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Synthesis of 7-Azidofurazano[3,4-*b*]tetrazolopyrazine and Isomer's Structure in Different Polarity Solvents

TAO GUO, MIN LIU, JUN JIANG, SHAO-JUN QIU* and ZHONG-XUE GE

Xi'an Modern Chemistry Research Institute, Xi'an 710065, P.R. China

*Corresponding author: Fax: +86 29 88220423; Tel: +86 29 88294436; E-mail: shaojqiu@yahoo.com

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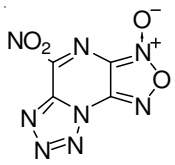
7-Azidofurazano[3,4-*b*]tetrazolopyrazine (FSZPA) was synthesized *via* methoxylation, nitration hydrazinolysis and azidation, using 2,6-dichloropyrazine as a starting material. The structures of 7-azidofurazano[3,4-*b*]tetrazolopyrazine and intermediates were identified by FTIR, NMR and elemental analysis. ^{15}N and ^{13}C NMR spectra showed three isomer forms resulting from the reversible opening and closing between asido and tetrazole depending on polarity of the solvents.

Key Words: Furoxan, Furazan, Pyrazine, Nucleophilic.

INTRODUCTION

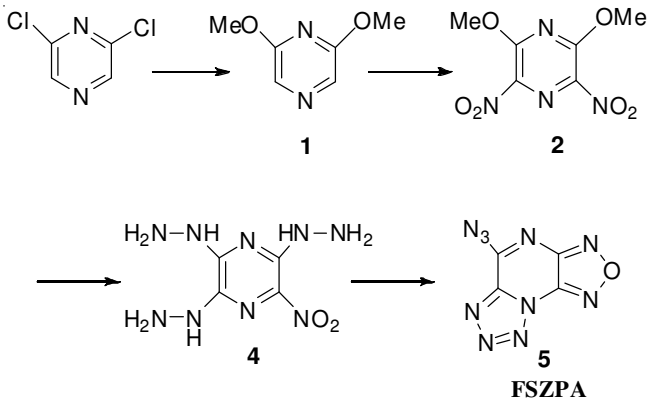
In recent years, nitrogen heterocyclic compounds with high nitrogen and less hydrogen and even without hydrogen, showing high generation enthalpy and high density, are developed to use as a new type of energetic materials. A series of studies on five- or six-membered nitrogen containing heterocyclic compounds and their derivatives have been carried out. DNBF and CL-14 are the typical examples[1-3]. As we known, the increase of energy density is observed when introducing furazan or tetrzole substituent into aromatic rings. Furoxans and tetrazoles was tried to introduce into pyrazine ring by Guillou and co-workers to synthesize 7-nitrofuraxan-[3,4-*b*]tetrazolopyrazine (FTZPN) (**Scheme-I**), but eventually the final product was 7-azidofurazano[3,4-b]tetrazolopyrazine (FSZPA)[4,5] (**Scheme-II**).



FTZPN

Scheme-I

In this work, we synthesized 7-azidofurazano[3,4-*b*]tetrazolopyrazine and discussed the mechanism of methoxylation, nitration, nucleophilic substitution, denitrification and cyclization. Furthermore, we examined that FSZPA had not less than three isomers. The dependency relationship between the structure of FSZPA isomers and solvents polarity was also investigated by ^{15}N and ^{13}C NMR spectroscopy.



Scheme-II

EXPERIMENTAL

2,6-Dimethoxypyrazine (1): To the stirred sodium methylate solution (115.7 g, 0.6 mol) was added 2,6-dichloropyrazine (29.8 g, 0.2 mol) in batches at 80 ºC. After refluxing for 18 h, the reaction was cooled. The mixture was poured into ice water and extracted with ether, dried over Na_2SO_4 and concentrated to give compound **1** (27.2 g, 97 %) as white crystals. m.p. 36-38 ºC (Lit. 38-39 ºC[6]); ^1H NMR [$(CD_3)_2CO$, 500 MHz] δ: 4.05 (s, 6H, $-OCH_3$), 7.85 (s, 2H, CH); ^{13}C NMR [$(CD_3)_2CO$, 125 MHz] δ: 52.9 ($-OCH_3$), 124.5 (-COMe), 159.2 (-CN). Anal. calcd. for $C_6H_6N_2O_6$: C, 31.31; H, 2.63; N, 24.34. Found: C, 31.03; H, 2.62; N, 24.02.

2,6-Dimethoxy-3,5-dinitropyrazine (2): 20 % oleum (300 mL) and fuming nitric acid (200 mL) were chilled in an ice bath and compound **1** (1.5 g, 0.1 mol) was added slowly. The solution was stirred at 0-2 ºC for 0.5 h and then heated to room temperature for 3 h. The reaction mixture was poured into cold water. The precipitate was filtered off, washed with water and dried in air to yield compound **2** (14.8, 65 %) as a yellow powder. m.p. 155-157 ºC (Lit. 154 ºC[7]); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ : 57.6 (-OCH_3), 131.6 (-C-OMe), 156.1 (-C-NO_2); IR (KBr, ν_{max}, cm^{-1}): 3033, 3058, 1581, 1542, 1273 cm^{-1}; Anal. calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.71; N 20.0. Found: C, 51.38; H, 5.66; N, 19.84.

2,6-Diamino-3,5-dinitropyrazine (3): A solution of aqueous ammonia (28 %, 10 mL) was added to compound **2** (5.0 g, 21.7 mmol) in acetonitrile (85 mL). The solution was refluxed for 2 h. After cooling, the precipitated solid was filtered off, washed with diethyl ether and dried in air to give compound **3** (3.9 g, 90 %) as orange powder. m.p. 327-330 ºC [Lit. > 300 ºC (dec.)][8]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 126.1 (-C-OMe), 156.1 (-C-NO_2). Anal. calcd. for $C_4H_4N_6O_4$: C 24.01, H 2.01, N, 42.00. Found: C, 24.37; H, 1.93; N, 41.48.

2,3,6-Trihydrazino-5-nitropyrazine (4): Hydrazine hydrate was dropwise added to the mixture of compound **2** (2.0 g, 9.5 mmol) in absolute ethanol (80 mL) at -78 ºC in 20 min. The solution was stirred at -78 ºC for 2 h. The precipitate was filtered off, washed with ethanol and dried in air to give compound 4 (1.4 g, 97 %) as a brown solid. m.p. 201-204 ºC; IR (KBr, ν_{max}, cm^{-1}): 3368, 3322, 3280, 1478. Anal. calcd. for $C_4H_9N_9O_2$: C, 22.33; H, 4.22; N, 61.50. Found: C, 21.60; H, 4.70; N, 59.48.

7-Azidofurazano[3,4-*b*]tetrazolopyrazine (5): Method 1: A mixture of compound **4** (0.6 g, 2.8 mmol) in dry acetonitrile (20 mL) was chilled at -40 ºC and the solution of NO_2BF_4 (2.4 g) in acetonitrile (20 mL) was added slowly. After stirring for 30 min, the solution was poured into cold water. The aqueous phase was extracted with diethyl ether (30 mL × 2) and organic fraction was dried over $MgSO_4$ and concentrated to give compound **5** (0.12 g, 24 %) as a white crystals. m.p. 79-81 ºC.

Method 2: The compound **4** was dissolved in acetic acid and the temperature was then chilled to -5 ºC. A solution of $NaNO_2$ (1.7 mol/L,15 mL) was added dropwise with vigorous stirring while maintaining the temperature below 3 ºC for 2 h and then poured into ice water. The aqueous phase was extracted with diethyl ether (30 mL × 2) and organic phase was dried over $MgSO_4$ and concentrated to dryness to give compound **5** (0.11 g, 20 %) as a white crystals. m.p. 79-81 ºC.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.2 (C1-5AA), 150.9 (C5-5AA); ^{13}C NMR [$(CD_3)_2CO$, 125 MHz] δ: 138.8 (C7-5AT), 140.7 (C5-5AT), 150.1 (C1-5AT), 151.5 (C8-5AT); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 139.1 (C8-5TT), 141.2 (C1-5TT); ^{15}N NMR ($CDCl_3$, 36 MHz) δ: 249.4 (N12-5AA); ^{15}N NMR [$(CD_3)_2CO$, 36 MHz] δ : 252.1 (N15-5AT), 361.3 (N12-5AT); ^{15}N NMR (DMSO-d_6, 36 MHz) δ: 360.8 (N12-5TT). Anal. calcd for $C_4N_{10}O$: C, 23.54; N, 68.62. Found: C, 24.08; N, 68.94.

^{1}H NMR, ^{13}C NMR and ^{15}N NMR spectra (NMR) analysis were recorded on a Bruker AV500 nuclear magnetic resonance spectrometer. Room-temperature Fourier transform infrared (FTIR) spectra were recorded in the range 400-4000 cm^{-1} on a Thermo Nicolet NEXUS870 spectrometer using the KBr pellet technique. Elemental analysis was obtained by using an Elementar VARI-EL-3 Vario elemental analyzer.

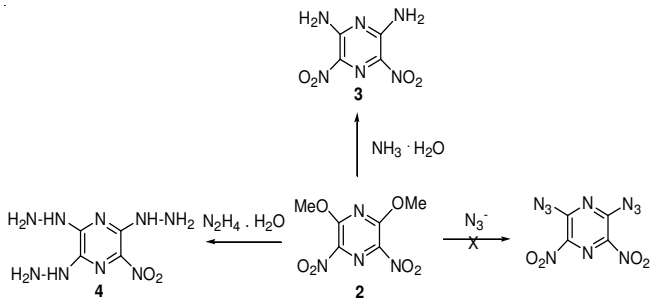
RESULTS AND DISCUSSION

Nucleophilic substitution and nitration on pyrazine ring: Methoxylation gave 73 % compound **1** by using the concentration of sodium methoxide less than 20 %, while the yield of compound **1** was obviously increased with the concentration more than 28 %. Interestingly, using methanolic sodium methoxide (2 equiv) at reflux for 3.5 h, this resulted in compound **1** along with small amounts of the monometoxylated byproduct. Moreover, the separation was difficult by recrystallization or column chromatography. Therefore, 97 % yield of compound **1** was obtained by employing the methanolic sodium methoxide (3 equiv) at reflux temperature for 18 h. As we known, electronegativity of nitrogen was larger than that of carbon, which results in the lower electron density of carbon atom and imbalance of electron density in nitrogen heterocyclic ring like pyrazines and pyridines. Thus, the nitration reaction of electron-deficient heterocycles did not undergo electrophilic substitution under normal conditions unless substituted with electron-donating substituents. The electron density of carbon atom was even much lower due to 2,6-dichloropyrazine containing two electron-withdrawing chlorine atoms, which led to the nitration reaction hardly to occur even in high temperature conditions. In contrast, nitration of compound **2**, 6-dimethoxypyrazine by forming far more electron-rich pyrazine ring system, which was obtained from the substitutions of methoxy groups in 2,6-dichloropyrazine rings, gave the dinitrated compound **2** easily in nitric-sulfuric acid at room temperature.

Influence of different nucleopilic reagent: In order to introduce the furoxan and tetrazole rings in 7-nitrofuraxan[3,4-b]tetrazolopyrazine, this meant to the synthesis of the precursor 2,6-diazido-3,5-dinitropyrazine (**Scheme-III**), in which the furoxan ring could be obtained by nitrogen removal of intramolecular between the azido and *ortho* nitro group. 2,6-Diazido-3,5-dinitropyrazine could be prepared by the direct nucleophilic substitution of a methoxy group or by the replacement of a diazonium moiety by the N_3^- ions. In later case, that implied the preparation of a diamino or of a dihydrazino compound like, respectively, compounds **3** and **4**. Therefore, our attention was turned to investigate the nucleophilic substitution reactions with compound **2**.

The direct displacement of methoxy group by N_3^- ions gave no reaction in compound **2**. On the other hand, compound **3** was successfully achieved using aqueous ammonia in acetonitrile at atmospheric pressure. However, treatment of compound **3** with sodium nitrite followed by sodium azide was found to be ineffective to form the diazido precursor 2,6-diazido-3,5-dinitropyrazine. The reason may be that electron-withdrawing effect of nitro group greatly reduced both the reactivity of the amino group and the stability of the diazonium salts. Using

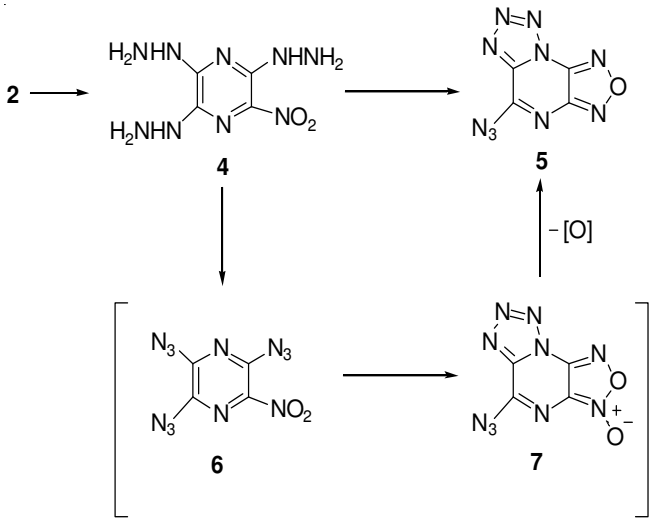
other nucleophiles only either led to extensive decomposition of compound **2**, or gave no reaction. Eventually, compound **4** as a brown solid was given in yield 97 % by employing hydrazine hydrate in ethanol at -78 ºC for 2 h.



Scheme-III

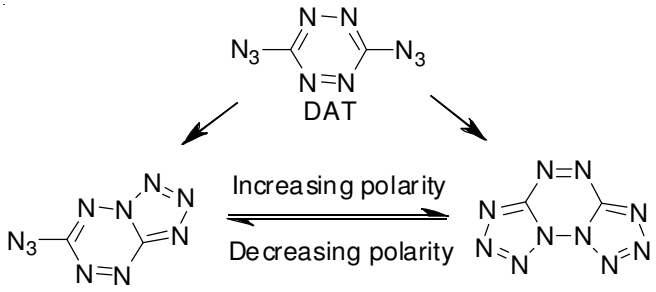
Cyclization reactions of furazan and tetrazole: Based upon the reasearch of the transformation of hydrazines into azides using dinitrogen tetroxide and clay supported ferric nitrate[9,10], we undertook a nitrosation reaction for compound **4** with two kinds of nitrosating reagents *i.e.*, nitrosonium tetrafluoroborate and sodium nitrite in acetic acid. Both of nitrosating regents gave compound **5** as white crystals in about 20 % yield. Compound **5** contained a tetrazole ring along with an azido substituent and a quite unexpected furazan ring instead of the expected furoxan.

The compound **2** was treated with hydrazine hydrate to lead to compound **4** rather than gave the 2,6-dihydrazino-3,5-dinitropyrazine, which involved a nucleophilic aromatic substitution of one of the nitro group adjacent to intracyclic nitrogen by a hydrazine group in compound **2**.[11] Compound **4** underwent nitrosation reaction to form intermediate **6** with three azidos and then led to intermediate **7** with a furoxan and tetrazole side ring by eliminating N_2 in heating, which might be followed by a remarkable reduction of the furoxan into a furazan side ring eventurally, akin to dismutation. This reduction process has actually been reported in the past for some functionalized furoxans upon treatment with hydrogen peroxide in trifluoroacetic acid[12], which would explain the lower yield of compound **5** obtained (**Scheme-IV**).



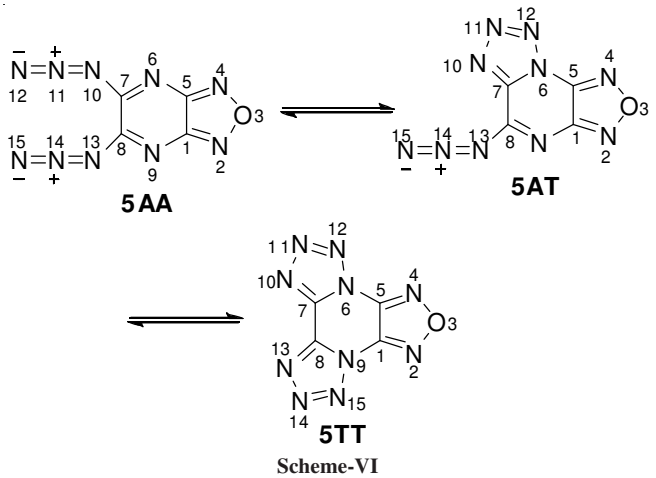
Scheme-IV

Effect of solvent polarity on structure of isomers: In nitrogen heteroaromatic ring the tetrazole ring nitrogen atom could be easily formed between nitrogen atom and its adjacent azido in polarity solvents. As reported in literature, the azido of 3,6-diazidotetrazine along with its adjacent nitrogen atom gradually transformed into tetrazole ring with increasing polarity of solvents[13]. (**Scheme-V**)



Scheme-V

In this work, we investigated the relations between different isomers of compound **5** and polarity of solvents. Based on significant difference of ^{15}N NMR chemical shifts featured by tetrazole ring and azido, the ^{13}C and ^{15}N NMR in different polarity solvents showed that compound **5** would have three isomeric forms in solution (Table-1). The ^{13}C NMR spectrum displayed two sets of signals of different chemical shifts. The ^{15}N NMR signals at 250 ppm and 360 ppm were generally attributed to the azide function displacement and tetrazole rings, respectively. In deuterated chloroform, ^{15}N NMR signal at 249.4 ppm along with ^{13}C NMR signals at 149.2 ppm and 150.9 ppm would belong to an open diazido **5AA**. On the other hand, the ^{15}N NMR signals at 252.3 ppm and 362.9 ppm as well as ^{13}C NMR signals at 138.2 ppm, 149.6 ppm and 151.7 ppm would be assigned to the monotetrazole **5AT**. (**Scheme-VI**)



Scheme-VI

Even more interesting, another phenomenon was observed in deuterated acetone. The ^{15}N NMR signal at 252.1 ppm and 361.3 ppm along with ^{13}C signals at 138.8, 140.7, 150.1 and 151.5 ppm corresponded to the **5AT** form. On the other hand, the ^{15}N NMR signals at 360.2 ppm along with ^{13}C NMR signals at 138.7 and 140.4 ppm would only come from a tetracyclic form **5TT** featuring two tetrazole rings in its structure.

Furthermore, a similar pattern was observed in deuterated dimethylsulfoxide. The ^{15}N NMR signals at 139.1 ppm as well as ^{13}C NMR signals at 141.2 ppm were attributed to the tetrazole rings.

TABLE-1
^{13}C AND ^{15}N NMR CHEMICAL SHIFTS FOR THE AZIDE (A) AND TETRAZOLE (T) IN CHLOROFORM, ACETONE AND DMSO OF COMPOUND **5**

Atom	Solvent	5AA	5AT	5TT
C1	$CDCl_3$	149.2	149.6	
	Acetone-d_6		150.1	140.4
	DMSO-d_6			141.2
C5	$CDCl_3$	149.2	140.3	
	Acetone-d_6		140.7	140.4
	DMSO-d_6			141.2
C7	$CDCl_3$	150.9	138.2	
	Acetone-d_6		138.8	138.7
	DMSO-d_6			139.1
C8	$CDCl_3$	150.9	151.7	
	Acetone-d_6		151.5	138.7
	DMSO-d_6			139.1
N12	$CDCl_3$	249.4	362.9	
	Acetone-d_6		361.3	360.2
	DMSO-d_6			360.8
N15	$CDCl_3$	249.4	252.3	
	Acetone-d_6		252.1	360.2
	DMSO-d_6			360.8

The ^{13}C and ^{15}N NMR spectra indicated that the equilibrium of three isomers of compound **5** depended on the polarity of solvents. Indeed, the equilibrium appeared to be displaced towards diazido **13AA** in chloroform, more towards the mono-tetrazole **13AT** in acetone and completely towards the bi-tetrazole **13TT** in dimethylsulfoxide, respectively. This result was in agreement with the observations of on 6- and 8-substituted tetrazolo[1,5-*a*]pyridines[14,15]. It was concluded that an open diazido was gradually transformed into tetrazole ring from nonpolar solvents to polar solvents.

Conclusion

In conclusion, 7-azidofurazano[3,4-*b*]tetrazolopyrazine has been synthesized by a nucleophilic aromatic substitution of a nitro group adjacent to nitrogen atom using hydrazine hydrate, nitrosation reaction and cyclization. An unexpected dismutation involving the transformation between furoxan and furazan has been described. Furthermore, our studies based on ^{13}C and ^{15}N NMR data have shown that in different solvents compound **5** exists in equilibrium between three isomeric forms **5AA**, **5AT** and **5TT** relaying on the polarity of solvents.

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