction (85% yield; *syn*:*anti* 90:10). Higher amount of the catalyst did not improve the results to a great extent. The role of the catalyst in this transformation could be activation of the nitroalkane component[16] (Fig. 1).

Representative results of the coupling reaction using IBS are summarized in Table 1. It was observed that under similar reaction conditions, a wide range of anilines containing electron-withdrawing as well as electron-donating groups such as nitro, fluoro, chloro, methyl, methoxy, and ester underwent condensation with excellent selectivity in high yields. Benzaldehydes carrying different functional groups were subjected to the coupling reactions and in all cases high selectivity was observed. Both nitroethane and nitropropane worked very well under the present reaction conditions. Although the general experimental procedure was based on 2 mmol scale reaction, 50 mmol reactions produced similar results. Under the same reaction conditions, this condensation reaction proceeded sluggishly when aliphatic aldehydes and amines were used as the starting material and yielded a mixture of products. The desired products could not be isolated.

The structure of major *syn* diasteroisomer was assigned on the basis of ^{1}H NMR analysis[17] by comparison with the known *anti* isomer (Table 1, entry 4).[18] Generally, the signal of the proton α to the nitro moiety of the major *syn* isomer shifted downfield with respect to its counterpart in the minor *anti* isomer. Furthermore,

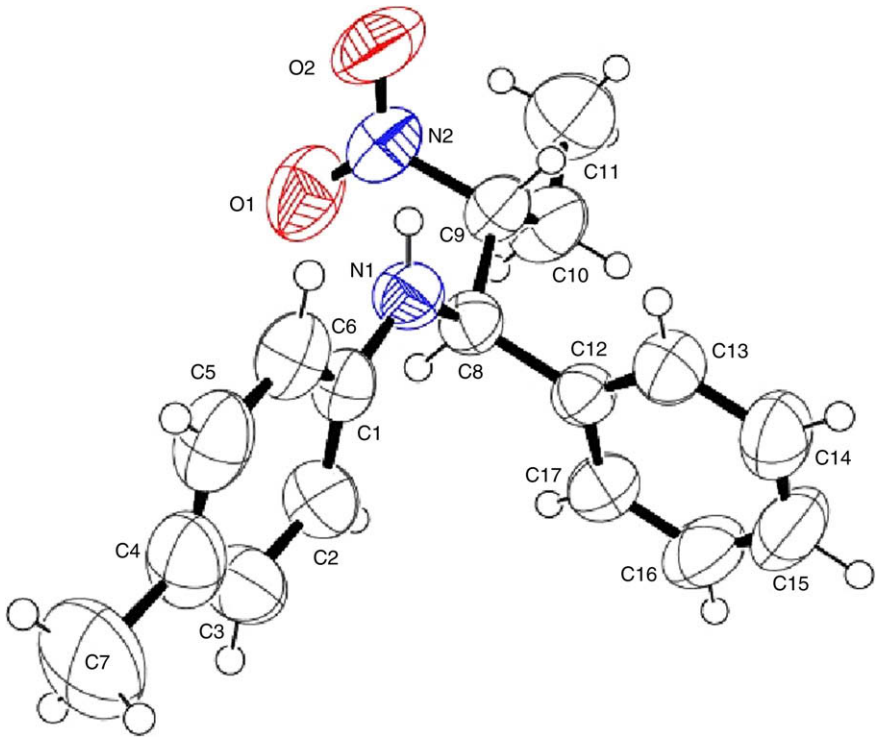

Figure 2. X-ray structure of *syn* 1-phenyl-1-(*p*-tolylamino)-2-nitrobutane.

the two geminal protons of the methylene moiety are superimposed in the ^{1}H NMR spectrum in the major *syn* isomer. This observation is consistent with previous reports contained in the chemical literature.[11a] In addition, the *anti* isomer of 1-phenyl-1-(4-methoxyphenylamino)-2-nitrobutane (Table 1, entry 4) is reported in the literature as a liquid.[19] We obtained the major isomer as a pale yellow solid and the minor isomer as pale yellow oil. The structure of *syn* 1-phenyl-1-(*p*-tolylamino)-2-nitrobutane (Table 1, entry 3) was also confirmed by single-crystal X-ray analysis (Fig. 2).[20] All these observations indicate that the major *syn* isomer was formed predominantly under the present reaction conditions.

The reusability of the catalyst is an important benefit especially for the commercial applications. Thus, the recovery and reusability of the catalyst were investigated. After completion, the reaction mixture was extracted with ether (10 mL × 3) to obtain the desired products. The catalyst, left in the reaction vessel was dried under vacuum and was reused for subsequent reactions. It showed the same activity as a fresh catalyst without loss of activity in terms of both yields and selectivity. After five recycles, the catalyst had a high activity in terms of both yields and selectivity (86%, *syn*:*anti* 93:7 for entry 1, Table 1).

In conclusion, imidazole-based zwitterionic-type molten salts are a new class of catalysts for the aza-Henry reaction, generating high selectivity in excellent yields. Most significantly, the *syn*-β-nitroamine was obtained predominantly under the present reaction conditions. Advantages offered by this method are: (i) mild reaction conditions (room temperature), (ii) excellent selectivity, (iii) high yields, (iv) no waste production, and (v) reusability of catalyst. To the best of our knowledge, this is the first report of aza-Henry reaction, promoted by a zwitterionic-type molten salt under solvent-free conditions. The investigation of the mechanism of this reaction and the use of chiral zwitterions are underway and will be reported in due course.

Acknowledgments

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15. *Synthesis of 1-phenyl-1-phenylamino-2-nitropropane* (Table 1, entry 1): A mixture of benzaldehyde (202 μL, 2 mmol), aniline (182 μL, 2 mmol), and nitroethane (144 μL, 2 mmol) was stirred in the presence of 4-(1-imidazolium)butane sulfonate (41 mg, 10 mol %) at room temperature for 60 h (TLC). After completion, the reaction mixture was extracted with diethyl ether (10 mL × 3). Evaporation of solvent furnished the product β-nitroamine. The major *syn* isomer was isolated by column chromatography (hexane/ether 9:1) as a pale yellow solid (433 mg, 85%). Direct recrystallization of the reaction mixture from ether–hexane (3:2) also afforded the pure *syn* isomer. Mp 109–110 °C; IR (KBr) 3413, 1595, 1512, 1330 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 5H), 7.08 (t, J = 7.6 Hz, 2H), 6.67 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 7.9 Hz, 2H), 4.99 (d, J = 4.5 Hz, 1H), 4.95–4.87 (m, 1H), 4.45 (br, 1H), 1.52 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9, 137.4, 129.6 (2C), 128.9 (2C), 128.4, 126.9 (2C), 118.7, 114.0 (2C), 86.4, 60.7, 13.7; Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.11; H, 6.16; N, 10.78.The catalyst, left in the reaction vessel was dried under vacuum and was reused for subsequent reactions.
16. In this reaction, the zwitterionic-type molten salt may act as a bifunctional organocatalyst similar to thiourea-catalyzed aza-Henry reaction. Takemoto and co-workers have postulated a mechanism for the nitro-Mannich reaction involving thiourea activation of the nitroalkane.[11c]
17. *Data for syn 1-phenyl-1-(4-methoxyphenylamino)-2-nitrobutane* (Table 1, entry 4): mp 98–100 °C; IR (KBr) 2997, 1552, 1510, 1228, 1178, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 5H), 6.66 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 4.68–4.62 (m, 2H), 4.21 (br, 1H), 3.66 (s, 3H), 2.10–1.95 (m, 1H), 1.63–1.55 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H). Data for *anti* isomer is reported in the literature.[17]
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20. CCDC 733796 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.