A Novel Approach for the Synthesis of Highly Fluorescent Pyrrolo[1,2-*b*]pyridazines

Florea Dumitrașcu,[a] Mino R. Caira,*[b] Bogdan Drăghici,[a] Miron Teodor Căproiu,[a] Dan G. Dumitrescu[a]

[a] Centre of Organic Chemistry 'C. D. Nenitzescu', Romanian Academy, Spl. Independentei 202B, 060023 Bucharest, Romania

[b] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
Fax +27(21)6897499; E-mail: Mino.Caira@uct.ac.za

Received 26 June 2007

Abstract: Pyrrolo[1,2-*b*]pyridazine derivatives were synthesized for the first time by 1,3-dipolar cycloaddition reaction between mesoionic 1,3-oxazolo[3,2-*b*]pyridazinium-2-oxides and acetylenic dipolarophiles. The isolation and characterization of the stable mesoionic oxazolo[3,2-*b*]pyridazines are also presented.

Key words: 1,3-dipolar cycloaddition, mesoionic oxazolopyridazine, pyrrolo[1,2-*b*]pyridazines, Michael addition, hydrogenation

Pyrrolopyridazine derivatives have various biological applications,[1–6] and their fluorescent properties have been investigated for potential uses in sensors, lasers, and semiconductor devices.[7–11]

The synthesis and properties of pyrrolo[1,2-*b*]pyridazine derivatives were reviewed in 1977 by Kuhla and Lombardino.[12] Subsequently, new methods for the synthesis of these compounds were described, which can be classified into two main approaches. The first comprises condensation reactions, such as the condensation of oxazolo[3,2-*b*]pyridazinium perchlorates with malonitrile, ethyl cyano acetate and ethyl malonate in the presence of sodium ethoxide,[13] the condensation of 1,4,7-triketones with hydrazine followed by dehydrogenation,[14] the condensation of cyanacetic acid hydrazide with 3-bromo-1,1,3-tricyano-2-phenylpropene,[15] and the reaction between 3-chloropyridazines with propargylic alcohol in the presence of a $Pd(PPh_3)_2Cl_2$–CuI with diethylamine as the reaction medium.[16] The second path is based on cycloaddition reactions, such as the cycloaddition of dimethyl acetylenedicarboxylate to the Reissert compound of pyridazine,[17] the 1,3-dipolar cycloaddition of pyridazinium dichloromethylide generated by the carbene method,[18] and the cycloaddition of alkylidene cyclopropane derivatives to pyridazine in the presence of $Pd(PPh_3)_4$.[19] Unsubstituted pyrrolo[1,2-*b*]pyridazine **1** was obtained by Flitsch and Kramer (Figure 1).[20]

One of the most versatile synthetic routes for obtaining pyrroles, fused pyrroles, and derived ring systems is via 1,3-dipolar cycloaddition reactions between acetylenic dipolarophiles and mesoionic oxazolones, so called münchnones.[21a–g] Due to their usually low stability, they are mostly generated in situ in the presence of the dipolarophile. The traditional Huisgen synthesis of münchnones,[22a,b] involving cyclodehydration of *N*-acylamino acids, usually with acetic anhydride or other acid anhydrides, is still the method of choice due to its simplicity, although other synthetic methods have since been discovered.[21a,b]

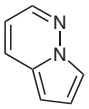

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Figure 1 Unsubstituted pyrrolo[1,2-*b*]pyridazine

A survey of the literature indicated that mesoionic oxazolo[3,2-*b*]pyridazin-2-ones and their reactions leading to pyrrolo[1,2-*b*]pyridazines have not been reported to date.

Herein we report a new method for the synthesis of highly fluorescent pyrrolo[1,2-*b*]pyridazines, namely 1,3-dipolar cycloaddition between mesoionic oxazolo[3,2-*b*]pyridazine-2-ones and dimethyl acetylenedicarboxylate (DMAD) as dipolarophile.

The starting materials for the synthesis of pyrrolo[1,2-*b*]pyridazine derivatives were 3(2*H*)-pyridazinone acetic acids **2a–d** and propanoic acids **6a–d**, respectively (structures in Scheme 1). The compounds **2** and **6** were easily prepared by a documented procedure[23a–f] consisting of an N-alkylation of 3(2*H*)-pyridazinones[24a–d] with esters of bromoacetic and bromopropanoic acid followed by alkaline hydrolysis.

The synthesis of pyrrolopyridazines was performed by treatment of acids **2a–d** with DMAD in acetic anhydride at 90 °C for three hours. By this method the new compounds **5a–d** were obtained in good yield (53–60%) as yellow crystals which showed high fluorescence both in solution and in the solid state (Scheme 1). The mechanism involves the generation in the first step of the previously unknown mesoionic structures **3** by cyclodehydration of acids **2** through the action of acetic anhydride. Under reaction conditions the intermediate adducts **4**, resulting from mesoionic 1,3-dipole and dipolarophile (DMAD), lose carbon dioxide giving fused pyrroles **5**. The elemental analysis and NMR spectroscopy confirmed the structure of the compounds **5**.[25]

SYNLETT 2008, No. 6, pp 0813–0816
Advanced online publication: 11.03.2008
DOI: 10.1055/s-2008-1042929; Art ID: D19107ST

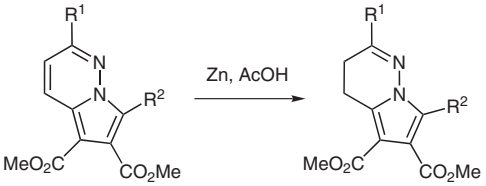
It is interesting to note that under similar reaction conditions and in the absence of DMAD from the acetic acid anhydride medium, the mesoionic compounds **3b** and **3d**, were isolated as yellow precipitates. The mesoionic structure was assigned on the basis of NMR spectroscopy.[26] Thus, in the ^{1}H NMR spectra, the presence of a methyl group grafted to the 3-position of the oxazole ring is evidenced by a singlet and the two protons of the pyridazine moiety by two doublets. The most characteristic feature in the ^{13}C NMR spectra for the mesoionic structure is the strongly shielded signal for methyl groups (δ = 6.9 ppm and 7.0 ppm), as well as the presence of the deshielded (to ca. δ = 160 ppm) signals attributed to the mesoionic carbonyl group. The values of chemical shifts for the methyl groups in the ^{13}C NMR spectra of compounds **3b** and **3d** are close to those from pyrrolopyridazine **5**. This represents good evidence that the methyl radical is grafted to the C-3 carbon atom of the five-membered heteroaromatic ring.

The münchnones generated from 2-[2(3*H*)pyridazin-1-yl]acetic acids **6a–d**, under similar reaction conditions, reacted with DMAD via two parallel routes (Scheme 1). The resulting mixture consisted of the expected pyrrolopyridazine derivatives **7a–d** along with variable amounts of mesoionic oxazolo[3,2-*b*]pyridazin-2-ones **8a–d**.[27] The formation of these latter compounds could be explained by the Michael addition of DMAD to the mesoionic münchnone ring in the 3-position. The Michael addition is well known in the series of pyrrole and condensed pyrrole derivatives,[28a–g] but to our knowledge there are no such examples in the class of münchnones.

The assignment of the configuration of the Michael adducts **8** was deduced from the off-resonance spectrum of compound **8a** on the basis of the $^3J_{C–H}$ coupling constant. The value of the ^3J constant between H-10 and C-9 is found to be 11.5 Hz, whereas $^3J_{C-3–H-10}$ presented a value of 6.5 Hz. These values for $^3J_{C–H}$ provide strong evidence for a *trans* configuration of the alkene moiety. The correlation method between the values of $^3J_{C–H}$ and configuration was successfully applied in the case of trisubstituted alkenes and buten-2-ene-1,4-dioates substituted in the 2-position with an aryl or pyrrole ring.[28g,29a–c]

It must be mentioned that the mesoionic compounds **8a–d** are more stable in protic solvents (e.g., water or methanol) than their analogues containing a methyl group in the oxazole moiety (**3b** and **3d**). The optical properties of mesoionic oxazolones **8** were recently reported.[30a,b]

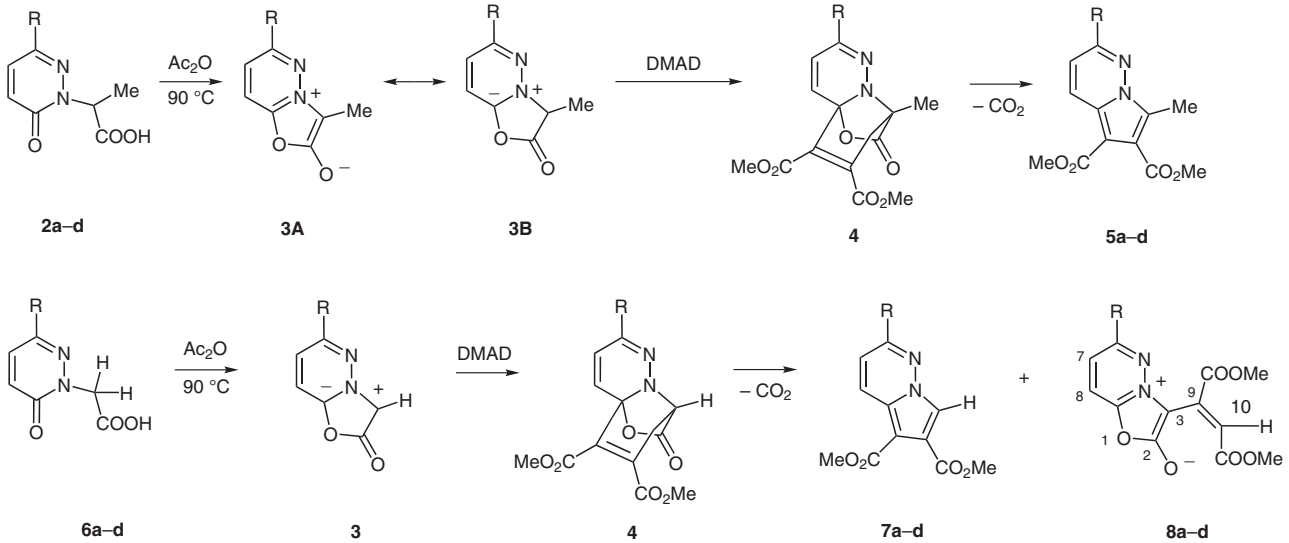
The chemical properties of pyrrolopyridazines include the transformation of the functional groups substitution and oxidation reactions.[12,28c] Herein we report their selective hydrogenation (Scheme 2). The reduction was performed with Zn in AcOH under reflux to give 3,4-dihydroderivatives **9a–c**.[31]



a: $R^1 = R^2 = Me$; **b**: $R^1 = Ph$, $R^2 = H$; **c**: $R^1 = 4\text{-}MeC_6H_4$, $R^2 = H$

Scheme 2 Reductive hydrogenation of pyrrolo[1,2-*b*]pyridazines

The stereostructure for a representative compound in this series (**9b**, $R^1 = Ph$, $R^2 = H$) was determined by X-ray crystal structure analysis[32] which showed that in the novel 6,5-bicyclic system present, the ring N1 → C6 has a conformation between that of a half-chair and a twist boat (Figure 2). Endocyclic torsion angles (average e.s.d. 0.2°)



a: R = Me; **b**: R = Ph; **c**: R = 4-MeC_6H_4; **d**: R = 4-ClC_6H_4

Scheme 1 Synthesis of pyrrolo[1,2-*b*]pyridazines

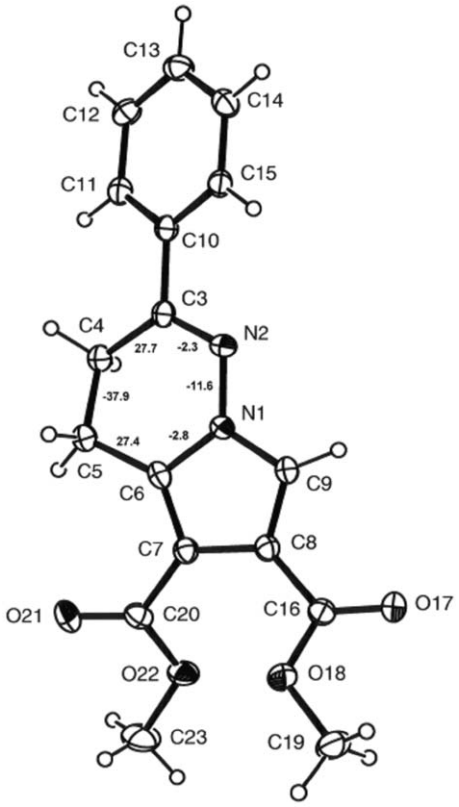


Figure 2 X-ray crystal structure of **9b** (R^1 = Ph, R^2 = H) with thermal ellipsoids drawn at the 50% level

defining the exact conformation are included in Figure 2. As found in 2-(4-chlorophenyl)-7-methyl-pyrrolo[1,2-*b*]pyridazine,[33] the phenyl group in **9** is not coplanar with the pyrrolopyridazine moiety. Here, the angle between the least-squares planes through the phenyl and pyrrole rings is 27.3(1)°.

Acknowledgment

M.R.C. thanks the University of Cape Town for research support.

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(25) **General Procedure for the Synthesis of Compounds 5**
3 (2*H*)-Pyridazinone acid **2** (5 mmol) were suspended with stirring in Ac_2O (5 mL) and then DMAD (5.5 mmol) was added.The reaction mixture was kept at ca. 90 °C for 3−4 h. The pyrrolopyridazine derivatives **5** were isolated by filtration or by evaporation of the solvent. In the latter case, the crude product was purified by recrystallization or by column chromatography using CH_2Cl_2 as eluent.

Dimethyl 2,7-Dimethylpyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (5a)
Colorless crystals from EtOH with mp 135−136 °C; yield 60%. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.87; H, 5.70; N, 10.93. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 2-Me), 2.61 (s, 3 H, 7-Me), 3.89, 3.95 (2 s, 6 H, 2 MeO), 6.76 (d, 1 H, *J* = 9.3 Hz, H-3), 8.27 (d, 1 H, *J* = 9.3 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.7 (7-Me), 21.8 (2-Me), 51.3, 52.2 (2 MeO), 101.6 (C-5), 116.3 (C-3), 117.7, 127.6, 128.3 (C-4a, C-6, C-7), 127.5 (C-4), 152.4 (C-2), 163.8, 166.3 (2 COO).

(26) **General Procedure for the Synthesis of Compounds 3**
Acid **6b** or **6d** (1 g) in Ac_2O (3 mL) was kept at ca. 90 °C for 3 h. The yellow precipitate was filtered and washed with Ac_2O and then with anhyd Et_2O.
3-Methyl-6-phenyloxazolo[3,2-*b*]pyridazinium-2-oxide (3b)
Yellow crystals from Ac_2O with mp 199–202 °C; yield 72%. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.43; H, 4.78; N, 12.70. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, 3-Me), 7.31, 7.36 (2 d, 2 H, *J* = 8.8 Hz, H-7, H-8), 7.48–7.53, 7.89–7.94 (2 m, 5 H, H-2′, H-3′, H-4′, H-5′, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9 (3-Me), 94.7 (C-3), 110.0, 112.3 (C-7, C-8), 126.7, 129.0 (C-2′, C-3′, C-5′, C-6′), 130.2 (C-4′) 134.6 (C-1′), 138.4 (C-8a), 153.9 (C-6), 160.4 (2-CO).

(27) **General Procedure for the Synthesis of 7 and 8**
The experimental procedure for compounds **7** and **8** was similar to those for pyrrolopyridazines **5**. The two compounds were isolated by column chromatography using neutral alumina (Merck 200–20 mesh) and CH_2Cl_2 as eluent.
Dimethyl 2-Methylpyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (7a)
Colorless crystals from EtOH with mp 89–91 °C; yield 22%. Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 59.34; H, 5.21; N, 10.50. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 2-Me), 3.91, 3.92 (2 s, 6 H, 2 MeO), 6.75 (d, 1 H, *J* = 9.3 Hz, H-3), 7.92 (s, 1 H, H-7), 8.26 (d, 1 H, *J* = 9.3 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (2-Me), 51.4, 52.1 (2 MeO), 103.4 (C-5), 117.3 (C-3), 117.9, 128.7 (C-4a, C-6, C-7), 121.0 (C-7), 128.2 (C-4), 153.4 (C-2), 163.7, 164.5 (2 COO).
Dimethyl 3-[(*E*)-(Buten-2-yl-1,4-dioate)]-6-methyloxazolo[3,2-*b*]pyridazinium-2-oxide (8a)
Yellow crystals from MeCN with mp 180−183 °C; yield 39%. Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.59; H, 4.33; N, 9.74. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, 6-Me), 3.76, 3.99 (2 s, 6 H, 2 MeO), 6.97 (s, 1 H, =CHCOO), 7.21 (d, 1 H, *J* = 8.8 Hz, H-7), 7.45 (d, 1 H, *J* = 9.3 Hz, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (6-Me), 51.7, 52.9 (2 MeO), 94.2 (C-3), 109.5 (C-10), 113.1 (C-8), 121.5 (C-7), 135.6 (C-9), 140.8 (C-8a), 155.4 (C-6), 156.8 (2-CO), 166.1, 166.7 (2 COO). Off-resonance NMR experiment: $J_{C\text{-}3\text{–}H\text{-}10}$ = 6.3 Hz; $J_{9\text{-}CO\text{–}H\text{-}10}$ = 11.5 Hz.

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(31) **General Procedure for the Synthesis of Compounds 9**
Esters **5** or **6** (2 mmol) were dissolved in AcOH (10 mL) and under reflux was added Zn powder (3 mmol) over a period of 3 h. The reaction was monitored by ^{1}H NMR or TLC. In the case when the reaction was found to be incomplete, Zn (1 mmol) was added and refluxing was continued for ca. 2 h. The hot reaction mixture was filtered and the precipitate was washed with AcOH. The AcOH was removed and the residue was purified by column chromatography.
Dimethyl 2-Phenyl-3,4-dihydropyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (9b)
Colorless crystals from EtOH with mp 145–147 °C; yield 77%. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.72; H, 5.33; N, 9.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.92 (t, 2 H, *J* = 8.1, 8.0 Hz, 3-CH_2), 3.26 (t, 2 H, *J* = 8.1, 8.0 Hz, 4-CH_2), 3.84, 3.87 (2 s, 6 H, 2 MeO), 7.46−7.48 (m, 3 H, H-3′, H-4′, H-5′), 7.54 (s, 1 H, H-7), 7.85–7.88 (m, 2 H, H-2′, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (4-CH_2), 21.2 (3-CH_2), 51.4, 51.5 (2 MeO), 109.7, 113.9, 127.2 (C-4a, C-5, C-6), 125.5 (C-7), 126.4, 128.7 (C-2′, C-3′, C-5′, C-6′), 131.0 (C-4′), 135.2 (C-1′), 160.0 (C-2), 164.0, 165.5 (2 COO).

(32) Crystal data for **9b** (R^1 = Ph, R^2 = H): $C_{17}H_{16}N_2O_4$; colorless plate; *M* = 312.32, orthorhombic, *Pbca*, *a* = 8.1844(2) Å, *b* = 13.4925(3) Å, *c* = 27.0683(6) Å, *V* = 2989.1(1) Å^3, *Z* = 8, *T* = 113(2) K, F_{000} = 1312, *R*1 = 0.0440, *wR*2 = 0.1089. The CCDC deposition number is 651836.

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