NITRILES IN HETEROCYCLIC SYNTHESIS: 1-CYANOFORMANILIDE AS PRECURSOR FOR A VARIETY OF HETEROCYCLIC RING SYSTEMS

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Abstract - A variety of polyfunctionally substituted azoles and azines could be synthesized utilizing 1-cyanoformanilide (1) as a precursor.

During recent years, we have maintained a strong interest for the synthesis of novel heterocyclic ring systems utilizing readily obtainable and functionally substituted nitriles as starting materials[2-6]. Recently, the synthetic potentialities of nitriles in heterocyclic synthesis have been reviewed[7-9]. In connection with our continuous efforts in this area, we were attracted by the notable characteristic of 1-cyanoformanilide (1), which contains a potentially nucleophilic nitrogen atom in the α position with respect to the cyano function, as a precursor for a variety of polyfunctional azoles and azines which were not observed previously[8]. To our knowledge, literature survey reveals that only little attention has been given to the utility of 1-cyanoformanilide (1) for the synthesis of heterocyclic ring systems[10,11]. Therefore, it was decided to design a specifically synthetic program to explore scopes, limitations and generality of 1-cyanoformanilide (1) as a precursor in preparing various heterocycles.

Thus in our laboratories, 1[12] reacted with an equimolar amount of salicylic acid in absolute ethanol in presence of catalytic amount of triethylamine under reflux for 3 h to afford a product of molecular formula $C_{15}H_{10}N_2O_3$. Keeping in view the various possibilities offered by this reaction, the 4H-1,3-benzoxazine structure 3a was proposed for the reaction product based on its ir spectrum which revealed the absence of nitrile stretching absorption band and the presence of the NH stretching band at 3450-3300 cm^{-1} and a benzamidocarbonyl group at 1710 cm^{-1} together with ring carbonyl at 1680 cm^{-1}. The ^1H-nmr spectrum of 3a revealed the presence of a multiplet signal at δ 7.35-7.40(9H)ppm assigned for the aromatic protons as well as one broad and D_2O exchangeable proton signal at δ 10.34 ppm assigned for the NH proton. Formation of 3a

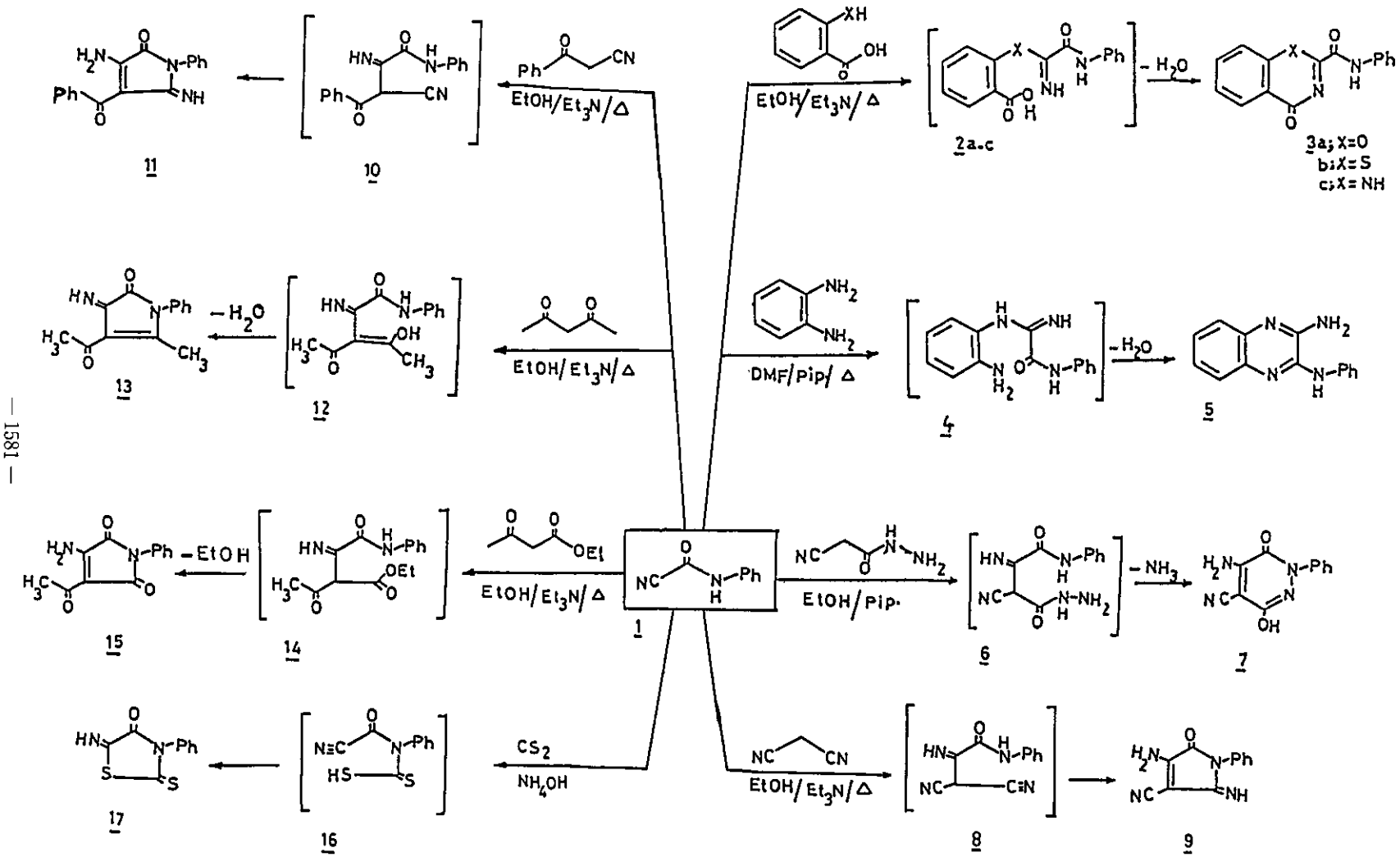
is assumed to take place via formation of the intermediate 2a followed by elimination of water molecule. At this point, the reagent would now come into range with potentially interesting consequences. Thus similarly 1 reacted with thiosalicylic acid as well as with anthranilic acid under the same conditions to yield the corresponding 4H-1,3-benzothiazine and 4H-quinazolone derivatives 3b and 3c in good yields respectively. The assigned structures for compounds 3b and 3c were based on analytical and spectral data (cf. Table 1 and 2). The reaction of 1 with o-phenylenediamine afforded the quinoxaline derivative 5. The analytical and spectral data of 5 are entirely consistent with the proposed structure. Formation of 5 proceeds via intermediacy of the adduct 4 followed by water elements elimination (cf. Scheme).

To assess the scope and generality of this methodology of heterocyclic synthesis, we next move to examine the reactivity of 1 towards some polyfunctionally active methylene reagents. Thus, it was found that 1 reacted with 2-cyanoethanoic acid hydrazide on warming and then standing for 15 h at room temperature in absolute ethanol in the presence of catalytic amount of piperidine to give the corresponding pyridazine derivative 7 via intermediate formation of 6 followed by loss of ammonia molecule. Also the reaction of 1 with malononitrile in refluxing absolute ethanol in the presence of 3 drops of triethylamine for 4 h afforded the pyrrole derivative 9. The identity of the product in each case, was established on the basis of elemental analyses and spectral data (cf. Table 1 and 2).

Compound 1 reacted with an equimolar amount of benzoylacetonitrile in refluxing ethanol catalyzed with 5 drops of triethylamine for 6 h to give the pyrrole derivative 11. Similarly 1 reacted with acetylacetone and ethyl acetoacetate in refluxing ethanolic triethylamine solutions for 3 h to yield the corresponding pyrrole derivatives 13 and 15 respectively (cf. Scheme). Structures of compounds 13 and 15 were identified based on analytical and spectral data (cf. Table 1 and 2).

Finally, it was found that 1 reacted with an equimolar amount of carbon disulphide in aqueous ammonium hydroxide solution at room temperature, on standing overnight with constant stirring, to give the 1,3-thiazolone derivative 17. Formation of 17 is assumed to proceed via cylization of the adduct 16, which finds parallelism to the previously reported thiopyran formation utilizing activated nitriles and carbon disulphide[13].

In conclusion, we consider that the above results presented in this paper, indirectly extend and broaden our knowledge in the area of heterocyclic synthesis and demonstrate a new generally applicable methodology for constructing a variety of heterocyclic ring systems. Work along the expansion of this methodology is now in progress.


EtOH/Et3N/Δ
EtOH/Et3N/Δ
- H2O
3a; X=O
b; X=S
c; X=NH
EtOH/Et3N/Δ
DMF/Pip/ Δ
- H2O
EtOH/Et3N/Δ
- H2O
EtOH/Et3N/Δ
EtOH/Pip.
- NH3
CS2
NH4OH
EtOH/Et3N/Δ

Scheme

Table 1: List of the newly prepared compounds.

Compound* (Colour)	Mp (°C)	Yield (%)	Mol.Formula (Mol.Weight)	Compound (Colour)	Mp (°C)	Yield (%)	Mol.Formula (Mol.Weight)
3a (white)	189	72	$C_{15}H_{10}N_2O_3$ (266.24)	9 (yellow)	196	76	$C_{11}H_8N_4O$ (212.19)
3b (yellow)	156	69	$C_{15}H_{10}N_2O_2S$ (282.31)	11 (yellow)	172	60	$C_{17}H_{13}N_3O_2$ (291.30)
3c (yellow)	178	75	$C_{15}H_{11}N_3O_2$ (265.26)	13 (yellow)	165	82	$C_{13}H_{12}N_2O_2$ (228.24)
5 (orange)	210	70	$C_{14}H_{12}N_4$ (236.26)	15 (yellow)	181	79	$C_{12}H_{10}N_2O_3$ (230.21)
7 (yellow)	226	68	$C_{11}H_8N_4O_2$ (228.20)	17 (yellow)	203	62	$C_9H_6N_2OS_2$ (222.27)

*All compounds reported were obtained in analytically pure state and give elemental analyses in agreement with their proposed structures.

Table 2: Ir and ^{1}H-nmr data for compounds listed in Table 1.

Compound	Ir, selected bands (cm^{-1})	^{1}H-nmr (DMSO-d_6) δ ppm
3a	3450-3300 (NH); 3050 (arom. CH); 1710, 1680 (CO); 1620 (C=N and δ NH).	7.35-7.40 (m, 9H, arom. protons); 10.34 (s, br, 1H, NH).
3b	3460-3300 (NH); 2950 (arom. CH); 1710, 1670 (CO); 1610 (C=N and δ NH).	7.28-7.39 (m, 9H, arom. protons); 10.36 (s, br, 1H, NH).
3c	3450-3330 (NH); 3040 (arom. CH); 1700, 1680 (CO); 1620 (C=N and δ NH).	7.34-7.40 (m, 9H, arom. protons); 9.90-10.01 (2s, br, 2H, 2NH).
5	3445-3300 (NH_2, NH); 2980 (arom. CH); 1615 (C=N, δ NH_2 and δ NH).	4.56 (s, 2H, NH_2); 7.28-7.40 (m, 9H, arom. protons); 9.98 (s, br, 1H, NH).
7	3420-3280 (OH, NH_2); 3010 (arom. CH); 2220 (CN); 1680 (CO); 1620 (C=N and δ NH_2).	4.51 (s, 2H, NH_2); 7.30-7.39 (m, 5H, arom. protons); 12.12-12.32 (s, br, 1H, OH).
9	3450-3310 (NH_2, NH); 3000 (arom. CH); 2210 (CN); 1690 (CO); 1620 (C=N, δ NH_2 and δ NH).	4.52 (s, 2H, NH_2); 7.29-7.41 (m, 5H, arom. protons); 10.01-10.30 (s, br, 1H, NH).
11	3450-3300 (NH_2, NH); 3040 (arom. CH); 1680 (CO); 1615 (C=N, δ NH_2 and δ NH).	4.56 (s, 2H, NH_2); 7.30-7.41 (m, 10H, arom. protons); 10.00-10.31 (s, br, 1H, NH).
13	3450-3310 (NH); 3040 (arom. CH); 3020, 2910 (CH_3); 1700, 1680 (CO); 1620 (C=N and δ NH).	1.12-1.78 (2s, br, 6H, $2CH_3$); 7.51 (m, 5H, arom. protons); 10.10-10.32 (s, br, 1H, NH).

Table 2 continued

Compound	Ir, selected bands (cm^{-1})	^{1}H-nmr (DMSO-d_6) δ ppm
15	3445-3300 (NH_2); 3050 (arom. CH); 3020, 3000 (CH_3); 1710, 1690 (CO); 1620 (δ NH_2).	1.80 (s, 3H, CH_3); 6.49 (s, 2H, NH_2); 7.05-7.21 (m, 5H, arom. protons).
17	3420-3340 (NH); 3040 (arom. CH); 1680 (CO); 1630 (C=N and δ NH); 1200 (C=S).	7.29-7.35 (m, 5H, arom. protons); 10.23 (s, br, 1H, NH).

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