



*Dedicated to the memory of
Academician Bogdan C. Simionescu (1948–2024)*

SYNTHESIS OF 3-NITROPYRROLO[1,2-*a*]BENZIMIDAZOLES AND 2-NITROPYRROLO[1,2-*a*]QUINOXALINES VIA MULTICOMPONENT REACTIONS

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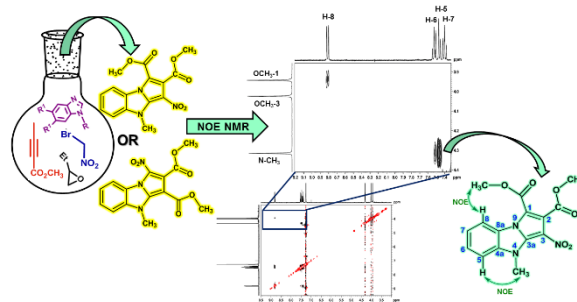
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Novel pyrrolo[1,2-*a*]benzimidazoles and pyrrolo[1,2-*a*]quinoxalines bearing a nitro group on the pyrrole ring were synthesized *via* one-pot multicomponent reactions of 1-substituted benzimidazoles with dimethyl acetylenedicarboxylate and bromonitromethane. All synthesized compounds were structurally characterized by IR, NMR and HRMS spectroscopy.



INTRODUCTION

N-Bridgehead pyrroloazoles and pyrrolodiazines are important compounds for both medicinal chemistry and materials science.¹ Many of these *N*-heterocyclic ring systems, including pyrrolo[1,2-*a*]benzimidazoles, and pyrrolo[1,2-*a*]quinoxalines, are versatile synthetic scaffolds, intensively investigated for their biological properties and as building blocks for the discovery of novel bioactive molecules. Thus, pyrrolo[1,2-*a*]benzimidazole

skeleton is a constituent of a range of DNA cross-linkers that mimic the mitomycin antitumour activity against various lines of human cancer cells.^{2–5} Pyrrolo[1,2-*a*]quinoxaline ring system is the core of many compounds that showed antimycobacterial activity against *Mycobacterium tuberculosis*,⁶ antiparasitic activity,⁷ central dopamine antagonist activity,⁸ and proved to be potent and selective 5-HT₃ receptor agonists.⁹ Some pyrrolo[1,2-*a*]quinoxaline derivatives shown potential anti-hepatitis C virus activity,¹⁰ antiproliferative activities on the human

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leukemic cell lines U937, K562 and the breast cancer cell line MCF7.¹¹ Several reviews reporting synthetic methods and biological activities of pyrrolo[1,2-*a*]benzimidazoles,^{12,13} and pyrrolo[1,2-*a*]quinoxalines^{14,15} have been published. Many synthetic methods toward these compounds include [3+2] dipolar cycloaddition reactions of diazinium ylides with electron-deficient alkenes or alkynes. The multicomponent synthetic methodology combined with [3+2] dipolar cycloaddition reactions proved an effective synthetic tool toward novel structures employing simple starting materials. Our group has developed a synthetic protocol to access a variety of *N*-bridgehead fused heterocyclic compounds based on the one-pot, three components reactions of *N*-heterocycle compounds with 2-halocarbonyl compounds and alkyne dipolarophiles in the presence of an epoxide which is playing the role of reaction medium and acid scavengers.¹⁶⁻²¹ Continuing our interest in this field we investigated the possibility to obtain novel *N*-bridgehead pyrrolodiazines bearing a nitro group on the pyrrole ring with the aim to achieve novel potentially bioactive functionalized derivatives *via* the transformation of nitro group. Several 1-nitro-substituted indolizine and pyrrolo[2,1-*a*]isoquinoline derivatives were achieved by one-pot, three-component reactions of pyridine and isoquinoline compounds with dialkyl acylenedicarboxylates and bromonitromethane.²² Aiming to explore the potential of this protocol and to achieve novel *N*-bridgehead pyrroloazoles and pyrrolodiazines carrying a nitro group on the pyrrole ring we investigated the one-pot three-component reactions of 1-substituted benzimidazoles with dimethyl acylenedicarboxylate and bromonitromethane. Here, we present novel pyrrolo[1,2-*a*]benzimidazoles and pyrrolo[1,2-*a*]quinoxaline-4-ones bearing a nitro group on the pyrrole ring obtained *via* multicomponent reactions of 1-substituted benzimidazole derivatives with dimethyl acylenedicarboxylate and bromonitromethane in 1,2-epoxybutane.

RESULTS AND DISCUSSION

The reactions of various 1-substituted benzimidazoles **1** with dimethyl acetylene dicarboxylate (DMAD) and bromonitromethane in an epoxide gave 3-nitro-1,2-dicarbomethoxy-pyrrolo[1,2-*a*]benzimidazoles **2** along with 2-nitro-3-carbomethoxy-pyrrolo[1,2-*a*]quinoxaline-4-ones **3**. The reactions were carried out either by mixing the starting compounds under stirring in propylene oxide at room temperature and continuing the stirring for 40 hours, or by mixing the starting compounds under stirring at room temperature in 1,2-epoxybutane and heating the reaction mixtures at reflux temperature for 24 hours (Scheme 1). In the propylene oxide at room temperature even after 40 hours about 30–50 % from the initial amounts of 1-substituted benzimidazoles are present in the final reaction mixtures. When the reactions were carried out in 1,2-epoxybutane at reflux temperature after 24 hours the final reaction mixtures contain only small amounts of starting 1-substituted benzimidazoles. The HPLC analysis of crude reaction products shown that both 3-nitro-1,2-dicarbomethoxy-pyrrolo[1,2-*a*]benzimidazoles **2** and 2-nitro-3-carbomethoxy-pyrrolo[1,2-*a*]quinoxaline-4-ones **3** were formed in all these reactions in various ratios. Based on these data, all reactions of 1-substituted benzimidazoles **1** with dimethyl acylenedicarboxylate and bromonitromethane were performed in 1,2-epoxybutane at reflux temperature for 24 hours (Table 1). In the reactions of 1-benzyl benzimidazole **1b** and 1-ethyl-5,6-dimethyl benzimidazole **1d**, respectively, with dimethyl acylenedicarboxylate and bromonitromethane in 1,2-epoxybutane at reflux temperature smaller amounts of the corresponding pyrrolo[1,2-*a*]quinoxalinones **3b** and **3d**, respectively, were formed (Table 1) and, unfortunately, compounds **3b** and **3d** could not be isolated from the reaction mixtures.

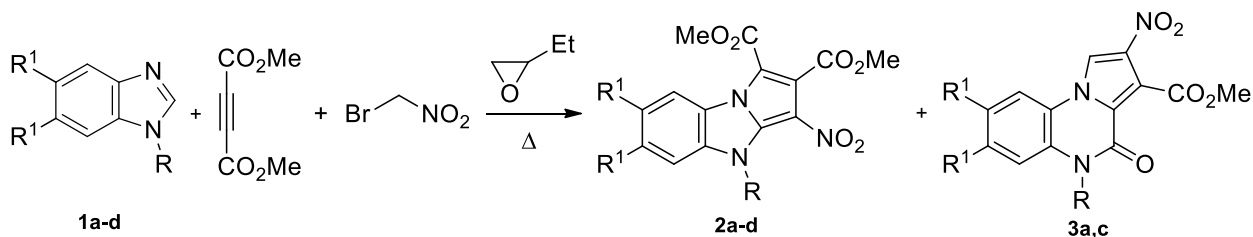
Table 1

HPLC data for the reaction products ^a

Starting compound	Retention time (min) for:		Ratio of peaks areas (2/3) ^b
	2	3	
1a	2.87	2.57	1.24
1b	2.85	2.64	2.42
1c	2.86	2.64	1.30
1d	2.83	2.63	3.04

^a reaction conditions: 24 h, 1,2-epoxybutane, reflux temperature

^b calculated from HPLC chromatograms



a: R = Me, R¹ = H; **b:** R = benzyl, R¹ = H; **c:** R = benzyl, R¹ = Me; **d:** R = Et, R¹ = Me

Scheme 1 – The reactions of 1-substituted benzimidazoles with DMAD and bromonitromethane.

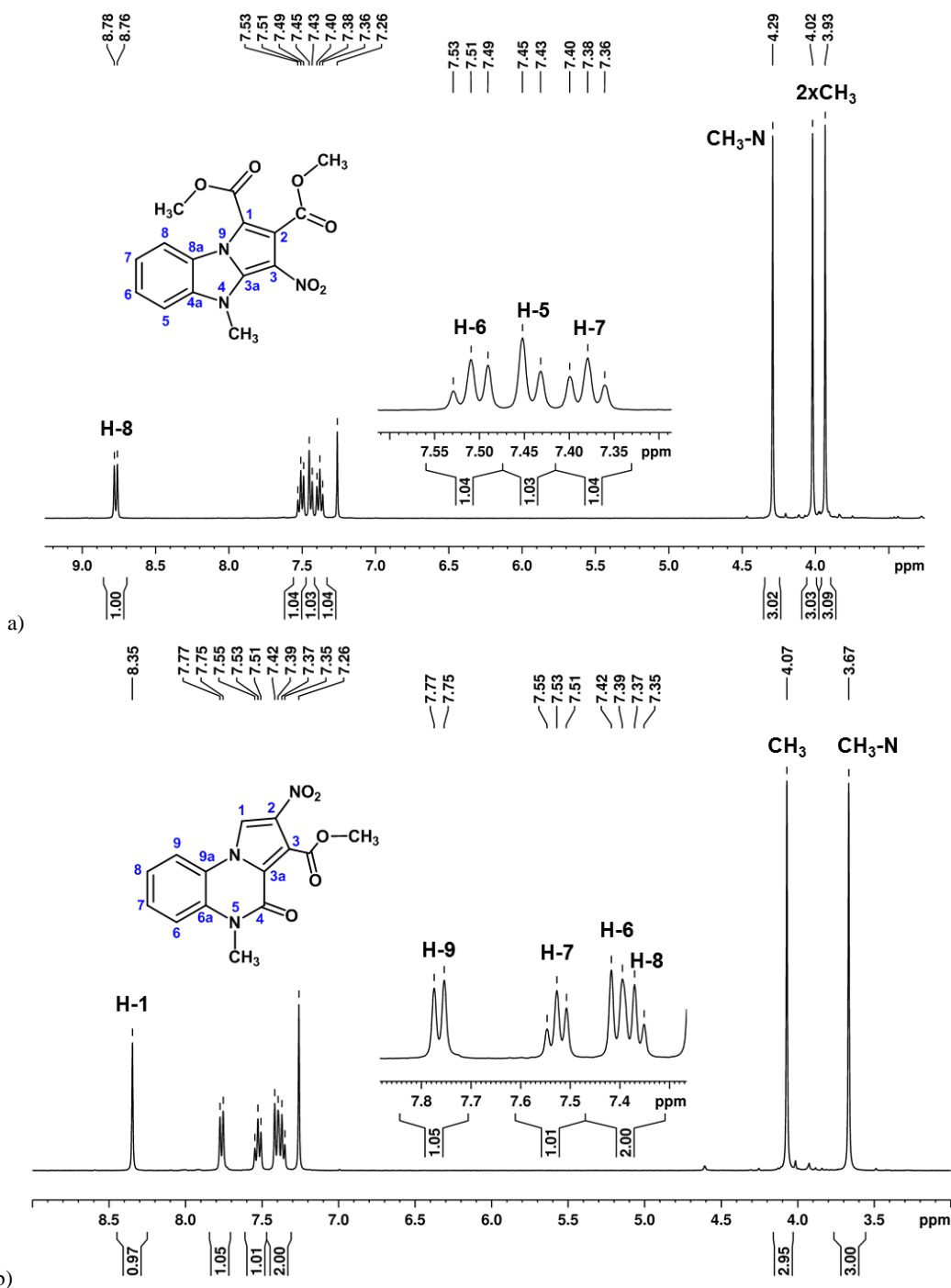


Fig. 1 – The proton spectra associated with (a) pyrrolo[2,1-*b*]benzimidazole **2a** and (b) pyrrolo[1,2-*a*]quinoxalinone **3a**, both recorded in CDCl₃, at 400 MHz. Signals assignments are annotated to the figure.

Pyrrolo[1,2-*a*]benzimidazole carrying a nitro group in the position 1 could eventually be formed as a result of the alkylating reaction of 1-substituted benzimidazole with bromonitromethane followed by the reaction with DMAD. However, 1-substituted nitro derivatives were not isolated probably due to the higher reactivity of DMAD.

The structures of all isolated compounds were verified by chemical and spectral analysis, including IR, NMR and HRMS. Thus, the presence of nitro groups has been confirmed in all cases by IR spectra (two bands around 1300 and 1500 cm^{-1}) and the relative number of N and O atoms was proved by the isotopic pattern of the HRMS spectra. The substitution positions have been derived from various NMR experiments. The molecular weights have been confirmed by high-resolution mass spectrometry (HRMS). The proton and carbon signals have been unambiguously assigned based on 2D NMR experiments like H,H-COSY, H,C-HSQC and H,C-HMBC. The formation of either pyrrolo[1,2-*a*]benzimidazoles or pyrrolo[1,2-*a*]quinoxalinones was evident from the proton spectra, as exemplified in Fig. 1 for the pair **2a-3a**. The benzimidazole compounds included in this study are totally substituted on the pyrrole cycle with one nitro group and two carbomethoxy units that resonate around 3.9 and 4.0 ppm. A characteristic signal for the benzimidazole residue is the doublet around 8.8 ppm. The presence of quinoxalinone pair is indicated by the presence of only one carbomethoxy resonating around 4.0 ppm and a singlet at approximately 8.3 ppm, associated with the pyrrole proton.

When the starting compounds were 1-substituted 5,6-dimethyl-benzimidazoles, the resulted pyrrolo[1,2-*a*]benzimidazoles (**2c** and **2d**) could be differentiated by the singlet from 8.5 ppm and the same two singlets from 3.9 and 4.0 ppm due to carbomethoxy units. The pair product pyrrolo[1,2-*a*]quinoxalinone (**3c**) is identified by the three low field singlets at 7.0, 7.5 ppm (benzimidazole protons) and 8.3 ppm (pyrrole proton) and the high field singlet from 4.0 ppm due to only one carbomethoxy group.

The position of nitro group in both pyrrolo[1,2-*a*]benzimidazoles and pyrrolo[1,2-*a*]quinoxalinones was established from Nuclear Overhauser Effects (NOEs) identified between methoxy protons and benzimidazole or quinoxalinone protons, as exemplified in Fig. 2 for the same pair of products **2a-3a**. In the case of pyrrolo[1,2-*a*]benzimidazole **2a**, there is a visible NOE interaction between the protons from one of the methoxy group and the H-8 proton, indicating a spatial proximity of less than 5 Å. This effect is possible only if the methoxy group is in position 1 on the pyrrole cycle. As there is no NOE interaction between the second methoxy and the methyl ($\text{CH}_3\text{-N}$) protons, we concluded that the nitro group is in position 3 on the pyrrole cycle, spatially closer to $\text{CH}_3\text{-N}$, as illustrated in Fig. 2a. A similar reasoning was applied for the pyrrolo[1,2-*a*]quinoxalinone **3a**. The NOE interactions identified for this derivative were between the pairs of protons H-9 with H-1 and $\text{CH}_3\text{-N}$ with H-6. In order to comply with the experimental NOE findings, the nitro group has to be in position 2 of the pyrrole cycle, as illustrate in Fig. 2b.

The reaction pathway for the one-pot three component reactions of 1-substituted benzimidazole **1** with DMAD and bromonitromethane involves most probably the initially formation a 1,3-dipole type structure **A** by the reaction of highly reactive DMAD with the corresponding 1-substituted benzimidazole, followed by the successive reaction with bromonitromethane implying the formation of a benzimidazolium cation **B** and the intermediate carbanion **C**.²² The 1,3-proton shift of the resulted intermediate **D** followed by the cyclization of intermediate **E** led to the primary cycloadduct **F**. The elimination of HBr and spontaneous aromatization of primary cycloadduct **F** gave the 3-nitro-pyrrolo[1,2-*a*]benzimidazole **2** (Scheme 2, route a).

The formation of the 2-nitropyrrolo[1,2-*a*]quinoxaline-4-one **3** took place by imidazole ring-opening initiated by the deprotonation of the cycloadduct **F** followed by recyclization of the resulting pyrrole **G** involving the carbomethoxy C=O group and dehydrogenative aromatization (Scheme 2, route b).^{19,23,24}

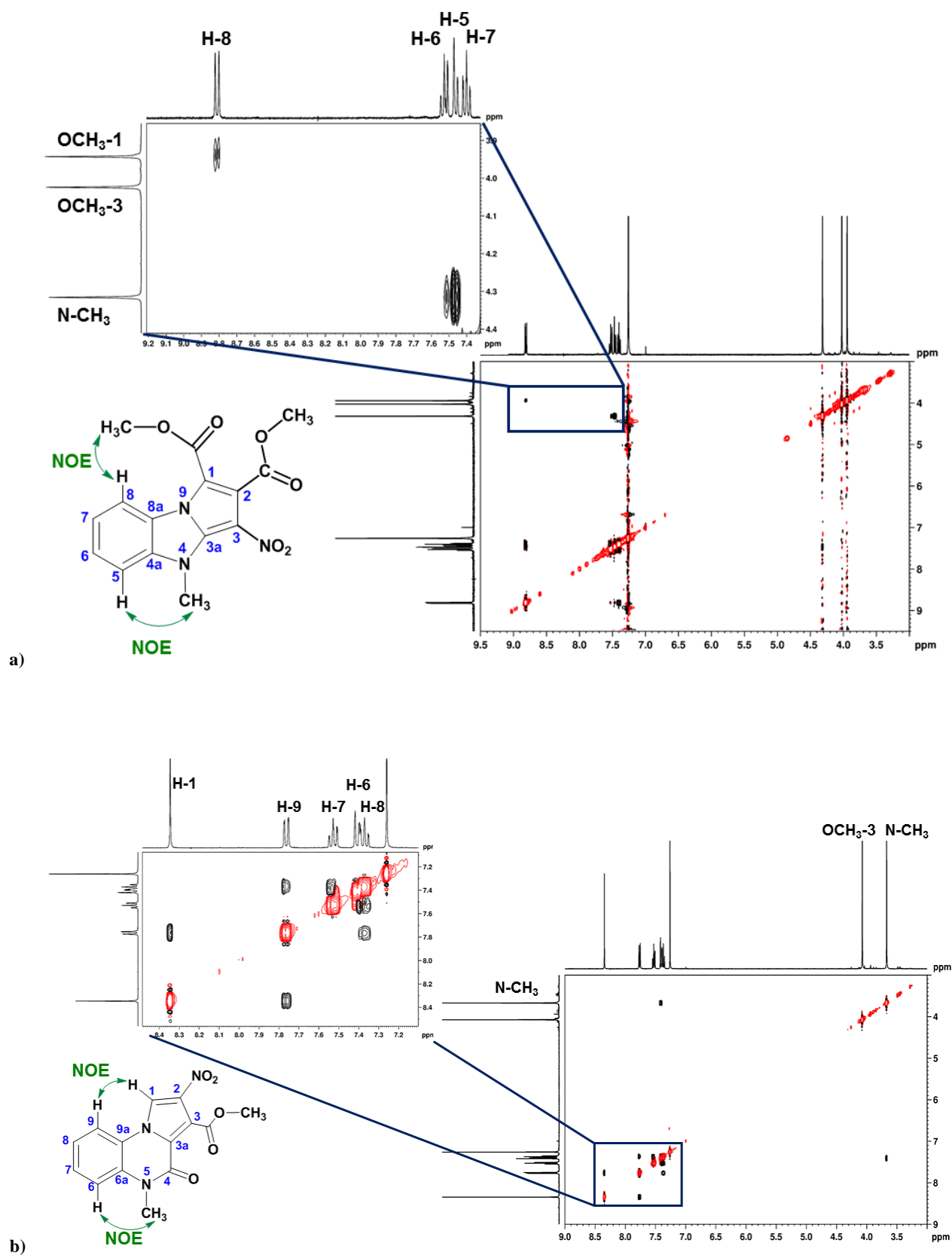
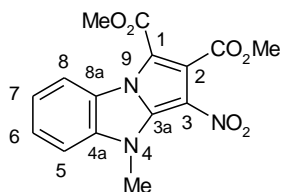


Fig. 2 – The H,H-NOESY spectra associated with (a) pyrrolo[1,2-*a*]benzimidazole **2a** and (b) pyrrolo[1,2-*a*]quinoxalinone **3a**, both recorded in CDCl_3 , at 400 MHz. The expanded regions of the NOESY spectra underline the through space proton-proton interaction signals (NOEs) that have been used to establish the position of the nitro group on the pyrrole cycle.

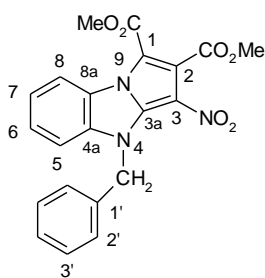
giving the 3-nitropyrrolo[1,2-*a*]benzimidazole **2**. The filtrate was concentrated under vacuum to dryness and the residue was chromatographed on a SiO₂ packed column by eluting with EtOAc:hexane (1:4 v/v) yielding pyrrolo[1,2-*a*]quinoxalin-4-one **3**.

Dimethyl 3-nitro-4-methylpyrrolo[1,2-*a*]benzimidazole-1,2-dicarboxylate (2a).



Yellow crystals (0.85 g, yield 51%), mp 219–220 °C. IR (KBr, cm⁻¹): 3149, 2954, 1733, 1663, 1528, 1444, 1342, 1280, 1248, 1076. ¹H NMR (400.1 MHz, CDCl₃, δ (ppm)): 3.93 (3H, s, CH₃-1), 4.02 (3H, s, CH₃-2), 4.29 (3H, s, CH₃-4), 7.38 (1H, t, ³J = 8.0 Hz, H-7), 7.44 (1H, d, ³J = 8.0 Hz, H-5), 7.51 (1H, t, ³J = 8.0 Hz, H-6), 8.77 (1H, d, ³J = 8.0 Hz, H-8). ¹³C NMR (100.6 MHz, CDCl₃, δ (ppm)): 32.8 (CH₃-4), 52.5 (CH₃-1), 53.3 (CH₃-2), 109.6 (C-1), 110.2 (CH-5), 116.9 (CH-8), 123.1 (CH-7), 125.1 (C-2), 125.8 (CH-6), 126.0 (C-8a), 136.2 (C-3a), 136.7 (C-4a and C-3), 159.5 (COO-1), 163.6 (COO-2). ¹⁵N NMR (40.5 MHz, CDCl₃, δ (ppm)): 109.5 (N-4), 165.8 (N-9). HRMS-ESI (m/z): [M+Na]⁺ for C₁₅H₁₃N₃NaO₆, calcd. 354.0697, found 354.0704.

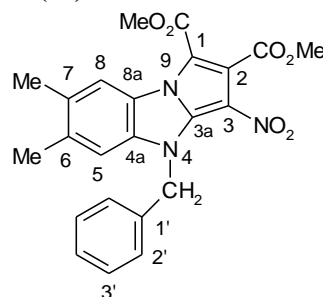
Dimethyl 3-nitro-4-benzylpyrrolo[1,2-*a*]benzimidazole-1,2-dicarboxylate (2b).



Yellow crystals (0.98 g, yield 48%), mp 213–215 °C. IR (KBr, cm⁻¹): 3027, 2952, 1744, 1716, 1579, 1544, 1478, 1419, 1343, 1289, 1260, 1229, 1195, 1147, 1076. ¹H NMR (400.1 MHz, CDCl₃, δ (ppm)): 3.94 (3H, s, CH₃-1), 4.02 (3H, s, CH₃-2), 6.02 (2H, s, CH₂), 7.20 (2H, d, ³J = 8.0 Hz, H-2'), 7.26–7.30 (3H, overlapped signals, H-3' and H-4'), 7.35–7.40 (1H, m, H-7), 7.44–7.45 (2H, overlapped signals, H-5 and H-6), 8.81 (1H, d, ³J = 8.0 Hz, H-8). ¹³C NMR (100.6 MHz, CDCl₃, δ (ppm)): 49.1 (CH₂), 52.5 (CH₃-1), 53.3 (CH₃-2), 109.8 (C-1),

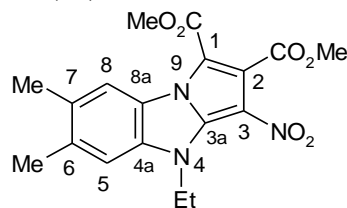
111.1 (CH-5), 117.1 (CH-8), 123.3 (CH-7), 125.1 (C-2), 125.9 (CH-6), 126.2 (C-8a), 126.7 (CH-2'), 128.2 (CH-4'), 129.0 (CH-3'), 135.7 (C-1'), 135.8 (C-3a), 136.2 (C-4a and C-3), 159.5 (COO-1), 163.6 (COO-2). ¹⁵N NMR (40.5 MHz, CDCl₃, δ (ppm)): 122.5 (N-4), 168.2 (N-9). HRMS-ESI (m/z): [M+Na]⁺ for C₂₁H₁₇N₃NaO₆, calcd. 430.1010, found 430.1017.

Dimethyl 3-nitro-4-benzyl-6,7-dimethylpyrrolo[1,2-*a*]benzimidazole-1,2-dicarboxylate (2c).



Yellow crystals (0.94 g, yield: 43%), mp 245–246 °C. IR (KBr, cm⁻¹): 2950, 1728, 1704, 1586, 1541, 1483, 1437, 1353, 1282, 1226, 1151, 1071. ¹H NMR (400.1 MHz, CDCl₃, δ (ppm)): 2.37 (3H, s, CH₃-6), 2.41 (3H, s, CH₃-7), 3.94 (3H, s, CH₃-1), 4.01 (3H, s, CH₃-2), 5.99 (2H, s, CH₂), 7.16–7.18 (3H, overlapped signals, H-5 and H-2'), 7.25–7.30 (3H, overlapped signals, H-3' and H-4'), 8.55 (1H, s, H-8). ¹³C NMR (100.6 MHz, CDCl₃, δ (ppm)): 20.4 (CH₃-7), 20.6 (CH₃-6), 49.0 (CH₂), 52.4 (CH₃-1), 53.3 (CH₃-2), 109.6 (C-1), 111.3 (CH-5), 117.1 (CH-8), 124.6 (C-8a), 124.8 (C-2), 126.6 (CH-2'), 128.0 (CH-4'), 128.9 (CH-3'), 132.6 (C-7), 134.6 (C-4a and C-3), 135.4 (C-6), 135.5 (C-3a), 136.1 (C-1'), 159.6 (COO-1), 163.7 (COO-2). ¹⁵N NMR (40.5 MHz, CDCl₃, δ (ppm)): 120.7 (N-4), 167.1 (N-9). HRMS-ESI (m/z): [M+Na]⁺ for C₂₃H₂₁N₃NaO₆, calcd. 458.1323, found 458.1325.

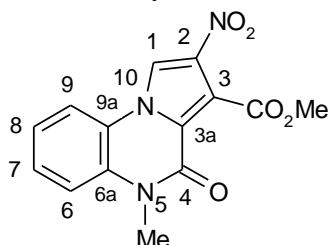
Dimethyl 3-nitro-4-ethyl-6,7-dimethylpyrrolo[1,2-*a*]benzimidazole-1,2-dicarboxylate (2d).



Yellow crystals (1.05 g, yield 56%), mp 224–226 °C. IR (KBr, cm⁻¹): 2951, 1748, 1715, 1587, 1536, 1482, 1429, 1362, 1290, 1221, 1139, 1069. ¹H NMR (400.1 MHz, CDCl₃, δ (ppm)): 1.47 (3H, t, ³J

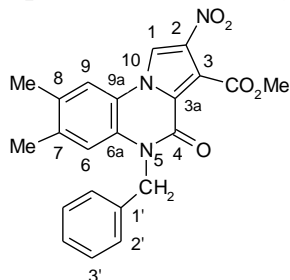
= 7.0 Hz, CH₃-Et), 2.42 (3H, s, CH₃-7), 2.43 (3H, s, CH₃-6), 3.93 (3H, s, CH₃-1), 4.02 (3H, s, CH₃-2), 4.78 (2H, q, ³J = 7.0 Hz, CH₂-Et), 7.20 (1H, s, H-5), 8.51 (1H, s, H-8). ¹³C NMR (100.6 MHz, CDCl₃, δ (ppm)): 15.8 (CH₃-Et), 20.3 (CH₃-7), 20.6 (CH₃-6), 41.1 (CH₂-Et), 52.4 (CH₃-1), 53.3 (CH₃-2), 109.5 (C-1), 110.5 (CH-5), 117.0 (CH-8), 124.5 (C-8a), 124.8 (C-2), 132.2 (C-7), 134.0 (C-4a and C-3), 135.2 (C-6), 135.3 (C-3a), 159.6 (COO-1), 163.8 (COO-2). ¹⁵N NMR (40.5 MHz, CDCl₃, δ (ppm)): 124.8 (N-4), 167.7 (N-9). HRMS-ESI (m/z): [M+Na]⁺ for C₁₈H₁₉N₃NaO₆, calcd. 396.1166, found 396.1185.

Methyl 2-nitro-4-oxo-5-methylpyrrolo[1,2-a]quinoxaline-3-carboxylate (3a).



Pale yellow crystals (0.61 g, yield 40%), mp 258–260 °C. IR (KBr, cm⁻¹): 3146, 2952, 1733, 1664, 1616, 1529, 1496, 1443, 1342, 1280, 1245, 1165, 1075. ¹H NMR (400.1 MHz, DMSO-d₆, δ (ppm)): 3.57 (3H, s, CH₃-5), 3.91 (3H, s, CH₃-3), 7.39 (1H, t, ³J = 8.0 Hz, H-8), 7.55 (1H, t, ³J = 8.0 Hz, H-7), 7.60 (1H, d, ³J = 8.0 Hz, H-6), 8.40 (1H, d, ³J = 8.0 Hz, H-9), 9.37 (1H, s, H-1). ¹³C NMR (100.6 MHz, DMSO-d₆, δ (ppm)): 28.5 (CH₃-5), 52.9 (CH₃-3), 113.8 (C-3), 116.5 (CH-9), 116.7 (CH-6), 117.1 (CH-1), 120.1 (C-3a), 121.8 (C-9a), 123.5 (CH-8), 128.4 (CH-7), 130.5 (C-6a), 135.0 (C-2), 153.0 (CO-4), 162.6 (COO). ¹⁵N NMR (40.5 MHz, DMSO-d₆, δ (ppm)): 129.7 (N-5), 172.7 (N-10). HRMS-ESI (m/z): [M+Na]⁺ for C₁₄H₁₁N₃NaO₅, calcd. 324.0591, found 324.0564.

Methyl 2-nitro-4-oxo-5-benzyl-7,8-dimethylpyrrolo[1,2-a]quinoxaline-3-carboxylate (3c).



Pale yellow crystals (0.71 g, yield: 35 %), mp 263–265 °C. IR (KBr, cm⁻¹): 3135, 2956, 1746,

1664, 1526, 1494, 1445, 1372, 1339, 1317, 1275, 1199, 1074. ¹H NMR (400.1 MHz, CDCl₃, δ (ppm)): 2.24 (3H, s, CH₃-7), 2.33 (3H, s, CH₃-8), 4.07 (3H, s, CH₃-3), 5.44 (2H, s, CH₂), 7.06 (1H, s, CH-6), 7.24–7.27 (3H, overlapped signals, H-2' and H-4'), 7.31 (2H, t, ³J = 7.0 Hz, H-3'), 7.49 (1H, s, H-9), 8.32 (1H, s, H-1). ¹³C NMR (100.6 MHz, CDCl₃, δ (ppm)): 19.4 (CH₃-8), 20.1 (CH₃-7), 45.3 (CH₂), 53.6 (CH₃-3), 113.4 (CH-1), 115.5 (C-3), 116.0 (CH-9), 118.0 (CH-6), 119.6 (C-9a), 120.3 (C-3a), 126.6 (CH-2'), 127.7 (CH-4'), 128.0 (C-6a), 129.0 (CH-3'), 133.1 (C-8), 135.5 (C-1'), 136.2 (C-2), 137.8 (C-7), 153.9 (CO-4), 163.0 (COO-3). ¹⁵N NMR (40.5 MHz, CDCl₃, δ (ppm)): 139.4 (N-5), 171.6 (N-10). HRMS-ESI (m/z): [M+Na]⁺ for C₂₂H₁₉N₃NaO₅, calcd. 428.1217, found 428.1218.

CONCLUSIONS

Novel pyrrolo[1,2-a]benzimidazoles and pyrrolo[1,2-a]quinoxaline-4-ones bearing a nitro group on the pyrrole ring have been synthesized *via* one-pot three-components reactions of 1-substituted benzimidazoles with dimethyl acetylenedicarboxylate and bromonitromethane in 1,2-epoxybutane. This synthetic route enables a reliable access to new nitro-substituted compounds which can be functionalized *via* the transformation of nitro group from the pyrrole ring.

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