Nitropyrazoles
2. Nitro-derivatives of dipyrazolo[3,4-b; 4',3'-e]pyrazine*

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Unsubstituted 1*H*,7*H*-dipyrazolo[3,4-b;4',3'-e]pyrazine has been synthesized for the first time starting from 5-amino-3-methyl-1-phenylpyrazole. Its nitration to form *C*- and *N*-dinitro-substituted derivatives has been studied. The molecular structure of 3,5-dinitro-1*H*,7*H*-dipyrazolo[3,4-b;4',3'-e]pyrazine has been established by X-ray structural investigation; the NH acidity of this compound and the orientation of its alkylation with bromoacetone have also been determined.

Key words: nitration, nitrodipyrazolo[3,4-b;4',3'-e]pyrazines, 1*H*,7*H*-dipyrazolo [3,4-b;4',3'-e]pyrazine.

Recently we developed a general approach to the synthesis of nitro derivatives of pyrazolo[4,3-c]pyrazole and showed that these compounds make it possible to prepare the previously unknown first member of the series.[1] Dipyrazolo[3,4-b;4',3'-e]pyrazine (DPP) is another poorly invesigated pyrazole-containing fused system. Compounds of the DPP series are of interest, since pyrazolopyrazines are known[2] to be pharmacologically active, so a similar system having an additional pyrazole ring naturally attracts attention. Interest in these compounds is caused as well by their luminescent properties.[3] However, among the DPP known, there are practically no compounds that allow versatile functionalization of this tricyclic system to be carried out. This restricts the synthetic possibilities in the DPP series. For example, *N*-unsubstituted DPP as well as those having easily transformed substituents are unknown.

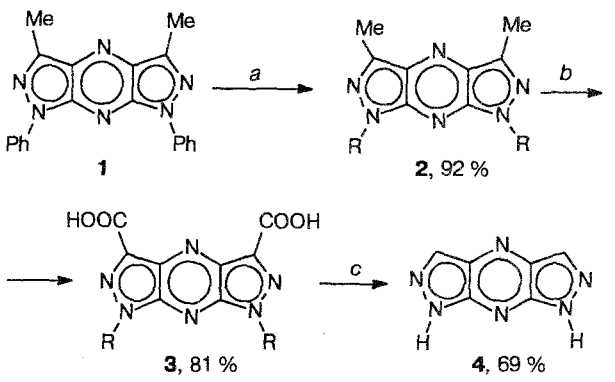
The advances in the chemistry of nitropyrazoles[4,5] provide reasons to hope that the first member of the series, unsubstituted DPP, and its nitro derivative can be attained on the basis of known techniques which include acidic nitration. The presence of C-nitro groups in the pyrazole ring would extend the possibilities of DPP functionalization by substantially facilitating reactions involving the NH-fragment[6] and by the possible conversion of the nitro-group into other groups[4] or the nucleophilic substitution of other groups for it.

For structural reasons and due to its availability we chose 3,5-dimethyl-1,7-diphenyldipyrazolo[3,4-b;4',3'-e]pyrazine (**1**) as the initial compound to accomplish this task. This compound was prepared by the condensation of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole with 5-amino-3-methyl-1-phenylpyrazole in acetic acid.[7]

The transition from compound **1** to unsubstituted DPP requires the removal of the *N*-phenyl substituents. This can be accomplished by the nitration of the benzene rings and their subsequent elimination in the form of 2,4-dinitrophenol in the presence of a base.[8] The methyl groups can be removed by oxidizing them to carboxylic groups followed by decarboxylation.

We chose conditions for the nitration of compound **1** with a mixture of nitric and sulfuric acids which gives bis(2,4-dinitrophenyl)DPP **2** in a nearly quantitative yield. Oxidation of compound **2** with sodium dichromate in sulfuric acid affords dicarboxylic acid **3** in a high yield. On heating dicarboxylic acid **3** in aqueous ammonia at 190 °C in an autoclave, it is converted into the unsubstituted dipyrazolo[3,4-b;4',3'-e]pyrazine (**4**), *i.e.*, decarboxylation and elimination of 2,4-dinitrophenol occur in one step (Scheme 1).

Scheme 1



R = 2,4-$(NO_2)_2C_6H_3$

a. HNO_3—H_2SO_4, 20°C, 48 h; *b*. H_2SO_4—$Na_2Cr_2O_7 \cdot 2H_2O$, 100°C, 10 h; *c*. 25 % aqueous solution of NH_3, 190—195°C, 6 h

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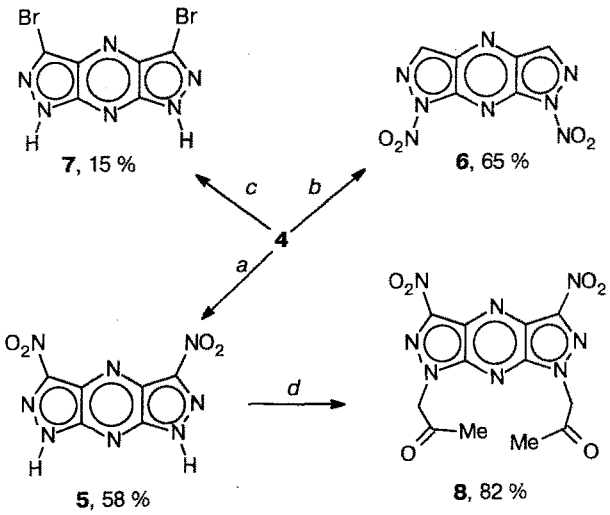
Unsubstituted DPP **4,** obtained for the first time, is a dark brown powder practically insoluble in any of the common organic solvents except DMSO. However, it dissolves readily in an aqueous alkaline solution to form the corresponding disalt. Compound **4** can be isolated from the resulting solution by treating it with an acid; this procedure was employed for purification of the compound.

We studied the acidic nitration of DPP **4** and have found that, in spite of the strong electron-withdrawing effect of the pyrazine moiety (due to the presence of two «pyridine» nitrogen atoms*), both pyrazole rings are nitrated (at the carbon atoms of the ring) on heating with a mixture of concentrated nitric (d = 1.5 g·cm^{-3}) and sulfuric acids to produce dinitro derivative **5** (Scheme 2).

Scheme 2



a. H_2SO_4—HNO_3, 70°C, 10 h; *b.* CF_3COOH—HNO_3—Ac_2O, 0—5°C, 2 h; *c.* NaOAc—CF_3COOH—Br_2, 80°C, 10 h; *d.* 1.LiOMe; 2.MeOH—dichloroethane, CH_3—CO—CH_2Br, 20°C, 5 h.

An examination of the effect of the acidity of the medium, the ratio between HNO_3 and H_2SO_4, and the temperature and duration of the process on the course of the reaction show that to obtain DPP **5** in a preparative yield (58 %) one should use a 4 : 1 (by volume) mixture of 96 % H_2SO_4 and HNO_3 at 70 °C. An increase in the acidity of the medium (100 % H_2SO_4—HNO_3, 3 : 1 (by volume)) at the same temperature results in a reduction in the yield of compound **5** to 25 %, possibly due to protonation of the original compound **4** which hinders nitration. An increase in the content of HNO_3 lowers the yield of the dinitro-substituted derivative **5**: with a 96 % H_2SO_4—HNO_3 ratio of 1 : 2 (by volume) the yield is 23 %, and when the ratio is 1 : 1 it is 10 %.

The acidity of compound **5** as a dibasic NH-acid, determined by the spectrophotometric method* (in water, at 20 °C), is: pK_{a1} = 4.33; pK_{a2} = 6.21 (the accuracy of the determination is ± 0.05 pK units). Thus, DPP **5** is a relatively strong NH-acid, as can be seen from the comparison of its pK_{a1} value with pK_a of 3-nitropyrazole, which is equal to 9.81.[10] These data indicate a very strong electron withdrawing effect of the annelated pyrazine fragment, which is even greater than that of the 4-NO_2 group (in 3,4-dinitropyrazole pK_a = 5.48).[10]

The structural features of compound **5** were determined by X-ray diffraction analysis (Fig.1). The crystals are rhombic, a = 6.029(1), b = 15.346(2), c = 9.656(3) Å, V = 893.4(3) Å^3, Z = 4, d = 1.860 g·cm^{-3}, space group $P_{bh}2_1$. The tricyclic framework of a molecule of **5** is planar to within ±0.02 Å. The nitro-group at the C(2) atom lies in the same plane as the tricyclic moiety, while that at C(10) is rotated around the C(10)—N(16) bond by an angle of 15.2°. The bond lengths in the molecule are close to their standard values:[11] the distribution of the bond lengths in the pyrazine ring is typical of an aromatic system, while the bond lengths in the pyrazole rings are prone to alternate. The molecules which are symmetrically connected in the crystal by the crystallographic n plane are combined into a chain through dipole-dipole interactions N(4)...O(15) (2.77 Å) and O(14)...N(16) (2.80 Å). Other intermolecular contacts are of the van der Waals type. The X-ray structural data imply that the NH-proton of crystalline compound **5** is located at the position 1 of the pyrazole ring, *i.e.*, at the nitrogen atom adjacent to the pyrazine ring.

It should be noted that nitration of DPP **4** carried out with a mixture of nitric acid and acetic anhydride (*i.e.*, with acetyl nitrate), instead of the nitric—sulfuric mixture, occurs at the NH-fragment, as in the case of other *N*-unsubstituted pyrazoles,[4] and yields *N,N'*-dinitro-substituted derivative **6**. Notice that the reaction is regiospecific and involves position 1 only, *i.e.*, the nitrogen atom adjacent to the pyrazine fragment (the verification of the structure of **6** is given below). *N*-Nitro-

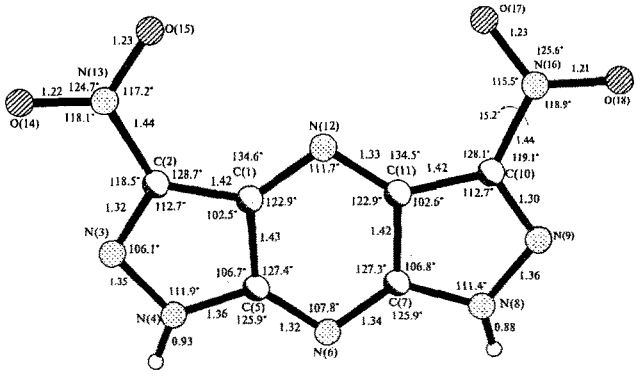


Fig. 1. Projection of a molecule of **6** on the plane of the heterocyclic nucleus

* The electron-withdrawing ability of a «pyridine» nitrogen atom is comparable with that of a nitro-group.[9]

* UV spectrum: for neutral molecule λ_{max} = 327 nm (lg ε = 4.27); for dianion λ_{max} = 330 nm (lg ε = 4.50). The procedure of determining the acidity of **5** and similar NH-azoles will be described in detail in a separate communication.

pyrazoles are known to undergo a thermal rearrangement which involves migration of the *N*-nitro-group to the vicinal carbon atom of the pyrazole ring ($N(1)—NO_2 \rightarrow C(5)—NO_2$).[4] The migration from N(1) to C(3), that is, over a nitrogen atom, is also possible, though in this case the reaction proceeds substantially more slowly. For compound **6** such a rearrangement ($N(1)—NO_2 \rightarrow C(3)—NO_2$) does not occur at all. Only its denitration to give DPP **4** takes place under the conditions of thermal isomerization (heating in benzonitrile for 10 h at 180 °C).

The ability of DPP **4** to enter electrophilic substitution reactions has been confirmed by its bromination with bromine in trifluoroacetic acid. The reaction is very slow due to very low solubility of compound **4**, however, after a prolonged heating with reflux we managed to obtain dibromide (**7**) in a low yield. It should be noted that *N*-unsubstituted dipyrazolo[3,4-b;4',3'-e]pyrazines turned out to be rather high-melting compounds (Table 1).

As we have expected (see above), compound **5** is readily alkylated at the nitrogen atom of the pyrazole ring. We examined the interaction of **5** with bromoacetone,[6] since *N*-acetonyl derivatives are of interest for their further transformations and as biologically active compounds.[5] Alkylation of the dilithium salt of compound **5** with bromoacetone in methanol affords the symmetrical diketone (**8**) in good yield. The reaction proceeds regiospecifically; it involves the N(1) atom only.

The structures of all of the compounds synthesized were determined using ^1H, ^{13}C, ^{14}N, and ^{15}N NMR spectroscopy (Table 2) and confirmed by the data from the IR spectroscopy and elemental analysis (Table 1). ^{13}C and ^{15}N NMR spectroscopic data allow one to establish the direction of *N*-nitration of DPP **4** and alkylation of the dinitro-derivative **5**. Actually, the presence of geminal spin-spin interaction of the pyrazine nitrogen atom (−57.95 ppm) with the proton at C(3), equal to 14.4 Hz, in the ^{15}N NMR spectrum points unambigiously to the presence of a NO_2-group at the N(1) atom.[6] In the case of diketone **8** the acetonyl groups are located at the N(1) atom as well; this is indicated by the presence of spin-spin interaction of the C(5) atom with the CH_2-protons of the acetonyl fragment. The ^{15}N NMR spectrum of compound **8** exhibits five signals: signals at −68.95 and −150.46 ppm assigned to the nitrogen atoms of the pyrazine ring, a signal at −25.69 ppm associated with the nitro group, and two triplets, at −45.72 ppm (N(2)) with $^3J_{N(2)—HCH2} = 3.0$ Hz and −205.40 ppm (N(1)) with $^2J_{N(1)—HCH2} = 1.3$ Hz. The presence of vicinal spin-spin interaction of N(2) with the CH_2-protons equal to 3.0 Hz also points to substitution at the N(1) atom.[6]

Experimental

3,5-Dimethyl-1,7-diphenyldipyrazolo[3,4-b;4',3'-e]pyrazine (1) was prepared according to the known procedure.[7] ^1H NMR spectra were recorded with a Bruker WM-250 spectrometer (operating on 250 MHz). ^{13}C, ^{14}N, ^{15}N NMR spectra were obtained using a Bruker AM-300 instrument (operating on 300 MHz for protons). Chemical shifts (δ) are referred to TMS (^{13}C, ^1H) or to CH_3NO_2 (^{14}N, ^{15}N). High-field chemical shifts are given with a minus. IR spectra were run on a Specord M-80 spectrometer for KBr disks, UV spectra were recorded with a Specord UV-VIS instrument. Melting and decomposition points were determined by differential thermal analysis (with a heating rate of 5 deg · min^{-1}). The reactions were monitored and the purity of the products was checked by TLC on Silufol UV-254 plates. The X ray structural study was performed using an Enraf-Nonius CAD-4 automatic diffractometer (Mo-*K*α radiation, $2\theta_{max} = 59.8°$). 738 reflections were registered, 457 of them had intensities $I \geq 3\sigma$. The structure was solved and refined in the anisotropic approximation using SHELX programs on a PC/AT computer, the final R was 7.8 %. The accuracy of the determination of bond lengths was ±0.008—0.010 Å and of bond angles was ±0.6—0.9°.

Table 1. Characteristics of dipyrazolo[3,4-b;4',3'-e]pyrazines **2—8**[a]

Compound	m.p. [dec.p.]/°C (solvent for crystallyzation)	IR, ν/cm^{-1}	Found / Calculated (%) C	H	N	Molecular formula
2	230 (acetone)	1535, 1345 (NO_2)	46.09 / 46.16	2.47 / 2.32	26.61 / 26.91	$C_{20}H_{12}N_{10}O_8$
3	134 (acetone)	3400 br. (OH) 1720 (CO) 1545, 1350 (NO_2)	41.50 / 41.39	1.36 / 1.39	24.12 / 24.14	$C_{20}H_8N_{10}O_{12}$
4	>350	3200—3000 (NH)	44.91 / 45.00	2.45 / 2.52	52.64 / 52.48	$C_6H_4N_6$
5	[305] (HNO_3)	3360 br. (NH) 1544, 1375 (NO_2)	28.61 / 28.81	0.78 / 0.81	45.26 / 44.79	$C_6H_2N_8O_4$
6	[124] (acetone)	1624, 1292 (NO_2)	28.52 / 28.81	0.79 / 0.81	45.02 / 44.79	$C_6H_2N_8O_4$
7	>350	3200—3100 br. (NH)	22.48 / 22.66	0.72 / 0.63	—	$C_6H_2Br_2N_6$
8	224 (acetone)	1740 (CO) 1540, 1375 (NO_2)	39.64 / 39.78	2.62 / 2.78	31.13 / 30.94	$C_{12}H_{10}N_8O_6$

[a] The authors wish to thank Ph. D. V. I. Gulevskaya for performing the differential thermographic analysis.

Table 2. The ^1H, ^{13}C, ^{14}N, and ^{15}N NMR spectral data[a] for dipyrazolo[3,4-b;4',3'-e]pyrazines (δ, in DMSO-d_6).[a]

Compound	^1H NMR	^{13}C NMR				^{15}N NMR
		C(3)	C(4)	C(5)	other C atoms	
1[b]	2.80 (s, 3-CH_3) 7.30 (t, Ph, J = 10.0) 7.54 (t, Ph, J = 7.5) 8.30 (d, Ph, J = 12.5)	150.92 q (J = 7.0)	136.12 d (J = 2.2)	150.58 d (J = 2.5)	11.39 (q, CH_3, J = 132.0); 123.47 (dq, Ph, J = 163.7; 4.1) 127.63 (dt, J = 163.0; 6.1); 129.52 (d, J = 162.8); 136.48 (t, J = 7.7)	−90.62 (q, N(2), J = 2.9)
2[b]	3.41 (s, 3-CH_3) 8.25 (d, Ph, J = 9.0) 8.65 (dd, Ph, J = 9.0; 2.5) 8.8 (d, Ph, J = 2.5)	149.31 q (J = 7.0)	135.44 q (J = 2.9)	145.48 s	11.76 (q, CH_3, J = 131.4) 121.58 (dd, Ph, J = 175.3; 4.7) 127.37 (d, Ph, J = 172.5) 128.02 (dd, Ph, J = 172.3; 5.2) 135.07 (Ph) 142.50 (Ph) 142.29 (Ph)	−16.76(NO_2)[c]
3[b]	8.15 (d, Ph, J = 8.8) 8.62 (dd, Ph, J = 8.8; 2.5) 8.85 (d, Ph, J = 2.5)	146.70 s	133.07 s	143.09 s	160.13 (s, COOH) 121.35 (d, Ph, J = 176.1) 128.49 (d, Ph, J = 176.4) 129.05 (d, Ph, J = 176.6) 134.14 (Ph) 140.09 (Ph) 141.77 (Ph)	—
4	8.50 (s, H^3) 13.68 (br.s, NH)	134.21 d (J = 183.9)	132.99 d (J = 10.5)	143.02 d (J = 4.4)	—	—
5	—	145.99 s	126.94 s	143.20 s	—	—
6[d]	8.89 (s, H^3)	137.70 d (J = 203.0)	136.45 d (J = 9.5)	140.98 d (J = 3.2)	—	−57.95 (d, N(2), J = 14.4) −131.41 (d, N(1), J = 8.9) −60.08 (NO_2)
7	—	144.31 s	122.03 s	131.14 s	—	—
8[b]	2.40 (s, CH_3) 5.79 (s, CH_2)	145.29 d (J = 2.1)	127.61 s	142.35 t (J = 2.6)	27.14 (q, CH_3, J = 128.6) 57.46 (tq, CH_2 J = 132.9; 2.1) 200.31 (q, CO, J = 8.0)	−25.69 (NO_2) −45.72 (t, N(2), J = 3.0) −205.40 (t, N(1), J = 1.3) −68.95 (N pyrazine) −150.46 (N pyrazine)

[a] The authors are grateful to B. I. Ugrak for recording the NMR spectra. [b] in $CDCl_3$. [c] ^{14}N NMR. [d] in acetone-d_6.

3,5-Dimethyl-1,7-bis(2,4-dinitrophenyl)dipyrazolo-[3,4-b;4',3'-e]pyrazine (2) Compound **1**[7] (2.5 g, 7.3 mmol) was dissolved in 17 mL of HNO_3 (d = 1.5 g · cm^{-3}), while the temperature was maintained below 20—25 °C, and 68 mL of concentrated H_2SO_4 was added. The mixture was stirred for 1 h, kept for 2 days at 20—25 °C, and poured into ice water. The precipitate was filtered off, washed with a small amount of acetone, and dried to give 3.5 g (92 %) of compound **2**.

3,5-Dicarboxy-1,7-bis(2,4-dinitrophenyl)dipyrazolo-[3,4-b;4',3'-e]pyrazine (3) Compound **2** (7.5 g, 14.4 mmol) was dissolved with stirring in 144 mL of conc. H_2SO_4 at 20—25 °C, and 12.5 g (42 mmol) of $Na_2Cr_2O_7 \cdot 2H_2O$ was added portionwise. The reaction mixture was held for 10 h at 100 °C, poured onto ice, and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$, and evaporated to yield 6.8 g (81 %) of dinitro-substituted derivative **3**.

1*H*,7*H*-Dipyrazolo[3,4-b;4',3'-e]pyrazine (4). Compound **3** (7.3 g, 13 mmol) and 150 mL of 25 % aqueous ammonia were placed in an autoclave and held at 190—195 °C for 6 h. Then the reaction mixture was evaporated to dryness, the residue was washed twice with water and 2—3 times with acetone, until the wash liquid was colorless. 1.4 g (69 %) of compound **4** as a dark brown powder was obtained. An additional purification was performed if necessary in the following way: 1 g of compound **4** was dissolved in a solution containing 0.8 g of KOH in 25 mL of water, the undissolved impurities were filtered off, and the solution was acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water and with acetone, and dried.

1*H*,7*H*-Dinitrodipyrazolo[3,4-b;4',3'-e]pyrazine (5). A solution of compound **4** (1 g, 6 mmol) in a mixture of 8 mL of HNO_3 (d = 1.5 g · cm^{-3}) and 32 mL of concentrated H_2SO_4 was held for 10 h at 70 °C, poured into water, neutralized with Na_2CO_3, and extracted twice with ethyl acetate. The organic layers were dried with $MgSO_4$ and evaporated, and the residue was washed with ether. 0.9 g (58 %) of compound **5** was obtained. If required further purification was accomplished by recrystallization from HNO_3 (d = 1.5 g · cm^{-3}).

1,7-Dinitrodipyrazolo[3,4-b;4',3'-e]pyrazine (6). To a suspension of compound **4** (1 g, 6 mmol) in 6 mL of CF_3COOH were added 1 mL of HNO_3 (d = 1.5 g · cm^{-3}) and then 2.6 mL of acetic anhydride at 0—5 °C. The mixture was stirred at this temperature for 2 h and poured into water. The precipitate was filtered off and washed with water to yield 1.0 g (65 %) of compound **6**.

3,5-Dibromodipyrazolo[3,4-b;4',3'-e]pyrazine (7). Br_2 (0.6 mL, 10.3 mmol) was added to a suspension of compound **4** (0.5 g, 3.1 mmol) and 0.75 g (0.9 mmol) of NaOAc in 20 mL of trifluoroacetic acid, and the mixture was held for 10 h at 80 °C. The hot reaction mixture was filtered from the unreacted dipyrazolopyrazine **4**, the filtrate was cooled, and the precipitate formed was filtered off to afford 0.15 g (15 %) of compound **7**.

1,7-Diacetonyl-3,5-dinitrodipyrazolo[3,4-b;4',3'-e]pyrazine (8). To 6 mL of a 1 *N* solution of LiOMe in 50 mL of methanol were added compound **5** (1 g, 4 mmol) and then 1.68 g (12.4 mmol) of bromoacetone in 7 mL of dichloroethane. The mixture was stirred for 5 h at ~20 °C, and the precipitate was filtered off and washed with ether to give 1.2 g (82 %) of compound **8**.

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Nitropyrazoles
3.* The synthesis of *C*-(diformylmethyl)nitropyrazoles

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The double Vilsmeier formylation of the *C*-methyl group in pyrazole derivatives has been shown to occur when a nitro-group is in the adjacent position of the ring. A method for the synthesis of *C*-(diformylmethyl)nitropyrazoles based on this reaction has been developed.

Key words: formylation, trimethinium salts, *C*-(diformylmethyl)nitropyrazoles.

The derivatives of malonic dialdehyde are key compounds for the synthesis of various heterocyclic systems owing to their reactions with bifunctional nucleophiles. For this reason, it is of value to develop approaches to the introduction of the diformylmethyl moiety into heteroaromatic rings in order to obtain convenient starting compounds for the synthesis of bi- and polyheterocyclic systems.

The formylation of 4-nitropyrazolyl-1-acetic acid[3] is a known example of the formation of a diformylmethyl fragment at the N-atom of the pyrazole ring. However,

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