Dedicated to Prof. P.T. Frangopol on the occasion of his 75th anniversary

New Pyrrolo[1,2-b]pyridazine Derivatives by 1,3-Dipolar Cycloaddition of Mesoionic Oxazolopyridazinone

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*New pyrrolo[1,2-b]pyridazine derivatives **8a-f** were synthesized by 1,3-dipolar cycloaddition reaction between mesoionic 1,3-oxazolo[3,2-b]pyridazinium-2-oxides and diethyl or diisopropyl acetylenedicarboxylate as alkyne dipolarophiles. The structures of the new compounds were assigned by elemental analysis and NMR spectroscopy.*

Keywords: mesoionic oxazolo[3,2-b]pyridazin-2-one, 1,3-dipolar cycloaddition, pyrrolo[1,2-b]pyridazine

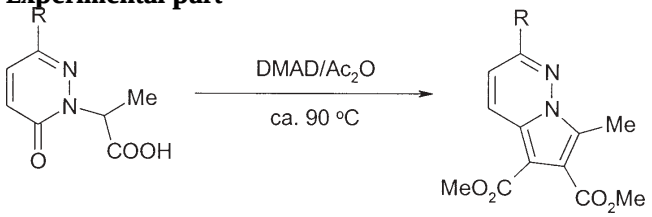
Although the first review of the synthetic pathways leading to pyrrolo[1,2-b]pyridazines appeared in 1977 [1], this research field is still of current interest. This is due to the very diverse properties of the pyrrolo[1,2-b]pyridazine scaffold, especially its spectroscopic behaviour, and thus, the possibility of obtaining OLEDs and other stable light-emitting organic substances [2-4]. Some potential medical applications for this system were also reported [5a-d]. Also, it was shown that the optical and biological properties are influenced by nature and number of substituents attached to the pyrrolopyridazine system.

The synthetic methods for the synthesis of pyrrolo[1,2-b]pyridazine derivatives can be classified into two main approaches. The first consists of condensation reactions [6a-e] and the second is based on cycloaddition reactions [7a-c].

Recently, [8] was reported a new method (scheme 1) for the synthesis of pyrrolo[1,2-b]pyridazines by 1,3-dipolar cycloaddition reactions between mesoionic 1,3-oxazolo[3,2-b]pyridazinium-2-oxides and dimethyl acetylenedicarboxylate (DMAD).

Herein we report the synthesis and characterization of new blue organic luminophore pyrrolo[1,2-b]pyridazine derivatives by 1,3-dipolar cycloaddition reactions between mesoionic oxazolones with diethyl or diisopropyl acetylenedicarboxylate as acetylenic dipolarophiles, with the aim of obtaining a finer tuning of the fluorescent properties.

Experimental part



Scheme 1

Melting points were determined on a Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C.

General procedure for the synthesis of compounds 8a-f

3 mMol of 3(2*H*)pyridazinone acid **5** were suspended with stirring in 5 mL acetic anhydride and then 3.5 mmol of diethyl or diisopropyl acetylenedicarboxylate were added. The reaction mixture was kept at ca. 90°C for 3-4 h. After cooling, to the reaction mixture was added 10 mL ethanol and the solvents were evaporated by vacuum distillation. The residue was triturated with isopropanol and the pyrrolo[1,2-]pyridazine derivatives **8** were isolated by filtration. The raw product was purified by recrystallization from isopropanol or ethyl acetate.

Diethyl 7-methyl-2-phenyl-pyrrolo[1,2-b]pyridazine-5,6-dicarboxylate (**8a**). The product was recrystallized from isopropanol and fluorescent yellow crystals with mp 128-9°C were obtained; Yield 59 %. Anal. Calcd. $C_{20}H_{20}N_2O_4$: C 68.17; H 5.72; N 7.95. Found C 68.41; H 6.01; N 8.11.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31, 1.34 (2t, 6H, *J* = 7.1 Hz, 2MeCH$_2$); 2.63 (s, 3H, 7-Me); 4.28, 4.34 (2q, 4H, *J* = 7.1 Hz, 2OCH$_2$); 7.32 (d, 1H, *J* = 9.4 Hz, H-3); 7.42-7.50 (m, 3H, H-3', H-4', H-5'); 7.92-7.96 (m, 2H, H-2', H-6'); 8.38 (d, 1H, *J* = 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$): δ: 9.9 (7-Me); 14.4, 14.5 (2MeCH$_2$); 60.3, 61.4 (2OCH$_2$); 102.4 (C-5); 113.3 (C-3); 119.4, 127.9, 128.6 (C-4a, C-6, C-7); 126.9 (C-2', C-6'); 128.5 (C-4); 128.9 (C-3', C-5'); 130.1 (C-4'); 135.8 (C-1'); 151.9 (C-2); 163.5, 165.9 (2COO).

Diisopropyl 7-methyl-2-phenyl-pyrrolo[1,2-b]pyridazine-5,6-dicarboxylate (**8b**). The product was recrystallized from isopropanol and fluorescent yellow crystals with mp 117-8°C were obtained; Yield 62 %. Anal. Calcd. $C_{22}H_{24}N_2O_4$: C 69.46; H 6.36; N 7.36. Found C 69.77; H 6.61; N 7.52.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.37, 1.41 (2d, 12H, *J* = 6.3 Hz, 2 **Me**$_2$CH); 2.64 (s, 7-Me); 5.24, 5.30 (2 sept, 2H, *J* = 6.3 Hz, 2OCH); 7.32 (d, 1H, *J* = 9.4 Hz, H-3); 7.49-7.53 (m, 3H, H-3', H-4', H-5'); 7.97-8.03 (m, 2H, H-2', H-6'); 8.43 (d, 1H, 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$): δ: 9.8 (7-Me); 22.1, 22.2 (2**Me**$_2$CH); 67.7, 68.9 (2**Me**$_2$CH); 102.5 (C-5); 113.0 (C-3); 120.0, 127.8, 128.5 (C-4a, C-6, C-7); 127.0 (C-2', C-6'); 128.5 (C-4); 129.0 (C-3', C-5'); 130.1 (C-4'); 135.8 (C-1'); 151.8 (C-2); 163.0, 165.3 (2COO).

Diethyl 2-(4-methylphenyl)-7-methyl-pyrrolo[1,2-b]pyridazine-5,6-dicarboxylate (**8c**). The product was recrystallized from isopropanol or ethylacetate and

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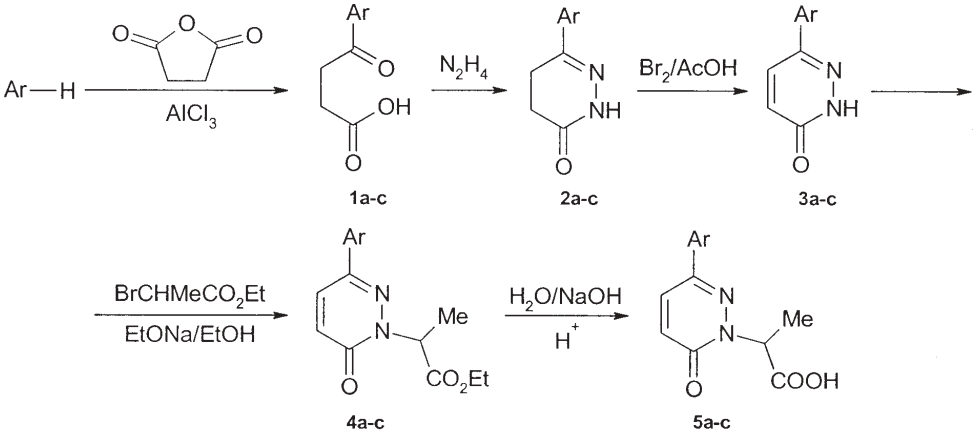


Scheme 2

a: Ar=C_6H_5; b: 4-MeC_6H_4; c: 4-ClC_6H_4

fluorescent yellow crystals with mp 108-110°C were obtained; Yield 61 %. Anal. Calcd. $C_{21}H_{22}N_2O_4$: C 68.84; H 6.05; N 7.65. Found C 69.18; H 6.33; N 7.92.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34, 1.36 (2t, 6H, *J* = 7.1 Hz, 2MeCH$_2$); 2.36 (s, 3H, 4'-Me); 2.63 (s, 3H, 7-Me); 4.27, 4.34 (2q, 4H, *J* = 7.1 Hz, 2OCH$_2$); 7.23 (d, 1H, *J* = 9.4 Hz, H-3); 7.25 (d, 2H, *J* = 8.3 Hz, H-3', H-5'); 7.82 (d, 2H, *J* = 8.3 Hz, H-2', H-6'); 8.37 (d, 1H, *J* = 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$): δ: 9.9 (7-Me); 14.4, 14.5 (2MeCH$_2$); 21.4 (4'-Me); 60.2, 60.3 (2OCH$_2$); 102.3 (C-5); 113.2 (C-3); 119.6, 127.9, 128.5 (C-4a, C-6, C-7); 126.8 (C-2', C-6'); 128.3 (C-4); 129.7 (C-3', C-5'); 133.0 (C-1'); 140.4 (C-4') 151.6 (C-2); 163.5, 165.9 (2COO).

Diisopropyl 2-(4-methylphenyl)-7-methyl-pyrrolo [1,2-b]pyridazine-5,6-dicarboxylate (**8d**). The product was recrystallized from ethyl acetate and fluorescent yellow crystals with mp 159-161°C were obtained; Yield 55 %. Anal. Calcd. $C_{23}H_{26}N_2O_4$: C 70.03; H 6.64; N 7.10. Found C 70.31; H 6.87; N 7.29.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.37, 1.41 (2d, 12H, *J* = 6.3 Hz, 2 **Me**$_2$CH); 2.40 (s, 3H, 4'-Me); 2.66 (s, 7-Me); 5.26, 5.31 (2 sept, 2H, *J* = 6.3 Hz, 2OCH); 7.25-7.29 (m, 3H, H-3, H-3', H-5'); 7.86 (d, 2H, *J* = 8.3 Hz, H-2', H-6'); 8.40 (d, 1H, *J* = 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 9.8 (7-Me); 21.4 (4'-Me); 22.0, 22.2 (2**Me**$_2$CH); 67.7, 68.9 (2**Me**$_2$CH); 102.6 (C-5); 113.0 (C-3); 119.9, 127.9, 128.6 (C-4a, C-6, C-7); 126.9 (C-2', C-6'); 128.3 (C-4); 129.7 (C-3', C-5'); 133.1 (C-1'); 140.4 (C-4') 151.7 (C-2); 163.0, 165.3 (2COO).

Diethyl 2-(4-chlorophenyl)-7-methyl-pyrrolo[1,2-b]pyridazine-5,6-dicarboxylate (**8e**). The product was recrystallized from isopropanol and fluorescent yellow crystals with mp 123-5°C were obtained; Yield 63 %. Anal. Calcd. $C_{20}H_{19}ClN_2O_4$: C 62.10; H 4.95; Cl 9.16; N 7.24. Found C 62.32; H 5.18; Cl 9.55; N 7.52.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.38, 1.42 (2t, 6H, *J* = 7.1 Hz, MeCH$_2$); 2.66 (s, 7-Me); 4.35, 4.44 (2q, 4H, *J* = 7.1 Hz, 2OCH$_2$); 7.23 (d, 1H, *J* = 9.4 Hz, H-3); 7.47 (d, 2H, *J* = 8.6 Hz, H-3', H-5'); 7.92 (d, 2H, *J* = 8.6 Hz, H-2', H-6'); 8.46 (d, 1H, *J* = 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$): δ: 9.8 (7-Me); 14.3, 14.5 (2**Me**CH$_2$); 60.3, 61.3 (2CH); 102.6 (C-5); 112.6 (C-3); 119.6, 127.8, 128.5 (C-4a, C-6, C-7); 128.2 (C-2', C-6'); 128.6 (C-4); 129.2 (C-3', C-5'); 134.1 (C-1'); 136.4 (C-4'); 150.6 (C-2); 163.4, 165.7 (2COO).

Diisopropyl 2-(4-chlorophenyl)-7-methyl-pyrrolo[1,2-b]pyridazine-5,6-dicarboxylate (**8f**). The product was recrystallized from ethyl acetate and fluorescent yellow crystals with mp 159-161°C were obtained; Yield 51 %. Anal. Calcd. $C_{22}H_{23}ClN_2O_4$: C 63.69; H 5.59; Cl 8.55; N 6.75. Found C 63.92; H 5.86; Cl 8.82; N 7.02.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.38, 1.42 (2d, 12H, *J* = 6.3 Hz, 2 **Me**$_2$CH); 2.65 (s, 7-Me); 5.26, 5.32 (2 sept, 2H, *J* = 6.3 Hz, 2OCH); 7.26 (d, 1H, *J* = 9.4 Hz, H-3); 7.46 (d, 2H, *J* = 8.7 Hz, H-3', H-5'); 7.92 (d, 2H, *J* = 8.7 Hz, H-2', H-6'); 8.44 (d, 1H, *J* = 9.4 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$):δ: 9.8 (7-Me); 22.0, 22.2 (2**Me**$_2$CH); 67.8, 69.0 (2**Me**$_2$CH); 102.9 (C-5); 112.5 (C-3); 120.3, 127.6, 128.5 (C-4a, C-6, C-7); 128.2 (C-2', C-6'); 128.7 (C-4); 129.3 (C-3', C-5'); 134.3 (C-1'); 136.4 (C-4'); 150.6 (C-2); 162.9, 165.2 (2COO).

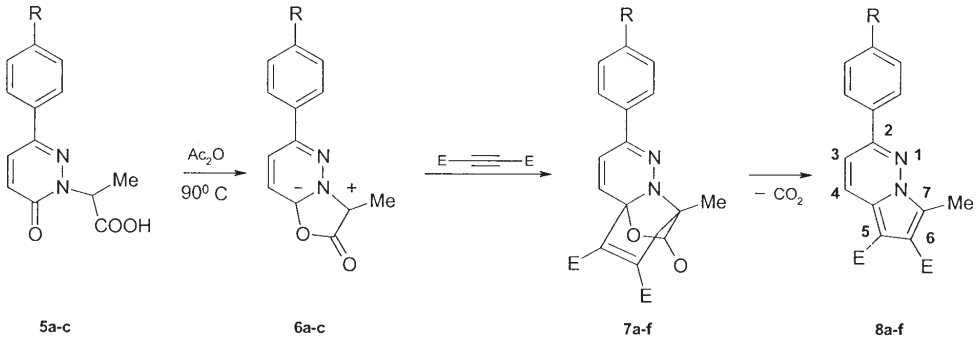
Results and discussion

The key intermediates in the synthesis of pyrrolo[1,2-b]pyridazines **8** were acids **5a-c**, which were obtained by a known procedure [9a-c] consisting of an *N*-alkylation of 3(2*H*)-pyridazinones **3** with ethyl esters of 2-bromopropanoic followed by alkaline hydrolysis and acidification (scheme 2). The 3(2*H*)-pyridazinones **3** were prepared by the reaction between ketoacids **1** and hydrazine, followed by dehydrogenation with bromine in acid acetic medium.

The synthesis of pyrrolopyridazines **8a-f** was achieved by the reaction between acids **5a-c** and diethyl or diisopropyl acetylenedicarboxylate as acetylenic dipolarophiles. The reaction was performed in acetic anhydride at 90°C for 3-4 h. By this method the new compounds **8a-f** (scheme 3) were obtained in moderate yields (51-63%) as yellow crystals which showed high fluorescence both in solution and in the solid state. The mechanism involves in the first step the formation of the mesoionic bicyclic structures **6** by action of acetic anhydride on acids **5a-c**. The mesoionic 1,3-dipoles react with the acetylenic dipolarophiles, giving the intermediates **7** which eliminate carbon dioxide under the reaction conditions, giving fused pyrrole[1,2-b]pyridazine derivatives **8a-f**. The structures of new compounds **8** were confirmed by elemental analysis and NMR spectroscopy.

In the H-NMR spectra of pyrrolopyridazines **8** the presence of a methyl group attached at the pyrrole ring is evidenced by a singlet with chemical shift in the range 2.63-2.67 ppm. The two protons (H-3 and H-4) of the pyridazine moiety appear as two doublets with the value of the coupling constant $^3J_{3,4}$ = 9.4 Hz. The proton H-4 (δ = 8.37-8.46 ppm) is deshielded by ca. 1.2-1.3 ppm with respect to H-3 (δ = 7.23-7.32 ppm) as a consequence of the steric and electronic effects of the 5-carboalkoxy group.

^{13}C-NMR spectra show all the expected signals. The values of the chemical shifts for the C-3 and C-4 of the 5-azaindolizine moiety in compounds **8** were established by C/H correlation experiments.



Scheme 3

a: R = H, E = CO_2Et; **b**: R= H, E = CO_2*i*Pr; **c**: R = Me, E = CO_2Et; **d**: R = Me, E = CO_2*i*Pr;
e: R = Cl, E = CO_2Et; **f**: R = Cl, E=CO_2*i*Pr

The atom C-2 (δ=150.6-151.6 ppm) of the pyrrolopyridazines **8** is the most deshielded with respect to the other atoms from the pyrrolopyridazine system, as it is part of a C-N double bond, and is also subjected to the supplementary deshielding effect of the aryl group at C-2.

The strong shielding observed for C-5 (δ = 102.3-102.6 ppm) is a consequence of its relative position β to the pyrrole nitrogen. Also, a small shielding of 1 ppm is observed due to the 7-methyl group, as compared to non 7-substituted compounds [8]. Furthermore, the effect of the 7-methyl group can be observed in the case of C-3 (δ = 112.5-113.2 ppm), which is shielded by ca. 1.5 ppm as compared to non 7-substituted pyrrolopyridazines (δ ~ 114.3 ppm). No such effect was observed for C-4, which appears consistently at δ = 128.3-129.0 ppm. C-7 (δ= 128.5 ppm) is deshielded by about 7 ppm by the presence of the 7-methyl group.

Conclusions

The bicyclic munchnones **6**, generated *in situ* from 2-[2(3*H*)pyridazinone-1-yl]propanoic acids **5** and acetic anhydride, reacted with diethyl or diisopropyl acetylenedicarboxylate giving highly fluorescent pyrrolo[1,2-b]pyridazine derivatives **8**. The structures of new compounds **8** were confirmed by elemental analysis and NMR spectroscopy.

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