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Dedicated to the memory of
Professor Ecaterina Ciorănescu-Nenitzescu (1909–2000)

NEW PYRROLO[1,2-b]PYRIDAZINE DERIVATIVES

Florea DUMITRAŞCU,[a*] Constantin DRĂGHICI,[a] Miron T. CĂPROIU,[a] Dan G. DUMITRESCU[a] and Marcel Mirel POPA[a]

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

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A series of pyrrolo[1,2-b]pyridazines were synthesized using a one-pot multicomponent reaction between pyridazine, 2-bromoacetophenones, 1-butyn-3-one as acetylenic dipolarophile and 1,2-epoxybutane as acid scavenger. The compounds were characterized using H-NMR and C-NMR spectroscopy.

INTRODUCTION

First synthesized in 1956 by Letsinger and Lasco,[1] pyrrolo[1,2-b]pyridazine still presents significant interest. This is due to its high fluorescence, interesting optical properties, and thus, the possibility of obtaining OLEDs and other stable light emitting organic substances. Furthermore, the various synthetic methods offer the ability to graft a number of substituents on this relatively simple scaffold and thus, the possibility to fine tune the optical[2-8] and/or the biological properties.[9-15] As testimony to the versatility of the pyrrolo[1,2-b]pyridazine system, the various syntheses and properties of such compounds have been the subject of two literature reviews 30 years apart.[16,17]

Taking into account the literature data available, the most facile syntheses of the pyrrolo[1,2-b]pyridazine scaffold consist of 1,3-dipolar cycloadditions, especially those between *N*-ylides and acetylenic or olefinic dipolarophiles.[18-23]

Multicomponent processes have the advantage of reducing reaction times and subsequent work-up procedures, and are also in agreement with some requirements of green chemistry. The multicomponent approach has been used in a large number of synthetic methods, and has also been successfully applied in 1,3-dipolar *N*-ylide cycloadditions.[24-26]

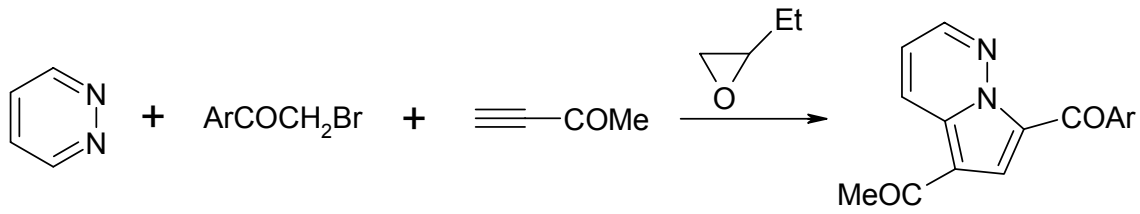
In order to expand our previous work, herein we report the synthesis and NMR characterization of six new 5-acetyl substituted pyrrolo[1,2-b]pyridazine derivatives using a one-pot multicomponent reaction between pyridazine, 2-bromoacetophenones, 1,2-epoxybutane as solvent and acid scavenger and 1-butyn-3-one as acetylenic dipolarophile.

RESULTS AND DISCUSSION

The synthesis of pyrrolo[1,2-b]pyridazines *via* N-ylides usually consists of two distinct stages: the synthesis of the intermediary piridazinium and the subsequent 1,3-dipolar cycloaddition. A closer inspection of the overall synthetic pathway showed us that a multicomponent approach was suitable for obtaining such compounds. Thus, pyrrolo[1,2-b]pyridazine derivatives **4** were synthesized by an one-pot, three-component reaction directly from pyridazine **1**, substituted phenacyl bromides **2** and 1-butyn-3-one **3** as dipolarophile in 1,2-epoxybutane at room temperature. This synthesis is a multi-step sequence of reactions, implying the consecutive quaternization, cycloimmonium-ylide generation, 1,3-dipolar cycloaddition and aromatization (Scheme 1).

The cycloaddition reaction between 1-butyn-3-one and pyridazinium *N*-ylides was found to be completely regioselective, as only one regioisomer could be observed by H-NMR spectroscopy.

* Corresponding author: fdumitra@yahoo.com

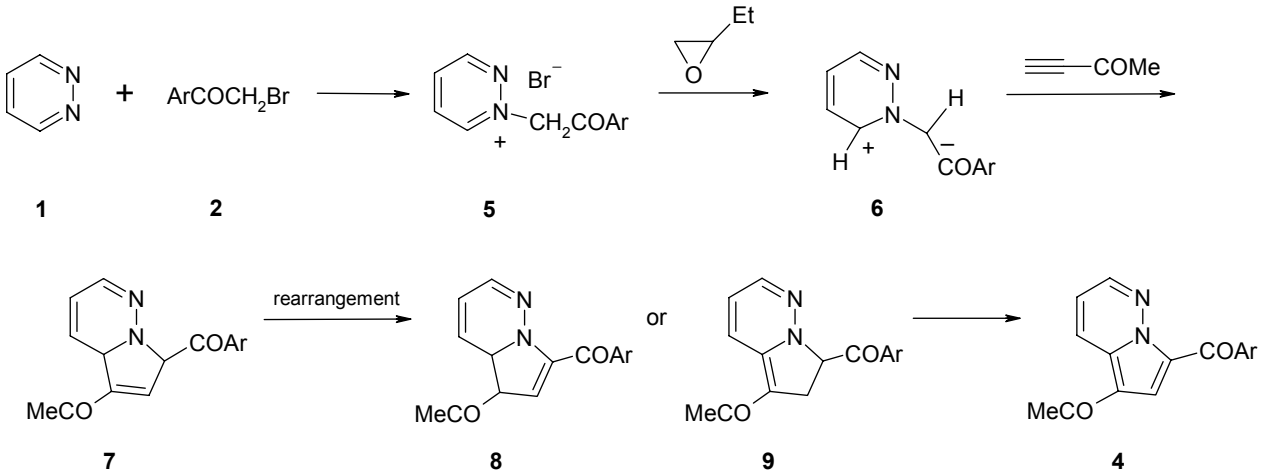


1 **2** **3** **4**

Ar: a = C_6H_5; b = 4-BrC_6H_4; c = 3-$O_2NC_6H_4$; d = 4-$O_2NC_6H_4$; e = 2-$MeOC_6H_4$; f = 4-$MeOC_6H_4$; g = 4-NCC_6H_4

Scheme 1

The reaction mechanism consists first in the reaction between pyridazine **1** and the bromoderivatives **2**, resulting in pyridazinium salts **5**. In the epoxide reaction medium, the bromide anion from the pyridazinium salts attacks the oxirane ring, resulting in the formation of the corresponding alkoxide. This, in turn, performs the actual deprotonation of the pyridazinium salts, generating *N*-ylide **6**. The *N*-ylide reacts with the activated alkyne, furnishing the primary cycloadduct **7** which undergoes *in situ* rearrangement to compounds **8** and **9**, which in turn suffer a dehydrogenation to fully aromatic pyrrolo[1,2-b]pyridazine **4** (Scheme 2).



1 **2** **5** **6** **7** **8** **9** **4**

Scheme 2

The structure of pyrrolopyridazines **4** 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 compounds **4**, the three protons (H2, H3, H4) from the pyridazine moiety appear as an ABC system with the following coupling constants: $^3J_{3,4}$ = 9.2 Hz, $^3J_{2,3}$ = 4.5 Hz and $^4J_{2,4}$ = 1.9 Hz. Due to the spatial proximity of the acetyl group in position 5, the most deshielded proton is H-4, at 8.86-8.93 ppm. The proton H-2 is also strongly deshielded because it is part of a C-N double bond. The signal for H-6 proton is a sharp singlet with a chemical shift in the range 7.63-7.69 ppm ($CDCl_3$).

The chemical shifts for the carbon atoms from pyrrolopyridazines **4** were assigned by using heteronuclear H-C correlation experiments (HETCOR). The atom C-2 (δ = 144.9-145.3 ppm) from the pyrrolopyridazines **4** is highly deshielded in respect with the other atoms from the pyrrolopyridazine system, as it is part of a C-N double bond. The two carbonyl groups appear at 181.8-184.5 ppm for the COAr moiety and at 193.4-193.8 ppm for the COMe one.

Additional evidence for the pyrrolopyridazine compounds was provided by FT-IR spectroscopy. The most characteristic features are the bands corresponding to the carbonyl groups (~1640 and ~1660 cm^{-1}). Also features characteristic to each compound are found: the cyano group which appears as a medium to strong band at 2216 cm^{-1} in

4g and the two NO_2 vibrations appear at around 1350 cm^{-1} and 1527 cm^{-1} in compounds **4c** and **4d**.

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 ^1H and 75 MHz for ^{13}C. Supplementary evidence was given by HET-COR and COSY experiments. FT-IR spectra were recorded on a Brucker Vertex 70 spectrometer.

General procedure for preparation of pyrrolo[1,2-b]pyridazines 4

5 Mmol of pyridazine, 5 mmol phenacyl bromide and 5 mmol 1-butyn-3-one were dissolved in 50 mL 1,2-epoxybutane and the mixture was stirred for 12 hours (with protection against moisture). The 1,2-epoxybutane was removed *in vacuum* and residue was treated with ethanol and then the precipitate was filtered off. The crude product was purified by column chromatography using standardized neutral alumina (Aluminiumoxid 90) and methylene chloride as eluent.

5-Acetyl-7-benzoyl-pyrrolo[1,2-b]pyridazine (**4a**)

The product was recrystallized from methanol and colorless crystals with mp 153-5 °C were obtained. Yield 61%. Anal. Calcd. $C_{16}H_{12}N_2O_2$: C 72.72, H 4.58, N 10.60. Found: C 72.98, H 4.77, N 10.42. IR (ATR, cm^{-1}): 1638 (CO); 1655(CO); 3055 (CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.54 (3H, s, MeCO); 7.21 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.51-7.56 (2H, m, H-3', H-5'); 7.59-7.66 (1H, m, H-4'); 7.65 (1H, s, H-6); 7.89-7.93 (2H, m, H-2', H-6'); 8.57 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.89 (1H, dd, *J* = 9.2, 1.9 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (2-MeCO); 113.8 (C-5); 118.8 (C-3); 124.8 (C-6); 126.7 (C-7); 128.6 (C-3', C-5'); 129.1 (C-4); 129.6 (C-2', C-6'); 132.5 (C-4');133.2 (C-4a); 139.2 (C-1'); 145.0 (C-2); 184.5 (COAr); 193.8 (COMe).

5-Acetyl-7-(4-bromobenzoyl)- pyrrolo[1,2-b]pyridazine (**4b**)

The product was recrystallized from ethanol and colorless crystals with mp 138-140 °C were obtained. Yield 58 %. Anal. Calcd. $C_{16}H_{11}BrN_2O_2$: C 56.00, H 3.23, Br 23.28, N, 8.16. Found: C 56.31, H 3.44, Br 23.56, N, 8.40. IR (ATR, cm^{-1}): 1629 (CO); 1633 (CO); 3053; (CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (3H, s, MeCO); 7.22 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.66 (1H, s, H-6); 7.65, 7.77 (2H, 2d, *J* = 8.5 Hz, H-2', H-3', H-5', H-6'); 8.56 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.90 (1H, dd, *J* = 9.2, 1.9 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.8 (MeCO); 113.8 (C-5); 118.9 (C-3); 124.5 (C-6); 126.2 (C-7); 127.4 (C-4'); 129.1 (C-4); 131.0, 131.9 (C-2', C-3', C-5', C-6'); 133.3 (C-4a); 137.8 (C-1'); 145.1 (C-2); 183.3 (COAr); 193.4 (COMe).

5-Acetyl-7-(3-nitrobenzoyl)-pyrrolo[1,2-b]pyridazine (**4c**)

The product was recrystallized from acetonitrile and colorless crystals with mp 215-7 °C were obtained. Yield 66 %. Anal. Calcd. $C_{16}H_{11}N_3O_4$: C 62.14; H 3.58; N 13.59. Found: C 62.01; H 3.24; N 13.72. IR (ATR, cm^{-1}): 1349 (NO_2); 1527 (NO_2); 1655 (CO); 1697 (CO); 3053(CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (3H, s, 2-Me); 7.26 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.69 (1H, s, H-6); 7.76 (1H, t, *J* = 8.0 Hz, H-5'); 8.20-8.24 (1H, m, H-4'); 8.45-8.49 (1H, m, H-6'); 8.58 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.69 (1H, t, *J* = 1.9 Hz, H-5'); 8.93 (1H, dd, *J* = 9.2, 1.9 Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (2-MeCO); 114.2 (C-5); 119.4 (C-3); 124.2 (C-4'); 124.8 (C-6); 125.8 (C-7); 129.2 (C-4); 129.9 (C-6') 133.7 (C-4a); 135.0 (C-2'); 140.5 (C-1'); 145.1 (C-2); 148.2 (C-3'); 181.8 (COAr); 193.4 (COMe).

5-Acetyl-7-(4-nitrobenzoyl)-pyrrolo[1,2-b]pyridazine (**4d**)

The product was recrystallized from acetonitrile and pale yellow crystals with mp 221-2 °C were obtained. Yield 62 %. Anal. Calcd. $C_{16}H_{11}N_3O_4$: C 62.14; H 3.58; N 13.59. Found: C 62.42; H 3.41; N 13.81. IR (ATR, cm^{-1}): 1346 (NO_2); 1504 (NO_2); 1645 (CO); 1663(CO); 3079; (CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.54 (3H, s, MeCO); 7.29 (dd, 1H, *J* = 9.2, 4.5 Hz, H-3); 7.66 (s, 1H, H-6); 8.02 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.39 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 8.59 (dd, 1H, *J* = 4.5, 1.9 Hz, H-2); 8.93 (dd, 1H, *J* = 9.2, 1.9, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (MeCO); 114.3 (C-5); 119.6 (C-3); 123.9 (C-3', C-5'); 125.1 (C-6); 126.0 (C-7); 129.3 (C-4); 130.3 (C-2', C-6'); 133.9 (C-4a); 144.5 (C-1'); 145.3 (C-2); 150.0 (C-4'); 182.5 (COAr); 193.4 (COMe).

5-Acetyl-7-(2-methoxybenzoyl)- pyrrolo[1,2-b]pyridazine (**4e**)

The product was recrystallized from ethanol and colorless crystals with mp 132-3 °C were obtained. Yield 51 %. Anal. Calcd. $C_{17}H_{14}N_2O_3$: C 69.38; H 4.79; N 9.52. Found: C 69.69; H 4.97; N 9.69. IR (ATR, cm^{-1}): 1169 (C-O); 1647 (CO); 1695 (CO); 3057 (CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.51 (3H, s, 2-Me); 3.71 (3H, s, 2-MeO); 7.00 (1H, d, *J* = 8.8 Hz, H-3'); 7.08 (1H, dt, *J* = 7.4, 0.8, H-5'); 7.19 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.60 (1H, s, H-6); 7.48-7.52 (2H, m, H-4', H-6'); 8.52 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.86 (1H, dd, *J* = 9.2, 1.9, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (2-MeCO); 55.8 (MeO); 111.6 (C-2'); 113.9 (C-5); 118.7 (C-3); 120.7 (C-5'); 125.1 (C-6); 128.2 (C-7); 129.0 (C-4); 129.6. 132.1 (C-4', C-6'); 130.0 (C-2'); 133.1 (C-4a); 144.8 (C-2); 157.5 (C-2'); 184.0 (COAr); 193.8 (COMe).

5-Acetyl-7-(4-methoxybenzoyl)- pyrrolo[1,2-b]pyridazine (**4f**)

The product was recrystallized from ethyl acetate and colorless crystals with mp 174-6 °C were obtained. Yield 57 %. Anal. Calcd. $C_{17}H_{14}N_2O_3$: C 69.38; H 4.79; N 9.52. Found: C 69.11; H 4.48; N 9.74. IR (ATR, cm^{-1}): 1171 (C-O); 1642 (CO); 1697 (CO); 3054 (CH aromatic).

^1H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (3H, s, 2-Me); 3.91 (3H, s, 2-MeO); 7.01 (2H, d, *J* = 8.8 Hz, H-3', H-5'); 7.14 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.63 (1H, s, H-6); 7.84 (2H, d, *J* = 8.5 9*+Hz, H-3', H-5'); 7.91 (2H, d, *J* = 8.8 Hz, H-2', H-6'); 8.52 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.86 (1H, dd, *J* = 9.2, 1.9, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (2-MeCO); 57.7 (MeO); 113.5 (C-5); 114.0 (C-3', C-5'); 118.4 (C-3); 123.7 (C-6); 127.0 (C-7); 129.1 (C-4); 131.6 (C-1'); 132.8 (C-2', C-6'); 132.8 (C-4a); 144.9 (C-2); 163.5 (C-4'); 183.5 (COAr); 193.7 (COMe).

5-Acetyl-7-(4-cyanobenzoyl)- pyrrolo[1,2-b]pyridazine (**4g**)

The product was recrystallized from ethanol colorless crystals with mp 202-4 °C were obtained. Yield 56 %. Anal. Calcd. $C_{17}H_{11}N_3O_2$: C 70.58; H 3.83; N 14.52. Found: C 70.80; H 3.51; N 14.77. IR (ATR, cm^{-1}): 1644 (CO); 1663 (CO); 2216 (CN); 3046 (CH aromatic).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (3H, s, 2-Me); 7.27 (1H, dd, *J* = 9.2, 4.5 Hz, H-3); 7.64 (1H, s, H-6); 7.84 (2H, d, *J* = 8.5 Hz, H-3', H-5'); 7.98 (2H, d, *J* = 8.5 Hz, H-2', H-6'); 8.59 (1H, dd, *J* = 4.5, 1.9 Hz, H-2); 8.93 (1H, dd, *J* = 9.2, 1.9, Hz, H-4).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.9 (2-MeCO); 114.2 (C-5); 115.7 (CN); 118.1 (C-4'); 119.4 (C-3); 124.9 (C-6); 125.8 (C-7); 129.3 (C-4); 129.8 (C-2', C-6'); 132.5 (C-3', C-5'); 133.7 (C-4a); 142.8 (C-1'); 145.2 (C-2); 182.6 (COAr); 193.4 (COMe).

CONCLUSIONS

Seven new pyrrolo[1,2-b]pyridazines **4** with an acetyl group grafted in the 5 position were synthesized by a one-pot multicomponent reaction between pyridazine, phenacyl bromides and 1-butyn-3-one in the presence 1,2-epoxybutane as reaction medium and acid scavenger. The regioselectivity of the reaction was evidenced by NMR spectroscopy. All the compounds were characterized by NMR and IR spectroscopy.

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