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Studies on the Homodienyl-[1,5]-Hydrogen Shift in Vinylaziridines

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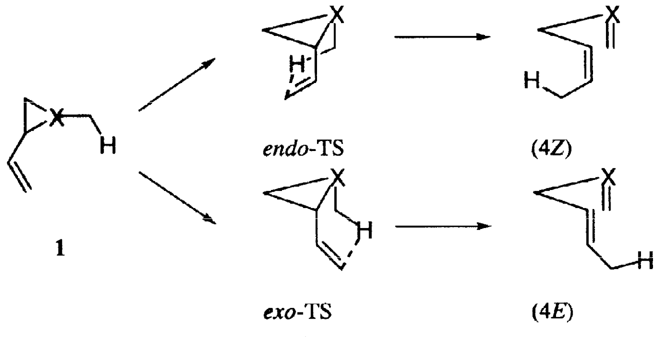
Abstract: The homodienyl-[1,5]-hydrogen shift in vinylaziridines has been investigated and the substituent effects observed in the reaction have been studied qualitatively.

Keywords: Amines, aziridines, rearrangements.

Pericyclic reactions have traditionally played an important role in synthetic organic chemistry. Several reasons for this can be identified, but the introduction of the Woodward-Hoffmann selection rules and the frontier molecular orbital (FMO) theory by Fukui, are particularly noteworthy since they introduce a large degree of predictability, and hence usefulness, to this class of reactions.[1] Although these theories clearly differentiate between allowed and forbidden processes there can exist stereoelectronic variants within an allowed transformation that have considerable differences in activation energy, the reasons for which are not always obvious. One illustrative example is the homodienyl-[1,5]-hydrogen shift, or retro-ene reaction, in vinylcyclopropanes (Scheme 1, X=CH).[2,3] For this case it is known that (4*Z*)-1,4-hexadiene is formed in preference to the (4*E*)-isomer upon pyrolysis of **1**, which can be rationalized by invoking a concerted *endo*-TS.[4] In subsequent ab initio quantum mechanical calculations it has been shown that the stereochemical outcome is the result of a stabilizing orbital overlap of the breaking C-H bond with the breaking C-C bond of the cyclopropane, which is maximized in the *endo*-TS.[5] In an ongoing investigation of ring-expansions in strained heterocycles we had a ready access to variously functionalized vinylaziridines. Since the homodienyl-[1,5]-hydrogen shift in these compounds has been described in only a few cases (Scheme 1, X=N),[6-14] and considering the lack of information on substituent and related effects, we became interested in studying these issues and comparing them with pertinent data from the vinylcyclopropane series.[15,16]



Scheme 1.

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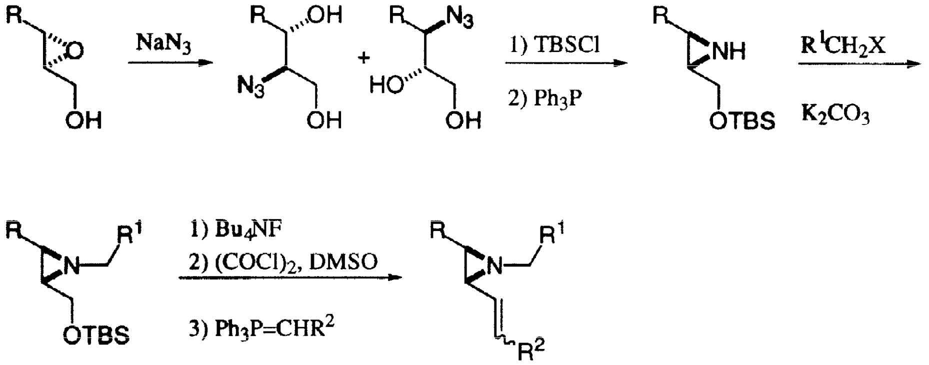
The synthesis of aziridines **2a-j**, **4**, **5** have been described previously and will only be briefly commented upon (Scheme 2).[17] Ring-opening of the parent scalemic epoxy alcohol prepared by the Sharpless asymmetric epoxidation (ee>95%) with sodium azide gave a regioisomeric mixture of azido diols. Protection of the primary hydroxyl groups followed by ring-closure then afforded the *N*-H aziridine. *N*-Alkylation of this material and conversion into the corresponding vinylaziridine by deprotection, Swern oxidation (**5**) and Wittig olefination completed this seven-step sequence. The *cis*-derivative **4** was prepared as a racemate by starting from the corresponding epoxy alcohol and following the same route.

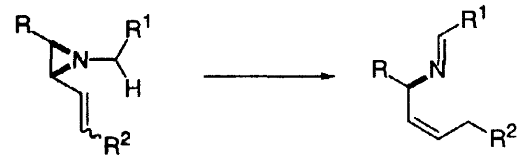


Scheme 2.

The homodienyl-[1,5]-hydrogen shift in vinylaziridines **2a-j** to give **3a-j** were performed by refluxing a solution of the substrate in benzene (0.03 M) and carefully monitoring the progress of the reaction by ^{1}H NMR spectroscopy. In Table 1 is reported the times required for complete conversion (>98%) of the starting materials into products, except for entry 10 which did not reach completion even after prolonged heating. In all cases, except for entry 6 (*vide infra*), only a single isomer of the products was formed. The stereochemistry of the olefinic portion of the products **3a-j** was determined from their ^{1}H NMR spectra which showed the expected vinylic coupling constants for (*Z*)-alkenes (J=9-11 Hz), or by NOESY spectroscopy. For the imine moiety no nOes was observed for the CH-proton and the assigned (*E*)-geometry is based on the proposed transition state structure, the exception being **3f** which was formed as a mixture of imine isomers (*E*:*Z* 1:1, entry 6). The first set of experiments was intended to probe the effects of varying the R-group on the reaction time (Table 1, entries 1-4). The rearrangement of **2a-d** into **3a-d** proceeds smoothly and without any significant differences in reaction time. Since the variations in R-groups are of a steric nature it is perhaps not surprising that these substrates behave similarly, but it is interesting to note that the reaction temperature required for completion of these rearrangements is considerably lower than that needed in the vinylcyclopropane series.[2,18] The selective formation of **3a-d** can be rationalized by transition-state structure **6**, which resembles that suggested for the analogous rearrangement in vinylcyclopropanes.[5] The main features of **6** are (i) to secure a close proximity between the rearrangement origin and terminus since only the nitrogen invertomer in which the vinyl group, adopting an *endo* orientation, and the *t*-butyl acetate moiety are *cis* can participate in the reaction, and (ii) that the *t*-butyl acetate group adopts an *exo* orientation, probably for steric reasons. Structure **6** then correctly accounts for the observed products and a recent kinetic investigation of the rearrangement of **2d** into **3d** supports a concerted reaction pathway.[19]

The necessity of having both the rearrangement origin and terminus *cis* with respect to each other was verified when attempting to rearrange *cis*-2,3-disubstituted vinylaziridine **4** which exist as a single nitrogen invertomer, presumably with the *N*-substituent *trans* to the other ring substituents. Refluxing a solution of **4** in benzene for extended periods gave no reaction while the use of higher temperatures (>100 °C) resulted in complete decomposition.

Table 1. The homodienyl-[1,5]-hydrogen shift in vinylaziridines **2a-j**.[a]

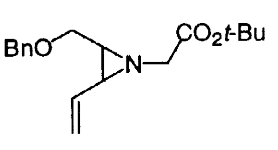


2 **3**

Entry	Substrate	R	R^1	R^2	Time (h)[b]
1	**2a**	*n*-C_6H_{13}	CO_2*t*-Bu	H	2.5
2	**2b**	*c*-C_6H_{11}	CO_2*t*-Bu	H	2.4
3	**2c**	$BnOCH_2$	CO_2*t*-Bu	H	2.7
4	**2d**	*t*-Bu	CO_2*t*-Bu	H	2.3
5	**2e**	*t*-Bu	*n*-C_6H_{13}	H	8.2
6	**2f**	*t*-Bu	C≡CH	H	1.7[c]
7	**2g**	*t*-Bu	Ph	H	1.0
8	**2h**	*t*-Bu	CO_2*t*-Bu	(*E*)-CH_2OTBDPS	10
9	**2i**	*t*-Bu	CO_2*t*-Bu	(*E*)-CO_2Et	18
10	**2j**	*t*-Bu	CO_2*t*-Bu	(*Z*)-Me	168[d]

[a] All reactions were run in refluxing benzene (0.03 M) under an atmospheric pressure of nitrogen. Imines **3** were isolated in quantitative yields and as a single diastereomer unless otherwise stated. [b] Time for complete consumption (>98%) of the starting material. [c] **3f** was formed as a mixture of *E*/*Z* imines (1:1). [d] 66% conversion.

Next the influence of the *N*-substituent was studied (Table 1, entries 4-7). It was found that aziridines **2d**, **f**, **g**, having substituents that can interact with the rearrangement origin by conjugation, reacted faster than *N*-heptyl derivative **2e**, which probably reflects a stabilizing interaction of these substituents on the aromatic-like transition state leading to products.[20] Interestingly, **3f** was formed as a mixture of imine diastereomers, which was verified by reduction to yield amine **7** as a single isomer ($NaBH_4$, MeOH, 97%).[21] This decrease in selectivity can be explained by examining structure **6**. When the steric bulk of the *N*-substituent is reduced the normal *exo* preference of this group is diminished and reaction through an *endo* conformation becomes feasible, as is probably the case for **2f** having the sterically least demanding R^1-group in the series. This should be compared to the [1,5]-hydrogen shift in 1,1-diethyl-2-vinylcyclopropane which results in the formation of a mixture of (2*E*,5*Z*)- and (2*Z*,5*Z*)-3-ethylhepta-2,5-diene in approximately equal amounts, which was explained by invoking similar arguments.[22] However, when rearranging *N*-alkyl derivative **2e** imine **3e** was produced as a single isomer and only when using **2f** an isomeric mixture of products were formed. It is reasonable to assume that the different selectivities at the rearrangement origin are a consequence of the shorter bond lengths in aziridines (C-N: 1.48Å, C-C: 1.46Å)[23] as compared to cyclopropane (C-C: 1.54Å),[24] resulting in a more compact transition state for the vinylaziridine case in which subtle steric interactions could be expressed as enhanced selectivity.



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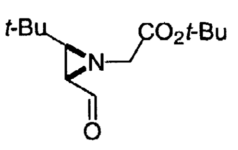

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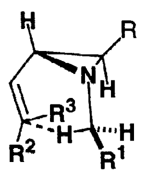

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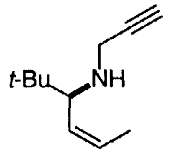

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Finally, the effect of varying the steric requirements at the rearrangement terminus was briefly examined (Table 1, entries 4, 8-10). Comparison of entries 4 and 8 shows that a *trans* alkyl substituent slows down the reaction somewhat and similar observations have been made in the vinylcyclopropane series.[4] For that case, however, it was suggested that the observed effect was not due to steric interactions in the transition state. Rearrangement of **2i** was found to be somewhat slower than that of **2h**, but requiring substantially longer reaction times that the parent substrate **2d**. Relating to vinylcyclopropanes it was originally reported that α,β-unsaturated esters had shorter half-lives than the unsubstituted analoges which seems to be in conflict to more recent findings, and at present we have no explanation for this discrepancy.[18] The introduction of a *cis* substituent on the rearrangement terminus has a dramatic influence on the reaction time, the rearrangement of **2j** reaching only 66% conversion after prolonged heating. This can be understood as a consequence of the *endo* preference of the vinyl group in structure **6** and introduction of a *cis* substituent should result in steric interactions and longer reaction times. Attempts to rearrange aldehyde **5** resulted in decomposition of the starting material, although analogous derivatives have been successfully rearranged in the vinylcyclopropane series.[25,26]

In conclusion, it has been shown that the homodienyl-[1,5]-hydrogen shift in vinylaziridines proceeds under milder conditions than the analogous rearrangement in vinylcyclopropanes. Substituents that can stabilize the concerted transition state by conjugation has a beneficial influence on the reaction rate while steric interactions at the rearrangement terminus retard the reaction.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-300 MHz spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as solvent. *J* Values are given in Hz. IR spectra were run on a Perkin-Elmer Spectrum One spectrophotometer and only the strongest/structurally most omportant peaks are listed. Optical rotations were measured on a Perkin-Elmer Polarimeter 241 at the sodium D line and at ambient temperatures. Benzene was dried over 4Å molecular sieves. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen.

General procedure for the rearrangement of vinylaziridines **2**. A solution of the vinylaziridine in benzene (0.03 M) was heated to reflux and the disappearance of the starting material was monitored by ^{1}H NMR spectroscopy or TLC. When the reaction was completed the solvent was removed to give the corresponding imine **3** in quantitative yield (except for **3j**, see Table 1) as judged by ^{1}H NMR spectroscopic analysis.

Imine **3a**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H), 5.63 (dq, 1H, J=11.2, 6.6 Hz), 5.55-5.46 (m, 1H), 4.16 (m, 1H), 1.62 (dd, 3H, J=6.6, 1.4 Hz), 1.53 (s, 9H), 1.45 (m, 2H), 1.32-1.18 (m, 8H), 0.96 (m 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 153.3, 131.1, 126.1, 82.3, 67.0, 36.1, 31.7, 29.1, 28.0, 25.0, 22.6, 14.1, 13.3; IR (neat) 1735, 1710 cm^{-1}; $[\alpha]_D$ -2.33 (*c* 0.84, $CHCl_3$); Exact mass calcd for $C_{16}H_{30}NO_2$ (M+H): 268.2277. Found: 268.2274.

Imine **3b**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (s, 1H), 5.59 (m, 1H), 5.44 (dq, 1H, J=11.0, 6.8 Hz), 3.70 (t, 1H, J=8.5 Hz), 1.80-1.44 (m, 5H), 3.37 (dd, 3H, J=6.8, 1.8 Hz), 1.31 (s, 9H), 1.18-0.71 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 153.4, 129.9, 126.4, 82.3, 72.7, 42.3, 30.2, 29.2, 28.0, 26.5, 26.2, 25.9, 13.4; IR (neat) 2925, 1738 cm^{-1}; $[\alpha]_D$ -40.0 (*c* 0.35, $CHCl_3$); Exact mass calcd for $C_{16}H_{28}NO_2$ (M+H): 266.2120. Found: 266.2127.

Imine **3c**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1H), 7.30 (m, 5H), 5.70 (dq, 1H, J=10.9, 6.7 Hz), 5.56 (tq, 1H, J=10.9, 1.5 Hz), 4.54 (s, 2H), 4.46 (m, 1H), 3.68 (dd, 1H, J=9.7, 8.0 Hz), 3.56 (dd, 1H, J=9.7, 4.7 Hz), 1.65 (dd, 3H, J=6.7, 1.5 Hz), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 155.3, 138.2, 128.4, 128.2, 127.8, 127.6, 127.1, 82.4, 73.1, 72.3, 66.9, 28.0, 13.4; IR (neat) 2978, 1740 cm^{-1}; $[\alpha]_D$ -10.3 (*c* 1.74, $CHCl_3$); Exact mass calcd for $C_{18}H_{26}NO_3$ (M+H): 304.1913. Found: 304.1921.

Imine **3d**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (s, 1H), 5.65 (m, 2H), 3.83 (d, 1H, J=8.5 Hz), 1.64 (d, 3H, J=5.2 Hz), 1.53 (s, 9H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 153.5, 128.4, 126.7, 82.1, 75.9, 35.5, 28.0, 26.5, 13.5; IR (neat) 1740, 1710 cm^{-1}; $[\alpha]_D$ -88.1 (*c* 0.70, $CHCl_3$); Exact mass calcd for $C_{14}H_{26}NO_2$ (M+H): 240.1964. Found: 240.1979.

Imine **3e**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (t, 1H, J=5.1 Hz), 5.66-5.49 (m, 2H), 3.51 (d, 1H, J=8.5 Hz), 2.23 (dt, 2H, J=7.1, 5.1 Hz), 1.61 (d, 3H, J=5.2 Hz), 1.50 (m, 2H), 1.41-1.17 (m, 6H), 1.89 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 130.2, 124.9, 76.5, 35.8, 34.9, 31.6, 29.0, 26.6, 26.3, 22.5, 14.0, 13.5; IR (neat) 1655 cm^{-1}; $[\alpha]_D$ -57.0 (*c* 1.35, $CHCl_3$); Exact mass calcd for $C_{15}H_{30}N$ (M+H): 224.2378. Found: 224.2371.

Imine **3f**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, assigned from a mixture of isomers) δ 7.50 (m, $1H_{min}$), 7.47 (m, $1H_{maj}$), 5.71-5.47 (m, $2H_{maj}$, $2H_{min}$), 4.50 (d, $1H_{min}$, J=9.3 Hz), 3.71 (d, $1H_{maj}$, J=8.6), 1.72 (m, $3H_{min}$), 1.63 (m, $3H_{maj}$), 0.92 (s, $9H_{maj}$, $9H_{min}$); ^{13}C NMR ($CDCl_3$, 75 MHz, as a mixture of isomers) δ 142.8, 140.3, 128.7, 128.6, 126.3, 126.1, 84.4, 80.9, 78.6, 71.5, 35.7, 35.4, 26.5, 26.2, 13.9, 13.5; IR (neat) 3300, 2090, 1610 cm^{-1}; Exact mass calcd for $C_{11}H_{18}N$ (M+H): 164.1439. Found: 164.1432.

Imine **3g**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (s, 1H), 7.78 (m, 2H), 7.40 (m, 3H), 5.76-5.60 (m, 2H), 3.82 (d, 1H, J=8.5 Hz), 1.72 (d, 3H, J=5.1 Hz), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3, 136.8, 130.2, 129.9, 128.4, 128.1, 125.3, 76.1, 35.6, 26.7, 13.6; IR (neat) 1645 cm^{-1}; $[\alpha]_D$ -194.9 (*c* 2.51, $CHCl_3$); Exact mass calcd for $C_{15}H_{22}N$ (M+H): 216.1752. Found: 216.1743.

Imine **3h**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (m, 5H), 7.41 (m, 6H), 5.62 (m, 2H), 3.65 (m, 3H), 2.33 (m, 2H), 1.53 (s, 9H), 1.05 (s, 9H), 0.89 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 153.6, 135.6, 134.8, 133.8, 129.6, 129.0, 128.6, 127.7, 82.1, 63.4, 35.3, 31.4, 28.0, 26.9, 26.6, 19.2; IR (neat) 2957, 1745, 1650 cm^{-1}; $[\alpha]_D$ -46.2 (*c* 0.47, $CHCl_3$); Exact mass calcd for $C_{31}H_{46}NO_3Si$ (M+H): 508.3247. Found: 508.3245.

Imine **3i**. Slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (s, 1H), 5.79 (m, 2H), 4.13 (q, 2H, J=7.2 Hz), 3.72 (m, 1H), 3.10 (m, 2H), 1.52 (s, 9H), 1.25 (t, 3H, J=7.2 Hz), 0.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 161.9, 154.0, 130.7, 123.7, 82.2, 76.5, 60.8, 35.5, 33.7, 28.0, 26.5, 14.2; IR (neat) 2959, 1745, 1710 cm^{-1}; $[\alpha]_D$ +14.3 (*c* 0.76, $CHCl_3$); Exact mass calcd for $C_{17}H_{30}NO_4$ (M+H): 312.2175. Found: 312.3180.

Amine **7**. To a solution of imine **3f** (28.0 mg, 0.172 mmol) in MeOH (1 mL) was added $NaBH_4$ (7 mg, 0.185 mmol). After stirring at room temperature for 45 min., acetone (0.5 mL) was added and the resultant mixture was stirred for an additional 15 min. Removal of the solvents and flash chromatography (EtOAc:Heptane 1:6) gave amine **7** as a colorless oil (27.5 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71 (dq, 1H, J=11.0, 7.0 Hz), 5.14 (br t, 1H, J=11.0 Hz), 3.42 (dd, 1H, J=16.9, 2.6 Hz), 3.30 (d, 1H, J=11.0 Hz), 3.21 (dd, 1H, J=16.9, 2.2 Hz), 2.15 (m, 1H), 1.67 (br d, 3H, J=7.0 Hz), 0.87 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.8, 128.1, 83.0, 70.6, 61.4, 36.0, 34.2, 26.5, 13.7; IR (neat) 3308, 2951, 2099 cm^{-1}; $[\alpha]_D$ +80.3 (*c* 2.98, $CHCl_3$); Exact mass calcd for $C_{11}H_{20}N$ (M+H): 166.1596. Found: 166.1603.

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