ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS : NOVEL SYNTHESIS OF PYRIDAZINES, PYRIDINES, PYRAZOLES AND POLYFUNCTIONALLY SUBSTITUTED BENZENE DERIVATIVES

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Abstract- Knoevenagel condensation of benzoylacetonitrile with malononitrile afforded the corresponding ylidene derivative which could be converted into pyridazine derivative on coupling with benzenediazonium chloride and cyclization. Similarly benzoylacetonitrile underwent self condensation to yield either the benzene derivative or the ylidene derivative. The latter could be converted into a variety of heterocyclic derivatives on reaction with malononitrile, ethyl cyanoacetate, hydrazine hydrate and benzenediazonium chloride.

Polyfunctionally substituted nitriles are highly reactive reagents that have been extensively utilised in heterocyclic synthesis[1,2]. Recently we have reported that phenacyl thiocyanate undergoes Knoevenagel condensation with malononitrile and ethyl cyanoacetate[4] to yield thiocyanatophenacylidenemalononitrile and thiocyanatophenacylidenecyanoacetate derivatives which were converted into a variety of otherwise not readily accessible, polyfunctional heterocycles. We have been interested to see if such Knoevenagel condensations can be effected with 3-oxoalkanonitriles as the condensation products looked to be very useful in heterocyclic synthesis. It has been found that benzoylacetonitrile 1 (0.1 mole) reacts with malononitrile (0.1 mole) when refluxed in pyridine (100 ml) for 3 h followed by dilution with water to yield the condensation product 2. Structure of 2 was supported by spectral data and by its chemical reactivity. Thus, 2 coupled with benzenediazonium chloride in ethanolic sodium acetate to yield the corresponding hydrazone 3 (or its possible tautomers). Compound 3 cyclized on reflux in acetic acid for 2 h to yield the pyridazine-6-imine derivative 4. Structure 4 finds support from IR spectrum which revealed C=N absorption at 1660 cm^{-1} similar to that reported to

pyridazine-6-imine[5] and from follow of the MS fragmentation pattern. Benzoylacetonitrile 1 underwent self condensation on boiling in pyridine to yield a product of molecular formula $C_{27}H_{17}N_3O$ (M^+=399). Two isomeric structures seemed possible (cf. structures 5 and 6). Structure 6 was established for the reaction product based on its inactivity toward reagents expected to effect ready condensation with 5 (eg. hydrazines, hydroxylamine)[6]. Further support for the proposed structure was obtained from spectral data (IR and MS) which can be only intelligably interpreted in terms of structure 6.

Compound 1 (0.1 mol) could be successfully dimerized when heated at 120°C in presence of ammonium acetate (0.1 mol) or cyanoacetamide (0.15 mol). Several tautomeric forms seemed possible for the reaction product. However, spectral data revealed that it exists in solid state and in solutions in the dienol form 8. Thus, IR revealed two highly conjugated CN bands and the absence of absorption of CO or C=NH group and the presence of OH absorption which excludes other tautomeric forms (cf. 7 and 9). ^{1}H NMR also revealed a pattern that can only be interpreted in terms of structure 7. Compound 7 could be converted into a variety of novel heterocycles. Thus, it coupled with benzenediazonium chloride to yield the hydrazone 10 which could be cyclized into 11 on reflux in acetic acid. Compound 11 could be directly obtained via heating equimolecular amounts of phenylhydrazonobenzoylacetonitrile 14 with benzoylacetonitrile and ammonium acetate at 150°C for 30 min. When 7 (0.1 mol) was refluxed with malononitrile (0.1 mol) in pyridine (30 ml) the products which can be formulated as 12a or isomeric 13a were obtained. The pyridine structure 13a was ruled out as the molecule failed to couple with aromatic diazonium salts in contrast to expected behaviour of compounds of similar structure[7-9]. This finds parallelism to the reported formation of pyranes on treatment of 1 with malononitrile via condensation of malononitrile with 1 and subsequent addition of 1 to the double bond[10]. Moreover, the reaction product underwent readily ring opening on reflux in alkaline solutions. Compound 7 reacted with hydrazines in refluxing ethanol to yield amidrazone 15 which could be cyclized on boiling in DMF into the pyrazole derivative 16. Structure 16 was based on ^{1}H NMR. Compound 16 could not be cyclized into a pyrazolopyridine derivative under a variety of conditions expected to effect such cylization. This leads to the conclusion that it exists in the form presented in which CN group is trans to the amino group.

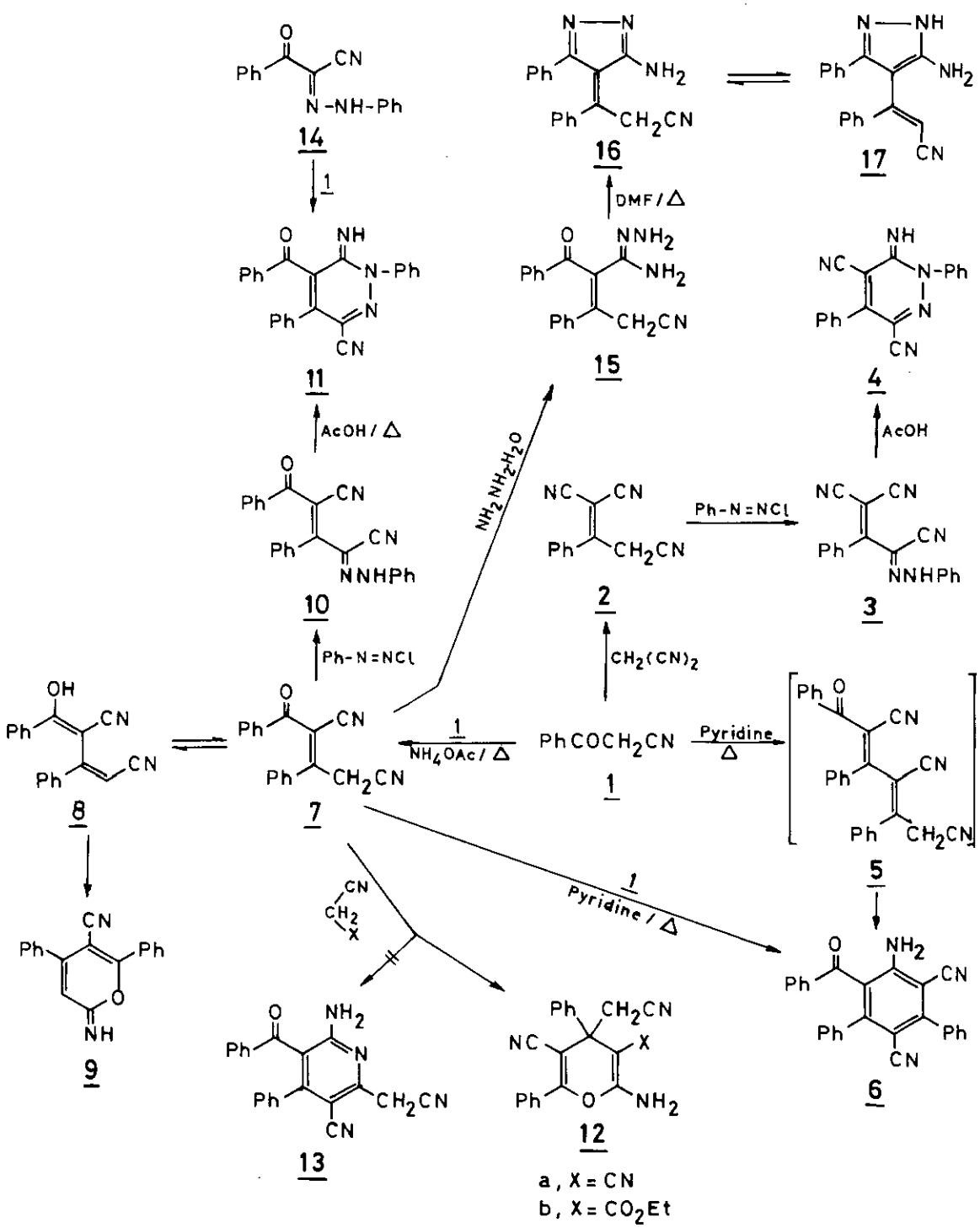
14
1
11
AcOH / Δ
10
Ph-N=NCl
NH2NH2H2O
16
DMF / Δ
15
17
4
AcOH
2
Ph-N=NCl
3
CH2(CN)2
1
1
NH4OAc / Δ
Pyridine
Δ
8
7
5
1
Pyridine / Δ
9
6
13
12
a, X = CN
b, X = CO2Et

Table 1 : List of compounds 2, 3, 4, 6, 7, 10, 11, 12a,b, 15 and 16

Compound*	Solvent of cryst.	Colour	MP (°C)	Yield %	IR $\lvert cm^{-1} \rvert$ (Selected bands)
2+1	MeOH	brown	80	65	2200, 2210, 2220 (3 CN); 1650 (C = N).
3+2	MeOH	yellow	200	80	3300 (NH); 2150, 2220 (CN); 1620 (C = N and δ NH).
4+3	MeOH	yellow	250	75	3400 (NH); 2220, 2230 (CN); 1660 (C = N); 1610 (δ NH).
6+4	EtOH	yellow	285	85	3350 (NH_2); 2220, 2225 (2 CN); 1680 (CO); 1630 (C = N and δ NH_2).
7	DMF	yellow	282	60	2190, 2210 (2 CN); 1650 (CO).
10	EtOH	brown	195	85	3500 (NH); 2190, 2210 (2 CN); 1600 (C = N and δ NH).
11	EtOH	brown	230	70	3400, 3280 (NH); 2220 (CN); 1660 (C = N); 1610 (δ NH).
12a	EtOH	brown	190	50	3400, 3280 (NH_2); 2220, 2200 (CN); 1620 (C = N and δ NH_2).
12b	EtOH	brown	223	50	3380, 3180 (NH_2); 2210, 2200 (CN): 1670 (CO); 1620 (C = N and δ NH_2).
15	EtOH/ Dioxan	brown	180	55	3400 (NH and NH_2); 2210 (CN); 1590 (C = N, δNH and δ NH_2).
16	DMF	brown	228	50	3500 ~ 3400 (NH and NH_2); 2225 (CN); 1595 (C = N δ NH and δ NH_2).

* Satisfactory elemental analysis for all the newly synthesized compounds were obtained.

\+ 1, M^+ = 193; 2 , M^+ = 297; 3, M^+ = 297; 4, M^+ = 399.

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