

NEW SYNTHETIC APPROACH FOR PYRAZOLO|3,4-b|PYRAZINES  
AND ISOXAZOLO|4,5-b|PYRAZINES

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**Abstract** - A new synthetic approach has been developed for the synthesis of pyrazolo|3,4-b|pyrazines (7) and isoxazolo-|4,5-b|pyrazines (22) from the corresponding substituted pyrazines.

In almost all synthetic approaches to pyrazolo|3,4-b|pyrazines the bicyclic system has been prepared from 4,5-diaminopyrazoles and 1,2-dicarbonyl compounds.<sup>1-7</sup> However, there is one report on the synthesis of this bicyclic system from 2-chloro-3-cyano-5,6-diphenylpyrazine, but without details.<sup>8</sup> The purpose of this communication is to describe some new syntheses of this and a related system from appropriate substituted pyrazines on the basis of recently reported neighboring group participation.<sup>9</sup>

The amidoxime **1**<sup>10</sup>, when heated in the presence of N,N-dimethylformamide dimethyl acetal (DMFDMA) in toluene, was transformed into a mixture of the corresponding pyrazolo|3,4-b|pyrazine (**4**), formamidine (**8**) and N,N-dimethylurea<sup>11</sup> (**9**). The yield of these products depends on the quantity of DMFDMA used. With 1.2 mole of DMFDMA (3 h under reflux) the yields of compounds **4**, **8** and **9** were 36%, 14% and 8% with 15% of the starting compound recovered, whereas with 2.3 moles of DMFDMA (6 h under reflux) the above products were formed in 35%, 28% and 10% yield. With large excess of DMFDMA (5 min at 75 °C) and in the absence of toluene as solvent, only compounds **8** and **9** were obtained in 66% and 12% yield. Compound **4** had mp 247-250 °C (from water); m/e 163 (M<sup>+</sup>) and  $\delta$  nmr (CF<sub>3</sub>COOH) 8.56 and 8.98 (d, H<sub>5</sub> and H<sub>6</sub>, J<sub>5,6</sub> = 2.6 Hz), 8.27 (s, CHO). The compound was deformylated with dilute hydrochloric acid (1:1) to give the amino compound **7**, mp 244-246 °C (from ethanol); m/e 135 (M<sup>+</sup>) and  $\delta$  nmr (DMSO-d<sub>6</sub>) 7.92 and 8.00 (d, H<sub>5</sub> and H<sub>6</sub>, J<sub>5,6</sub> = 2.1 Hz). This compound could be prepared also from 2-chloro-3-cyanopyrazine (**10**) and hot ethanolic hydrazine hydrate in 53% yield.

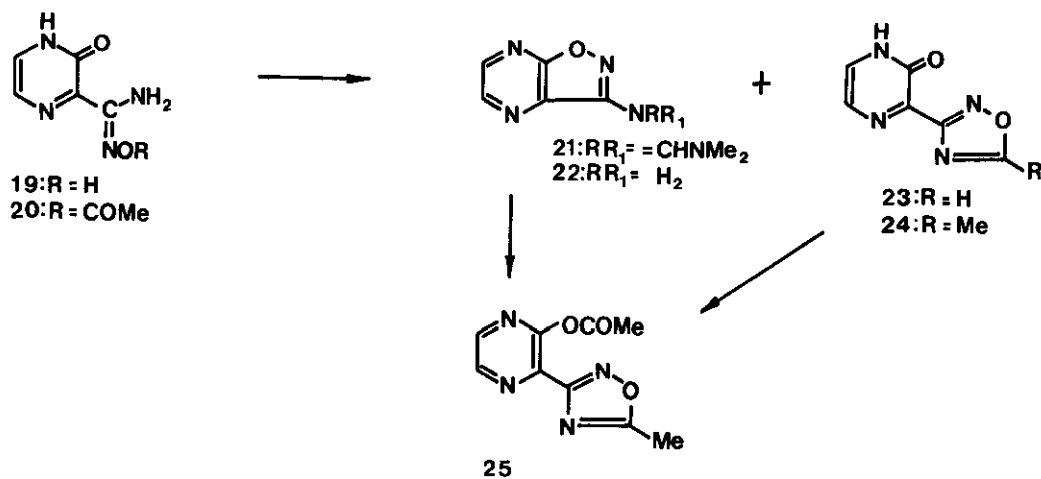
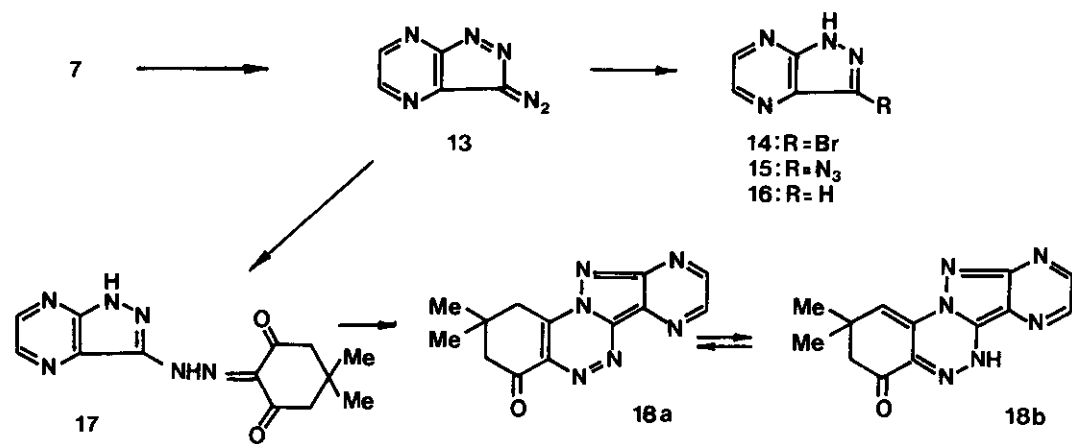
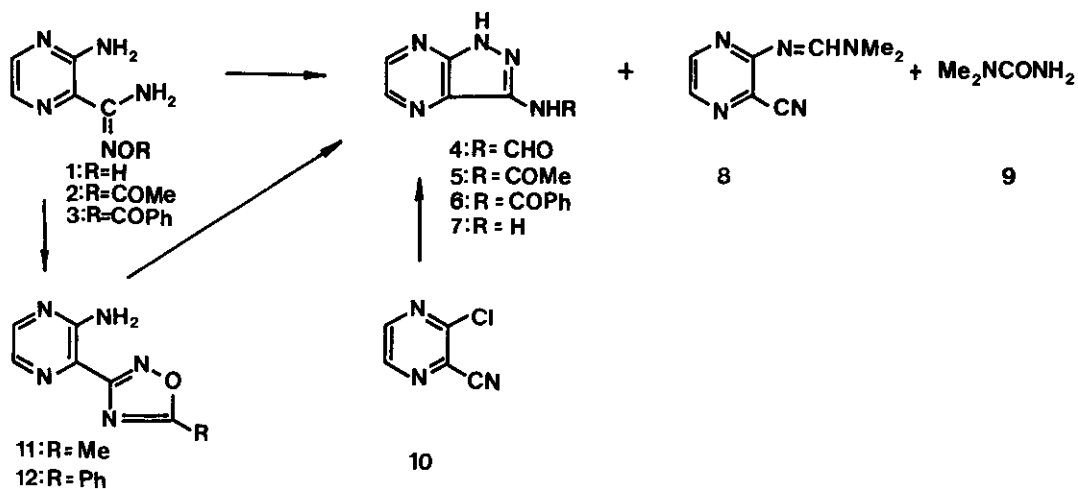
In another approach, 2-amino-3-(1,2,4-oxadiazolyl-3)pyrazines **11** or **12** were used as starting material. These compounds were prepared from **1** by acylation of the amidoxime functional group with acetic anhydride or benzoyl chloride (in chloroform solution in the presence of triethylamine) at room temperature to give **2** or **3**, both in 97% yield.<sup>10</sup> These compounds, when heated in glacial acetic acid were transformed into the oxadiazolyl derivatives, i.e. **11** in 72% yield (mp 217-219 °C (from ethanol); m/e 177 (M<sup>+</sup>) and **12** in 86% yield (cyclization to **12** was performed pre-

ferentially in the presence of hot polyphosphoric acid), mp 220-223 °C (from ethanol and *N,N*-dimethylformamide); *m/e* 239 ( $M^+$ ). These two oxadiazolyl derivatives, 11 and 12, could be transformed into the corresponding pyrazolo[3,4-*b*]pyrazines 5 and 6 upon heating in *N,N*-dimethylformamide in the presence of sodium ethoxide (yield 60% and 95%, respectively). Compound 5 had mp 300-303 °C (dec) (from methanol and *N,N*-dimethylformamide; *m/e* 177 ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.57 (s, H<sub>5</sub> and H<sub>6</sub>), 2.10 (s, Me) and compound 6 had mp 231-234 °C (from ethanol); *m/e* 239 ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.56 (s, H<sub>5</sub> and H<sub>6</sub>), and Ph group 8.00 (m, H<sub>2</sub>- and H<sub>6</sub>-), 7.55 (m, H<sub>3</sub>- and H<sub>4</sub>- and H<sub>5</sub>-). Upon hydrolysis with 10% aqueous sodium hydroxide (1 h under reflux) compound 5 was transformed into the amino compound 7.

3-Aminopyrazolo[3,4-*b*]pyrazine 7 is a useful synthon and can be transformed into a stable diazo compound (13), mp 180 °C (dec) (from chloroform and petroleum ether); *m/e* 146 ( $M^+$ ) and  $\delta$  nmr (CDCl<sub>3</sub>) 8.31 and 8.41 (d, H<sub>5</sub> and H<sub>6</sub>, *J*<sub>5,6</sub> = 2.1 Hz). This compound, upon treatment with 48% aqueous hydrobromic acid, is converted in 84% yield into the 3-bromo compound (14), mp 278-281 °C (from ethanol); *m/e* 198 ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.63 (s, H<sub>5</sub> and H<sub>6</sub>). With hydroxylamine hydrochloride the diazo compound is transformed into the corresponding azide (15) in 91% yield, mp 163-165 °C (dec) (from ethanol); *m/e* 161 ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.43 and 8.50 (d, H<sub>5</sub> and H<sub>6</sub>, *J*<sub>5,6</sub> = 2.1 Hz). Upon irradiation ( $\lambda$  = 254 nm) of a methanolic solution of the diazo compound the parent bicycle (16) was obtained in 53% yield, mp 183-186 °C (sublimed at 150-160 °C/1.3 kPa) (lit.,<sup>1,6</sup> mp 198-200 °C); *m/e* ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.5 (s, H<sub>3</sub>), 8.57 and 8.63 (d, H<sub>5</sub> and H<sub>6</sub>, *J*<sub>5,6</sub> = 2.3 Hz).

The diazo compound coupled with 5,5-dimethylcyclohexane-1,3-dione to afford first the corresponding hydrazone (17) (or tautomeric form), mp 190-193 °C (cyclization is taking place at the mp) (from ethanol); *m/e* 286 ( $M^+$ ). The hydrazone, when heated in *N,N*-dimethylformamide, is transformed in 70% yield into a tetracyclic derivative (18), mp 213-216 °C (from ethanol); *m/e* 268 ( $M^+$ ). Contrary to the pyridine analog,<sup>13</sup> this tetracycle exists in solution in an equilibrium of both tautomeric forms 18a and 18b. In dimethyl sulphoxide the ratio is about 5:2 and in trifluoroacetic acid about 16:1, respectively.

There are only few representatives of the isoxazolo[4,5-*b*]pyrazine system<sup>14,15</sup> and they were prepared from the corresponding substituted isoxazoles. As shown above, the ortho amino function in the pyrazine ring can participate with the oxadiazolyl ring in the formation of a fused pyrazole. Therefore, we have anticipated that in the same manner a hydroxyl functional group may be involved in the formation of a fused isoxazolo ring. In fact, we were able to synthesize in this way the isoxazolo[4,5-*b*]pyrazine ring system as follows. The amidoxime 19 or its acetyl derivative (20) were transformed with DMFDMA into the bicyclic product (21), mp 130-132 °C (from methanol); *m/e* 191 ( $M^+$ ) and  $\delta$  nmr (DMSO-*d*<sub>6</sub>) 8.76 (s, CH) 8.59 and 8.73 (d, H<sub>5</sub> and H<sub>6</sub>, *J*<sub>5,6</sub> = 2.5 Hz), 5.16 (s, Me) 3.07 (s, Me). In addition, the oxadiazolo derivative (23) was isolated, mp 194-196 °C (from ethanol and *N,N*-dimethylformamide); *m/e* 164 ( $M^+$ ) and  $\delta$  nmr (CF<sub>3</sub>COOH) 9.12 (s, H<sub>5</sub>-), 7.78 and 7.98 (d, H<sub>5</sub> and H<sub>6</sub>, *J*<sub>5,6</sub> = 3.9 Hz). The amidoxime (19) afforded after short heating (5 min at 75 °C) with this reagent (DMFDMA) both products in 21% and 13% yield, respectively. On the other



hand, if the ratio of reactants was 1 : 2.7 and after heating a chloroform solution for 1.5 h under reflux, only the bicyclic product 21 was obtained in 68% yield. Similarly, the acetylated amidoxime (20) afforded under these conditions both products in low yield (6% of 21 and 28% of 23), the bicycle being the minor product. The formamidine (21 is easily transformed (1 min heating with 5% aqueous sodium hydroxide) into the corresponding amino derivative (22) in 39% yield, mp 207-208 °C (from ethanol); m/e 136 (M<sup>+</sup>) and  $\delta$  nmr (DMSO-d<sub>6</sub>) 8.58 and 8.68 (d, H<sub>5</sub> and H<sub>6</sub>, J<sub>5,6</sub> = 2.5 Hz). The amino compound is transformed with hot formic acid after 5 min into compound 23 (50% yield) together with a small amount of 3-cyanopyrazin-2-one, which becomes the only reaction product after prolonged treatment (3 h). The isoxazole part of the bicycle is also opened under the influence of acetic anhydride and from compound 22 the oxadiazolyl derivative 25 is obtained in 78% yield, mp 250-253 °C (dec) (from methanol); m/e 220 (M<sup>+</sup>) and  $\delta$  nmr (DMSO-d<sub>6</sub>) 8.77 and 8.91 (d, H<sub>5</sub> and H<sub>6</sub>, J<sub>5,6</sub> = 2.4 Hz), 2.71 (s, Me), 2.38 (s, COMe). This product is in turn obtained also by acetylation of 24 in 89% yield.

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