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Base-free conjugate addition of aliphatic nitro compounds to enones in BmimNTf$_2$: a recyclable synthesis of γ-nitro ketones

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ABSTRACT

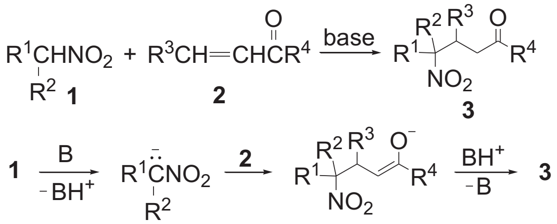
A base-free, recyclable approach for the conjugate addition of aliphatic nitro compounds to enones to give γ-nitro ketones is presented. Reactions are carried out in an ionic liquid with a basic anionic moiety, such as BmimNTf$_2$, as the solvent, under mild conditions (25 °C for 24 h). The IL medium could be recycled several times without any appreciable loss of activity, after a simple extraction procedure for the separation of the reaction product.

1. Introduction

The base-promoted conjugate addition of aliphatic nitro compounds **1** to enones **2** is a powerful method for the synthesis of γ-nitro ketones **3**,[1] which are very useful synthetic intermediates for the preparation of a variety of fine chemicals.[2]

The classical reaction conditions involve the use of a base, necessary for the α-deprotonation of **1** with formation of the corresponding carbanion, followed by the nucleophilic attack of the latter to the β-carbon of the enone **2** with formation of the enolate of a γ-nitro ketone, protonation of which then affords the final product **3** (Scheme 1, B=base).[1]

In this work, we report the first example of conjugate addition of aliphatic nitro compounds **1** to enones **2** in an ionic liquid (IL) solvent, such as BmimNTf$_2$. Owing to the intrinsic basicity of the solvent, our method allows the formation of γ-nitro ketones **3** in good yields in the absence of external bases; moreover, the reaction medium can be recycled several times without appreciable loss of activity.



Scheme 1. Mechanism of base-promoted conjugate addition of aliphatic nitro compounds **1** to enones **2** to give γ-nitro ketones **3** (B=base).

2. Results and discussion

1-Nitrooctane **1a** and methyl vinyl ketone **2a** were used as model substrates for assessing the reactivity of aliphatic nitro compounds with enones in an IL as the solvent. The results obtained by reacting **1a** with **2a** in the presence of Et$_3$N as the base and in several classical ILs, such as BmimBF$_4$, BmimOTf, BmimPF$_6$, and BmimCl, are shown in Table 1, entries 1–4. As can be seen, the expected 5-nitrododecan-2-one **3aa** was formed in all cases, even though the use of BmimCl required a higher temperature and led to a lower product yield (entry 4).

In any case, these results confirmed the possibility to use an IL as the reaction medium for this kind of reaction. The use of ILs in organic synthesis has recently attracted great attention, due to the

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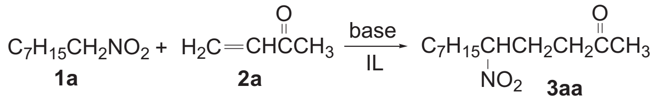
Table 1
Reactions of 1-nitrooctane **1a** with methyl vinyl ketone **2a** in different ionic liquids (ILs)[a]



$$C_7H_{15}CH_2NO_2 + H_2C{=}CH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[IL]{base} C_7H_{15}\underset{NO_2}{\underset{|}{C}H}CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$$

1a **2a** **3aa**

Entry	Solvent	T (°C)	Base	Run[b]	Yield of **3aa**[c] (%)
1	$BmimBF_4$	25	Et_3N[d]	1	60
2	BmimOTf	25	Et_3N[d]	1	46
3	$BmimPF_6$	25	Et_3N[d]	1	57
4	BmimCl	80	Et_3N[d]	1	42
5	$BmimNTf_2$	25	None	1	60
				2	59
				3	60
				4	58
				5	58
				6	57

[a] All reactions were carried out for 24 h in the given ionic liquid as the solvent (0.2 mmol of **1a** per mL of solvent) with a **2a**/**1a** molar ratio of 1.2.
[b] Run 1 corresponds to the first experiment, the next runs to recycles. See text for details.
[c] Isolated yield based on starting **1a**.
[d] 20 mol % with respect to **1a**.

very important characteristics of these non-conventional solvents: they are stable, non-flammable, non-volatile, recyclable, and in some cases may even promote organic reactions.[3] In order to further improve our initial results, we then turned out our attention to the use of an IL with a basic anionic moiety, such as $BmimNTf_2$. The use of this IL, in fact, could permit the formation of **3aa** from **1a** and **2a** in the absence of an external base, making the whole process more simple and convenient. When we allowed **1a** to react with **2a** in $BmimNTf_2$ at 25 °C for 24 h in the absence of any external base, **3aa** was indeed formed in 60% isolated yield, thus confirming the validity of our hypothesis (Table 1, entry 5, Run 1). We also tested the possibility to recycle the solvent several times, after extracting the reaction product with Et_2O. As can be seen from the results reported in Table 1, entry 5, Runs 2–6, the IL could be recycled up to five times without appreciable loss of activity.

The next experiments were aimed at generalizing the process to the use of different nitro compounds and enones. The results obtained using other simple and functionalized nitro compounds, shown in Table 2, demonstrate that the process is quite general, the corresponding γ-nitro ketones being consistently formed in fair to good yields (51–73%). We have also tested the medium recyclability in other two cases (Table 2, entries 1 and 6), and the possibility to recycle the IL several times, without significant decrease of activity, was confirmed.

3. Conclusion

In conclusion, in this work we have reported the first example of the use of ILs as reaction media for the conjugate addition of aliphatic nitro compounds **1** to enones **2** for the synthesis of γ-nitro ketones **3**. We have found that an IL with a basic anionic moiety, such as $BmimNTf_2$, may allow the reaction to occur in the absence of any external base. Moreover, the IL medium could be recycled several times without any appreciable loss of activity, after a simple extraction procedure for the separation of the reaction product.

4. Experimental section

4.1. General

Melting points were determined with a Reichert Thermovar apparatus. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker DPX Avance 300 spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in parts per million and in hertz, respectively. IR spectra were taken with a Jasco FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC–MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone+5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh).

4.2. Preparation of substrates and ionic liquids

Enones were commercially available (Aldrich, Fluka) and were used as received. Nitro compounds **1b**, **1f**, **1g**, **1j** were commercially available. Compounds **1a**, **1c**, **1e**, **1i** were synthesized by halide displacement as reported in the literature.[4a] Compound **1d** was synthesized by nitration and protection of the methyl vinyl ketone.[4b] 2-Phenylnitroethane **1h** was obtained by reduction of β-nitrostyrene.[4c] Ionic liquids $BmimNTf_2$,[5] BmimOTf[6] were prepared according to literature procedures. All the other ionic liquids were prepared as we previously described.[7]

4.3. General procedure for the synthesis of γ-nitro ketones 3 in $BmimNTf_2$ (Tables 1 and 2)

To a stirred solution of **1** (0.42 mmol) in $BmimNTf_2$ (2 mL) was added the enone **2** (0.51 mmol) under nitrogen, and the resulting mixture was allowed to stir at 25 °C (Table 1, entry 5 and Table 2, entries 1–9, 11) or 40 °C (Table 2, entry 10) for 24 h. The product was extracted with Et_2O (6×2.5 mL), and the residue, after elimination of Et_2O under vacuum, was used as such for the next recycle (see below). The collected ethereal phases were concentrated and the product purified by column chromatography (SiO_2, hexane/AcOEt from 95:5 to 70:30) to give γ-nitro ketones **3**. The isolated yields obtained in each experiment are reported in Tables 1 and 2.

4.4. Recycling procedure (Tables 1 and 2)

To the residue obtained as described above were added **1** (0.42 mmol) and **2** (0.51 mmol), dissolved in Et_2O. Et_2O was removed under vacuum, and then the same procedure described above was followed.

4.5. Characterization of products

*4.5.1. 5-Nitrododecan-2-one (**3aa**).* Yield: 58 mg, 60% (Table 1, entry 1). Yellow oil. IR (film): ν=2932 (s), 1719 (s), 1443 (s), 1359 (s), 1163 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=4.52–4.43 (m, 1H, $CHNO_2$), 2.50–2.43 (m, 2H, CH_2CO), 2.14 (s, 3H, Me), 2.12–2.03 (m, 2H, CH_2CH_2CO), 2.01–1.89 [m, 1H, $CH_3(CH_2)_5CHHCHNO_2$], 1.75–1.63 [m, 1H, $CH_3(CH_2)_5CHHCHNO_2$], 1.38–1.17 [m, 10H, $CH_3(CH_2)_5$], 0.86 (t, 3H, J=6.8 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=206.7, 88.2, 39.2, 34.2, 31.8, 30.32, 29.2, 29.1, 27.6, 25.9, 22.8, 14.3; GC–MS: m/z=229 (M^+, absent), 109 (9), 83 (30), 69 (27), 55 (32), 43 (100); Anal. Calcd for $C_{12}H_{23}NO_3$ (229.32): C, 62.85; H, 10.11; N, 6.11; found C, 62.90; H, 10.19; N, 6.07.

*4.5.2. 5-Nitrodecan-2-one (**3ba**).* Yield: 51 mg, 60% (Table 2, entry 1). Yellow oil. IR (film): ν=2930 (s), 1720 (s), 1441 (s), 1361 (s), 1167 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=4.58–4.42 (m, 1H, $CHNO_2$), 2.48 (t, 2H, J=6.9 Hz, CH_2CO), 2.21–1.86 [m, 4H, $CH_2CH(NO_2)CH_2$], 2.15 (s, 3H, Me), 1.47–1.16 [m, 6H, $CH_3(CH_2)_3$], 0.87 (t, 3H, J=6.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=206.7, 88.2, 39.2, 34.1, 31.2, 30.2, 27.6, 25.6, 22.5, 14.1; GC–MS: m/z=201 (M^+, absent), 137 (7), 95