Pergamon

Tetrahedron 55 (1999) 13809–13818

TETRAHEDRON

New Perspectives in Oxazole Chemistry. 3.[1] Homo- and Hetero-Domino Processes of 4-Nitro Derivatives

Rodolfo Nesi,* Stefania Turchi,* Donatella Giomi, Andrea Danesi

Dipartimento di Chimica Organica 'Ugo Schiff' dell'Università - Centro di Studio del CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Via Gino Capponi 9, I-50121 Firenze, Italy

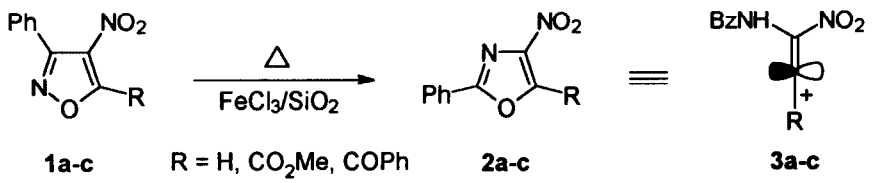
Received 16 July 1999; revised 6 September 1999; accepted 23 September 1999

Abstract

Addition - ring opening of the nitrooxazole **2a** with diverse amino nucleophiles afforded directly the polyfunctionalized nitroenamines **7a-g** in good to excellent yields. At the same time, highly diastereoselective cascade reactions, easily performed both on **2a-c** with the ynamine **8** and **2b** with the enol ether **13**, led to the novel polycyclic systems **12a-c** and **15**, respectively.

1. Introduction

The increasing interest in domino processes over the past decade[2] is widely justified by the possibility of building up simple molecules as well as more complex targets by one-pot reactions, carried out under suitable established conditions, which do not require isolation of the intermediates involved in the spontaneous sequences.



1a-c R = H, CO_2Me, COPh **2a-c** **3a-c**

Scheme 1

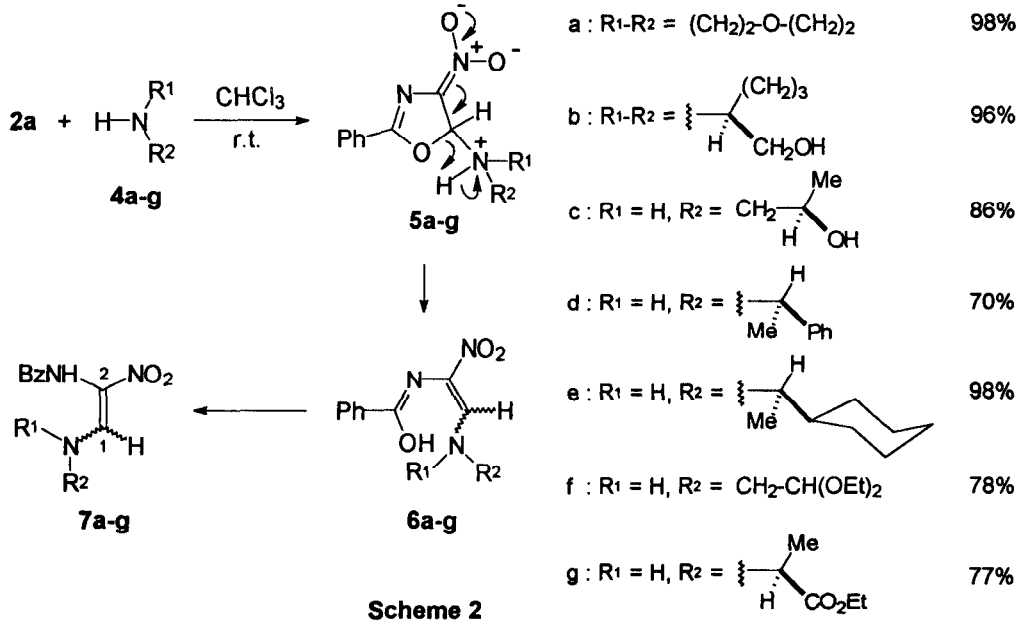
*Fax: 0039-055-2476964, E-mail: nesi@chimorg.unifi.it

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00864-9

Recent results from our laboratory clearly showed that the nitrooxazoles **2a-c**, first available in reasonable yields by thermal isomerization of the corresponding isoxazoles **1a-c** in the presence of a catalytic amount of the anhydrous $FeCl_3$-SiO_2 reagent (Scheme 1), can be regarded as synthetic equivalents of the nitrovinyl cations **3a-c** for a novel effective access to nitroenamine derivatives with a few primary and secondary amines.[1] In order to expand the scope of this strategy, we decided to investigate the reactivity of **2a** towards compounds **4a-g**; the possibility of carrying out other domino reactions upon the same substrates with different counterparts was also explored.

2. Results and discussion

When **2a** was allowed to react with a very small excess of morpholine (**4a**) in chloroform at room temperature, compound **7a** was obtained in 98% yield by a three-step hetero-domino process involving the oxazoline **5a** and the corresponding ring opening product **6a** as key intermediates (Scheme 2).

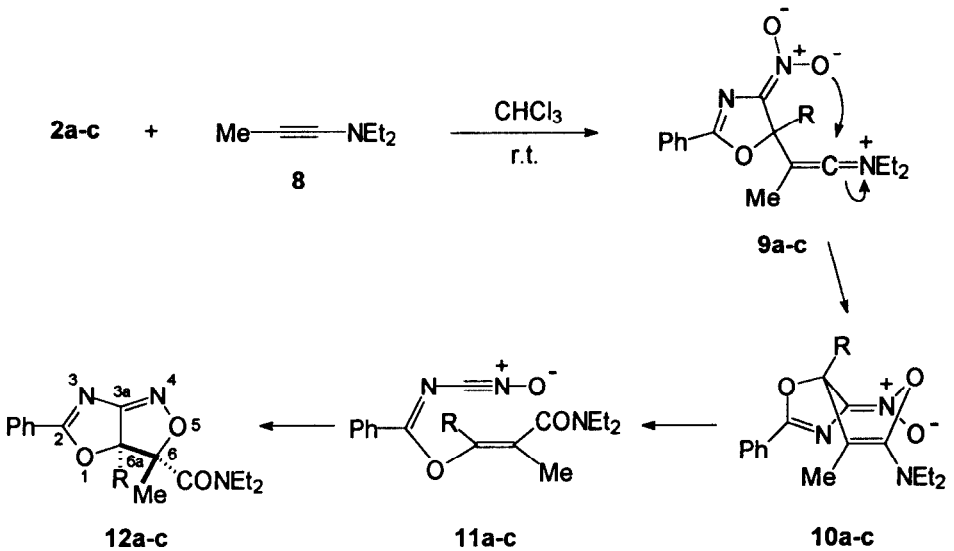


Scheme 2

A total chemoselectivity was observed with the aminoalcohols **4b** and **4c** which afforded under the same conditions the polyfunctionalized nitroenamines **7b** and **7c** as the only products. In an analogous fashion, the homochiral compounds **7d** and **7e** were prepared in very good yields by treatment of **2a**

with (*R*)-1-phenylethylamine (**4d**) and (*R*)-1-cyclohexylethylamine (**4e**), respectively. Finally, the same nitrooxazole easily reacted both with the protected aminoaldehyde **4f** and the aminoester **4g** to give **7f** and **7g** in 77-78% yields.

It is well known that both nitrocyclopentene[3] and some five-membered nitro heterocycles[4] reacted with ynamines affording, through [4+2] oxazine cycloadducts, polycyclic isoxazolines whose structure was firmly established by X-ray analyses.

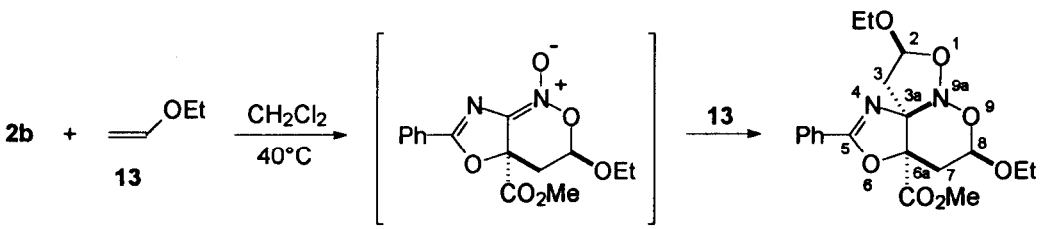


Scheme 3

Treatment of the nitrooxazoles **2a-c** with a small excess of 1-diethylaminopropyne (**8**) in chloroform at room temperature enabled us to isolate in 52-63% yields compounds **12a-c**,[5] the first derivatives of the hitherto unknown oxazolo[4,5-*c*]isoxazole system, as a result of a four-step hetero-domino process (Scheme 3). In the light of the exclusive *cis* stereochemistry always observed for the R and $CONR_2$ groups in the diverse isoxazolines,[3,4] a concerted retro-hetero Diels-Alder ring opening of the bicyclic intermediates **10a-c** followed by intramolecular cycloadditions of the resulting nitrile oxides **11a-c** into **12a-c**, appears to be preferred to an alternative homolytic cleavage of the N-O bond, previously suggested for similar species,[3,4a] leading to diradicals as precursors of the final products.

Efforts to exploit **2a** as a nitroalkene heterodiene for a direct entry into spiro tricyclic nitroso acetals[6] with ethyl vinyl ether (**13**) were unsuccessful: careful chromatographic workup of the very

complex reaction mixture achieved at 40°C in anhydrous dichloromethane, did not give any desired compound. Conversely, despite a remarkable decrease in reactivity, a clean reaction was observed under the same conditions with the nitroester **2b** and we succeeded in isolating the diastereomer **15** in 76% yield; its formation can be accounted for on the basis of a pericyclic homo-domino process involving a [4+2] cycloaddition of the nucleophilic dienophile **13** upon the C=C–N=O moiety of **2b**, followed by a 1,3-dipolar cycloaddition of the same reagent with the nitronate adduct **14** (Scheme 4).[7]



14 **15**

Scheme 4

The proposed stereochemistry, arising from highly preferential *endo* and *exo/syn* transition states for the sequential steps, was supported by the analogous structure of the largely predominant reaction product of the nitroisoxaxole **1b** with **13**, unambiguously determined by an X-ray analysis.[8]

The structures of the new products followed from analytical and spectral evidence (Experimental). Particularly, whereas compound **7a**, containing a symmetrical tertiary amino group, exists exclusively in DMSO-d_6 solution in the *E* configuration,[9] as indicated by the lack of duplications in the ^{1}H- and ^{13}C-NMR spectra and the presence in the former of a diagnostic signal at δ 8.53 for the strongly deshielded H-1, a conformational equilibrium between *EE* and *EZ* forms[9] (*ca.* 50%) must be taken into consideration for **7b** in the same solvent, as suggested by its ^{1}H NMR pattern exhibiting two singlets of comparable intensities at δ 8.73 and 8.76 for the olefinic proton. On the contrary, the nitroenamines **7c-g** were shown to exist as mixtures of *E,E* and *Z,E* isomers (3:1 to 6:1), whose proportions were inferred from the relative intensities of their amide NH singlets at δ 9.51-9.61 and 9.78-9.84.

As for the binuclear systems **12a-c**, all the resonances of the skeleton carbons were easily identified at δ 178.0-180.65 (C-2), 175.9-179.1 (C-3a), 96.75-101.7 (C-6), and 91.8-102.9 (C-6a). Finally, while the H-2 and H-8 protons of **15** gave rise to doublets of doublets at δ 5.86 and 5.12 in

the ^{1}H NMR pattern, two doublets were detected in the ^{13}C coupled spectrum at δ 110.35 and 97.9 for the corresponding anomeric carbons.

3. Conclusion

The 4-nitrooxazole system, previously employed as a very reactive partner for normal [4+2] cycloadditions with several 4π counterparts,[10] was confirmed as a valuable synthon for several nitroenamine derivatives; moreover, by virtue of a wide reactivity, it has been advantageously used for the construction of polycyclic skeletons by efficient and selective domino reactions.

4. Experimental

General Procedures. Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were measured as KBr pellets with a Perkin-Elmer 881 spectrophotometer; unless otherwise stated, ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 solutions with a Varian Gemini instrument operating at 200 MHz and 50 MHz, respectively. Chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz); the values in square brackets refer to the most evident resonances of the minor isomer; the relative assignment of the ^{13}C NMR resonances was achieved by the use of coupled spectra and long-range heteronuclear correlation experiments. Elemental analyses were obtained with a Perkin-Elmer 2400 Analyzer. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatographies, respectively. Petroleum ether refers to the fractions of b.p. 40-70°C. All the reactions were carried out in a screw-capped tube (Pyrex N. 13).

Synthesis of the Nitroenamines 7a-f. General procedure.

The amine (0.51 mmol) was added to a solution of the nitrooxazole (0.5 mmol) in chloroform (1.5 ml) and the mixture was stirred at room temperature for 24h; the solvent was then removed under reduced pressure.

A. The residue obtained by reaction of **2a** with morpholine (**4a**) (0.044 g, 0.044 ml) was taken up in *n*-pentane (2-3 ml), filtered, and dried to give (*E*)-2-benzoylamino-1-(morpholin-4-yl)-2-

nitroethylene (**7a**) (0.136 g, 98%). An analytical sample, obtained as a pale yellow solid by crystallization from AcOEt, gradually darkened above 170°C and melted with decomposition at 173°C; IR ν 3251, 3066, 2930, 2849, 1643, 1475, 1268, 1228 cm^{-1}; ^1H NMR δ 3.50-3.75 (m, 8H), 7.48-7.64 (m, 3H), 7.92-8.03 (m, 2H), 8.53 (s, 1H), 9.83 (s, 1H); ^{13}C NMR δ 66.4 (t), 118.1 (s), 128.0 (d), 128.9 (d), 132.4 (d), 133.3 (s), 144.2 (d), 166.7 (s). Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.45; H, 5.30; N, 15.00.

B. The crude product of **2a** with L-prolinol (**4b**) (0.052 g, 0.050 ml) was washed with the minimum amount of anhydrous ether to yield (*E*)-2-benzoylamino-1-[(*S*)-2-hydroxymethylpyrrolidin-1-yl]-2-nitroethylene (**7b**) (0.140 g, 96%) which crystallized from AcOEt/ether as pale yellow needles, m.p. 141-142°C dec; $[\alpha]^{21}_D$ = +26.3 (*c* 1.39, $CHCl_3$); IR ν 3432, 3268, 2943, 1660, 1631, 1468, 1404, 1254 cm^{-1}; ^1H NMR δ 1.60-2.0 (br m), 3.25-3.98 (br m), 5.17 (br s), 7.42-7.68 (m), 7.84-8.02 (m), 8.73 (s), [8.76 (s)], [9.81 (s)], 9.83 (s);^{13}C NMR δ 23.7 (t), 26.2 (t), [26.4 (t)], 47.8 (t), [48.1 (t)], 63.6 (t), [63.8 (t)], 66.3 (d), 118.5 (s), [118.6 (s)], 128.1 (d), 128.85 (d), 132.3 (d), 133.5 (s), 143.3 (d), [166.85 (s)], 167.7 (s). Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.40; H, 5.95; N, 14.60.

C. Operating as above, the reaction product of **2a** with (*R*)-1-amino-2-propanol (**4c**) (0.038 g, 0.040 ml) afforded 2-benzoylamino-1-[(*R*)-2-hydroxypropylamino]-2-nitroethylene (**7c**) (0.114 g, 86%), m.p. 111-112°C dec (from AcOEt/ether); $[\alpha]^{21}_D$ = –30.2 (*c* 1.03, acetone); IR ν 3425, 3344, 3264, 1660, 1411, 1364, 1217 cm^{-1}; ^1H NMR δ 1.06 (d, *J* = 6.1 Hz), [1.09 (d, *J* = 6.0 Hz)], 3.10-3.45 (m), 3.62-3.88 (m), 4.83 (d, *J* = 4.7 Hz), [5.01 (d, *J* = 4.8 Hz)], 7.48-7.65 (m), 7.92-8.17 (m), 8.44 (d, *J* = 14.4 Hz), [9.35-9.62 (br m)], 9.59 (s), [9.81 (s)]; ^{13}C NMR δ 20.7 (q), [20.8 (q)], 55.3 (t), [55.95 (t)], [65.55 (d)], 66.0 (d), [115.4 (s)], 118.5 (s), 127.9 (d), 128.3 (d), 128.4 (d), 128.6 (d), 131.9 (d), 132.1 (s), 133.5 (s), 133.8 (d), 147.65 (d), [149.4 (d)], 165.9 (s), [167.2 (s)]. Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.20; H, 5.60; N, 16.05.

D. Chromatographic workup [petroleum ether/AcOEt (5:2 v/v) as eluent] of the crude reaction product of **2a** with the amine **4d** (0.062 g, 0.065 ml) gave 2-benzoylamino-2-nitro-1-[(*R*)-1-phenylethylamino]ethylene (**7d**) (R_f = 0.15, 0.109 g, 70%) as a pale yellow solid that, after crystallization from *n*-pentane/ether, gradually softened above 55°C and melted at 62-63°C; $[\alpha]^{24}_D$ = –119.8 (*c* 1.375, $CHCl_3$); IR ν 3286, 3065, 2978, 2940, 1650, 1479, 1261 cm^{-1}; ^1H NMR δ 1.54 (d, *J* = 7.0 Hz), [1.66 (d, *J* = 7.0 Hz)], 4.89 (sbr quintet, *J* = 7.0 Hz), 7.25-7.64 (m), [7.75 (d, *J* = 14.3 Hz)],

7.90-8.09 (m), 8.42-8.63 (m), 9.61 (s), [9.68 (sbr dd, J = 14.3 and 7.0 Hz)], [9.81 (s)]; ^{13}C NMR δ [21.8 (q)], 22.0 (q), 57.6 (d), [58.2 (d)], [115.75 (s)], 118.9 (s), 126.4 (d), 127.5 (d), 128.2 (d), 128.3 (d), 128.6 (d), 131.9 (d), 133.7 (s), 143.4 (s), 145.3 (d), [146.9 (d)], 165.9 (s), [167.1 (s)]. Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.70; H, 5.45; N, 13.70.

E. The residue of the reaction of **2a** with **4e** (0.065 g, 0.075 ml) was washed twice with *n*-pentane (2-3 ml) and dried to yield 2-benzoylamino-1-[(*R*)-1-cyclohexylethylamino]-2-nitroethylene (**7e**) (0.155 g, 98%), m.p. 113-114°C (from ether); $[\alpha]^{23}_D$ = –104.4 (*c* 0.935, $CHCl_3$); IR ν 3294, 3064, 2930, 2851, 1679, 1650, 1399, 1377, 1228 cm^{-1}; ^{1}H NMR δ 0.80-1.40 (m), 1.16 (d, J = 6.7 Hz), [1.26 (d, J = 6.7 Hz)], 1.55-1.82 (br m), 3.21-3.42 (m), [4.05-4.36 (m)], 7.45-7.68 (m), 7.80-8.05 (m), 8.43 (d, J = 14.3 Hz), [9.25-9.40 (br m)], 9.51 (s), [9.78 (s)]; ^{13}C NMR δ 18.4 (q), 25.7 (t), 26.0 (t), 28.8 (t), 29.0 (t), [42.7 (d)], 43.2 (d), 60.3 (d), [60.5 (d)], [115.2 (s)], 118.0 (s), 127.5 (d), 127.8 (d), 128.3 (d), 128.6 (d), 129.4 (d), 131.8 (d), 132.0 (s), 133.9 (s), 146.0 (d), [147.9 (d)], 165.7 (s), [167.0 (s)]. Anal. Calcd. for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.50; H, 7.15; N, 13.05.

F. The crude product obtained from **2a** and aminoacetaldehyde diethylacetal (**4f**) (0.068 g, 0.074 ml), was subjected to flash chromatography [petroleum ether/AcOEt (1:1 v/v) as eluent] to give 2-benzoylamino-1-(2,2-diethoxyethylamino)-2-nitroethylene (**7f**) (R_f = 0.2, 0.126 g, 78%). An analytical sample, obtained by crystallization from *n*-pentane/ether, gradually softened above 75°C and melted at 82-83°C; IR ν 3291, 3070, 2977, 2931, 1655, 1474, 1270, 1226, 1120, 1063 cm^{-1}; ^{1}H NMR δ 1.14 (t, J = 7.0 Hz), [1.15 (t, J = 7.0 Hz)], 3.42-3.77 (m), 4.49 (t, J = 5.2 Hz), [4.66 (t, J = 5.2 Hz)], 7.48-7.57 (m), 7.92-8.08 (m), 8.44 (d, J = 14.5 Hz), [9.38 (sbr dt, J = 14.5 and 7.0 Hz)], 9.60 (s), [9.81 (s)]; ^{13}C NMR δ 15.2 (q), 50.2 (t), [51.1 (t)], 62.45 (t), [100.65 (d)], 101.2 (d), [115.7 (s)], 118.8 (s), 127.8 (d), 128.2 (d), 128.3 (d), 128.6 (d), 131.9 (d), 132.05 (s), 133.4 (s), 133.6 (d), 147.5 (d), [149.3 (d)], 165.9 (s), [167.1 (s)]. Anal. Calcd. for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.50; H, 6.65; N, 13.25.

Ethyl (S)-2-[N-(2-benzoylamino-2-nitroethen-1-yl)amino]propionate (7g).

Triethylamine (0.052 g, 0.071 ml, 0.51 mmol) was added to the nitrooxazole **2a** (0.095 g, 0.5 mmol) and L-alanine ethyl ester hydrochoride (**4g**) (0.078 g, 0.51 mmol) in choroform (1.5 ml), and the mixture was stirred at room temperature for 24h. Chromatographic workup [petroleum ether/AcOEt (1:1 v/v) as eluent] of the yellow-brown residue left by removal of the solvent, gave compound **7g** (R_f = 0.36, 0.118 g, 77%) as a pale yellow semi-solid product. An analytical sample

was obtained by dissolution in anhydrous ether, filtration, evaporation to dryness and prolonged evacuation at room temperature (10^{-2} mmHg); $[\alpha]^{24}_D$ = +34.7 (*c* 1.075, $CHCl_3$); IR ν 3317, 3060, 2980, 2954, 1731, 1652, 1470, 1266 cm^{-1}; ^1H NMR δ 1.21 (t, *J* = 7.1 Hz), [1.23 (t, *J* = 7.1 Hz)], 1.39 (d, *J* = 7.2 Hz), [1.51 (d, *J* = 7.2 Hz)], 4.07-4.24 (m), 4.39-4.58 (m), 7.46-7.69 (m), 7.90-8.07 (m), 8.20 (sbr dd, *J* = 14.1 and 8.0 Hz), 8.48 (d, *J* = 14.1 Hz), [9.65 (sbr dd, *J* = 14.1 and 8.2 Hz)], 9.60 (s), [9.84 (s)]; ^{13}C NMR δ 14.0 (q), 17.6 (q), [18.2 (q)], 55.7 (d), [55.9 (d)], 61.1 (t), [61.3 (t)], [116.15 (s)], 119.4 (s), 127.7 (d), 128.2 (d), 128.3(d), 128.5 (d), 131.85 (d), 132.05 (d), 133.3 (s), 133.6 (s), 145.7 (d), [146.9 (d)], 165.8 (s), [167.1 (s)], [171.3 (s)], 171.7 (s). Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 55.05; H, 5.65; N, 13.50.

Reactions of the Nitroderivatives ***2a-c*** *with 1-Diethylaminopropyne* ***(8)****: Synthesis of Compounds* ***12a-c****. General Procedure.*

A solution of the nitrooxazole (0.5 mmol) and the ynamine (0.75 mmol) in chloroform (1.5 ml) was stirred at room temperature for 24h. Removal of the solvent under reduced pressure left a residue that was dried and subjected to flash chromatography with petroleum ether/AcOEt (3:1 v/v) as eluent.

A. Treatment of **2a** (0.095 g) with **8** (0.083 g, 0.102 ml) gave (*6SR, 6aSR*)-6,6a-dihydro-6-(*N,N*-diethylcarbamoyl)-6-methyl-2-phenyloxazolo[4,5-*c*]isoxazole (**12a**) (R_f = 0.47, 0.092 g, 61%) which crystallized from ether as colourless needles, m.p. 126-127°C ; IR ν 3060, 3029, 2982, 2944, 1628, 1539, 1355, 1327, 1294 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.57 (s, 3H), 3.12-3.82 (m, 4H), 6.35 (s, 1H), 7.45-7.68 (m, 3H), 8.12-8.17 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 12.3 (q), 14.4 (q), 16.2 (q), 41.0 (t), 42.3 (t), 91.8 (d), 96.75 (s), 125.85 (s), 128.8 (d), 129.6 (d), 134.3 (d), 167.8 (s), 179.1 (s), 180.65 (s). Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.90; H, 6.15; N, 13.70.

B. Reaction of **2b** (0.124 g) with **8** afforded methyl (*6SR, 6aSR*)-6,6a-dihydro-6-(*N,N*-diethylcarbamoyl)-6-methyl-2-phenyloxazolo[4,5-*c*]isoxazole-6a-carboxylate (**12b**) (R_f = 0.32, 0.093 g, 52%) as colourless needles, m.p. 181-182°C (from ether); IR ν 3071, 2986, 1770, 1625, 1544, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 3H), 3.22-3.54 (m, 3H), 3.71-3.94 (m, 1H), 3.75 (s, 3H), 7.45–7.70 (m, 3H), 8.18-8.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5 (q), 14.5 (q), 19.2 (q), 41.75 (t), 42.6 (t), 53.1 (q), 97.5 (s), 99.9 (s), 125.3 (s), 128.9

(d), 129.9 (d), 134.6 (d), 165.0 (s), 167.3 (s), 175.9 (s), 180.0 (s). Anal. Calcd. for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.05; H, 5.85; N, 11.75.

C. Treatment of **2c** (0.147 g) with **8** yielded (*6SR, 6aSR*)-6a-benzoyl-6,6a-dihydro-6-(*N,N*-diethylcarbamoyl)-6-methyl-2-phenyloxazolo[4,5-*c*]isoxazole (**12c**) (R_f = 0.33, 0.128 g, 63%) as a pale yellow solid that, after crystallization from ether, gradually darkened above 185°C and melted at 191.5-192°C ; IR ν 3060, 2972, 1692, 1621, 1541, 1292, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.77 (s, 3H), 3.06-3.49 (m, 3H), 3.73-3.91 (m, 1H), 7.32-7.62 (m, 6H), 7.96-8.06 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.3 (q), 14.6 (q), 19.7 (q), 41.5 (t), 42.6 (t), 101.7 (s), 102.9 (s), 125.2 (s), 127.8 (d), 128.8 (d), 129.5 (d), 129.9 (d), 132.5 (d), 134.3 (d), 135.4 (s), 167.1 (s), 176.8 (s), 178.0 (s), 196.0 (s). Anal. Calcd. for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.20; H, 5.75; N, 10.55.

Methyl(2SR, 3aSR, 6aRS, 8RS)-2,8-Diethoxyhexahydro-5-phenyl-1,6,9-trioxa-4,9a-diazacyclopent[d] indene-6a-carboxylate (15).

A solution of the nitroester **2b** (0.124 g, 0.5 mmol) and ethyl vinyl ether (0.754 g, 1 ml, 10.4 mmol) in anhydrous dichloromethane (2 ml) was stirred at 40°C for 11 days; evaporation to dryness under reduced pressure left a brown oily residue that was subjected to flash chromatography with petroleum ether/AcOEt 5:1 v/v as eluent. After the unreacted **2b** was obtained from the first band (R_f = 0.62, 0.065 g), the second one afforded compound **15** (R_f = 0.30, 0.071 g, 76% based on the recovered starting material) as a pale yellow semi-solid product. An analytical sample was obtained by dissolution in the above solvent, filtration, evaporation to dryness and rapid evacuation at room temperature (10^{-2} mmHg); IR ν 3060, 2979, 2940, 1744, 1647, 1448, 1330, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 2.17 (dd, *J* = 13.9 and 8.1 Hz, 1H), 2.21 (dd, *J* = 13.6 and 1.8 Hz, 1H), 2.56 (dd, *J* = 13.3 and 7.1 Hz, 1H), 2.75 (dd, *J* = 13.9 and 6.6 Hz, 1H), 3.47-3.78 (m, 3H), 3.82 (s, 3H), 3.87-4.02 (m, 1H), 5.12 (dd, *J* = 8.1 and 6.6 Hz, 1H), 5.86 (dd, *J* = 7.1 and 1.8 Hz, 1H), 7.35-7.56 (m, 3H), 7.96-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.0 (q), 15.1 (q), 33.8 (t), 39.9 (t), 52.9 (q), 63.3 (t), 65.45 (t), 86.0 (s), 97.4 (d), 104.7 (s), 110.35 (d) 126.0 (s), 128.2 (d), 129.0 (d), 132.4 (d), 164.8 (s), 170.2 (s). Anal. Calcd. for $C_{19}H_{24}N_2O_7$: C, 58.16; H, 6.16; N, 7.14. Found: C, 58.50; H, 6.30; N, 6.80.

5. Acknowledgement

Support of this work by Consiglio Nazionale delle Ricerche (CNR) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) is gratefully acknowledged.

6. References and notes

1. Part 2: Nesi, R.; Giomi, D.; Turchi, S. *J. Org. Chem.* **1998**, *63*, 6050.
2. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
3. van Eijk, P.J.S.S.; Overkempe, C.; Trompenaars, W.P.; Reinhoudt, D.N.; Manninen, L. M.; van Hummel, G. J.; Harkema, S. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 27.
4. (a) de Wit, A.D.; Trompenaars, W.P.; Reinhoudt, D.N.; Harkema, S.; van Hummel, G. J. *Tetrahedron Lett.* **1980**, 1779; (b) Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S.; Dapporto, P.; Paoli, P. *Tetrahedron Lett.* **1991**, *32*, 6223.
5. According to their *trans* arrangement, no positive NOE effect was observed between the vicinal methyl and hydrogen of **12a**.
6. For a comprehensive review on this topics, see: Denmark, S.E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
7. Attempts to isolate or detect this intermediate under milder conditions failed.
8. Unpublished results.
9. For the correct meaning of the stereochemical terminology, see reference 1.
10. Nesi, R.; Turchi, S.; Giomi, D. *J. Org. Chem.* **1996**, *61*, 7933.