Tetraacetylethylene and Nitrile Oxides: Synthesis of Spirofuranisoxazoles

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trans and *cis*-3-Hexen-2,5-dione, **2**, reacted with nitrile oxides to give 4,5-dihydroisoxazoles **3a-c** with the *trans* configuration. On the contrary the reaction between 3,4-diacetyl-3-hexen-2,5-dione, **1**, with nitrile oxides yielded 3-aryl-8,9-diacetyl-7-hydroxy-7-methyl-1,6-dioxa-2-azaspiro[4.4]nona-3,8-dienes **9a-e**. The reaction is completely regiospecific. The cycloadducts show ring-open chain tautomerism.

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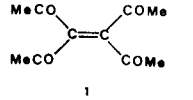
Alkenes bearing electron withdrawing groups easily react with 1,3-dipoles to give cycloadducts which can turn into aromatic systems. Thus 3,4-diacetyl-3-hexen-2,5-dione or tetraacetylethylene, **1**, and 3-hexen-2,5-dione or diacetylethylene, **2**, reacted with nitrilimines to give the corresponding acetylpyrazoles [1].

The behaviour of the ketone **2** with nitrile oxides is completely analogous giving the dihydroisoxazoles **3a-c**. In the ^{1}H-nmr spectra the coupling constants are diagnostic in the structural assignments, since for all isoxazolines the $J_{4,5}$ value is in the range 4.3-6.0 Hz and is consistent with the hitherto reported values for *trans* protons in 4,5-dihydroisoxazoles [2,3]. The *cis* isomers show larger $J_{4,5}$ values.

Starting both from *cis*- and *trans*-diacetylethylene **2a** and **2b**, we isolated only the *trans*-cycloadducts **3a-c**. Since the 1,3-dipolar cycloadditions are stereospecific, this result demonstrates that in every case an isomerisation takes place, which leads to the more stable isomer. The 4,5-dihydroisoxazoles **3a-c** are not very stable but they change into the aromatic isoxazoles **4** and **5**. The rate of this transformation is influenced by the nature of the arylnitrile oxide: in fact in the case of the 2,6-dichlorobenzonitrile oxide the isoxazoline **3c** is not stable enough to be purified, while in the case of 4-chlorobenzonitrile oxide **3a** we could not find a trace of the corresponding aromatic isoxazoles **4a** and **5a**. Compound **3b** has an intermediate behaviour: all the three products were isolated and characterized.

Scheme 1



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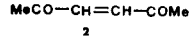

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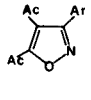
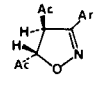


4 a-c



3 a Ar = 4-ClC$_6$H$_4$
b Ar = 4-NO$_2$C$_6$H$_4$
c Ar = 2,6-Cl$_2$C$_6$H$_3$

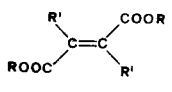
5 a-c

The ^{1}H-nmr spectra of the isoxazoles **4b** and **4c** show, beside the aromatic protons, only the methyl signals of the acetyl groups, while those of the monoacetylisoxazoles **5b** and **5c** are characterized by the presence of a signal at δ 9.1 diagnostic of 5-unsubstituted isoxazoles.

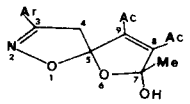
Tetrasubstituted alkenes such as tetracarbethoxy- **6** and diacetyldicarbethoxyethylene **7** do not react with nitrile oxides, possibly as a consequence of steric hindrance, even if it cannot be excluded an electronic effect. Contradicting data are reported in the literature for the planar tetracyanoethylene. While a paper [4a] states that 2,4,6-trimethylbenzonitrile oxide reacts with tetracyanoethylene giving the corresponding isoxazole, another paper [4b] reports that nitrile oxides react with the cyano groups giving oxadiazole derivatives.

Although tetraacetylethylene **1** is a nonplanar tetrasubstituted alkene [5,6], it reacts with nitrile oxides **8a-e**, but it did not give the expected isoxazoles. The cycloadducts obtained were assigned the structure of 3-aryl-8,9-diacetyl-7-hydroxy-7-methyl-1,6-dioxa-2-azaspiro[4.4]nona-3,8-dienes **9a-e** on the basis of spectral data and chemical behaviour.

Scheme 2



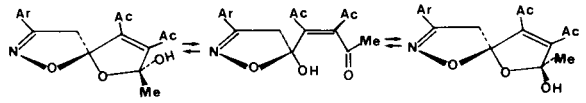
6 R' = COOR
7 R' = COMe



9 a Ar = 4-ClC$_6$H$_4$
b Ar = 4-NO$_2$C$_6$H$_4$
c Ar = 2,6-Cl$_2$C$_6$H$_3$
d Ar = 4-MeC$_6$H$_4$
e Ar = C$_6$H$_5$

The ir spectra show strong bands at *ca.* 3400, 1690 and 1640 cm^{-1} attributable to OH, CO and C=C groups respectively. The nmr spectra display the presence of an equilibrium mixture of two diastereoisomers. The equilibrium position is reached within a few minutes. For instance in the case of **9a** in deuteriochloroform the ratio between the two diastereoisomers **A** and **B** is 69:31, while in hexadeuteriodimethyl sulphoxide it is 55:45. The open form **C** could not be detected.

Scheme 3



9A 9C 9B

The main isomer **A** shows three singlets at δ 1.65, 2.34 and 2.54 attributable to the three methyl groups, an AB system at δ 3.64 (J = 17.8 Hz), a broad singlet at 3.80 for the OH group and AA'BB' system at 7.47 (J = 8.7 Hz) for the aromatic ring.

On the basis of the chemical shift of the methylene group (δ = 3.6-3.7) for all cycloadducts **9a-e** we discarded the regioisomer **10** for which a value at lower field is expected (δ = 4.3-4.4). The 5*RS*,7*SR* stereochemistry for the main diastereoisomer is revealed by the higher shift of the methyl group at 7-position (δ = 1.65) which is a direct result of the influence of the oxygen atom of the isoxazoline ring. Molecular models indicate that the stereoisomers **A** show minor strain than the isomer **B** where there is some congestion between the methyl group at 7 position and the isoxazoline methylene group.

The observed regioselectivity may be explained in terms

Table 1

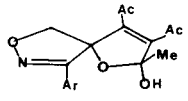
Analytical and Spectral Data of Compounds **3-5, 9, 13-16**

Compound	Yield %	Mp (°C) solvent	Formula	Analysis % Calcd./Found C	H	N	Cl	OH	IR, ν (cm⁻¹); CO	UV λ max (log ε)
3a	41	68-69 ether	$C_{13}H_{12}NClO_3$	58.76 59.01	4.52 4.55	5.27 5.26	28.44 28.02		1710	
3b	30	126-128 ether	$C_{13}H_{12}N_2O_5$	56.52 56.41	4.35 4.37	10.14 10.22			1720	
4b	10	122-125 ether	$C_{13}H_{10}N_2O_5$	56.93 56.52	3.65 3.40	10.22 10.44			1700, 1680	
4c	35	93-97 cyclohexane	$C_{13}H_9NCl_2O_3$	52.35 52.74	3.02 3.31	4.70 4.41	23.83 23.55		1710, 1680	
5c	40	118-120 ether	$C_{11}H_7NCl_2O_2$	51.56 51.58	2.73 2.60	5.47 5.22	27.73 27.41		1680	
9a	93.7	128-120 ether	$C_{17}H_{16}NClO_5$	58.37 58.14	4.58 4.57	4.01 3.97	10.16 9.78	3410	1690	
9b	95.1	165-168 benzene	$C_{17}H_{16}N_2O_7$	56.62 56.99	4.44 4.46	7.77 7.75		3410	1690	297 (3.90)
9c	88.8	178-180 benzene	$C_{17}H_{15}NCl_2O_5$	53.12 53.37	3.91 3.82	3.65 3.97	18.49 18.31	3410	1700	268 (4.20)
9d	82.5	119-122 ether	$C_{18}H_{19}NO_5$	65.64 65.85	5.81 5.84	4.25 4.06		3370	1690	260 (3.87)
9e	82.5	100-102 ether	$C_{17}H_{17}NO_5$	64.76 65.02	5.40 5.48	4.44 4.34		3340	1695	
13a	25	122-124 cyclohexane	$C_{19}H_{18}NClO_6$	58.24 58.06	4.60 4.45	3.58 3.82	9.07 8.91		1760, 1710	
13b	20	128-130 ether	$C_{19}H_{18}N_2O_8$	56.72 56.55	4.48 4.47	6.97 6.83			1750, 1700	
14a	24	92-94 ether	$C_{19}H_{18}NClO_6$	58.24 58.06	4.60 4.45	3.58 3.82	9.07 8.91		1750, 1690	
14b	19	47-49 ether	$C_{19}H_{18}N_2O_8$	56.72 56.68	4.48 4.41	6.97 6.72			1740, 1690	
15a	5	105-107 ether	$C_{19}H_{16}NClO_5$	61.04 60.72	4.28 4.20	3.75 3.78	9.50 9.29		1760, 1710	
15b	5	134-137 ether	$C_{19}H_{16}N_2O_7$	59.38 59.29	4.17 4.08	7.29 7.05			1760, 1705	
16a	7	102-104 ether	$C_{21}H_{20}NClO_7$	58.13 58.12	4.61 4.58	3.23 3.14	8.19 8.35		1760, 1740, 1695	
16b	8	128-130 ether	$C_{21}H_{20}N_2O_9$	56.76 56.50	4.50 4.38	6.31 6.20			1760, 1740, 1700	

of the relative magnitudes of the coefficients in the LUMO's and HOMO's of the 1,3-dipole and the dipolarophile, and is consistent with literature data [6,7].

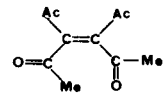
In these cycloaddition reactions no evidence for spiro adducts of type **10** or for cyclo adducts such as **11** could be obtained.

Scheme 4

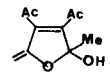


10

11



1



12

Formation of the spiro adducts **9** can be rationalized if we admit an equilibrium between tetraacetylethylene and the tautomeric cyclic form **12**. We have already hypothesized this intermediate **12** to justify the behaviour of the tetraketone **1** in various reactions [7,8]. Our efforts to isolate or to detect compound **12** by means of spectroscopic techniques were unsuccessful. The formation of com-

Table 2

^{1}H-nmr spectra of Compounds **3-5, 9, 13-16** [a]

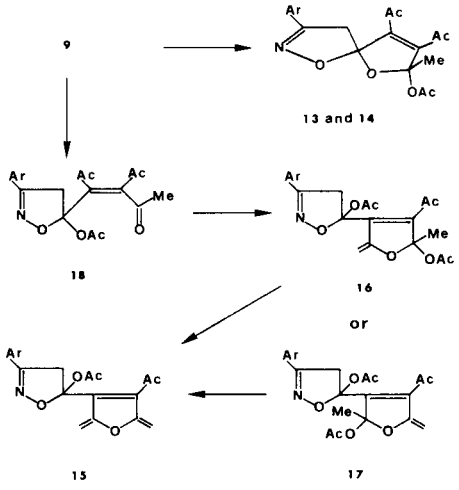
Compound	% [b]	Me	Ac	CH_2	CH	Ar	OH
3a			2.21, 2.38		4.80 (d, J = 4.3) 5.15 (d, J = 4.3)	7.50 (AA'BB', J = 9.0)	
3b			2.29, 2.42		4.94 (d, J = 4.3) 5.27 (d, J = 4.3)	8.06 (AA'BB', J = 9.0)	
3c			2.03, 2.43		4.95 (d, J = 6.0) 5.60 (d, J = 6.0)	7.42	
4b			2.59, 2.74			8.08 (AA'BB', J = 9.0)	
4c			2.55, 2.77			7.38	
5b			2.42		9.16	8.08 (AA'BB', J = 9.0)	
5c			2.35		9.13	7.39	
9aA	69	1.65	2.34, 2.54	3.64 (AB, J = 17.8)		7.47 (AA'BB', J = 8.7)	3.80
9aB	31	1.84	2.37, 2.48	3.61 (AB, J = 17.8)		7.47 (AA'BB', J = 8.7)	3.80
9bA	78	1.67	2.35, 2.57	3.71 (AB, J = 18.0)		8.06 (AA'BB', J = 9.0)	3.66
9bB	22	1.86	2.38, 2.51	3.63 (AB, J = 18.3)		8.06 (AA'BB', J = 9.0)	3.66
9cA	65	1.67	2.40, 2.52	3.59 (AB, J = 17.8)		7.37 (m)	3.75
9cB	35	1.84	2.35, 2.46	3.59 (AB, J = 18.7)		7.37 (m)	3.75
9dA	70	1.65, 2.39	2.34, 2.53	3.66 (AB, J = 17.6)		7.38 (AA'BB', J = 8.0)	3.54
9dB	30	1.83, 2.39	2.38, 2.48	3.63 (AB, J = 17.4)		7.38 (AA'BB', J = 8.0)	3.54
9eA	65	1.64	2.33, 2.53	3.67 (AB, J = 18.0)		7.28-7.57 (m)	3.91
9eB	35	1.83	2.36, 2.46	3.65 (AB, J = 18.0)		7.28-7.57 (m)	3.91
13a		1.88	2.10, 2.38, 2.41	3.63 (AB, J = 18.0)		7.48 (m)	
13b		1.90	2.14, 2.30, 2.46	3.69 (AB, J = 18.4)		8.05 (AA'BB', J = 9.0)	
14a		1.79	2.05, 2.33, 2.37	3.70 (AB, J = 18.2)		7.50 (AA'BB', J = 9.0)	
14b		1.82	2.08, 2.36, 2.40	3.77 (AB, J = 18.9)		8.07 (AA'BB', J = 9.0)	
15a			2.09, 2.53	3.73 (AB, J = 18.1)	5.26 (q, J = 2.3) 4.32 (d, J = 3.0) 4.66 (d, J = 3.0)	7.53 (AA'BB', J = 9.0)	
15b			2.11, 2.55	3.75 (AB, J = 19.0)	5.26 (q, J = 2.4) 4.30 (d, J = 3.1) 4.70 (d, J = 3.1)	8.06 (AA'BB', J = 9.0)	
16a		1.84	2.07, 2.08, 2.48	3.70 (AB, J = 18.4)	5.24 (q, J = 1.6)	7.50 (AA'BB', J = 8.7)	
16b		1.85	2.08, 2.09, 2.50	3.78 (AB, J = 18.6)	5.25 (q, J = 2.1)	8.07 (AA'BB', J = 9.0)	

[a] The signals are singlets, unless otherwise stated. [b] Isomeric ratios of the two diastereoisomers **A** and **B** calculated from nmr spectra.

pounds **9** demonstrate the presence of **12** in solution since it is trapped by the nitrile oxides.

Some attempts were made in order to trap the two tautomers **A** and **B**. The reaction of the spiro adducts **9a** and **9b** with acetic anhydride in the presence of traces of *N,N*-dimethyl-4-aminopyridine gave rise to a mixture of four compounds which were separated by column chromatography. The slowest compounds, which accounted for *ca.* 25% and 20% yield respectively, were assigned the structures **13** and **14**. The minor components of the mixture which account for *ca.* 5% and 7% yield respectively, were tentatively assigned the structures **15** and **16** or **17** on the basis of analytical and spectral data.

Scheme 5



The mechanism for the formation of compounds **13-16** (or **17**) may be rationalised keeping in mind ring-chain tautomerism. The acetic anhydride reacts with the closed form yielding the stereoisomers **13** and **14** and with the open form leading to the intermediate **18**. This intermediate may behave as tetraacetylethylene giving rise to a ring closure to yield compound **16** or **17**: both can lose water by acetic anhydride action to give compound **15**.

Table 3

^{13}C-NMR Spectra of Compounds **9b**, **9c**, and **9e** [a]

	9b [b]	**9c** [b]	**9e** [c]
Me	25.8, 26.7, 29.2 29.5, 30.2, 30.4	25.8, 26.8, 29.1 29.4, 30.1, 30.4	25.0, 26.9, 29.8 30.0, 30.3, 30.4
C-4	42.4, 42.6	45.1, 45.3	43.1, 43.5
C-7	106.8, 107.9	106.7, 107.8	107.1, 108.0
C-5	114.8, 115.3	114.1, 114.6	114.6, 114.8
C-Ar	124.0-148.3	127.3-133.9	126.9-130.9
C-8, C-9	135.1, 135.3 152.6, 152.9	134.9, 135.0 152.8, 153.1	137.3, 140.9 148.1, 150.9
C-3	156.7, 156.8	154.9, 155.0	158.1, 158.3
CO	185.4, 195.6 198.8, 199.1	195.2, 195.4 198.8, 199.0	196.5, 197.3 198.3, 198.6

[a] They are a mixture of the diastereoisomers **A** and **B**. [b] In DMSO-d_6. [c] In deuteriochloroform.

EXPERIMENTAL

Melting points were taken on a Kofler melting point apparatus and are uncorrected. Unless otherwise stated, the ^{1}H-nmr spectra were recorded for deuteriochloroform solutions with a Hitachi-Perkin-Elmer apparatus R-600 instrument and ^{13}C-nmr spectra with a Varian FT-80 A spectrometer; chemical shifts (J in Hz) are reported downfield from internal tetramethylsilane. The ir spectra were recorded on a Perkin-Elmer 782 spectrophotometer using samples in potassium bromide pellets.

Materials.

The nitrile oxides were prepared by conventional methods [3]. The following compounds were prepared by the literature procedure cited: tetraacetylethylene, **1** [2], *cis*-and *trans*-diacetylethylene **2**, [9], 2,3-diacetylfumarate, **7**, [10]. Ethene-1,1,2,2-tetracarboxylate, **6**, was purchased from Fluka.

General Procedure of the Reaction of Aryl Nitrile Oxides **8a-c** with Diacetylethylene **2**.

To a solution of diacetylethylene **2** (2.6 mmoles) in methylene chloride (10 ml) was slowly added a solution of the arylnitrile oxide **8a-c** (2.6 mmoles) in methylene chloride (6 ml). The mixture was refluxed for 7 hours. The solution was evaporated to give a residue which was resolved by column chromatography using petroleum ether containing an increasing amount of ether as eluent. Compounds **3a-c**, **4b,c**, and **5b,c**, were obtained and further purified by recrystallization (see Table 1 and Table 2 for analytical and spectral data).

General Procedure of the Reaction of Arylnitrile Oxides **8a-e** with Tetraacetylethylene **1**.

To a solution of tetraacetylethylene **1** (5 mmoles), in methylene chloride (30 ml), was slowly added a solution of the arylnitrile oxide **8a-e** (5 mmoles) in methylene chloride (20 ml) at 0°. The solution was stirred at room temperature for 24 hours. The solution was evaporated to give a residue which was crystallized to yield the cycloadducts **9a-e** (see Table 1, Table 2, and Table 3 for analytical and spectral data).

Tables 1-3

General Procedure of the Reaction of the Cycloadducts **9a** and **9b** with Acetic Anhydride.

To a solution of the cycloadducts **9a** and **9b** (2.86 mmoles) in triethylamine (3.9 mmoles) was added 4,4-dimethylaminopyridine (0.1 mmole) followed by acetic anhydride (5.8 mmoles). The mixture was stirred at room temperature for 1 hour and basified with a solution of sodium carbonate. The solution was extracted with chloroform and the extracts were dried and evaporated. Column chromatography of the residue, eluted with ether-petroleum ether mixture first in a ratio 2:1, then in a ratio 1:1, gave in order of mobility compounds **15**, **16**, **13**, and **14** (see Table 1 and Table 2 for analytical and spectral data).

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