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NEW PYRROLES FROM QUINAZOLINIUM N1-YLIDES AND ACETYLENIC DIPOLAROPHILES

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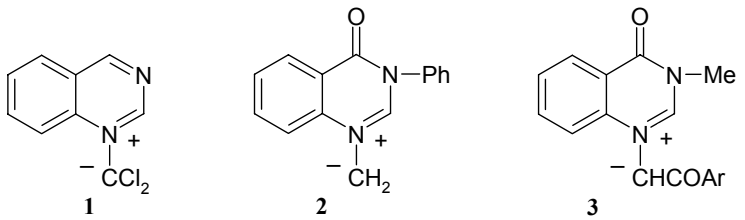
The new pyrroles **8a,b** were obtained by one-pot reaction from N1-quinazolinum bromides and non-symmetrical acetylenic dipolarophiles. Structural characterizations were based on IR and NMR spectroscopy as well as on single crystal X-ray diffraction.

INTRODUCTION

Our interest in pyrroloazines[1] led us to investigate a new route for the synthesis of pyrrolo[1,2-*a*]quinazoline.[2] This ring system received a growing interest in the past twenty years and a number of synthetic methods have been considered for its synthesis.[3] As some of the key methods for obtaining pyrroloazines, *N*-ylide 1,3-dipolar cycloaddition reactions were also investigated for this ring system. The first attempt consisting of the use of quinazolinium dichloro *N*-ylide **1** resulted in a mixture of isomeric pyrroloquinazolines.[4] The use of unsubstituted ylide **2** resulted in *N*-substituted pyrroles or pyrroloquinazolines depending on the dipolarophile used.[5]



1 **2** **3**

Scheme 1

During our investigations on the cycloaddition reaction between monosubstituted ylides **3** and acetylenic dipolarophiles with the aim of obtaining pyrroloquinazolines, we observed the unexpected formation of tri- and tetra-substituted pyrroles in moderate to good yields.[2] The reaction represents a new synthetic route to substituted N-arylpyrroles in a simple one-pot procedure starting from available materials. The structural variety of the obtained pyrroles is provided by the acetylenic dipolarophiles, only one substituted quinazoline being used as starting material. The interest in pyrrole chemistry arises from the possibility of functionalization of this ring system which will

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result in enhanced biological activity, as well as the employment of pyrroles as starting materials in organic syntheses.[6]

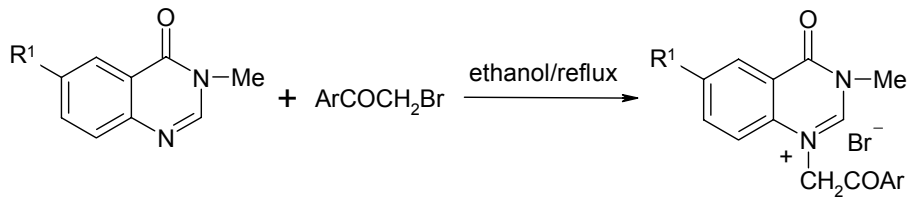
Herein we report the synthesis and structural characterization of new pyrroles obtained by the *in situ* rearrangement of the dihydropyrrolo[1,2-a]quinazoline intermediate obtained in the 1,3-dipolar cycloaddition of monosubstituted quinazolinium ylides with non-symmetrical acetylenic dipolarophiles.

RESULTS AND DISCUSSION

The key intermediates for synthesis of the pyrroles **8** were quinazolinium bromides **6**. As in the case of quinazoline the quaternization reaction takes place predominantly at N3. 3-methyl-4(3*H*)-quinazolinone **4** was used as starting compound in order to obtain the key intermediate **6**. Bromides **6** were obtained in good yield by refluxing in ethanol 3-methyl-4(3*H*)quinazolin-4-ones **4** and bromoacephenones **5** (Scheme 2).

The final product, trisubstituted pyrrole **8**, is obtained using a well-proven one-pot experimental procedure[2] consisting of refluxing salts **6** with 3-butyn-2-one and ethyl propiolate respectively, in 1,2-epoxybutane as solvent and acid scavenger (Scheme 3).

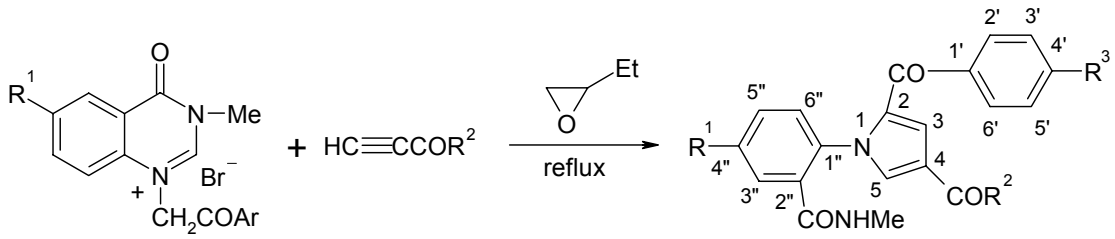
The reaction mechanism consists in the opening of the oxirane ring by the bromide anion, followed by the generation of the *N*-ylide and subsequent cycloaddition in the presence of the dipolarophile. This leads to the formation of an unstable dihydropyrrolo[1,2-*a*]quinazoline, which is transformed *in situ* by ring opening to trisubstituted pyrroles **8a,b**.



4a,b **5a,b** **6a,b**

6a: R^1 = H, Ar = 4-$NO_2C_6H_5$; **6b**: R^1 = Cl, Ar = C_6H_5

Scheme 2



6a,b **7** **8a,b**

8a: R^1 = H, R^2 = Me, R^3 = 4-NO_2; **8b**: R^1 = Cl, R^2 = OEt, R^3 = H

Scheme 3

The salts **6** and the corresponding N-arylpyrroles **8** were characterized by IR and NMR spectroscopy including COSY and HETCOR experiments. The IR spectra of the bromides **6** present the characteristic bands for the carbonyl groups at 1652 and 1689 cm^{-1} for the carbonyl group in the aroyl moiety and at 1707 cm^{-1} and 1714 cm^{-1} for the carbonyl group (amide group) in the quinazoline moiety. The characteristic vibrations of the NO_2 group could also be observed at 1297 and 1527 cm^{-1} respectively for the compound **6a**. The most characteristic signal in the ^{1}H-NMR spectra of the salts is a singlet at 10.06 ppm and 9.80 ppm respectively, corresponding to the H-2 hydrogen, which is strongly deshielded due to its position with respect to the two nitrogen atoms. The ^{13}C-NMR spectra present the expected signals for such compounds, the characteristic signals at δ ~157 and δ ~188 ppm corresponding to the carbonyl groups and the signal at δ ~154 ppm of the carbon C-2. For the compound **6a**, carbon C-4' in the benzoyl moiety (δ = 151.3 ppm) is

strongly deshielded due to the nitro group directly attached to it.

The most characteristic band in the IR spectra of the pyrroles **8** found at 3324-3395 cm^{-1} corresponds to the CONH group. This is proof for the quinazoline ring opening, leading to an *N*-arylpyrrole derivative. The carbonyl bands appear in the 1630-1707 cm^{-1} range due to the conjugation within the molecule. Also the absorption bands of the NO_2 group are present at 1287 and 1524 cm^{-1} for the pyrrole **8a**. The ^{1}H-NMR spectra of compounds **8** are in accordance with the proposed structures. The hydrogens H-3 and H-5 of the pyrrole moiety appear as two doublets with the coupling constant J = 1.6 Hz at 7.23 and 7.29 ppm and 7.67 and 7.59 ppm, respectively. The NH hydrogen appears as a quartet with J = 4.9 Hz at 6.40 ppm for pyrrole **8a** and 6.72 ppm for the pyrrole **8b**, due to the coupling with the hydrogen atoms in the methyl group. In the ^{13}C-NMR spectra the most characteristic signals are those of the carbon C-5 which appear at ~135 ppm, strongly deshielded due to its direct bonding to the nitrogen atom in the pyrrole moiety. For the pyrrole **8a** another characteristic is the carbon C-4' in the benzoyl moiety, which is strongly deshielded by the influence of the NO_2 and appears at around 150 ppm.

In the H-NMR spectra of compound **8b**, an interesting multiplicity of the signals of the protons in the ethyl moiety could be observed. Due to steric hindrance, free rotation about the bond C1″-N is prevented. Thus, the methylene protons in the ester are magnetically non-equivalent which will result in the splitting of their signal. Thus, the expected quartet at 4.09-4.33 ppm appears split into a multiplet. The methyl group appears as a triplet which is the expected signal. Another interesting observation could be made for the ^{13}C-NMR spectra of the compounds **8a** and **8b**. The C-4 carbon atom appears at different chemical shifts due to the substituents. Thus, in the case of **8a** C-4 appears at 126 ppm slightly deshielded by the presence of the acyl group. In the compound **8b** the C-4 appears at 117 ppm due to the weaker influence of the substituent. Another interesting feature is the chemical shift of the carbon in the carbonyl group of the acyl moiety which appears at 192 ppm, whereas in the ester moiety it appears at 163 ppm. By comparison of the spectra of compounds **8a** and **8b** the chemical shift of the carbonyl group in the amide was assigned unequivocally at δ ~165 ppm.

For both compounds **6** and **8**, spectral data are in good agreement with the proposed structures. In order to provide additional structural proof and to investigate the stereochemistry and crystal packing of molecules **8a** and **8b**, crystals were grown for X-ray analysis from a 1:1 methylene chloride:ethanol mixture by slow evaporation. Structure solution and refinement of these two new analogues followed previously published procedures[2] and their crystallographic details are provided in ref. 7. Fig. 1 shows the molecular conformations and Table 1 lists geometrically equivalent torsion angles in the two molecules.

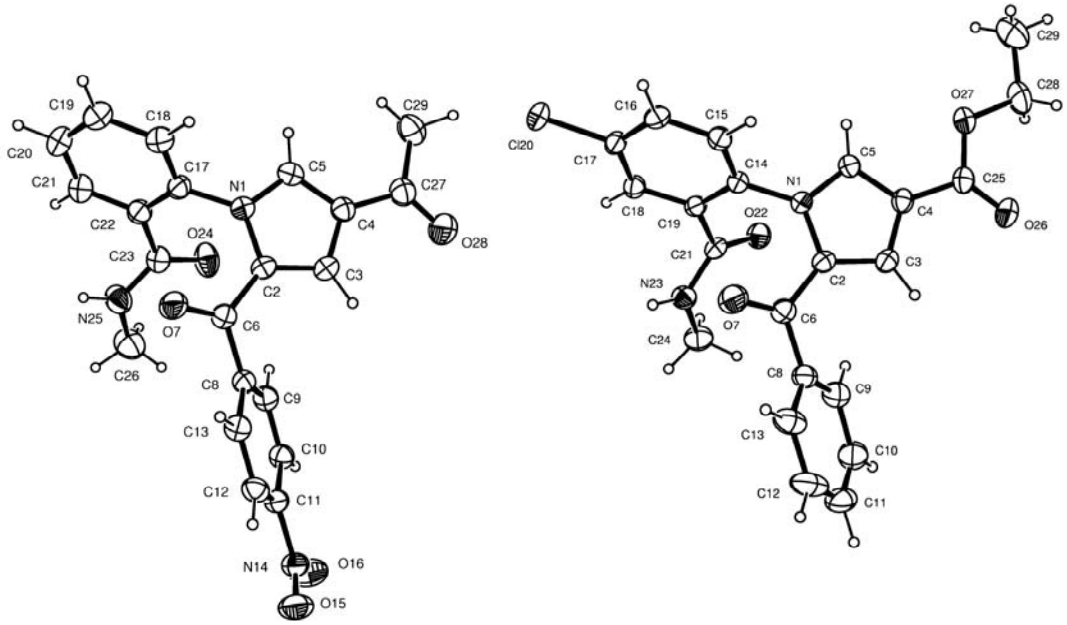


Fig. 1 – Molecular structures of **8a** (left) and **8b** (right) with thermal ellipsoids drawn at the 50% probability level.

Visual comparison of the molecules in Fig. 1 suggests that common fragments are orientated similarly with respect to the pyrrole ring as reference and this is confirmed by the listed torsion angles. The magnetic non-equivalence of the methylene protons in **8b**, observed in solution as a result of hindered rotation about the N-Ar bond, is mirrored in the solid state where the dihedral angle between the rings linked by this bond is -63.2(2)°.

Given the close similarity in molecular conformations, it was interesting to note that molecules of **8a** and **8b** do not associate in the same way in the crystals analyzed. As illustrated in Fig. 2, two distinct hydrogen-bonded motifs were observed, one creating a centrosymmetric dimer in **8a** and a second yielding an infinitely extended molecular array in the crystal of **8b**, propagated by the twofold screw axis.

Table 1

Selected torsion angles defining the solid-state conformations of molecules **8a** and **8b**

8a:Torsion angle	Value (°)	**8b**:Torsion angle	Value (°)
C2-N1-C17-C22	-59.3(3)	C2-N1-C14-C19	-63.2(2)
N1-C17-C22-C23	1.6(3)	N1-C14-C19-C21	-4.2(2)
C17-C22-C23-O24	-38.8(3)	C14-C19-C21-O22	-50.7(2)
C3-C4-C27-O28	-0.6(3)	C23-C24-C25-O26	7.3(2)
N1-C2-C6-O7	-17.1(3)	N1-C2-C6-O7	-16.7(2)
N1-C2-C6-C8	163.8(2)	N1-C2-C6-C8	165.0(1)
C2-C6-C8-C9	-44.2(3)	C2-C6-C8-C9	-36.2(2)

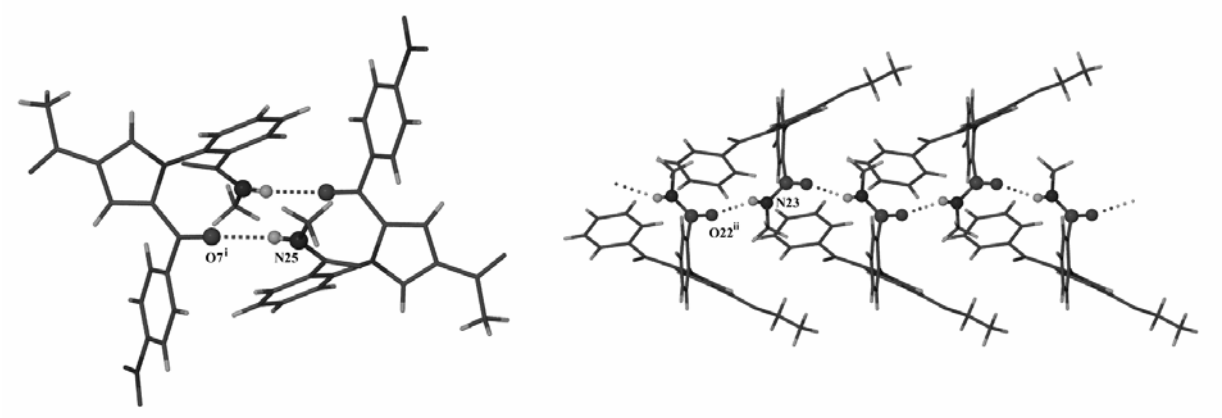


Fig. 2 – Hydrogen bonded motifs in **8a** (left) and **8b** (right).

While the hydrogen bond donor function (N-H) is the same for both molecules, the acceptor atoms are chemically distinct. In **8a**, the functional group N25-H25 is the hydrogen bond donor to acceptor carbonyl oxygen atom $O7^{i}$ (i = *3-x, 2-y, -1-z*) of the 4-nitrobenzoyl moiety, the unique hydrogen bond $N25\text{-}H25\cdots O7^{i}$ having N···O = 2.909(2) Å (Fig. 2, left). Instead, in **8b** the N23-H23 group forms an intermolecular hydrogen bond with the amide carbonyl oxygen atom $O22^{ii}$ of a 2_1-related molecule (Fig. 2, right) and the result is an infinite chain of molecules parallel to the crystal *b*-axis. The hydrogen bond $N23\text{-}H23\cdots O22^{ii}$ (ii = *3/2-x, 1/2+y, 3/2-z*) is stronger than that in **8**a, having N···O = 2.833(2) Å. Additional C-H···O hydrogen bonds stabilize the crystal structures of both **8a** and **8b**.

Yet another H-bonded motif – in this case one with a distinctly 'spiral' geometry – was observed in the crystal structure of the analogue dimethyl 2-benzoyl-1-(2-methylaminocarbonylphenyl)pyrrole-3,4-dicarboxylate,[2] whose molecular conformation is again similar to those of **8a** and **8b**. The three modes of intermolecular hydrogen bonding observed thus far (dimeric, linear, spiral) may reflect specific cases of crystal polymorphs of the individual compounds; the presence of multiple hydrogen-bond acceptor oxygen atoms suggests that crystal polymorphism may well be a feature of the solid-state chemistry of these new compounds. This aspect could be relevant in the case of pharmacologically active N-arylpyrroles.

EXPERIMENTAL

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus.

The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. Supplementary evidence was given by HETCOR and COSY experiments.

General procedure for obtaining the salts 6

5 mmol of quinazolinone-4-one **4** and 5 mmol of corresponding bromoacetophenone **5,** in 40 mL ethanol were heated at reflux for 24 hours. The solvent was partly removed by evaporation and the mixture was left overnight at room temperature. The solid was filtered and recrystallized from EtOH.

1-[2-(4-Nitrophenyl)-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (6a). Colourless crystals with mp 227-229 ^{o}C were crystallized from EtOH; Yield 79 %. Anal. Calcd. $C_{17}H_{14}BrN_3O_4$: C 50.51, H 3.49, Br 19.77, N 10.40. Found C 50.88, H 3.21, Br 19.50, N 10.69. IR (KBr, cm^{-1}): 1297, 1527, 1652, 1707, 2933, 3062.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.88 (s, 3H, MeN); 6.51 (s, 2H, CH_2); 7.45 (d, 1H, *J* = 8.5 Hz, H-8); 7.84 (t, 1H, *J* = 7.8 Hz, H-6); 7.99 (dt, 1H, *J* = 8.5 Hz, 1.65 Hz, H-7); 8.34 (s, 4H, H-3', H-5', H-2', H-6'); 8.53 (dd, 1H, *J* = 7.8 Hz, 1.65 Hz, H-5) 10.06 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.1 (MeN); 59.0 (CH_2); 117.3 (C-8); 129.5 (C-5); 124.4 (C-3', C-5'); 130.1 (C-2', C-6'); 130.8 (C-6); 119.5, 130.0, 137.0 (C-4a, C-8a, C-1'); 137.5 (C-7); 151.3 (C-4'); 154.1 (C-2); 157.3 (CONH); 188.5 (COAr).

6-Chloro-1-[2-phenyl-2-oxoethyl]-3-methyl-4(3*H*)quinazolinon-1-ium bromide (6b). Colourless crystals with mp 231-3 ^{o}C were crystallized from EtOH; Yield 76 %. Anal. Calcd. $C_{17}H_{14}BrClN_2O_2$: N 7.12. Found 7.44. IR (KBr, cm^{-1}): 1685, 1714, 2931, 3075.
^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 3.81 (s, 3H, MeN); 6.28 (s, 2H, CH_2); 7.32 (d, 1H, *J* = 8.8 Hz, H-8); 7.50-7.55 (m, 2H, H-3', H-5'); 7.68-7.73 (m, 1H, H-4'); 7.82 (dd, 1H, *J* = 8.8, 2.5 Hz, H-7); 8.01-8.06 (m, 2H, H-2', H-6'); 8.40 (d, 1H, *J* = 2.5 Hz, H-5); 9.80 (s, 1H, H-2).
^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 37.0 (MeN); 59.0 (CH_2); 119.2, 128.9, 136.4, 137.7 (C-5, C-7, C-8, C-4')); 120.8, 132.5, 136.2, 137.6 (C-4a, C-6, C-8a, C-1'); 128.8, 129.7 (C-2', C-3', C-5', C-6'); 154.3 (C-2); 156.7 (CONH); 188.5 (COAr).

General procedure for obtaining pyrroles 8

3 mmol quaternary salt **6** and 5 mmol of acetylenic dipolarophile in 30 mL 1,2-epoxybutane were heated at reflux for 70 hours. The solvent was partly removed by evaporation, 5 mL MeOH was added and the mixture was left overnight in the refrigerator. The solid was filtered and recrystallized from MeOH.

4-Acetyl-1-(2-methylaminocarbonylpheny)-2-(4-nitrobenzoyl)pyrrole (**8a**). Pale yellow crystals with mp 201-2 ^{o}C were crystallized from MeOH. Yield 69 % Anal. Calc. $C_{21}H_{17}N_3O_5$: C 64.45, H 4.38, N 10.74. Found: C 64.79, H 4.61, N 10.98. IR (KBr, cm^{-1}): 1287, 1524, 1660, 1645, 1707, 3069, 3113.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.44 (s, 3H, COMe); 2.68 (d, 1H, *J* = 4.9 Hz, MeNH); 6.40 (1H, q, *J* = 4.9 Hz, NH); 7.23 (d, 1H, *J* = 1.6, H-5); 7.28-7.31 (m, 1H, H-6"); 7.51-7.54 (m, 2H, H-4", H-5"); 7.62-7.63 (m, 1H, H-3"); 7.67 (d, 1H, *J* = 1.6, H-3); 8.03 (2H, d, *J* = 8.8 Hz, H-2', H-6') 8.32 (d, 2H, *J* = 8.8, H-2', H-6').
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 26.6, 27.4 (MeNH, MeO); 121.6 (C-3); 123.7 (C-3', C-5'); 127.3, 128.4, 129.5, 131.0 (C-3", C-4", C-5", C-6"); 126.2, 130.9, 134.4, 136.8 (C-2, C-4, C-1", C-2"); 130.6 (C-2', C-6'); 135.4 (C-5); 142.6 (C-1'); 150.3 (C-4'); 165.2 (CONH); 184.1 (COAr); 192.6 (COMe).

Ethyl 1-(4-chloro-2-methylaminocarbonylphenyl)-2-benzoylpyrrole-4-carboxylate (**8b**). Colourless crystals with mp 185-6 ^{o}C were crystallized from MeOH; Yield 77 %. Anal. Calc. $C_{22}H_{19}ClN_2O_4$: C 64.32, H 4.66, Cl 8.63, N 6.82. Found: C 64.71, H 4.97, Cl 8.93, N 7.11. IR (KBr, cm^{-1}): 1630, 1661, 1701, 3074, 3391.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, Me); 2.67 (d, 1H, *J* = 4.9 Hz, MeNH); 4.09-4.33 (m, 2H, CH_2); 6.72 (1H, q, *J* = 4.9 Hz, NH); 7.12 (d, 1H, *J* = 8.2 Hz, H-6"); 7.29 (d, 1H, *J* = 1.6, H-5); 7.40 (dd, 1H, *J* = 8.2, 2.5 Hz H-5"); 7.49-7.54 (m, 2H, H-3', H-5'); 7.59 (d, 1H, *J* = 1.6, H-3); 7.60-7.68 (m, 1H, H-4'); 7.63 (d, 1H, *J* = 2.5 Hz H-3"); 7.92-7.94 (m, 2H, H-3', H-5').
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.4 (Me-ethyl); 26.6 (MeNH); 60.6 (CH_2); 117.1 (C-4); 122.5 (C-3); 132.9, 135.3, 135.4, 136.4, 137.1 (C-2, C-1', C-1", C-2", C-4"); 128.5 (C-6"); 128.3 (C-3', C-5'); 129.0 (C-3"); 133.6, 134.9 (C-5, C-4'); 130.0 (C-2', C-6'); 130.7 (C-5"); 163.4 (COO); 166.2 (CONH); 186.4 (COAr).

CONCLUSIONS

New pyrroles were synthesized in order to extend the investigations on their structure. The compounds were fully characterized by IR and NMR spectroscopy. Hindered rotation around the N-Ar bond was proven by H-NMR spectroscopy. X-ray analysis of compounds **8a** and **8b** confirmed the predicted structures and further revealed different hydrogen bonding arrangements in their respective crystals.

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7. Crystal data for **8a**: $C_{21}H_{17}N_3O_5$, M = 391.38, yellow prism, 0.40 × 0.32 × 0.30 mm^3, triclinic, space group $P\ \bar{1}$ (No. 2), a = 9.1765(9), b = 10.3279(10), c = 11.2474(9) Å, α = 66.166(5), β = 89.352(6), γ = 78.928(4)°, V = 954.3(2) Å^3, Z = 2, D_c = 1.362 g/cm^3, F_{000} = 408, μ = 0.099 mm^{-1}.
Nonius Kappa CCD diffractometer, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, $2\theta_{max}$ = 51.5º, 9625 reflections collected, 3615 unique (R_{int} = 0.0610). Final *GooF* = 1.052, *R1* = 0.0534, *wR2* = 0.1086, *R* indices based on 2797 reflections with I >2σ(I) (refinement on F^2), 264 parameters, 0 restraints.
Crystal data for **8b**: $C_{22}H_{19}ClN_2O_4$, M = 410.84, colourless prism, 0.38 × 0.33 × 0.32 mm^3, monoclinic, space group $C2/c$ (No. 15), a = 24.1916(13), b = 9.0549(5), c = 18.4166(10) Å, β = 94.9560(10)°, V = 4019.1(4) Å^3, Z = 8, D_c = 1.358 g/cm^3, F_{000} = 1712, μ = 0.221 mm^{-1} (multiscan absorption corrections applied), Bruker Apex Duo diffractometer, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, $2\theta_{max}$ = 56.6º, 23377 reflections collected, 5011 unique (R_{int} = 0.0390). Final *GooF* = 1.046, *R1* = 0.0382, *wR2* = 0.1026, *R* indices based on 4389 reflections with I >2σ(I) (refinement on F^2), 264 parameters, 0 restraints.
Crystallographic data for the structural analyses of **8a** and **8b** have been deposited with the Cambridge Crystallographic Data Centre [CCDC no. 781857 (**8a**), 781858 (**8b**)]. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http:// www.ccdc.cam.ac.uk).