THE CHEMISTRY AND SYNTHETIC POTENTIALITIES OF β-KETOANILIDES: REACTION OF ETHYL CYANOACETATE WITH β-KETOANILIDES

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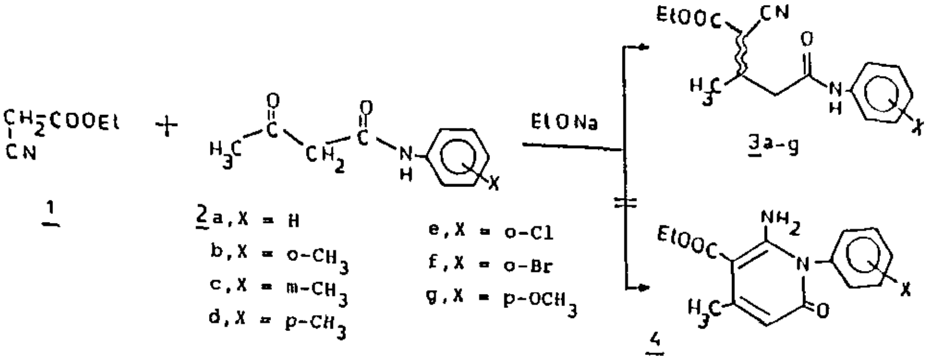
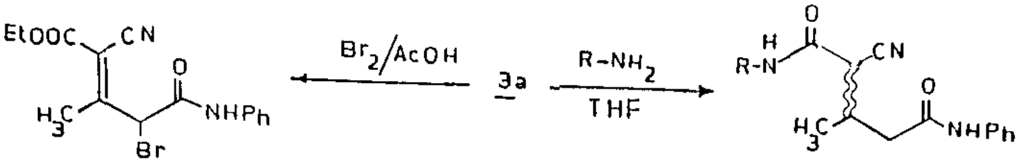
Abstract- Ethyl cyanoacetate reacts with β-ketoanilides 2a-g to give the simple Knoevenagel condensation products 3a-g. The reactivity of 3a towards a variety of chemical reagents was studied to give, in most cases, polyfunctionally substituted pyridine derivatives.

β-Ketoanilides are versatile reagents reported to react with activated nitriles to afford a variety of polyfunctionally substituted heterocycles and fused heterocyclic derivatives[1-3]. In previous publications, β-Ketoanilides were reported to react with malononitrile to afford the simple Knoevenagel condensation products together with pyridine derivatives[4,5]. In our laboratories, ethyl cyanoacetate (1) reacts with β-ketoanilides 2a-g under reflux in sodium ethoxide to afford readily, in each case, one separable product to which the Knoevenagel condensation products 3a-g and not the pyridine derivatives 4 were assigned based on elemental analyses as well as the spectral data. Thus, for example, analytical data of compound 3a analyzed for $C_{15}H_{16}N_2O_3$ ($M^+= 272$). ^1H NMR spectrum of 3a revealed the presence of a



singlet at δ 4.67(2H)ppm which corresponds to the non-coupled methylene protons and one D_2O exchangeable proton at δ 9.11(1H)ppm assigned for the NH proton. Also it shows a multiplet at δ 7.3-7.6(5H)ppm assigned for the phenyl protons, quartet at δ 4.12(2H)ppm as well as triplet at δ 1.71(3H)ppm assigned for the $-CH_2CH_3$ ester group. Further confirmation of the assigned structure 3a-g as well as its chemical reactivity has investigated through studying the behaviour of 3a towards some chemical reagents. Thus, 3a reacts with bromine in glacial acetic acid at room temperature to afford the α-bromoanilide derivative 5. On the other hand, compounds 6a,b were isolated in good yields on reacting 3a with aniline in refluxed ethanol and with phenylhydrazine in ethanol at room temperature respectively.



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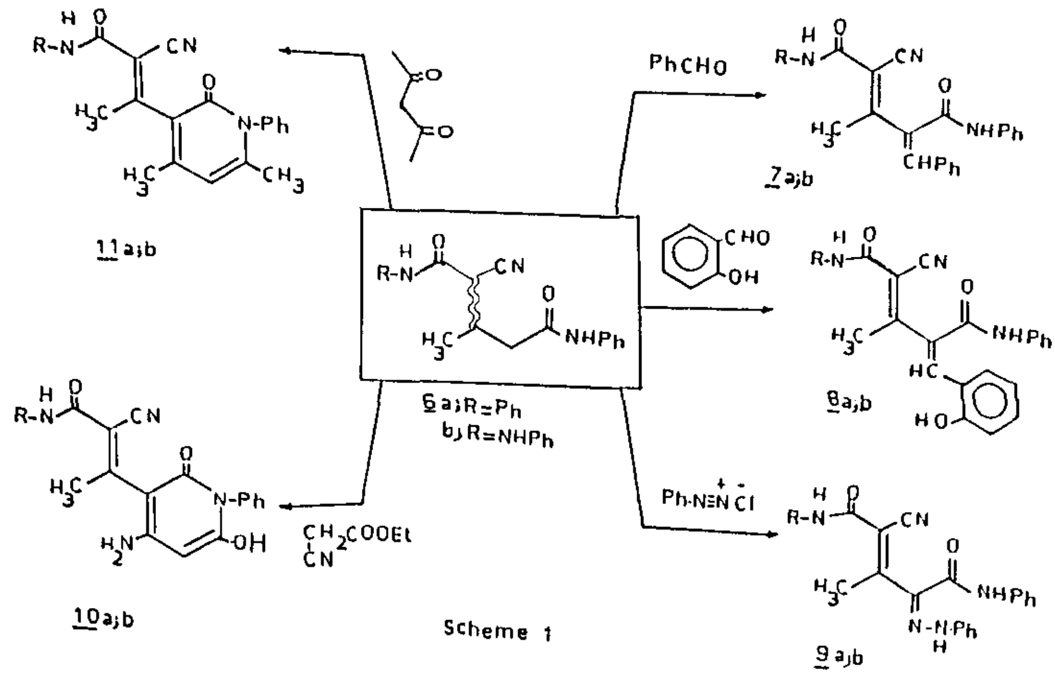
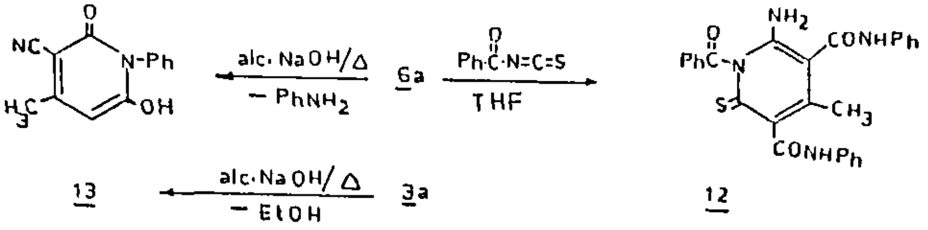
6a; R = Ph
b; R = NHPh

Next, the potential utilities and limitations of 6a,b for building up pyridine derivatives have been investigated. Thus, it has been found that 6a,b condensate with benzaldehyde and salicyaldehyde to afford the acyclic arylidene derivatives 7a,b and 8a,b respectively. However, our trials to cyclize 8a,b were unsuccessful. Compounds 6a,b coupled with equimolar amounts of benzenediazonium chloride in alkaline medium (pH=8) to yield the phenylhydrazone derivatives 9a,b respectively (cf. Scheme 1). On the other hand, compounds 6a,b were found to react with ethyl cyanoacetate in an oil bath at 140°C in presence of a catalytic amount of piperidine to afford 6-hydroxy-N-phenylpyridine-2-one derivatives 10a,b, based on their IR spectra which revealed the presence of the characteristic OH stretching band at 3600-3450 cm^{-1}. Formation of 10a,b were assumed to proceed via addition of the active methylene hydrogens of 6a,b to the cyano function of 1 followed by ethanol elimination. Similarly, compounds 6a,b reacted with acetylacetone under the same conditions to afford the corresponding N-phenylpyridine-2-one derivatives 11a,b which are in agreement with their analytical and spectral data (cf. Scheme 1).



Scheme 1

The difference in chemical reactivities of 6a and 6b towards some chemical reagents was also undertaken. Thus, 6a reacts with benzoyl isothiocyanate in refluxed sodium ethoxide-THF mixture to yield the pyridine derivative 12. Also 6a undergoes ready cyclization, in refluxed ethanolic-sodium hydroxide solution, into 6-hydroxy-N-phenylpyridine-2-one derivative 13, via loss of aniline. Compound 13 shows the characteristic OH strectching band at 3600-3450 cm^{-1} in its IR spectrum. Such pyridine derivative 13 was also obtained on boiling 3a, under the same condition, via loss of ethanol (both have the same finger print IR spectrum).



On the other hand, compound 6b reacts with malononitrile in an oil bath (140°C) and in presence of catalytic amount of piperidine to afford a product analyzed for $C_{20}H_{19}N_6O_2$. Two possible isomeric structures 14 and 15 were considered. However, the pyridine structure 14 was assigned for the reaction product based on ^1H NMR spectrum which reveals the presence of two D_2O exchangeable singlet signals at 4.68(2H)ppm and 5.23(2H)ppm corresponding to two NH_2 groups. Also, compound 6b reacts with trichloroacetonitrile in refluxed ethanol to afford the pyridine derivative 16. This is assumed to proceed via nucleophilic substitution of the trichloromethyl moiety by the ethoxide ion.

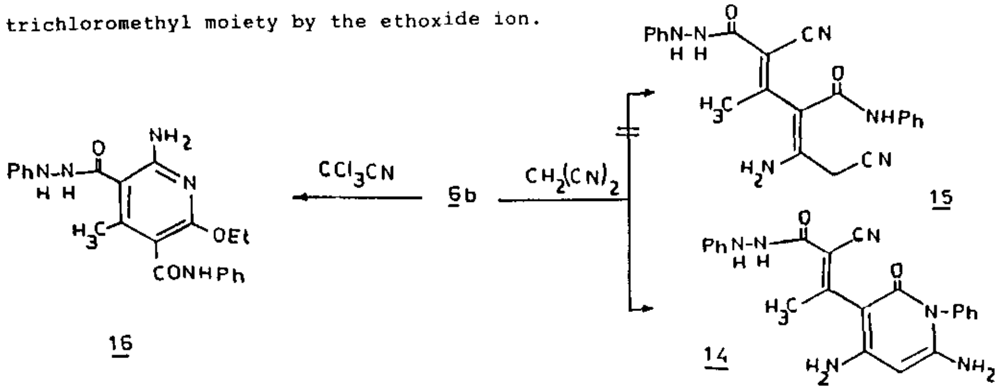


Table 1: List of compounds 3a-g, 5, 6a,b, 7a,b, 8a,b, 9a,b, 10a,b, 12, 13, 14 and 16 prepared.

Compd.*	Mp. (°C)	Yield (%)	Mol.Formul.	Compd*	Mp. (°C)	Yield (%)	Mol. Fromul.
3a	>300	82	$C_{15}H_{16}N_2O_3$	8a	190-1	79	$C_{26}H_{21}N_3O_3$
3b	175	79	$C_{16}H_{18}N_2O_3$	8b	150	75	$C_{26}H_{22}N_4O_3$
3c	186	80	$C_{16}H_{18}N_2O_3$	9a	115-6	75	$C_{25}H_{21}N_5O_2$
3d	205	81	$C_{16}H_{18}N_2O_3$	9b	263	71	$C_{25}H_{22}N_6O_2$
3e	160	77	$C_{15}H_{15}N_2O_3Cl$	10a	>300	69	$C_{22}H_{18}N_4O_3$
3f	270	79	$C_{15}H_{15}N_2O_3Br$	10b	>300	65	$C_{22}H_{19}N_5O_3$
3g	235-6	76	$C_{16}H_{18}N_2O_4$	11a	280-2	60	$C_{24}H_{21}N_3O_2$
5	215	70	$C_{15}H_{15}N_2O_3Br$	11b	141-2	63	$C_{24}H_{22}N_4O_2$
6a	151	73	$C_{19}H_{17}N_3O_2$	12	110	65	$C_{24}H_{22}N_4O_3S$
6b	>300	70	$C_{19}H_{18}N_4O_2$	13	280-1	69	$C_{12}H_{10}N_2O_2$
7a	180-1	75	$C_{26}H_{21}N_3O_2$	14	>300	64	$C_{22}H_{20}N_6O_2$
7b	>300	76	$C_{26}H_{22}N_4O_2$	16	>300	68	$C_{22}H_{23}N_5O_3$

*All compounds reported were obtained in pure state and give elemental analyses and spectral data (IR and ^{1}H NMR) in agreement with their proposed structures.

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