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Studies in 3-oxy-assisted 3-aza Cope rearrangements†

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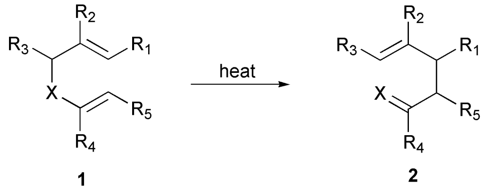
On thermolysis appropriately substituted *N*-silyloxy-*N*-allyl enamines undergo smooth 3,3-sigmatropic rearrangments to the corresponding *N*-silyloxy imino ethers.

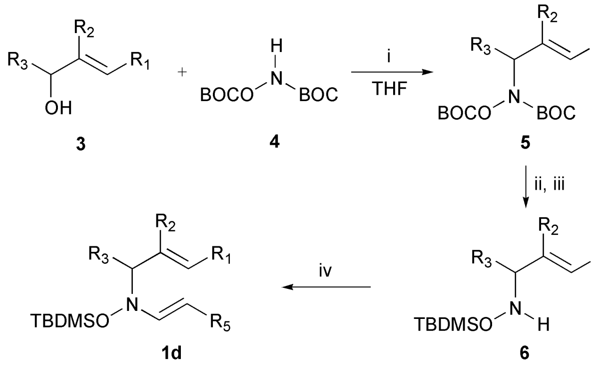
Cope rearrangement is an important reaction in organic synthesis. This pericyclic process involving 1,5-hexadienes generally proceeds under drastic conditions (*i.e.* high temperatures and prolonged reaction times) and in poor to modest yield[1] [eqn. (1); **1a** to **2a**]. The 3-aza analogue of the above reaction involving uncharged molecules, first reported by Hill,[2] also requires high temperatures for the rearrangements to occur [eqn. (1); **1b** to **2b**]. Although the presence of an ether functionality at C-3 [eqn. (1); **1c** to **2c**] in the all carbon framework has been found to improve the overall efficiency of the process,[3] the effect of such a substituent in the 3-aza version is so far not reported. We disclose in this communication the first experimental realisation with the latter type of functionality which consists of thermolysis of a number of *N*-silyloxy-*N*-allyl enamines [eqn. (1); **1d** to **2d**] and show that the corresponding 3,3-sigmatropic rearrangement products, the oxime-ethers **2d**, are obtained in good to excellent yields.



(1)

a) X = CH$_2$ b) X = NR c) X = CHOR d) X = NOSiMe$_2$CMe$_3$

O-Silyl-*N*-allyl hydroxylamines were secured as follows: the appropriate allyl alcohol **3** and *N,O-bis-tert*-butoxycarbonyl hydroxylamine (**4**) were condensed by Mitsunobu's method[4] to give the corresponding *N*-allyl-*O*-acyl hydroxamic acid **5** (Scheme 1). Removal[5] of the protecting groups from these substances provided the corresponding hydroxylamines. *O*-Silylation[6] of the latter furnished the title compounds **6**. They underwent nucleophilic addition smoothly[7] to ethynyl-*p*-tolylsulfone and methyl propiolate to provide the *N*-silyloxy-*N*-allyl enamines **1d** required for our study (Scheme 1, Table 1).‡



TBDMS = SiMe$_2$CMe$_3$

Scheme 1 *Reagents and conditions*: i, diisopropylazodicarboxylate, PPh$_3$; THF, rt; ii, CF$_3$CO$_2$H (4 eq.), CH$_2$Cl$_2$, rt; iii, TBDMSCl, imidazole, DMF, rt; iv, HC≡CR$_5$ (1 eq.), CH$_3$CN or CH$_2$Cl$_2$, rt.

Table 1 Michael addition products **1d** from *O*-silyl hydroxylamines **6**

#	Allyl alcohol **3**	*O*-Silyl hydroxylamine **6** yield[a](%)	1,4-Addition product **1d**[b]	Yield[a] (%)
1	$R_1 = R_2 = R_3 = H$	63	$R_5 = SO_2Tol$	70
2	$R_1 = R_3 = H; R_2 = Me$	60	$R_5 = SO_2Tol$	72
3	$R_2 = R_3 = H; R_1 = Me$	58	$R_5 = SO_2Tol$	76
4	$R_1 = R_2 = H; R_3 = Me$	24	$R_5 = SO_2Tol$	78
5	$R_1 = R_3 = H; R_2 = Ph$	62	$R_5 = SO_2Tol$	77
6	$R_2 = R_3 = H; R_1 = Ph$	87	$R_5 = SO_2Tol$	75
7	$R_1 = R_2 = R_3 = H$	63	$R_5 = CO_2Me$	70

[a] Isolated yields. [b] R_4 = H , Tol = *p*-MeSO$_2$C$_6$H$_4$

The thermal rearrangements of the above substances were conducted in *o*-dichlorobenzene under reflux (188 °C) (*ca.* 0.03 M) and the results are collected in Table 2.§

Examination of the Table shows that the reactions occur in consistently good yield to provide the oxime ethers **2d** as a mixture of the *syn* and *anti* isomers. Under virtually identical experimental conditions the cyclohexyl enamines **1b** (R = cyclohexyl; $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = SO_2Tol$ or $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CO_2Me$) *showed no tendency to undergo the aza-Cope reaction, underlining the importance of the silyloxy group in promoting the rearrangement.*

The occurrence of 1,3-shifts in these reactions is excluded because of the presence of the characteristic 2H multiplet due to *H*$_2$C=CH group in the ^{1}H NMR spectra of the products **2d** (Table 2; entries 3 and 6) centred at *ca.* δ 5.0 ppm and the absence of the same in that of **2d** (entry 4). In those reactions, wherein two stereogenic centres are created in the products (Table 2; entries 3 and 6), high diastereoselection was observed. The oxime pair, in each case, contained one predominant diastereomer (>80% by ^{1}H NMR analysis).

Table 2 Rearrangement of N-silyloxy enamines **1d** to oxime ethers **2d**

#	Enamine **1d**	Reaction Time (min)	Oxime ether **2d** yield[a] (%)	Ratio *syn*:*anti*[b]
1	$R_1 = R_2 = R_3 = H; R_5 = SO_2Tol$	80	82	63:37
2	$R_1 = R_3 = H; R_2 = Me; R_5 = SO_2Tol$	70	81	82:18
3	$R_2 = R_3 = H; R_1 = Me; R_5 = SO_2Tol$	165	79	50:50
4	$R_1 = R_2 = H; R_3 = Me; R_5 = SO_2Tol$	25	80	50:50
5	$R_1 = R_3 = H; R_2 = Ph; R_5 = SO_2Tol$	15	80	99:1
6	$R_2 = R_3 = H; R_1 = Ph; R_5 = SO_2Tol$	240	78	37:63
7	$R_1 = R_2 = R_3 = H; R_5 = CO_2Me$	60	80	60:40

[a] Isolated yields. [b] By ^{1}H NMR (see, ref. 8).

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† Dedicated with respect to the late Professor T. R. Govindachari.

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In conclusion, the first examples of 3-silyloxy-assisted 3-aza Cope reactions are reported. They are shown to occur in good to excellent yields.

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Notes and references

‡ All addition products **1d** were deduced (^{1}H NMR) to possess the *trans* arrangement of the olefinic bond bearing the electron withdrawing group R_5.

§ Typical experimental procedure: *trans*-1-*N*-allyl-*N*-(*tert*-butyldimethylsilyloxy)amino-2-(*p*-tolylsulfonyl)ethylene (**1d**, Table 2, entry 1) (25 mg), in *o*-dichlorobenzene (2 mL), was heated under reflux until all the starting material had been consumed (80 min) (tlc control, silica, Et_2O : *n*-hexane 1 : 3, as eluent). Evaporation of the solvent under reduced pressure, followed by purification of the residue by ptlc, gave the product, a viscous oil (20.5 mg, 82% yield), as a mixture of *syn* and *anti* oxime-ethers (**2d**, Table 2, entry 1). Selected spectroscopic data: IR (neat) 1642, 1597, 1325, 1252, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.42 and 2.43 (3H, two s), 4.90–5.15 (2H, m), 6.82 and 7.36 (1H, two d).

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