1,3-Dipolar Cycloadditions of Nitrile Oxides with 4-Carbethoxymethyleno-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]oxadiazole

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The (*E*)- and (*Z*)-α,β-unsaturated esters, **3** and **4** are prepared by applying a Wittig reaction on the ketone **1**. Stable nitrile oxides are added to the stable (*E*)-isomer **3** resulting to the formation of the spiro-derivatives **7**, whereas with the unstable nitrile oxides a second stereoisomer **8** is also formed. Mesitonitrile oxide reacts also with the ketone **1** to give the spiro-cycloadduct **10**. The assignment of regio-isomers **7** was deduced from their spectral data as well as from some molecular orbital considerations.

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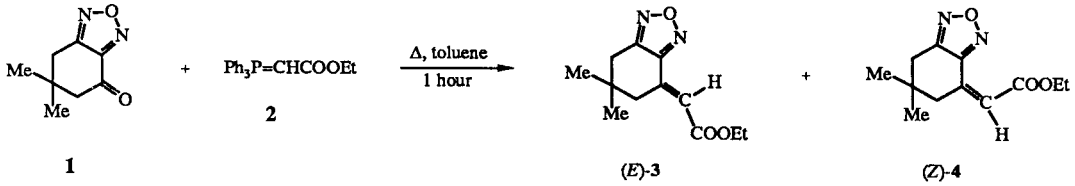
Nitrile oxides have been known to react with α,β-unsaturated carboxylic esters to give a mixture of 2-isoxazoline-4-carboxylic esters and 5-carboxylic esters [1], the regiochemistry of the products mainly being dictated by the substituent electronic effects and secondary by the nature of the nitrile oxide [1,2].

More recently, from the 1,3-dipolar cycloaddition reaction of β-(1-imidazolyl)-α,β-unsaturated carboxylic esters with acetonitrile oxide, the 3-(2-oxo-1-imidazolyl)-α,β-unsaturated carboxylic esters were isolated [3] through cycloaddition of the dipole to the relatively active C=N double bond of the imidazole instead to C=C double bond. On the other hand, 1,3-dipoles are known to add to ketone C=O bonds activated by adjacent electron withdrawing groups [4]. Cycloadditions of nitrile oxides with non-activated carbonyl compounds have been performed in the presence of boron trifluoride as catalyst [5].

It looked, therefore, interesting to investigate the possibility of 1,3-dipolar cycloadditon reactions between nitrile oxides and the α,β-unsaturated esters **3** and **4** and also the ketone **1** in order to examine the influence of the adjacent oxadiazole ring to the reactivity and regioselectivity of the cycloaddition.

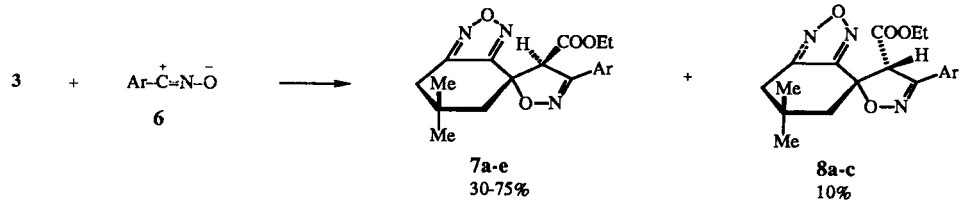
The α,β-unsaturated esters (*E*)-3 and (*Z*)-4 were prepared by applying a Wittig reaction on 4-oxo-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]oxadiazole (**1**) with phosphorus ylide **2** (Scheme 1). The reaction products **3** and **4** were separated by column chromatography and the major and faster moving component was assigned to the (*E*)-isomer **3** on account of the chemical shift of the C-5 methylene protons, which resonated in the ^{1}H nmr downfield (δ 3.05, as a slightly broadened singlet) due to the neighboring carbethoxy group. In addition, the vinylic proton being "adjacent" to the heterocyclic ring resonated downfield at δ 6.92. The minor and slower moving component (*Z*)-isomer **4** showed for the C-5 methylene protons an upfield singlet at δ 2.44 (slightly broadened) and a singlet at δ 6.14 for the vinylic proton. The C-7 methylene protons

Scheme 1



1 **2** (*E*)-**3** (*Z*)-**4**

Scheme 2



7a-e 30-75% **8a-c** 10%

a, Ar = Ph
b, Ar = 4-$CH_3C_6H_4$-
c, Ar = 4-ClC_6H_4-
d, Ar = 2,4,6-$(CH_3)_3C_6H_2$-
e, Ar = 2,6-$Cl_2C_6H_3$-

were observed, as expected, for both isomers at about δ 2.76.

The minor isomer **4** was unstable and was partially converted, even at room temperature, probably to the tautomeric isomer **5**, as deduced from spectral data and therefore no cycloaddition reactions were attempted with this isomer.

The major and stable (*E*)-isomer **3** reacted with a series of nitrile oxides **6a-e** to give the cycloadducts **7** (Table) in 30-75% yield (Scheme 2). However, after crystallization of **7a-c**, isolated from the reaction of (*E*)-**3** with the unstable nitrile oxides **6a-c**, the ^{1}H nmr of the residue showed the presence of a second minor stereoisomer **8** which was formed in less than 10% yield. This stereoisomer **8** could not be isolated in pure form and was examined as a mixture with **7**.

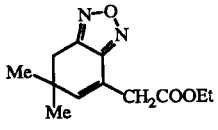
The formation of **8** could be attributed to a partial isomerization of (*E*)-**3** to (*Z*)-**4** because of the presence of triethylamine during the reaction process. This aspect is supported from a test experimental carried out on (*E*)-**3** which in the presence of triethylamine gave an 8:1 mixture of (*E*)-**3** and (*Z*)-**4**.

The assignment of **7** to the predominant stereoisomer was based on the chemical shift of the isoxazoline ring proton which was observed downfield at δ 4.69 for **7a**. It is also noted that the isoxazoline ring proton of **8a** was observed at δ 4.47.

The possible regioisomeric structure **9** could be excluded on the basis of the chemical shifts of the isoxazoline ring proton in comparison with analogous cycloadducts and furthermore its formation should be sterically hindered.

Table
Physical, Spectral and Analytical Data for the Spiro-cycloadducts **7** and **10**

Compound	Yield %	Mp °C	IR (Nujol) cm^{-1} νCO	^{1}H-NMR ppm (deuteriochloroform)	Formula (Molecular Weight)	Analysis % Calcd/Found C	H	N	MS, m/e (Relative Intensity, %)
7a	48	72-74	1730	1.15 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.16 (s, 6H, CMe_2), 2.09 and 2.25 (2 x d, J = 14.5 Hz, 2H, 7-CH_2), 2.57 and 2.94 (2 x d, J = 17.0 Hz, 2H, 5-CH_2), 4.20 (q, J = 8.0 Hz, 2H, CH_2CH_3), 4.69 (s, 1H, CH), 7.33-7.83 (m, 5H, ArH)	$C_{19}H_{21}N_3O_4$ (355.39)	64.21 64.14	5.96 6.08	11.82 11.79	355 (M^+, 3), 281 (3), 236 (1), 190 (7), 119 (100)
7b	52	156-158	1730	1.16 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.19 (s, 6H, CMe_2), 2.09 and 2.25 (2 x d, J = 14.5 Hz, 2H, 7-CH_2), 2.36 (s, 3H, *p*-Me), 2.57 and 2.93 (2 x d, J = 16.0 Hz, 2H, 5-CH_2), 4.21 (q, J = 8.0 Hz, 2H, CH_2CH_3), 4.66 (s, 1H, CH), 7.20 and 7.57 (2 x d, J = 8.5 Hz, 4H, ArH)	$C_{20}H_{23}N_3O_4$ (369.42)	65.03 65.00	6.26 6.22	11.37 11.24	369 (M^+, 100), 296 (43), 236 (4), 190 (10), 133 (46)
7c	29	125-127	1730	1.16 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.20 (s, 6H, CMe_2), 2.12 and 2.24 (2 x d, J = 13.5 Hz, 2H, 7 -CH_2), 2.59 and 2.92 (2 x d, J = 17.5 Hz, 2H, 5-CH_2), 4.21 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.65 (s, 1H, CH), 7.39 and 7.63 (2 x d, J = 8.0 Hz, 4H, ArH)	$C_{19}H_{20}ClN_3O_4$ (389.83)	58.54 58.45	5.17 5.12	10.78 11.00	391/389 M^+, 5), 318/316 (2), 236 (1), 190 (8), 155/153 (100)
7d	75	135-137	1740	1.06 (t, J = 6.5 Hz, 3H, CH_2CH_3), 1.17 (s, 6H, CMe_2), 2.03 and 2.35 (2 x d, J = 15.0 Hz, 2H, 7-CH_2), 2.26 (s, 3H, *p*-Me), 2.44 (s, 6H, *o*-Me), 2.53 and 2.92 (2 x d, J = 17.0 Hz, 5-CH_2), 4.04 (q, J = 6.5 Hz, 2H, CH_2CH_3), 4.96 (s, 1H, CH), 6.89 (s, 2H, ArH)	$C_{22}H_{27}N_3O_4$ (397.48)	66.48 66.60	6.85 7.00	10.57 10.63	397 (M^+, 1), 323 (1), 236 (2), 190 (6) 161 (100)
7e	77	97-99	1725	1.04 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.16 and 1.20 (2 x s, 2 x 3H, CMe_2), 1.99 and 2.33 (2 x d, J = 14.5 Hz, 2H, 7-CH_2), 2.52 and 2.94 (2 x d, J = 17 Hz, 2H, 5-CH_2), 4.06 (q, J = 7.0 Hz, 2H, CH_2CH_3), 5.52 (s, 1H, CH), 7.28-7.53 (m, 3H, ArH)	$C_{19}H_{19}Cl_2N_3O_4$ (424.28)	53.79 53.70	4.51 4.58	9.90 10.03	427/425/423 (M^+, 8), 354/352/350 (7), 236 (100), 190 (58), 191/189/187 (5)
10	92	93-94	–	1.13 and 1.19 (2 x s, 2 x 3H, CMe_2), 2.28 (s, 3H, *p*-Me), 2.32 (s, 2H, 5-CH_2), 2.42 (s, 6H, *o*-Me), 2.78 (s, 2H, 7-CH_2), 6.93 (s, 2H, ArH)	$C_{18}H_{21}N_3O_3$ (327.38)	66.04 65.78	6.47 6.24	12.84 12.78	327 (M^+, 24), 166 (100), 161 (11), 146 (45)



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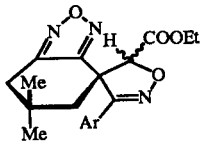


9

The observed chemical shifts for the isoxazoline ring protons in **7a** and **8a** are very similar to those reported in the literature [6,7] for analogous systems. In addition, the isoxazoline ring proton of **9** would resonate at about δ 5.50 [6,7].

Frontier molecular orbital considerations of the reacting systems also favor formation of the regio-isomer **7**. Assuming that the cycloaddition of nitrile oxides is LUMO-dipole controlled reaction [8], the orbital coefficient of the bis-substituted ethylene carbon atom in the HOMO of the dipolarophile should be smaller than the coefficient of the carbon bearing the carbethoxy group. Thus, the preferred orbital interactions must be similar to that illustrated in the Figure, leading to the proposed regioisomer **7**. The same regioselectivity was also observed in several other cycloadditions [9].

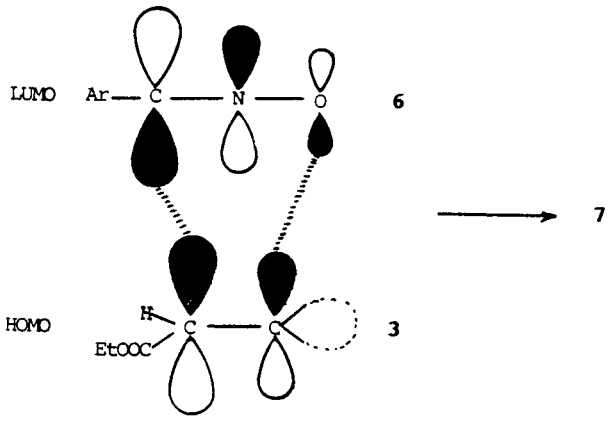
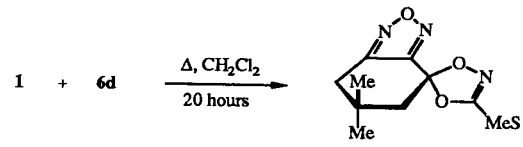


Figure. Preferred HOMO-LUMO interactions between **3** and **6**.

From the above cycloadditions with nitrile oxides it can be concluded that the reactivity of the ester (*E*)-**3** is reduced compared to methyl crotonate and methyl cinnamate [1] and the oxygen atom of the dipole preferentially attacks the bis-substituted ethylene carbon atom, leading to 4-carbethoxy-spiro-isoxazolines **7**. It is also mentioned that in the cycloaddition of benzonitrile oxides with methyl crotonates and cinnamates the regioisomeric ratio of 4- and 5-isoxazoline carboxylates was found [1] approximately 7:3.

Finally, the dipolarophility of the starting ketone **1**, towards nitrile oxides **6** was also examined and was found that **1** was unreactive and only with mesitonitrile oxide **7d**, a spiro dioxazoline cycloadduct **10** was isolated in 92% yield (Scheme 3).

Scheme 3



10

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 297 spectrophotometer. The ^{1}H nmr spectra, reported in δ units, were recorded with a Bruker AW 80 spectrometer with tetramethylsilane as internal standard in deuteriochloroform solutions. Mass spectra were obtained at 70 eV using a Hitachi-Perkin-Elmer RMU-6L mass spectrometer. Elemental analysis were performed with a Perkin-Elmer 240B CHN analyzer. Silica gel (Merck 60, 70-230 mesh) was used for the column chromatography.

Literature procedures were followed in the preparation of 4-oxo-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]oxadiazole **1** [10,11], (carbethoxymethyleno)triphenylphosphorane **2** [12], mesitonitrile oxide **6d** and 2,6-dichlorobenzonitrile oxide **6e** [13]. Benzonitrile oxide **6a**, 4-methylbenzonitrile oxide **6b** and 4-chlorobenzonitrile oxide **6c** were prepared *in situ* from the corresponding *N*-phenylbenzohydrazonoyl chlorides [14] and triethylamine.

4-Carbethoxymethyleno-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*]-[1,2,5]oxadiazoles (*E*)-**3** and (*Z*)-**4**.

A stirred solution of **1** (3.65 g, 22 mmoles) and **2** (8.7 g, 25 mmoles) was refluxed in dry toluene (250 ml) for 1 hour. After evaporation of the solvent the gummy residue was chromatographed (*n*-hexane-ethyl acetate 20:1) to give in elution order:

Compound (*E*)-**3** had mp 45-47° (3.65 g, 70%); ir (Nujol): 1720, 1710, 1640 cm^{-1}; ^{1}H nmr: δ 1.04 (s, 6H, CMe_2), 1.32 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.76 (s, 2H, 7-CH_2), 3.05 (s, 2H, 5-CH_2), 4.23 (q, J = 7.0 Hz, 2H, CH_2CH_3), 6.92 (s, 1H, CH); ms: m/z 236 ($M^{+\cdot}$, 31), 221 (13), 190 (25), 175 (32), 162 (100).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.12; H, 7.02; N, 12.01.

Compound (*Z*)-**4** was an oil (1.05 g, 20%); ir (Nujol): 1740, 1660 cm^{-1}; ^{1}H nmr: δ 1.06 (s, 6H, CMe_2), 1.31 (t, J = 8.0 Hz, 3H, CH_2CH_3), 2.44 (s, 2H, 5-CH_2), 2.77 (s, 2H, 7-CH_2), 4.29 (q, J = 8.0 Hz, 2H, CH_2CH_3), 6.14 (s, 1H, CH); ms: m/z 236 ($M^{+\cdot}$, 31), 221 (12), 190 (32), 175 (22), 162 (100).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.98; H, 6.86; N, 11.84.

The slower moving and minor isomer (*Z*)-**4** was unstable and was converted by standing at room temperature to a 1:1 mixture with the tautomeric compound **5**. Complete conversion to **5** was achieved by refluxing a chloroform solution of (*Z*)-**4** for 30 hours.

Compound **5** had ir (Nujol): 1730, 1720 cm^{-1}; ^{1}H nmr: δ 1.06 (s, 6H, CMe_2), 1.23 (t, J = 8.0 Hz, 3H, CH_2CH_3), 2.87 (s, 2H, 7-CH_2), 3.40 (s, 2H, 5-CH_2), 4.15 (q, J = 8.0 Hz, 2H, CH_2CH_3), 6.02 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.95; H, 6.89; N, 11.92.

General Procedure for the Reaction of 4-(Carbethoxymethyleno)-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]oxadiazole (*E*)-**3** with the Unstable Nitrile Oxides **6a-c**.

To a solution of the carbethoxymethylenooxadiazole (*E*)-**3** (0.47 g, 2 mmoles) and hydrazonoyl chloride (2 mmoles) in dry dichloromethane (30 ml), triethylamine (0.2 g, 2 mmoles) was added slowly under stirring. The reaction mixture was stirred for 24 hours at 25°, while additional quantities of hydrazonoyl chloride (2 mmoles) and triethylamine (2 mmoles) were added every 8 hours. The solution was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The gummy residue was chromatographed on a silica gel column (eluted with a mixture of *n*-hexane-ethyl acetate 10:1) to give a mixture of the stereoisomers **7** and **8**. By addition of ether-*n*-hexane to the stereoisomeric mixture the major stereoisomer **7** was crystallized. However, it was not possible to obtain from the remaining mixture, pure samples of the minor isomer **8**, therefore it was examined as a mixture with **7**. Analytical and spectral data of **7** are given in the Table.

The selected ^{1}H nmr spectral data of **8**, given below, were deduced after substraction of the peaks corresponding to **7**, whereas elemental analyses refer to the isomeric oily mixtures of **7** and **8**.

Compound **8a** was obtained in 8% yield; ^{1}H nmr: δ 1.12 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.16 (s, 6H, CMe_2), 2.62 and 2.82 (2 x d, J = 16.0 Hz, 5-CH_2), 4.01 (q, J = 8.0 Hz, 2H, CH_2CH_3), 4.47 (s, 1H, CH).

Anal. Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.48; H, 6.20; N, 12.00.

Compound **8b** was obtained in 11% yield; ^{1}H nmr: δ 1.16 (t, J = 8.0 Hz, 3H, CH_2CH_3), 1.19 (s, 6H, CMe_2), 2.36 (s, 3H, *p*-Me), 2.62 and 2.81 (2 x d, J = 17.5 Hz, 2H, 5-CH_2), 4.04 (q, J = 8.0 Hz, 2H, CH_2CH_3), 4.48 (s, 1H, CH).

Anal. Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.26; N, 11.37. Found: C, 65.25; H, 6.07; N, 11.21.

Compound **8c** was obtained in 5% yield; ^{1}H nmr: δ 1.16 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.20 (s, 6H, CMe_2), 2.64 and 2.84 (2 x d, J = 17.0 Hz, 2H, 5-CH_2), 4.03 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.48 (s, 1H, CH).

Anal. Calcd. for $C_{19}H_{20}ClN_3O_4$: C, 58.54; H, 5.17; N, 10.78. Found: C, 58.27; H, 5.10; N, 10.95.

The stereoisomers **7a** and **8a** were also prepared [15] in 68% and 13% respectively, as follows: To an ether solution of the ester (*E*)-**3** (0.47 g, 2 mmoles) was added dropwise a solution of benzonitrile oxide (2 mmoles) in ice-cooled ether. The reaction mixture was then stirred at 20° for 24 hours, washed twice with water, dried with sodium sulfate and the solvent was evaporated. Crystallization of **7a** was achieved by addition of ether-*n*-hexane. Additional amounts of **7a** as mixture with **8a** remained in the filtrate.

General Procedure for the Reaction of 4-(Carbethoxymethyleno)-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]oxadiazole (*E*)-**3** with the Stable Nitrile Oxides **6d,e**.

A solution of carbethoxymethylenooxadiazole (*E*)-**3** (0.7 g, 3 mmoles) and nitrile oxides **6d,e** (3-10 mmoles) in dry dichloromethane (15 ml) was refluxed for 25 hours hours until tlc control experiments did not show the presence of free nitrile oxide. Then the dichloromethane solution was washed with water, dried over sodium sulfate and the solvent was removed *in vacuo*. From the residue the cycloaddition product **7** was crystallized by addition of ether-*n*-hexane mixture. Analytical and spectral data are summarized in the Table.

Reaction of 4-Oxo-4,5,6,7-tetrahydro-6,6-dimethylbenzo[*c*][1,2,5]-oxadiazole **1** with Mesitonitrile Oxide **6d**.

A solution of ketone **1** (0.33 g, 2 mmoles) and mesitonitrile oxide **6d** (0.97 g, 6 mmoles) in dry dichloromethane (15 ml) was refluxed for 20 hours until tlc control experiments did not show the presence of free mesitonitrile oxide. The mixture was then washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the gummy residue was recrystallized from ethanol giving the cycloaddition product **10**. Analytical and spectra data of **10** are given in the Table.

Partial Isomerization of (*E*)-**3** to (*Z*)-**4** in Triethylamine Solution.

Carbethoxymethylenooxadiazole (*E*)-**3** (0.24 g, 1 mmole) was added to a 10% solution of triethylamine in dry dichloromethane (10 ml) and the mixture remained under stirring at 25° for 25 hours. Then the mixture was washed with water, dried over sodium sulfate and the solvent was evaporated under reduced pressure. ^{1}H nmr of the residue showed that it was an 8:1 mixture of (*E*)-**3** and (*Z*)-**4**.

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