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

Olga Bortolini,* Antonio De Nino, Loredana Maiuolo,* Beatrice Russo, Giovanni Sindona and Amedeo Tocci

Dipartimento di Chimica, Università della Calabria, Via Bucci 12 C, 87036 Rende (CS), Italy

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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.
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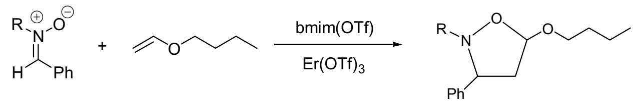
The 1,3-dipolar cycloaddition reactions represent the favourite method for the construction of five-membered heterocycles, important frameworks of various natural products.[1] In particular the 1,3-dipolar cycloadditions of nitrones with alkenes afforded isoxazolidines, which are interesting intermediates 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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Keywords: 1,3-Dipolar cycloadditions; Isoxazolidines; Ionic liquids; Er(III) catalyst.

* Corresponding authors. Tel.: +39 0984 492850; fax: +39 0984 493307 (O.B.); tel.: +39 0984 492853 (L.M.); e-mail addresses: o.bortolini@unical.it; maiuolo@unical.it

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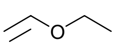
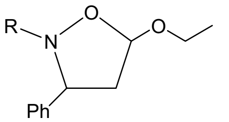
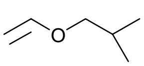
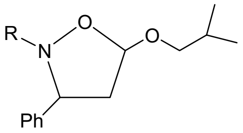
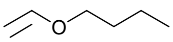
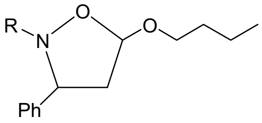
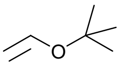
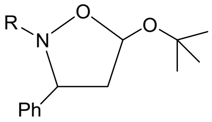
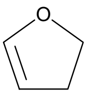
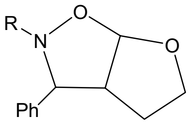
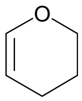
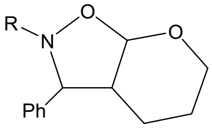
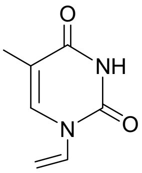
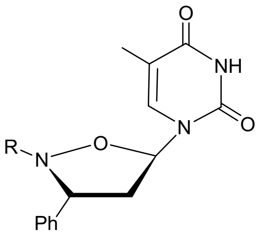
Table 1. Reaction of nitrone **1a** (1 mmol) with butyl vinyl ether **2**, in different experimental conditions

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.

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