Cycloaddition Reactions of 3-Methyloxazolium-5-olates to 4-Arylidene-5(4*H*)-isoxazolones

Francesca Clerici, Emanuela Erba, Pierluigi Mornatti, and Pasqualina Trimarco*

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano,
Via Venezian, 21, I-20133 Milano, Italy

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The unstable cycloadducts formed from benzylideneisoxazolones **2** and oxazolium-5-olates **1** undergo CO_2 elimination to afford the stereoisomeric substituted 3,7-diazaspiro[4,4]nonane derivatives **3**, which were isolated in one case (**3a, b**). On further reaction, compounds **3** are transformed into pyrrole-3-carboxylic acids **4**. Reaction paths and regiochemical behaviour are discussed.

Cycloadditions-Reaktionen von 3-Methyloxazolium-5-olaten an 4-Aryliden-5(4*H*)-isoxazolone

Die instabilen Cycloaddukte, die aus den Benzylidenisoxazolen **2** und Oxazolium-5-olaten **1** gebildet werden, erleiden CO_2-Eliminierung zu den stereoisomer substituierten 3,7-Diazaspiro[4,4]nonan-Derivaten **3**, die in einem Fall (**3a, b**) isoliert wurden. Durch weitere Reaktionen werden die Verbindungen **3** in die Pyrrol-3-carbonsäuren **4** übergeführt. Reaktionswege und regiochemisches Verhalten werden diskutiert.

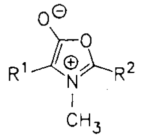
N-substituted oxazolium-3-olates ("Münchnones") are known to react as 1,3-dipoles in 1,3-dipolar cycloaddition reactions[1,2]. However, the regiochemical features of these reactions are far from being completely clarified. Previously, we described a synthetic path to substituted pyrrole-3-carbaldehydes by rearrangement of the cycloadditon products from Münchnones and 4-methylene-*v*-triazolines[3]. As a further contribution both to the synthetic chemistry of substituted pyrroles and to the understanding of the regiochemical behaviour of Münchnones, we now report our results concerning the reactions of oxazolium-5-olates with 4-arylidene-5(4*H*)-isoxazolones.

Benzylideneisoxazolone **2a** was treated with a slight excess of oxazolium-5-olate **1a** in refluxing toluene. The reaction was complete within 10–15 min and was accompanied by CO_2 elimination, affording a mixture of the stereoisomeric spirane pyrrolinoisoxazoles **3a, b**. The products could be separated by fractional crystallization, and their structure was assigned on the basis of analytical and spectroscopic data.

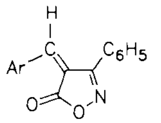
In the IR spectrum, compounds **3a, b** show a strong carbonyl absorption at $\nu = 1790\ cm^{-1}$, which is in good agreement with published data for 4,4-disubstituted 5(4*H*-isoxazolones[4]. The singlets for $N-CH_3$ and 6-H are at $\delta = 2.63$ and 5.02 for **3b** and at $\delta = 2.52$ and 4.80 for **3a**, in agreement with the proposed structure. By considering molecular models, the 5*R**,6*S** configuration was assigned to compound **3b** and the 5*R**,6*R** configuration to **3a** since in the former, the signal associated with 6-H should be shifted to lower field due to deshielding by the CO group, as observed. This agrees with the fact that in the spectrum of **3b** the signals for the 6-phenyl group are present at higher field than for **3a**. It was found that both **3a** and **3b** are converted into a stereoisomeric mixture when a chloroform or methanol solution was kept at room temperature for some days. On standing for longer periodes both **3a** and **3b** underwent a relatively slow transformation to afford *N*-methyl-2,4,5-triphenylpyrrole-3-carboxylic acid (**4a**) and benzonitrile. This reaction was comparatively fast (complete within a few minutes) at the reflux temperature of chloroform or methanol.

1a showed similar behaviour on reaction with **2b–e** as with **2a**, as did **1i** and **1j** on reaction with **2a**. However, spirane intermediates were never isolated in a pure condition, but were converted directly into the corresponding pyrrolecarboxylic acids **4b–d, m–o**, respectively.

In another series of experiments, unsymmetrically substituted Münchnones were used. The reactions were performed as described above. From the reactions of **2a** with **1b–h** reaction mixtures were obtained containing the corresponding spirane products **3**. As expected, four products were pres-



1	R^1	R^2
a	C_6H_5	C_6H_5
b	C_6H_5	$C_6H_4-CH_3-(4)$
c	C_6H_5	$C_6H_4-OCH_3-(4)$
d	$C_6H_4-OCH_3-(4)$	C_6H_5
e	$C_6H_4-Cl-(4)$	$C_6H_4-OCH_3-(4)$
f	$C_6H_4-OCH_3-(4)$	$C_6H_4-Cl-(4)$
g	C_6H_5	CH_3
h	CH_3	C_6H_5
i	$C_6H_4-Cl-(4)$	$C_6H_4-Cl-(4)$
j	$C_6H_4-OCH_3-(4)$	$C_6H_4-OCH_3-(4)$



2	Ar
a	C_6H_5
b	$C_6H_4-CH(CH_3)_2-(4)$
c	$C_6H_4-NO_2-(4)$
d	$C_6H_4-OCH_3-(4)$
e	2-thienyl

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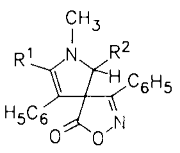
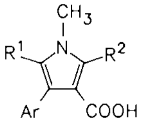
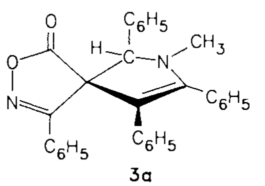


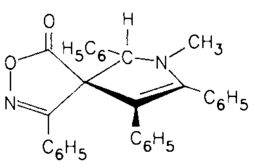
3	R^1	R^2
a	C_6H_5	C_6H_5(5*R**, 6*R**)
b	C_6H_5	C_6H_5(5*R**, 6*S**)
c	C_6H_5	$C_6H_4-CH_3$-(4)
d	$C_6H_4-CH_3$-(4)	C_6H_5
e	C_6H_5	$C_6H_4-OCH_3$-(4)
f	$C_6H_4-OCH_3$-(4)	C_6H_5
g	$C_6H_4-OCH_3$-(4)	C_6H_4-Cl-(4)
h	C_6H_4-Cl-(4)	$C_6H_4-OCH_3$-(4)
i	C_6H_5	CH_3
j	CH_3	C_6H_5



4	R^1	R^2	Ar
a	C_6H_5	C_6H_5	C_6H_5
b	C_6H_5	C_6H_5	$C_6H_4-CH(CH_3)_2$-(4)
c	C_6H_5	C_6H_5	$C_6H_4-NO_2$-(4)
d	C_6H_5	C_6H_5	$C_6H_4-OCH_3$-(4)
e	C_6H_5	$C_6H_4-CH_3$-(4)	C_6H_5
f	$C_6H_4-CH_3$-(4)	C_6H_5	C_6H_5
g	C_6H_5	$C_6H_4-OCH_3$-(4)	C_6H_5
h	$C_6H_4-OCH_3$-(4)	C_6H_5	C_6H_5
i	$C_6H_4-OCH_3$-(4)	C_6H_4-Cl-(4)	C_6H_5
j	C_6H_4-Cl-(4)	$C_6H_4-OCH_3$-(4)	C_6H_5
k	C_6H_5	CH_3	C_6H_5
l	CH_3	C_6H_5	C_6H_5
m	C_6H_4-Cl-(4)	C_6H_4-Cl-(4)	C_6H_5
n	$C_6H_4-OCH_3$-(4)	$C_6H_4-OCH_3$-(4)	C_6H_5
o	C_6H_5	C_6H_5	2-thienyl



3a



3b

ent (i.e. two regioisomers, each as a pair of enantiomers), and this was confirmed by the signals in the ^{1}H-NMR spectrum associated with the CH group. A separation into the pure isomers proved to be difficult, owing mainly to the tendency of products **3** to decompose spontaneously to the corresponding acids **4**. Accordingly, we were not able to assign each NMR signal unequivocally to a particular isomer. However, by analogy with the NMR features of **3a** and **3b**, we could assign the pair of lower field signals to the 5*R**,6*S** regioisomers. The relative intensities of the signals of each pair allowed a rough estimation of the regioisomer ratio. The same ratio was measured between the isomeric pyrrolecarboxylic acids **4** produced by thermolysis of the crude mixture of spiranes **3**. In all cases, the isomeric acids could be satisfactorily separated and fully characterized.

The structures of the isomeric acids were assigned as follows. The known 2-methyl-3,5-diphenylpyrrole[1] and 2,3-diphenyl-5-methylpyrrole[1] were produced by thermal decarboxylation of **4l** and **4k**, respectively, thus confirming their structure. When considering their ^{1}H-NMR spectra, it was found that for **4k** the signal associated with the CH_3 group is present at lower field than the corresponding signal for **4l** ($\Delta\delta = 0.5$), as expected. By analogy, the lower field signals in the spectra of all acids were consistently assigned to the substituent adjacent to the carboxyl group, thus establishing the structure. A confirmation was obtained by decarboxylation of acid **4g**. 2,3-Diphenyl-5-(4-methoxyphenyl)pyrrole was obtained whose structure was confirmed by an NOE experiment, in which a positive effect (10%) was observed between the signals associated with 4-H and the *ortho*-hydrogens of the 4-methoxyphenyl group.

Discussion

The high reactivity of arylideneisoxazolones towards Münchnones, which is well substantiated by the above examples, allows the use of this reaction for the preparation of desired pyrrolecarboxylic acids. The whole process may be explained as follows (Scheme 1). Cycloadducts are formed by a 1,3-dipolar cycloaddition of the Münchnones to the exocyclic double bond of compounds **1**; these are unstable and undero loss of CO_2 and prototropic tautomerization to spiranes **3**. Clearly, the stereochemical features of this process cannot be inferred from the configuration of the products because of the impossibility of isolating the intermediates, but some considerations about the regiochemistry can be presented instead. When unsymmetrically substituted Münchnones were used, four products **3** were obtained as a consequence of the formation of two regioisomers (both as diastereoisomeric pairs). These led in turn, to two isomeric pyrrolecarboxylic acids. The ratio of these isomers was measured by ^{1}H NMR of the crude reaction mixtures (Table 1). It is assumed that the same ratio also applied to their spirane precursors **3**. Because of their instability in solution, they could not be easily analyzed, but it was confirmed, both on pure **3a** and pure **3b**, that the transformation of **3** into **4** occurs quantitatively. The diaryl-substituted Münchnones **1c – f** reacted with moderate regioselectivity; the major reaction products were the pyrroles derived from linkage of the CH group of **2** to the carbon atom of the azomethine ylide system bearing the less electron-rich substituent. A greater selectivity was shown by the isomeric **1g** and **1h**, which displayed a clear tendency to link the *C*$-CH_3$ carbon to the CH group of **2**. These results are not immediately understandable in the light of the mechanistic hypothesis of the simple MO approach[5], since a very high selectivity is expected.

Scheme 1

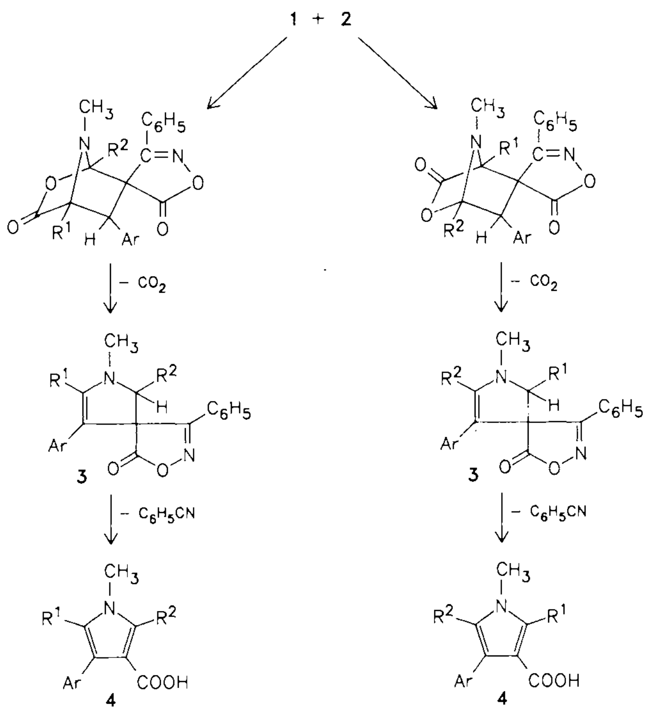


Table 1. Isomer ratios of products **4**

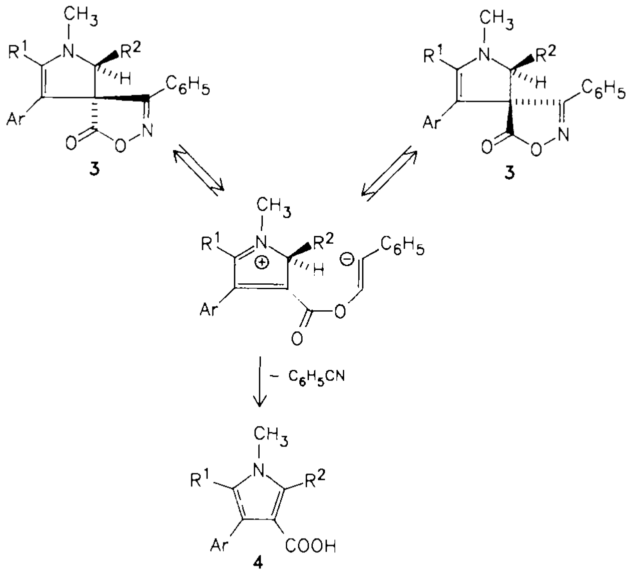
Münchnones	5(4*H*)-Isoxazolones	Products **4** (ratio)
1b	**2a**	**4e**:**4f** (50:50)
1c	**2a**	**4g**:**4h** (60:40)
1d	**2a**	**4g**:**4h** (60:40)
1e	**2a**	**4i** :**4j** (35:65)
1f	**2a**	**4i** :**4j** (15:85)
1g	**2a**	**4k**:**4l** (20:80)
1h	**2a**	**4k**:**4l** (20:80)

Assuming for the HOMO and LUMO of the dipole, the energy values calculated for the azomethine ylide system[6] and for the dipolarophile the data reported for α,β-unsaturated esters[7,8], this reaction should be classified as a $\mathrm{LUMO_{dipolarophile}/HOMO_{dipole}}$-controlled process.

The larger coefficient in the LUMO of **2** lies on the CH group. According to our experimental results it seems that in all cases a larger coefficient in the dipole HOMO should be assigned to the carbon bearing the more electron-withdrawing substituent for compounds **1b**–**f**, and to the carbon bearing the methyl group for Münchnones **1g**,**h**. An acceptable picture is as follows: taking into account that i) in the Münchnone system the HOMO coefficient is known to be strongly influenced by substituents of the ring, ii) an increase of electron density at a particular site should increase the coefficient magnitude, and iii) the Münchnones have extensively delocalized structures, in which the C-substituents are generally involved, one concludes that in the case of compounds **1g**,**h** the coefficient on $C-CH_3$ is magnified by the inductive electron-releasing effect of the substituent, thus determining the observed regioselectivity. On the other hand, aryl groups in compounds **1c**–**f** affect the whole diaryl azomethine ylide system by conjugation. By virtue of the push-pull effect of mutually electron-donating and -withdrawing substituents, a charge distribution results, in which the electron density on the C-atom bearing the more electron-poor group is enhanced with respect to the basic system, thus increasing the corresponding coefficient in the HOMO.

As far as the transformations of spirane compounds **3** are concerned, the following applies: the epimerization, which was observed in solution can be explained only by a ring chain tautomerism, possibly through opening of the isoxazolone ring as shown in Scheme 2. A zwitterionic intermediate is produced, which is in equilibrium with both stereoisomers or, alternatively, can also undergo an irreversible benzonitrile elimination to form the final pyrrole derivative.

Scheme 2



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Experimental

Melting points are uncorrected: Büchi 150 (capillary) apparatus. – IR spectra: Perkin-Elmer 197 and Philips SP 3 200 S spectrophotometers. – ^{1}H-NMR spectra, $(CH_3)_4Si$ as internal standard in the solvent indicated: Varian EM 360, EM 390 and Bruker AC 200 instruments. – ^{13}C-NMR spectra (50.327 MHz), $(CH_3)_4Si$ as internal standard: Bruker AC 200 instrument. – Column chromatography was performed on silica gel with petroleum ether (40–60°C)/ethyl ether (3:7).

Oxazolium-5-olates: Compounds **1a**,**c**, and **d**[9] and **1g**,**h**, and **j**[3] have been already described.

4-(4-Chlorophenyl)-2-(4-methoxyphenyl)-3-methyloxazolium-5-olate (**1e**): The hitherto unknown *C*-(4-chlorophenyl)-*N*-methylglycine hydrochloride was prepared in a similar manner to *N*-methyl-*C*-phenylglycine[10] starting from 4-chlorobenzaldehyde and methylamine hydrochloride. – Yield 24%; m.p. 225°C (MeOH). – IR (nujol): ν = 1730 cm^{-1}. – ^{1}H NMR (D_2O/NaOD): δ = 1.90 (s, 3H, NCH_3), 3.66 (s, 1H, CH), 6.94–7.06 (m, 4H, aryl-H).

$C_9H_{11}Cl_2NO_2$ (236.1) Calcd. C 45.78 H 4.69 N 5.93
Found C 45.50 H 4.61 N 5.84

The *C*-(4-chlorophenyl)-*N*-methylglycine hydrochloride (15 g, 6.35 mmol) was suspended in 10% NaOH (112 ml). A solution of 4-methoxybenzoyl chloride (15.3 g, 8.97 mmol) in CCl_4 (20 ml) was added with vigorous stirring at room temp. Stirring was continued for 1.5 h, and the reaction mixture, acidified to pH 2 with 10% HCl, yielded a gummy material. The doughy residue was separated, washed several times with CCl_4 (150 ml), and the solution dried with Na_2SO_4 and evaporated to yield an oily product. – Yield 74%. – IR ($CHCl_3$): ν = 1725 cm^{-1}, 1610 (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.80 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 6.25 (br. s, 1H, CH), 6.70–7.55 (m, 8H, aryl-H), 9.10 (br. s, 1H, OH, H/D exchange with D_2O).

N-(4-Methoxybenzoyl)-*N*-methyl-*C*-(4-chlorophenyl)glycine (6.5 g, 1.94 mmol) was suspended in acetic anhydride (35 ml) and heated at 55°C for 10 min. The solution was evaporated under reduced pressure, and the yellow crystalline solid taken up in ether and filtered. – Yield 51%; m.p. 176°C. – IR (nujol): ν = 1690 cm^{-1} (C=O). – ^{1}H-NMR ($CDCl_3$): δ = 3.78 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 6.8–7.8 (m, 8H, aryl-H).

$C_{17}H_{14}ClNO_3$ (315.6) Calcd. C 64.66 H 4.46 N 4.43
Found C 64.71 H 4.61 N 4.30

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-3-methyloxazolium-5-olate (**1f**): As **1e**, from *C*-(4-methoxyphenyl)-*N*-methylglycine[3] (10 g, 4.36 mmol) and 4-chlorobenzoyl chloride (8.76 g, 5.05 mmol). – Yield 76%. – IR (nujol): ν = 1720 cm^{-1}, 1620 (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.74 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 6.20 (br. s, 1H, CH), 6.67–7.85 (m, 8H, aryl-H), 9.50 (br. s, 1H, OH, H/D exchange with D_2O). – The gummy 4-chlorobenzoyl derivative was suspended in acetic anhydride (60 ml) and heated at 50°C for 15 min. After evaporation at reduced pressure the residue was washed several times with ether yielding a yellow crystalline product. – Yield 63%; m.p. 153°C (Et_2O). – IR (nujol): ν = 1690 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 6H, NCH_3 and OCH_3), 6.8–7.7 (m, 8H, aryl-H).

$C_{17}H_{14}ClNO_3$ (315.6) Calcd. C 64.66 H 4.46 N 4.43
Found C 64.75 H 4.66 N 4.37

2,4-Bis(4-chlorophenyl)-3-methyloxazolium-5-olate (**1i**): As **1e**, from *C*-(4-chlorophenyl)-*N*-methylglycine hydrochloride (see above) (15 g, 6.35 mmol) and 4-chlorobenzoyl chloride (12.7 g, 7.31 mmol). Yield 69%. – IR ($CHCl_3$): ν = 1725 cm^{-1}, 1620 (C=O). – ^{1}H-NMR ($CDCl_3$): δ = 2.75 (s, 3H, NCH_3), 6.25 (br. s, 1H, CH), 7.0–7.55 (m, 8H, aryl-H), 9.18 (br. s, 1H, OH, H/D exchange with D_2O). – The gummy product was suspended in acetic anhydride (85 ml) and heated at 50–55°C for 15 min. After evaporation at reduced pressure the residue was worked up as for **1e** and **1f**. – Yield 73%; m.p. 173°C (EtOH). – IR (nujol): ν = 1690 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 3H, NCH_3), 7.20–7.65 (m, 8H, aryl-H).

$C_{16}H_{11}Cl_2NO_2$ (320.2) Calcd. C 60.02 H 3.46 N 4.37
Found C 59.79 H 3.54 N 4.42

Arylideneisoxazolones **2a–e**: Compounds **2a, c, d** were prepared by reported methods[11,12] from 3-phenylisoxazol-5-one and the appropriate aldehyde. **2b** and **2e** were obtained similarly.

(Z)-4-(4-Isopropylphenyl)methylene-3-phenyl-5(4H)-isoxazolone (**2b**): Yield 44%; m.p. 170°C (*i*Pr_2O). – IR (nujol): ν = 1740 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 1.38 (d, *J* = 7 Hz, 6H, 2 CH_3), 3.05 [dq, *J* = 7 Hz, 1H, $CH(CH_3)_2$], 7.20–8.40 (m, 14H, aryl-H).

$C_{19}H_{17}NO_2$ (291.3) Calcd. C 78.32 H 5.88 N 4.81
Found C 78.02 H 6.02 N 4.63

(Z)-3-Phenyl-4-(2-thienyl)methylene-5(4H)-isoxazolone (**2e**): Yield 54%; m.p. 183°C (CH_3COOH). – IR ($CHCl_3$): ν = 1740 cm^{-1} (C=O). – ^{1}H NMR ([D_6]DMSO): δ = 7.20–7.40 and 8.22–8.50 (2 m, 3H, 2-thienyl), 7.52–7.82 (m, 5H, aryl-H), 8.2 (s, 1H, CH).

$C_{14}H_9NO_2S$ (255.3) Calcd. C 65.86 H 3.55 N 5.48
Found C 65.62 H 3.56 N 5.39

(5R,6R*)-7-Methyl-2-oxa-4,6,8,9-tetraphenyl-3,7-diazaspiro[4.4]nona-3,8-dien-1-one* (**3a**) *and (5R*,6S*)-7-Methyl-2-oxa-4,6,8,9-tetraphenyl-3,7-diazaspiro[4.4]nona-3,8-dien-1-one* (**3b**): From 2.50 g (10 mmol) of **2a** and 3 g (12 mmol) of **1a** in toluene (70 ml) according to the standard procedure (see below). The crude mixture, taken up in benzene, afforded compound **3a** as the initial crystalline product. On addition of pentane, the mother liquor yielded a second crystalline solid, which was identified as **3b**.

3a: Yield 31%; m.p. 161°C (C_6H_6). – IR (nujol): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.52 (s, 3H, NCH_3), 4.80 (s, 1H, 6-H), 6.75–7.65 and 8.1–8.3 (2 m, 20H, aryl-H).

$C_{31}H_{24}N_2O_2$ (456.5) Calcd. C 81.55 H 5.30 N 6.14
Found C 81.31 H 5.44 N 6.07

3b: Yield 16%; m.p. 107°C (benzene/pentane). – IR (nujol): 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 3H, NCH_3), 5.02 (s, 1H, 6-H), 6.75–7.70 (m, 20H, aryl-H).

$C_{31}H_{24}N_2O_2$ (456.5) Calcd. C 81.55 H 5.30 N 6.14
Found C 81.18 H 5.44 N 6.07

1-Methyl-2,4,5-triphenylpyrrole-3-carboxylic Acid (**4a**): a) A mixture of cycloadducts **3a** and **3b** (1 g, 2.2 mmol) was heated in refluxing methanol (30 ml) until the starting material had disappeared (TLC). After solvent evaporation, the crude **4a** was crystallized and analyzed. – Yield 83.6%; m.p. 213°C (dec.; EtOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.35 (s, 3H, NCH_3), 7.0–8.3 (m, 15H, aryl-H).

$C_{24}H_{19}NO_2$ (353.4) Calcd. C 81.56 H 5.42 N 3.96
Found C 81.06 H 5.40 N 4.09

b) From pure **3a** (0.9 g, 1.97 mmol) according to above method. – Yield 91%.

c) From pure **3b** (0.5 g, 1.09 mmol) according to above method. – Yield 81%.

Standard Procedure for the Reaction of Isoxazolones **2** *with Münchnones* **1b–j**: The arylideneisoxazolones **2** were dissolved in boiling anhydrous toluene. The Münchnones **1** were added in several portions over 15–20 min under N_2 and at reflux temp. The reaction solution was heated for 15 min at reflux and evaporated to yield a crude mixture of cycloadducts **3**. Compounds **3** were dissolved in methanol and heated to reflux until the starting material had disappeared (TLC).

After evaporation, the crude pyrrolecarboxylic acids **4** were purified according to method a), b), or c).

a) The residue was crystallized from an appropriate solvent.

b) The residue was separated by fractional crystallization.

c) The residue was chromatographed on a silica gel column eluted with ethyl ether/petroleum ether (40–60°C) (3:7).

4-(4-Isopropylphenyl)-1-methyl-2,5-diphenylpyrrole-3-carboxylic Acid (**4b**): From 2 g (6.8 mmol) of **2b** and 2.56 g (10.2 mmol) of **1a** in toluene (70 ml), according to the standard procedure, and purified by method a). – Yield 40%; m.p. 218–220°C (*i*PrOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, *J* = 7 Hz, 6H, 2 CH_3), 2.85 (dq, *J* = 7 Hz, 1H, CHMe), 3.30 (s, 3H, NCH_3), 6.88–7.58 (m, 14H, aryl-H).

$C_{27}H_{25}NO_2$ (395.5) Calcd. C 81.99 H 6.37 N 3.54
Found C 82.14 H 6.42 N 3.46

1-Methyl-4-(4-nitrophenyl)-2,5-diphenylpyrrole-3-carboxylic Acid (**4c**): From 2.05 g (6.9 mmol) of **2c** and 2.25 g (8.9 mmol) of **1a** in toluene (70 ml), according to the standard procedure, and purified by method a). – Yield 51%; m.p. 219–220 (dec.; *i*PrOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ([D_6]DMSO): δ = 3.29 (s, 3H, NCH_3), 6.28 (br. s, 1H, OH, H/D exchange with D_2O), 7.10–8.18 (m, 14H, aryl-H).

$C_{24}H_{18}N_2O_4$ (398.4) Calcd. C 72.35 H 4.55 N 7.03
Found C 72.12 H 4.68 N 6.94

4-(4-Methoxyphenyl)-1-methyl-2,5-diphenylpyrrole-3-carboxylic Acid (**4d**): From 2.00 g (7.16 mmol) of **2d** and 2.55 g (10.15 mmol) of **1a** in toluene (70 ml), according to the standard procedure, and purified by method a). – Yield 36%; m.p. 230°C (*i*PrOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.30 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.68 (d, *J* = 9 Hz, 2H, aryl-H), 7.13 (d, *J* = 9 Hz, 2H, aryl-H), 7.13–7.60 (m, 10H, aryl-H).

$C_{25}H_{21}NO_3$ (383.4) Calcd. C 78.30 H 5.52 N 3.65
Found C 78.48 H 5.52 N 3.59

1-Methyl-2,5-diphenyl-4-(2-thienyl)pyrrole-3-carboxylic Acid (**4o**): From 2.00 g (7.84 mmol) of **2e** and 2.36 g (9.4 mmol) of **1a** in toluene (60 ml), according to the standard procedure, and purified by method a). – Yield 43%; m.p. 194°C (CH_2Cl_2). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.28 (s, 3H, NCH_3), 6.75–7.50 (m, 13H, aryl-H).

$C_{22}H_{17}NO_2S$ (359.4) Calcd. C 73.51 H 4.77 N 3.89
Found C 73.31 H 4.72 N 3.94

1-Methyl-2-(4-methylphenyl)-4,5-diphenylpyrrole-3-carboxylic Acid (**4e**) *and 1-Methyl-5-(4-methylphenyl)-2,4-diphenylpyrrole-3-carboxylic Acid* (**4f**): From 1.80 g (7.23 mmol) of **2a** and 2.26 g (8.67 mmol) of **1b** in toluene (60 ml), according to the standard procedure, and purified by method b).

3c,d (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 4.74, 4.77, 4.96, 5.00 (4 s, 1H, 6-H).

4e: Yield 19%; m.p. 220°C (CH_2Cl_2/*n*-pentane). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3H, $PhCH_3$), 3.30 (s, 3H, NCH_3), 7.00–7.48 (m, 14H, aryl-H).

$C_{25}H_{21}NO_2$ (367.4) Calcd. C 81.71 H 5.76 N 3.81
Found C 81.54 H 5.66 N 3.79

4f: Yield 45%; m.p. 224°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H, $PhCH_3$), 3.30 (s, 3H, NCH_3), 7.05–7.36 (m, 14H, aryl-H).

$C_{25}H_{21}NO_2$ (367.4) Calcd. C 81.71 H 5.76 N 3.81
Found C 81.93 H 5.49 N 3.75

2-(4-Methoxyphenyl)-1-methyl-4,5-diphenylpyrrole-3-carboxylic Acid (**4g**) *and 5-(4-Methoxyphenyl)-1-methyl-2,4-diphenylpyrrole-3-carboxylic Acid* (**4h**): From 2.15 g (8.6 mmol) of **2a** and 2.65 g (9.4 mmol) of **1c** in toluene (70 ml), according to the standard procedure, and purified by method c).

3e,f (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR (C_6D_6): δ = 4.82, 4.84, 5.15 (3 s, 1H, 6-H).

4g: Yield 29%; m.p. 209°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.27 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 6.85–7.45 (m, 14H, aryl-H).

$C_{25}H_{21}NO_3$ (383.4) Calcd. C 78.31 H 5.52 N 3.65
Found C 78.51 H 5.54 N 3.74

4h: Yield 12%; m.p. 217°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.24 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 6.6–7.45 (m, 14H, aryl-H).

$C_{25}H_{21}NO_3$ (383.4) Calcd. C 78.31 H 5.52 N 3.65
Found C 78.21 H 5.47 N 3.63

2-(4-Methoxyphenyl)-1-methyl-4,5-diphenylpyrrole-3-carboxylic Acid (**4g**) *and 5-(4-Methoxyphenyl)-1-methyl-2,4-diphenylpyrrole-3-carboxylic Acid* (**4h**): From 8.5 g (34 mmol) of **2a** and 10.5 g (37.3 mmol) of **1d** in toluene (200 ml), according to the standard procedure, and purified by method b).

3e,f (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 4.73, 4.75, 4.95, 4.97 (4 s, 1H, 6-H).

4g: Yield 39%.

4h: Yield 22%.

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-3-carboxylic Acid (**4i**) *and 5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-3-carboxylic Acid* (**4j**): From 1.64 g (6.6 mmol) of **2a** and 2.40 g (7.6 mmol) of **1e** in toluene (60 ml), according to the standard procedure, and purified by method c).

3g,h (crude mixture): IR ($CHCl_3$): 1790 cm^{-1} (C=O). – ^{1}H NMR (C_6D_6): δ = 4.72, 4.81, 5.05, 5.15 (4 s, 1H, 6-H).

4i: Yield 16%; m.p. 205°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.22 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 6.78–7.42 (m, 13H, aryl-H).

$C_{25}H_{20}ClNO_3$ (417.8) Calcd. C 71.85 H 4.82 N 3.35
Found C 71.63 H 4.92 N 3.00

4j: Yield 38%; m.p. 213°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 3.25 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 6.95–7.39 (m, 13H, aryl-H).

$C_{25}H_{20}ClNO_3$ (417.8) Calcd. C 71.85 H 4.82 N 3.35
Found C 72.00 H 5.05 N 3.42

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-3-carboxylic Acid (**4i**) *and 5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-3-carboxylic Acid* (**4j**): From 2.17 g (8.7 mmol) of **2a** and 3.00 g (9.9 mmol) of **1f** in toluene (70 ml), according to the standard procedure, and purified by method b).

3g,h (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 4.76, 4.98 (2 s, 1H, 6-H).

4i: Yield 4%.

4j: Yield 44%.

1,2-Dimethyl-4,5-diphenylpyrrole-3-carboxylic Acid (**4k**) *and 1,5-Dimethyl-2,4-diphenylpyrrole-3-carboxylic Acid* (**4l**): 0.94 g (3.8 mmol) of **2a** and 1.00 g (4.8 mmol) of *N*-acetyl-*N*-methyl-*C*-phenylglycine[11] were dissolved in anhydrous toluene (50 ml). The mixture was heated at reflux to completely dissolve the reagents, and a solution of dicyclohexylcarbodiimide (DCC) (1.01 g, 4.8 mml) in anhydrous toluene (20 ml) was then added dropwise at room temp. After 20 min, dicyclohexylurea (DCU) was filtered off and the filtrate evaporated under reduced pressure. The crude mixture of **3i,j** was worked up as described in the standard procedure and purified by method c).

3i,j (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 4.66, 4.87 (2 s, 1H, 6-H).

4k: Yield 9%; m.p. 205°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.42 (s, 3H, NCH_3), 7.0–7.6 (m, 10H, aryl-H).

$C_{19}H_{17}NO_2$ (291.3) Calcd. C 78.38 H 5.88 N 4.80
Found C 78.49 H 5.70 N 4.74

4l: Yield 25%; m.p. 226°C (*i*PrOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 2.18 (s, 3H, CH_3), 3.35 (s, 3H, NCH_3), 7.20–7.50 (m, 10H, aryl-H).

$C_{19}H_{17}NO_2$ (291.3) Calcd. C 78.38 H 5.88 N 4.88
Found C 78.17 H 5.81 N 4.74

1,2-Dimethyl-4,5-diphenylpyrrole-3-carboxylic Acid (**4k**) *and 1,5-Dimethyl-2,4-diphenylpyrrole-3-carboxylic Acid* (**4l**): 2.53 g (10.2 mmol) of **2a** and 2.7 g (13.0 mmol) of *N*-benzoyl-*N*-methylalanine[1] were dissolved in anhydrous toluene (80 ml). The mixture was heated at reflux to completely dissolve the reagents and then cooled to room temp. 2.73 g (13 mmol) of DCC, dissolved in anhydrous toluene (50 ml), was added dropwise to the mixture. After 20 min, DCU was filtered off and the filtrate evaporated under reduced pressure. The crude mixture of **3i,j** was worked up as described in the standard procedure and purified by method b).

3i,j (crude mixture): IR ($CHCl_3$): ν = 1790 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 4.62, 4.84 (2 s, 1H, 6-H).

4k: Yield 7%.

4l : Yield 35%.

2,5-Bis(4-chlorophenyl)-1-methylpyrrole-3-carboxylic Acid (**4m**): From 1.75 g (7.02 mmol) of **2a** and 2.50 g (7.80 mmol) of **1i** in toluene (60 ml), as described in the standard procedure, and purified by method a). – Yield 58%; m.p. 211°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 3.18 (s, 3H, NCH_3), 6.95–7.45 (m, 13H, aryl-H), 8.2 (br. s, 1H, OH H/D exchange with D_2O).

$C_{24}H_{17}Cl_2NO_2$ (422.3) Calcd. C 68.25 H 4.06 N 3.31
Found C 67.95 H 4.23 N 3.28

2,5-Bis(4-methoxyphenyl)-1-methyl-4-phenylpyrrole-3-carboxylic Acid (**4n**): From 0.79 g (3.17 mmol) of **2a** and 1.10 g (3.50 mmol) of **1j**[3] in toluene (40 ml), as described in the standard procedure, and purified by method a). – Yield 53%; m.p. 233°C (MeOH). – IR (nujol): ν = 1665 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 3.26 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3 in C_6H_4 at C-5), 3.87 (s, 3H, OCH_3 in C_6H_4 at C-2), 6.80–7.42 (m, 13H, aryl-H).

$C_{26}H_{23}NO_4$ (413.4) Calcd. C 75.52 H 5.60 N 3.39
Found C 75.11 H 5.97 N 3.54

CAS Registry Numbers

1a: 13712-75-9 / **1b**: 66380-06-1 / **1c**: 28750-90-5 / **1d**: 28609-00-9 / **1e**: 117711-97-4 / **1f**: 117711-98-5 / **1g**: 72726-10-4 / **1h**: 81156-07-2 / **1i**: 117711-99-6 / **1j**: 78994-82-8 / **2a**: 36298-61-0 / **2b**: 117712-00-2 / **2c**: 61588-01-0 / **2d**: 36298-62-1 / **2e**: 117734-17-5 / **3a**: 117712-01-3 / **3b**: 117712-02-4 / **3c** (isomer 1): 117712-20-6 / **3c** (isomer 2): 117712-30-8 / **3d** (isomer 1): 117712-21-7 / **3d** (isomer 2): 117712-31-9 / **3e** (isomer 1): 117712-22-8 / **3e** (isomer 2): 117712-32-0 / **3f** (isomer 1): 117712-23-9 / **3f** (isomer 2): 117712-33-1 / **3g** (isomer 1): 117712-24-0 / **3g** (isomer 2): 117712-34-2 / **3h** (isomer 1): 117712-25-1 / **3h** (isomer 2): 117712-35-3 / **3i** (isomer 1): 117712-26-2 / **3i** (isomer 2): 117712-36-4 / **3j** (isomer 1): 117712-27-3 / **3j** (isomer 2): 117712-37-5 / **4a**: 117712-03-5 / **4b**: 117712-04-6 / **4c**: 117712-05-7 / **4d**: 117712-06-8 / **4e**: 117712-07-9 / **4f**: 117712-08-0 / **4g**: 117712-09-1 / **4h**: 117712-10-4 / **4i**: 117712-11-5 / **4j**: 117712-12-6 / **4k**: 117712-13-7 / **4l**: 117712-14-8 / **4m**: 117712-15-9 / **4n**: 117712-16-0 / **4o**: 117712-17-1 / *C*-(4-chlorophenyl)-*N*-methylglycine: 117712-18-2 / 4-chlorobenzaldehyde: 104-88-1 / methylamine hydrochloride: 593-51-1 / 4-methoxybenzoyl chloride: 100-07-02 / *C*-(4-methoxyphenyl)-*N*-methylglycine: 117712-19-3 / 4-chlorobenzoyl chloride: 122-01-0 / *N*-acetyl-*N*-methyl-*C*-phenylglycine: 35746-37-3 / *N*-(4-chlorobenzoyl)-*C*-(4-methoxyphenyl)-*N*-methylglycine: 117712-28-4 / *C*-(4-chlorophenyl)-*N*-(4-chlorobenzoyl)-*N*-methylglycine: 117734-18-6 / *N*-(4-methoxybenzoyl)-*N*-methyl-*C*-(4-chlorophenyl)glycine: 117712-29-5 / *N*-benzoyl-*N*-methylalanine: 69994-40-7

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