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CARBO- AND HETEROCYCLIZATION REACTIONS OF 2-(4-MORPHOLINYL)-1-PHENYLPROPENE AND NITROOLEFINS

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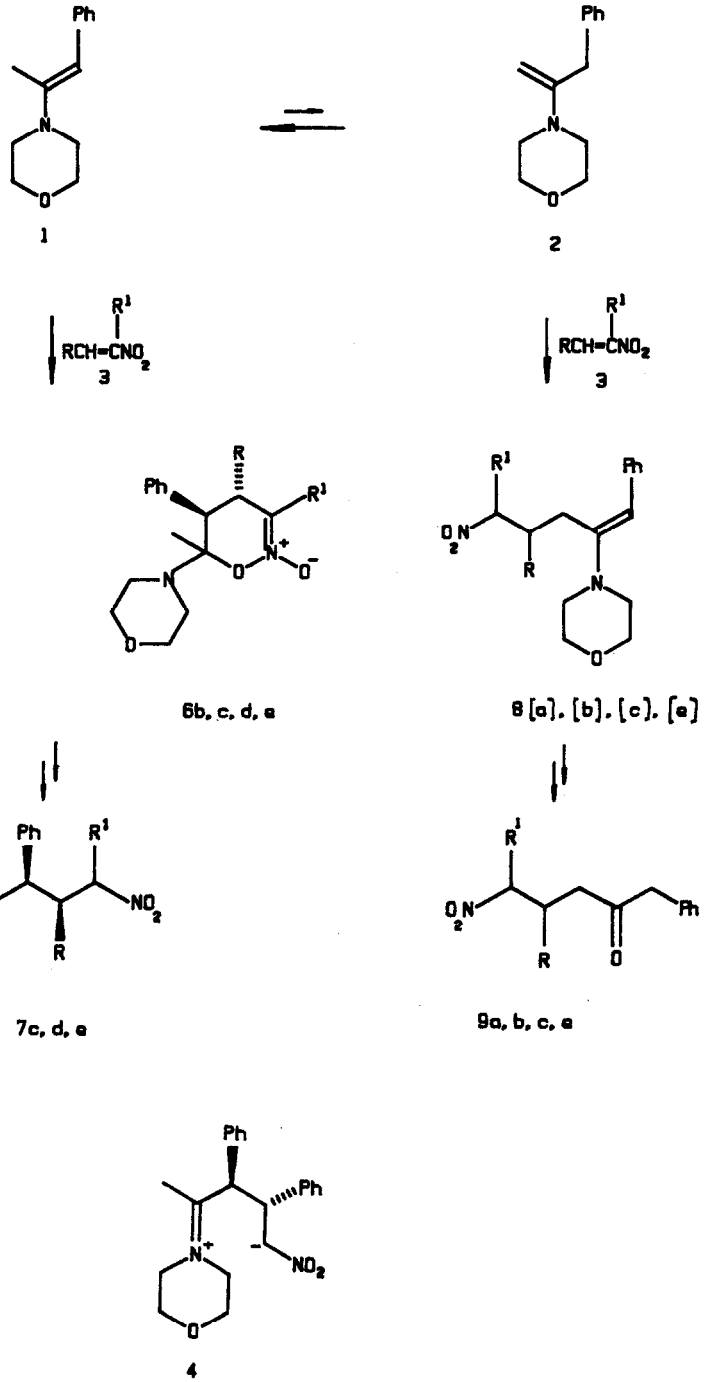
Abstract - The title enamine may exist in two double bond isomers. Both forms react with the nitroolefins under different conditions to afford, after hydrolysis, regioisomeric γ-nitroketones. γ-Dicarbonyl compounds are isolated from the hydrolysis at pH 2 of the 1,2-oxazine N-oxide systems, which in some cases have also been separated.

The enamine 1[1-4] was reacted with a series of nitroolefins 3, both linear and cyclic in nature, which are listed in Scheme 1.[5] The reactions were carried out in the absence of solvent because in that case yields were much higher. In each case the product of kinetic control was a 4- and/or 6-membered cyclization product, isolated as single diastereoisomer. The high diastereoselectivity is the first important feature of these reactions, the second one being their reversibility (with the exception of one case), which determines a different reaction course, as a consequence of the existence of an equilibrium in the substrate 1, already found for the N,N-dimethyl analog in the reaction with 2,4-dinitrofluorobenzene.[6]

In the reaction with ß-nitro-styrene 3a (Scheme 1) the only product isolated was the cyclobutane derivative 5a, whose stereochemistry, as for two out of four chiral centres, is a consequence of the type of attack of the nitroolefin onto the substrate, both reagents being in E configuration. The nucleophilic prochiral centre of the enamine and the electrophilic prochiral centre of the nitroolefin in fact approach each other in the Re*-Re* manner,[7] thus determining the relative configuration of the carbon atoms of the firstly formed single bond. The chirality of the carbon atoms bearing the nitro group and the morpholine ring respectively is uncertain because in the collapse of the carbanion onto the iminium carbon atom in the dipolar intermediate 4, a double configuration may arise.

On standing in $CDCl_3$, the cyclobutane 5a reverted completely into the reactants within 24 hours. They reacted again, the enamine substrate in the form of the double bond isomer 2, to give the Michael-type adduct 8a which could not be isolated as pure compound but only identified by IR and ^1H NMR

Scheme 1

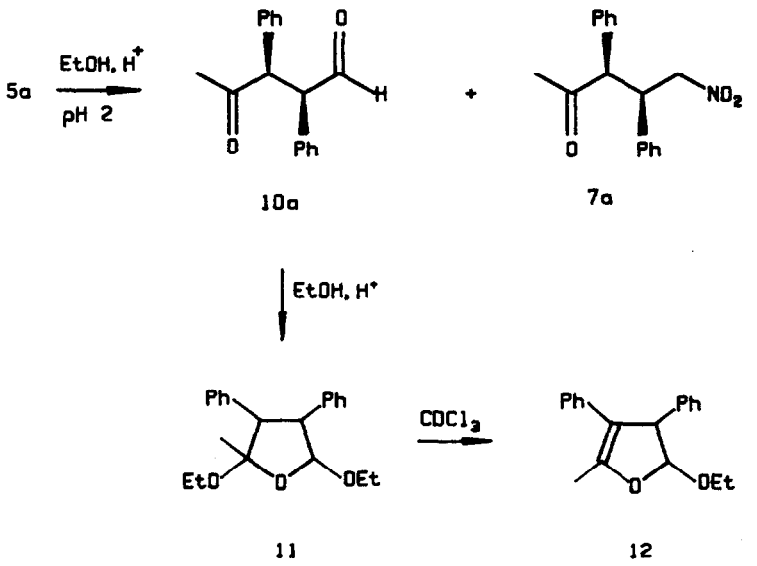


	R	R^1
a	Ph	H
b	Ph	Me
c	Me	Ph
d	$(CH_2)_3$	
e	$(CH_2)_4$	

spectroscopy. In fact it underwent rapid hydrolysis in the solvent itself to the corresponding γ-nitroketone **9a** (Scheme 1).

When the cyclobutane adduct **5a** was hydrolysed at pH 5 the γ-nitroketone **7a** was isolated as single diastereoisomer. On the other hand hydrolysis carried out at pH 2 led to the corresponding γ-ketoaldehyde **10a** and the γ-nitroketone **7a** in ratio 3:1. (Scheme 2).

Scheme 2



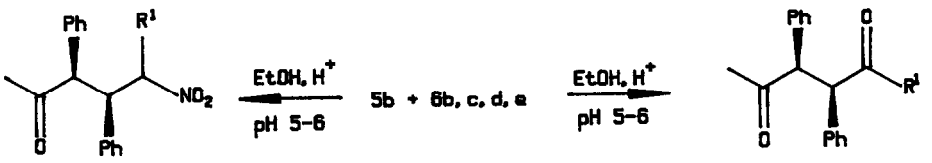
The ketoaldehyde, which is the result of a Nef-type reaction, was not stable under the reaction conditions and it cyclized rapidly to the corresponding tetrahydrofuran derivative **11**. Also this latter compound converted subsequently into the dihydrofuran derivative **12**, by loss of ethanol, when dissolved in chloroform. The isolation of the Nef product **10a** is interesting as it is the first example of this type of reaction occurring on a derivative from an enamine and ß-nitro-styrene.

When the nitroolefin was 2-nitro-1-phenyl-propene **3b**, the formation of the corresponding cyclobutane adduct **5b** was accompanied by the formation of the [4+2] heterocyclization product **6b**, evidently for steric reasons, the nucleophilic centre of the olefin being bulkier than in the previous case.

The ratio **5b**:**6b** was about 1:3 and it did not vary within the range -30 °C - 25 °C. Unfortunately, the two products could not be separated, neither by crystallization nor by flash cromatography, and therefore all the subsequent reactions have been performed on the mixture. In a protic solvent both compounds **5b** and **6b** went back to the reactants, the former more rapidly, as evidentiated by ^{1}H NMR spectra run at regular intervals. The reaction

took the other course, through the isomer 2, to give eventually, after hydrolysis, the ketone 9b as a pair of diastereoisomers. Hydrolysis of the mixture 5b and 6b carried out at pH 2, led to the γ-diketone 10b[8,9] as a single diastereoisomer (Scheme 3).

Scheme 3



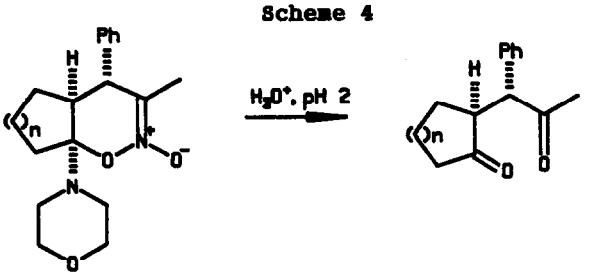
7c, d, e

10b, c, d, e

When the olefin carbon atom bearing the nitro group was even bulkier, as in 1-nitro-1-phenyl-propene 3c, the only product formed was the six-membered heterocyclic derivative 6c, as single diastereoisomer. The high diastereoselectivity of the reaction was again confirmed by the obtainement of a single -diketone 10c,[10] by hydrolysis of the heterocycle 6c performed at pH 2. Hydrolysis of the 1,2-oxazine N-oxide derivative 6c, performed at pH 5, allowed the isolation of the γ-nitroketone 7c, while the γ-nitroketone 9c was obtained leaving the heterocycle 6c in a solvent and allowing the reaction to take the other course. Surprisingly, this second route was not followed by the 1,2-oxazine N-oxide 6d, obtained in quantitative yield from the enamine 1 and 1-nitrocyclopentene 3d. In methanol it underwent the heterocyclic ring fission to the corresponding Michael-type adduct which was not isolated. The subsequent hydrolysis furnished the γ-nitroketone 7d as a pair of diastereoisomers, the double configuration being relative to the nitromethine carbon atom.[11] Conversely, hydrolysis of the 1,2-oxazine N-oxide 6d itself resulted in the formation of a single γ-diketone 10d, in which the two chiral centers have the configuration shown in Scheme 3. This is confirmed by the fact that the same compound was obtained by acidic hydrolysis of the already known heterocycle 13 derived from 2-nitro-1-phenyl-propene and 1-(4-morpholinyl)-cyclopentene (Scheme 4).[12]

The reaction between the substrate 1 and 1-nitrocyclohexene 3e followed the usual route furnishing the expected 1,2-oxazine N-oxide derivative 6e first and, through its reversion into the reactants, the γ-nitroketone 9e as single diastereoisomer, after hydrolysis of the nitroalkylated enamine intermediate 8e. The γ-diketone 10e was obtained directly from the heterocycle 6e by hydrolysis at pH 2. The same γ-diketone was prepared from the acidic hydrolysis of the corresponding 1,2-oxazine N-oxide 14 obtained from morpholinocyclohexene (Scheme 4).[12]

Scheme 4



n=1: 13 n=2: 14 n=1: 10d n=2: 10e

In conclusion, differently from the results reported in the literature,[6] in the present case a double reactivity has been observed for the enamine derived from benzylmethylketone. When the reagents are reacted neat, it is possible to separate the products of kinetic formation, which are always cyclic in nature. In solution, an equilibrium is rapidily estabilished between the cycloadducts and the reagents, the enamine partecipating in the last step as the less substituted form 2. The nitroolefins attack this latter form preferentially, to yield eventually, after hydrolysis, the γ-nitroketones 9. In some cases it is also possible to separate their regioisomers 7, performing the hydrolysis of the cycloadducts at pH 5. On the other hand, the γ-dicarbonyl compounds 10 are formed only by hydrolysis of the cycloadducts 6, carried out at pH 2. Conversion of the γ-nitroketones into the corresponding dicarbonyl compounds is not possible, at least under our acidic conditions.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded in nujol mulls on a Perkin-Elmer 1320 spectrometer. ^{1}H NMR spectra were measured on a Varian 360 A (60 MHz) and on a Bruker WP-80 (80 MHz) spectrometers using deuterochloroform as solvent and tetramethylsilane as internal standard. ^{13}C NMR were recorded on a Bruker WP-80 (20.1 MHz). Mass spectra were obtained on a VG 7070 spectrometer at 70 eV. TLC were performed on Whatman K6F silica gel plates. Flash chromatography was performed on Merck silica gel 60 (230-400 mesh), under pressure of nitrogen.

Synthesis of the reactants

The enamine 1 [m.p.71 °C (lit.[1] 66-68 °C)] was prepared from benzyl-methyl-ketone and morpholine by the method of W.White and T.A.Weingarten.[13]

ß-Nitro-styrene (3a) was used as purchased (Aldrich), 2-nitro-1-phenyl-propene (3b) was prepared in accordance with ref 14, 1-nitro-1-phenyl-propene (3c) in accordance with ref 15 and the cyclic nitroolefins 3d and

3e in accordance with E.Corey.[16]

Reaction of 2-(4-morpholinyl)-1-phenyl-propene (1) with ß-nitro-styrene [2R*-(3R, 4R or 4S, 1R or 1S)]-2,3-Diphenyl-1-methyl-1-(4-morpholinyl)-4-nitro-cyclobutane (5a)

The nitroolefin 3a (0.74 g, 4.9 mmoles) was added to the enamine 1 (1.0 g, 4.9 mmoles) and the reagents mixed intimately. After 10 min, the solid formed was filtered with the aid of a small amount of dry ether and it was identified as 5a (1.05 g, 82% yield), m.p. 128-130 °C (Found: C, 72.00; H, 7.01; N, 7.89. $C_{21}H_{24}N_2O_3$ requires: C, 71.57; 6.86; N, 7.95%); IR, ν_{max}, cm^{-1}: 1600, 1500, 770, 750, 710, 700 (Ph), 1535, 1360 (NO_2), 1120 (C-O-C); ^1H NMR, δ: 7.5 (s, 5 H, Ph), 7.4 (s, 5 H, Ph), 5.1 (d, J 9.0 Hz, 1 H, $CHNO_2$), 4.5 (dd, J_1 9.0 Hz, J_2 11.0 Hz, 1 H, CHPh), 3.8 (m, 4 H, CH_2OCH_2), 3.6 (d, J 11.0 Hz, 1 H, CHPh), 2.8 (m, 4 H, CH_2NCH_2), 1.1 ppm (s, 3 H, Me); MS: M^+ 352 (4), 306 (19), 292 (13), 218 (15), 203 (52), 202 (58), 193 (14), 149 (39), 130 (10), 117 (23), 115 (36), 104 (44), 91 (100), 77 (69).

The cyclobutane 5a was left in $CDCl_3$; after 24 h the nitroalkylated enamine 1,4-diphenyl-2-(4-morpholinyl)-5-nitro-1-pentene [8a] was detected: IR, ν_{max}, cm^{-1}: 1620 (C=C), 1550 (NO_2); ^1H NMR, δ: 5.8 (s, C=CH), 4.6 ppm (m, CH_2NO_2).

The cyclobutane 5a was dissolved in methanol. After standing at r.t. for 2 h the solvent was evaporated and the resulting oily residue was hydrolysed at pH 2 in ethanol and 10% HCl for 1 h. After the usual workup, the ketone 9a was purified by flash chromatography (eluant: light petroleum-ethylacetate 4:1) and identified as 1,4-diphenyl-5-nitro-2-pentanone, m.p. 65 °C, from methanol (Found: C, 71.89; H, 5.95; N, 4.76. $C_{17}H_{17}NO_3$ requires: C, 72.07; H, 6.05; N, 4.84%); IR, ν_{max}, cm^{-1}: 1705 (C=O), 1600, 1500 (Ph), 1540, 1360 (NO_2); ^1H NMR, δ: 7.4 (m, 10 H, Ph), 4.7 (m, 2 H, CH_2NO_2), 4.1 (m, 1 H, CHPh), 3.7 (s, 2 H, CH_2Ph), 2.9 ppm (d, J 7.0 Hz, CH_2CO); ^{13}C NMR: 205.3 (s), 138.7 (s), 133.4 (s), 129.4 (2 d), 129.0 (3 d), 127.9 (2 d), 127.4 (3 d), 79.2 (t), 50.4 (t), 44.2 (t), 38.9 ppm (d); MS: 236 (1), 192 (5), 145 (25), 131 (15), 117 (15), 104 (30), 91 (100).

Hydrolysis of the cyclobutane 5a

The cyclobutane adduct 5a was hydrolysed in ethanol-water, at pH 5-6, to give, after the usual workup, the γ-nitroketone 7a which was identified as (3R*,4R*)-3,4-diphenyl-5-nitro-2-pentanone, m.p. 139 °C (Found, C 71.98; H 6.12; N 4.76. $C_{17}H_{17}NO_3$ requires: C, 72.07; H, 6.05; N, 4.84%); IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 1500, 750, 700 (Ph), 1540, 1360 (NO_2); ^1H NMR, δ: 7.1 (m, 10 H, Ph), 4.9 (m, 2 H, CH_2NO_2), 4.03 (m, 2 H, 2 CHPh), 2.1 ppm (s, 3 H, MeCO); ^{13}C NMR: 206 (s), 136.1 (s), 135.3 (s), 128.9 (2 d), 128.5 (2 d), 128.2 (2 d), 127.8 (2 d), 127.5 (2 d), 78.5 (t), 61.5 (d), 46.1 (d), 29.8 ppm (q); MS: 236 (0.8), 193 (38), 180 (21), 115 (25), 105

(21), 104 (21), 103 (12), 91 (88), 77 (21), 43 (100).

When carried out in ethanol and 10% HCl at pH 2 for 30 min, hydrolysis of **5a** led to a 25:25:50 mixture of compounds **7a**, **10a** and **11** which were separated on flash chromatography (eluant: light petroleum-ethylacetate 9:1). The compound **10a** was identified as (2R*, 3R*)-2,3-diphenyl-4-oxo-2-pentanal, oil, IR, ν_{max}, cm^{-1}: 1720, 1700 (C=O), 1600, 1500, 750, 700 (Ph); ^1H NMR, δ: 9.9 (s, 1 H, HC=O), 7.3 (m, 10 H, Ph), 4.5 (m, 2 H, 2 CHPh), 2.2 ppm (s, 3 H, MeCO); ^{13}C NMR: 207 (s), 198 (d), 134.7 (s), 132.7 (s), 129.7 (2 d), 128.8 (4 d), 127.7 (2 d), 127.0 (2 d), 61.7 (d), 60.0 (d), 29.3 ppm (q); MS: M^+ 252.11655 ($C_{17}H_{16}O_2$: 252.11502) (2), 237 (1), 224 (8), 210 (14), 192 (30), 181 (30), 165 (12), 105 (28), 103 (32), 91 (28), 77 (28), 43 (100). The compound **11** was attributed the structure of 2,5-diethoxy-3,4-diphenyl-2-methyl-tetrahydrofuran, m.p. 74 °C, IR, ν_{max}, cm^{-1}: 1620, 1600, 740, 700 (Ph), 1100 (C-O-C); ^1H NMR, δ: 7.4 (m, 10 H, Ph), 5.1 (d, J 6.0 Hz, 1 H, CH-OEt), 3.6 (m, 6 H, 2 CHPh and 2 OCH_2CH_3), 1.4 (s, 3 H, Me), 1.2 ppm (2 t, 6 H, 2 CH_3CH_2). MS: 281.15384 ($C_{19}H_{21}O_2$: M - OC_2H_5: 281.15414) (16), 252 (39), 238 (100), 223 (16), 209 (31), 193 (42), 181 (21), 178 (21), 165 (18), 133 (19), 115 (26), 105 (66), 91 (42), 77 (24), 43 (52). In chloroform solution, **11** was rapidly converted into **12**, which was given the structure of 2,3-dihydro-3,4-diphenyl-2-ethoxy-5-methyl-furan, oil, IR, ν_{max}, cm^{-1}: 1650 (O-C=C), 1595, 1495, 750, 690 (Ph), 1100 (C-O-C). ^1H NMR, δ: 7.3, 7.2 (2 s, 10 H, Ph), 5.3 (d, J 3.0 Hz, 1 H, CH-OEt), 4,3 (m, 1 H, CHPh), 3,6 (q, 2 H, CH_3CH_2O), 2.2 (s, 3 H, MeC=C), 1.2 ppm (t, 3 H, CH_3CH_2); ^{13}C NMR: 133.8 (s), 129.8 (s), 128.8 (2 d), 128.1 (2 d), 127.8 (2 d), 127.3 (2 d), 127.0 (d), 125.5 (d), 110.2 (d), 64.0 (t), 58.9 (d), 15.2 (q), 13.7 ppm (q). MS: M^+ 280.14761 ($C_{19}H_{20}O_2$: 280.14632) (50), 251 (16), 237 (39), 234 (19), 223 (10), 209 (23), 205 (37), 191 (70), 178 (28), 165 (14), 131 (19), 129 (18), 115 (21), 105 (37), 91 (39), 77 (28), 43 (100).

Reaction of 2-(4-morpholinyl)-1-phenyl-propene (1) with 2-nitro-1-phenyl-propene (3b)

The nitroolefin **3b** (1.64 g, 9.8 mmoles) was added to the enamine **1** (2.0 g, 9.8 mmoles) at 0 °C. After 1 h, the solidified mass was washed with dry ether. It resulted to be a 3:1 mixture of [4R*-(4 α, 5ß, 6α or 6ß)]-5,6-dihydro-3,6-dimethyl-4,5-diphenyl-6-(4-morpholinyl)-4H-1,2-oxazine N-oxide (**6b**) and [2R*-(3R, 4R or 4S, 1R or 1S)]-1,4-dimethyl-2,3-diphenyl-1-(4-morpholinyl)-4-nitro-cyclobutane (**5b**). IR, ν_{max}, cm^{-1}: 1620 (C=N), 1600, 1500, 700 (Ph), 1530 (NO_2), 1120 (C-O-C); ^1H NMR, δ: 7.3 (m, 10 H, Ph), 3.8, 3.5 (m, 6 H, CH_2OCH_2, CHMe, CHPh), 3.0 - 2.8 (2 m, 4 H, CH_2NCH_2), 1.9 (s, 2.25 H, MeC=N), 1.6 (s, 2.25 H, MeC-N), 1.5 (s, 0.75 H, MeC-NO_2), 1.1 ppm (s, 0.75 H, MeC-N).

The mixture **5b** and **6b** was allowed to stand in $CDCl_3$; after 48 h the

nitroalkylated enamine 1,4-diphenyl-2-(4-morpholinyl)-5-nitro-1-hexene [8b] was detected: IR, ν_{max}, cm^{-1}: 1620 (C=C), 1545 (NO_2); ^1H NMR, δ: 5.4 (s, C=CH), 4.8 (m, $CHNO_2$), 1.2 ppm (d, J 7 Hz , $C\underline{H}_3CH$).

The mixture 5b and 6b was dissolved in methanol; after 72 h at r.t. hydrolysis carried out at pH 2 gave, after the usual workup, a 1:1 mixture of the γ-nitroketones 9b and 9'b, which were separated on flash chromatography (eluant: light petroleum-ethylacetate 9:1).

1,4-Diphenyl-5-nitro-2-hexanone (9b)

M.p. 68 °C (Found: C, 72.85; H, 6.30; N, 4.76. $C_{18}H_{19}NO_3$ requires: C, 72.71; H, 6.44; N, 4.71%); IR, ν_{max} ($CDCl_3$), cm^{-1}: 1705 (C=O), 1600, 1500, 770, 750, 700 (Ph), 1540, 1340 (NO_2); ^1H NMR, δ: 7.3 (m, 10 H, Ph), 4.9 (m, 1 H, $CHNO_2$), 3.7 (m and s, 3 H, $C\underline{H}_2Ph$, $C\underline{H}Ph$), 3.0 (m, 2 H, CH_2CO), 1.5 ppm (d, J 7.0 Hz, 3 H, Me); ^{13}C NMR: 206.1 (s), 133.2 (s), 129.4 (2 d) 128.8 (2 d), 128.2 (2 d), 127.9 (2 d), 127.2 (2 d), 85.9 (d), 50.7 (t), 44.8 (d), 43.2 (t), 16.8 ppm (q); MS: 250.13306 ($C_{18}H_{18}O$ = $C_{18}H_{19}NO_3$ - HNO_2: 250.13576) (1), 207 (4), 176 (25), 159 (17), 149 (18), 131 (14), 118 (39), 105 (18), 91 (100).

1,4-Diphenyl-5-nitro-2-hexanone (9'b)

Oil, IR, ν_{max} ($CDCl_3$), cm^{-1}: 1700 (C=O), 1600, 1495, 760, 740, 700 (Ph), 1540, 1350 (NO_2); ^1H NMR, δ: 7.3 (m, 10 H, Ph), 4.8 (dq, J_1 7.0 Hz, J_2 7.0 Hz, 1 H, $CHNO_2$), 3.9 (m, 1 H, $C\underline{H}Ph$), 3.6 (s, 2 H, $C\underline{H}_2Ph$), 1.3 ppm (d, J 7.0 Hz, 3 H, Me); ^{13}C NMR: 205.1 (s), 131.5 (s), 129.3 (d), 129.0 (2 d), 128.8 (2 d), 128.2 (2 d), 127.8 (2 d), 127.1 (d), 87.0 (d), 50.6 (t), 45.5 (d), 44.3 (t), 17.7 ppm (q); MS: M^+ 297.13987 ($C_{18}H_{19}NO_3$: 297.13648) (0.03), 251 (0.78), 206 (2.3), 159 (10), 131 (10), 117 (15), 104 (37), 91 (100).

Hydrolysis of the mixture 5b,6b

The mixture 5b, 6b was hydrolysed at pH 2 under the usual conditions for 20 min, to yield a single diastereoisomer of the corresponding γ-diketone 10b, which was identified as (3R*,4R*)-3,4-diphenyl-2,5-hexanedione, m.p.109-110°C, (Found C, 81.17; H, 6.81; O, 12.01. $C_{18}H_{18}O_2$ requires: C, 80.95; H, 6.95; O, 12.10%).IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 740, 700 (Ph). ^1H NMR, δ: 7.1 (m, 10 H, Ph), 4.5 (s, 2 H, 2 $C\underline{H}$Ph), 2.1 ppm (s, 6 H, 2 MeCO); ^{13}C NMR: 208 (s), 135.7 (s) 128.9 (2 d), 128.7 (2 d), 127.4 (d), 62.1 (d), 29.2 ppm (q); MS: M^+ 266.13217 ($C_{18}H_{18}O_2$: 266.13067), (1.6), 224 (13), 206 (11), 181 (27), 105 (5), 103 (7), 43 (100).

Reaction of 2-(4-morpholinyl)-1-phenyl-propene (1) with 1-nitro-1-phenyl-propene (3c)

[4S*-(4α, 5β, 6α or 6β)]-5,6-dihydro-3,5-diphenyl-6-(4- morpholinyl)-4H-1,2-oxazine N-oxide (6c).

The nitroolefin 3c (1.2 g, 7.3 mmoles) was added to the enamine 1 (1.5 g, 7.3 mmoles) at 0 °C. After a few hours the solid formed was filtered (1.35

g, 50% yield) and identified as 6c, m.p. 126-128 °C (Found:C, 72.0; H, 7.11; N, 7.17. $C_{22}H_{26}N_2O_3$ requires: C, 72.11; H, 7.15; N, 7.64%); IR, ν_{max}, cm^{-1}: 1585 (C=N), 1595, 1490, 770, 750, 700 (Ph), 1110 (C-O-C); ^1H NMR, δ: 7.9 (m, 2 H, o-ArH), 7.5 (m, 8 H, m- and p-ArH, Ph), 3.7 (m, 6 H, CH_2OCH_2, CHMe, CHPh), 3.0 (m, 4 H, CH_2NCH_2), 1.4 (s, 3 H, Me), 1.1 ppm (d, J 6.0 Hz, 3 H, Me); MS: M^+ 366 (0.5), 336 (0.5), 320 (5), 315 (3), 230 (40), 203 (50), 202 (35), 163 (18), 117 (100), 115 (85), 91 (85), 77 (18).

The heterocycle 6c was left in $CDCl_3$; after 24 h the enamine 1,5-diphenyl-4-methyl-2-(4-morpholinyl)-5-nitro-1-pentene [8c] was detected: IR, ν_{max}, cm^{-1}: 1620 (C=C), 1540 (NO_2); ^1H NMR, δ: 5.8 (C=CH); 5.2 (d, J 11 Hz, $CHNO_2$), 2.1 (m, $CHCH_3$), 1.0 ppm (d, J 7 Hz, CH_3CH).

Treatment of the heterocycle 6c with methanol, followed by hydrolysis at pH 2, led to a 50:25:25 mixture of γ-nitroketones 7c, obtained as single diastereoisomer, 9c and 9'c, obtained as pair of diastereoisomers.

(3R*,4S*,5R* or 5S*)-3,5-Diphenyl-4-methyl-5-nitro-2-pentanone (7c)

M.p. 151-153 °C, from methanol (Found: C, 72.80; H 6.28; N, 4.80. $C_{18}H_{19}NO_3$ requires: C, 72.71; H, 6.44; N, 4.71%); IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 1495, 740, 700 (Ph), 1550, 1360 (NO_2); ^1H NMR, δ: 7.4 (m, 10 H, Ph), 5.2 (d, J 10.0 Hz, 1 H, $CHNO_2$), 3.6 (m, 2 H, CHMe, CHPh), 2.0 (s, 3 H, MeCO), 0.6 ppm (d, J 7.0 Hz, 3 H, Me); ^{13}C NMR: 206 (s), 130.2 (2 d), 129.9 (2 d), 129.0 (2 d), 129.7 (2 d), 128.1 (2 d), 94.1 (d), 60.3 (d), 37.3 (d), 29.3 (q), 12.7 ppm (q); MS: 267 (0.6), 251.14315 ($C_{18}H_{19}O$ = M - NO_2: 251.14358) (5), 149 (10), 115 (17), 107 (45), 105 (30), 91 (33), 77 (20), 43 (100).

1,5-Diphenyl-4-methyl-5-nitro-2-pentanone (9c)

Oil, IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 1500, 740, 700 (Ph), 1540, 1350 (NO_2), ^1H NMR, δ: 7.5 (s, 5 H, Ph), 7.3 (m, 5 H, Ph), 5.5 (d, J 11.0 Hz, 1 H, $CHNO_2$), 3.5 (s, 2 H, CH_2Ph), 3.0 (m, 1 H, CHMe), 2.3 (m, 2 H, CH_2CO), 1.1 ppm (d, J 7.0 Hz, 3 H, Me); ^{13}C NMR: 206.2 (s), 133.5 (s), 133.2 (s), 130 (2 d), 129.1 (2 d), 128.8 (2 d), 128.2 (2 d), 127.2 (2 d), 96.1 (d), 50.6 (t), 43.8 (t), 33.4 (d), 16.9 ppm (q); MS: 267 (1), 251.14562 ($C_{18}H_{19}O$ = $C_{18}H_{19}NO_3$ - NO_2: 251.14358) (5), 175 (11), 118 (10), 117 (19), 107 (25), 105 (14), 91 (100).

1,5-Diphenyl-4-methyl-5-nitro-2-pentanone (9'c)

Oil, IR, ν_{max}, cm^{-1}: 1705 (C=O), 1600, 1500, 740, 700 (Ph), 1540, 1350 (NO_2); ^1H NMR, δ: 7.5 (s, 5 H, Ph), 7.3 (m, 5 H, Ph), 5.4 (d, J 11.0 Hz, 1 H, $CHNO_2$), 3.7 (s, 2 H, CH_2Ph), 3.1 (m, 1 H, CHMe), 2.6 (m, 2 H, CH_2CO), 0.7 ppm (d, J 7.0 Hz, 3 H, Me). ^{13}C NMR: 206 2 (s), 133.5 (s), 133.1 (s), 129.2 (2 d), 129.0 (2 d), 128.6 (2 d), 128.0 (2 d), 127.0 (2 d), 95.9 (d), 50.6 (t), 44.9 (t), 33.4 (d), 16.0 (q); MS: M^+ 297.13108 ($C_{18}H_{19}NO_3$: 297.13648) (0.1), 267 (0.4), 251 (1.3), 118 (12), 117 (33), 115 (24), 107 (12), 105 (21), 92 (33), 91 (100), 77 (15).

Hydrolysis of the 1,2-oxazine-N-oxide 6c

Hydrolysis of the 1,2-oxazine-N-oxide 6c carried out at pH 5-6 gave the corresponding γ-nitroketone 7c in quantitative yield; when it was performed at pH 2, a single diasteroisomer of the corresponding γ-diketone 10c was isolated and identified as (2R*,3R*)-1,3-diphenyl-2-methyl-1,4-pentanedione.

Reaction of 2-(4-morpholinyl)-1-phenyl-propene (1) with 1- nitrocyclopentene (3d)

[5aS*-(5aα,6α,7α or 7β)]-3,4,5,5a,6,7-hexahydro-7-methyl-7-(4- morpholinyl)-6-phenyl-cyclopenta[c]-1,2-oxazine N-oxide (6d)

The nitroolefin 3d (0.4 g, 3.4 mmoles) was added to the enamine 1 (0.7 g, 3.4 mmoles) in dry ether, at 0 °C. After 24 h, a crystalline product was separated (0.8 g, 80% yield) and identified as 6d, m.p. 96-98 °C (Found: C, 68.20; H, 7.55; N, 8.62. $C_{18}H_{24}N_2O_3$ requires: C, 68.33; H, 7.65; N, 8.55%); IR, ν_{max}, cm^{-1}: 1645 (C=N), 1600, 1490, 760, 700 (Ph), 1115 (C-O-C); ^1H NMR, δ: 7.4 (s, 5 H, Ph), 3.7 (m, 4 H, CH_2OCH_2), 3.0 (m, 6 H, CH_2NCH_2, CHPh, H-5a), 2.0 (m, 6 H, $(CH_2)_3$), 1.2 ppm (s, 3 H, Me); MS: M^+ 316 (24), 286 (5), 270 (33), 203 (100), 202 (46), 117 (26), 115 (33), 91 (67).

Treatment of the heterocycle 6d with either methanol or chloroform, followed by hydrolysis at pH 2 , furnished after the usual workup a 1:4 mixture of two γ-nitroketones 7d and 7'd, which were separated on flash chromatography (eluant: light petroleum-ethylacetate 9:1).

(1R*,1'S*,2'R* or 2'S*)-1-(-2'-nitrocyclopentyl)-1-phenyl-2-propanone (7d)

M.p.55°C, IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 820, 750, 700 (Ph), 1540, 1350 (NO_2); ^1H NMR, δ: 7.3 (m, 5 H, Ph), 4.6 (m, 1 H, $CHNO_2$), 3.7 (d, J 9.0 Hz, 1 H, CHPh), 3.3 (m, 1 H, H-1), 2.0 (s, 3 H, MeCO), 1.8 ppm (m, 6 H, $(CH_2)_3$); ^{13}C NMR: 206.1 (s), 135.3 (s), 128.2 (2 d), 127.9 (2 d), 126.0 (d), 89.1 (d), 61.6 (d), 45.9 (d), 32.2 (t), 28.8 (t), 28.0 (q), 22.8 ppm (t). MS: 201.12719 ($C_{14}H_{17}O$ = M - NO_2: 201.12793) (3), 175 (27), 157 (25), 129 (24), 115 (16), 107 (26), 91 (47), 43 (100).

(1R*,1'S*,2'R* or 2'S*)-1-(-2'-nitrocyclopentyl)-1-phenyl-2- propanone (7'd)

M.p. 89°C, (Found C, 68.10; H, 6.85; N, 5.60. $C_{14}H_{17}NO_3$ requires: C, 68.00; H, 6.93; N, 5.66%); IR, ν_{max}, cm^{-1}: 1700, (C=O), 1600, 1495, 840, 740, 700 (Ph), 1540, 1350 (NO_2); ^1H NMR, δ: 7.2 (m, 5 H, Ph), 5.1 (m, 1 H, $CHNO_2$), 3.5 (d, J 11.0 Hz, 1 H, CHPh), 2.8 (m, 1 H, H-1), 2.0 (s, 3 H, MeCO), 1.3 ppm (m, 6 H, $(CH_2)_3$); ^{13}C NMR: 205.7 (s), 135.8 (s), 128.2 (2 d), 127.3 (2 d), 126.9 (d), 88.1 (d), 58.9 (d), 47.1 (d), 29.4 (t), 28.3 (q), 26.7 (t), 21.2 ppm (t). MS: 201 (1) 175 (10), 157 (13), 129 (15), 115 (15), 105 (14), 91 (32), 77 (16), 67 (19), 43 (100).

Hydrolysis of the 1,2-oxazine N-oxide 6d

Hydrolysis of the heterocycle 6d carried out at pH 2 furnished

quantitatively the corresponding γ-diketone **10d**, which was identified as (1R*, 1S'*)-1-(-2'-oxocyclopentyl)-1-phenyl-2-propanone, oil, IR, ν_{max}, cm^{-1}: 1740, 1700 (C=O), 1600, 1495, 740, 700 (Ph); ^1H NMR, δ: 7.3 (m, 5 H, Ph), 3.9 (d, J 8.0 Hz, 1 H, CHPh), 3.2 (m, 1 H, H-1), 1.8 ppm (m, 6 H, $(CH_2)_3$); ^{13}C NMR: 217.9 (s), 203 (s), 133.6 (s), 128.9 (4 d), 127.6 (d), 58.5 (d), 51.9 (d), 37.2 (t), 29.4 (q), 27.3 (t), 20.4 ppm (t). MS: 217 (0.3), M^+ 216.11562 ($C_{14}H_{16}O_2$: 216.11502) (0.5), 174 (28), 156 (27), 145 (19), 129 (19), 117 (27), 115 (30), 91 (88), 77 (17), 43 (100).

Reaction of 2-(4-morpholinyl)-1-phenyl-propene (1) with 1-nitrocyclohexene (3e)

[6aR*-(6aα, 7α, 8α or 8β)]-3,4,5,6,7,8-hexahydro-6aH-8-methyl-8-(4-morpholinyl)-7-phenyl-benzo[c]-1,2-oxazine N-oxide (6e)

The nitroolefin **3e** (0.53 g, 4.2 mmoles) was added to a solution of the enamine **1** (0.86 g, 4.2 mmoles) in dry ether. After 3 h, the crystalline product precipitated, **6e**, was filtered (1.2 g, 90% yield), m.p. 112-114 °C (Found:C, 69.21; H, 8.03; N, 8.39. $C_{19}H_{26}N_2O_3$ requires: C, 69.06; H, 7.93; N, 8.40%); IR, ν_{max}, cm^{-1}: 1605 (C=N), 790, 760, 700 (Ph), 1110 (C-O-C); ^1H NMR, δ: 7.3 (m, 5 H, Ph), 3.7 (m, 4 H, CH_2OCH_2), 3.2 (d, J 8.0 Hz, 1 H CHPh), 2.9 (m, 5 H, CH_2NCH_2, H-6a), 1.7 (m, 8 H, $(CH_2)_4$), 1.3 ppm (s, 3 H, Me); MS: M^+ 330 (4), 284 (5), 203 (100), 202 (72), 117 (25), 115 (37), 91 (43), 81 (88), 77 (25).

When the heterocycle **6e** was left in $CDCl_3$, after 24 h the nitroalkylated enamine 2-(4-morpholinyl)-3-(2-nitrocycloexyl)-1-phenyl-1-propene [**8e**] was detected: IR, ν_{max}, cm^{-1}: 1610 (C=C), 1540 (NO_2); ^1H NMR, δ: 5.7 (CH=C), 4.3 ppm (m, $CHNO_2$).

The oxazine **6e** was dissolved in methanol. After 72 h, the solution was acidified to pH 2 with 10% HCl. The residue obtained after extraction with ether was chromatographed (eluant: light petroleum-ethylacetate 9:1) and the γ-nitroketones **7e** and **9e** were separated. Compound **9e** was identified as 3-(2-nitrocyclohexyl)-1-phenyl-2-propanone, oil, IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 1495, 740, 700 (Ph), 1540, 1350 (NO_2); ^1H NMR, δ: 7.3 (m, 5 H, Ph), 4.3 (m, 1 H, $CHNO_2$), 3.7 (s, 2 H, CH_2Ph), 2.4 (d, J 5.0 Hz, CH_2CO), 1.6 ppm (m, 9 H, $(CH_2)_4CH$). ^{13}C NMR: 206.1 (s), 133.8 (s), 129.4 (2 d), 128.8 (2 d), 127.1 (d), 85.0 (d), 50.5 (t), 42.9 (t), 34.2 (d), 28.3 (t), 27.1 (t), 23.3 (t), 21.1 ppm (t). MS: 215.14318 ($C_{15}H_{18}O$ = M - NO_2: 215.14358) (1), 170 (3), 139 (4), 122 (4), 91 (100), 81 (10). The compound **7e** was given the structure of (1R*,1'S*,2'R* or 2'S*)-1-(2'-nitrocyclohexyl)-1-phenyl-2-propanone, m.p. 114-116 °C (Found: C, 69.12; H, 7.18; N, 5.40. $C_{15}H_{18}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%); IR, ν_{max}, cm^{-1}: 1700 (C=O), 1600, 760, 720, 700 (Ph), 1540 (NO_2); ^1H NMR, δ: 7.3 (m, 5 H, Ph), 4.2 (m, 1 H, $CHNO_2$), 3.6 (d, J 4.0 Hz, 1 H, CHPh), 2.9 (m, 1 H, H-1), 2.1 (s, 3 H,

MeCO), 1.6 ppm (m, 8 H, $(CH_2)_4$). ^{13}C NMR: 206.1 (s), 134.5 (s), 130.1 (2 d), 128.9 (2 d), 127.2 (d), 88.7 (d), 59.9 (d), 41.0 (d), 31.9 (t), 29.2 (q), 26.9 (t), 24.5 (t), 24.1 ppm (t). MS: 215 (6), 189 (17), 171 (40), 129 (30), 115 (17), 107 (20), 91 (53), 81 (27), 43 (100).

Hydrolysis of the 1,2-oxazine N-oxide 6e

Hydrolysis of the heterocycle 6e carried out in methanol at pH 2 gave quantitatively the corresponding γ-diketone 10e, identified as (1R*, 2S*)-1-(-2-oxo-cyclohexyl)-1-phenyl-2-propanone, m.p.105 °C from methanol (Found: C, 78.30; H, 7.90. $C_{15}H_{18}O_2$ requires: C, 78.23; H, 7.88%); IR, ν_{max}, cm^{-1}: 1710, 1700 (C=O), 1600, 1500, 740, 700 (Ph); ^1H NMR, δ: 7.2 (s, 5 H, Ph), 3.8 (d, J 11.0 Hz, 1 H, CHPh), 3.0 (m, 1 H, CHCO), 2.3 (m, 2 H, CH_2CO), 2.1 (s, 3 H, Me), 1.5 ppm (m, 6 H, $(CH_2)_3$). ^{13}C NMR: 212 (s), 207.5 (s), 133.6 (s), 128.9 (2 d), 128.8 (2 d), 127.5 (d), 58.9 (d), 53.6 (d), 42.2 (t), 31.9 (t), 28.8 (q), 25.1 ppm (t); MS: 231 (2), M^+ 230.13185 ($C_{15}H_{18}O_2$: 230.13067) (2), 188 (49), 170 (32), 159 (10), 143 (17), 97 (31), 91 (97), 77 (17), 43 (100).

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