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An unexpected synthesis of 7-azidofurazano[3,4-*b*]tetrazolopyrazine

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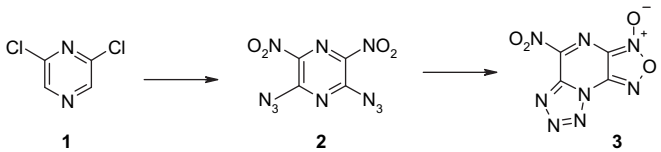
ABSTRACT

In the course of our program focused on the preparation of high-nitrogen content heterocyclic compounds, we wish to report an original synthesis of the tricyclic 7-azidofurazano[3,4-*b*]tetrazolopyrazine via an unprecedented reaction between 2,6-dimethoxy-3,5-dinitropyrazine and hydrazine hydrate. This compound was identified by an X-ray diffraction analysis. Further studies of its structure by ^{15}N and ^{13}C NMR spectroscopy were carried out in different solvents. This allowed us to observe a noteworthy equilibrium involving three forms resulting from the reversible opening of a tetrazole ring.

1. Introduction

The starting point of this work stems from our research on the preparation of heterocyclic compounds with a high-nitrogen content for their potential applications in a variety of fields including energetic materials featuring furazan/furoxan and tetrazole rings.[1] Increase of energy is observed when introducing furazan or furoxan rings to aromatic nitro substrate; known examples are DNBF and CL14.[2,3] Higher gains are achievable by replacing benzene ring with nitrogen aromatic cycles or by substituting furazan/furoxans by tetrazoles. With in mind the preparation of original polyheterocyclic compounds, we focused on the chemistry of pyrazine as the core ring system, which has only received little attention in the past.[4] We thus started from the available 2,6-dichloropyrazine (**1**) in order to introduce furoxans and tetrazoles rings on this frame. The synthetic approach involves preparation of the azido nitro precursor **2** and the study of the cyclisation to get furoxan and tetrazole rings (Scheme 1).



Scheme 1. Synthetic approach.

As reported by Pagoria and co-workers, nitration of the electron-deficient 2,6-dichloropyrazine (**1**) only gave a low yield of an unidentified mixture of products. In contrast, nitration of 2,6-dimethoxypyrazine (**4**), which is far more electron-rich pyrazine ring system, gave 65% of the dinitrated compound **6**.[5]

In order to increase the ring system electron density, we set to methoxylate compound **1**. Interestingly, using methanolic sodium methoxide (5 equiv) at reflux for 3.5 h, this led to 2,6-dimethoxypyrazine (**4**) in moderate 66% yield along with 22% of the monometoxylated product (**5**).[6a] Moreover, their separation by recrystallization or chromatography over silica gel proved difficult. Eventually, a better 98% yield of **4** was obtained by heating the same reagents in a sealed tube at 125 °C for 18 h with a larger excess of sodium methoxide (10 equiv). The nitration of **4** is an illustration of the classical approach to the synthesis of nitro-substituted heterocycles. In general electron-deficient heterocycles such as pyrazines or pyridines do not undergo electrophilic substitution reactions under normal conditions unless substituted with electron-donating substituents (Scheme 2).

The presence of the two annelated furoxan and tetrazole rings in the final product **3** implies the preparation of the azido precursor **2**. A furoxan ring could be readily obtained through the intramolecular thermal cyclization of a nitro group with a azide functionality with the concomitant elimination of a dinitrogen molecule.[6b,c] The precursor **2** could be prepared by the direct

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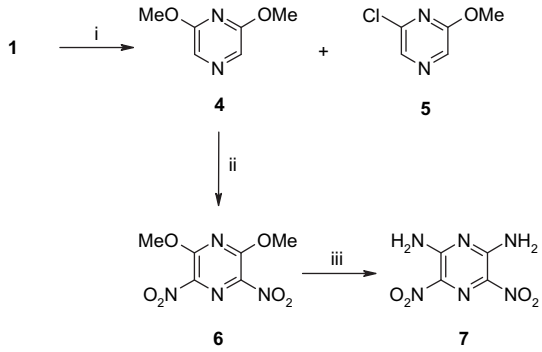

Scheme 2. Reagents and conditions: (i) NaOMe, MeOH, reflux, 3.5 h; (ii) HNO_3/H_2SO_4, 15 °C, 30 min then RT, 2 h; (iii) NH_4OH, MeCN, 65 °C, 18 h.

nucleophilic substitution of chlorine atom or of a methoxy group or by the replacement of a diazonium moiety by the N_3^- ions. In this latter case, the preparation of a diamino or of a dihydrazino compound like, respectively, **7** and **8** has to be envisioned. We thus turned our attention to nucleophilic substitution reactions with compound **6** and a variety of nucleophiles. As depicted in Table 1, direct S_NAr displacement of methoxy group by N_3^- ions gave no reaction. On the other hand, as reported by Pagoria and co-workers, amination of **6** was achieved successfully using aqueous ammonia in acetonitrile at atmospheric pressure to yield 70% of the 2,6-diamino-3,5-dinitropyrazine (**7**).[5] The ^{13}C NMR analysis is in close agreement with the reported chemical shifts of this compound.[7] However, treatment of **7** with sodium nitrite followed by sodium azide was found to be ineffective to form the diazido precursor **2**. It was thus thought that electron-withdrawing effect of nitro group greatly altered both the reactivity of the amino group and the stability of the diazonium derivative. In another approach, demethylation of **6** was attempted with several reagents. Trials using KI,[8] BBr_3,[9] $NaSSiMe_3$[10] gave no reaction (entries 4–6) whereas the use of KOH (entry 7) only led to extensive decomposition.

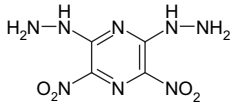

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Table 1
Reagents employed in the attempted azidation of 2,6-dimethoxy-3,5-dinitropyrazine (**6**)

Entry	Reagents	Result
1	NaN_3, CH_3COOH, 80 °C	No reaction
2	NaN_3, NH_4NO_3, MeCN, 80 °C	No reaction
3	NH_4OH then $NaNO_2/NaN_3$, CH_3COOH/H_2SO_4	Compound **7** (70%)
4	KI, EtOH, 80 °C	No reaction
5	BBr_3, CH_2Cl_2, 0 °C<T<25 °C	No reaction
6	$NaSSiMe_3$, dimethyl-2-imidazolidinone, 180 °C	No reaction
7	KOH 1M, [18-crown-6], THF, 25 °C	Several decomposition products
8	$NH_2NH_2{\cdot}H_2O$, MeCN, 0 °C	Polymerization
9	$NH_2NH_2{\cdot}H_2O$, EtOH, −78 °C	Precipitate insoluble in DMSO

Eventually, we surveyed the use of hydrazine hydrate in acetonitrile at 0 °C and observed an encouraging polymerisation process (entry 8). This polymerisation could be avoided by running the reaction at −78 °C in ethanol for 2 h (entry 9). The resulting precipitate was washed in ethanol and filtered off to give a brown solid in 97% yield. The characterization of this compound was very difficult due to its lack of solubility in DMSO as well as the absence of aromatic protons. Nevertheless, we used this uncharacterized compound in the next reaction step.

Based upon the analogy of the transformation of hydrazines into azides using dinitrogen tetroxide[11] and clay supported ferric nitrate,[12] we undertook a nitrosation reaction with two nitrosating reagents: nitrosonium tetrafluoroborate and sodium nitrite in acetic acid.[13,14] Both reagents led to the isolation of a substance as white crystals in a moderate 30% yield. X-ray diffraction allowed its structural elucidation. As depicted in Figure 1, compound **9** has a tricyclic structure featuring a tetrazole ring along with an azido substituent and a quite unexpected furazan side ring instead of the expected furoxan (Fig. 1).[15]

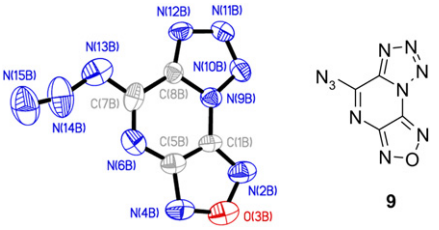
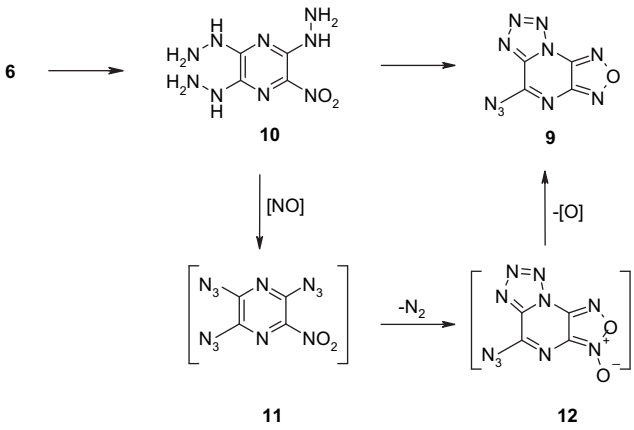


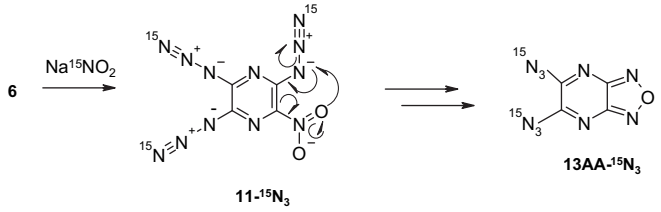
Figure 1. X-ray structure of compound **9**.

We suggest the following transformations to explain the occurrence of this unexpected compound. Treatment of **6** with hydrazine hydrate did not allow the isolation of the expected compound **8** but led to a remarkable triple substitution reaction giving intermediate **10**, which involves a nucleophilic aromatic substitution displacement of one of the nitro group of compound **6** by a hydrazine group. Doddi and co-workers have actually reported the displacement of a nitro group adjacent to intracyclic nitrogen by strong nucleophiles.[16]

Upon nitrosation the triazido intermediate **11** could occur, which must lead to two cyclisations and thus to a furoxan-bearing tricyclic specie **12**. This must be followed by a remarkable reduction of the furoxan into a furazan side ring (Scheme 3). Few related processes, akin to a dismutation, have actually been reported in the past for some functionalized furoxans upon treatment with hydrogen peroxide in trifluoroacetic acid.[17] In fact such a dismutation would explain the moderate yield of compound **9** obtained. The same reaction was done using ^{15}N sodium nitrite to give an azido intermediate **13** containing three labelled nitrogen (Scheme 4). However, upon the formation of the furazan ring, since an elimination of N_2 takes place along with the loss of one of the terminal ^{15}N



Scheme 3. Reaction pathway for the synthesis of **9**.



Scheme 4. Nitrosation of **6** with radiolabelled sodium nitrite.

atom, the resulting reaction product features two labelled nitrogen one on the tetrazole ring and the other one on the azido group.

The ^{13}C and ^{15}N NMR analysis of this ^{15}N-enriched compound **13** in deuterated solvents of different polarity (chloroform and acetone) pointed out another remarkable feature.

In deuterated chloroform, the ^{13}C spectrum displays two sets of signals of different intensities (Fig. 2). Based on the significant differences of the ^{15}N NMR shift between a tetrazole ring and an azide function, the existence of two isomeric forms could be inferred in solution. The ^{15}N signals at 250 ppm are fairly typical of the azide function displacement whereas the signals at 360 ppm are generally attributed to tetrazole rings (Fig. 3).[18] Indeed, the major ^{15}N signal at 249.5 ppm along with ^{13}C signals at 149.0 ppm and 150.7 ppm would belong to an open diazido **13AA**. On the other hand, the minor set of ^{15}N signals at 250.1 ppm and 360.5 ppm as well as ^{13}C signals at 138.3 ppm, 140.1 ppm, 149.9 ppm and 151.9 ppm would belong to the monotetrazole **13AT** (Table 2).

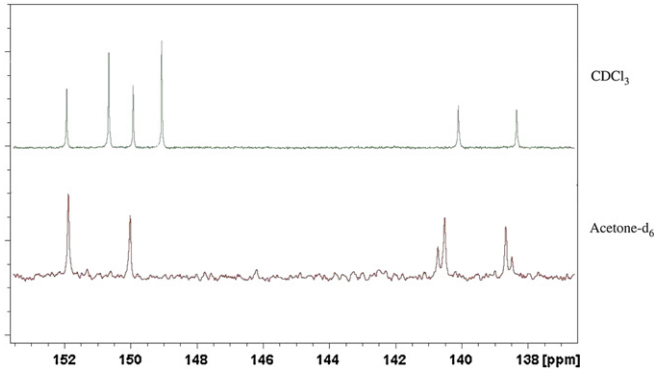


Figure 2. ^{13}C spectra of **13** in $CDCl_3$ and acetone-d_6.

Even more interesting, a second equilibrium was observed in deuterated acetone. The major set of ^{15}N signal at 250.1 ppm and 360.5 ppm along with ^{13}C signals at 138.6 ppm, 140.5 ppm, 150.0 ppm and 151.8 ppm correspond to the **13AT** form. On the other hand, the minor ^{15}N signals at 360 ppm along with ^{13}C signals at 138.5 and 140.7 ppm can only come from a tetracyclic form **13TT** featuring two tetrazole rings in its structure. A similar pattern was observed in deuterated DMSO.

The ^{13}C and ^{15}N NMR data pointed out that the equilibrium between three entities depends sensitively of the chosen solvent (Scheme 5).[19] Indeed, the equilibrium appears to be displaced towards diazido **13AA** in chloroform, and more towards the mono- and bis-tetrazole **13AT** and **13TT**, respectively, in acetone and DMSO. This conclusion is in accordance with the observations of Cmoch and co-workers on 6- and 8-substituted tetrazolo[1,5-*a*]pyridines.[20,21] Moreover, it is very clear that **13AT** seems to be the most stable form as it is the only one, which exists both in these three solvents and in the solid state (as white orthorhombic crystals with a density of 1.725 g/cm^3 were identified).

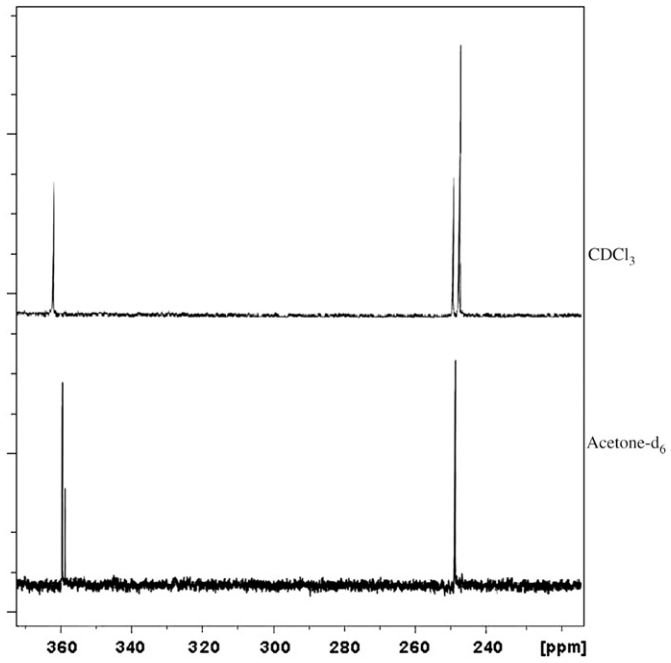
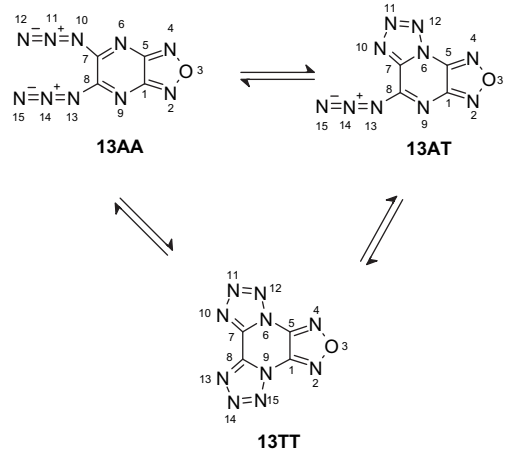


Figure 3. ^{15}N spectra of **13** in $CDCl_3$ and acetone-d_6.

Table 2
^{13}C and ^{15}N NMR chemical shifts (ppm) for the azide (A) and tetrazole (T) in $CDCl_3$ and acetone-d_6 of compound **13**

Nucleus	Solvent	13AA	13AT	13TT
C1	$CDCl_3$	149.0	149.9	
	Acetone		150.0	140.7
C5	$CDCl_3$	149.0	140.1	
	Acetone		140.5	140.7
C7	$CDCl_3$	150.7	138.3	
	Acetone		138.6	138.5
C8	$CDCl_3$	150.7	151.9	
	Acetone		151.8	138.5
N12	$CDCl_3$	249.5	363.1	
	Acetone		360.5	360.0
N15	$CDCl_3$	249.5	252.2	
	Acetone		250.1	360.0



Scheme 5. Equilibrium between tetrazole (T) and azide (A) forms of compound **13**.

In conclusion, we have reported an original synthesis of 7-azidofurazano[3,4-*b*]tetrazolopyrazine via an unprecedented

nucleophilic aromatic substitution of a nitro group using hydrazine hydrate. Very few reports related to this unexpected transformation have been described.[16,22] Furthermore, our studies based on ^{13}C and ^{15}N NMR analysis have shown that in solution compound **13** exists in equilibrium between three isomeric forms of which the monotetrazole **13AT** is the most stable. There are practically no data in the literature on the presence of three entities **13AA**, **13AT** and **13TT** describing the remarkable behaviour of **13** with the result of the coexistence of two tetrazole–azide equilibria.[23,24]

2. Experimental

2.1. General

Melting points were measured on a Kofler bench and are uncorrected. ^1H NMR, ^{13}C NMR and ^{15}N NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz, 100 MHz and 28.9 MHz, respectively. ^1H and ^{13}C chemical shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. ^{15}N chemical shift are reported with respect to liquid NH_3. Infrared spectra are collected in KBr pellets with Nicollet IMPACT 400D instrument. Elemental analyses were obtained by the laboratoire de Microanalyse, CNRS.-ICSN, 91198 Gif/Yvette, France. Column chromatography was performed over Merck silica gel 60 (0.035–0.070 mm). Mass spectra were measured on Hewlett Packard 5989B instrument using the atmospheric electrospray ionisation system. X-ray intensity data were collected on a Bruker X8-APEX2 CCD area-detector diffractometer using Mo $K\alpha$ radiation (λ=0.71073 Å). Nine sets of narrow data frames were collected at different values of θ, for 6 and 3 initial values of φ and ω, respectively, using 0.5° increments of φ or ω.[25,26] The crystal structure (Fig. 1) has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 727691.

2.2. 2,6-Dimethoxypyrazine 4

A solution of 2,6-dichloropyrazine (3 g, 20 mmol) in methanolic sodium methoxide, prepared from Na (11 g, 2 mol) in dry methanol (100 mL), was stirred and refluxed for 18 h. The solution was evaporated to dryness and the residue was dispersed in hydrochloric acid 3 N (30 mL) and extracted with ether (3×50 mL). The organic layer was washed with water (5×50 mL), dried over sodium sulphate and concentrated to dryness to give compound **4** (3 g, 99%) as white crystals. Mp 40–41 °C (cf. Ref. 19: 48–49 °C); ^1H ($CDCl_3$): 7.79 (s, 2H); 3.98 (s, 3H). ^{13}C ($CDCl_3$): 54.1; 124.1; 160.4. Anal. Calcd for $C_6H_8O_2N_2$: C, 51.42; H, 5.65; N, 19.99. Found: C, 51.40; H, 5.77; N, 19.90.

2.3. 2,6-Dimethoxy-3,5-dinitropyrazine 6

Sulphuric acid (28 mL) and fuming nitric acid (20 mL) were chilled in an ice bath and compound **4** (1.5 g, 10 mmol) was added slowly. The solution was stirred at chilled conditions for 30 min then warm to room temperature for 3 h. The reaction mixture was poured into 100 mL of cold water. The precipitate was filtered off, washed with water and dried in air to yield compound **6** (1.5 g, 65%) as a yellow powder. Mp 155–157 °C (cf. Ref. 4: 154 °C). ^1H ($CDCl_3$): 4.33 (s, 3H). ^{13}C ($CDCl_3$): 57.6; 131.6; 156.1. Anal. Calcd for $C_6H_6O_6N_2$: C, 31.31; H, 2.63; N, 24.34. Found: C, 31.03; H, 2.62; N, 24.02.

2.4. 2,6-Diamino-3,5-dinitropyrazine 7

A solution of aqueous ammonia (0.1 mL) was added to compound **6** (100 mg, 0.43 mmol) in acetonitrile (10 mL). The solution was refluxed for 18 h. After cooling the reaction, the precipitated solid was filtered off, washed with ether and dried in air to give compound **7** (60 mg, 70%) as orange powder. Mp 300–350 °C (decomp.) (cf. Ref. 5: 355–360 °C). ^1H ($CDCl_3$): 8.21 (br, s, 4H). ^{13}C ($CDCl_3$): 126.1; 151.6. Anal. Calcd for $C_4H_9O_2N_9$: C, 24.01; H, 2.01; N, 42.00. Found: C, 24.37; H, 1.93; N, 41.48. These analytical data are determined for the crude material.

2.5. 2,3,5-Trihydrazino-6-nitropyrazine 10

A mixture of compound **6** (200 mg, 0.86 mmol) in absolute ethanol was chilled at −78 °C and hydrazine hydrate (0.2 mL, 1.72 mmol) was added. The solution was stirred at chilled conditions for 2 h. The precipitate was filtered off, washed with ethanol and dried in air to give compound **10** (194 mg, 97%) as a brown solid. Mp 200 °C (decomp.). IR ν/cm^{-1}: 3437, 3430, 3426, 1480. Anal. Calcd for $C_4H_9O_2N_9$: C, 22.33; H, 4.22; N, 58.58. Found: C, 21.60; H, 4.70; N, 61.50. These analytical data are determined for the crude material.

2.6. 7-Azidofurazano[3,4-*b*]tetrazolopyrazine 9

2.6.1. Method A. A mixture of compound **10** (300 mg, 1.30 mmol) in dry acetonitrile (10 mL) was chilled at −40 °C and $NOBF_4$ (1.2 g, 10.4 mmol) was added slowly. The solution was stirred for 30 min and poured into 20 mL of cold water. The aqueous phase was extracted with ethyl acetate (3×50 mL) and the organic fraction was dried over $MgSO_4$ and concentrated to dryness. The residue was purified by chromatography over silica gel (ethyl acetate/pentane 1/9) to yield compound **9** (60 mg, 24%) as white cristals. Mp 79.5 °C (cf. Ref. 13: 88 °C). ^{13}C ($CDCl_3$): 150.2; 151.8. ^{13}C (acetone-d_6): 142.0; 143.9; 153.4; 155.2. ^{13}C (DMSO-d_6): 140.9; 143.2. ^{15}N ($CDCl_3$): 249.5. ^{15}N (acetone-d_6): 250.1; 360.6. Anal. Calcd for C_4ON_{10}: C, 23.54; H, 0.00; N, 68.62; O, 7.84. Found: C, 24.08; H, 0.00; N, 66.94; O, 8.01.

2.6.2. Method B. The compound **10** (300 mg, 1.3 mmol) was dissolved in acetic acid (10 mL) and the temperature was then adjusted to −5 °C and a solution of $NaNO_2$ (720 mg, 10.4 mmol) in water (10 mL) was added dropwise with vigorous stirring while maintaining the temperature below 3 °C. The reaction mixture was allowed to proceed at 0 °C for 2 h and poured into 100 mL of ice water. The aqueous phase was extracted with ethyl acetate and the organic fraction was dried over $MgSO_4$ and concentrated to dryness. The residue was purified by chromatography over silica gel (ethyl acetate/pentane 1/9) to yield compound **9** (55 mg, 20%) as white crystals.

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