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

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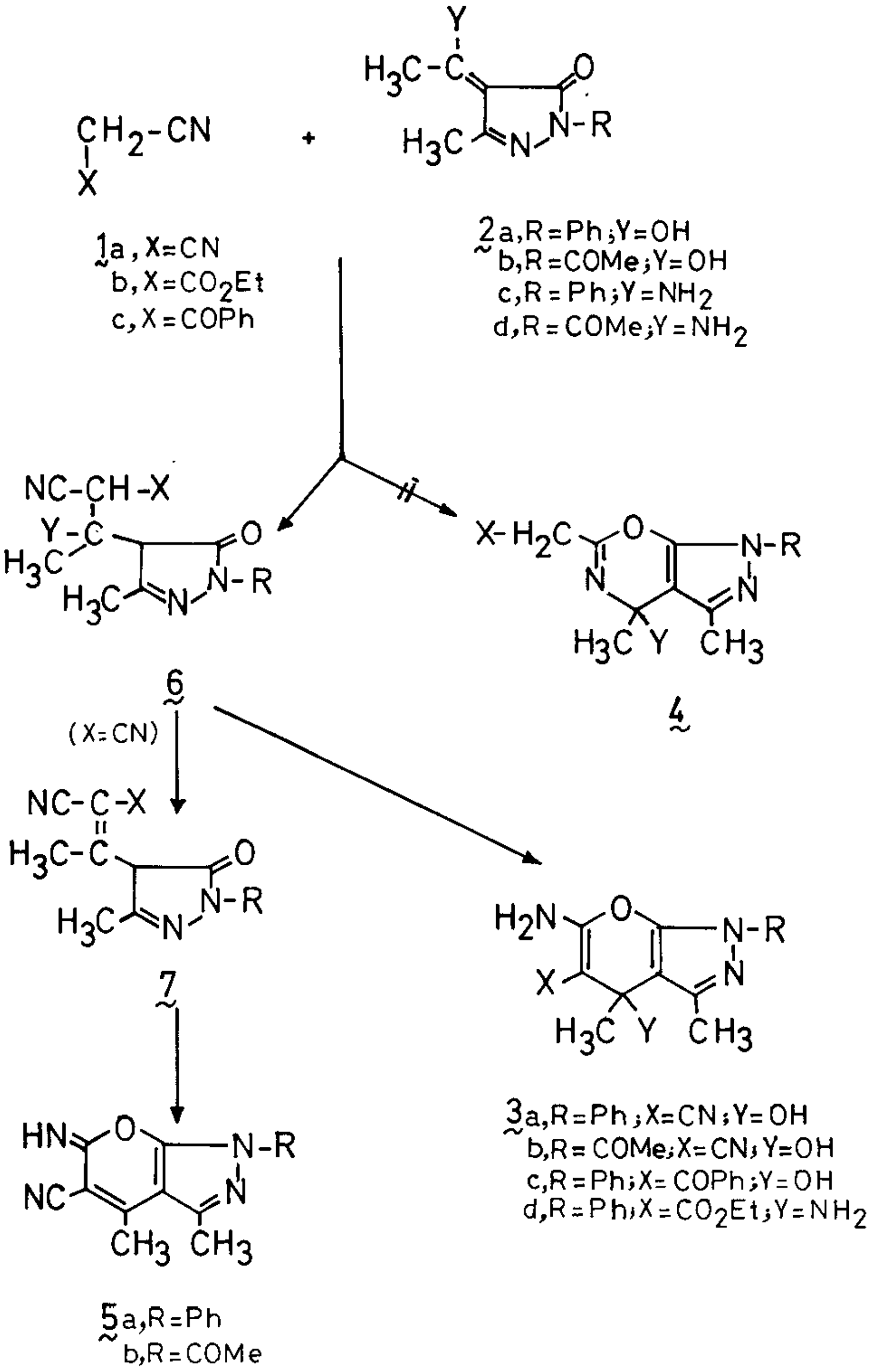
Abstract - A novel synthesis of pyrano[2,3-c] pyrazoles via the reaction of β-functional nitriles with 4-α-hydroxyethylene- and 4-α-aminoethylene-3-methyl-2-pyrazolin-5-one derivatives is reported.

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[1,2] we have, recently, reported a novel synthesis of pyranoazoles via reaction of 4-arylideneazolones with β-functional nitriles.[3,4] In continuation of this work we report here the results of our investigation on the reaction of the β-functional nitriles 1a-c with the 4-α-hydroxyethylene- and 4-α-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 β-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 ^{1}H NMR spectra. Thus, the IR spectra of the products revealed absorption bands characteristic for OH, NH_2, CN and C=C groups. ^{1}H NMR revealed also two methyl signals, NH_2 and aromatic protons multiplet. These data can only be intelligibly interpreted in terms of structure 3. Similarly 1c reacted with 2a


CH2-CN
X
+
Y
H3C-C
O
N-R
H3C
N
1a, X=CN
b, X=CO2Et
c, X=COPh
2a, R=Ph; Y=OH
b, R=COMe; Y=OH
c, R=Ph; Y=NH2
d, R=COMe; Y=NH2
NC-CH-X
Y-C
H3C
O
N-R
H3C
N
6
X-H2C
O
N-R
N
N
H3C Y CH3
4
(X=CN)
NC-C-X
H3C-C
O
N-R
H3C
N
7
H2N
O
N-R
X
N
H3C Y CH3
3a, R=Ph; X=CN; Y=OH
b, R=COMe; X=CN; Y=OH
c, R=Ph; X=COPh; Y=OH
d, R=Ph; X=CO2Et; Y=NH2
HN
O
N-R
NC
N
CH3 CH3
5a, R=Ph
b, R=COMe

to yield 3c.

In contrast to the behaviour of 2a,b toward malononitrile, 2c,d reacted with the same reagent to yield products of molecular formula corresponding to addition of 1a to 2c,d and ammonia elimination. Structure 5 was established for these products based on spectral data. Thus the IR spectra of 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}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 2a,b toward 1a and in contrast to the behaviour of the enamino derivative 2c, compound 1b reacted with 2c to yield a 1:1 adduct for which structure 3d was assigned based on spectral data.

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

Now the behaviour of several other hydroxyalkylidene-and aminoalkylideneazolones toward 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 3a-d and 5a,b.

Compound[•]	Solvent of cryst.	Colour	M.p. (^{o}C)	Yield (%)	Mol. Formula
3a	DMF/$H_2$0	yellow	>300	65	$C_{15}H_{14}O_2N_4$
3b	Acetone	yellow	>300	62	$C_{11}H_{12}O_3N_4$
3c	DMF/$H_2$0	brown	185	60	$C_{21}H_{19}O_3N_3$
3d	Acetone	colourless	262	55	$C_{17}H_{20}O_3N_4$
5a	DMF/$H_2$0	brown	165	72	$C_{15}H_{12}ON_4$
5b	DMF/$H_2$0	yellow	>300	70	$C_{11}H_{10}O_2N_4$

[•] Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

Table 2: IR and ^1H NMR data of compounds **3a-d** and **5a,b**.

Comp.	IR, cm^{-1}	^1H NMR(DMSO), δ ppm.
3a	3470(OH); 3340, 3240(NH_2); 2220 (CN) and 1650(C=C and C=N).	2.2(t, 3H, CH_3); 2.4(t, 3H, CH_3); 4.5 (s, br, 2H, NH_2) and 7.0-7.7(aromatic and OH protons).
3b	3350(OH); 3200(NH_2); 2220(CN); 1700(CO) and 1640(C=C and C=N).	1.9(s, 3H, CH_3); 2.0(s, 3H, CH_3); 2.2 (s, 3H, CH_3) and 3.0(s, br, 3H, NH_2 and OH).
3c*	3600-3400(OH); 3280(NH_2) and 1640(CO).	
3d*	3500-3400(chelated NH_2); 3080 (NH_2); 1740(ester CO) and 1620 (C=C and C=N).	
5a	3400, 3300, 3120(NH); 2220(CN) and 1640(C=N).	2.0(s, 3H, CH_3); 2.5(s, 3H, CH_3); 7.2 ~ 7.8(m, 5H, aromatic protons) and ~ 11.0(s, br, 1H, NH).
5b	3300-3100(NH); 2220(CN) and 1650(CO).	2.0(s, 3H, CH_3); 2.1(s, 3H, CH_3); 2.2 (s, 3H, CH_3) and ~10.8(s, br, 1H, NH).

* Compound is insoluble in all tested ^1H NMR solvents.

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