NITRILES IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF SOME NEW PYRIDINE, PYRIDAZINE AND PYRIMIDINE DERIVATIVES

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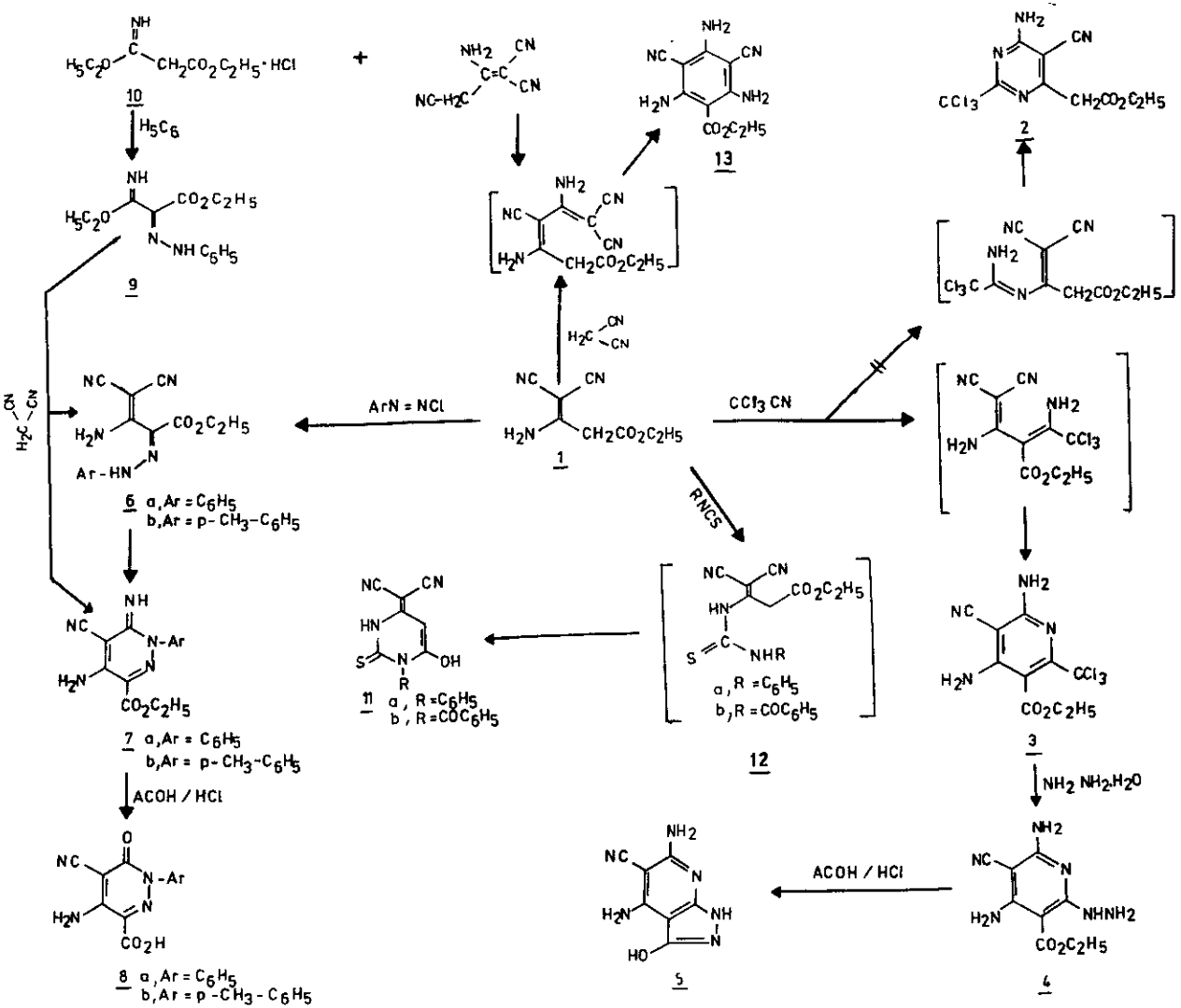
Abstract - Pyrimidine, pyridazine, pyridine and pyrazolopyrimidine derivatives were synthesised from 3-amino-2-cyano-4-ethoxycarbonylcrotononitrile (1) as a starting material.

In connection with our previous interest in developing new approaches for synthesis of heterocycles utilising readily obtainable starting materials,[1,2] we report here the synthesis of a variety of new heterocycles utilising the recently synthesized 3-amino-2-cyano-4-ethoxycarbonylcrotononitrile (1). Thus compound 1 (0.01 mole) reacted with trichloroacetonitrile (0.01 mole) in refluxing ethanol (30 ml) catalyzed with a few drops of triethylamine for 3 h to yield a 1:1 adduct. Two isomeric structures were considered (cf. 2 and 3). Structure 2 was ruled out based on ^{1}H-NMR which revealed absence of a methylene group. The formation of 3 is thus assumed to take place via addition of the active methylene moiety in 1 to the nitrile and cyclization. The formation of 3 from reaction of 1 with trichloroacetonitrile ressembles the reported formation of pyridine derivative from reaction of 2-amino-1,1',3-tricyanopropene with trichloroacetonitrile.[3] This is different from the general behaviour of enaminonitriles. The later affords pyrimidines on reaction with trichloroacetonitrile.[4,5] The presence of active methylene in 1 and in aminotricyanopropene lead to reaction with trichloroacetonitrile to occur exclusively at this CH_2.

Compound 3 (0.01 mole) reacted with hydrazine hydrate (0.01 mole) in refluxed ethanol (20 ml) for 3 h to yield the hydrazine derivative 4. Compound 4 (0.01 mole) could be successfully cyclised into 5 on refluxing (2h) in acetic (30 ml)-hydrochloric acid (2 ml) mixture. Compound 1 (0.01 mole) coupled with aromatic diazonium chlorides to yield products which may be formualted as 6 or isomeric 7. IR spectrum however could be utilized to rule out structure 7 as it indicated the presence of two CN groups. Attempted cyclization of 6 into 7 on reflux in acetic acid was unsuccessfull. Compound 6 (0.01 mole) was converted into 8 on refluxing (2 h) in acetic (30 ml)-hydrochloric acid (2 ml) mixture most likely via intermediacy of 7. Compound 7a was obtained as a by-product from reaction of 9 (0.01 mole) with malononitrile (0.01 mole) in refluxing ethanol (20 ml) catalyzed with a few drops of


10
9
13
2
1
6 a, Ar = C6H5
b, Ar = p-CH3-C6H5
ArN = NCl
CCl3 CN
RNCS
7 a, Ar = C6H5
b, Ar = p-CH3-C6H5
ACOH / HCl
11 a, R = C6H5
b, R = COC6H5
12
a, R = C6H5
b, R = COC6H5
3
NH2 NH2H2O
4
ACOH / HCl
5
8 a, Ar = C6H5
b, Ar = p-CH3-C6H5

piperidine for 3h. The major product was however compound 6a. Compound 9 was obtained via coupling of the imidate 10 with benzenediazonium chloride.

Compound 1 (0.01 mole) reacted with 0.01 mole of either phenyl isothiocyanate or benzoyl isothiocyanate in refluxing dioxane (30 ml) for 3 h to yield the pyrimidines 11a,b respectively. Compounds 11a,b are assumed to be formed via addition of amino function in 1 to the unsaturated linkage in the isothiocyanate affording 12 which cyclized via loss of ethanol into 11.

Compound 1 (0.01 mole) reacts with malononitrile (0.01 mole) in refluxing ethanol (20 ml) catalyzed with few drops of piperidine for 3 h to give a 1:1 adduct. Several possible structures seemed possible. Structure 13 was established based on identity of the reaction product with the product of reaction of compound 10 (0.01 mole) with 3-amino-2,4-dicyanocrotononitrile (0.01 mole) in refluxing ethanol (20 ml) catalyzed with a few drops of piperidine for 3 h.

All compounds described were obtained in good yields and a variety of new heterocycles because now available.

Table : List of compounds newly synthesized.

Compound*	Solvent	Mp(°C)	Yield (%)	Mol Formula	IR, selected bands (cm^{-1})
3	ethanol	140	80	$C_{10}H_9N_4O_2Cl_3$	3460, 3320 (NH_2), 2210 (CN), 1690(C=O)
4	ethanol	190	80	$C_9H_{12}N_6O_2$	3450, 3320(NH_2), 2210(CN), 1680 (CO).
5	DMF/H_2O	>300	65	$C_7H_6N_6O$	3460(OH); 3320, 3220 (NH_2,NH) 2210 (CN), 1680 (C=O).
6a	ethanol	270	70	$C_{14}H_{13}N_5O_2$	3340, 3220 (NH_2, NH), 2220, 2210 (two CN), 1720 (C=O).
6b	methanol	245	80	$C_{15}H_{15}N_5O_2$	3340, 3240 (NH_2, NH), 2220, 2210 (two CN), 1710 (C=O).
7a	ethanol	>300	40	$C_{14}H_{13}N_5O_2$	3340,3240(NH_2,NH),2220(CN),1710(C=O)
8a	acetic acid	198	80	$C_{12}H_8N_4O_3$	3460 (OH); 3340, 3240 (NH_2), 2220 (CN) and 1690 (C=O).
8b	acetic acid	>300	70	$C_{13}H_{10}N_4O_3$	3520 (OH), 3400, 3200 (NH_2), 2220 (CN), 1680 (C=O).
11a	ethanol	>300	60	$C_{13}H_8N_4OS$	3340, 3320 (NH_2), 2225, 2200 (two CN), 1710 (C=O).
11b	DMF/H_2O	>300	65	$C_{14}H_8N_4O_2S$	br 3340-3200 (NH_2), 2220, 2200 (two CN), 1690 (C=O).
13	acetic acid	>300	70	$C_{11}H_{11}N_5O_2$	3400, 3300 (NH_2); 2220, 2200 (CN), 1700 (C=O).

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

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