

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-iodomethylisoxazoli-

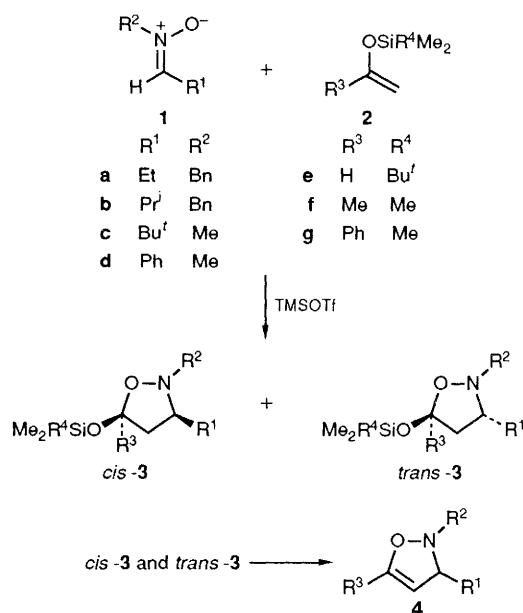
dines.² The second route is based on the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf), as an activator, in cycloaddition reaction of nitrones with allyltrimethylsilane to give 5-trimethylsilylmethylisoxazolidines at temperatures lower than 20 °C.³

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 (%)	<i>cis</i> -3 : <i>trans</i> -3 ratio ^b	Yield 4 (%)
				<i>T</i> /°C	<i>t</i> /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, ¹H NMR (300 MHz) and ¹³C NMR spectroscopy and mass spectrometry, and give correct elementary analyses. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Yields refer to ¹H 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.

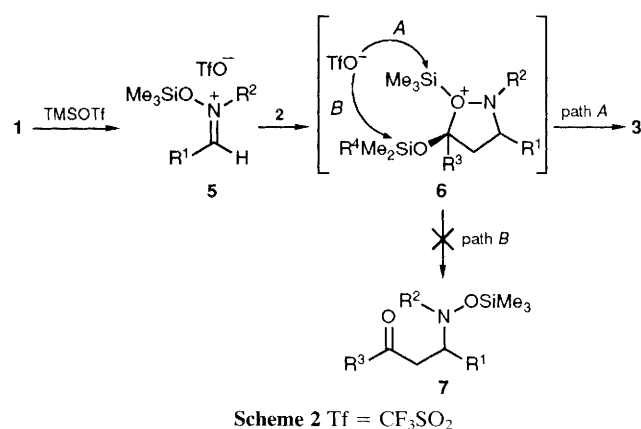


Scheme 1 Bn = benzyl

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

[†] When 2e was used, upon analysis of the reaction mixture by ¹H 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.

Scheme 2 Tf = CF₃SO₂

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.

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*-siloxyiminium 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.

[‡] 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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