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The first ionic liquids promoted conjugate addition of azide ion to α,β-unsaturated carbonyl compounds

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Abstract—The first, highly efficient conjugate addition of azide ion to α,β-unsaturated carbonyl compounds promoted by the simple recyclable ionic liquids, bmimPF_6 and bmimBF_4, are described.

β-Amino esters and lactones are vital constituents of many natural and unnatural products.[1] A new and common synthetic strategy to prepare β-amino carbonyl compounds is the conjugate addition of nitrogen nucleophiles (e.g., HN_3) to the α,β-unsaturated carbonyl compounds.[2] Traditionally, conjugated addition of hydrogen azide to the α,β-unsaturated carbonyl compounds reported previously was mainly studied in acidic media (HN_3 in HOAc, etc.) with very poor conversion.[3] In 1997, Lakshmipathi and Rao[4] reported an efficient Lewis base-catalyzed conjugate addition of hydrogen azide (15 equiv in benzene) to enones (1 equiv) to form β-azido esters or lactones at elevated temperature (353 K). Miller and co-workers[5] have reported an improved protocol for the β-azidation of α,β-unsaturated carbonyl compounds. The method employed $TMSN_3$ (4 equiv) and HOAc (4 equiv) as azide source. While several impressive advances have been made in the aza-Michael reactions,[6] there is a need for the development of flexible strategies that will accommodate a range of structure types. In the present letter, we reported an exceedingly mild synthesis of β-azido carbonyl compounds. Advantages of the protocol include high-yielding reaction that can be conducted at ambient temperature in recyclable ionic liquids, bmimPF_6 and bmimBF_4, and the use of readily available and stable NaN_3 as the azide source.

Room temperature ionic liquids such as bmimPF_6 and bmimBF_4 are finding growing application as alternative media for separation and organic transformations.[7] The desirable advantages of ionic liquids such as the lack of vapour pressure, wide liquid range and thermal stability have made them exceptional reaction media and environmentally benign solvents. Accordingly, they are emerging as novel replacements for volatile organic synthesis and transformations.[8] Surprisingly however, there is no report on ionic liquids promoted conjugate addition of hydro azide or azide ion to α,β-unsaturated carbonyl compounds. Herein we first reported the conjugate addition reaction in ionic liquids and developed a new procedure of this aza-Michael reaction with NaN_3 directly.

We speculated that premixing of NaN_3 and acetic acid (HOAc) would initiate a disproportion reaction leading to controlled stoichiometries of HN_3 with the production of sodium acetate as a by-product.[9] Introduction of α,β-unsaturated ketones in the presence of an amine catalyst could then lead to conjugate addition. In the initial studies, similar to previous reports,[5,9] treatment of cyclohexenone with 4 equiv NaN_3 and 4 equiv HOAc in the presence of catalytic quantities (20 mol %) of Et_3N (CH_2Cl_2, at room temperature) for 20 h resulted in a clean conversion to azido ketone in low yield (35% yield) (Scheme 1). Moreover, under the reaction condition, the mixture was difficult to stir in CH_2Cl_2. Then this reaction was performed under the same condition in ionic liquids, such as bmimPF_6 and bmimBF_4, bmimBr, and a survey of Lewis bases revealed that there is reasonable generality with respect to the Lewis base that is employed (Table 1).

Keywords: Conjugate addition; Enone; Ionic liquid; Azide.

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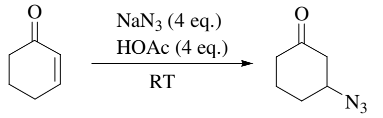


Scheme 1.

Table 1. Evaluation of Brönsted bases as catalysts in the aza-conjugate addition reactions in ionic liquids

Entry	Catalyst[a]	Ionic liquids	Yield (%)[b]
1	Et_3N	$BmimPF_6$	92
2	Pyridine	$BmimPF_6$	95
3	*N*-Methylimidazole	$BmimPF_6$	79
4	Et_3N	BmimBr	Trace
5	Cinchonine	BmimBr	43
6	*N*-Methylimidazole	BmimBr	13
7	Pyridine	$BmimBF_4$	90
8	Cinchonine	$BmimBF_4$	85
9	—[c]	$BmimPF_6$	89
10	—[c]	$BmimBF_4$	90

[a] All reactions were carried out using 1 mmol of cyclohexenone, 20 mmol% amine catalyst, 4 mmol of NaN_3 and 4 mmol HOAc in 2 mL ionic liquids at room temperature for 20 h.

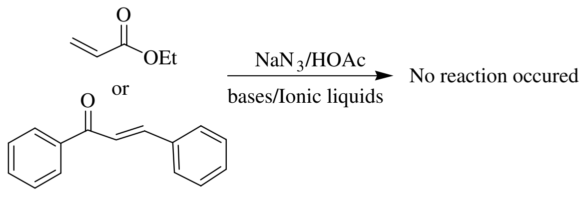
[b] Isolated yield.

[c] No addition of Brönsted bases (amine catalyst).

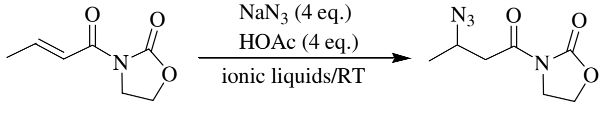
Triethylamine and the other aromatic heterocycles are proved comparably competent as catalysts, resulting in high isolated yield (92–95%) in ionic liquids, $bmimBF_4$ and $bmimPF_6$. Interestingly, cinchonine was an equally efficient catalyst in this aza-Michael reaction (entries 5, 8). However, under the same conditions, all these Lewis bases were less efficient catalysts in bmimBr (entries 4–6). An explanation for the ionic liquid-dependent changes in reaction that it is an ionic liquid promoted aza-Michael reaction (entries 9, 10), and the Brönsted base catalyst has a limited catalytic activity.

In the process of exploring other α,β-unsaturated carbonyl compounds that might serve as suitable substrates for the conjugate addition, we found that ethyl acrylate and chalcone did not undergo reaction under the above conditions, or even in the presence of a stoichiometric amount of amine base in $bmimPF_6$ or $bmimBF_4$ (Scheme 2).

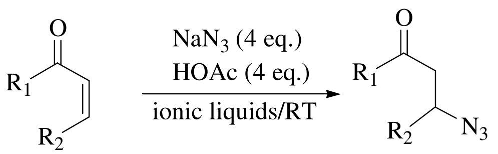
Instead, the crotonate derivative of 2-oxazolidinone is processed under the conditions reported (no addition of Brönsted bases) above to afford the azide derivate in 92% yield (Scheme 3). It can be explained that there existed intramolecular activation.



Scheme 2.



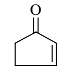
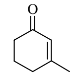
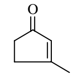
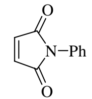
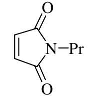
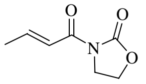
Scheme 3.



Scheme 4.

We then turned our attention to examining the substrate scope under the reaction condition of no addition of base catalyst (Scheme 4, Table 2). A typical procedure was as follows: a mixture of the cyclic enone (1 mmol), HOAc (4 mmol) and NaN_3 (4 mmol) was stirred in 2 mL ionic liquid ($bmimPF_6$ or $bmimBF_4$) at room temperature for 20 h. After addition of aqueous $NaHCO_3$, the products were extracted with ethyl ether and purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent. Several cyclic α,β-unsaturated ketones were proved to be excellent substrates for this aza-Michael reaction. In addition to cyclohexenone, cyclopentenone was transformed to the corresponding azidoketone in high yield in the present aza-Michael reaction (entries 1, 2). *N*-Phenyl maleimide and *N*-propyl maleimide were also effective substrates in this aza-Michael reaction (entries 6, 7). Unfortunately, 3-methyl cyclohexenone and 3-methyl cyclopetenone were not appropriate substrates in this aza-Michael reaction (entries 3–5).

Table 2. Other α,β-unsaturated carbonyl compounds for catalytic aza-conjugate addition reactions in ionic liquids[10]

Entry[a]	Enones	Ionic liquids	Yield (%)[b]
1 2		$BmimPF_6$ $BmimBF_4$	82 86
3 4		$BmimPF_6$ $BmimBF_4$	38 42
5		$BmimPF_6$	Trace
6		$BmimBF_4$	62
7		$BmimPF_6$	60
8		$BmimBF_4$	92

[a] All reaction were performed in ionic liquids and no addition of base catalyst.

[b] Isolated yields.

To check the efficiency of recycling ionic liquids (bmimPF_6), cyclohexenone was subjected to the conjugate addition of azide ion, after four runs, the yield of corresponding azido ketone was very high (86–89%).[11]

In conclusion, we have first demonstrated that the conjugate addition of azide ion to α,β-unsaturated carbonyl compounds could be promoted by simple recyclable ionic liquids, bmimPF_6 and bmimBF_4. The present reaction with its mild reaction conditions opens a novel entry to synthesis of β-azido carbonyl compounds using sodium azide and HOAc in ionic liquids.

Acknowledgements

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10. All the known products were identified by GC–MS (Agilent 6890N GC/5973N MS, HP-5MS).
11. Recycling study of ionic liquids: After extraction with diethyl ether to separate the products, the ionic liquid layer was washed by aqueous $NaHCO_3$, water and the residue water was removed in vacuum and the resulting ionic liquid layer was reused for the next run.