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VINYLAMINES—XV[1]

UNUSUAL STEREOCHEMICAL COURSE IN NITROALKYLATION OF BIASED ENAMINIC SYSTEMS

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Abstract—Reactions between 1-nitropropene and 3-phenyl-, 3-*t*-butyl- and 4-*t*-butyl-cyclohexanone enamines are described. Both parallel and antiparallel attacks of the olefin on the substrates are possible.

Antiparallel attack of electrophilic reagents on cyclohexanone enamines occurs due to stereoelectronic effects.[2] Only when steric hindrance inhibits such an approach, does the parallel attack take place,[1,3] i.e. the reaction is subject to steric approach control. On the other hand, systems like enols (which are isoelectronic with enamines) undergo alkylation by both parallel and antiparallel attack in almost equal amounts.[4]

In the present work we have found that morpholine enamines derived from 4-*t*-butyl-, 3-*t*-butyl- and 3-phenyl-cyclohexanone show analogous behaviour towards 1-nitropropene, although no steric hindrance such as would force the reaction to the unusual parallel attack seem to be present.

When the Δ^6 isomer of **1a** reacts with 1-nitropropene (1NP) (Chart 1), two enaminic adducts **2a** and **3a** are isolated, in the ratio of 67:33 (Table 1). The acidic hydrolysis of **2a**, carried out under non-epimerizing conditions (i.e. pH = 6–7), produces the ketone **4a**, while **3a** gives the ketone **6a**. Unlike **4a**, which undergoes complete epimerization† by treatment with TsOH in refluxing benzene to give the isomer **5a**, **6a** does not epimerize.‡

The epimerization of **4a**, like that of all our ketones which undergo isomerization, obviously occurs at C2, "via" keto-enolic tautomerism. Actually the Cα is not epimerizable; its hydrogen being of paraffinic nature. On the other hand, even when the Cα hydrogen is benzylic, the epimerization does not take place at Cα under our conditions.[1]

Therefore the β-nitroisopropyl group must be axial in **4a** and equatorial in **6a**. Consequently, **2a** and **3a** are derived from two different types of attack of the nitroolefin on **1a**.

It is known that 1NP exists largely in the *trans* configuration.[5] However, the configuration of 1NP is unimportant as it has been shown that the stereochemical behaviour of *cis* and *trans* electrophilic olefins with enaminic substrates is the same.[6] In fact the stereochemistry of our reactions depends only upon the size of the methyl group of electrophylic carbon.

During the approach of 1NP to the substrate, the methyl group assumes an *exo* position with regard to the cyclohexenic ring, in order to avoid strong interactions with axial hydrogens of the ring itself. Consequently, we have assigned the *threo* configuration§ to **2a** and **3a**. **4a** and **6a** have therefore the same configuration as the enamines from which they are derived that is cis-*threo*, while the trans-*erythro* configuration can be assigned to **5a** (Chart 1).

The stereochemical course of the reaction of 1NP with the Δ^6 isomer of **1b** follows the same course as the one of the Δ^6 form of **1a**.

The Δ^1 isomer, differently to the Δ^6 form, is subject to parallel attack only, as the antiparallel one would involve very strong steric interactions between the entering group and the C3 substituent. The alkylated enamine **7a** in fact produces a ketone **8a** which does not undergo epimerization. The trans-*threo* configuration can thus be assigned to **8a** and consequently to **7a** (Chart 1).

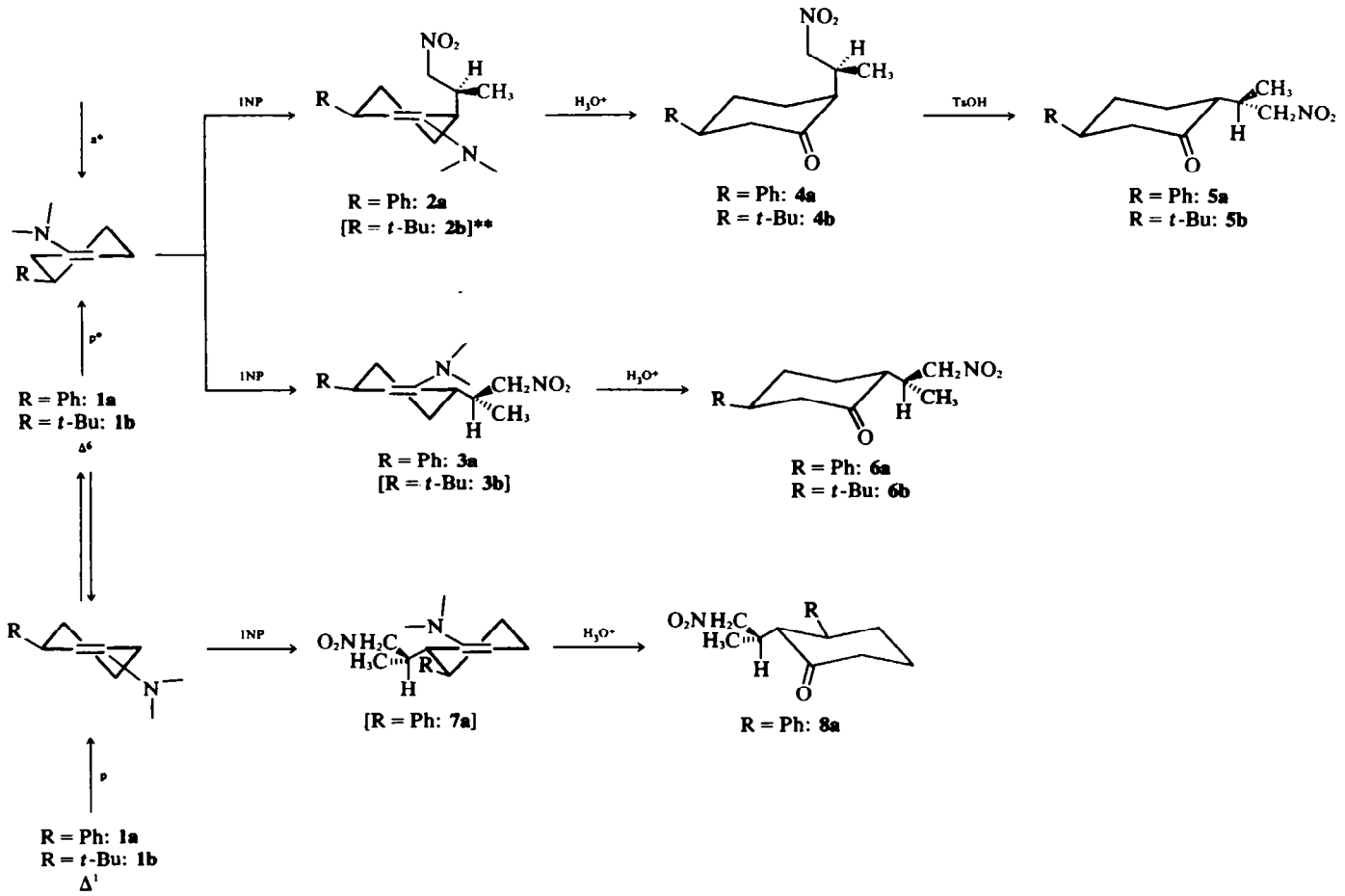
1-Morpholino-4-*t*-butyl-cyclohexene **9** also undergoes nitroalkylation by both parallel and antiparallel attack and gives the trisubstituted enamines **10** and **11**, in the ratio of 60:40 (Chart 2 and Table 1). The trans-*threo* configuration can be attributed to the enamine **10**, since the subsequent ketone **12**, obtained from hydrolysis of **10**, is a kinetic control product. In fact, by acidic epimerization under our usual conditions, **12** changes into

†No traces of the parent ketone can be detected, at least within the limits of experimental errors (2% for NMR analysis).

‡The ketone **6a** is obtained unchanged after attempted epimerization.

§This nomenclature is derived from the sequence rules:

C2: $CO > CH_2 > H$; Cα: $CH_2NO_2 > CH_3 > H$



*a: antiparallel attack; p: parallel attack.
**The compounds in brackets were not isolated.

CHART 1.

CHART 2.

Table 1

Enamines from	Δ^1/Δ^6 (from areas of NMR vinylic proton signals)	Ratio (2,3/2,5) disubstituted ketones	Antiparallel/ parallel attack
3-phenyl-cyclohexanone	~100/~0	20/80	67/33*
3-*t*-butyl-cyclohexanone	45/55	10/90	67/33*
4-*t*-butyl-cyclohexanone	—	—	60/40

*This ratio is referred to the percentages of adducts obtained from the Δ^6 isomers.

its more stable bisequatorial stereoisomer **13**. On the other hand, the ketone **14**, resulting from the hydrolysis of **11**, does not epimerize; therefore the configuration of both **11** and **14** must be cis-*threo*.

All the stereochemical assignments have been confirmed by NMR analysis. As can be seen in Table 2, all the ketones to which the same structure has been assigned, show the same patterns and chemical shifts for the nitromethylenic proton signals.

Table 2

Configuration and conformation of the β-nitroisopropyl group	Pattern	Compounds	Chemical shift (δ)	J (Hz)
Threo axial		**4a**	4·29	—
		4b	4·22	—
		12	4·23	—
Erythro equatorial		**5a**	4·50	12·8
		5b	4·44	12·5
		13	4·53	12·8
Threo equatorial		**6a**	4·43	6·75
		6b	4·44	6·75
		14	4·48	6·75

Enamines **2a**, **2b** and **10** are hydrolysed completely in 3 h, whereas **3a**, **3b** and **11** require at least 24 h. The different rates are due firstly to the poor overlap between the unshared nitrogen electrons and the double bond in enamines in which the substituent at C6 is equatorial. Secondly, the difference in energy between the dipolar intermediates involved is very high, owing to Johnson strain[7] in the equatorial intermediate **16** (Chart 3). This fact too supports the above statements.

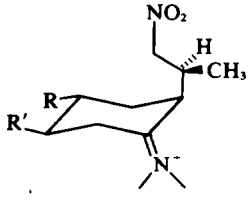
Finally, the existence of an equilibrium between the Δ^1 and Δ^6 forms in the 3-substituted enamines, already demonstrated,[1] has received further confirmation.

EXPERIMENTAL

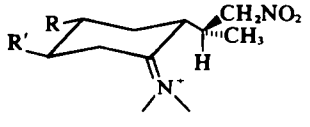
All m.ps are uncorrected. IR spectra were recorded with a Perkin–Elmer 257 Spectrophotometer and NMR spectra with a Jeol JNM-C-60HL Spectrometer with TMS as internal standard. Plates for analytical TLC were spread with Silica gel G (Merck) and columns were prepared using extra pure SiO_2 Merck (70-325 mesh ATMS).

Reaction of 1-*morpholino*-3-*phenyl*-*cyclohexene* (**1a**) *with* 1-*nitropropene*

1-Nitropropene (1·5 g, 17 mmoles) in dry ether was added to a soln of **1a** (4·2 g, 17 mmoles). The mixture was kept at 5° for 24 h. After removal of the solvent, an oil was obtained. IR spectrum (CCl_4): 1640 cm^{-1} (C=C–N); 1600, 1580, 753, 700 cm^{-1} (Ph); 1550, 1380 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 5·06 δ (C=C<u>H</u>, t(J = 4·5 Hz), 0·2H);



16 ax



16 eq

R = *t*-Bu; R′ = H
R = H; R′ = *t*-Bu

CHART 3.

4·93 δ (C=CH, d(J = 4·05 Hz), 0·8H); 4·25 δ (CH_2NO_2, m, 2H); 0·95 δ (CH_3, d(J = 4·5 Hz); 0·85 δ (CH_3, d(J = 4·5 Hz). The oily crude product was crystallized from benzene–ligroin. A solid product, **2a**, was firstly obtained, m.p. 86–88°, from methanol. (Found: C, 69·5; H, 7·98; N, 8·53. $C_{19}H_{26}N_2O_5$ requires: C, 69·06; H, 7·98; N, 8·48%). IR spectrum (Nujol): 1642 cm^{-1} (C=C–N); 1599, 1490, 702, 685 cm^{-1} (Ph); 1551, 1339 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·25 δ (Ph, m, 5H); 5·00 δ (C=CH, d(J = 4·5 Hz), 1H); 4·35 δ (CH_2NO_2, doublet of quartets, AB part of ABX system (J_{AB} = 12·0 Hz), 2H); 3·74 δ (CH_2–O–CH_2, m, 4H); 0·98 δ (CH_3, d(J = 6·75 Hz), 3H). From the mother liquors **3a** separated, m.p. 106–8° from methanol (Found: C, 69·4; H, 7·96; N, 8·50. $C_{19}H_{26}N_2O_5$ requires: C, 69·06; H, 7·93; N, 8·48%). IR spectrum (Nujol): 1636 cm^{-1} (C=C–N); 1600, 1488, 762, 700 cm^{-1} (Ph); 1548, 1340 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·24 δ (Ph, m, 5H); 4·98 δ (C=CH, broad singlet (W_H = 5·25 Hz), 1H); 4·35 δ (CH_2NO_2, 2H); 3·74 δ (CH_2–O–CH_2, m, 4H); 0·90 δ (CH_3, d(J = 6·75 Hz), 3H). The ratio **2a**:**3a** was determined by the method described by Purdy[5] and resulted to be 2:1.

The enamine **2a** (1·4 g, 4·2 mmoles) underwent acidic hydrolysis with acetic acid (2·63 g, 4·2 mmoles) in acetone-water for 24 h and the mixture was extracted with benzene. Removal of the solvent left an oil which solidified by treatment with light petroleum **4a** m.p. 65–66°, from *n*-hexane (Found: C, 68·4; H, 7·38; N, 5·08. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). IR spectrum ($CDCl_3$): 1700 cm^{-1} (CO); 1600, 1490, 753, 700 cm^{-1} (Ph); 1552 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·16 δ (Ph, m, 5H); 4·29 δ (CH_2NO_2, d(J = 6·75 Hz), 2H); 3·40 δ (CHPh, m, 1H); 1·00 δ (CH_3, d(J = 6·75 Hz), 3H).

4a underwent acidic equilibration with TsOH in refluxing benzene for 12 h, and gave a 9:1 mixture of **5a** and **4a**. **5a** was separated from the mixture by fractional crystallization, m.p. 82–85°, from benzene-*n*-hexane (Found: C, 68·85; H, 7·42; N, 5·33. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). IR spectrum (Nujol): 1702 cm^{-1} (CO); 1600, 1500, 762, 753, 703 cm^{-1} (Ph); 1548 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·21 δ (Ph, m, 5H); 4·50 δ (CH_2NO_2, doublet of quartets, AB part of ABX system (J_{AB} = 12·8 Hz), 2H); 1·14 δ (CH_3, d(J = 6·75 Hz), 3H).

The enamine **3a** (0·2 g, 0·6 mmoles) was hydrolysed in a mixture acetone–water with acetic acid (0·038 g, 0·6 mmoles). Extraction with ether and removal of the solvent left an oil which crystallized from light petroleum **6a** m.p. 65–67° (Found: C, 68·90; H, 7·25; N, 5·20. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). IR spectrum (Nujol): 1700 cm^{-1} (CO); 1600, 752, 720, 690 cm^{-1} (Ph); 1550 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·25 δ (Ph, m, 5H); 4·43 δ (CH_2NO_2, d(J = 6·75 Hz), 2H); 1·06 δ (CH_3, d(J = 6·75 Hz), 3H).

A portion of hydrolysed crude reaction product was chromatographed (eluent: acetone–benzene 0·1–0·4%). **8a** was isolated as an oil (Found: C, 68·80; H, 7·66; N, 5·25. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). IR spectrum (film): 1705 cm^{-1} (CO); 1600, 1585, 758, 732 cm^{-1} (Ph); 1545, 1345 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 7·32 δ (Ph, m, 5H); 4·25 δ (CH_2NO_2, m, 2H); 1·05 δ (CH_3, d(J = 6·75 Hz), 3H).

Reaction of 1-*morpholino*-3 (*and* 5)-t-*butyl-cyclohexene* (**1b**) *with* 1-*nitropropene*

1-Nitropropene (2·23 g, 0·01 moles) was added to a soln of **1b** (0·87 g, 0·01 moles) in dry ether. Removal of the solvent left an oil. IR spectrum (film): 1640 cm^{-1} (C=C–N); 1550, 1380 cm^{-1} (NO_2); 1260 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·93 δ (C=CH, d(J = 2·6 Hz), 1H); 4·32 δ (CH_2NO_2, m, 2H). The crude enaminic mixture was hydrolysed with acetic acid (0·6 g, 0·01 moles) in acetone–water. Extraction with ether and removal of the solvent gave an oil which was treated with light petroleum. A solid product **4b** separated, m.p. 69–70° (Found: C, 64·4; H, 9·57; N, 5·82. $C_{13}H_{23}NO_3$ requires: C, 64·70; H, 9·61; N, 5·80%). IR spectrum (Nujol): 1595 cm^{-1} (CO); 1550, 1350 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 4·22 δ (CH_2NO_2, 2H); 1·05 δ (CH_3, d(J = 6·5 Hz)); 0·90 δ (*t*-Bu, s). The crystallization mother liquors were concentrated and chromatographed (eluent: benzene). **6b** was separated, m.p. 45–46°, from light petroleum (Found: C, 64·6; H, 9·57; N, 5·84. $C_{13}H_{23}NO_3$ requires: C, 64·7; H, 9·61; N, 5·80%). IR spectrum (Nujol): 1710 cm^{-1} (CO); 1550 cm^{-1} (NO_2); 1238 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·44 δ (CH_2NO_2, d(J = 6·75 Hz), 2H); 0·90 δ (CH_3, d(J = 6·75 Hz)); 0·89 δ (*t*-Bu, s). The ratio **4b**:**6b** was 2:1. Attempts made in order to separate the compound 2-(β-nitroisopropyl)-3-*t*-butyl-cyclohexanone **8b** failed, but it was detected by TLC.

The ketone **4b** was equilibrated with TsOH in refluxing benzene for 1 h. The stereoisomer **5b** was isolated, m.p. 45–46° (Found: C, 64·3; H, 9·57; N, 5·84. $C_{13}H_{23}NO_3$ requires: C, 64·7; H, 9·61; N, 5·80%). IR spectrum (Nujol): 1712 cm^{-1} (CO); 1550 cm^{-1} (NO_2). NMR spectrum ($CDCl_3$): 4·44 δ (CH_2NO_2, doublet of quartets, AB part of ABX system (J_{AB} = 12·5 Hz), 2H); 1·09 δ (CH_3, d(J = 6·75 Hz)); 0·89 δ (*t*-Bu, s).

Reaction of 1-*morpholino*-4-t-*butyl-cyclohexene* **9** *with* 1-*nitropropene*

1-Nitropropene (1·7 g, 0·02 moles) in dry ether was added to a soln of **9** (4·5 g, 0·02 moles). After removal of the solvent, the semisolid residue solidified in light petroleum **10** m.p. 85–87° (Found: C, 66·03; H, 9·96; N, 9·03. $C_{17}H_{30}N_2O_3$ requires: C, 65·77; H, 9·74; N, 9·02%). IR spectrum (Nujol): 1645 cm^{-1} (C=C–N); 1550, 1365 cm^{-1} (NO_2); 1262 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·96 δ (CH=C, m); 4·66 δ (CH_2NO_2, doublet of quartets, AB part of ABX system (J_{AB} = 12·3 Hz)); 1·03 δ (CH_3, d(J = 6·75 Hz)), 0·90 δ (*t*-Bu, s). The enamine **11** was isolated from the mother liquors m.p. 94–95°, from light petroleum (Found: C, 65·64; H, 9·99; N, 8·95. $C_{17}H_{30}N_2O_3$ requires: C, 65·77; H, 9·74; N, 9·02%). IR spectrum (Nujol): 1647 cm^{-1} (C=C–N); 1550, 1362, 1349 cm^{-1} (NO_2); 1258 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 5·01 δ (C=CH, m (W_H = 10 Hz)); 4·34 δ (CH_2NO_2); 3·73 δ (CH_2–O–CH_2, m, 4H), 0·90 δ (*t*-Bu, s), 0·84 δ (CH_3, d). The ratio **10**:**11** was 3:2.

The enamine **10** (0·63 g, 2 mmoles) was hydrolysed with acetic acid (0·12 g, 2 mmoles) in acetone–water for 3 h and the mixture was extracted with ether. The extracts, after eliminating the solvent, gave an oil. IR spectrum (film): 1708 cm^{-1} (CO); 1548, 1378, 1365 cm^{-1} (NO_2); 1215 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·23 δ (CH_2NO_2, 2H); 0·99 δ (CH_3, d(J = 6·75 Hz)); 0·86 δ (*t*-Bu, s). The compound **12** formed a 2,4-dinitrophenylhydrazone derivative, m.p. 184–6°, from methanol (Found: C, 54·3; H, 6·60; N, 16·3. $C_{19}H_{27}N_5O_6$ requires: C, 54·15; H, 6·46; N, 16·6%).

The product **12** was equilibrated with TsOH in refluxing benzene for 1 h. An oil was separated **13**. IR spectrum (film): 1708 cm^{-1} (CO), 1545, 1378, 1365 cm^{-1} (NO_2); 1235 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·35 δ (CH_2NO_2, m, AB part of ABX system (J_{AB} = 12·8 Hz), 2H); 1·2 δ (CH_3, d(J = 6·75 Hz)); 0·98 δ (*t*-Bu, s). The

product **13** formed a 2,4-dinitrophenylhydrazone derivative, m.p. 165–6°, from methanol (Found: C, 54·20; H, 6·52; N, 6·41. $C_{19}H_{27}N_5O_6$ requires: C, 54·15; H, 6·46; N, 16·62%).

The enamine **11** (0·628 g, 2 mmoles) in acetone was treated with acetic acid (0·12 g, 2 mmoles) in water, for 24 h. After eliminating the solvent, the mixture was extracted with ether. The extracts left an oil, **14**. IR (film): 1710 cm^{-1} (CO); 1550, 1380, 1369 cm^{-1} (NO_2); 1240 cm^{-1} (*t*-Bu). NMR spectrum ($CDCl_3$): 4·48 δ ($C\underline{H}_2NO_2$, d(J = 6·75 Hz), 2H); 1·04 δ ($C\underline{H}_3$, d(J = 6·75 Hz)); 0·95 δ (*t*-Bu, s). The compound **14** formed a 2,4-dinitrophenylhydrazone derivative, m.p. 152–3°, from methanol (Found: C, 54·18; H, 6·50; N, 16·51. $C_{19}H_{27}N_5O_6$ requires: C, 54·15; H, 6·46; N, 16·62%).

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