NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRIDAZINE DERIVATIVES

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Abstract — The crotononitriles 1a-c coupled with aryldiazonium salts to yield either the acyclic hydrazones or azahydrazones depending on coupling reaction conditions. Both hydrazones and azodrazones could be cyclized to the corresponding pyridazine derivatives. Direct formation of pyridazines on coupling 1b and 1c with aryldiazonium salts was observed. Structures of reaction products are confirmed by spectral and analytical data.

Nitriles are versatile reagents and their utulity in organic synthesis is now receiving considerable interest.[1-3] In the last few years we have been involved in a program aiming to develop new efficient procedures for the synthesis of polyfunctionally substituted heterocycles utilizing simple laboratory available functionally substituted nitriles as starting materials.[4-6] As a part of this work we have investigated the possible utility of propenenitrile derivatives 1a-c for synthesis of pyridazines. Although it has been reported[7] that 1a does not couple with aromatic diazonium salts we have found that 1a-c coupled readily with aryldiazonium salts under our conditions. The nature of the coupling products was found to be dependent on the applied coupling reaction conditions and the nature of the substituents on 1. Thus, 1a (0.01 mole) coupled with aryldiazonium salts (prepared from 0.02 mole of the aromatic amine and the appropiate amounts of hydrochloric acid and sodium nitrite) in ethanol (30 ml) containing 6.0 g of sodium acetate, utilizing previously reported coupling procedure,[8] to yield brown coupling products. ^{13}C-NMR of these products revealed that they are the acyclic azahydrazones 2a,b and not the isomeric 3a,b as they revealed signals for two C=N carbons. When 2a,b (0.01 mole) were refluxed for 2 h in aqueous acetic acid (30 ml, 70 %), the pyridazin-6-ones (4a,b) were obtained in slmost quantitative yields. The formation of 4 is assumed to be formed via intermediacy of the imines 3 which, however, could not be isolated. Compounds 4a,b were also formed on coupling 1b (0.01 mole) with aryldiazonium salts (0.02 mole) in ethanolic sodium acetate.

Again the arylhydrazones (5a,b) are the assumed reaction intermediates which could not be isolated in a pure form.

In contrast to the behaviour of 1a towards aryldiazonium salts in ethanolic sodium acetate solutions, 1a (0.01 mole) coupled with aryldiazonium salts (0.01 mole) in acetic acid (30 ml) and in the presence of sodium acetate (5.0 g) to yield the hydrazones 6a,b which afforded the pyridazin-6-imine (7a,b) on heating above their melting points. Compounds 6a,b (0.01 mole) could be converted into 2a,b on coupling with aryldiazonium salts (0.01 mole) in ethanolic sodium acetate solutions.

Compound (1c; 0.01 mole) was also coupled with aryldiazonium salt (0.01 mole) to yield hydrazones which could not be isolated in pure form but the pyridazin-6-imines (8a,b) were isolated on short reflux (1h) of the hydrazones in acetic acid (30 ml).

The formation of hydrazones on coupling of 1a,b with aryldiazonium salts finds a parallism to the reported[9,10] readily coupling of 1d-f with aryldiazonium salts and the cyclization of the formed coupling products. The results, however, reveal the presence of electron withdrawing substituent on the methyl group in 1 which is not necessarily for coupling reaction to take place as has been recently reported.[11] The methyl group adjacent to activated double bond with two cyano or cyano and ester function on the β-carbon is sufficiently acidic to react with aryldiazonium salts.

Although 1d was reported[11] to afford 9 on coupling with benzenediazonium salt and cyclization of the formed hydrazone, trials to repeat these results in our laboratories revealed that this synthetic route is highly unefficient as 1d is obtainable only in low yield and dimerises quickly on storage. Thus we developed more efficient synthesis of 9 via heating equimolecular amounts of 10 with ethyl cyanoacetate in presence of ammonium acetate at 160°C (bath T.) for 2h.

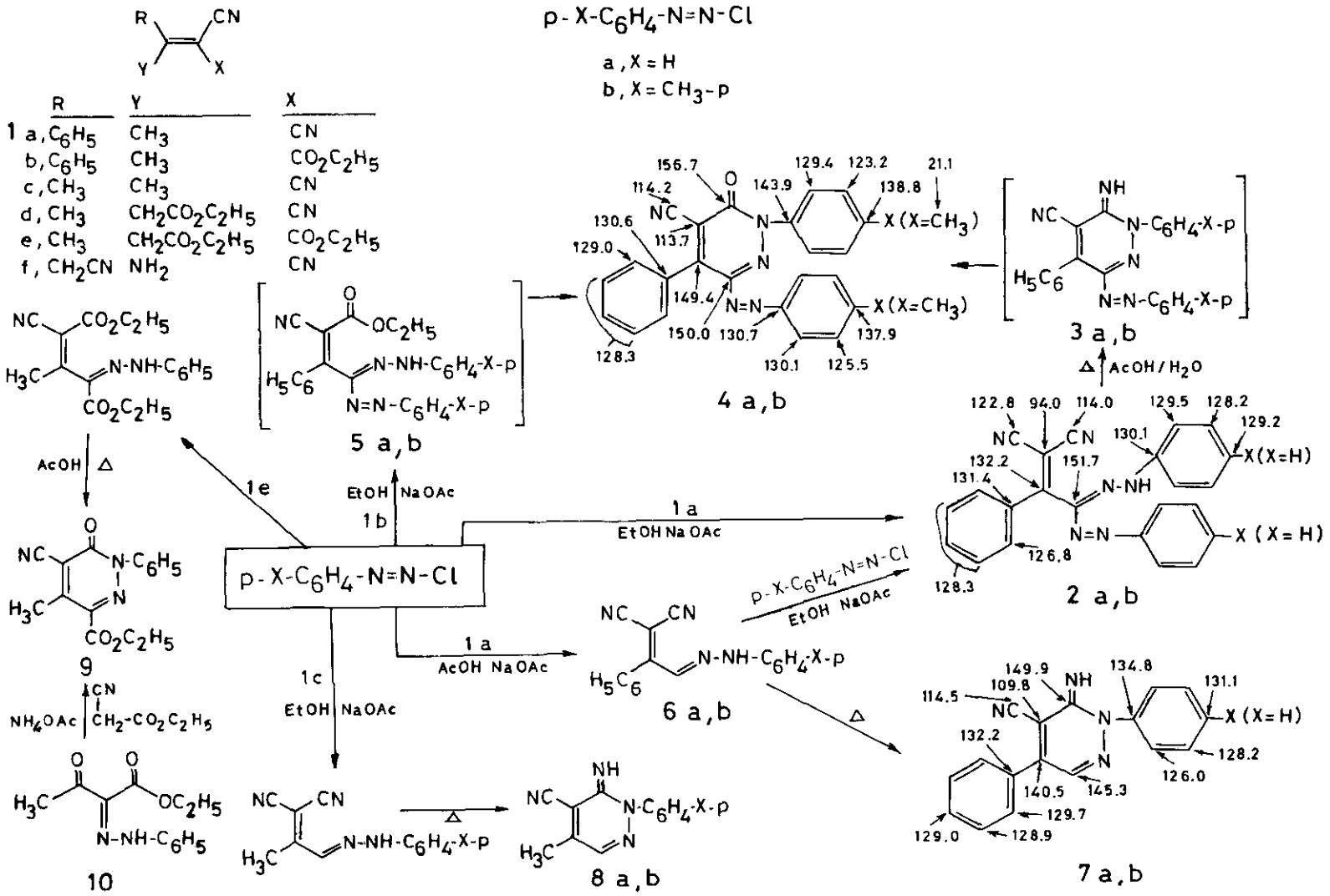
R
CN
Y
X
p-X-C6H4-N=N-Cl
a, X = H
b, X = CH3-p
R Y X
1 a, C6H5 CH3 CN
b, C6H5 CH3 CO2C2H5
c, CH3 CH3 CN
d, CH3 CH2CO2C2H5 CN
e, CH3 CH2CO2C2H5 CO2C2H5
f, CH2CN NH2 CN
5 a,b
4 a,b
3 a,b
AcOH / H2O
AcOH Δ
1e
EtOH NaOAc
1b
1a
EtOH Na OAc
p-X-C6H4-N=N-Cl
1a
AcOH NaOAc
p-X-C6H4-N=N-Cl
EtOH NaOAc
1c
EtOH NaOAc
9
NH4OAc
CH2-CO2C2H5
10
6 a,b
2 a,b
8 a,b
7 a,b

Table: List of compounds newly synthesized.

Compound*	Solvent	Colour	Mp (°C)	Yield (%)	Mol Formula
2a	ethanol	brown	205	70	$C_{23}H_{16}N_6$
2b	ethanol	brown	197	78	$C_{25}H_{20}N_6$
4a	acetic acid	red	240	80	$C_{23}H_{15}N_5O$
4b	acetic acid	red	230	82	$C_{25}H_{19}N_5O$
6a	acetic acid	red	135	50	$C_{17}H_{12}N_4$
6b	acetic acid	red	155	60	$C_{18}H_{14}N_4$
7a	ethanol	orange	173	80	$C_{17}H_{12}N_4$
7b	ethanol	orange	150	80	$C_{18}H_{14}N_4$
8a	acetic acid	red	117	60	$C_{12}H_{10}N_4$
8b	acetic acid	red	120	70	$C_{13}H_{12}N_4$
9	acetic acid	colourless	150	80	$C_{15}H_{13}N_3O_3$

*Satisfactory elemental analyses, IR, ^{1}H-NMR and mass spectra for all the newly synthesized compounds were obtained.

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