Conversion of nitrosobenzenes to isoxazolidines: an efficient cascade process utilizing reactive nitrone intermediates†

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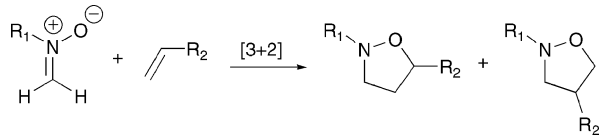
Reactive nitrones can be generated directly *in situ* by an unusual reaction of nitrosobenzene with styrene.

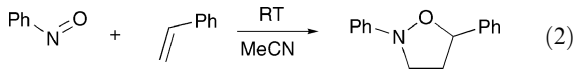
Efficiency is a central concept in modern organic synthesis. Cascade reactions, where multiple bond-forming events occur in one synthetic operation, not only encourage efficiency but also reduce waste by eliminating extra steps and often tedious purifications.[1,2] In this *communication*, we report the efficient, regioselective one-pot synthesis of a variety of isoxazolidines from commercially available starting materials. Isoxazolidines are often used as intermediates in the synthesis of complex molecules,[3,4] and are frequently present in biologically active compounds.[5–7] They are valuable intermediates because the N–O bond can be easily cleaved under mild reducing conditions to afford 1,3-amino alcohols, which themselves are highly valuable synthetic building blocks.[8] The most common method for the synthesis of isoxazolidines involves the 1,3-dipolar cycloaddition of a nitrone with an alkene to simultaneously generate an O–C and C–C bond, as well as up to three stereocenters (eqn (1)).[9–15]



(1)

Because of the utility of the isoxazolidines, a wide variety of synthetic approaches toward the precursor nitrones have been reported.[16,17] Among these synthetic methods, the acid-catalyzed condensation of N-monosubstituted hydroxylamines with carbonyl compounds and the oxidation of N,N-disubstituted hydroxylamines or secondary amines are the most general.[13] A neutral, non-oxidative pathway to nitrones, particularly reactive methylene nitrones, which are generally too reactive to isolate, would be beneficial.[18]

The high reactivity of aromatic nitroso compounds[19] led us to investigate their reactivity with olefins incapable of undergoing the nitroso ene reaction.[20] This led us to a discovery of a useful yet previously undeveloped reactivity pattern for nitroso compounds. We observed formation of isoxazolidines simply by combining nitrosobenzene and styrene in MeCN at RT for 12–48 h (eqn (2)). The reaction produces a slightly higher yield of product in DMSO, however, for ease of removal, we chose to employ MeCN as solvent, with minimal loss in reaction rate and yield (<10%).

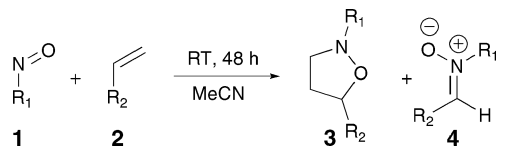


(2)

Table 1 summarizes the results of several cycloaddition reactions between various substituted styrenes and nitrosobenzenes in MeCN after 48 h. Yields of the isoxazolidines were best when a moderate excess of styrene (4 equiv.) was employed. Larger excesses did not significantly improve the isolated yields of these isoxazolidines. Electron rich styrenes generally give higher yields than electron deficient styrenes, but the unsubstituted parent styrene was the best substrate in this reaction, producing 49% of pure isoxazolidine (Table 1, entry 1). A by-product in these reactions is the substituted nitrone **4**, which helped in our mechanistic analysis (*vide infra*). We confirmed the structure of the products **3** by routine analytical methods, including 2D NMR spectroscopy (see ESI†). In addition, the structure of **3b** was confirmed by single crystal X-ray analysis, cementing our analysis and structural assignment of these products.[21]

Experiments to probe the influence of temperature were undertaken in refluxing MeCN (82 °C). The reactions at elevated temperature afforded the more hindered trisubstituted isoxazolidines **5** in addition to the disubstituted isoxazolidines which were formed at room temperature (Table 2).

Table 1 Room temperature cycloadditions[a]



1 **2**

Entry	R_1	R_2	Product	Yield (%)[b]
1	Ph (**1a**)	Ph (**2a**)	**3a**	49
2	Ph (**1a**)	2-MePh (**2b**)	**3b**	48
3	Ph (**1a**)	4-MeOPh (**2c**)	**3c**	48
4	Ph (**1a**)	3-ClPh (**2d**)	**3d**	31
5	Ph (**1a**)	4-*t*-BuPh (**2e**)	**3e**	30
6	Ph (**1a**)	4-CF_3Ph (**2f**)	**3f**	40
7	Ph (**1a**)	2-BrPh (**2g**)	**3g**	35
8	Ph (**1a**)	4-BrPh (**2h**)	**3h**	48
9	4-BrPh (**1b**)	Ph (**2a**)	**3i**	40

[a] **1** (0.25 mmol), **2** (1.0 mmol), and anhydrous MeCN (4 mL) were used. [b] Yield of isolated products; maximum possible yield: 50%.

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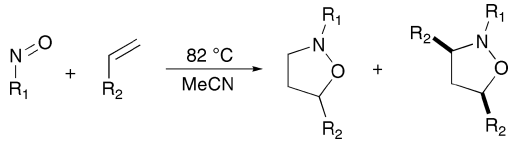
Table 2 Elevated temperature cycloadditions[a]



1 2 3 5

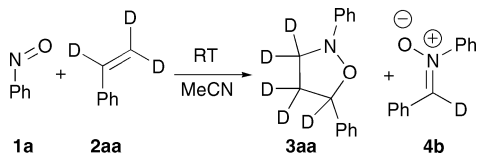
Entry	R_1	R_2	Product	Yield (%)[b]
1	Ph (**1a**)	Ph (**2a**)	**3a**/**5a**	49/40
2	Ph (**1a**)	2-MePh (**2b**)	**3b**/**5b**	41/41
3	Ph (**1a**)	4-MeOPh (**2c**)	**3c**/**5c**	48/39
4	Ph (**1a**)	3-ClPh (**2d**)	**3d**/**5d**	30/32
5	Ph (**1a**)	4-*t*-BuPh (**2e**)	**3e**/**5e**	33/30
6	Ph (**1a**)	4-CF_3Ph (**2f**)	**3f**/**5f**	38/25
7	Ph (**1a**)	2-BrPh (**2g**)	**3g**/**5g**	40/33
8	Ph (**1a**)	4-BrPh (**2h**)	**3h**/**5h**	48/40
9	4-BrPh (**1b**)	Ph (**2a**)	**3i**/**5i**	40/21

[a] **1** (0.25 mmol), **2** (1.0 mmol), and anhydrous MeCN (4 mL) were used. [b] Yield of isolated products; maximum possible yield: 50%.

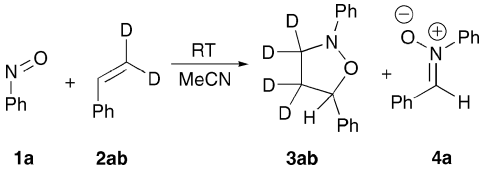
We confirmed the structure and stereochemistry of these *endo* [3 + 2] cycloadducts by the usual methods. In addition, the structure of **5b**, including the relative *cis* stereochemistry of the newly formed 5-membered ring, was confirmed by X-ray crystallography.[21]

We were intrigued by the mechanism of this reaction and in hopes of developing a synthetically useful cascade process, we undertook a mechanistic analysis of the reaction. Our hypothesis was that a nitrone-involved dipolar cycloaddition was responsible for formation of the isoxazolidines.[22] Our goal was to determine if and how nitrones were being formed under the reaction conditions.

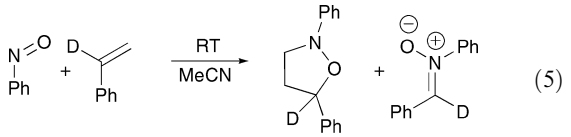
In a room temperature experiment employing CD_3CN as solvent, the reaction of nitrosobenzene **1a** with styrene **2a** produced 2,5-diphenylisoxazolidine **3a** and *N*-benzylideneaniline oxide **4a**, with no deuterium incorporation in either product. When the deuterated styrenes **2aa**, **2ab**, and **2ac** were individually subjected to the usual reaction conditions (PhNO, MeCN, RT), the products incorporated deuterium as indicated in eqn (3)–(5). These data point to cleavage of the C=C bond of the styrene moiety as a key step in the mechanism. As additional confirmation, we utilized two ^{13}C labelled styrenes (eqn (6)–(7)). These experiments confirmed that cleavage of the alkene bond must be occurring along the reaction pathway, and accounted for all the carbons in the starting material and products.



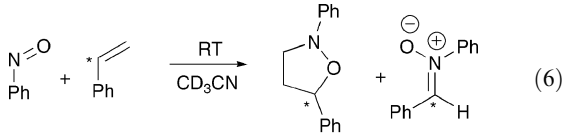
1a 2aa 3aa 4b (3)



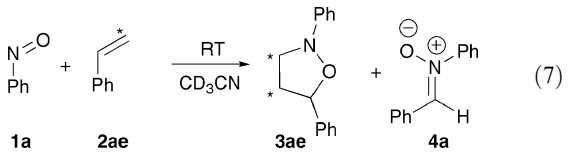
1a 2ab 3ab 4a (4)



1a 2ac 3ac 4b (5)



1a 2ad 3ad 4c (6)

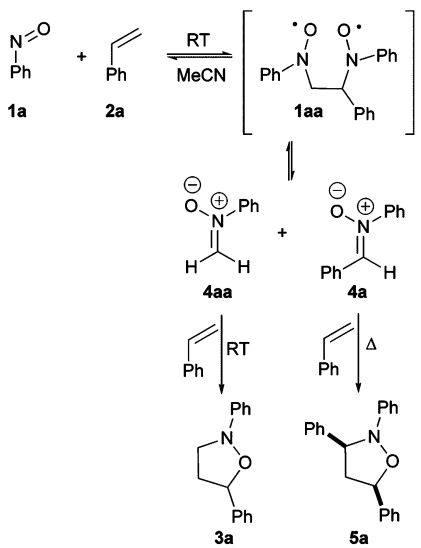


1a 2ae 3ae 4a (7)

It is noteworthy that the alkenes without adjacent electron stabilizing groups, including allyl alcohol, allyl bromide, and 1-octene, do not produce nitrones or cycloadducts under the standard reaction conditions. Nitrosobenzenes appear to be converted to nitrones only upon reaction with styrenes.

A preliminary proposed reaction pathway is outlined in Scheme 1. The combination of nitrosobenzene and styrene in a 2 : 1 ratio produces two nitrone molecules, one substituted (**4a**) and one unsubstituted (**4aa**) *via* an unstable intermediate 2 : 1 adduct of nitrosobenzene and styrene such as bis-nitroxide radical **1aa**. While we do not have direct evidence for **1aa** and cannot rule out other possibilities, we propose a bis-nitroxide radical intermediate not only due to their rich chemistry[23–26] but also more importantly the implication of nitroxide radical formation in the early stages of the nitroso ene reaction,[27,28] which may have a parallel in this reaction.

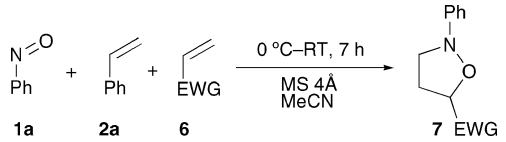
Regardless of the exact nature of the 2 : 1 adduct, the formation of unsubstituted nitrone **4aa** cannot be disputed, and this reactive dipole undergoes an immediate cycloaddition at RT with the excess styrene present. The substituted nitrone **4a** is not reactive towards dipolar cycloaddition at room

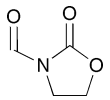


1a 2a 1aa 4aa 4a 3a 5a

Scheme 1 Proposed reaction sequence.

Table 3 Trapping of the unsubstituted nitrone with dipolarophiles[a]



Entry	EWG	Product	Yield (%)[b]
1	CHO (**6a**)	**7a**	86[c]
2	CN (**6b**)	**7b**	65
3	CO_2Me (**6c**)	**7c**	78
4	$C(O)NMe_2$ (**6d**)	**7d**	82
5	C(O)Et (**6e**)	**7e**	74
6	 (**6f**)	**7f**	81

[a] **1a** (1.0 mmol), **2a** (2.0 mmol), **6** (0.5 mmol), and anhydrous MeCN (2 mL) were used. [b] Yield of isolated product. [c] Isolated as the primary alcohol after $NaCNBH_3$ reduction.

temperature and can be isolated from the reaction mixture before undergoing cycloaddition with styrene. However, **4a** will undergo cycloaddition with styrene when heated.

With this data in hand, we pursued the synthetically useful goal of trapping the reactive nitrone **4aa** *in situ* with a dipolarophile that is more reactive than the styrene employed for generation of the **4aa**. For instance, when nitrosobenzene, acrylamide, and styrene are combined at RT (Table 3 entry 4), the desired 5-substituted oxazolidine can be isolated in 82% yield in a single step from inexpensive, commercially available materials. No cycloadduct derived from the more plentiful, but less reactive dipolarophile styrene was observed when the reaction was started at 0 °C and allowed to warm to RT. Other reasonable cycloadducts can be isolated as shown in Table 3 with use of an appropriate monosubstituted dipolarophile. The reactions are highly regioselective, with no evidence of formation of the 4-substituted products observed (^{1}H NMR spectroscopy). Methyl methacrylate, a disubstituted olefin, is also a suitable dipolarophile, yielding the expected cycloadduct in 52% yield. However, 1,2-substituted olefins, such as methyl crotonate, were unreactive in this cycloaddition at room temperature.

In summary, we have demonstrated the useful formation of nitrones from nitrosobenzenes and monosubstituted aromatic styrenes, which can undergo a cyclization with electron-deficient alkenes to afford isoxazolidines in a single reaction flask. A [3 + 2] dipolar cycloaddition is clearly implicated by the available mechanistic data. The reaction allows for the rapid assembly of various substituted isoxazolidines directly from nitrosobenzenes, electron deficient alkenes, and styrene. The synthetically useful reactions described in Table 3 proceed with good yields and under convenient reaction conditions, but in contrast to typical syntheses that require 3 or more total steps, this cascade provides direct access to 5-substituted isoxazolidines in a single step from commercially available starting materials.

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Notes and references

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