The Products of an Imino Diels–Alder Reaction with 2-Trimethylsilyloxycyclohexadiene: Synthesis, *X*-Ray Crystal Structures, and Mechanistic Implications

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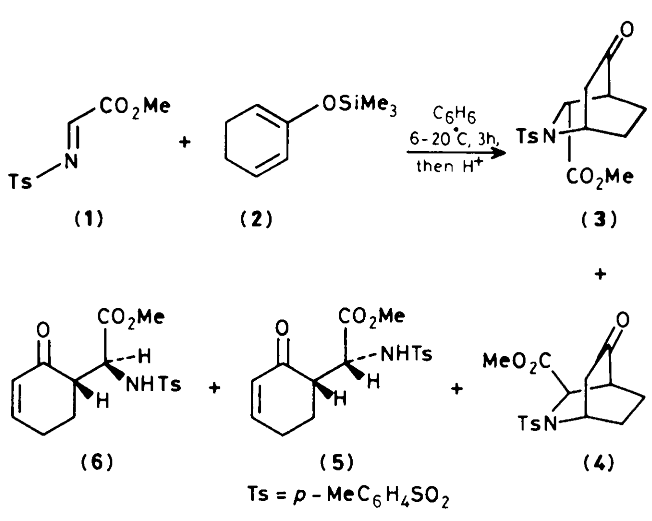
The reaction of the *N*-tosyl imino-ester (**1**) with 2-trimethylsilyloxycyclohexadiene (**2**) followed by acidic work-up shows a divergence in pathways: at low temperature in polar solvents the cyclohexenones (**5**) and (**6**) (*X*-ray) are favoured, whereas at higher temperatures the bicyclic ketones (**3**) and (**4**) (*X*-ray) are the predominant products.

The reaction of the *N*-tosyl imino-ester (**1**) with 2-trimethylsilyloxycyclohexadiene (**2**) has previously been used by us to prepare azabicyclo[2.2.2]octanone precursors for the synthesis of naturally occurring piperidine alkaloids of the *Prosopis* family.[1,2] In order to optimise the diastereoselectivity and yield we have investigated the effect of solvents, Lewis acids, and temperature, and in the course have discovered the formation of 'aldol' products (**5**) and (**6**) in addition to the bicyclic products (**3**) and (**4**).

The imine (**1**) used for the addition was prepared in anhydrous tetrahydrofuran (THF) from the $BF_3.OEt_2$-catalysed reaction of methyl glyoxylate[3] and *N*-sulphinyltoluene-*p*-sulphonamide,[4] and was distilled before use. Reaction of the imine (**1**) with 2-trimethylsilyloxycyclohexa-1,3-diene (**2**)[5] in benzene at room temperature (the reagents were mixed at 5 °C owing to the exothermicity of mixing) followed by mild acidic work-up (20% solution of 0.0005 M HCl in THF) gave mainly the bicyclic adducts (**3**) (47%) and (**4**) (18.5%) and two

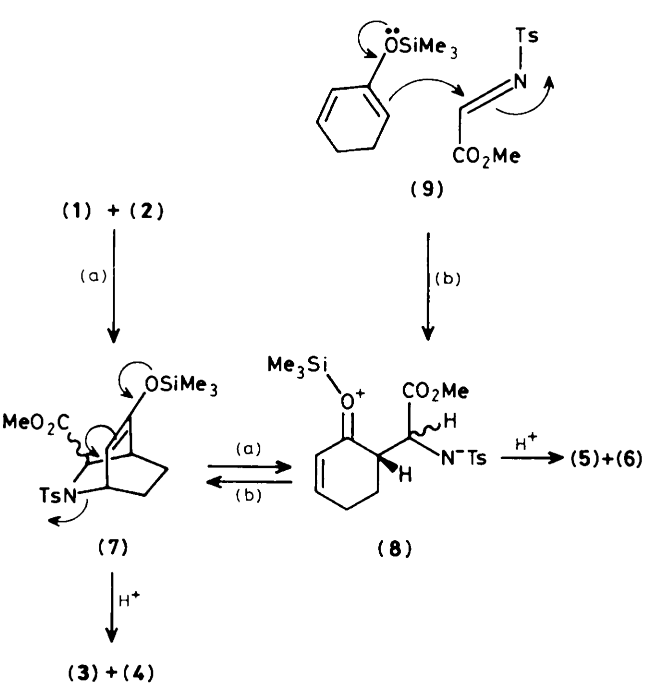


minor products which were identified as the cyclohexenones (**5**) (6%) and (**6**) (2%).† The structure of the *endo*-product (**4**), m.p. 126—127 °C (dichloromethane–hexane) was confirmed by *X*-ray analysis.‡ The geometry of the nitrogen atom is, as expected, planar rather than tetrahedral, the torsion angle being 160.4(2)°. This probably indicates delocalisation of the nitrogen lone pair into the sulphonamide.[6] By contrast, the only other reported azabicyclo[2.2.2]octanone crystal structure was of a *N*-methyl derivative where no lone pair delocalisation was possible,[7] and the N atom was tetrahedral, with the relevant torsion angle 145.2°.

Although assignment of relative stereochemistry to the cyclohexenones was impossible from an analysis of the spectroscopic data, the minor product (**6**), m.p. 95—96 °C (dichloromethane–hexane) afforded crystals suitable for *X*-ray diffraction, and the structure shown was assigned on this basis.‡

The major bicyclic product is stereochemically related to the minor cyclohexenone (**6**) and *vice versa*. Indeed, Michael cyclisations of (**5**) and (**6**) can be induced under acidic and basic conditions.[8] Three clear mechanistic possibilities for the formation of (**3**)—(**6**) emerge:

(a) A hetero Diels–Alder reaction between (**1**) and (**2**) would produce cycloadducts (**7**). These could undergo partial retro-Michael reaction to give *N*-silylated cyclohexenones (**8**). Acidic work-up of these silylated species would afford (**3**)—(**6**).



Mechanisms (a) and (b) for the formation of (**3**)—(**6**).

(b) A Mukaiyama 'aldol' reaction[9] between (**1**) and (**2**) would yield (**8**) directly. These could cyclise under Michael conditions to (**7**).

(c) Mechanisms (a) and (b) could occur simultaneously in competition, as suggested by Danishefsky for the analogous hetero Diels–Alder reaction of carbonyl compounds.[10]

In order to test these possibilities a series of reactions has been carried out under a variety of conditions in which solvent (C_6H_6, CH_2Cl_2, THF, MeCN), temperature (from −78 to 45 °C), and Lewis acid (BF_3, $AlCl_3$, $TiCl_4$) have been systematically varied. It has thus been possible to define conditions in which either bicyclic or 'aldol' products predominate.§ The general trend which emerges is an increasing proportion of bicyclic products with diminished solvent polarity and increased reaction temperature. Reasonably high diastereoselectivity is observed within each type of reaction product, but in opposing stereochemical senses. Thus the preference for (**3**) (up to 5:1) over (**4**) may be due to a cycloaddition transition state in which the bulky *N*-tosyl prefers to avoid steric interactions,[11] while allowing the favourable secondary orbital interactions of the ester C=O to prevail. The low-temperature (Lewis acid) preference for (**5**) (up to 4:1) over (**6**) is best accommodated in an open transition state (**9**) which minimises steric interactions between the CO_2Me and the Me_3Si groups. These stereochemical preferences are consistent with the observations noted in the accompanying Communication.[12] Taken together they imply the dual mechanism explanation suggested above in option (c).

Cycloaddition of silyloxydienes to unactivated imines under mild Lewis acid catalysis has been observed by Danishefsky

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† All new compounds exhibited spectroscopic and analytical data in accordance with the assigned structure.

‡ *Crystal data for* (**4**): $C_{16}H_{19}NO_5S$, M = 337.38, monoclinic, $C2/c$ (no. 15), a = 22.297(2), b = 7.720(1), c = 20.825(2) Å, β = 112.86(1)°, U = 3303.1 Å^3, D_c = 1.356 g cm^{-3}, Z = 8, $F(000)$ = 1424, $\mu(\text{Mo-}K_\alpha)$ = 1.76 cm^{-1}. 4850 reflections measured ($5 \leqslant 2\theta \leqslant 45°$) on a Stoe–Siemens AED diffractometer, averaged to give 1761 unique observed reflections with $F \geqslant 4\sigma(F)$. Structure solved by direct methods, and refined by full-matrix least squares, with all non-hydrogen atoms anisotropic, to R and R_w values of 0.049 and 0.054.

Crystal data for (**6**): $C_{16}H_{19}NO_5S$, M = 337.38, triclinic, $P\bar{1}$ (no. 2) a = 8.685(1), b = 10.159(1), c = 11.087(2) Å, α = 98.85(1), β = 112.86(1), γ = 114.74(1)°, U = 849.5(2) Å^3, D_c = 1.319 g cm^{-3}, Z = 2, $F(000)$ = 356, $\mu(\text{Mo-}K_\alpha)$ = 18.64 cm^{-1}. 2906 reflections measured ($5 \leqslant 2\theta \leqslant 120°$) on a Nicolet R3 mμ diffractometer, averaged to give 2301 unique observed reflections with $F \geqslant 4\sigma(F)$. Structure solved by direct methods, and refined by full matrix least squares, with all non-hydrogen atoms anisotropic, to R and R_w values of 0.048 and 0.058.

For both structures, atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ Benzene, 6—20 °C, 3 h, 74% overall yield, (**3**):(**4**):(**5**):(**6**) = 56:10:26:8; MeCN/$AlCl_3$ −40 to 20 °C, 2.5 h, 60% overall yield, (**3**):(**4**):(**5**):(**6**) = 10:3:77:10.

and other research groups,[13] but the divergence in pathways as noted in this Communication has not previously received attention.[14] The reaction of (**1**) with stereochemically defined enol ethers in an asymmetric sense has great potential for the enantioselective synthesis of β-amino carbonyl compounds.¶

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References

1 A. B. Holmes, J. Thompson, A. J. G. Baxter, P. R. Raithby, and J. Dixon, *J. Chem. Soc., Chem. Commun.*, 1983, 1490; A. B. Holmes, J. Thompson, A. J. G. Baxter, and J. Dixon, *ibid.*, 1985, 37.
2 T. N. Birkinshaw and A. B. Holmes, *Tetrahedron Lett.*, 1987, **28**, 813.
3 J. M. Hook, *Synth. Commun.*, 1984, **14**, 83.
4 G. Kresze and W. Wucherpfennig, 'Newer Methods of Preparative Organic Chemistry,' ed. W. Foerst, Verlag Chemie, Weinheim/Bergstr., 1968, Vol. 5, p. 115.
5 C. Girard and J. M. Conia, *Tetrahedron Lett.*, 1974, 3327.
6 A. Kalman, M. Czugler, and G. Argay, *Acta Crystallogr., Sect. B*, 1981, **37**, 868.
7 F. Khuong-Huu, A. Chiaroni, and C. Riche, *Tetrahedron Lett.*, 1981, **22**, 733.
8 T. N. Birkinshaw, A. B. Holmes, and P. M. Mayne, manuscript in preparation.
9 T. Mukaiyama, T. Izawa, and K. Saigo, *Chem. Lett.*, 1974, 323; T. Mukaiyama, *Org. React.*, 1982, **28**, 203.
10 S. J. Danishefsky, E. Larson, D. Askin, and N. Kato, *J. Am. Chem. Soc.*, 1985, **107**, 1246.
11 S. M. Weinreb and R. R. Staib, *Tetrahedron*, 1982, **38**, 3087.
12 T. N. Birkinshaw, A. B. Tabor, A. B. Holmes, and P. R. Raithby, following communication.
13 J. F. Kerwin, Jr. and S. Danishefsky, *Tetrahedron Lett.*, 1982, **23**, 3739; J. P. Vacca, *Tetrahedron Lett.*, 1985, **26**, 1277; K. M. Ryan, R. A. Reamer, R. P. Volante, and I. Shinkai, *Tetrahedron Lett.*, 1987, **28**, 2103; S. Danishefsky, M. E. Langer, and C. Vogel, *Tetrahedron Lett.*, 1985, **26**, 5983; S. Danishefsky and C. Vogel, *J. Org. Chem.*, 1986, **51**, 3915.
14 Y. Ueda and S. C. Maynard, *Tetrahedron Lett.*, 1985, **26**, 6309.

¶ Since the submission of this manuscript the study of a related reaction has been reported (T. J. Sowin and A. I. Meyers, *J. Org. Chem.*, 1988, **53**, 4154).