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REINVESTIGATION OF THE REPORTED SYNTHESIS OF NAPHTHO[2',1'-4,5]-THIAZOLO[2,3-c][1,2,4]TRIAZEPINES

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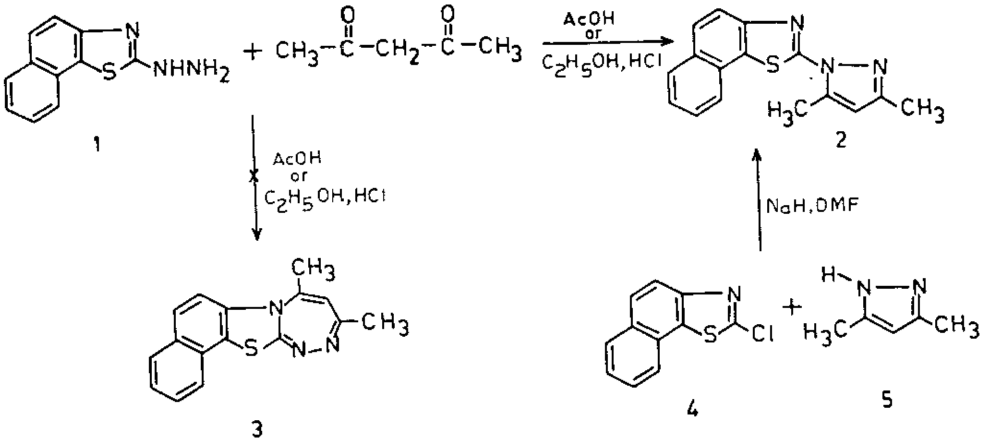
Abstract - The reaction of 2-hydrazinonaphtho[2,1-d]thiazole with 1,3-diketones affords 2-pyrazolylnaphtho[2,1-d]thiazoles rather than naphtho[2',1'-4,5]thiazolo[2,3-c][1,2,4]triazepines as previously reported. The structure assignment is based on nmr (^{1}H and ^{13}C) and mass spectral data and an unambigious synthesis.

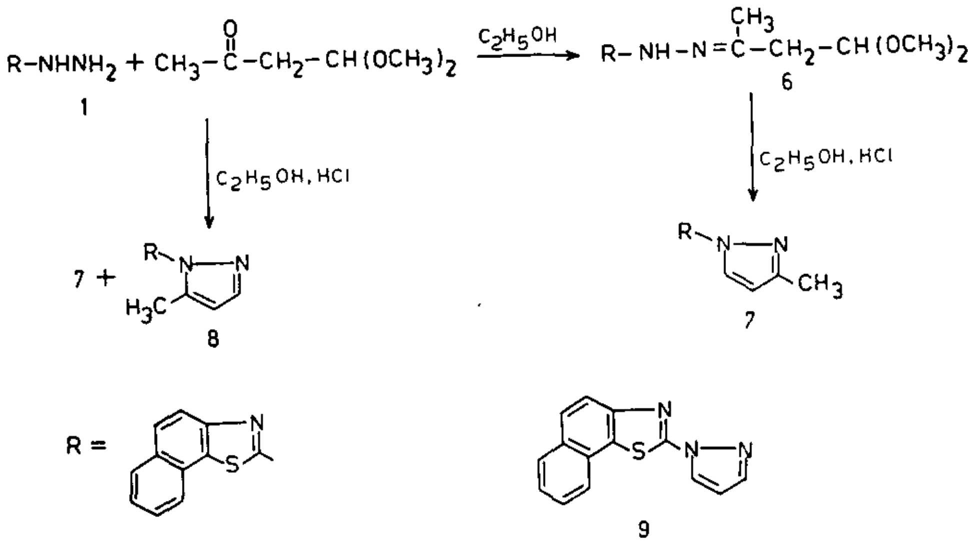
The reaction of hydrazines with 1,3-diketones leads to the formation of pyrazoles.[1] However, heterocyclic hydrazines have been reported to behave in divergent manner.[2-4] Whereas the expected pyrazoles are reported in such reactions,[2] others have reported isomeric structures - diazepines[3] or triazepines.[4] Structure of many of these reported 7-membered heterocycles has been reinvestigated recently by us[5,6] and Peet et al.[7] and it was conclusively established that all such structures are in error and need correction. In continuation of this study, we recently noted a report by Jain and Soni of the formation of triazepines by treating 2-hydrazinonaphtho[2,1-d]thiazole with 1,3-diketones.[8] Such a structure appeared untenable on the basis of our past experience. Furthermore, the ^{1}H nmr values, reported for the compounds,[8] were in excellent correspondence with thos recorded for a large number of related pyrazole derivatives.[5,6] It was, therefore, decided to reinvestigate this reaction.

Condensation of 2-hydrazinonaphtho[2,1-d]thiazole (**1**) with pentane-2,4-dione either in glacial acetic acid or in ethanolic HCl afforded a crystalline compound, mp 159°C, whose ^{1}H nmr spectrum displayed sharp signals of three proton intensity at δ 2.31 and 2.77 assigned to C_3-CH_3 and C_5-CH_3 and a signal of one proton intensity at δ 6.01 assigned to C_4-H, besides the aromatic protons. Although the mp of the product was at variance (mp 99-100°C),[8] the ^{1}H nmr signals and elemental analysis left us in no doubt about the identicality of the two samples. An examination of ^{13}C nmr spectrum of this compound revealed signals at δ 152.06, 110.15 and 142.32 in agreement with the values recorded for carbon atoms C_3, C_4, and C_5 of pyrazole ring.[9] Furthermore, the mass spectrum exhibited ions at m/z 184 and 95 corresponding to the ions generated by simple cleavage of the heterocyclic moieties through the C-N bond. These spectroscopic data suggested the product to be a pyrazole, **2**, rather than the isomeric triazepine, **3**.



The pyrazole structure was conclusively established by its alternate synthesis. Treatment of 2-chloronaphtho[2,1-d]thiazole **(4)** with the sodium salt of 3,5-dimethyl-1H-pyrazole **(5)** in DMF provided **2**, which was identical in all respects with the reaction product obtained from **1** and pentane-2,4-dione.

To further generalize the formation of pyrazole derivatives in such reactions, pentane-2,4-dione was replaced by acetylacetaldehyde dimethyl acetal and malonaldehyde bis-(dimethyl acetal). Treatment of **1** with acetylacetaldehyde dimethyl acetal in ethanol provided the corresponding hydrazone, **6**, which was cyclized by refluxing the product in ethanolic HCl to produce **7**. The ^{1}H nmr spectrum of **7** displayed a sharp three-proton singlet at δ 2.38 assigned to C_3-CH_3 and two doublets of one proton each at δ 6.28 and 8.33 (J=2.5 Hz) of pyrazole ring due to C_4 and C_5-H, respectively, along with the aromatic protons. The other isomeric product **(8)** was obtained by refluxing **1** with acetylacetaldehyde dimethyl acetal in ethanolic HCl. The mixture of two products (tlc and ^{1}H nmr) was separated by column chromatography affording, besides **7**, the other isomer identified as **8**. The ^{1}H nmr spectrum of **8** was characterized by signals at δ 2.85 (s, 3H, C_5-CH_3), 6.24 (d, J=1.0 Hz, 1H, C_4-H) and 7.63 (d, J=1.0 Hz, 1H, C_3-H), besides aromatic protons. The formation of **8** could be envisaged by the fact that formyl group generated by hydrolysis of acetylacetaldehyde dimethyl acetal forms the hydrazone, firstly, with **1** which in turn undergoes cyclization to **8**.



The deshielding of C_5-CH_3 as compared to C_3-CH_3 can be rationalized on the basis of the lone pair effect of the nitrogen atom of the naphthothiazole ring or perhaps hydrogen bonding and consequent planarity of the system.[9] It was also expected that the hydrogens attached to C_5 and C_3 should behave in the same manner. 2-(Pyrazol-1-yl)naphtho[2,1-d]-thiazole (**9**) obtained by refluxing **1** and malonaldehyde bis(dimethyl acetal) in ethanolic HCl indeed showed these characteristics. The ^1H nmr spectrum of **9** displayed signals at δ 6.51 (dd, J=2.5 and 1.5 Hz, 1H), 7.76 (d, J=1.5 Hz, 1H) and 8.48 (d, J=2.5 Hz, 1H) which are readily assigned to hydrogens attached at C_4, C_3, and C_5 of the pyrazole moiety, respectively.[9] These assignments were confirmed by spin decoupling experiments.

The ^{13}C nmr spectrum of **9** exhibited signals at δ *143.17, 109.20, 127.52 assigned to* carbon atoms C_3, C_4, and C_5 of pyrazole ring. However, analysis of ^{13}C nmr spectra of the isomeric products (**7** and **8**) showed that carbon atom C_3, C_4, and C_5 in **7** resonated at δ 153.19, 109.54, and 127.54, whereas in **8**, these carbons resonated at 143.26, 110.53 and 141.78 respectively. Such a downfield shift of carbon atom C_3 in **7** and C_5 in **8** is expected only when a hydrogen is substituted by a methyl group.[10]

EXPERIMENTAL

Melting points are uncorrected. The ir spectra (nujol) were recorded on a Beckman IR-20 spectrophotometer. The ^1H nmr spectra were recorded on R-32 Perkin Elmer (90 MHz) and on Bruker (400 MHz) instruments, whereas ^{13}C nmr spectra were recorded on Bruker (100 MHz) and Varian XL-100 instruments. All the spectra were run in deuteriochloroform using TMS as internal standard. The mass spectra were measured with a Hewlett Packard GC/MS 5985 apparatus at 70eV. 3,5-Dimethyl-1H-pyrazole, acetylacetaldehyde dimethyl acetal and malonaldehyde bis(dimethyl acetal) were commercially available (Aldrich). 2-Chloronaphtho[2,1-d]thiazole and 2-hydrazinonaphtho[2,1-d]thiazole were prepared according to the literature procedure.[8,11]

2-(3,5-Dimethylpyrazol-1-yl)naphtho[2,1-d]thiazole (2)

a A mixture of **1** (1.075 g, 5 mmol) and pentane-2,4-dione (0.5 ml, 5 mmol) in 30 ml of glacial acetic acid was refluxed for 2 h. The crystalline solid so obtained on cooling the mixture was passed through a short column of silica gel using chloroform as eluent to afford **2** crystallised from chloroform, mp 159°C (lit.[8] mp 99-100°C), yield 1.2 g (85%). ^{1}H Nmr δ : 2.31 (s, 3H, C_3-CH_3), 2.77 (s, 3H, C_5-CH_3), 6.01 (s, 1H, C_4-H), 7.45-7.56 (m, 2H, C_7-H and C_8-H), 7.79 (d, 1H, J=8.8 Hz, C_4-H), 7.87-7.92 (m, 3H, C_5-H, C_6-H, and C_9-H). ^{13}C Nmr δ : 13.62, 13.87, 110.15, 121.23, 124.52, 125.44, 126.96, 127.01, 127.94, 128.91, 129.13, 130.65, 142.32, 149.49, 152.06, 160.84. Ms, m/z (rel. int.): 279[M]$^+$ (100), 278(18), 264(12), 263(6), 238(11), 237(25), 200(13), 185(15), 184(4), 158(22), 140(73), 95(15). Anal. Calcd for $C_{16}H_{13}N_3S$: C, 68.81; H, 4.65; N, 15.05. Found : C, 68.71; H, 4.62; N, 14.85.

2 was also obtained by refluxing **1** and pentane-2,4-dione for 2 h in ethanolic HCl in 80% yield.

b 3,5-Dimethyl-1H-pyrazole **5** (384 mg, 4 mmol) was added slowly to a suspension of dry sodium hydride (60%) (144 mg, 6 mmol) in 20 ml of N,N-dimethylformamide. After a few min of stirring, **4** (876 mg, 4 mmol) was added and the mixture was heated in an oil bath at 140-150°C for 20 h. The mixture was cooled, diluted with water and extracted with chloroform to give **2** crystallised from chloroform, mp 159°C, yield 215 mg (30%). The physical and spectroscopic data were identical to those of **2** obtained from 1 and pentane-2,4-dione using the procedure of Jain and Soni.[8]

2-(3-Methylpyrazol-1-yl)naphtho[2,1-d]thiazole (7)

A solution of **1** (1.075 g, 5 mmol) and acetylacetaldehyde dimethyl acetal (660 mg, 5 mmol) in ethanol (30 ml) was stirred at room temperature for 1 h and left over night. The solid which separated out was filtered and washed with ethanol to give hydrazone **6** crystallised from ethanol, mp 212°C, yield 1.15 g (80%). Ir: 3200 cm^{-1} (NH stretching). ^{1}H Nmr δ : 1.90 (s, 3H, CH_3), 2.68 (d, 2H, J=5.5Hz, -CH_2-CH-), 3.41 (s, 6H, 2xOCH_3), 4.73 (t, 1H, J=5.5 Hz, $-CH_2-CH-$), 7.43-7.58 (m, 2H, C_7-H and C_8-H), 7.70-7.91 (m, 4H, C_4-H, C_5-H, C_6-H, and C_9-H). This hydrazone **6** (658 mg, 2 mmol) was refluxed in ethanol (20 ml) containing 1 ml of 10 N HCl for 2 h. The concentrated solution was cooled, the solid so obtained was crystallised from ethanol to afford **7**, mp 168°C, yield 360 mg (68%). ^{1}H Nmr δ : 2.38 (s, 3H, C_3-CH_3), 6.28 (d, 1H, J=2.5 Hz, C_4-H), 7.44-7.55 (m, 2H, C_7-H and C_8-H), 7.86-7.89 (m, 3H, C_5-H, C_6-H, and C_9-H), 8.00 (d, 1H, J=8.8 Hz, C_4-H), 8.33 (d, 1H, J=2.5 Hz, C_5-H). ^{13}C Nmr δ : 13.78, 109.54, 120.81, 120.98, 124.33, 125.53, 127.03, 127.54, 128.01, 128.93, 129.26, 130.70, 148.97, 153.19, 159.80. Ms, m/z (rel. int.) : 265$[M]^+$ (100), 264(9), 224(10), 223(3), 185(7), 184(2), 158(7), 140(27), 81(3). Anal. Calcd for $C_{15}H_{11}N_3S$: C, 67.92; H, 4.15; N, 15.85. Found : C, 68.01; H, 4.13; N, 15.91.

7 was also obtained by refluxing **1** (1.075 g, 5 mmol) and acetylacetaldehyde dimethyl acetal (660 mg, 5 mmol) in ethanol (30 ml) containing 1 ml of 10 N HCl for 2.5 h. On cooling a solid separated out, which was found to be a mixture of two compounds (tlc and ^{1}H nmr). Column chromatographic separation of the mixture over silica gel using chloroform-benzene (60 : 40) as eluent afforded **8** which was crystallised from chloroform, mp 150-151°C, yield 400 mg (30%). ^{1}H Nmr δ : 2.85 (s, 3H, C_5-CH_3), 6.24 (d, 1H, J=1.0 Hz, C_4-H), 7.46-7.57 (m, 2H, C_7-H and C_8H), 7.63 (d, 1H, J=1.0 Hz, C_3-H), 7.83 (d, 1H, J=8.8 Hz, C_4-H), 7.89-7.95 (m, 3H, C_5-H, C_6-H, and C_9H). ^{13}C Nmr δ : 13.31, 110.53, 120.54, 124.85, 125.48, 126.53, 127.83, 127.97, 128.02, 128.19, 129.70, 141.78, 143.26, 149.44, 160.96. Ms, m/z (rel. int.) : 265$[M]^+$ (100), 264(9), 238(6), 237(13), 185(11), 184(2), 158(8), 140(25), 81(4). Anal. Calcd for $C_{15}H_{11}N_3S$: C, 67.92; H, 4.15; N, 15.85. Found : C, 67.83; H, 4.07; N, 15.61.

The other compound separated was identical to **7** (mp, mmp, ir and ^{1}H nmr), yield 600 mg(15%).

2-(Pyrazol-1-yl)naphtho[2,1-d]thiazole (9)

A mixture of **1** (645 mg, 3 mmol) and malonaldehyde bis(dimethyl acetal) (492 mg, 3 mmol) in ethanol (20 ml) containing 1.5 ml of 10 N HCl was refluxed for 3 h. On concentrating and cooling the mixture, a crystalline solid separated out, which was filtered and crystallised from ethanol to give **9**, mp 135°C, yield 520 mg (67.5%). ^{1}H Nmr δ : 6.51 (dd, 1H, J=2.5 and 1.5 Hz, C_4-H), 7.45-7.58 (m, 2H, C_7-H and C_8-H), 7.76 (d, 1H, J=1.5 Hz, C_3 -H), 7.85-7.96 (m, 4H, C_4-H, C_5-H, C_6-H, and C_9-H), 8.48 (d, 1H, J=2.5 Hz, C_5-H). ^{13}C Nmr δ : 109.20, 120.98, 124.32, 125.77, 127.14, 127.52, 127.74, 127.94, 128.97, 129.54, 130.79, 143.17, 148.83, 159.79. Anal. Calcd for $C_{14}H_9N_3S$: C, 66.93; H, 3.58; N, 16.73. Found : C, 66.87; H, 3.58; N, 16.29.

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