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1,3-Cycloaddition of nitrones in ionic liquids catalyzed by Er(III): an easy access to isoxazolidines

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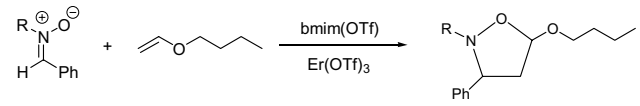
Abstract—1,3-Dipolar cycloadditions of nitrones with alkenes afforded the corresponding isoxazolidines in ionic liquids in the presence of $Er(OTf)_3$. The ionic liquid and the catalyst are recycled up to five times without any specific treatment or loss of activity. Extension of the procedure to the synthesis of isoxazolidinyl nucleosides has been investigated.

The 1,3-dipolar cycloaddition reactions represent the favourite method for the construction of five-membered heterocycles, important frameworks of various natural products.[1] In particular the 1,3-dipolar cycloadditions of nitrones with alkenes afforded isoxazolidines, which are interesting intermediates for the synthesis of β-amino alcohols and alkaloids[2,3] or, more recently, of cyclic and bicyclic 4'aza analogues of 2′,3′-dideoxynucleosides,[4] the isoxazolidinyl nucleosides active against HIV 'in vitro' tests.[5,6] One of the major drawbacks of this kind of reactions, however, is the drastic experimental conditions required to obtain cycloadducts in satisfactory yields. Lewis acid catalysis has been used to enhance reaction rates providing, in the same time, a strict control on regio-, diastero-, and enantioselectivity.[7] In the Lewis acid-catalyzed 1,3-dipolar cycloaddition the coordination of the Lewis acid to the oxygen atom of nitrone gives a dominant $LUMO_{nitrone}$–$HOMO_{alkene}$ interaction, making this approach more selective.[7b]

The use of ionic liquids (ILs)[8] as support for organic synthesis, in particular in cycloaddition reactions, has been described in some recent publications.[9] Ionic liquids have received in latest years a good deal of attention since classical organic reactions can be performed in these media with great advantages (yield and selectivity) as compared to conventional conditions. Taking into account the advantages offered by ILs, we have combined our past experience in the field of cycloadditions[4] and catalysis with the versatile properties of ILs[10] with the aim to find new routes for appealing isoxazolidine synthesis.

Initially we have focused our attention on the cycloaddition of the model *N*-benzyl *C*-phenyl nitrone **1a** with dipolarophile butyl vinyl ether **2**, catalyzed by $Er(OTf)_3$ in bmim(OTf) (1-butyl-3-methyl imidazolium, $TfO^- = CF_3SO_3^-$)[11] at room temperature.



1a R=CH_2Ph **1b** R=Me — **2** — **3a** **3b**

As shown in Table 1, the presence of the catalyst, its loading and increasing amounts of the dipolarophile strongly influence the reaction rates. For a ratio **1a**/**2**/$Er(OTf)_3$ of 1:20:0.2 an almost complete conversion to cycloaddition product **3a** is observed in reasonable reaction times (3 h), at room temperature (entry 8). A similar conversion and yield may be obtained employing a lower amount of alkene but a higher temperature (entry 6). Compared to conventional conditions the cycloaddition reactions performed in ionic liquids are much faster and

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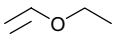
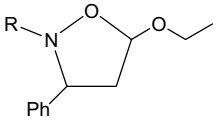
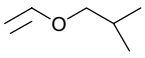
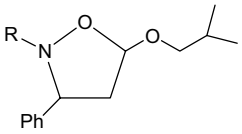
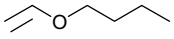
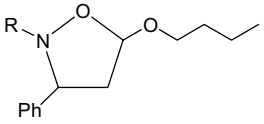
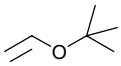
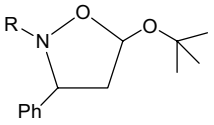
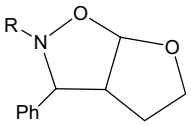
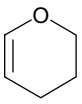
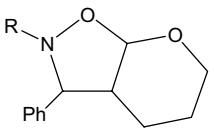
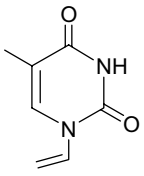
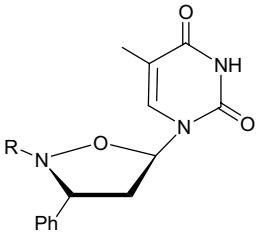
Table 1. Reaction of nitrone **1a** (1 mmol) with butyl vinyl ether **2**, in different experimental conditions

Entry	Alkene **2** (mmol)	$Er(OTf)_3$ (mmol)	*T* (°C)	Solvent	Time (h)	Conversion, % (Yield, %)	**3a** *endo*:*exo* ratio
1	20	—	25	bmim(OTf)	2	—	—
2	5	0.1	25	bmim(OTf)	3	64 (60)[a]	[b]
3	5	0.2	25	bmim(OTf)	1	64	53:47
4	5	0.2	100	bmim(OTf)	1	15	54:46
5	15	0.2	25	bmim(OTf)	1	75	60:40
6	15	0.2	100	bmim(OTf)	3	92 (89)	51:49
7	20	0.2	25	bmim(OTf)	1	80 (78)	63:37
8	20	0.2	25	bmim(OTf)	3	96 (90)	62:38
9	20	0.2	25	MeOH	3	22 (18)	60:40
10	20	0.2	110	Toluene	3	65 (50)	65:35

[a] Determined by GC analysis with an internal standard.
[b] Not determined.

Table 2. Reaction of *N*-benzyl *C*-phenyl nitrone **1a** and *N*-methyl *C*-phenyl nitrone **1b** with various alkenes catalyzed by $Er(OTf)_3$ in bmim(OTf) at 25 °C

Entry	Nitrone	Alkene	Time (h)	Product R = CH_2Ph or CH_3		Conversion, % (Yield, %)[a]	*endo*:*exo* ratio
1	**1a**		3		**3c**[16]	96 (91)	60:40
2	**1b**		1		**3d**[17]	99	40:60
3	**1a**		3		**3e**	99 (95)	57:43
4	**1b**		3		**3f**	84	39:61
5	**1a**		3		**3a**[13a]	96 (90)	62:38
6	**1b**		3		**3b**	75	40:60
7	**1a**		5		**3g**[18]	70 (65)	77:23
8	**1b**		1[b]		**3h**[14]	99	37:63
9	**1a**		1[b]		**3i**[14]	99 (95)	26:74
10	**1b**		0.5[b]		**3l**[14]	99	25:75
11	**1a**		5[b]		**3m**	66 (63)	36:64
12	**1b**		3		**3n**	75	42:58
13	**1a**		48		**3o**	30[c]	62:38

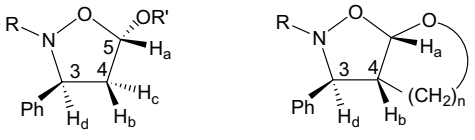
[a] Determined by GC analysis with an internal standard.
[b] Reaction performed at 0 °C.
[c] 2.5 mL of IL is used in this case.

selective. As an example, the reaction between **1a** and **2**, catalyzed by $Er(OTf)_3$ (0.2 mmol) afforded cycloaddition derivative **3a** after 3 h in MeOH in 22% conversion and 18% yield (entry 9) and in refluxing toluene in 65% conversion, 50% yield (entry 10), respectively.

Isolation of the cycloadduct is simple and straightforward. Work-up consisted in the dilution of reaction mixture with water and extraction of isoxazolidine with diethyl ether, followed by purification of the product by flash chromatography and NMR analysis to establish the *endo*:*exo* ratio. Furthermore, water was removed from the aqueous phase under vacuum and the ionic liquid, containing the $Er(OTf)_3$, was reused up to five times without loss of activity nor selectivity; conversion 96%, *endo*:*exo* ratio 62:38 after five cycles. We have intentionally stopped the recycle at the fifth cycle, however we are convinced that this process may be carried on many more times.

To explore the potential of this procedure we have extended the protocol, optimized as shown in Table 1, to *N*-methyl *C*-phenyl nitrone **1b** and to many different alkenes, obtaining in all cases the corresponding isoxazolidines in rather good conversions and yields, Table 2. The reaction of nitrones **1a**,**b** with the vinyl ethers of Table 2 is highly regioselective, affording exclusively 5-substituted isoxazolidines, in agreement with the literature reports.[7a] In a typical procedure 1 mmol of nitrone was mixed with 0.2 mmol of $Er(OTf)_3$ in bmim(OTf) 1 mL under stirring, at room temperature. After 30 min, 20 mmol of dipolarophile were added and the progress of the reaction was monitored by GC analysis. The mixture was then poured into water and extracted with Et_2O to obtain the desired isoxazolidines and to recover the ionic liquid containing the catalysts, as described in previous paragraphs.

The observed regio- and stereochemical outcome of these cycloadditions have been established by detailed ^1H NMR spectroscopic analysis.[12] In particular for monocyclic derivatives **3a**–**h**, the difference in the chemical shifts of the two protons at C(4) position of the *endo* derivative is smaller than that in the *exo* adduct.[13] For bicyclic derivatived **3i**–**n** the stereoselectivity has been obtained by comparison with the literature data using the resonances of proton H_a.[14]



endo monocyclic isomer *endo* bicyclic isomer (n=2,3)

As shown in Table 2 the *endo*:*exo* selectivity is rather modest, in agreement with the literature reports that, however, refer to reactions in conventional solvents.[13,14] At the moment we have no explanation why the *endo*:*exo* ratio overturns by passing from *N*-benzyl *C*-phenyl nitrone **1a** to *N*-methyl *C*-phenyl nitrone **1b**.

Worthy of note the reaction occurs also with vinyl nucleobases as 1-vinyl thymine to afford the corresponding cycloaddition product **3o**, although in moderate yield, entry 13 of Table 2.[15] We have already mentioned the pharmaceutical importance of these isoxazolidinyl nucleosides and efforts are currently under way in order to optimize yields and selectivities of these specific reactions.

In conclusion we have shown that 1,3-dipolar cycloadditions of nitrones with alkenes in the presence of $Er(OTf)_3$ may be conveniently carried out in ionic liquids at room temperature with the obtainment of the corresponding isoxazolidines in good conversions and yields. The ionic liquid and the catalyst may be recycled several times without loss of activity nor selectivity.

Acknowledgement

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Supplementary data

Supplementary data (selected spectrometric (EI, APCI–MS) data of the isoxazolidines) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.219.

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12. ^{1}H NMR spectral data for the cycloaddition derivatives ($CDCl_3$): **3a** see Ref. 13a; **3b** (*exo*) δ (*J* Hz) 0.91 (t, 3H, CH_3, $J = 7.2$); 1.33–1.44 (m, 2H); 1.48–1.58 (m, 2H); 2.33–2.43 (m, 1H, H_b); 2.61 (s, 3H, CH_3); 2.84–2.94 (m, 1H, H_c); 3.15 (dd, 1H, $J = 7.37$, 9.45); 3.41 (t, 1H, H_d, $J = 8.40$); 3.66 (dd, 1H, $J = 6.20$, 9.45); 5.16 (dd, 1H, H_a, $J = 3.06$, 6.41); 7.25–7.50 (m, 5H, Ar); **3b** (*endo*) δ (*J* Hz) 0.98 (t, 3H, CH_3, $J = 7.2$); 1.39–1.46 (m, 2H); 1.52–1.62 (m, 2H); 2.42–2.52 (m, 1H, H_b); 2.53–2.63 (m, 1H, H_c); 2.80 (s, 3H, CH_3); 3.22 (dd, 1H, J= 6.55, 9.30); 3.58 (dd, 1H, $J = 6.85$, 9.30); 4.00 (dd, 1H, H_d, $J = 6.17$, 9.84); 5.20 (d, 1H, H_a, $J = 4.68$); 7.25– 7.45 (m, 5H, Ar); **3c** see Ref. 16; **3d** see Ref. 17; **3e** (*exo*) δ (*J* Hz) 0.89 (d, 3H, CH_3, $J = 6.61$); 0.91 (d, 3H, CH_3, $J = 6.61$); 1.87 (m, 1H); 2.24–2.38 (m,1H, H_b); 2.82–2.94 (m, 1H, H_c); 3.15 (dd, 1H, $J = 6.76$, 9.31); 3.46 (dd, 1H, $J = 6.76$, 9.31); 3.62–3.74 (m, 2H); 4.15 (d, 1H, $J = 14.57$); 5.12 (dd, 1H, H_a, J= 2.70, 6.31); 7.15–7.52 (m, 10H, Ar); **3e** (*endo*) δ (*J* Hz) 0.96 (d, 3H, CH_3, $J = 6.76$); 0.99 (d, 3H, CH_3, $J = 6.76$); 1.92 (m, 1H); 2.40–2.51 (m, 1H, H_b); 2.58–2.68 (m, 1H, H_c); 3.18 (dd, 1H, $J = 7.27$, 9.31); 3.46 (dd, 1H, $J = 6.90$, 9.31); 4.15 (s, 2H); 4.21 (dd, 1H, H_d, $J = 6.30$, 10.36); 5.17 (d, 1H, H_a, $J = 4.80$); 7.18–7.51 (m, 10H, Ar); **3f** (*exo*) δ (*J* Hz) 0.94 (d, 3H, CH_3, $J = 6.70$); 0.95 (d, 3H, CH_3, $J = 6.70$); 1.96 (m, 1H); 2.31–2.41 (m, 1H, H_b); 2.58 (s, 3H, CH_3); 2.85–2.95 (m,1H, H_c); 3.17 (dd, 1H, $J = 7.39$, 9.46); 3.43 (t, 1H, H_d, $J = 8.38$); 3.68 (dd, 1H, $J = 6.21$, 9.46); 5.16 (dd, 1H, H_a, $J = 3.06$, 6.41); 7.25– 7.50 (m, 5H, Ar); **3f** (*endo*) δ (*J* Hz) 0.94 (d, 3H, CH_3, $J = 6.70$); 0.96 (d, 3H, CH_3, $J = 6.70$); 1.90 (m, 1H); 2.40–2.50 (m, 1H, H_b); 2.55–2.65 (m, 1H, H_c); 2.82 (s, 3H, CH_3); 3.20 (dd, 1H, $J = 6.51$, 9.27); 3.59 (dd, 1H, $J = 6.90$, 9.27); 4.04 (dd, 1H, H_d, $J = 6.21$, 9.96); 5.17(d, 1H, H_a, $J = 4.73$); 7.20–7.40 (m, 5H, Ar);**3g** see Ref. 18; **3h**, **3i**, **3l** see Ref. 14; **3m** 2–benzyl-3-phenyl-1,8-dioxa-2-aza-bicyclo[4.3.0]nonane (*exo*) δ (*J* Hz), 1.41–1.64 (m, 2H, 5-H), 1.75–1.91 (m, 2H, 6-H), 3.33–3.54 (m, 1H, H_b), 3.79–4.05 (m, 5H, CH_2Ph, H_d, 7-H), 5.88–5.95 (m, 1H, H_a), 7.05–7.60 (m, 10H, Ar); (*endo*) 1.60–1.74 (m, 2H, 5-H), 1.95–2.20 (m, 2H, 6-H), 3.11–3.23 (m, 1H, H_b), 3.62–4.08 (m, 3H, CH_2Ph; H_d), 4.10–4.18 (m, 2H, 7-H), 5.90–6.02 (m, 1H, H_a), 7.10–7.52 (m, 10H, Ar); **3n** 2-methyl-3-phenyl-1,8-dioxa-2-aza-bicyclo[4.3.0]nonane (*exo*) δ (*J* Hz) 1.52–1.70 (m, 2H, 5-H), 1.72–1.84 (m, 2H, 6-H), 2.71 (s, 3H, CH_3), 3.21–3.32 (m, 1H, H_b), 3.76–3.88 (m, 1H, H_d), 3.98–4.10 (m, 1H, 7-H), 5.74–5.81 (m, 1H, H_a), 7.20–7.41 (m, 5H, Ar); (*endo*) 1.62–1.74 (m, 2H, 5-H), 1.83–1.98 (m, 2H, 6-H), 2.56 (s, 3H, CH_3), 3.16–3.22 (m, 1H, H_b), 3.55–3.89 (m, 3H, H_d, 7-H), 5.87–5.94 (m, 1H, H_a), 7.25–7.50 (m, 5H, Ar).
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