TRIMETHYLSILYL TRIFLATE-PROMOTED [2+3] DIPOLAR CYCLOADDITION OF NITRONES WITH ALLYLTRIMETHYLSILANE

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Abstract - 3-Alkyl-5-trimethylsilylmethylisoxazolidines are accessible in good yields and at temperatures ≤ 20°C, by the trimethylsilyl triflate-promoted reaction of allyltrimethylsilane with aliphatic nitrones.

Recently, we have devised a route to isoxazolidines by iodocyclization of *O*-silylated homoallylic hydroxylamines, prepared by allylation of nitrones with allylic Grignard reagents.[2] In the course of our further studies in this area, we were particularly interested in a one-pot synthesis of *O*-trimethylsilyl homoallylic hydroxylamines via trimethylsilyl triflate (TMSOTf) catalyzed reaction of nitrones with allyltrimethylsilane.[3] This reaction was reported to occur when conjugated nitrones deriving from benzaldehyde, 3-pyridinecarboxaldehyde and ethyl glyoxylate were allowed to react with allyltrimethylsilane and TMSOTf in CH_2Cl_2 at room temperature. We envisioned to extend a similar intermolecular 1,3-addition process to aliphatic nitrones, and we found that the reaction of *unconjugated* *Z*-nitrones (**1a-f**)[4] with allyltrimethylsilane, in the presence TMSOTf at ≤ 20°C in CH_2Cl_2, afforded a mixture of *cis*- and *trans*-3-alkyl-5-trimethylsilylmethylisoxazolidines (**4**), with no traces of homoallylic hydroxylamines. By a formal point of view, we got the same products expected by the classical [2+3] dipolar cycloaddition of nitrones with allyltrimethylsilane, which is reported to take place at temperatures higher than 100°C.[5] The high reactivity exhibited by aliphatic nitrones in the TMSOTf-promoted cycloaddition reaction could be attributed to the formation of an intermediate *N*-silyloxyiminium ion (**2**), which successively reacts with allyltrimethylsilane to give isoxazolidines (**4**) via the oxonium ion (**3**), as depicted in Scheme 1. The reaction of the *N*-silyloxyiminium ion (**2**) with the nucleophilic C=C bond of allyltrimethylsilane can occur, in principle, via a stepwise process involving an intermediate β-silyl carbonium ion, or through a concerted mechanism characterized by an asynchronous

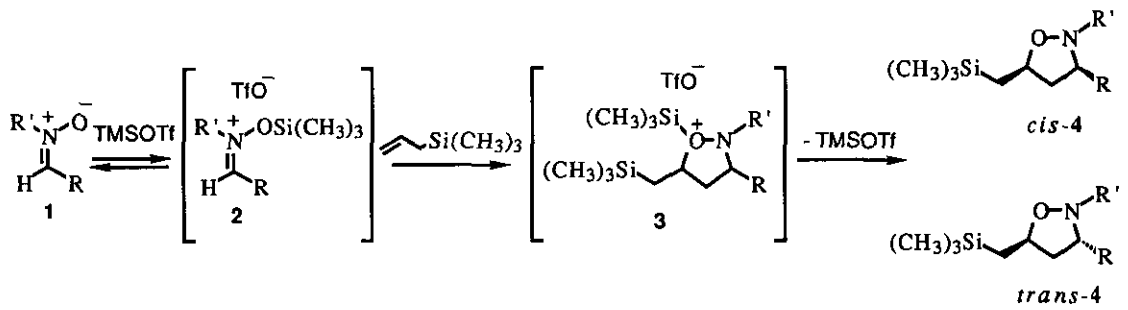
transition state. In principle, a catalytic amount of TMSOTf should be adequate, but, in the experiments listed in Table 1, we used 10% molar excess with respect to the nitrone in order to get good conversions in acceptable reaction times. A catalytic effect similar to that exhibited by TMSOTf could also be anticipated in the case of other strong silylating agents. We indeed observed that nitrones, in the presence of allyltrimethylsilane (5 equiv.) and iodine (1.2 equiv.) which give *in situ* trimethylsilyl iodide, gave isoxazolidines (**4**) in moderate yield (Entry 3).

The results collected in Table 1 show that, when R is a primary or secondary alkyl group, the reactions promoted by TMSOTf afforded ~ 60% yields of *cis*-**4** and *trans*-**4** (Entries 1, 2 and 4). The sterically demanding pivalaldehyde nitrones (**1d-e**) showed the lowest reactivity (Entries 5-8), while the α-alkoxy substituent activated nitrone (**1f**), deriving from *D*-glyceraldehyde, which displayed the highest reactivity among the nitrones examined, affording excellent yields of isoxazolidines at -30°C and in short reaction time (Entry 9).

The diastereomeric *cis*-**4** and *trans*-**4** were analyzed by gas chromatography, and samples of diastereomerically pure isoxazolidines were obtained by preparative liquid chromatography.[6] The assignement of relative stereochemistry was established by the difference in ^{1}H nmr (300 MHz) chemical shifts ($\Delta\delta$) of the H4 methylene protons, wherein $\Delta\delta$ for *cis* is higher than $\Delta\delta$ *trans*-isoxazolidines (**4**)[7] (see Table 2).

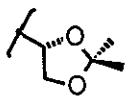
Regarding the stereochemical outcome of the cyclization reactions, the results depicted in Table I did not show appreciable diastereoselectivities. Low levels of selectivity in the intermolecular [2+3] dipolar cycloaddition of aldonitrones and monosubstituted alkenes are frequently observed[5,8] as a consequence of the small energy difference between *endo* and *exo* transition states. However it is to be noted that formation of *cis*-**4** was favored by primary R groups (Entries 1,2), while α-branching in the R substituent (Entries 4-8) favored the formation of *trans*-**4**. In the case of chiral nitrone (**1f**) (Entry 9) four cyclized products are expected as the faces of nitrone are diastereotopic. Unfortunately, nitrone (**1f**) did not display an appreciable diastereofacial selectivity[9] giving four isomers in the ratio 2:1:1:1, as detected by gas chromatography going from the lowest to the highest retention time. The first pair of peaks correspond to two trans products as determined by ^{1}H nmr analysis of chromatographic fractions enriched in the various isomers.

We are presently studying the extension of the TMSOTf-promoted cycloaddition of nucleophilic alkenes with nitrones as a valuable tool to synthesize the isoxazolidine ring system under mild conditions.



Scheme 1

Table 1. Synthesis of Isoxazolidines **4**.[a]

Entry		Nitrone **1** R	R'	reaction temp.(°C)	reaction time (h)	Yield **4** (%)	*cis/trans* ratio[b]
1	**1 a**	CH_3	CH_2Ph	- 15	42	61	61/39
2	**1 b**	C_2H_5	CH_2Ph	- 15	48	63	62/38
3[c]	**1 b**	C_2H_5	CH_2Ph	20	48	25	58/42
4	**1 c**	$(CH_3)_2CH$	CH_2Ph	0	48	60	43/57
5	**1 d**	$(CH_3)_3C$	CH_2Ph	0	48	40	30/70
6	**1 d**	$(CH_3)_3C$	CH_2Ph	20	8	57	35/65
7	**1 e**	$(CH_3)_3C$	CH_3	0	48	48	20/80
8	**1 e**	$(CH_3)_3C$	CH_3	20	6	44	15/85
9	**1 f**		CH_2Ph	- 30	3	89	35/65

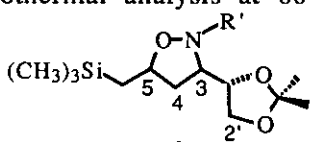
(a) In a typical procedure, TMSOTf (2.2 mmol) in CH_2Cl_2 (2 ml) was added drop by drop to a solution of nitrone (**1**) (2 mmol) and allyltrimethylsilane (4 mmol) in dry CH_2Cl_2 (18 ml) cooled at the desired temperature under argon. After stirring for the time reported in the Table 1, the reaction was quenched with 10% aq. $NaHCO_3$ (3 ml) and extracted with CH_2Cl_2 (3 x 20 ml). Isoxazolidines are purified by flash chromatography using cyclohexane-ethyl acetate (97:3). (b) Determined by gas chromatographic analysis of the crude reaction mixture. (c) Trimethylsilyl iodide used as the promoter.

Table II. ^{1}H Nmr Data for Isoxazolidines (**4**).

Product (R_t)[a]	^{1}H Nmr (300 MHz, $CDCl_3$) δ, ppm
cis-**4 a** (10.0)	7.45-7.20(m, 5H, ArH), 4.38-4.25(m, 1H, H5), 3.97(d, J =13.2, 1H, CH_2Ph), 3.90(d, J =13.2, 1H, CH_2Ph), 3.20-3.05(m, 1H, H3), 2.53 (ddd, J = 6.7, 6.7, 12.0, 1H, H4), 1.55(ddd, J =6.7, 8.2, 12.0,1H, H4), 1.15(d, J =6.4, 3H, CH_3), 1.07(dd, J =4.6, 14.0, 1H, CH_2Si), 0.88 (dd, J =8.4, 14.0, 1H, CH_2Si), 0.00(s, 9H, $SiMe_3$).
trans-**4 a** (8.8)	7.45-7.20(m, 5H, ArH), 4.19-4.08(m, 1H, H5), 3.96(d, J =13.7, 1H, CH_2Ph), 3.82(d, J =13.7, 1H, CH_2Ph), 2.80-3.05(m, 1H, H3), 2.12-1.87(m, 2H, H4), 1.15(d, J =6.4, 3H, CH_3), 1.09(dd, J =5.3, 14.0, 1H, CH_2Si), 0.82 (dd, J =9.1, 14.0, 1H, CH_2Si), 0.00(s, 9H, $SiMe_3$).
cis-**4 b** (13.0)	7.27-7.05(m, 5H, ArH), 4.32-4.13(m, 1H, H5), 3.90(d, J =12.9, 1H, CH_2Ph), 3.72(d, J =12.9, 1H, CH_2Ph), 2.82(quin, J =7.2, 1H, H3), 2.40 (dt, J =7.2, 11.9, 1H, H4), 1.55-1.20(m, 1H, H4), 1.52-1.36 (m, 2H, CH_2), 0.92(dd, J =6.3, 14.0, 1H, CH_2Si), 0.72(t, J =7.4, 3H, CH_3), 0.66-0.77 (m, 1H, CH_2Si), -0.12(s, 9H, $SiMe_3$).
trans-**4 b** (11.4)	7.27-7.05(m, 5H, ArH), 4.07-3.95(m, 1H, H5), 3.84(d, J =12.9, 1H, CH_2Ph), 3.72(d, J =12.9, 1H, CH_2Ph), 2.73-2.55(m, 1H, H3), 1.95-1.71 (m, 2H, H4), 1.33-1.19 (m, 2H, CH_2), 0.95(dd, J =4.6, 13.9, 1H, CH_2Si), 0.79(t, J =7.4, 3H, CH_3), 0.77-0.66 (m, 1H, CH_2Si), -0.12(s, 9H, $SiMe_3$).
cis-**4 c** (11.7)	7.50-7.20(m, 5H, ArH), 4.42-4.28(m, 1H, H5), 4.07(d, J =13.3, 1H, CH_2Ph), 3.82(d, J =13.3, 1H, CH_2Ph), 2.76(q, J =7.5, 1H, H3), 2.43 (ddd, J =5.5, 7.5, 12.0, 1H, H4), 1.72-1.60(m, 1H, H4), 1.82-1.55 (m, 1H, CH), 1.06(dd, J =6.4, 14.0, 1H, CH_2Si), 0.91(d, J =6.6, 3H, CH_3), 0.85(d, J =6.6, 3H, CH_3), 0.83(dd, J =7.8, 14.0, 1H, CH_2Si), 0.00(s, 9H, $SiMe_3$).
trans-**4 c** (13.6)	7.50-7.20(m, 5H, ArH), 4.12-4.00(m, 1H, H5), 3.96(d, J =13.7, 1H, CH_2Ph), 3.85(d, J =13.7, 1H, CH_2Ph), 2.80-2.68(m, 1H, H3), 2.19-2.07 (m, 2H, H4), 1.82-1.55(m, 1H, CH), 1.09(dd, J =5.5, 14.0, 1H, CH_2Si), 0.93(d, J =6.6, 3H, CH_3), 0.90(d, J =6.6, 3H, CH_3), 0.82(dd, J =8.8, 14, 1H, CH_2Si), 0.00(s, 9H, $SiMe_3$).
cis-**4 d** (12.8)	7.52-7.21(m, 5H, ArH), 4.42-4.27(m, 1H, H5), 4.12(d, J =13.3, 1H, CH_2Ph), 3.76(d, J =13.3, 1H, CH_2Ph), 2.88(t, J =7.9, 1H, H3), 2.31 (ddd, J =5.8, 8.4, 12.7, 1H, H4), 1.72-1.60(m, 1H, H4), 1.05-0.95(m, 1H, CH_2Si), 0.90-0.75(m, 1H, CH_2Si), 0.86(s, 9H, CH_3), 0.00(s, 9H, $SiMe_3$).
trans-**4 d** (12.1)	7.52-7.21(m, 5H, ArH), 4.10-3.98(m, 1H, H5), 4.05(d, J =13.7, 1H, CH_2Ph), 3.98(d, J =13.7, 1H, CH_2Ph), 2.78(dd, J =2.7, 9.6, 1H, H3), 2.16 (ddd, J =2.7, 5.8, 12.5, 1H, H4), 1.82(dt, J =9.6, 12.5, 1H, H4), 1.12(dd, J =5.8, 14.0, 1H, CH_2Si), 0.92(s, 9H, CH_3), 0.82(dd, J =9.0, 14.0, 1H, CH_2Si), 0.00(s, 9H, $SiMe_3$).

cis-**4e**[b] (8.2)	4.46-4.28(m, 1H, H5), 2.70(s, 3H, NCH_3), 2.62(t, *J* =6.4, 1H, H3), 2.34-2.18 (m, 1H, H4), 1.72-1.63(m, 1H, H4), 1.20-1.05(m, 1H, CH_2Si), 0.86(s, 9H, CH_3), 0.90-0.72(m, 1H, CH_2Si), 0.00(s, 9H, SiMe3).
trans-**4e**[b] (7.6)	4.02-3.85(m, 1H, H5), 2.75(s, 3H, NCH_3), 2.46(dd, *J* =3.5, 10.1, 1H, H3), 2.10 (ddd, *J* =3.5, 5.6, 12.3, 1H, H4), 1.82(dt, *J* =10.1, 12.3, 1H, H4), 1.08(dd, *J* =5.6, 14.0, 1H, CH_2Si), 0.92(s, 9H, CH_3), 0.78(dd, *J* =9.6, 14.0, 1H, CH_2Si), 0.00(s, 9H, SiMe3).
cis-**4f**[c] (10.8)	7.52-7.21(m, 5H, ArH), 4.48-4.38(m, 1H, H5), 4.11(d, *J* =12.6, 1H, CH_2Ph), 4.08-3.88(m, 2H, H2'), 3.79(d, *J* =12.6, 1H, CH_2Ph), 3.50-3.35(m, 1H, H1'), 3.15(dt, *J* =4.6, 8.2, 1H, H3), 2.63 (ddd, *J* =6.9, 8.2, 12.8, 1H, H4), 1.83 (ddd, *J* =4.6, 8.5,1 2.8, 1H, H4), 1.34(s, 3H, CH_3), 1.32(s, 3H, CH_3), 1.07(dd, *J* =5.6, 14.0, 1H, CH_2Si), 0.89(dd, *J* =8.7, 14.0, 1H, CH_2Si), 0.00(s, 9H, SiMe3).
cis-**4f'**[c] (11.7)	7.52-7.21(m, 5H, ArH), 4.25-3.95(m, 3H, H5,H1',H2'), 4.12(d, *J* =13.7, 1H, CH_2Ph), 4.00(d, *J* =13.7, 1H, CH_2Ph), 3.80(dd, *J* =6.0, 8.4, 1H, H2'), 3.31(q, *J* =7.0, 1H, H3), 2.40 (ddd, *J* =6.0, 8.0, 12.4, 1H, H4), 1.92-1.70 (m, 1H, H4), 1.36(s, 3H, CH_3), 1.32(s, 3H, CH_3), 1.06(dd, *J* =5.9, 12.9, 1H, CH_2Si), 0.87(dd, *J* =8.5, 12.9, 1H, CH_2Si), 0.00(s, 9H, SiMe3).
trans-**4f''**[c] (10.2)	7.52-7.21(m, 5H, ArH), 4.36(d, *J* =14.0, 1H, CH_2Ph), 4.30-3.88 (m, 3H, H5, H1', H2'), 3.88(d, *J* =14.0, 1H, CH_2Ph), 3.71(dd, *J* =7.1, 8.1 1H, H2'), 3.04(ddd, *J* =6.5, 7.7, 9.5, 1H, H3), 2.10-1.75 (m, 2H, H4), 1.41(s, 3H, CH_3), 1.33(s, 3H, CH_3), 1.05(dd, *J* =5.8, 14.0, 1H, CH_2Si), 0.81(dd, *J* =8.5, 14.0, 1H, CH_2Si), 0.00(s, 9H, SiMe3).
trans-**4f'''**[c] (10.6)	7.52-7.21(m, 5H, ArH), 4.32-3.88(m, 5H, H5,1',2',CH_2Ph), 3.62-3.50(m, 1H, H2'), 3.20-3.10(m, 1H, H3), 2.45-2.35 (m, 1H, H4), 1.91-1.62(m, 1H, H4), 1.35(s, 3H, CH_3), 1.30(s, 3H, CH_3), 1.17(dd, *J* =6.3, 14.2, 1H, CH_2Si), 0.90(dd, *J* =8.5, 14.2, 1H, CH_2Si), 0.00(s, 9H, SiMe3).

(a) Retention times (R_t) are given in min and refer to isothermal analyses performed at 150°C, unless otherwise stated, with a 30 m Supelcowax capillary column (0.25 μm film thickness) using a 2.5 ml/min hydrogen flow. (b) Isothermal analysis at 80°C. (c) Numbering of isoxazolidines (**4f**) is given as in Structure **A**. The nmr spectra refer to chromatographic fractions enriched in the given isomer. The *cis-trans* descriptors refer to the stereochemistry of the isoxazolidine ring. The relative stereochemistry of C1' and C3 could not be determined by nmr spectroscopy in the case of *trans*-**4f''** and **4f'''**, while, on the basis of previous findings in our laboratory,[10] we can assign the (3S) configuration to *cis*-**4f** and the (3R) configuration to *cis*-**4f'**.



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ACKNOWLEDGEMENTS

We thank the Fondazione " G. Marconi " and TPV Materie Plastiche for awarding a fellowship to DDD, and the Italian C. N. R. (Progetto Finalizzato Chimica Fine 2) for financial support.

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Received, 30th June, 1992