Trimethylsilyl Trifluoromethanesulfonate Promoted [3 + 2] Dipolar Cycloaddition of Nitrones and Silyl Enol Ethers: an Efficient Route to 5-Siloxyisoxazolidines

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The reaction of silyl enol ethers and nitrones, in the presence of trimethylsilyl trifluoromethanesulfonate, gives 5-siloxyisoxazolidines in excellent yield under fairly mild conditions.

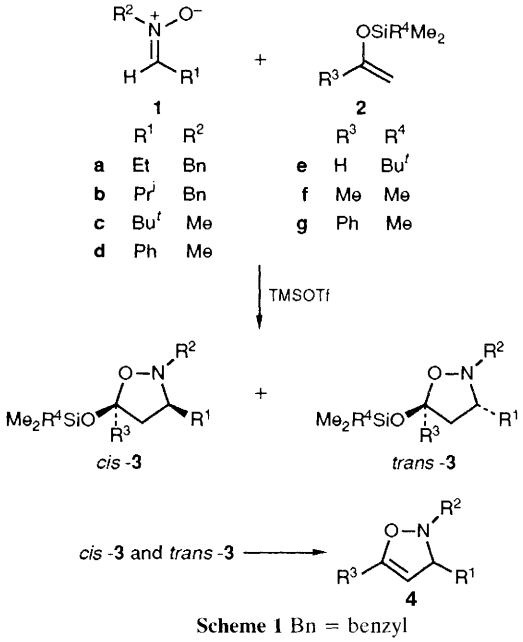
The [3 + 2] dipolar cycloaddition of nitrones and alkenes represents the most powerful route to isoxazolidines.[1] We have recently reported two alternative methods for the synthesis of 3,5-disubstituted isoxazolidines *via* [CNO + CC] ring forming reactions. Our first approach involves allylation of nitrones (using allylic magnesium or zinc derivatives) followed by *O*-silylation to give *O*-silylated hydroxylamines which, on iodocyclization, afford 5-iodomethylisoxazolidines.[2] The second route is based on the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf), as an activator, in cycloaddition reaction of nitrones with allyltrimethylsilane to give 5-trimethylsilylmethylisoxazolidines at temperatures lower than 20 °C.[3]

We now report that aldonitrones **1** and trialkylsilyl enol ethers **2** undergo an analogous TMSOTf catalysed cycloaddition reaction affording regioselectively 5-trialkylsiloxyisox-

Table 1

Run	Nitrone	Silyl enol ether	TMSOTf /equiv.	Reaction conditions		Yield[a] **3** (%)	*cis*-**3** : *trans*-**3** ratio[b]	Yield **4** (%)
				T/°C	*t*/h			
1	**1a**	**2e**	0.1	0	72	42	58 : 42	17
2	**1a**	**2e**	0.1	20	24	64	50 : 50	32
3	**1a**	**2e**	1.0	−10	24	92	70 : 30	0
4	**1b**	**2e**	1.0	−10	30	95	38 : 62	0
5	**1c**	**2e**	1.0	0	30	89	45 : 55	0
6	**1d**	**2e**	1.0	0	30	87	36 : 64	0
7	**1a**	**2f**	1.0	0	24	91	35 : 65	6
8	**1b**	**2f**	1.0	0	24	88	40 : 60	8
9	**1d**	**2f**	1.0	0	24	77	40 : 60	15
10	**1a**	**2g**	1.0	0	27	76[c]	50 : 50	19[c]
11	**1b**	**2g**	1.0	0	24	74[c]	55 : 45	21[c]

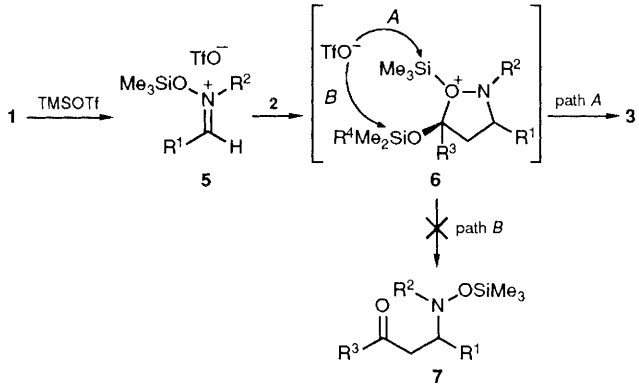
[a] Unless otherwise stated, yields refer to the isolated products after flash column chromatography. With the exceptions of runs 5, 10 and 11, *cis* and *trans* **3** are easily separated and fully characterized by IR, ^{1}H NMR (300 MHz) and ^{13}C NMR spectroscopy and mass spectrometry, and give correct elementary analyses. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yields refer to ^{1}H NMR analysis of the crude reaction mixture. The purification of **3** by flash chromatography is not possible since it gets almost quantitatively converted into **4**.



Scheme 1 Bn = benzyl

azolidines **3** (Scheme 1), as a mixture of *cis* and *trans* isomers, in excellent yields and under mild conditions. On the other hand, in the absence of TMSOTf, high temperature (xylene, reflux) is required in order to achieve the classical thermal [3 + 2] cycloaddition of nitrones and trialkylsilyl enol ethers.[4]

As reported in Table 1, the cycloaddition of nitrone **1a** and silyl enol ether **2e** was first examined in the presence of 10 mol% of TMSOTf at 0 and 20 °C (runs 1,2). In the first case only a moderate yield of *cis* and *trans* **3** was obtained, after 3 days, together with formation of the 2,3-dihydroisoxazole **4** (run 1). In run 2, almost quantitative conversion into **3** and **4** was observed after 24 h. However, the use of 1 equiv. of TMSOTf at −10–0 °C (runs 3–9) allowed us to optimize the formation of isoxazolidines **3**. Thus, when the aldonitrone **1a** (1 mmol) and acetaldehyde silyl enol ether **2e** (1.3 mmol) were reacted in the presence of TMSOTf (1 mmol), in dichloromethane (10 ml) at −10 °C (run 3), the cycloadduct **3** was exclusively obtained. Complete suppression of 2,3-dihydroisoxazole **4** was also achieved in runs 4–6 using silyl enol ether **2e**.† The elimination of trimethylsilanol from **3**, to form **4**, was noticed to be faster when silyl enol ethers derived from ketones were used; since substitution at C-5 stabilises the double bond in compound **4**. In fact, when acetone silyl enol ether **2f** was used, very good yields of 5-disubstituted isoxazolidines **3** were still obtained, although a small amount of **4** was isolated‡ (runs 7–9). Moreover, acetophenone silyl enol ether **2g** (runs 10, 11) afforded **4** in an even greater amount, as expected for the efficient conjugative stabilization of the 2,3-dihydroisoxazole double bond by the C-5 phenyl substituent.



Scheme 2 Tf = CF_3SO_2

Concerning the role played by TMSOTf, we believe that the activation energy required for the formation of the new carbon–carbon bond is reduced to a significant extent by the silylation of nitrone to afford *N*-siloxyimminium ion **5**, which then gives the oxonium ion **6**, an immediate precursor of **3** (Scheme 2, path *A*).§ In all the experiments reported in Table 1, β-(*N*-hydroxylamino)-aldehydes or ketones **7**, derived from path *B*, were not detected.

In conclusion, TMSOTf catalysed [3 + 2] dipolar cycloaddition of nitrones with silyl enol ethers represents a convenient route for the synthesis of 5-siloxyisoxazolidines which are potentially useful synthetic intermediates being masked forms of Mannich products.

† When **2e** was used, upon analysis of the reaction mixture by ^{1}H NMR, we observed scrambling of trialkylsilyl group in products **3**, as indicated by the presence of small amounts (<5%) of 5-trimethylsiloxyisoxazolidines as well as 5-*tert*-butyldimethylsiloxyisoxazolidines.

‡ Pure *cis* and *trans* 5-methyl-5-trimethylsiloxyisoxazolidines (runs 7–9) were found to be moderately unstable, since they undergo both partial equilibration and elimination on keeping for a prolonged time at room temperature.

§ The cyclization process may take place stepwise *via* a preliminary 1,3-addition of **2** to **5**, followed by cyclization of the intermediate β-silyl carbonium ion, but, the possibility of a concerted pericyclic mechanism cannot be ruled out.

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