Cycloaddition Reactions of (*Z*)-*β*-Siloxyacrylonitriles with Enones: Synthesis of 4*H*-Pyrans and Dihydro-2*H*-pyrans

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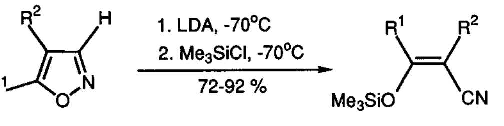
Reaction of (*Z*)-*β*-siloxyacrylonitriles **1** with enones **2** afforded 4*H*-pyrans **3** and dihydro-2*H*-pyrans **4** regio- and stereoselectively. A concerted hetero-Diels–Alder process is proposed.

In a recent publication[1] we reported a general method for the synthesis of (*Z*)-*β*-siloxyacrylonitriles from isoxazoles (Scheme 1) and we noted that this new family of silyl enol ethers showed a great potential as versatile synthetic intermediates in heterocyclic chemistry. They can be easily converted into *β*-enaminoketones[1,2] of wide application in the synthesis of alkaloids[3] and other biologically active compounds.[4,5] Some time ago,[6] we also studied the dienophilic activity of (*Z*)-*β*-siloxyacrylonitriles toward homo- and heterodienes and we proved the reaction to be of interest in the field of heterocyclic synthesis.



Scheme 1

In this paper, we report the cycloaddition reactions of (*Z*)-*β*-siloxyacrylonitriles **1** with enones **2** as a simple and efficient route to 4*H*-pyrans **3** and dihydro-2*H*-pyrans **4**. Diels–Alder reactions of 1-oxabuta-1,3-dienes have been well known for many years and have been thoroughly investigated by Tietze[7] and Desimoni.[8] Although the participation of siloxybutadienes (silyl dienol ethers) in Diels–Alder and hetero-Diels–Alder reactions has been extensively studied,[9,10] the ability of silyl enol ethers to behave as dienophiles in cycloaddition reactions with inverse electron demand has not been thoroughly explored.[11] Cava et al.[12] have reported the reaction of the monosilyl derivative of biacetyl with reactive dienes which gives *α*-hydroxy ketones after hydrolysis of the adducts and recently, Mizukami[13] has also used silyl enol ethers with oxybutadiene derivatives.

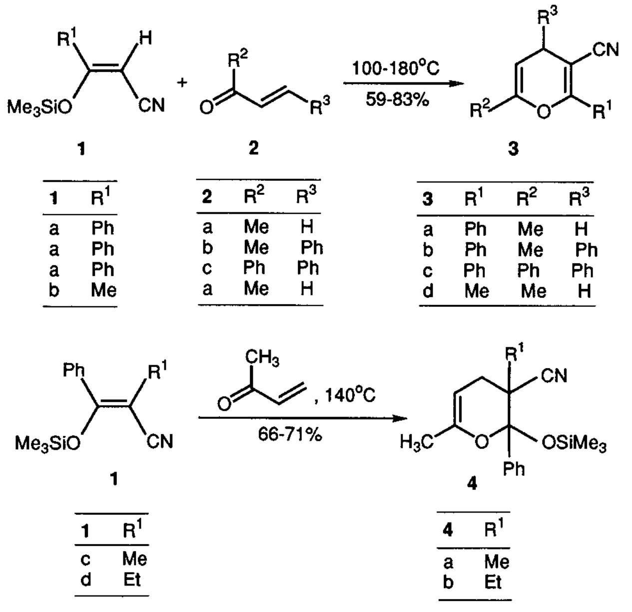
Table. Reaction of (*Z*)-*β*-Siloxyacrylonitriles **1** with Enones **2**

Compound	Enone	Temperature (°C)	Time (h)	Product[a]	Yield[b] (%)
1a	**2a**	120	2	**3a**	83
1a	**2b**	140	2	**3b**	77
1a	**2c**	180	4	**3c**	59
1b	**2a**	100	1.5	**3d**	68
1c	**2a**	140	1.5	**4a**	71
1d	**2a**	140	2	**4b**	66

[a] Products purified by flash chromatography (silica gel, eluent: CH_2Cl_2). Satisfactory microanalyses obtained: C ± 0.3; H ± 0.2; N ± 0.2.

[b] Yield of pure isolated product.

We have now found that (*Z*)-*β*-siloxyacrylonitriles **1a–d** undergo cycloaddition reactions when heated with *α*,*β*-unsaturated ketones **2a–c** leading to 4*H*-pyrans **3a–d** and dihydro-2*H*-pyrans **4a,b** in very acceptable yields[14] (Scheme 2, Table).



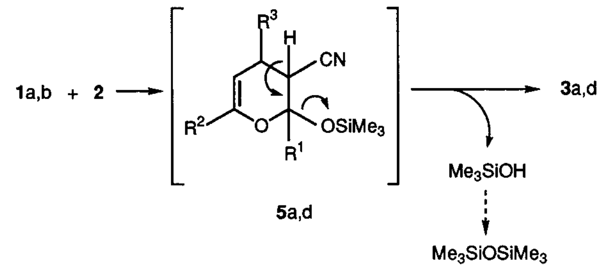
1	R1	2	R2	R3	3	R1	R2	R3
a	Ph	a	Me	H	a	Ph	Me	H
a	Ph	b	Me	Ph	b	Ph	Me	Ph
a	Ph	c	Ph	Ph	c	Ph	Ph	Ph
b	Me	a	Me	H	d	Me	Me	H

1	R1
c	Me
d	Et

4	R1
a	Me
b	Et

Scheme 2

The reaction takes place in a sealed glass ampule, without solvent, at temperatures around 140 °C (Table). All attempts to achieve the reaction in standard glass equipment using high boiling point solvents (diglyme etc.) gave very poor yields. After heating, the ampule is opened and the brownish crude mixture poured into saturated NH_4Cl and extracted with diethyl ether. Trisubstituted (*Z*)-*β*-siloxyacrylonitriles **1a,b** give directly pyrans **3a–d** after hydrolysis; however NMR of the crude shows that pyrans **3a–d** are present in the mixture, to some extent, before hydrolysis. We were not able to isolate adducts **5a–d** presumably due to the easy elimination of silanol from the adducts (Scheme 3). Tetrasubstituted (*Z*)-*β*-siloxyacrylonitriles **1c,d** cannot undergo elimination and they react with methyl vinyl ketone leading to 3,4-dihydro-2-siloxy-2*H*-pyrans **4a,b** as single diastereomers. It should be noted that the reaction shows high regioselectivity. Although we cannot be definitive about the mechanism of the cycloaddition and the degree of concertedness of the reaction, a concerted pathway seems to be preferred to a two-step addition process in view of the high stereoselectivity shown by the reaction (GC/MS shows that **4a,b** are single homogeneous compounds) and the lack of open chain products in all the studied reactions. Participation of a silyl enol ether as the alkene component in a Diels–Alder reaction is unusual,[12] but our results are not surprising if we assume that the essential feature in a Diels–Alder reaction is that the two components should have complementary electronic character.[15] In this case, an electron poor oxabutadiene **2** and an electron rich dienophile **1** are used, and the cycloaddition seems to proceed according to a Diels–Alder reaction with inverse electron demand.



Scheme 3

In summary, (*Z*)-β-siloxyacrylonitriles, easily available from isoxazoles, react with enones providing a convenient route to 4*H*-pyrans for which not many known procedures of synthesis have been reported in the literature.[14]

All reagents were of commercial quality from freshly opened containers, or were purified before use. Organic solvents were purified by standard procedures. Melting points are uncorrected. Preparation of (*Z*)-β-siloxyacrylonitriles **1** was described in a previous article.[1] IR spectra were recorded on a Mattson Cygnus-100 FT spectrometer. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker WP-200-5Y spectrometer. Purification of products were performed by flash chromatography on silica gel 60 (Macherey-Nagel, 230–400 mesh). GC/MS were recorded on a Hewlett-Packard 5988-A equipped with HP-1 Crosslinke Methyl-Silicone Gum capillary columns. For the new compounds **3a–d** and **4a,b** satisfactory microanalyses were obtained C $\pm$ 0.27, H $\pm$ 0.19, N $\pm$ 0.21.

4*H*-Pyrans 3 and Dihydro-2*H*-Pyrans 4; General Procedure:

The enone **2** (2 mmol) and the (*Z*)-β-siloxyacrylonitrile **1** (2.1 mmol) were placed in a 2.5 mL fire-sealed ampule. The mixture was heated in a thermostated oven; the temperatures and the times are indicated in the Table for each experiment. After cooling, the yellow-brownish crude product was poured into satd NH_4Cl solution (5 mL) at 0 °C and extracted with Et_2O (2 × 5 mL). The organic layer was dried ($MgSO_4$) and the solvent rotoevaporated to leave a residue which was purified by flash chromatography (CH_2Cl_2) to give the final products **3** and **4** (Table).

CAUTION! occasionally, explosion of the ampule may occur. A careful sealing of the ampule is recommended.

Selected spectroscopic data:

3a: yield: 83 %; viscous oil.

IR (film): ν = 3045, 2925, 2210, 1620, 1605, 1580, 760, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.38–8.27 (m, 5 H, C_6H_5), 4.63 (dd, J = 5.8, 9.1 Hz, 1 H, =CH), 2.89 (dd, J = 0.7, 9.1 Hz, 1 H, C*H*H), 2.82 (dd, J = 0.7, 5.8 Hz, 1 H, CH*H*), 2.22 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 170.7, 154.6, 137.4, 131.3, 129.3, 128.5, 117.1, 91.6, 74.9, 23.5, 19.5.

EI-MS: m/z (%) = 197 (17, M^+), 196 (13, M^+-1), 182 (25), 77 (30), 70 (100), 55 (82), 43 (50).

3b: yield: 77 %; mp 72–74 °C (EtOH).

IR (CCl_4): ν = 2217, 1610, 1605, 1587, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.24–8.04 (m, 10 H, Ar–H), 4.91 (d, J = 4.2 Hz, 1 H, =CH), 3.87 (d, J = 4.2 Hz, 1 H, CH), 2.26 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 173.4, 153.9, eight peaks between 141.8 and 127.1 (Ph groups), 116.7, 95.1, 76.4, 33.2, 23.1.

EI-MS: m/z (%) = 273 (21, M^+), 272 (15, M^+-1), 258 (10), 196 (65), 146 (100), 103 (7), 77 (19), 43 (42).

3c: yield: 59 %; mp 117–118 °C (EtOH).

IR (CCl_4): ν = 2223, 1600, 1580, 1500, 695 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.15–8.21 (m, 15 H, Ar–H), 5.37 (d, J = 3.85 Hz, 1 H, =CH), 4.11 (d, J = 3.85 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 175.2, 157.4, twelve peaks between 143.1 and 127.7 (Ph groups), 118.2, 88.9, 76.6, 35.6.

EI-MS: m/z (%) = 335 (30, M^+), 334 (10, M^+-1), 258 (21), 233 (37), 230 (5), 208 (85), 131 (100), 128 (16), 105 (23), 77 (28), 39 (31).

3d: yield: 68 %; bp 55–60 °C/Torr.

IR (film): ν = 3020–2870, 2235, 1645, 1220 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.48 (dd, J = 3.9, 6.7 Hz, 1 H, =CH), 2.69 (m, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 168.8, 153.6, 117.1, 91.2, 76.1, 25.3, 21.9, 18.9.

EI-MS: m/z (%) = 135 (3, M^+), 134 (9, M^+-1), 120 (18), 94 (31), 92 (21), 70 (100), 43 (47).

4a: yield: 71 %; viscous oil.

IR (film): ν = 2213, 1662, 1580, 1485, 740, 695 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.25–7.80 (m, 5 H, C_6H_5), 4.70 (m, 1 H, =CH), 2.35 (m, 2 H, CHH), 2.02 (d, J = 1.9 Hz, 3 H, CH_3C=), 1.37 (s, 3 H, CH_3C), 0.13 [s, 9 H, $(CH_3)_3Si$].

^{13}C NMR ($CDCl_3$): δ = 152.8, 143.1, 129.5, 129.3, 127.2, 124.7, 120.4, 89.8, 33.5, 25.6, 16.8, 8.3, 0.2.

EI-MS: m/z (%) = 301 (0.3, M^+), 300 (1, M^+-1), 286 (9), 224 (7), 212 (33), 166 (11), 90 (16), 73 (39), 70 (100), 55 (61), 43 (51).

4b: yield: 66 %; viscous oil.

IR (film): ν = 2205, 1660, 1595, 1480, 820, 745, 690 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.25–7.70 (m, 5 H, C_6H_5), 4.78 (br t, J = 4.9 Hz, 1 H, =CH), 2.28 (m, 2 H, $=CCH_2$), 2.03 (br s, 3 H, CH_3C=), 1.55 (q, J = 8.1 Hz, 2 H, CH_2CH_3), 1.01 (t, J = 8.1 Hz, 3 H, CH_2CH_3), 0.14 [s, 9 H, $(CH_3)_3Si$].

EI-MS: m/z (%) = 314 (0.8, M^+-1), 300 (3), 226 (27), 91 (15), 90 (19), 73 (58), 70 (100), 55 (79), 43 (40).

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