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A NOVEL APPROACH FOR THE SYNTHESIS OF PYRROLO[1,2-b]PYRIDAZINE DERIVATIVES

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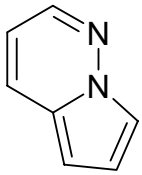
The reaction of *N*-phenacylpyridazinium bromides **3** and **7** with acrylonitrile as activated olefinic dipolarophile gave in the presence of triethylamine and the oxidant tertrakis-pyridinecobalt(II) dichromate (TPCD) in DMF at 90 ºC pyrrolo[1,2-b]pyridazine derivatives **6** and **8**. Structural proof for the compounds was provided by elemental analysis and NMR spectroscopy, including COSY and HETCOR experiments.

INTRODUCTION

The synthesis and properties of pyrrolo[1,2-b]pyridazines were reviewed by Kuhla and Lombardino in 1976[1] and the parent compound was obtained by condensation of 1-aminopyrrole with β-hydroxyacrolein diethylacetal.[2] Even though after 1976 new methods for the synthesis of pyrrolo[1,2-b]pyridazine derivatives were reported[3a-g], the 1,3-dipolar cycloaddition reactions of pyridazinium *N*-ylides continue to be the most important method for the preparation of pyrrolo[1,2-b]pyridazine derivatives.[4a-f]



Pyrrolo[1,2-b]pyridazine

The pyrrolo[1,2-b]pyridazine derivatives are interesting due to their biological and optical properties.[5-15] The high fluorescence of pyrrolo[1,2-b]pyridazines in solution and in solid state recommends them in the design of novel optically active materials. Also, it was demonstrated that the optical properties are influenced by the nature and numbers of substituents grafted on the pyrrolopyridazine system.[11-15]

Herein we report the one pot synthesis of potential blue organic luminophors pyrrolo[1,2-b]pyridazine derivatives by 1,3-dipolar cycloaddition reactions between pyridazinium *N*-ylides and acrylonitryle as dipolarophile and in the presence of the oxidant reagent tetrakis-pyridine cobalt (II) dichromate (TPCD).

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reactions of pyridazinium *N*-ylides with acrylonitrile were reported to give 5-cyano-4a,5,6,7-tetrahydropyrrolo [1,2-b]pyridazine derivatives of type **5** (Scheme 1).[16a-c] As it was mentioned above the optical properties of pyrrolopyridazine can be influenced by the nature of the substituents. In order to obtain new pyrrolopyridazine derivatives having attached at the pyrrole moiety a cyano group, the possibility of aromatization of the 5-cyano-4a,5,6,7-tetra-hydropyrrolo[1,2-b]pyridazines to the corresponding pyrrolo[1,2-b]pyridazines was investigated.

According to the literature data, tetrakis-pyridine cobalt (II) dichromate [$Py_4Co(HCrO_4)_2$]; TPCD is an oxidant reagent which was used with

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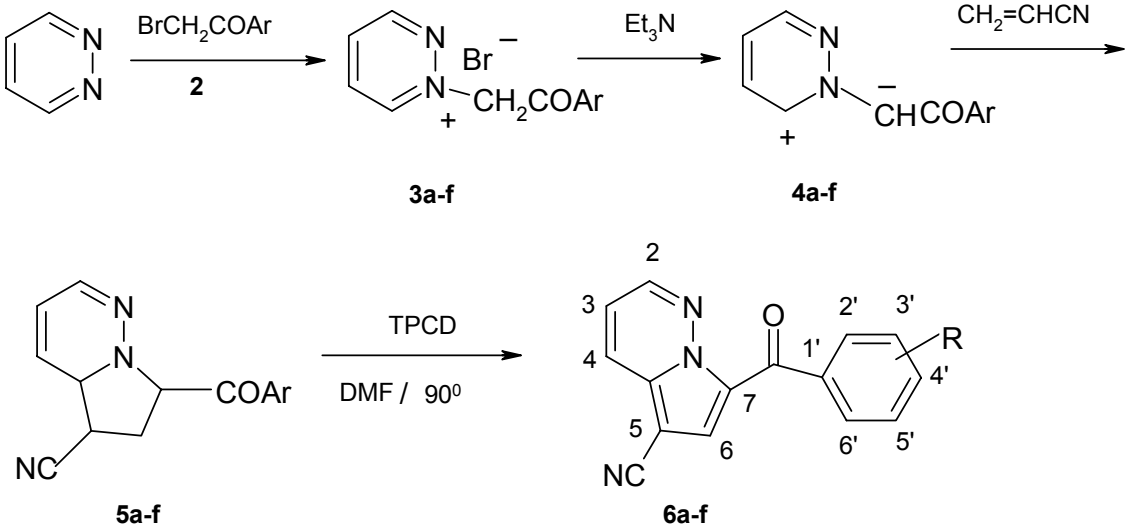
good results for the oxidation of alcohols, as well as the dehydrogenation of cycloadducts resulted by the reaction between heteroaromatic *N*-ylides and olefinic or acetylenic dipolarophiles.[17a-f]

The intermediates for the synthesis of pyrrolopyridazines **6**, pyridazinium bromides **3**, were easily prepared by *N*-alkylation of pyridazine **1** with 2-bromoacetophenones **2** in acetone at room temperature (Scheme 1). The tetrahydroderivatives **5** (Scheme 1) were prepared from pyridazinium bromides and acrylonitrile in the presence of triethylamine in dichloromethane. Usually, the pyridazinium *N*-ylides are unstable compounds and they are generated *in situ* by the reaction between *N*-alkylated pyridazinium salts and triethylamine. After the reaction mixture was washed with water to remove the triethylammonium bromide, the dichloromethane was evaporated and the residue containing the tetrahydroderivatives **5** was treated with TPCD in DMF at 80-90ºC to give in good yields 7-aroyl-5-cyano-pyrrolo[1,2-b]pyridazines **6**. It must be mentioned that the primary cycloadducts **5** were found to be unstable in solution due their tendency to oxidize with oxygen from air,[16a] but more stable in solid state as previously reported.[16a-c]

The pyrrolopyridazine derivatives **6** were obtained more easily by a "one pot" reaction from bromides **3**, acrylonitrile, triethylamine and TPCD, in DMF at 90 °C.

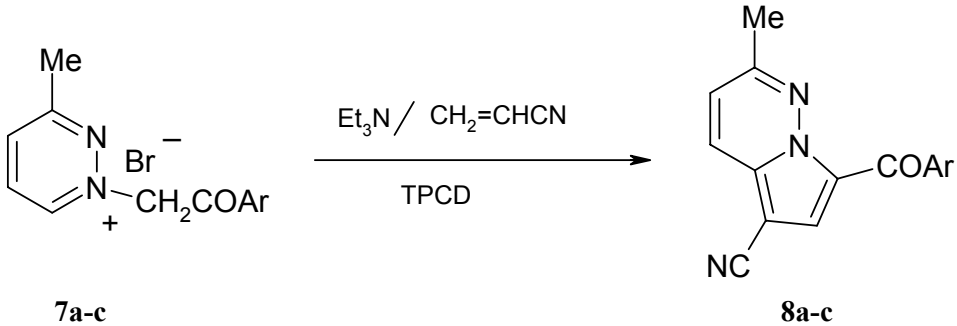
The cycloaddition reaction between acrylonitrile and pyridazinium *N*-ylides was found to be completely regioselective, as only one regioisomer could be observed by H-NMR spectroscopy.



Ar: a = C_6H_5; b = 4-$C_6H_4C_6H_5$; c = 4-FC_6H_4; d = 3-BrC_6H_4; e = 4-BrC_6H_4; f = 3-$O_2NC_6H_4$; g = 4-$O_2NC_6H_4$

Scheme 1

Similarly, starting from 3-methylpyridazine and 2-bromoacetophenones, 3-methylpyridazinium bromides **7a-c** were obtained and subsequently transformed in the corresponding 2-methyl-pyrrolopyridazine derivatives **8a-c** by treatment with acrylonitrile in the presence of triethylamine and TPCD in DMF at 90 °C.



Ar: a = C_6H_5; b = 4-BrC_6H_4; c = 4-$OMeC_6H_4$

Scheme 2

The structure of pyrrolopyridazines was confirmed by NMR spectroscopy. The chemical shifts for hydrogen and carbon atoms were established on the basis of multiplicity, the magnitude of the coupling constants, as well as by classical two dimensional H/H and H/C correlations. In the NMR spectra of nitriles **6**, the three protons (H2, H3, H4) from the pyridazine moiety appear as an ABC system with the following coupling constants: $^{3}J_{2,3}$ = 4.5 Hz, $^{4}J_{2,4}$ = 1.9 Hz and $^{3}J_{3,4}$ = 9.2 Hz. In the 2-methyl derivatives **8**, the two protons from the pyridazine ring appear as two doublets with $^{3}J_{3,4}$ = 9.2 Hz. The proton H-2 in the compounds **6** is strongly deshielded because it is part of a C-N double bond. The signal for H-7 proton is a sharp singlet with a chemical shift in the range 7.55-7.60 ppm ($CDCl_3$). The signal for H-7 proton is a sharp singlet with a chemical shift in the range 7.55-7.60 ppm ($CDCl_3$).

The chemical shifts for the carbon atoms from pyrrolopyridazines **6** were assigned by using heteronuclear H-C correlation experiments (HETCOR). The atom C-2 (δ = 144.8-145.7 ppm) from the pyrrolopyridazines **6** is highly deshielded in respect with the other atoms from the pyrrolopyridazine system, as it is part of a C-N double bond. The grafting of a methyl group in the 2 position of pyrrolopyridazine moiety has a deshielding effect at positions 2 with about 9 ppm, The strong shielding observed for C-5 (δ around 84 ppm) is a consequence of its relative β positions to the pyrrole nitrogen, as well as the effect of cyano group. By comparsion with 7-aroyl-5-carboethoxy-pyrrolopyridazines,[4e] where the cyano group was replaced with an ester group, the chemical shift for C-2 is around of 105 ppm.

Additional evidence for the pyrrolopyridazine compounds was provided by FT-IR spectroscopy. The most characteristic features are the peaks corresponding to the cyano group which appears in the range 2213-2226 cm^{-1} and the carbonyl group (1635-1646 cm^{-1}).

EXPERIMENTAL

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. Supplementary evidence was given by HETCOR and COSY experiments. FT-IR spectra were recorded on a Brucker Vertex 70 spectrometer.

General procedure for preparation of pyridazinium bromides 3

10 Mmol of pyridazine and 10 mmol 2-bromoacetophenone in acetone(50-100 mL) were kept at room temperature for 24 h or refluxed for six hours with stirring. The precipitate was filtered and was washed with acetone to give bromide 3 which was used in the next step without further purification.

General procedure for preparation of pyrrolo[1,2-b]pyridazines 6

5 Mmol of pyridazinium bromides **3** and 15 mmoles of acrylonitrile in 30 mL DMF were treated under stirring and at room temperature with 0.7 mL (5 mmol) triethylamine. After 30 min. was added 3 g TPCD and at the reaction mixture was heated at 80-90 ºC for 4 h. Then the mixture was cooled at room temperature and 50 mL 5% aqueous HCl were added and the precipitated was filtered and air dried. The crude product was purified by chromatography with a short column (Aluminium oxide 90 standardized, chloroform).

7-Benzoyl-5-cyano-pyrrolo[1,2-b]pyridazine (**6a**). The product was recrystallized from acetonitrile and colorless crystals with mp 165-7 °C were obtained. Yield 57%. Anal. Calcd. $C_{15}H_9N_3O$: C 72.87, H 3.67, N 16.99. Found: N, C 73.11, H 3.94, N 17.24. IR (ATR, cm^{-1}): 1644 (CO); 2225 (CN); 3059 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.20 (dd, 1H, *J* = 9.2, 4.5 Hz, H-3); 7.55 (s, 1H, H-6); 7.48-7.53 (m, 2H, H-3', H-5'); 7.58-7.64 (m, 1H, H-4'); 7.84-7.88 (m, 2H, H-2', H-6'); 8.14 (dd, 1H, *J* = 9.2, 1.9 Hz, H-4); 8.57 (dd, 1H, *J* = 4.5, 1.9 Hz, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 84.4 (C-5); 114.0 (CN); 117.7 (C-3); 125.0 (C-6); 125.9 (C-4); 127.2 (C-7); 128.6 (C-3', C-5'); 129.5 (C-2', C-6'); 132.8 (C-4'); 134.7 (C-4a); 138.5 (C-1'); 144.8 (C-2); 183.6 (COAr).

7-(4-Phenylbenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6b**). The product was recrystallized from benzene or acetonitrile as colorless crystals with mp 213-4 ºC were obtained. Yield 69%. Anal. Calcd. $C_{21}H_{13}N_3O$: C 78.00, H 4.05, N 12.99. Found: C 78.34, H 4.29, N 13.16. IR (ATR, cm^{-1}): 1635 (CO); 2224 (CN); 3053 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, 1H, 9.2, 4.5, H-3); 7.34-7.39 (m, 1H, H-4"); 7.41-7.47 (m, 2H, H-3", H-5"); 7.57 (s, 1H, H-6); 7.58-7.62 (m, 2H, H-2", H-6"); 7.69 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 7.92 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 8.11 (dd, 1H, *J* = 9.2, 1.7, H-4); 8.53 (dd, 1H, *J* = 4.5, 1.7, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 84.6 (C-5); 114.4 (CN); 118.1 (C-3); 125.3 (C-6); 126.1 (C-4); 127.2 (C-7); 127.5, 128.6, 129.3, 130.4 (9C, C-2', C-3', C-5', C-6', C-2", C-3", C-4", C-5", C-6"); 135.0 (C-4a); 135.0 (C-1'); 137.1 (C-1'); 140.0 (C-1"); 145.0 (C-2); 145.9 (C-4'); 183.4 (COAr).

7-(4-Fluorobenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6c**).The product was recrystallized from acetonitrile and colorless crystals with mp 211-2 °C were obtained. Yield 53 %. Anal. Calcd. $C_{15}H_8FN_3O$: N 15.84. Found: N 16.01. IR (ATR, cm^{-1}): 1644.0 (CO); 2225 (CN); 3070; 3135 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (dd, 1H, *J* = 9.2, 4.5 Hz, H-3); 7.26 (t, 2H, *J* = 8.9 Hz, H-3', H-5'); 7.56 (s, 1H, H-6); 7.93 (dd, 2H, *J* = 8.9, 5.3 Hz, H-2', H-6'); 8.18 (dd, 1H, *J* = 9.2, 1.9 Hz, H-4); 8.58 (dd, 1H, *J* = 4.5, 1.9 Hz, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 84.4 (C-5); 114.0 (CN); 115.7 (d, *J* = 22.1 Hz, C-3', C-5'); 117.8 (C-3); 124.7 (C-6); 126.0 (C-4); 127.0 (C-7); 132.1 (d, *J* = 9.6 Hz, C-2', C-6'); 134.4 (C-4a); 134.4 (d, *J* = 2.8 Hz, C-1'); 144.8 (C-2); 165.6 (d, *J* = 225.9 Hz, C-4'); 182.1 (COAr).

7-(3-Bromobenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6d**). The product was recrystallized from acetonitrile and colorless crystals with mp 205-7 °C were obtained. Yield 55 %. Anal.

Calcd. $C_{15}H_8BrN_3O$: N 12.88. Found: N 13.07. IR (ATR, cm^{-1}): 1642 (CO); 2223 (CN); 3066; 3094; 3127 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, 1H, *J* = 9.2, 4.5, H-3); 7.40 (t, 1H, *J* = 7.9 Hz, H-3'); 7.56 (s, 1H, H-6); 7.72-7.79 (m, 2H, H-4', H-6'); 7.98 (t, 1H, *J* = 1.8 Hz, H-2'); 8.17 (dd, 1H, *J* = 9.2, 1.7 Hz, H-4); 8.59 (dd, 1H, *J* = 4.5, 1.7 Hz, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 84.6 (C-5); 113.9 (CN); 118.1 (C-3); 122.8 (C-3'); 125.4 (C-6); 125.9 (C-4); 126.8 (C-7); 127.9 (C-6'); 130.1 (C-5'); 132.2 (C-2'); 135.0 (C-4a); 135.6 (C-4'); 140.0 (C-1'); 144.9 (C-2); 181.9 (COAr).

7-(4-Bromobenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6e**). The product was recrystallized from acetonitrile or nitromethane and colorless crystals with mp 207-9 °C were obtained. Yield 55 %. Anal. Calcd. $C_{15}H_8BrN_3O$: N, 12.88. Found: N, 13.11. IR (ATR, cm^{-1}): 1643 (CO); 2223 (CN); 3064; 3093; 3127 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 7.38 (s, 4H, H-2', H-3', H-5', H-6'); 7.44 (dd, 1H, *J* = 9.2, 4.5, H-3); 7.75 (s, 1H, H-6); 8.30 (dd, 1H, *J* = 9.2, 1.9, H-4); 8.72 (dd, 1H, *J* = 4.5, 1.9).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 84.3 (C-5); 112.6 (CN); 120.1 (C-3); 127.6 (C-6); 128.6 (C-4); 126.1 (C-7); 129.4 (C-4'); 131.2, 132.4 (C-2', C-3', C-5', C-6'); 135.9 (C-1'); 136.8 (C-4a); 145.7 (C-2); 185.6 (COAr).

7-(3-Nitrobenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6f**). The product was recrystallized from acetonitrile or nitromethane and colorless crystals with mp 235-7 °C were obtained. Yield 50 %. Anal. Calcd. $C_{15}H_8N_4O_3$: N 19.17. Found: N 19.40. IR (ATR, cm^{-1}): 1348 (NO_2); 1531 (NO_2); 1646 (CO); 2230 (CN); 3073; 3094; 3126 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 7.44 (dd, 1H, *J* = 9.2, 4.5, H-3); 7.73 (s, 1H, H-6); 7.80 (t, 1H, *J* = 8.1, 7.8, H-5'); 8.23 (dt, 1H, *J* = 8.1, 7.8, H-6'); 8.31 (dd, 1H, *J* = 9.2, 1.9, H-4); 8.53 (ddd, 1H, *J* = 8.1, 2.3, 1.3,H-4'); 8.68 (dd, 1H, *J* = 2.3, 1.3, H-2'); 8.70 (dd, 1H, *J* = 4.5, 1.9, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 85.0 (C-5); 112.9 (CN); 120.0 (C-3); 124.4 (C-2'); 125.8 (C-7); 126.4 (C-6); 126.6 (C-4); 127.6 (C-4'); 130.5 (C-4'); 135.1 (C-6'); 136.5 (C-4a); 139.1 (C-1'); 145.7 (C-2); 148.3 (C-3'); 182.6 (COAr).

7-(4-Nitrobenzoyl)-5-cyano-pyrrolo[1,2-b]pyridazine (**6g**). The product was recrystallized from acetonitrile or nitromethane and pale yellow crystals with mp 245-7 °C were obtained. Yield 52 %. Anal. Calcd. $C_{15}H_8N_4O_3$: N 19.17. Found: N 19.38. IR (ATR, cm^{-1}): 1344 (NO_2); 1518 (NO_2); 1646 (CO); 2225 (CN); 3068; 3102; 3131 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 (dd, 1H, *J* = 9.2, 4.5, H-3); 7.60 (s, 1H, H-6); 8.01 (d, 2H, *J* = 8.9, H-2', H-6'); 8.22 (dd, 1H, *J* = 9.2, 1.9, H-4); 8.39 (d, 2H, *J* = 8.9, H-3', H-5'); 8.62 (dd, 1H, *J* = 4.5, 1.9, H-2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 85.2 (C-5); 113.6 (CN); 118.6 (C-3); 123.8 (C-3', C-5'); 125.7 (C-6); 126.1 (C-4); 126.5 (C-7); 130.2 (C-2', C-6'); 135.3 (C-4a); 143.4 (C-1'); 145.1 (C-2); 150.1 (C-4'); 181.6 (COAr).

7-Benzoyl-5-cyano-2-methyl-pyrrolo[1,2-b]pyridazine (**8a**). The product was recrystallized from ethanol and colorless crystals with mp 157-9 °C were obtained. Yield 57%. Anal. Calcd. $C_{16}H_{11}N_3O$: C 73.55; H 4.24; N 16.08. Found: C 73.81; H 4.55; N 16.32. IR (ATR, cm^{-1}): 1641 (CO); 2214 (CN).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.68 (s, 3H, Me); 7.09 (d, 1H, *J* = 9.2 Hz, H-3); 7.47 (s, 1H, H-6); 7.49-7.54 (m, 2H, H-3', H-5'); 7.59-7.65 (m, 1H, H-4'); 7.86-7.90 (m, 2H, H-2', H-6'); 8.03 (d, 1H, *J* = 9.2 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5 (Me); 84.2 (C-5); 114.7 (CN); 120.3 (C-3); 124.9 (C-6); 125.6 (C-4); 127.9 (C-7); 128.8 (C-3', C-5'); 129.7 (C-2', C-6'); 133.0 (C-4'); 133.9 (C-4a); 138.7 (C-1'); 154.5 (C-2); 184.0 (COAr).

7-(4-Bromobenzoyl)-5-cyano-2-methyl-pyrrolo[1,2-b]pyridazine (**8b**). The product was recrystallized from acetonitrile and colorless crystals with mp 219-220 °C were obtained. Yield 58%. Anal. Calcd. $C_{16}H_{10}BrN_3O$: C 56.49; H 2.96; Br 23.49; N 12.35. Found: C 56.88; H 3.22; Br 23.78; N 12.67. IR (ATR, cm^{-1}): 1638 (CO); 2220 (CN).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.65 (s, 3H, Me); 7.09 (d, 1H, *J* = 9.2 Hz, H-3); 7.45 (s, 1H, H-6); 7.65, 7.74 (2d, 4H, *J* = 8.6 Hz, H-2', H-3', H-5', H-6'); 8.02 (d, 1H, *J* = 9.2 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5 (Me); 84.4 (C-5); 114.5 (CN); 120.4 (C-3); 124.7 (C-6); 125.6 (C-4); 127.1 (C-7); 128.1 (C-4'); 131.3, 132.1 (C-2', C-3', C-5', C-6'); 133.9 (C-4a); 137.4 (C-1'); 154.6 (C-2); 182.8 (COAr).

7-(4-Methoxybenzoyl)-5-cyano-2-methyl-pyrrolo[1,2-b]pyridazine (**8c**). The product was recrystallized from ethyl acetate and colorless crystals with mp 173-5 °C were obtained. Yield 61 %. Anal. Calcd. $C_{17}H_{13}N_3O_2$: C 70.09; H 4.50; N 14.42. Found: C 70.34; H 4.67; N 14.58. IR (ATR, cm^{-1}): 1648 (CO); 2216 (CN).

^{1}H-NMR (300 Hz, $CDCl_3$) δ: 2.64 (s, 3H, Me); 3.91 (s, 3H, MeO); 7.00 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.05 (d, 1H, *J* = 9.2 Hz, H-3); 7.45 (s, 1H, H-6); 7.91 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.01 (d, 1H, *J* = 9.2 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5 (Me); 83.7 (C-5); 114.1 (C-3', C-5'); 114.9 (CN); 119.8 (C-3); 123.7 (C-6); 125.6 (C-4); 127.6 (C-7); 131.1 (C-1'); 132.3 (C-3', C-5'); 133.5 (C-4a); 154.5 (C-2); 163.9 (C-4'); 182.8 (COAr).

CONCLUSIONS

Ten new pyrrolo[1,2-b]pyridazine **6** and **8** with a cyano group in the pyrrole moiety were synthesized by reaction between *N*-phenacyl pyridazinium bromides and acrylonitrile in the presence Et_3N and TPCD as the oxidant reagent. The regioselectivity of the reaction was evidenced by NMR spectroscopy. All the compounds were characterized by NMR and IR spectroscopy.

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