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MESOIONIC TRIFLUOROACETYLATED 5-IMINO OXAZOLINES: A RE-EXAMINATION OF THE STRUCTURE USING ^{13}C NMR SPECTROSCOPY AND CYCLOADDITION REACTIONS

D. CLERIN, B. MEYER and J. P. FLEURY*
Laboratoire de Chimie Organique Générale,† Ecole Supérieure de Chimie, 68093 Mulhouse-Cedex, France

and

H. FRITZ
Ciba-Geigy AG, Basel, Switzerland

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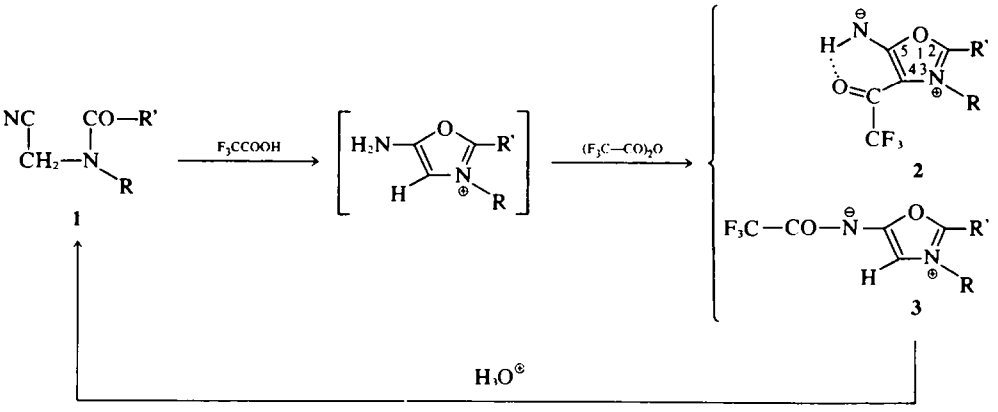
Abstract—The position of the trifluoroacetyl group in mesoionic 2,3-diaryl-5-imino oxazolines has been disputed. The natural abundance ^{13}C NMR spectra and the 1,3-dipolar cycloaddition product of the mesoionic oxazoline with the dimethylacetylenedicarboxylate are compatible with a structure in which the trifluoroacetyl group is bonded to the exocyclic 5-imino nitrogen.

Cyclisation of α-acylaminonitriles **1** in the presence of a mixture of trifluoroacetic acid and trifluoroacetic anhydride leads to acylated derivatives of mesoionic 5-imino oxazolines. This reaction was first described by Roesler and Fleury[1] who proposed a C-acylated structure **2** and later by Götz and Zeile[2] who assigned a N-acylated structure **3**.

However, none of these properties allows the structure of the product to be assigned unambiguously. Thus the absorption band at 3166 cm^{-1} may correspond to the νC_4–H of structure **3** already reported for related compounds,[3-5] but may also be explained equally well by the intramolecularely H-bonded νN–H of structure **2**. Various trifluoroacetamides **4–5** and trifluoromethyl-



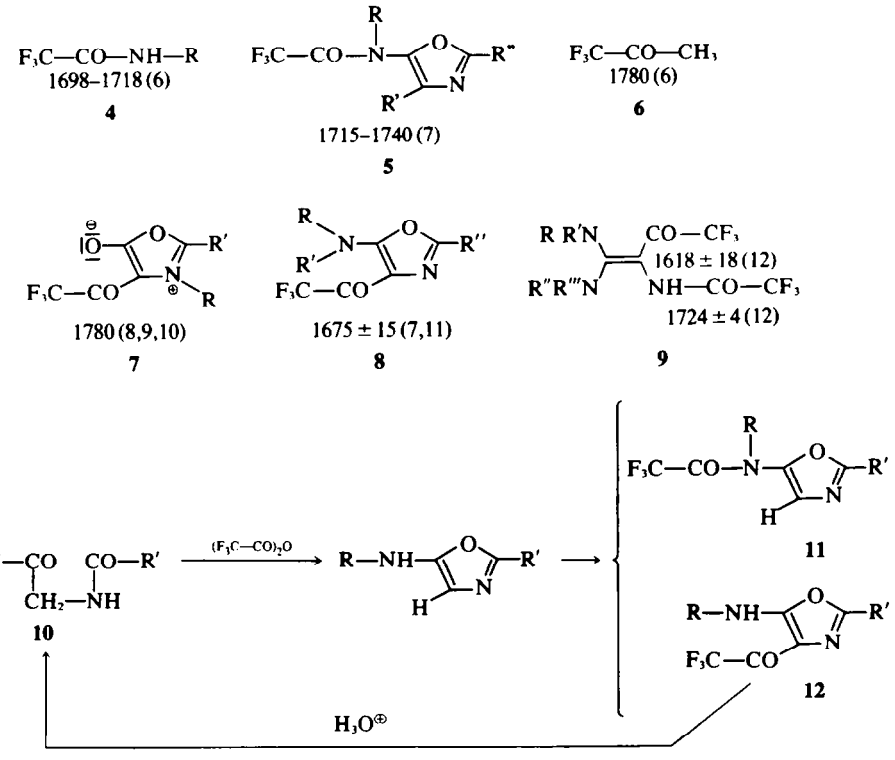
	R	R'	ref.
1a, 2a, 3a	CH_3	p-O_2N-C_6H_4	(this issue)
1b, 2b, 3b	C_6H_5	p-O_2N-C_6H_4	(1)
1c, 2c, 3c	p-H_3C-C_6H_4	C_6H_5	(1)
1d, 2d, 3d	C_6H_5	C_6H_5	(1)
1e, 2e, 3e	p-Cl-C_6H_4	C_6H_5	(1, 2)
1f, 2f, 3f	H_3C	H_3C	(2)
1g, 2g, 3g	$(H_3C)_2N$	H_3C	(2)

These mesoionic oxazolines are characterized by an IR absorption band near 3166 cm^{-1} and several absorptions between 1654 and 1570 cm^{-1}; the ^1H NMR spectrum shows a non exchangeable proton near 7·46 ppm. Furthermore, hydrolysis under mild acidic conditions yields starting nitrile **1**.

ketones **6–9** with the corresponding νCO values (cm^{-1}) are compiled as shown.

It appears that νCO of C-trifluoroacetyl derivatives can range from 1780 to 1600 cm^{-1}, whereas N-trifluoroacetyl absorption band is usually situated towards 1700 cm^{-1}. Considering the chemical behaviour in the 5-amino oxazole series, we have shown that competitive N- and C-trifluoroacetylation reactions may occur. Thus, when α-acylaminoamides **10** are treated with trifluoroacetic

†Laboratoire associé au C.N.R.S. No. 135.



anhydride, a mixture of oxazoles **11** and **12** is isolated.[7]

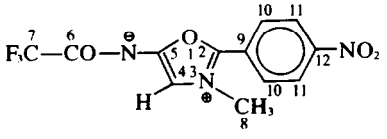
On the other hand, hydrolysis of compounds **11** and **12** under acidic conditions regenerates the starting amides, showing that ring opening and loss of the trifluoroacetyl group occur from a N- as well as a C-acylated compound.[7,11]

In this paper, we wish to report spectroscopic (^{13}C NMR data) and chemical (a 1,3-dipolar cycloaddition reaction product) proofs which are in agreement with one of these two structures.

RESULTS AND DISCUSSION

Our studies were performed on the 5-iminooxazoline obtained from nitrile **1a** (R = CH_3; R' = p-O_2N-C_6H_4).

^{13}C *NMR data.* ^{13}C NMR spectra were recorded in the Fourier mode at 25·2 MHz with proton noise and off resonance decoupling. The spectra clearly establish structure **3a** as the correct one, since the signal for C-4 appears as a doublet in the off resonance spectrum. To facilitate complete assignment of the signals, undecoupled spectra with sweep widths of 1000 Hz were recorded.



3a

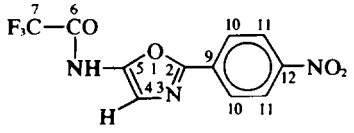


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Table 1. ^{13}C chemical shifts[a] and coupling constants[b] of 5-imino oxazoline **3a** and 5-amino oxazole **13**

Carbons	3a	13
6	159·99[c]	153·52[d]
5	159·45[e]	144·75[f]
12	149·32[g]	148·09[g]
2	147·78[h]	153·19[i]
10	130·40 (171)[j]	126·51 (169)[j]
9	126·71[k]	131·73[l]
11	124·36 (173)[m]	124·55 (172)[n]
7	117·82 (288)	115·38 (287)
4	107·48 (215)[p]	115·98 (210)
8	36·82 (not measured)	—

[a] At 25·2 MHz, DMSO-d6 solution, in ppm (±0·05 ppm) downfield from internal TMS; [b] in parenthesis ^1J in Hz accurate to ±0·5 Hz, ^2J, ^3J and ^4J in footnotes; [c] ^2J (C, F) = 33 Hz; [d] ^2J (C, F) = 39 Hz; [e] ^4J(C, F) = 1·5 Hz; ^2J(C, H_4) = 12·5 Hz; [f] ^4J(C, F) = 0 Hz; ^2J(C, H_4) = 15 Hz; [g] ^2J(C, H_{11}) = 3 Hz; ^3J (C, H_{10}) = 9 Hz; [h] ^3J (C, H_{10}) = 4 Hz; ^3J (C, H_4) = 8 Hz; ^3J (C, H_8) < 1 Hz; [i] ^3J (C, H_{10}) = 4 Hz; ^3J (C, H_4) = 12 Hz; [j] ^3J (C, H_{10}) = 7 Hz; [k] ^3J (C, H_{11}) = 8 Hz; [l] ^3J (C, H_{11}) = 7·5 Hz; [m] ^3J (C, H_{11}) = 5 Hz; [n] ^3J (C, H_{11}) = 4 Hz; [p] ^3J (C, H_8) = 3·5 Hz.

Chemical shifts and $^{13}C,H$ coupling constants of **3a** are given in Table 1 together with the values for the known oxazole **13**.[13]

The $^{13}C,H$ coupling constants given in the Table 1 are directly measured from line splittings of the spectra. No attempt was made to analyze the carbon spectra of the *p*-nitrophenyl rings, whose proton spectra are strongly coupled. The values of these couplings given in the Table 1 are therefore approximate but can be used with confidence as an aid in the assignment of carbon signals.

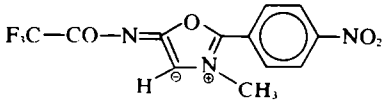
Assignment of the proton bearing carbons C-8, C-4, C-10 and C-11 is straightforward and requires no further comment. Likewise C-6 and C-7 are easily assigned because of their large and characteristic ^{13}C, ^{19}F coupling constants.[14]

The unambiguous differentiation between the signals of the quarternary carbons C-2, C-5, C-9 and C-12 is achieved by consideration of chemical shifts and ^{13}C, H coupling constants. Thus, the signals of C-9 and C-12 show the expected triplet splittings of about 8 Hz, caused by vicinal coupling with the aromatic protons; C-12 shows an additional triplet splitting (3 Hz) due to geminal coupling.

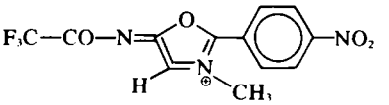
The signals for C-5 are split by a geminal coupling with H-4; in **3a** a small ^{13}C, ^{19}F coupling (1·5 Hz) is observed, which is absent in **13**. Finally, the C-2 signals are recognized by their vicinal couplings with H-4 and the aromatic protons H-10.

A comparison of the chemical shifts of **3a** and **13** shows that large differences occur in the chemical shifts of the oxazole ring carbons, C-5 being deshielded by 14·8 ppm in **3a** and C-4 and C-2 being shielded by 8·5 and 5·4 ppm respectively.

These results demonstrate that the dipolar structure **3a** does not completely describe the charge distribution in this molecule, but that negative charge is delocalized into the oxazole ring according to structures **3'a** and **3''a**:



3'a



3''a

The chemical shifts of C-4 and C-5 are similar to values recently reported by Hearn and Potts for methylsydnone and related mesoionic compounds.[15] These authors also concluded, that C-4 carries high electron density, in agreement with ESCA-investigations and ab initio SCF-MO calculations on N-methylsydnone.[16]

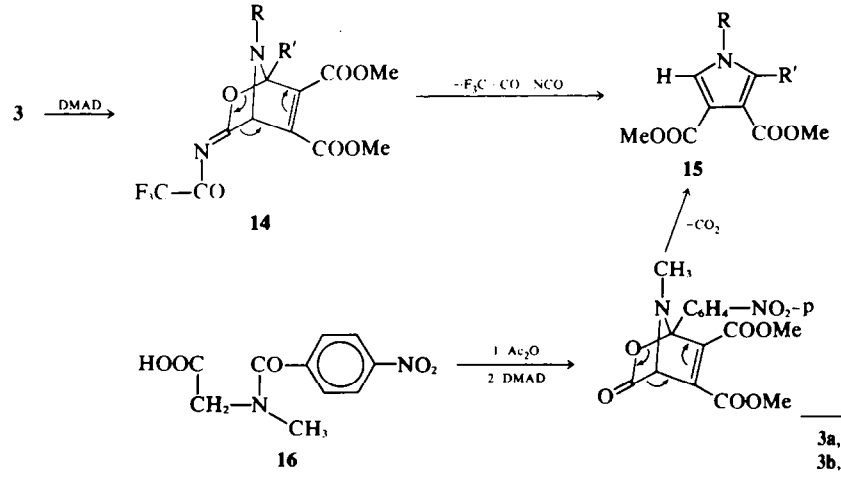
1,3-Dipolar cycloaddition reaction. For several years, 1,3-dipolar cycloaddition reactions involving mesoionic ring systems as 1,3-dipoles and various dipolarophiles, have been reported in the literature.[17-19] Such reactions have been used for the synthesis of a large variety of heterocyclic compounds such as: pyrroles,[4,18,20-23] thiophenes,[24,25] pyridones[24] and pyrazoles.[4,23,26] It has been shown that the 1,3-dipolar cycloaddition reaction proceeds through an unstable 1:1 primary adduct which rearranges to more stable heterocycles already mentioned above, while small molecules are evolved, i.e. carbon dioxide,[9,18,20,25,26] carbonyl sulphide,[23] isocyanates,[4,21,22,25] N-benzoyl N'-phenyl carbodiimide.[5] In some cases the primary 1:1 adduct has been isolated and well characterized.[4,5,23,27] When **3a–b** were allowed to react with dimethylacetylene dicarboxylate (DMAD) in boiling dry dioxane, pyrroles **15a–b** were formed with yields in excess of 75%. By analogy with the 1,3-dipolar cycloadditions mentioned above, the reaction presumably involves initial formation of an unstable bicyclic adduct **14** with subsequent elimination of trifluoroacetylisocyanate. Pyrrole **15a** has also been prepared from N-paranitrobenzoylsarcosine **16** according to the method described by Huisgen *et al.*[18]

Structures **15a** and **15b** were confirmed by their ^{13}C NMR spectra. Chemical shifts and coupling constants are given in Table 2. The carbons of the N-phenyl ring in **15b** were assigned using the characteristic fine structure of the signals of the undecoupled spectrum.[28] Differentiation between C-3 and C-4, and C-6 and C-6' was not possible, since $^2J_{(C_4,H_3)} = {}^3J_{(C_3,H_3)}$ and $^3J_{(C_6,H_3)} = {}^4J_{(C_6',H_3)}$ in both compounds (Table 2).

The present results show that the cyclisation reaction of α-acylaminonitriles of type **1** in the presence of trifluoroacetic anhydride leads to mesoionic 5-imino oxazolines bearing a trifluoroacetyl group on the exocyclic 5-imino nitrogen atom. 1,3-Dipolar cycloaddition reaction with dimethylacetylene dicarboxylate yields N-substituted pyrroles via a 1:1 bridged adduct across the 4,2 positions of the mesoionic ring.

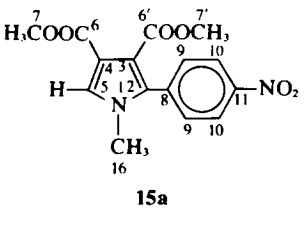
EXPERIMENTAL

All m.ps were taken in capillaries using a Büchi apparatus. Spectral characteristics were determined on the following

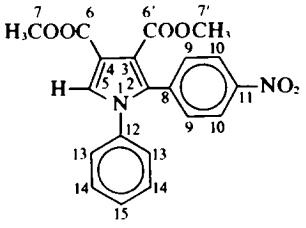


	R	R'
3a, 15a	CH_3	p-O_2N-C_6H_4
3b, 15b	C_6H_5	p-O_2N-C_6H_4

Table 2. ^{13}C chemical shifts[a] and coupling constants[b] of pyrroles **15a** and **b**



15a



15b

Carbons	15a	15b
6; 6'	165·23; 163·82[c]	165·47; 163·58[c]
11	147·87[d]	147·34[e]
12	—	138·01[f]
8	136·89[g]	136·50[h]
2	134·41[i]	132·78[i]
9	131·37 (167)[j]	131·15 (167)[k]
14	—	129·70 (163)
5	129·06 (191)[l]	129·05 (193)
15	—	128·69 (163)[m]
13	—	125·93 (164)
10	123·57 (171)[n]	123·24 (171)[n]
4; 3	116·57; 115·13[o]	118·26; 116·23[o]
7; 7'	51·92; 51·57	52·33; 51·73
	(not measured)	(not measured)
16	35·47 (not measured)	—

[a] At 25·2 MHz, $CDCl_3$ solution; in ppm (±0·05 ppm) downfield from TMS; [b] in parenthesis ^1J in Hz accurate to ±0·5 Hz, ^2J, ^3J and ^4J in footnotes; [c] $^3J_{(C,H_7)} = {}^3J_{(C,H_{7'})} = 4{\cdot}0$ Hz; $^3J_{(C,H_5)} = {}^4J_{(C,H_3)} = 1{\cdot}0$ Hz; [d] $^2J_{(C,H_{10})} = 3{\cdot}5$ Hz; $^3J_{(C,H_9)} = 9{\cdot}5$ Hz; [e] $^2J_{(C,H_{10})} = 3{\cdot}0$ Hz; $^3J_{(C,H_9)} = 9{\cdot}0$ Hz; [f] $^3J_{(C,H_{14})}$ and $^3J_{(C,H_5)}$ not observable because of overlapping signals; [g] $^3J_{(C,H_{10})} = 8{\cdot}0$ Hz; [h] $^3J_{(C,H_{10})} = 8{\cdot}5$ Hz; [i] $^3J_{(C,H_5)}$ and $^3J_{(C,H_9)}$ not observable because of overlapping signals; [j] $^3J_{(C,H_9)} = 7{\cdot}0$ Hz; [k] $^3J_{(C,H_9)} = 8{\cdot}0$ Hz; [l] $^3J_{(C,H_{15})} = 3{\cdot}5$ Hz; [m] $^3J_{(C,H_{13})} = 7{\cdot}0$ Hz; [n] $^3J_{(C,H_{10})} = 4{\cdot}0$ Hz; [o] $^2J_{(C,H_5)} = {}^3J_{(C,H_5)} = 6{\cdot}5$ Hz.

instrumentation: IR, Perkin-Elmer Model 21 spectrophotometer; ^1H NMR, Varian T-60 and Varian A-60A spectrometers, using TMS as internal standard; ^{13}C NMR, Varian XL-100/15 Fourier Transform spectrometer operating at 25·15 MHz with solutions containing *ca.* 200 mg of compound per ml solvent and using TMS as internal standard.

Microanalysis were performed by the Departement of Microanalysis, Centre National de la Recherche Scientifique, Strasbourg, France.

N-(p-*Nitrobenzoyl*) N-*methyl aminoacetonitrile* **1a**. Methylaminoacetonitrile hydrochloride (10·6 g, 0·1 mol) dissolved in N NaOH (100 ml) was added with stirring to a cooled soln (8–10°) of *p*-nitrobenzoyl chloride (20·5 g, 0·11 mol) in ether (150 ml). Additional N NaOH was added until the mixture was just alkaline (about 100 ml during 1 hr). The mixture was stirred for an additional 0·5 hr, the ppt was collected and the ether soln separated and evaporated to dryness to give an additional amount of product. It was crystallized from water–EtOH: 17·5 g (80%), m.p. 88–89°; IR (KBr) 1635 (s) (CO), 1605 (m) (C=C), 1515, 1350 (s) (NO_2) cm^{-1}; PMR ($CDCl_3$) 3·15 (s, 2, CH_2), 4·47 (s, 3, N–CH_3) 7·60–8·38 (q, 4, aromatic) ppm. (Found: C, 54·69; H, 4·07; N, 19·03. Calc. for $C_{10}H_9N_3O_3$: C, 54·79; H, 4·11; N, 19·18%).

2-p-*Nitrophenyl* 3-*methyl* 5-*trifluoroacetylimino oxazole* **3a**. Nitrile **1a** (2·2 g, 0·01 mol), trifluoroacetic anhydride (10 g, 0·05 mol) and trifluoroacetic acid (6 g, 0·05 mol) were stirred for 30 min at room temp. The soln was concentrated under vacuum and the residue treated with dry ether. The yellow ppt was crystallized from acetonitrile: 2·8 g (89%), m.p. 234–235° (dec); IR (KBr) 3200 (m) (CH), 1635, 1622, 1595, 1565 (s) (CO, C=N, C=C), 1525, 1342 (s) (NO_2), 1297–1125 (s) (CF_3) cm^{-1}; PMR (acetone-d_6) 4·34 (s, 3, N–CH_3) 7·65 (s, 1, 4-H), 8·30–8·70 (q, 4, aromatic) ppm. (Found: C, 45·64; H, 2·73; N, 13·54. Calc. for $C_{12}H_8F_3N_3O_4$: C, 45·71; H, 2·54; N, 13·33%). The mesoionic compound **3b** (R = C_6H_5; R' = O_2N–C_6H_4) was obtained in 85% yield, according to the procedure described in Ref. 1.

2-p-*Nitrophenyl*-5-(N-*trifluoroacetyl*) *amino oxazole* **13** was obtained in 56% yield according to the method reported in Ref. 13.

1-*Methyl*-2-p-*nitrophenyl*-3,4-*dimethoxycarbonyl pyrrole* **15a**

From **3a**. Mesoionic compound **3a** (3·1 g, 0·01 mol), dimethylacetylene dicarboxylate (2·8 g, 0·02 mol) and dry dioxane (100 ml) were heated under reflux for 1 hr. The solvent was removed under vacuum and the pale-yellow residue thus obtained was crystallized from EtOH: 2·5 g (78%); m.p. 153·5–154·5°; IR (KBr) 3175 (m) (CH), 1709 (s) (CO), 1608 (m) (C=C), 1524, 1344 (s) (NO_2) cm^{-1}. PMR ($CDCl_3$) 3·59 (s, 3, N–CH_3), 3·72, 3·85 (s, 6, $COOCH_3$), 7·38 (s, 1,5-H), 7·54–8·41 (q, 4, aromatic) ppm. (Found: C, 56·60; H, 4·40; N, 8·90. Calc. for $C_{15}H_{14}N_2O_6$: C, 56·60; H, 4·40; N, 8·80%).

From N-p-*nitrobenzoylsarcosine* **16**. N-*p*-Nitrobenzoylsarcosine (5 g, 0·021 mol) and Ac_2O (50 ml) were maintained at 70° for 5 min. Then, dimethylacetylene dicarboxylate (5 g, 0·035 mol) was added and the mixture kept at 80° for 15 min while CO_2 was evolved. The excess of Ac_2O was removed under vacuum and the residual yellow oil, was treated with cold water until a solid product was formed: 5·9 g (88%), identical to the compound obtained from **3a**.

1-*Phenyl*-2-p-*nitrophenyl*-3,4-*dimethoxycarbonyl pyrrole* **15b**. Reaction of **3b** with dimethylacetylene dicarboxylate was performed under the same conditions as described for **15a**. Compound **15b** was crystallized from acetone as pale-yellow needles: 3·0 g (79%); m.p. 191–192°; IR (KBr) 3135 (m) (CH), 1715 (s) (CO), 1605 (s) (C=C), 1515, 1346 (s) (NO_2) cm^{-1}; PMR ($CDCl_3$) 3·73, 3·81 (s, 6, CH_3), 6·8–8·0 (m, 10, 5-H and aromatic) ppm. (Found: C, 63·18; H, 4·28; N, 7·48. Calc. for $C_{20}H_{16}N_2O_6$: C, 63·16; H, 4·21; N, 7·37%).

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