

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS  
OF 4-HYDROXY- AND 4-AMINOPYRANO[2,3-c]PYRAZOLES

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Abstract - A novel synthesis of pyrano[2,3-c]pyrazoles via the reaction of  $\beta$ -functional nitriles with 4- $\alpha$ -hydroxyethylene- and 4- $\alpha$ -aminoethylene-3-methyl-2-pyrazolin-5-one derivatives is reported.

As a part of our program directed for development of new procedures for the synthesis of azoles and fused azoles as potential CNS regulants and antimetabolites in purine biochemical reactions<sup>1,2</sup> we have, recently, reported a novel synthesis of pyranoazoles via reaction of 4-arylideneazolones with  $\beta$ -functional nitriles.<sup>3,4</sup> In continuation of this work we report here the results of our investigation on the reaction of the  $\beta$ -functional nitriles 1a-c with the 4- $\alpha$ -hydroxyethylene- and 4- $\alpha$ -aminoethylene-3-methyl-2-pyrazolin-5-one derivatives 2a-d. The synthesised compounds are interesting for biological activity studies and for utility in further chemical transformations.

Thus, in a typical procedure equimolecular amounts of the  $\beta$ -functional nitriles (20 mmol) and 2a-d are refluxed in pyridine (30 ml) for 2 h. Removal of pyridine followed by trituration with ethanol afforded either 1:1 adducts or condensation products depending on the nature of the activated nitrile derivative and on the nature of the pyrazolone. Thus, it has been found that 1a reacts with 2a,b to yield 1:1 adducts. Two theoretically possible structures were considered (cf. structures 3a,b and 4 and Table 1). Structure 4 was readily eliminated based on IR and <sup>1</sup>H NMR spectra. Thus, the IR spectra of the products revealed absorption bands characteristic for OH, NH<sub>2</sub>, CN and C=C groups. <sup>1</sup>H NMR revealed also two methyl signals, NH<sub>2</sub> and aromatic protons multiplet. These data can only be intelligibly interpreted in terms of structure 3. Similarly 1c reacted with 2a



to yield  $\underline{3c}$ .

In contrast to the behaviour of  $\underline{2a,b}$  toward malononitrile,  $\underline{2c,d}$  reacted with the same reagent to yield products of molecular formula corresponding to addition of  $\underline{1a}$  to  $\underline{2c,d}$  and ammonia elimination. Structure  $\underline{5}$  was established for these products based on spectral data. Thus the IR spectra of  $\underline{5a,b}$  revealed the absence of absorption for ring CO and showed absorption characteristic for C=NH, one conjugated CN group and NH (cf. Table 2). Moreover,  $^1\text{H}$  NMR of the products also afforded further evidence for the cyclic structure as it revealed the absence of any resonance for pyrazole H-4.

Similar to the behaviour of  $\underline{2a,b}$  toward  $\underline{1a}$  and in contrast to the behaviour of the enamino derivative  $\underline{2c}$ , compound  $\underline{1b}$  reacted with  $\underline{2c}$  to yield a 1:1 adduct for which structure  $\underline{3d}$  was assigned based on spectral data.

The formation of  $\underline{3a-c}$  or  $\underline{5a,b}$  from reaction of  $\underline{1a-c}$  with  $\underline{2a-d}$  is assumed to proceed via Michael addition of  $\underline{1}$  to the activated double bond of  $\underline{2}$ . Thus acyclic intermediate Michael adducts  $\underline{6}$  were obtained which then either cyclise into  $\underline{3}$  or loose ammonia (in case of  $\underline{2c,d}$  with  $\underline{1a}$ ) to yield the acyclic ylidene derivative  $\underline{7}$ . Cyclisation of  $\underline{7}$  afforded the final isolable products  $\underline{5a,b}$ .

Now the behaviour of several other hydroxyalkylidene- and aminoalkylideneazolones toward  $\underline{1a-c}$  as well as other activated nitriles is under investigation. Work in progress will be the subject of another communication.

Table 1: List of the pyrano[2,3-c]pyrazole derivatives  $\underline{3a-d}$  and  $\underline{5a,b}$ .

Compound*	Solvent of crist.	Colour	M.p. (°C)	Yield (%)	Mol. Formula
$\underline{3a}$	DMF/H <sub>2</sub> O	yellow	>300	65	C <sub>15</sub> H <sub>14</sub> O <sub>2</sub> N <sub>4</sub>
$\underline{3b}$	Acetone	yellow	>300	62	C <sub>11</sub> H <sub>12</sub> O <sub>3</sub> N <sub>4</sub>
$\underline{3c}$	DMF/H <sub>2</sub> O	brown	185	60	C <sub>21</sub> H <sub>19</sub> O <sub>3</sub> N <sub>3</sub>
$\underline{3d}$	Acetone	colourless	262	55	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub> N <sub>4</sub>
$\underline{5a}$	DMF/H <sub>2</sub> O	brown	165	72	C <sub>15</sub> H <sub>12</sub> ON <sub>4</sub>
$\underline{5b}$	DMF/H <sub>2</sub> O	yellow	>300	70	C <sub>11</sub> H <sub>10</sub> O <sub>2</sub> N <sub>4</sub>

\* Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

Table 2: IR and  $^1\text{H}$  NMR data of compounds  $\underline{3a-d}$  and  $\underline{5a,b}$ .

Comp.	IR, $\text{cm}^{-1}$	$^1\text{H}$ NMR(DMSO), $\delta$ ppm.
$\underline{3a}$	3470(OH); 3340, 3240( $\text{NH}_2$ ); 2220 (CN) and 1650(C=C and C=N).	2.2(t, 3H, $\text{CH}_3$ ); 2.4(t, 3H, $\text{CH}_3$ ); 4.5 (s, br, 2H, $\text{NH}_2$ ) and 7.0-7.7(aromatic and OH protons).
$\underline{3b}$	3350(OH); 3200( $\text{NH}_2$ ); 2220(CN); 1700(CO) and 1640(C=C and C=N).	1.9(s, 3H, $\text{CH}_3$ ); 2.0(s, 3H, $\text{CH}_3$ ); 2.2 (s, 3H, $\text{CH}_3$ ) and 3.0(s, br, 3H, $\text{NH}_2$ and OH).
$\underline{3c}^*$	3600-3400(OH); 3280( $\text{NH}_2$ ) and 1640(CO).	
$\underline{3d}^*$	3500-3400(chelated $\text{NH}_2$ ); 3080 ( $\text{NH}_2$ ); 1740(ester CO) and 1620 (C=C and C=N).	
$\underline{5a}$	3400, 3300, 3120(NH); 2220(CN) and 1640(C=N).	2.0(s, 3H, $\text{CH}_3$ ); 2.5(s, 3H, $\text{CH}_3$ ); 7.2~7.8(m, 5H, aromatic protons) and ~11.0(s, br, 1H, NH).
$\underline{5b}$	3300-3100(NH); 2220(CN) and 1650(CO).	2.0(s, 3H, $\text{CH}_3$ ); 2.1(s, 3H, $\text{CH}_3$ ); 2.2 (s, 3H, $\text{CH}_3$ ) and ~10.8(s, br, 1H, NH).

\* Compound is insoluble in all tested  $^1\text{H}$  NMR solvents.

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