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Nitrile oxide cycloadditions in supercritical carbon dioxide†

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The regioselectivity of dipolar cycloadditions of mesitonitrile oxide to various dipolarophiles in supercritical carbon dioxide can be tuned by changes in density, the magnesium bromide-mediated cycloaddition to pent-1-en-3-ol proceeding with higher stereoselectivity than in most conventional solvents.

The [2 + 4] cycloaddition reaction has been studied in some detail in supercritical carbon dioxide (scCO$_2$) which has recently emerged as a promising environmentally benign alternative to conventional solvents for organic synthesis.[1,2] Regio- and stereoselectivity effects in the Diels–Alder reaction have been studied. Differing *exo*/*endo* reaction rates were observed as a function of solvent density[3] and the effects of Lewis acid have been reported.[4]

1,3-Dipolar [3 + 2] cycloaddition reactions have hardly been studied in scCO$_2$.[5] In this Communication we have selected the well known dipolar cycloaddition of mesitonitrile oxide to various dipolarophiles[6] to investigate the regioselectivity as a function of the variable density of the solvent which is readily realisable through pressure changes. We have also observed a highly stereoselective chelation-controlled dipolar cycloaddition to pentenol.

The scope of mesitonitrile oxide (MesCNO) cycloadditions in scCO$_2$ was demonstrated in the reactions with electron-deficient (entries 1–5), electron-rich (entries 6 and 7), hindered (entry 8) and strained (entry 9) dipolarophiles (Table 1). The reaction mixtures described in Table 1 (entries 1–9) are all homogeneous in scCO$_2$ under the specified conditions. These results show that cycloadditions occur with a diverse range of alkenes and alkynes in scCO$_2$ to give isoxazoles and isoxazolines in high yields.

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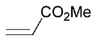
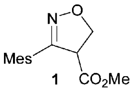
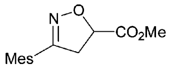
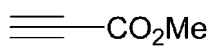
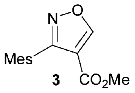
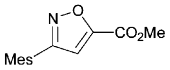
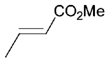
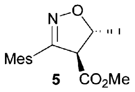
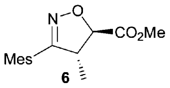
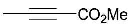
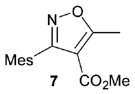
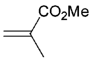
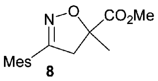
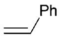
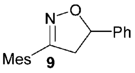
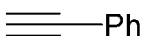
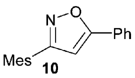
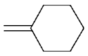
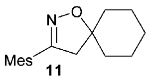
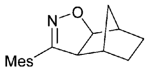
† Electronic supplementary information (ESI) available: Representative experimental procedures for cycloaddition of MesCNO to dipolarophiles and pentenol in scCO$_2$ and spectroscopic data for new compounds. See http://www.rsc.org/suppdata/cc/b4/b411561a/

Table 1 Cycloadditions of mesitonitrile oxide to alkenes and alkynes in scCO$_2$[a1]

Entry	Dipolarophile	Time (h)	Cycloadducts		Yield (%)/Ratio of isomers[b]
1		16	 1	 2	97 (**1**:**2**; 8.7:1)
2		16	 3	 4	97 (**3**:**4**; 2.9:1)
3		60	 5	 6	97 (**5**:**6**; 4.2:1)
4		60	 7		99
5		24	 8		98
6		24	 9		96
7		24	 10		97
8		60	 11		96
9		60	 12		96

[a] Reagents and conditions: MesCNO, dipolarophile (1 mole equiv.), scCO$_2$, 77 °C, 2600–2700 psi. [b] Based on ^{1}H NMR of crude products.

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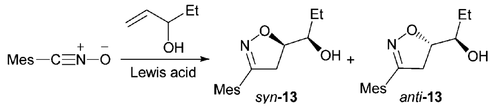
Table 2 Pressure (density) effects on the regioselectivity of the cycloaddition of mesitonitrile oxide to methyl propiolate in $scCO_2$ at 40 °C[a]

Entry	Pressure/psi)	Density/g mL^{-1}[7]	Ratio of **3** to **4**[b]
1	1180	0.294	3.1:1[c]
2	1230	0.350	2.6:1
3	1262	0.401	2.7:1
4	1323	0.515	2.8:1
5	1420	0.611	3.8:1
6	1645	0.670	2.8:1
7	2045	0.765	2.9:1
8	2540	0.814	2.5:1
9	2795	0.833	2.6:1

[a] Reagents and conditions: MesCNO, methyl propiolate (1 mole equiv.), $scCO_2$, 40 °C, 21 h. [b] Based on ^1H NMR of crude products. [c] Reaction mixtures (entries 1–9) are homogeneous under the specified conditions. †See ESI.

Table 3 Effect of Lewis acids on the cycloaddition of mesitonitrile oxide to pent-1-en-3-ol in $scCO_2$[a]



Entry	Lewis acid/mol equiv.	Ratio of *syn*:*anti*-isoxazoline **13**[b]	Yield (%)
1	None	62:38	96
2	LiCl (1)[c]	67:33	90
3	Li_2CO_3 (1)[c]	65:35	92
4	$ZnCl_2$ (1)[d]	74:26	91
5	$MgBr_2$ (0.5)[d]	85:15	93
6	$MgBr_2$ (1)[d]	92:8	92
7	$MgBr_2$ (5)[d]	94:6	92

[a] *Reagents and conditions*: MesCNO, pent-1-en-3-ol (1 mole equiv.), Lewis acid, $scCO_2$, 33 °C, 1100 psi, 16 h. [b] Based on ^1H NMR of crude products. [c] LiCl and Li_2CO_3 appear insoluble in the reaction mixtures. [d] $MgBr_2$ appears partially soluble in the reaction mixtures. †See ESI.

Owing to the high compressibility of $scCO_2$, chemical reactions carried out in this medium are potentially affected by pressure (and therefore density) variations. In the present study, the effects of pressure on the regioselectivity in the reaction of mesitonitrile oxide and methyl propiolate were examined at 40 °C (Table 2).

The experiments were conducted under high dilution (0.016 M). The density of the solution may therefore be assumed to be very close to that predicted for pure CO_2.[3,4] Inaccuracies in pressure measurement ($\pm$30 psi) due to small temperature fluctuations ($\pm$1 °C) contribute to errors in density estimations. Errors in density estimations are substantial at low pressures (near the critical pressure) but small to negligible at higher pressures.

The results (Table 2) indicate that 4-methoxycarbonylisoxazole **3** is the predominant regioisomer under the pressures tested at 40 °C. A maximum of 3.8:1 was observed at 1420 psi (0.611 g mL^{-1}). The data show that it is possible to tune the product ratios of **3** and **4** from 2.5:1 to 3.8:1 by simply altering the pressure/density of $scCO_2$. Whilst such a variation could be effected by changing the solvent (1.2:1 with MeOH and 3:1 with cyclohexane)[6] we have now demonstrated that this could also be achieved in the same solvent, simply by pressure/density adjustment of $scCO_2$.

Pioneering work by Kanemasa[8] showed that highly *syn*-selective nitrile oxide cycloadditions with α-substituted allylic alcohols could be achieved through chelation effects with Lewis acids. In particular, magnesium salts of allylic alcohols reacted rapidly with nitrile oxides, especially in non-coordinating solvents. The *syn*-selectivity arises from minimisation of allylic strain in the transition state. In the present work, the potential for chelation controlled stereoselective nitrile oxide cycloadditions in $scCO_2$ was investigated (Table 3).

Table 4 Solvent effects on $MgBr_2$-mediated cycloaddition of mesitonitrile oxide to pent-1-en-3-ol[a]

Entry	Solvent	Ratio of *syn*:*anti*-isoxazoline **13**[b]	Yield (%)
1	CO_2 (1100 psi)[c]	94:6	92
2	THF	74:26	93
3	EtOAc	92:8	93
4	MeOH	50:50	22
5	CH_2Cl_2	94:6	92
6	PhMe	95:5	86
7	n-C_6H_{14}	90:10	79
8	MeCN	92:8	61

[a] *Reagents and conditions*: MesCNO, pent-1-en-3-ol (1 mole equiv.), $MgBr_2$ (5 mole equiv.), 33 °C, 16 h. [b] Based on ^1H NMR of crude products. †See ESI.

Of the Lewis acids screened (LiCl, Li_2CO_3, $ZnCl_2$ and $MgBr_2$), the last mentioned gave rise to the most promising level of *syn*-selectivity for isoxazoline **13**. By increasing the amount of $MgBr_2$ from equimolar to a five-fold excess, the *syn*-selectivity was improved from 92:8 to 94:6 (Table 3, entries 6 and 7). We have also demonstrated that the yield and *syn*-selectivity for isoxazoline **13** obtained in CO_2 (Table 4, entry 1) rival those obtained in CH_2Cl_2 and toluene (Table 4, entries 5 and 6), and are generally higher than those seen in other conventional solvents (Table 4), thereby highlighting the merit of $scCO_2$ as an alternative reaction medium.

In summary, we have demonstrated the benefits of $scCO_2$ as a reaction medium for mesitonitrile oxide cycloadditions. The high compressibility of $scCO_2$ provides a distinct advantage over conventional organic solvents for controlling the regiochemistry of nitrile oxide cycloadditions through simple pressure (density) adjustments of CO_2. Finally, Lewis acid-mediated cycloadditions of mesitonitrile oxide with chiral allylic alcohols proceed in $scCO_2$ with yields and stereoselectivity generally surpassing those obtained in organic solvents.

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