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CHEMISTRY OF POLYHALOGENATED NITROBUTADIENES, 15: SYNTHESIS OF NOVEL 4-NITRO-3-AMINO-1*H*-PYRAZOLE-5-CARBALDEHYDES AND PYRAZOLO[3,4-*f*]INDAZOLE-4,8-DIONES

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Dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

Abstract – Condensation of 1-amino-1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienes **3a-e** with methylhydrazine leads to a series of uniquely persubstituted 4-nitropyrazoles **4a-e** bearing a dichloromethyl substituent in 5-position. Subsequent hydrolysis of this group applying aqueous sulfuric acid then gives interesting *push-pull*–substituted pyrazole-5-carbaldehydes **5a-e**. Upon hydrolysis of **4a-e** at harsher reaction conditions different pyrazolo[3,4-*f*]indazole-4,8-diones were also formed. A mechanism of the homo-condensation of carbaldehydes **5a,d** to the indazole derivatives **8-13** is proposed, and as an example the structure of 3,7-bis(dimethylamino)-1,6-dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,6*H*)-dione (**9**) has been confirmed by X-ray analysis.

INTRODUCTION

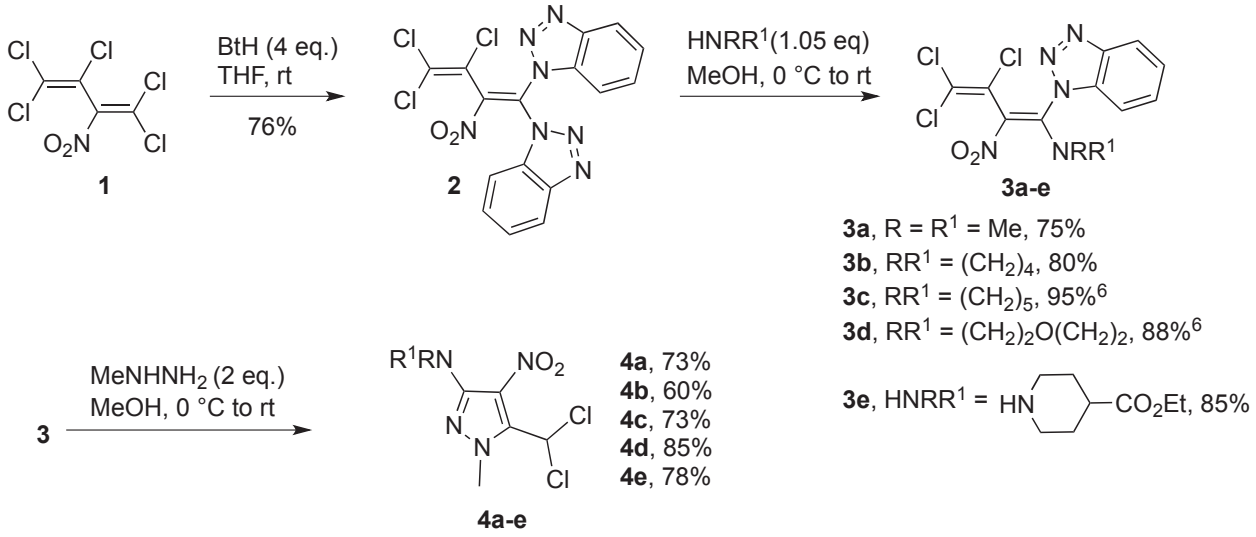
Halogenated nitrobutadienes are a relatively small group of unsaturated nitro compounds.[1] Among these, representatives with one or two nitro groups and additionally three to five halogen atoms are known. These halogenated nitrobutadienes are easily accessible via introduction of an activating and directing nitro group into polyhalogeno-1,3-butadienes,[2] which themselves can be obtained by dimerization of cheap industrial solvents such as trichloroethene and 1,2-dichloroethene and subsequent dehydrohalogenation-halogenation steps. Especially, the readily accessible perchloro-2-nitro-1,3-

butadiene (**1**) is one of the most attractive members of this rather new class of synthetically useful compounds.[3] Preliminary studies have already shown the enormous potential of **1** as a potent precursor for a variety of highly functionalized acyclic as well as (hetero)cyclic compounds.[4]

In the present paper, we mainly focus on recent progress in a) the synthesis of 3-amino-(5-(dichloromethyl)-1-methyl-4-nitro-1*H*-pyrazoles by condensation of 1-amino-1-(1*H*-benzo[*d*][1,2,3]-triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienes with methylhydrazine, b) hydrolysis of the dichloromethyl group in the synthesized pyrazoles to the formyl unit, and c) formation of different dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-diones from pyrazoles under different sulfuric acid catalysis conditions.

RESULTS AND DISCUSSION

Starting from perchloro-2-nitrobuta-1,3-diene (**1**), 1,1-bis(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene (**2**) is accessible in 76% yield.[5] The partial trans-amination of **2** with secondary aliphatic amines, such as dimethylamine, pyrrolidine, piperidine,[6] morpholine,[6] and ethyl piperidine-4-carboxylate in methanol at mild reactions conditions (0 °C to rt, 3-7 h) leads to the 1-(1*H*-benzo-[*d*][1,2,3]triazol-1-yl)-1-amino-3,4,4-trichloro-2-nitrobuta-1,3-dienes **3a-e** in good to very good yields (75-95%).[6] Thereby, again the benzotriazole substituent proves its powerful leaving group character finding versatile applications in organic chemistry.[7] Subsequent treatment of dienes **3a-e** with methyl-hydrazine at 0 °C to rt in methanol then provides the 4-amino-4-nitropyrazoles **4a-e** in 60-85% yield (Scheme 1).

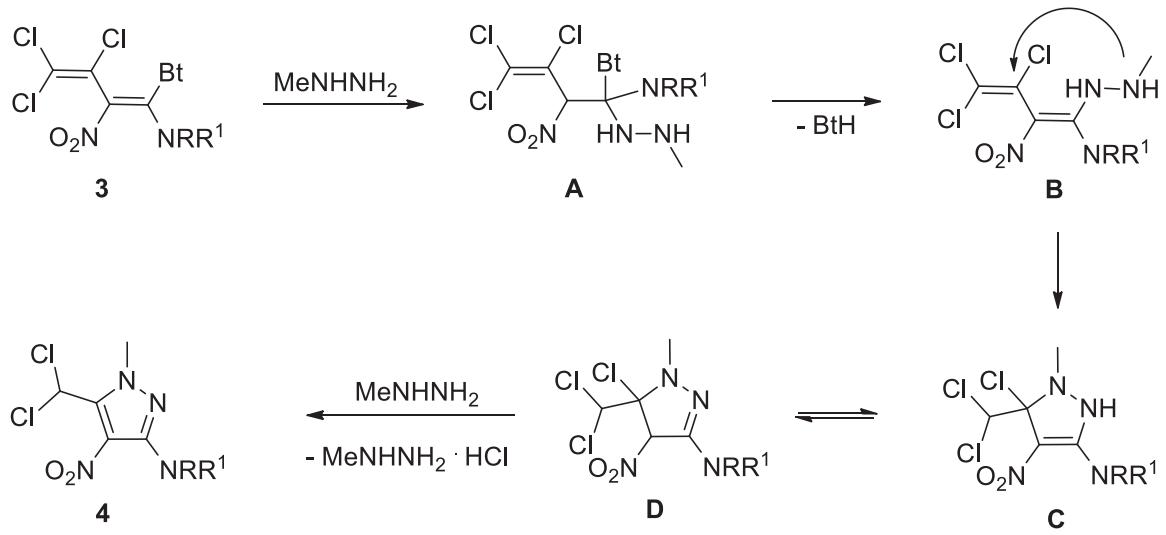


Scheme 1

The assumed mechanistic pathway for the formation of pyrazoles **4** from dienes **3** is depicted in Scheme 2. In detail, the electrophilic C1-atom in **3** is initially attacked by the NH_2 group of methylhydrazine to form

butene **A**. In contrast to this, the attack of the more nucleophilic NH unit of methylhydrazine is not observed probably due to sterical hindrance caused by the bulky benzotriazole fragment. After this nucleophilic addition, the elimination of benzotriazole as a leaving group from **A** results in diene **B**. Thereupon a remarkable ring closing reaction takes place, i. e. an intramolecular aza-Michael type addition, that leads to pyrazoline **C**. Tautomerisation to pyrazoline **D** and elimination of hydrochloric acid by means of a second equivalent of methylhydrazine reveals nitropyrazoles **4** (Scheme 2).

Previously, we described a similar pathway for the synthesis of 4-nitropyrazoles from di(arylamino)-2-nitrobutadienes or arylimino-2-nitrobut-2-enes and hydrazine hydrate or aryl hydrazines.[8] Such highly substituted nitropyrazoles were found to offer interesting biological activities. For example, 5-chloro-4-nitropyrazoles are intermediates for herbicides,[9a] certain 1-phenyl-4-nitropyrazoles,[9b] 5-amino-1-phenyl-4-nitropyrazoles,[9c] and aryl(dichloroacetamido)nitropyrazoles[9d] were prepared as herbicides and plant growth regulators. Other nitropyrazole derivatives are known to facilitate significant retinal function recovery after ischemic insult through the increase of ocular blood flow,[9e] and additionally, many 3-nitropyrazoles show antibacterial activity.[9f]

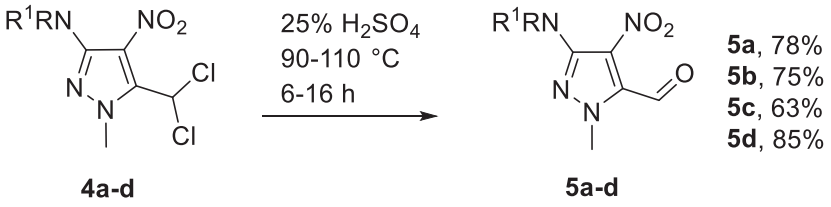


Scheme 2

In the course of our studies, the dichloromethyl group attached to the synthesized pyrazoles **4** should be converted into a formyl unit. For comparison, chloroform can be hydrolyzed to formyl chloride by conc. HNO_3 at 60 °C,[10] already, whereas benzal chloride is hydrolyzed to benzaldehyde upon treatment with aqueous HCl (100 °C, 3 h, 95-100% yield),[11a,b] in DMSO (100 °C, 2 h, 95% yield),[11c] in trimethyl orthoformate (237 °C, 24 h, 74%),[11d] or in boric acid (130 °C, 4 h, 85%).[11e] Also several methods for the synthesis of heterocyclic aldehydes from corresponding (dichloromethyl)heterocycles are known from the literature, for example pyrazoles (H_2SO_4-H_2O, 100-130 °C; 10-22 h),[12a] triazoles (100 °C, 2-3 h, Na_2CO_3,

H_2O, dioxane),[12b] benzimidazoles (i) AcONa, $Bu_4N^+Br^-$, PhMe, 3-4 h, 90 °C, ii) Na_2CO_3, $Bu_4N^+Br^-$, H_2O, 4-6 h, 40 °C),[12c] 1,3-benzodioxoles (AcOH, HCl, hexamethylenetetramine, H_2O, reflux),[12d] triazolo[5,1-*f*]-[1,6]naphthyridines (Me_2NH, H_2O, 5 h, 70 °C),[12e] imidazo[1,2-*a*]pyridines ($CaCO_3$, H_2O, reflux),[12f] thiophenes (HCO_2H, $ZnCl_2$, reflux),[12g] isoquinolines (DMSO, 150 °C),[12h] isothiazoles (i)H_2SO_4, H_2O, 125-130 °C, ii) NaOH, H_2O, rt, pH 6),[12i] isoxazoles (NaOMe, CH_2Cl_2),[12j] or pyrroles (H_2O, MeOH).[12k]

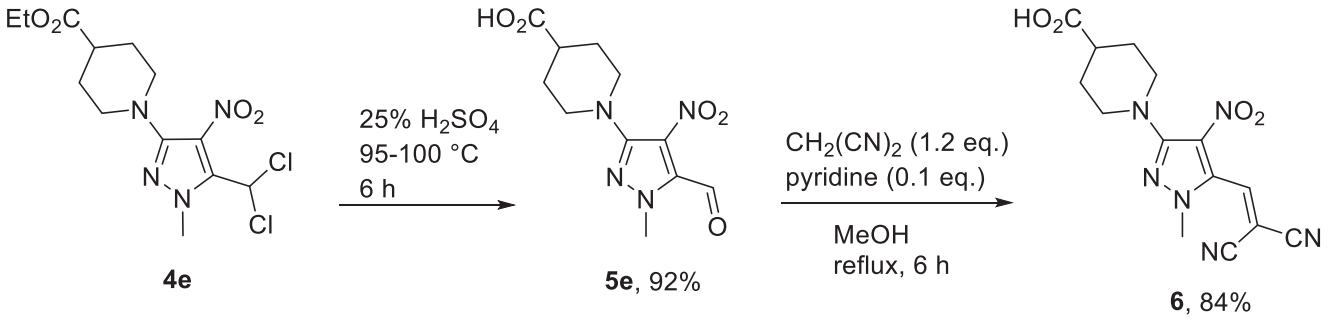
In the present case, we found that hydrolysis of pyrazoles **4a-d** with 25% aqueous sulfuric acid at 90-110 °C led to the carbaldehydes **5a-d** in moderate to good yields (63-85%) (Scheme 3). At lower temperatures (70-85 °C) the reaction rate was very low, whereas at elevated temperatures (115-140 °C) the formation of several by-products could be observed.



Scheme 3

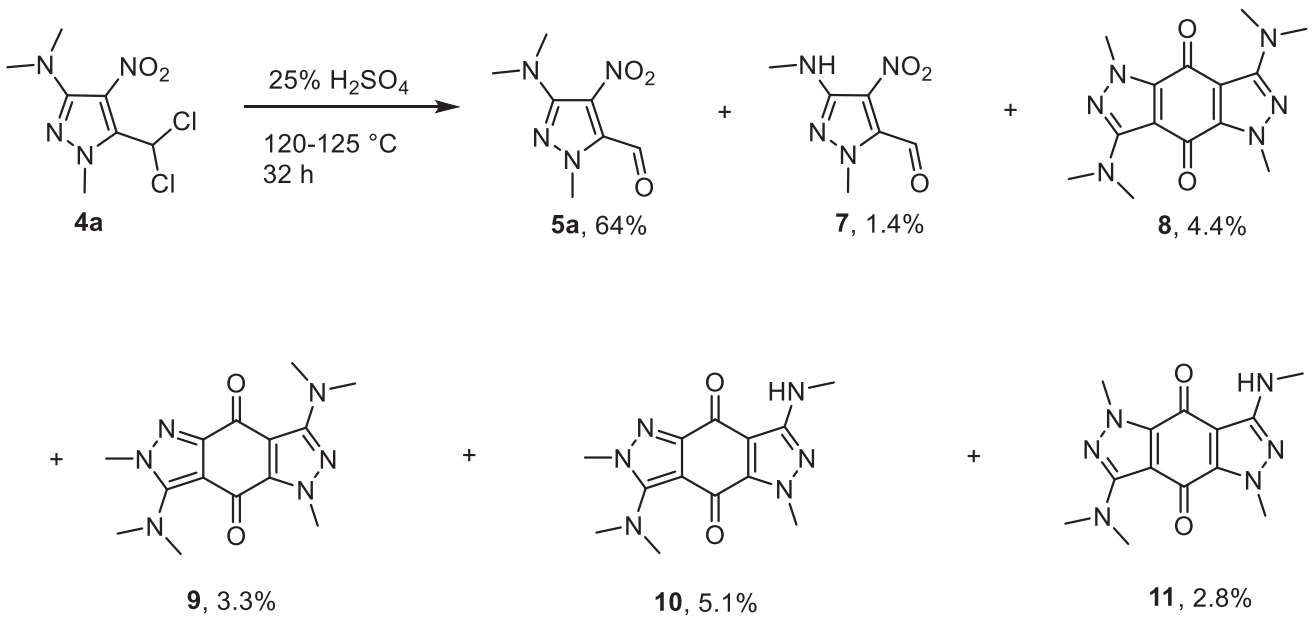
The products of this synthetic step should also allow for interesting application aside from their utilization as a synthetic intermediate, as formylpyrazoles have been found to exhibit remarkable DPPH radical scavenging ability,[13a] show antifungal and antibacterial activity,[13a-c] and were useful as antitumor[13d] or antidiabetic agents.[13e]

Treatment of ethyl carboxylate **4e** with 25% sulfuric acid at 95 °C resulted in hydrolysis of both the $CHCl_2$ and the CO_2Et group and thus was converted into acid **5e** in 92% yield. Via subsequent Knoevenagel condensation with malononitrile in the presence of a catalytic amount of pyridine the 5-dicyanovinyl-pyrazole **6** was obtained in 84% yield as a yellow solid (Scheme 4).



Scheme 4

Hydrolysis of pyrazole **4a** at harsher conditions (25% aq. H_2SO_4, but 120-125 °C for 32 h), gave smaller amounts of the carbaldehyde **5a** (64% yield), but provided structurally unexpected byproducts, additionally. Fortunately, a series of them could be isolated and characterized after twofold column chromatography: 3-methylaminopyrazole **7** (1.4% yield), 1,5-dimethylpyrazoloindazoledione **8** (4.4%), 1,6-dimethylpyrazoloindazoledione **9** (3.3%), 1,6-dimethyl-3-(methylamino)pyrazoloindazoledione **10** (5.1%), and 1,5-dimethyl-7-(methyl-amino)pyrazoloindazoledione **11** (2.8%) (Scheme 5).

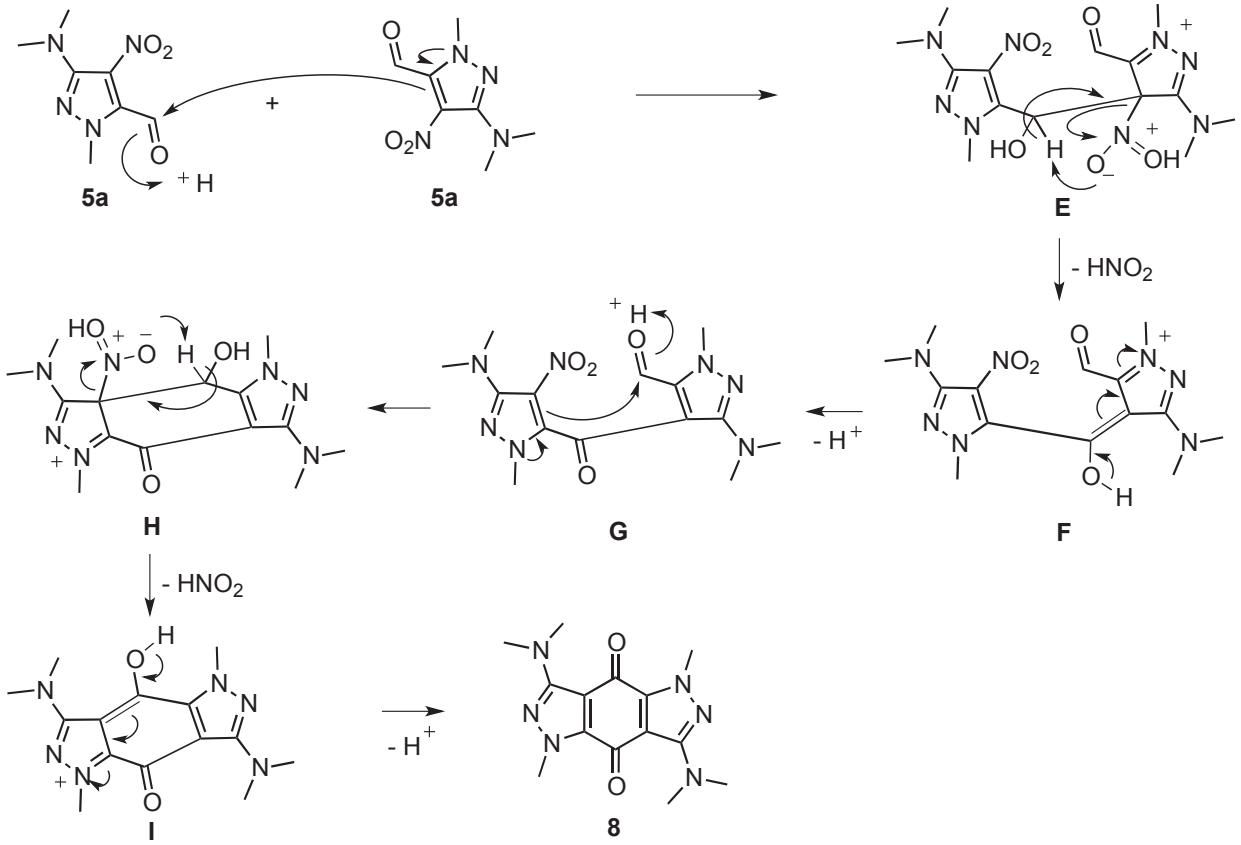


Scheme 5

Assumably, the methylamino derivative **7** is formed by thermal *N*-demethylation of dimethylamino-pyrazole **5a** at 120 °C, a reaction that is rarely found in literature. For example, it is known that *N,N*-dimethylanilines can be mono-*N*-demethylated by a non-heme oxoiron(IV) complex, i. e. $[(N_4Py)Fe^{IV}O]^{2+}$, (N_4Py=*N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine). This reaction is described as an electron transfer–proton transfer (ET–PT) process in acetonitrile at 25 °C.[14a] Other reaction conditions for *N*-demethylation of a Me_2N group are as follows: a) H_2 (300 psi), H_2O, MeOH, $Pd(OH)_2$, 8 h, rt,[14b], b) *t*-BuOOH, $FeCl_2$, MeOH, rt,[14c] c) HBr, KI, DMF, reflux,[14d] d) i) BrCN, Me_2CO, reflux, ii) HCl, H_2O, reflux,[14e] e) CaO, I_2, MeOH, THF, 0 °C.[14f]

The side-product indazoledione **8** is formed probably from carbaldehyde **5a** through a twofold elimination of nitrous acid (Scheme 6). Addition of the enamine unit of **5a** to the carbonyl group of a second molecule of **5a** gives alcohol **E**. Successive thermal 1,2-elimination of HNO_2 then provides

bispyrazolylketone **G**, from which in an analogous, but then intramolecular manner, the tricyclic ketoalcohol **H** is formed. Finally, elimination of nitrous acid results in the formation of pyrazoloindazoledione **8**. When **4a** is hydrolyzed under the same reaction conditions, but additionally under nitrogen, all compounds except of **10** are formed. Therefore, a radical mechanism cannot be excluded.



Scheme 6

Such pyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-diones are part of a very rare class of organic compounds. To the best of our knowledge, only a few publications on the synthesis from 1,4-benzoquinones and diazoalkanes or phenylhydrazine derivatives and some reactions of these tricyclic compounds are known.[15]

Summing up these side-products that result from forced hydrolysis of **4a** (scheme 5), the formation of indazoledione **9** is remarkable. It is probably obtained from indazoledione **8** through 1,2-migration of a methyl group.[16] The structural conclusions concerning this migration of a methyl group were confirmed by X-ray crystallography of compound **9** (Figure 1). In addition, the indazolediones **10** and **11** are obtained either by mono-*N*-demethylation of indazolediones **9** and **8**, respectively, or by condensation

between pyrazoles **5a** and **7** according to scheme 7. Alternatively, the formation of **10** is also conceivable from **11** via 1,2-migration of a methyl group.

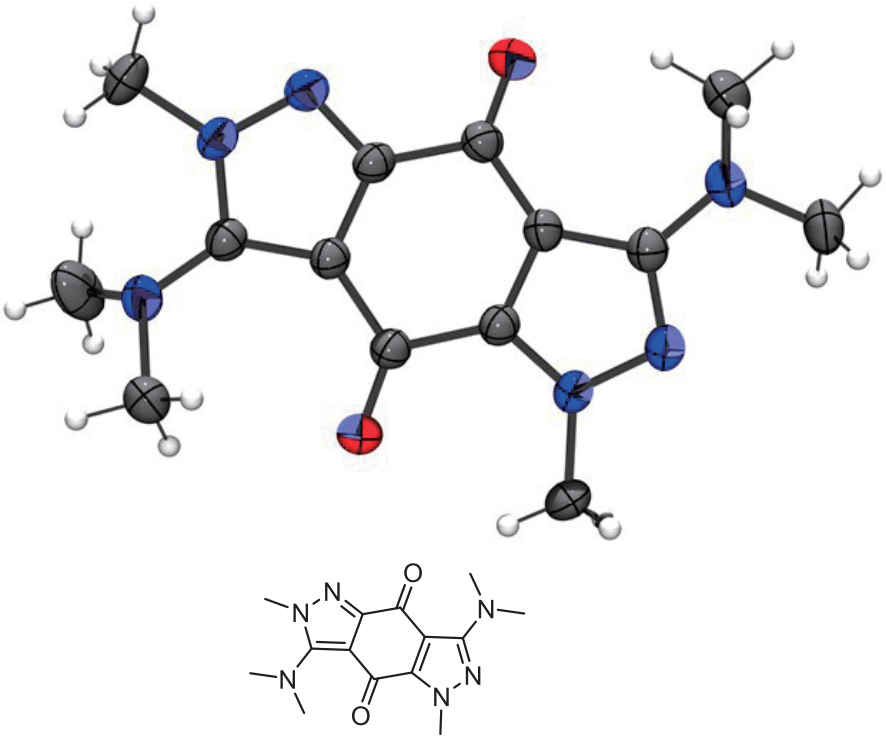
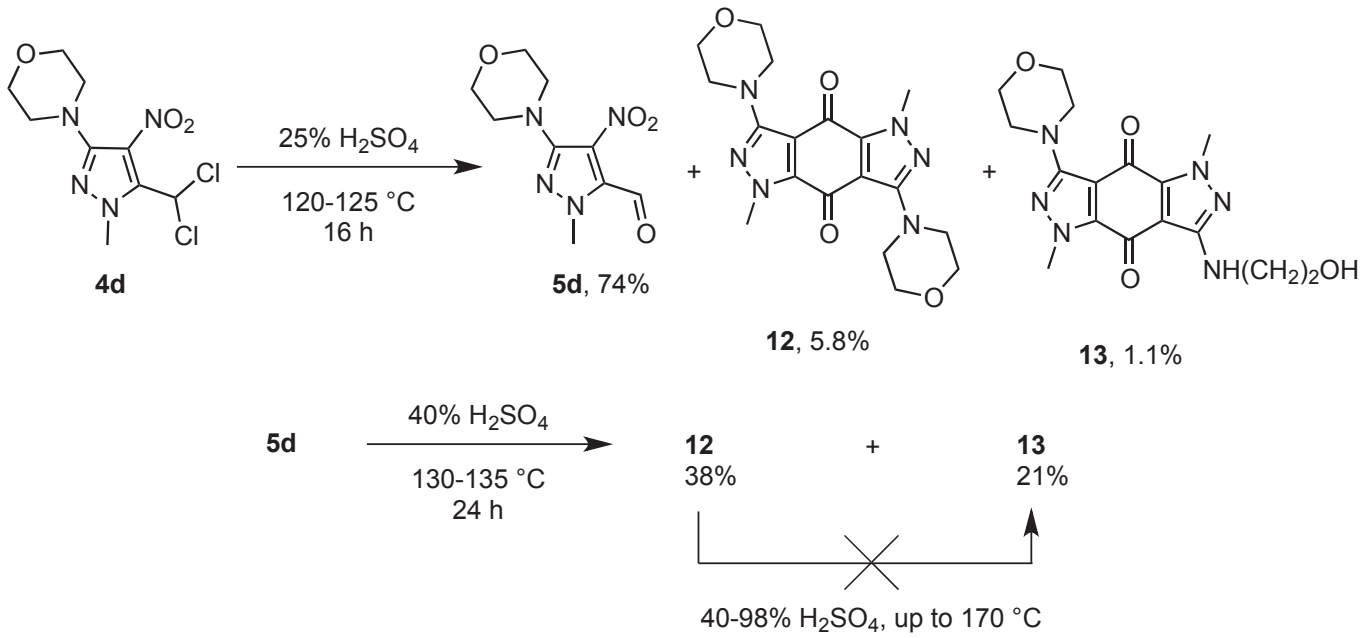


Figure 1. X-Ray crystal structure of 3,7-bis(dimethylamino)-1,6-dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,6*H*)-dione (**9**).[17, 18]

Additional hydrolysis of pyrazole **4d** applying the above mentioned relatively harsh reaction conditions (120-125 °C, in this case for only 16 h) gave the corresponding carbaldehyde **5d** in 74% yield and affords structurally similar byproducts. In this particular case, 1,5-dimethylpyrazoloindazoledione **12** (5.8%) and the hydroxo derivative **13** (1.1%) were isolated and characterized. Compound **12** was obtained similarly to the demethylation reactions in case of the hydrolysis of pyrazole **4a**, whereas alcohol **13** was obviously formed by an additional morpholine ring opening. Independently performed homo-condensation of carbaldehyde **5d** applying 40% sulfuric acid at 130-135 °C for 24 h also led to these indazole derivatives **12** and **13** in 38% and 21% yield, respectively. The ring opening of morpholine is known from the literature, e.g. via thermal treatment at 260-300 °C using a high-pressure reactor which affords ethanolamine and other breakdown products.[19a] Some morpholine derivatives can be *N*-dealkylated to the 2-aminoethanoles using either a) i) $NaIO_4$, $RuCl_3 \cdot x\ H_2O$, CCl_4, MeCN, rt, ii) KOH, H_2O, MeOH, 40°C,[19b] or b) mercury(II) EDTA complex, H_2O.[19c]

Surprisingly, several attempts to obtain alcohol **13** by morpholine ring opening of previously isolated dione **12** by means of conc. sulfuric acid (up to 98%) and high temperatures (up to 170 °C) were unsuccessful. In all these cases only slow decomposition of starting compound **12** was observed (Scheme 7).



Scheme 7

CONCLUSION

Once again, as published in the course of our series named chemistry of polyhalogenated nitrobutadienes, pentachloro-2-nitrobutadiene (**1**) was the starting material of choice for the synthesis of highly substituted heterocycles. Thereby, 3-amino-5-(dichloromethyl)-1-methyl-4-nitro-1*H*-pyrazoles **4a-e** were obtained from 1-amino-1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienes **3a-e** upon reaction with methyl hydrazine under mild conditions. Subsequent hydrolysis of pyrazoles **4a-e** with H_2SO_4/H_2O led to the formation of novel pyrazole-5-carbaldehydes **5a-e** as main products and different pyrazoloindazole-4,8-diones as side-products. The formation of the latter includes a remarkable methyl group migration. Assumable mechanistic pathways for the synthesis of **4a-e** from dienes **3a-e** and of indazoles **8-13** from carbaldehydes **5a,d** are given. The structure of 3,7-bis(dimethylamino)-1,6-dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,6*H*)-dione (**9**), i. e. the product of the methyl migration process, has been confirmed by X-ray analysis. In addition to synthetic significance, most of the synthesized compounds belong to classes of substances that reveal promising biological or even pharmacological activity.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus 520 and are uncorrected. Thin layer chromatography (TLC) was performed on Merck TLC-plates (aluminum based) silica gel 60 F 254. Separation of compounds and purifications were carried out by means of column chromatography on silica gel 60 (Merck). Petroleum ether as eluent had the boiling range 60–70 °C. FT-IR spectra were obtained in the range of 400 to 4000 cm^{-1} with a Bruker Vector 22 FT-IR spectrometer equipped with ALPHA's *Platinum ATR* single reflection diamond ATR module. Mass spectra were obtained on a Varian 320 MS Triple Quad GC/MS/MS instrument with a Varian 450-GC unit usually in direct mode with electron impact (70 eV). In the case of chlorinated compounds, all peak values of molecular ions as well as fragments refer to the isotopes ^{35}Cl. The elemental composition was confirmed by high-resolution EI and (+)-ESI mass spectrometry. All HRMS results were satisfactory in comparison to the calculated accurate masses of the molecular ions (±2 ppm, R ~ 10000). ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz): Avance III 600 MHz FT-NMR spectrometer (Bruker, Rheinstetten, Germany); ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Avance 400 FT-NMR spectrometer (also Bruker). ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz): DPX 200 FT-NMR spectrometer (also Bruker). ^{1}H and ^{13}C NMR spectra were referenced to the residual solvent peak: $CDCl_3$: δ = 7.26 (^{1}H), δ = 77.0 (^{13}C) ppm; DMSO-d_6: δ = 2.50 (^{1}H), δ = 39.7 (^{13}C) ppm. Chemical shifts δ are given in ppm. In most cases, peak assignments were accomplished by $^{1}H,^{13}C$-HSQC and $^{1}H,^{13}C$-HMBC NMR experiments. N-NMR spectra were externally referenced to nitromethane at 0.0 ppm.

Starting Material. Pentachloro-2-nitrobuta-1,3-diene (**1**) was synthesized according to the literature[3] from 2*H*-pentachlorobuta-1,3-diene with a 10:1 solution of 63% HNO_3 and 98% H_2SO_4 in 53% yield (bp 69–71 °C, 1 mbar). 1,1-Bis(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene (**2**) was prepared according to the literature[5] from nitrodiene **1** and 1*H*-benzotriazole in 76% yield. 1-Aminotrichloro-1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-nitrobutadienes **3c** and **3d** were prepared by previously reported procedures.[6] All spectral data were in accordance with the literature. All other chemicals used in this study were purchased from commercial sources.

Typical Procedure for the Preparation of Butadienes 3a-e.

(*E*)-1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-*N*,*N*-dimethylamino-2-nitrobuta-1,3-diene (**3a**). To a suspension of 4.37 g (10.00 mmol) of bisbenzotriazole derivative **2** in 70 mL of MeOH at 0 °C a solution of 2 M dimethylamine in MeOH (5.25 mL, 10.50 mmol) was added within 3 min. The resulting mixture was stirred for 2 h at 0-5 °C and additional 3 h at room temperature (rt). The precipitate was filtered off, washed with water (2 × 50 mL) and with cold MeOH (20 mL). After drying *in vacuo* **3a** was

obtained in 75% yield (2.72 g, yellow solid); mp 146-147 °C. IR: 2972, 2935, 1594, 1568, 1507, 1414, 1360, 1292, 1271, 1208, 1030, 906, 878, 813, 769, 755, 708, 656, 577 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.38-7.82 (m, 3H), 3.17 (s, 6H, 2 CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.6, 146.1, 132.3, 130.5 (CH), 126.0 (CH), 120.9 (CH), 120.8, 120.6, 110.6 (CNO_2), 110.3 (CH), 42.0 (CH_3). MS: *m/z* 361 [M^+, 2%], 326 [M^+ -Cl, 2%], 251 [6%], 197 [M^+ -NO_2 -benzotriazolyl, 50%], 162 [M^+ -NO_2 -benzotriazolyl -Cl, 40%], 147 [M^+ NO_2 -benzotriazolyl -Me, 39%]. HRMS (ESI) calcd for $C_{12}H_{11}Cl_3N_5O_2$ 361.9978 (M^++H), found: *m/z* 361.9982.

(*E*)-1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitro-1-pyrrolidinobuta-1,3-diene (**3b**). Reaction time: 2 h at 0 °C and 4 h at rt. Yield 80%. Yellow solid; mp 166-168 °C. IR: 2956, 2877, 1598, 1561, 1500, 1452, 1370, 1277, 1026, 904, 870, 809, 747, 706, 655, 571 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.40-7.78 (m, 3H), 3.15-4.20 (m, 4H, NCH_2), 1.80-2.38 (m, 4H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.7, 145.3, 132.1, 130.2 (CH), 127.2, 125.6 (CH), 123.5, 120.6 (CH), 116.5 (CNO_2), 110.3 (CH), 51.8 (2 NCH_2), 25.8 (CH_2), 24.5 (CH_2). MS: *m/z* 387 [M^+, 3%], 352 [M^+ -Cl, 2%], 313 [M^+ -NO_2 -N_2, 2%], 223 [M^+ -NO_2 -benzotriazolyl, 40%], 188 [M^+ -NO_2 -benzotriazolyl -Cl, 27%]. HRMS (ESI) calcd for $C_{14}H_{13}Cl_3N_5O_2$ 388.0135 (M^++H), found: *m/z* 388.0137.

Ethyl (*E*)-1-(1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl)piperidine-4-carboxylate (**3e**). Reaction time: 1 h at 0 °C and 6 h at rt. Yield 85%; yellow solid; mp 70-72 °C. IR: 2980, 1729 (CO), 1599, 1561, 1502, 1454, 1381, 1286, 1187, 1040, 903, 861, 809, 749, 707, 659, 573 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.36-7.85 (m, 3H), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.10-3.65 (m, 4H, NCH_2), 2.75 (br s, 1H, CO-CH), 2.00-2.33 (m, 4H, CH_2), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0 (CO), 148.0, 146.2, 132.4, 130.5 (CH), 125.9 (CH), 124.7, 121.0 (CH), 120.6, 111.7 (CNO_2), 110.3 (CH), 61.0 (OCH_2), 49.7 (2 NCH_2), 39.5 (CO-*C*H), 28.1 (CH_2), 27.7 (CH_2), 14.1 (CH_3). MS: *m/z* 473 [M^+, 2%], 428 [M^+ -OEt, 2%], 309 [M^+ -benzotriazolyl -NO_2, 13%], 274 [M^+ -NO_2 -benzotriazolyl -Cl, 5%]. HRMS (ESI) calcd for $C_{18}H_{19}Cl_3N_5O_4$ 474.0503 (M^++H), found: *m/z* 474.0505.

Typical Procedure for the Preparation of Pyrazoles 4a-e.

5-(Dichloromethyl)-3-dimethylamino-1-methyl-4-nitro-1*H*-pyrazole (4a). To a suspension of 3.63 g (10.00 mmol) of benzotriazole derivative **3a** in 70 mL of MeOH at 0 °C a solution of methylhydrazine (0.921 g, 20.00 mmol) in 3 mL of MeOH was added within 3 min. The resulting mixture was stirred for 1 h at 0-5 °C and for an additional 8 h at rt. After addition of ice water (300 mL) and 0.5 mL of conc. hydrochloric acid the mixture was extracted with CH_2Cl (3 × 100 mL). The combined organic layers were

washed with water (2 × 150 mL) and dried over anhydrous $CaCl_2$. Removal of the solvent *in vacuo* and subsequent flash column chromatography (petroleum ether / EtOAc 10:1) afforded pyrazole **4a** as a yellow oil, which solidified in the refrigerator (1.85 g, 73%). IR: 3045, 2955, 2861, 2799, 1571, 1489, 1347, 1260, 1190, 1059, 969, 864, 822, 747, 665, 582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, $^1J_{C-H}$ = 185.8 Hz, 1H, $CHCl_2$), 4.04 (s, $^1J_{C-H}$ = 142.6 Hz, 3H, Me), 2.84 (s, $^1J_{C-H}$ = 137.1 Hz, 6H, NMe_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 137.4, 119.6 (CNO_2), 57.7 ($CHCl_2$), 41.5 (NMe_2), 39.4 (NMe). ^{14}N NMR (28.9 MHz, $CDCl_3$): δ -5.7 (NO_2), -95.3 (=N-), -187.0 (NMe). The signal of the NMe_2 group was not detected probably due to an enormous half width. MS: *m/z* 252 [M^+, 3%], 235 [M^+ -OH, 2%], 217 [M^+ -Cl, 3%], 206 [M^+ -NO_2, 2%], 151 [M^+, 25%], 109 [100%]. HRMS (EI) calcd for $C_7H_{11}Cl_2N_4O_2$ 253.0259 (M^++H), found: *m/z* 253.0258.

5-(Dichloromethyl)-1-methyl-4-nitro-3-(pyrrolidin-1-yl)-1*H*-pyrazole (4b). Reaction time: 1 h at 0 °C and 5 h at rt. Yield 60%. Yellow solid; mp 45-47 °C. IR: 3042, 2970, 2873, 1573, 1482, 1390, 1362, 1319, 1276, 1214, 987, 870, 817, 746, 649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H, $CHCl_2$), 4.08 (s, 3H, Me), 3.35-3.45 (m, 4H, 2 NCH_2), 1.87-2.00 (m, 4H, 2 CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 136.7, 116.6 (CNO_2), 57.8 ($CHCl_2$), 50.0 (NCH_2), 39.3 (NMe), 25.4 (CH_2). MS: *m/z* 278 [M^+, 25%], 261 [M^+ -OH, 100%], 243 [M^+ -Cl, 24%], 232 [M^+ -NO_2, 12%], 208 [M^+ -pyrrolidinyl, 27%]. HRMS (EI) calcd for $C_9H_{12}Cl_2N_4O_2$ 278.0337 (M^+), found: *m/z* 278.0339.

5-(Dichloromethyl)-1-methyl-4-nitro-3-(piperidin-1-yl)-1*H*-pyrazole (4c). Reaction time: 1 h at 0 °C and 10 h at rt. Yield 73%. Yellow solid; mp 51-52 °C. IR: 3036, 2942, 2847, 1567, 1487, 1393, 1335, 1296, 1197, 1028, 951, 860, 825, 809, 749, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (s, 1H, $CHCl_2$), 4.09 (s, 3H, Me), 3.12-3.20 (m, 4H, 2 NCH_2), 1.76-1.58 (m, 6H, 3 CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.3, 137.7, 120.3 (CNO_2), 57.9 ($CHCl_2$), 51.0 (NCH_2), 39.6 (NMe), 25.4 (2 CH_2), 24.1 (CH_2). MS: *m/z* 292 [M^+, 10%], 275 [M^+ -OH, 26%], 259 [M^+ -OH -O, 28%], 257 [M^+ -Cl, 11%]. HRMS (EI) calcd for $C_{10}H_{14}Cl_2N_4O_2$ 292.0494 (M^+), found: *m/z* 292.0497.

5-(Dichloromethyl)-1-methyl-3-(morpholin-4-yl)-4-nitro-1*H*-pyrazole (4d). Reaction time: 1 h at 0 °C and 3 h at rt. Yield 85%. Yellow solid; mp 92-93 °C. IR: 3070, 2896, 2856, 1552, 1476, 1394, 1341, 1304, 1269, 1201, 1117, 1053, 959, 863, 833, 742, 652, 550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (s, 1H, $CHCl_2$), 4.12 (s, 3H, Me), 3.82-3.93 (m, 4H, 2 OCH_2), 3.23-3.28 (m, 4H, 2 NCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.4, 138.0, 120.5 (CNO_2), 66.4 (2 OCH_2), 57.7 ($CHCl_2$), 50.0 (2 NCH_2), 39.7 (NMe). MS: *m/z* 294 [M^+, 32%], 277 [M^+ -OH, 35%], 259 [M^+ -Cl, 24%], 231 [49%]. HRMS (EI) calcd for $C_9H_{12}Cl_2N_4O_3$ 294.0287 (M^+), found: *m/z* 294.0288.

Ethyl 1-(5-(dichloromethyl)-1-methyl-4-nitro-1*H*-pyrazol-3-yl)piperidine-4-carboxylate (4e). EtOH was used as a solvent. Reaction time: 2 h at 0 °C and 3 h at rt. Yield 78%, red oil. IR: 3044, 2957, 2831, 1727 (CO), 1552, 1479, 1392, 1335, 1259, 1183, 1041, 951, 854, 814, 736, 648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H, $CHCl_2$), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.05 (s, 3H, Me), 3.55 (ddd, *J* = 13.0, 4.0, 3.7 Hz, 2H, NCH_2), 2.84 (ddd, *J* = 12.6, 11.1, 2.8 Hz, 2H, NCH_2), 2.39-2.48 (m, 1H, COCH), 1.82-1.96 (m, 4H, CH_2), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4 (CO), 152.6, 137.7, 120.2 (CNO_2), 60.3 (OCH_2), 57.7 ($CHCl_2$), 49.3 (2 NCH_2), 40.7 (NMe), 39.5 (CHCO), 27.5 (2 CH_2), 14.1 (CH_3). MS: *m/z* 364 [M^+, 20%], 347 [M^+ -OH, 55%], 329 [M^+ -Cl, 12%], 319 [M^+ -OEt, 25%], 283 [M^+ -Cl -NO_2, 7%], 221 [100%]. HRMS (EI) calcd for $C_{13}H_{18}Cl_2N_4O_4$ 364.0705 (M^+), found: *m/z* 364.0705.

Typical Procedure for the Preparation of Carbaldehydes 5a-d.

3-(Dimethylamino)-1-methyl-4-nitro-1*H*-pyrazole-5-carbaldehyde (5a). At rt to 34 mL aqueous sulfuric acid (25% H_2SO_4) were added 2.53 g (10.00 mmol) of pyrazole **4a**. Subsequently, the resulting mixture was stirred for 16 h at 105-110 °C. After cooling to rt and addition of ice water (300 mL) the mixture was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with water (2 × 150 mL) and dried over anhydrous $CaCl_2$. Removal of the solvent *in vacuo* and subsequent flash column chromatography (petroleum ether / EtAc 10:1) afforded pyrazole **5a** as an orange oil, which solidified in the refrigerator (1.55 g, 78%), mp 77-78 °C. IR: 2963, 2921, 2805, 1685 (CO), 1578, 1484, 1365, 1327, 1256, 1136, 972, 857, 778, 584 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 10.38 (s, $^1J_{C\text{-}H}$ = 198.8 Hz, 1H, CHO), 4.05 (s, $^1J_{C\text{-}H}$ = 143.2 Hz, 3H, Me), 2.96 (s, $^1J_{C\text{-}H}$ = 137.5 Hz, 6H, NMe_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 181.9 (CH), 153.0, 134.5, 123.1 (CNO_2), 41.6 (NMe_2), 40.8 (NMe). MS: *m/z* 198 [M^+, 55%], 182 [M^+ -O, 60%], 164 [25%], 154 [M^+ -NMe_2, 27%], 152 [M^+ -NO_2, 18%]. HRMS (ESI) calcd for $C_8H_{15}N_4O_4$ 231.1093 (M^++MeOH+H), found: *m/z* 231.1088.

1-Methyl-4-nitro-3-(pyrrolidin-1-yl)-1*H*-pyrazole-5-carbaldehyde (5b). Reaction time: 8 h at 95-100 °C. Yield 75%. Yellow solid; mp 79-80 °C. IR: 2969, 2876, 1684 (CO), 1568, 1463, 1379, 1346, 1300, 1213, 1128, 967, 840, 758, 676, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.33 (s, 1H, CHO), 4.03 (s, 3H, Me), 3.42-3.46 (m, 4H, 2 NCH_2), 1.94-1.98 (m, 4H, 2 CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.6 (CH), 150.3, 134.0, 123.1 (CNO_2), 50.1 (NCH_2), 40.6 (NMe), 25.5 (CH_2). MS: *m/z* 224 [M^+, 48%], 207 [M^+ -OH, 100%], 194 [M^+ -CHO, 10%], 176 [M^+ -HNO_2 -H, 46%]. HRMS (EI) calcd for $C_9H_{12}N_4O_3$ 224.0909 (M^+), found: *m/z* 224.0912.

1-Methyl-4-nitro-3-(piperidin-1-yl)-1*H*-pyrazole-5-carbaldehyde (5c). Reaction time: 8 h at 105-110 °C. Yield 63%. Orange oil, which solidified in the refrigerator; mp 23-24 °C. IR: 2937, 1691 (CO), 1557, 1488, 1386, 1329, 1222, 1117, 1028, 950, 857, 775, 648 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 10.39 (s, 1H, CHO), 4.04 (s, 3H, Me), 3.19-3.27 (m, 4H, 2 NCH_2), 1.63-1.76 (m, 6H, 3 CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 182.0 (CH), 153.0, 135.0, 125.4 (CNO_2), 51.0 (NCH_2), 40.8 (NMe), 25.5 (2 CH_2), 24.1 (CH_2). MS: *m/z* 238 [M^+, 38%], 221 [M^+ -OH, 100%], 203 [37%], 192 [M^+ -NO_2, 8%]. HRMS (EI) calcd for $C_{10}H_{14}N_4O_3$ 238.1066 (M^+), found: *m/z* 238.1070.

1-Methyl-3-morpholino-4-nitro-1*H*-pyrazole-5-carbaldehyde (5d). Reaction time: 7 h at 90-95 °C. Yield 85%, orange solid; mp 75-76 °C. IR: 2983, 2914, 2858, 1692 (CO), 1553, 1487, 1379, 1338, 1257, 1205, 1118, 957, 864, 835, 779, 660, 550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 10.40 (s, 1H, CHO), 4.06 (s, 3H, Me), 3.79-3.89 (m, 4H, 2 OCH_2), 3.25-3.36 (m, 4H, NCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 181.8 (CH), 152.0, 135.1, 125.7 (CNO_2), 66.4 (OCH_2), 50.0 (NCH_2), 40.9 (NMe). MS: *m/z* 240 [M^+, 17%], 223 [M^+ -OH, 22%], 206 [9%], 193 [M^+ -HNO_2, 8%], 177 [33%]. HRMS (EI) calcd for $C_9H_{12}N_4O_4$ 240.0859 (M^+), found: *m/z* 240.0859.

1-(5-Formyl-1-methyl-4-nitro-1*H*-pyrazol-3-yl)piperidine-4-carboxylic acid (5e) was synthesized similar to **5a**. Reaction time: 6 h at 95-100 °C. After cooling to rt and addition of ice water the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over anhydrous $CaCl_2$. After removal of the solvent *in vacuo* and addition of Et_2O the resulting precipitate was filtered off and washed with Et_2O. Yield 92%, yellow solid; mp 185-186 °C. IR: 2963, 1685 (CO), 1551, 1475, 1390, 1332, 1232, 1201, 1041, 954, 834, 764, 633, 525 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H, CHO), 4.06 (s, 3H, Me), 3.69 (ddd, *J* = 13.0, 3.7, 3.7 Hz, 2H, NCH_2), 2.98 (ddd, *J* = 12.7, 11.1, 2.3 Hz, 2H, NCH_2), 2.53-2.62 (m, 1H, CH-CO), 1.91-2.10 (m, 4H, CH_2). Expectedly, the hydroxy group was not detected due to chemical exchange. ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.9 (CH), 180.5 (CO), 152.3, 135.1, 125.6 (CNO_2), 49.3 (2 NCH_2), 40.9 (NMe), 40.4 (CH), 27.4 (2 CH_2). MS: *m/z* 282 [M^+, 22%], 265 [M^+ -OH, 60%], 247 [M^+ -OH -H_2O, 20%], 235 [M^+ -HNO_2, 5%], 203 [100%], 190 [M^+ -CO_2H -HNO_2, 40%]. HRMS (EI) calcd for $C_{11}H_{14}N_4O_5$ 282.0964 (M^+), found: *m/z* 282.0967.

1-(5-(2,2-Dicyanovinyl)-1-methyl-4-nitro-1*H*-pyrazol-3-yl)piperidine-4-carboxylic acid (6). To the suspension of pyrazole **5e** (141 mg, 0.5 mmol) in 10 mL MeOH was added malononitrile (40 mg, 0.6 mmol) and pyridine (4 mg, 0.05 mmol). The resulting mixture was stirred for 6 h at 65 °C. Subsequently, the supernatant liquid was concentrated *in vacuo* to a volume of about 3 mL and was then cooled to 5 °C. The resulting precipitate was filtered off, washed with cold MeOH (1 mL), H_2O (2 × 5 mL), ET_2O (1 × 2

mL), and finally dried under reduced pressure to afford **6.** Yield 139 mg (84%), yellow solid; mp 206-207 °C. IR: 2962, 2836, 1688 (CO), 1557, 1486, 1391, 1333, 1235, 1041, 933, 826, 767, 620 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 12.26 (br s, 1H, OH), 8.71 (s, $^1J_{C-H}$ = 177.8 Hz, 1H, =CH), 3.84 (s, 3H, Me), 3.57 (d, *J* = 12.6 Hz, 2H, NCH_2), 2.92 (ddd, *J* = 12.6, 11.5, 1.9 Hz, 2H, NCH_2), 2.42-2.47 (m, 1H, CH-CO), 1.91 (dd, *J* = 13.5, 2.9 Hz, 2H, CH_2), 1.72 (dd, *J* =11.5, 3.6 Hz, 1H, CH_2), 1.66 (dd, *J* = 11.5, 3.6 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0 (CO), 153.7, 147.8 (=CH), 134.4, 123.7 (CNO_2), 112.7 (CN), 111.7 (CN), 92.7 (CCN), 49.3 (2 NCH_2), 39.7 (NMe), 39.1 (CH), 27.4 (2 CH_2). MS: *m/z* 330 [M^+, 17%], 313 [M^+ -OH, 32%], 285 [M^+ -CO_2H, 7%], 251 [5%], 203 [26%]. HRMS (ESI) calcd for $C_{14}H_{15}N_6O_4$ 331.1155 (M^++H), found: *m/z* 331.1157.

Hydrolysis of pyrazole 4a at 120-125 °C to pyrazoles 5a, 7, and indazoles 8-11. 7.59 g (30.00 mmol) of pyrazole **4a** were added at rt to 128 mL aqueous sulfuric acid (25% H_2SO_4), and the resulting mixture was stirred for 32 h at 120-125 °C. After cooling to rt and addition of ice water (700 mL) the mixture was extracted with CH_2Cl_2 (5 × 300 mL). The combined organic layers were washed with water (2 × 300 mL) and dried over anhydrous $CaCl_2$. Removal of the solvent *in vacuo* and subsequent flash column chromatography (at first petroleum ether / EtOAc in a 10:1 ratio, then 1:1) afforded pyrazole **5a** (3.81g, 64%), indazoles **9** (150 mg, 3.3%) and **10** (220 mg, 5.1%) as well as a mixture of compounds **7**, **8**, and **11**, respectively. The second flash column chromatography (petroleum ether / EtOAc 5:1) of mixture **7**, **8**, and **11** afforded indazole **8** (200 mg, 4.4%), pyrazole **7** (77 mg, 1.4%), and indazole **11** (121 mg, 2.8%), respectively.

1-Methyl-3-(methylamino)-4-nitro-1*H*-pyrazole-5-carbaldehyde (7). Yield 1.4%, yellow solid; mp 191-192 °C. IR: 3400, 1681 (CO), 1608, 1533, 1464, 1360, 1316, 1266, 1193, 1142, 1057, 907, 800, 758, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H, CHO), 6.09 (br s, 1H, NH), 4.07 (s, 3H, Me), 3.05 (d, *J* = 5.2 Hz, 3H, $HNCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.3 (CHO), 151.6, 133.2, 120.7 (CNO_2), 40.8 (NMe), 29.3 (NHMe). MS: *m/z* 184 [M^+, 100%], 166 [M^+ -H_2O, 6%], 149 [M^+ -H_2O -OH, 43%], 137 [M^+ -HNO_2, 10%], 109 [M^+ -NO_2 -CHO, 20%]. HRMS (EI) calcd for $C_6H_8N_4O_3$ 184.0596 (M^+), found: *m/z* 184.0600.

3,7-Bis(dimethylamino)-1,5-dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-dione (8). Yield 4.4%, red solid; mp 268-269 °C. IR: 2950, 2866, 2800, 1641 (CO), 1538, 1471, 1413, 1360, 1308, 1275, 1197, 1064, 980, 900, 753, 688, 594 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.10 (s, 6H, NMe), 3.08 (s, 12H, NMe_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (CO), 157.1, 140.5, 108.6, 41.3 (NMe_2), 38.9 (NMe). MS:

m/z 302 [M^+, 100%], 287 [M^+ -Me, 30%], 272 [M^+ -2Me, 10%], 258 [M^+ -NMe_2, 25%], 244 [M^+ -NMe_2 -Me + H, 33%]. HRMS (ESI) calcd for $C_{14}H_{19}N_6O_2$ 303.1569 (M^++H), found: *m/z* 303.1570.

3,7-Bis(dimethylamino)-1,6-dimethylpyrazolo[3,4-*f*]indazole-4,8(1*H*,6*H*)-dione (9). Yield 3.3%, red solid; mp 178-179 °C. IR: 2919, 2857, 2801, 1654 (CO), 1649 (CO), 1535, 1482, 1420, 1376, 1309, 1273, 1174, 1140, 1065, 988, 938, 770, 645, 568 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 3H, NMe), 3.82 (s, 3H, NMe), 3.08 (s, 6H, NMe_2), 2.97 (s, 6H, NMe_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (CO), 171.2 (CO), 157.2, 152.8, 149.3, 140.5, 111.2, 109.5, 42.7 (NMe_2), 41.3 (NMe_2), 38.9 (NMe), 36.5 (NMe). MS: *m/z* 302 [M^+, 100%], 287 [M^+ -Me, 55%], 272 [M^+ -2Me, 6%], 258 [M^+ -NMe_2, 25%], 244 [M^+ -NMe_2 -Me + H, 52%]. HRMS (ESI) calcd for $C_{14}H_{19}N_6O_2$ 303.1569 (M^++H), found: *m/z* 303.1571.

7-(Dimethylamino)-1,6-dimethyl-3-(methylamino)pyrazolo[3,4-*f*]indazole-4,8(1*H*,6*H*)-dione (10). Yield 5.1%, orange solid; mp 225-227 °C. IR: 3438, 2926, 2802, 1662 (CO), 1642 (CO), 1579, 1529, 1429, 1387, 1212, 1151, 1077, 980, 940, 756, 638, 609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.56 (q, *J* = 5.1 Hz, 1H, NH), 4.09 (s, 3H, NMe), 3.82 (s, 3H, NMe), 3.01 (d, *J* = 5.1 Hz, 3H, HNMe), 2.96 (s, 6H, NMe_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5 (CO), 171.1 (CO), 155.5, 153.2, 148.7, 138.8, 112.3, 107.4, 42.7 (NMe_2), 38.2 (NMe), 36.4 (NMe), 29.4 (HNMe). MS: *m/z* 288 [M^+, 100%], 273 [M^+ -Me, 55%], 258 [M^+ -2Me, 7%], 244 [M^+ -NMe_2, 26%], 230 [M^+ -NMe_2 -Me + H, 20%]. HRMS (ESI) calcd for $C_{13}H_{17}N_6O_2$ 289.1413 (M^++H), found: *m/z* 289.1414.

3-(Dimethylamino)-1,5-dimethyl-7-(methylamino)pyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-dione (11). Yield 2.8%, red solid; mp 250-251 °C. IR: 3414, 2855, 2801, 1641 (CO), 1579, 1527, 1475, 1408, 1368, 1308, 1251, 1142, 1074, 979, 904, 753, 713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.40 (br s, 1H, NH), 4.09 (s, 3H, NMe), 4.08 (s, 3H, NMe), 3.07 (s, 6H, NMe_2), 3.00 (s, 3H, HNMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (CO), 170.6 (CO), 157.7, 155.3, 140.0, 138.8, 112.3, 109.3, 106.5, 41.4 (NMe_2), 38.5 (NMe), 38.3 (NMe), 29.4 (HNMe). MS: *m/z* 288 [M^+, 100%], 273 [M^+ -Me, 43%], 258 [M^+ -2Me, 12%], 244 [M^+ -NMe_2, 20%], 230 [M^+ -NMe_2 -Me + H, 18%]. HRMS (ESI) calcd for $C_{13}H_{17}N_6O_2$ 289.1413 (M^++H), found: *m/z* 289.1413.

Hydrolysis of pyrazole 4d at 120-125 °C to pyrazole 5d, 7, and indazoles 12, 13. 2.95 g (10.00 mmol) of pyrazole **4d** were added at rt to 42.5 mL of aqueous sulfuric acid (25% H_2SO_4), and the resulting mixture was stirred for 16 h at 120-125 °C. After cooling to rt and addition of ice water (200 mL) the mixture was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) and dried over anhydrous $CaCl_2$. Removal of the solvent *in vacuo* and subsequent flash

column chromatography (at first petroleum ether / EtOAc 5:1, then 1:1) afforded pyrazole **5a** (1.78g, 74%) and indazoles **12** (112 mg, 5.8%) and **13** (20 mg, 1.1%), respectively.

1,5-Dimethyl-3,7-dimorpholinopyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-dione (12). Yield 5.8%, red solid; mp 312-314 °C. IR: 2974, 2902, 2859, 1648 (CO), 1534, 1479, 1452, 1378, 1309, 1279, 1195, 1113, 1074, 969, 903, 862, 754, 659, 555 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.12 (s, 6H, 2 NMe), 3.83-3.91 (m, 8H, 4 OCH_2), 3.47-3.56 (m, 8H, 4 NCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0 (CO), 156.4, 140.4, 109.2, 66.6 (OCH_2), 49.1 (NCH_2), 39.1 (NMe), 38.9 (NMe). MS: *m/z* 386 [M^+, 100%], 368 [M^+ -H_2O, 45%], 355 [M^+ -CH_3O, 40%], 343 [M^+ -C_2H_4O + H, 38%]. HRMS (ESI) calcd for $C_{18}H_{23}N_6O_4$ 387.1781 (M^++H), found: *m/z* 387.1782.

3-((2-Hydroxyethyl)amino)-1,5-dimethyl-7-morpholinopyrazolo[3,4-*f*]indazole-4,8(1*H*,5*H*)-dione (13). Yield 1.1%, red solid; mp 226-227 °C. IR: 3341, 2962, 2860, 1644 (CO), 1575, 1520, 1447, 1375, 1277, 1111, 965, 898, 861, 754, 729, 664, 551 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 5.77 (br s, 1H, NH), 4.10 (s, 3H, NMe), 4.04 (s, 3H, NMe), 3.84-3.88 (m, 6H, 3 OCH_2), 3.52-3.56 (m, 2H, NCH_2), 3.46-3.50 (m, 4H, 2 NCH_2), 2.83 (br s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.1 (CO), 170.7 (CO), 156.9, 154.7, 140.0, 138.6, 109.9, 106.6, 66.6 (2 OCH_2), 62.3 (OCH_2), 49.2 (2 NCH_2), 45.6 ($HNCH_2$), 38.7 (NMe), 38.4 (NMe). MS: *m/z* 360 [M^+, 45%], 342 [M^+ -H_2O, 25%], 329 [M^+ -CH_2OH, 28%], 311 [M^+ -H_2O -CH_2OH, 10%], 298 [M^+ -H_2O -C_2H_4OH + H, 20%]. HRMS (ESI) calcd for $C_{16}H_{21}N_6O_4$ 361.1624 (M^++H), found: *m/z* 361.1625.

Hydrolysis of carbaldehyde 5d at 130-135 °C to indazoles 12 and 13. 721 mg (3.00 mmol) of carbaldehyde **5d** were added at rt to 17 mL of aqueous sulfuric acid (25% H_2SO_4), and the resulting mixture was stirred for 24 h at 130-135 °C. After cooling to rt and subsequent addition of ice water (100 mL) the mixture was extracted with CH_2Cl_2 (6 × 80 mL). The combined organic layers were washed with water (2 × 100 mL) and dried over anhydrous $CaCl_2$. Removal of the solvent *in vacuo* followed by flash column chromatography (petroleum ether / EtOAc 2:1) gave indazole **12** (220 mg, 38%) and aminoalcohol **13** (114 mg, 21%), respectively.

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17. **X-Ray structure analysis for indazole 9. $C_{14}H_{18}N_6O_2$**, M = 302.33 g mol^{-1}**:** A suitable single crystal of the title compound was selected under a polarization microscope and mounted in a glass capillary (d = 0.3 mm). The crystal structure was determined by X-ray diffraction analysis using graphite monochromated Mo-K_α radiation (0.71073 Å) [T = 223(2) K], whereas the scattering intensities were collected with a single crystal diffractometer (STOE IPDS II). The crystal structure was solved by Direct Methods using SHELXS-97 and refined using alternating cycles of least squares refinements against F^2 (SHELXL-97).[18] All non-H atoms were located in Difference Fourier maps and were refined with anisotropic displacement parameters. The H positions were determined by a final Difference Fourier Synthesis.

$C_{14}H_{18}N_6O_2$ crystallized in the monoclinic space group $P2/c$ (no. 14), lattice parameters a = 8.262(2) Å, b = 17.645(4) Å, c = 11.319(2) Å, β = 117.97(2)°, V = 1457.3(5) Å^3, Z = 4, $d_{calc.}$ = 1.378 g cm^{-3}, F(000) = 640 using 2743 independent reflections and 272 parameters. $R1$ = 0.0535, $wR2$ = 0.1216 [$I > 2\sigma(I)$], goodness of fit on F^2 = 1.108, residual electron density = 0.341 and –0.285 e Å^{-3}.

Further details of the crystal structure investigations have been deposited with the Cambridge Crystallographic Data Center, CCDC 1415384. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44(1223)-336 033; e-mail: **fileserv@ccdc.ac.uk** or **http://www.ccdc.cam.ac.uk**).

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