REACTIONS WITH ACTIVATED NITRILES: SOME NEW APPROACHES FOR THE SYNTHESIS OF PYRIDINE DERIVATIVES

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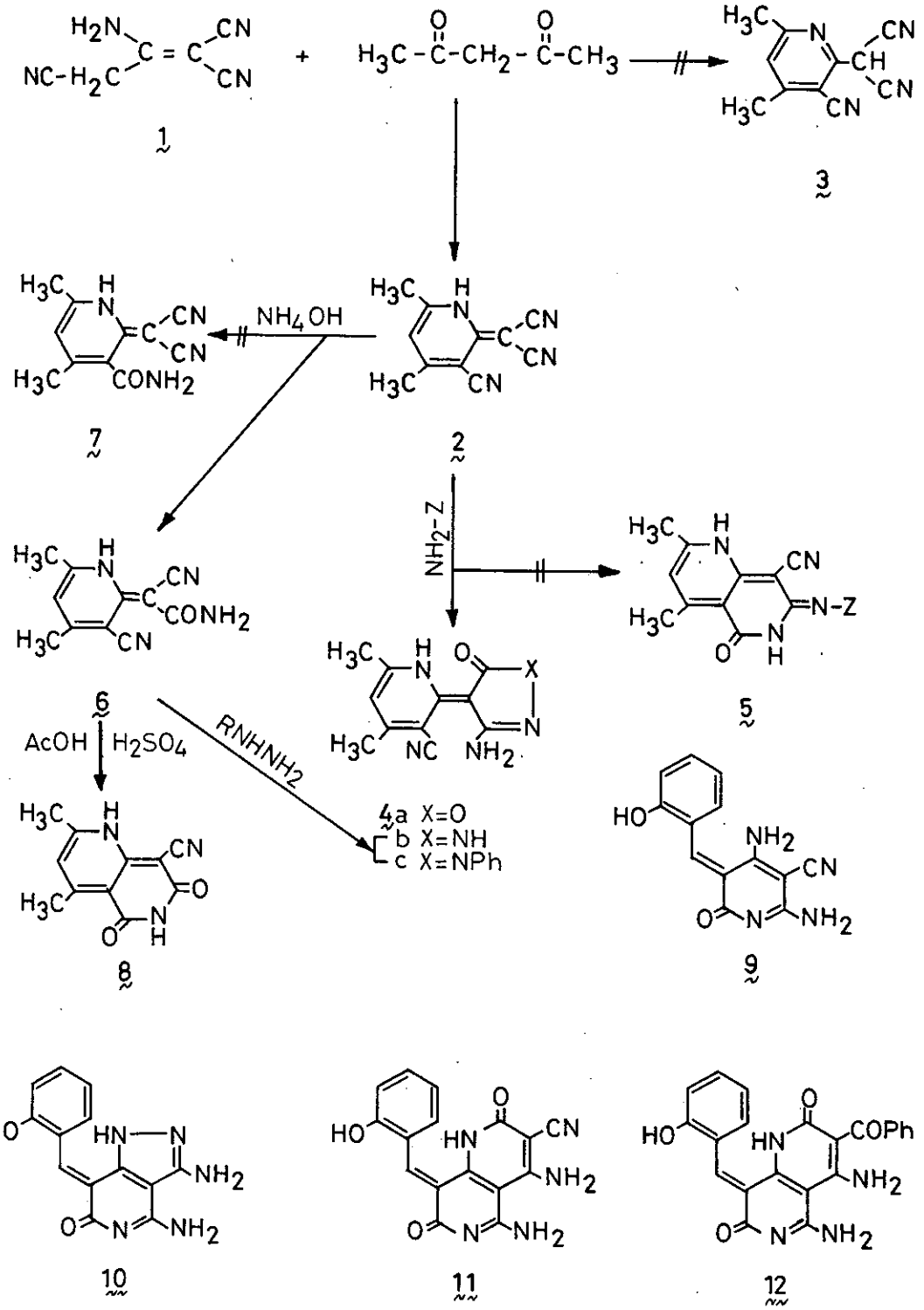
Abstract - The reaction of 2-amino-1,1,3-tricyanopropene (1) with acetylacetone and with salicylaldehyde gave the pyridine derivatives 2 and 9, respectively. Compounds 2 and 9 were transformed into pyridine derivatives 4 and pyrazolo[4,3-c]pyridine derivative 10 on treatment with hydrazines. 9 reacted with malononitrile and benzoylacetonitrile to give the pyrido[3,2-c]pyridine derivatives 11 and 12, respectively. The structures of the isolated products were established by the results of elemental analyses and IR and ^{1}H NMR spectral data.

Polyfunctional nitriles are versatile reagents and their utility in heterocyclic synthesis has received considerable attention. Previously, we have reported several new syntheses of azoles, fused azoles and azines utilising laboratory available activated nitrile derivatives as starting materials.[1-4] In the present work we report on the utility of the readily obtainable 2-amino-1,1,3-tricyanopropene (1) for the synthesis of several polyfunctional pyridine derivatives. The obtained products bear several functional substituents and appear promising for further chemical transformations and also for biological activity studies. Thus, it has been found that a solution of equimolecular amounts of 1 and acetylacetone in ethanol was refluxed for 2 h in the presence of piperidine as a catalyst to yield a product of molecular formula $C_{11}H_8N_4$. Two possible structures, 3-cyano-2-dicyanomethylene-4,6-dimethyl-1,2-dihydropyridine (2) and isomeric 3, were considered. Structure 2 was established by the results of IR spectrum which revealed absorption bands for NH and three different CN groups. If this compound is 3 it would be difficult to rationalize for the NH band. Also it may be anticipated that the two cyano bands at the dicyanomethyl substituent would be identical.


NH4OH
AcOH
H2SO4
RNHNH2
NH2-Z
4a X=O
b X=NH
c X=NPh

Compound 2 (0.01 mol) reacted with hydroxylamine and hydrazines (0.01 mol) (heating on a water bath for 1 h) to yield products which may be formulated as 4a-c or 5a-c. Structure 4 could be established for the products based on their stability toward the action of conc. H_2SO_4, a condition reported to effect cyclization of α-cyanoamidoximes and α-cyanohydrazones into the corresponding isoxazoles and pyrazoles.[4]

Compound 2 (1 g) reacted with ammonium hydroxide (20-21.5%, 5 ml, heating on a water bath for 30 min and the solid obtained on cooling was filtered, and washed with dil. HCl and then with water) to yield a product which may be 3-cyano-2-(carboxamidocyano)methylene-4,6-dimethyl-1,2-dihydropyridine (6) or isomeric 7. Structure 6 could be established for the reaction product based on its ready conversion into the pyrazole derivatives 4b,c on treatment with hydrazine hydrate and with phenylhydrazine, respectively. Several geometrical isomers for compound 6 are possible. However, compound 6 was established to exist in the E conformation based on its ready cyclization into 3-cyano-5,7-dimethyl-1,2,4,8-tetrahydropyrido[4,3-b]-pyridine-2,8-dione (8). Thus, compound 6 (1 g) when heated with conc. H_2SO_4 (2 ml) and glacial acetic acid (10 ml) at 100°C (bath temperature) for 1 h afforded a product which was identified as 8 based on the results of elemental analysis and spectral data.

In a previous paper[1] we have reported that the reaction of 1 with salicylaldehyde afforded, in contrast to literature reports[5], 3-cyano-2,4-diamino-5-salicylidene-5,6-dihydropyridin-6-one (9) which was established to exist in the conformation shown in Chart. In order to confirm further this structure we have extended our investigation to study the behaviour of 9 toward a variety of reagents. Thus, it has been found that a mixture of 9 (0.01 mol) and hydrazine hydrate (0.01 mol) in DMF (20 ml) was refluxed for 2 h and was concentrated in vacuo to give 3,4-diamino-7-salicylidene-1,6,7-trihydropyrazolo[4,3-c]pyridin-6-one (10).

Compound 9 (0.01 mol) reacted also with malononitrile (0.01 mol) and with benzoylacetonitrile (0.01 mol) in DMF (20 ml) under reflux for 2 h in the presence of piperidine (1 ml) to yield 3-cyano- and 3-benzoyl-4,5-diamino-1,2,7,8-tetrahydropyrido[3,2-c]pyridines 11 and 12, respectively. The structures of the obtained products were established by the results of elemental analyses and IR and ^{1}H NMR spectral data (cf. Table 2).

Compounds 10-12 were considered to exist in the conformations shown in Chart as they were derived from the E form of 9.

Table 1: List of the pyridine derivatives 2, 4a-c, 6, 8, 10, 11 and 12.

Compound*	Solvent of cryst.	Colour	M.p. (°C)	Yield (%)	Mol. Formula
2	$CHCl_3$/EtOH	greenish-yellow	271	75	$C_{11}H_8N_4$
4a	EtOH	yellow	255	90	$C_{11}H_{10}O_2N_4$
4b	$CHCl_3$/EtOH	yellow	295	85	$C_{11}H_{11}ON_5$
4c	$CHCl_3$/EtOH	brick red	127	70	$C_{17}H_{15}ON_5$
6	EtOH	yellow	280	90	$C_{11}H_{10}ON_4$
8	EtOH	brown	>300	60	$C_{11}H_9O_2N_3$
10	DMF/H_2O	reddish-brown	235	60	$C_{13}H_{11}O_2N_5$
11	DMF/H_2O	pale yellow	246	70	$C_{16}H_{11}O_3N_5$
12	DMF/H_2O	brownish-yellow	218	55	$C_{22}H_{16}O_4N_4$

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

Table 2: IR and ^1H NMR data.

Comp.	IR, cm^{-1}	^1H NMR(DMSO, EM-360 60 MHz), δ ppm.
2	3320(NH); 2230, 2210, 2190(three CN) and 1630(C=C).	2.1(s, 3H, CH_3); 2.17(s, 3H, CH_3); 5.0 (s, br, 1H, NH) and 6.7(s, 1H, pyridine-CH).
4a	3390, 3375, 3325(NH_2 and NH); 2230(CN); 1650(ring CO) and 1610 (C=N).	2.5(s, 3H, CH_3); 2.46(s, 3H, CH_3); 3.33(s, br, 2H, NH_2); 6.9(pyridine-CH) and 8.0(s, br, 1H, NH).
4b	3390, 3370, 3320(NH_2 and NH); 2220(CN); 1650(ring CO) and 1610 (C=N).	2.33(s, 3H, CH_3); 2.46(s, 3H, CH_3); 3.33(s, br, 2H, NH_2); 6.66(s, 1H, pyridine-CH) and 7.8(s, 2H, two NH).
4c	3390, 3365, 3320(NH_2 and NH); 2225(CN); 1660(ring CO) and 1610 (C=N).	2.17(s, 3H, CH_3); 2.7(s, 3H, CH_3); 3.5 (s, br, 2H, NH_2); 6.37(s, 1H, pyridine-CH); 6.66~7.7(m, 5H, aromatic protons) and 7.9(s, br, 1H, NH).

Table 2; Contd.

Comp.	IR, cm^{-1}	^1H NMR, δ ppm.
6	3395, 3380, 3320(NH_2 and NH); 2235, 2220(two CN); 1690(CO) and 1610(C=N).	2.25(s, 3H, CH_3); 2.42(s, 3H, CH_3); 3.5 (s, br, 2H, NH_2); 4.65(s, 1H, pyridine-CH) and 6.2(s, br, 1H, NH).
8	3350(NH); 2225(CN); 1660(ring CO) and 1610(C=C).	2.33(s, 3H, CH_3); 2.46(s, 3H, CH_3); 3.4 (s, br, 2H, two NH) and 6.66(s, 1H, pyridine-CH).
10*	3480(OH); 3365, 3350, 3320, 3120 (NH_2 groups); 1670~1640(ring CO and δNH_2) and 1605(C=N).	
11*	3500(OH); 3380, 3365, 3300, 3150 (NH_2 groups); 2210(CN); 1660 ~ 1620(ring CO and δNH_2)and 1610 (C=N).	
12	3490(OH); 3370, 3355, 3290, 3100 (NH_2 groups); 1655 ~1630(ring CO and δNH_2) and 1605(C=N).	4.2(s, br, 1H, NH); 7.15(m, 5H, aromatic protons) and 8.6(m. 10H, aromatic, two NH_2, vinylic and OH protons).

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

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