NITRILES IN HETEROCYCLIC SYNTHESIS: NEW ROUTE FOR THE SYNTHESIS OF PYRIDINE AND PYRIDO[2,3-d]PYRIDAZINE DERIVATIVES

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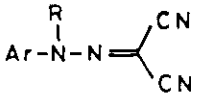
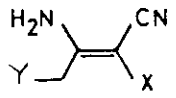
Abstract - Several new 2-cyanohydrazonomethyl pyridines and pyrido[2,3-d]-pyridazine derivatives were obtained via the reaction of arylhydrazono-nitriles with 2-amino-1,1,3-tricyanopropene and diethyl 3-amino-2-cyano-pent-2-ene-dicarboxylate.

The considerable biological activities of pyridazines and their condensed derivatives have led to an intensive research on methods of their synthesis[1-5]. In the last few years our group have reported several approaches to the synthesis of such compounds utilizing the laboratory available starting materials.[6-11] During this phase of our research we have reported a novel pyrimidine synthesis via the reaction of enaminonitriles with trichloroacetonitrile.[12] Recently Gewald and Hain[13] have shown that this synthetic approach affords pyridine when the enaminonitrile has methylene group in a suitable position. In order to define the scope and limitations of our pyrimidine synthesis we report here a facile synthesis of some pyridine and pyrido[2,3-d]pyridazine derivatives via the reaction of arylhydrazonomesoxalonitriles 1a-h with enaminonitriles 2a,b. Thus, it has been found that arylhydrazonomesoxalonitriles 1a-d react with 2-amino-1,1,3-tricyanopropene (2a) in refluxing ethanol and in presence of catalytic amount of triethylamine to afford 1:1 adducts. Several isomeric structures seemed possible (cf. structures 3-6 in Scheme 1). Structure 3 could be easily ruled out on the basis of ^{1}H NMR

which revealed the absence of signals for methylene protons. Structure 4 can also be eliminated based on the absence of H-5 pyrimidine signal. Thus the pyridine structure 5 or the pyrido[2,3-d]pyridazine 6 were considered. In order to assign either of these structures to the product, compound 2a reacted with



1 a, R = H ; Ar = C_6H_5 b, R = H ; Ar = $C_6H_4CH_3$(p-)
c, R = H ; Ar = C_6H_4Br(p-) d, R = H ; Ar = C_6H_4Cl(p-)
e, R = CH_3 ; Ar = C_6H_5 f, R = CH_3 ; Ar = $C_6H_4CH_3$(p-)
g, R = CH_3 ; Ar = C_6H_4Cl(p-) h, R = CH_3 ; Ar = $C_6H_4NO_2$(p-)



2 a, X = Y = CN
b, X = Y = CO_2Et

le-h under the same experimental conditions to afford 1:1 adducts for which structure 7 was established based on elemental analyses and spectral data. Since the uv spectra (ethanol) of compounds 7a-d showed two peaks at $\lambda_{max.}$ 258 and 380 nm, and proved to be completely different from those of the products of reaction of la-d with 2a which showed only one absorption peak (ethanol) at $\lambda_{max.}$ 430 nm. Therefore, if the latter products were in the monocyclic structure 5, they should reveal a uv pattern similar to that of 7. Thus structure 6 was established for the products of reaction of la-d with 2a. The formation of 6 and 7 is assumed to proceed via addition of the active methylene in 2a to one of the cyano groups in 1 followed by cyclization in case of la-d through the hydrazone N-H and the ortho cyano group in the intermediate 5 to afford 6 whereas such N-H is absent in case of le-h and therefore the final product is the monocyclic 7 without possibility of further cyclization.

Compound 2b also reacted with la-g to afford products of Michael addition followed by cyclization via ethanol elimination. Structure 8 seemed to be a suitable intermediate which leads to structure 9 in case of la-d and to 10 in case of le-g. (cf. Scheme 2). Structures 9 and 10 were inferred from both spectral and analytical data (cf. Tables 1 and 2). It is clear that several polysubstituted pyridines,

pyrido[2,3-d]pyridazinimine and pyrido[2,3-d]pyridazinone derivatives which are of potential biological activity[14] are now available from easily prepared starting materials and under simple experimental conditions.

Table 1: Physical data of the newly synthesized products.

Compound number	Yield %	Mp (°C)	Crystallization Solvent	Mol. Formula	Mol. Wt
6a	73	282(dec.)	DMF	$C_{15}H_{10}N_8$	302.298
6b	67	>300	DMF/ethanol	$C_{16}H_{12}N_8$	316.324
6c	72	229	DMF	$C_{15}H_9N_8Br$	381.194
6d	75	265	DMF	$C_{15}H_9N_8Cl$	336.743
7a	65	199-200	Ethanol	$C_{16}H_{12}N_8$	316.324
7b	83	270	Ethanol	$C_{17}H_{14}N_8$	330.352
7c	68	276	Ethanol/DMF	$C_{16}H_{11}N_8Cl$	350.817
7d	58	133	Ethanol	$C_{16}H_{11}N_9O_2$	350.769
9a	78	288	Dioxane	$C_{15}H_8N_6O_2$	304.264
9b	83	230	Ethanol/DMF	$C_{16}H_{10}N_6O_2$	318.264
9c	76	267	Ethanol/DMF	$C_{15}H_7N_6O_2Br$	383.160
9d	68	263-4	DMF	$C_{15}H_7N_6O_2Cl$	338.709
10a	73	196	Ethanol	$C_{18}H_{16}N_6O_3$	364.358
10b	77	178	Ethanol	$C_{19}H_{18}N_6O_3$	378.385
10c	71	108	Ethanol	$C_{18}H_{15}N_6O_3Cl$	398.851

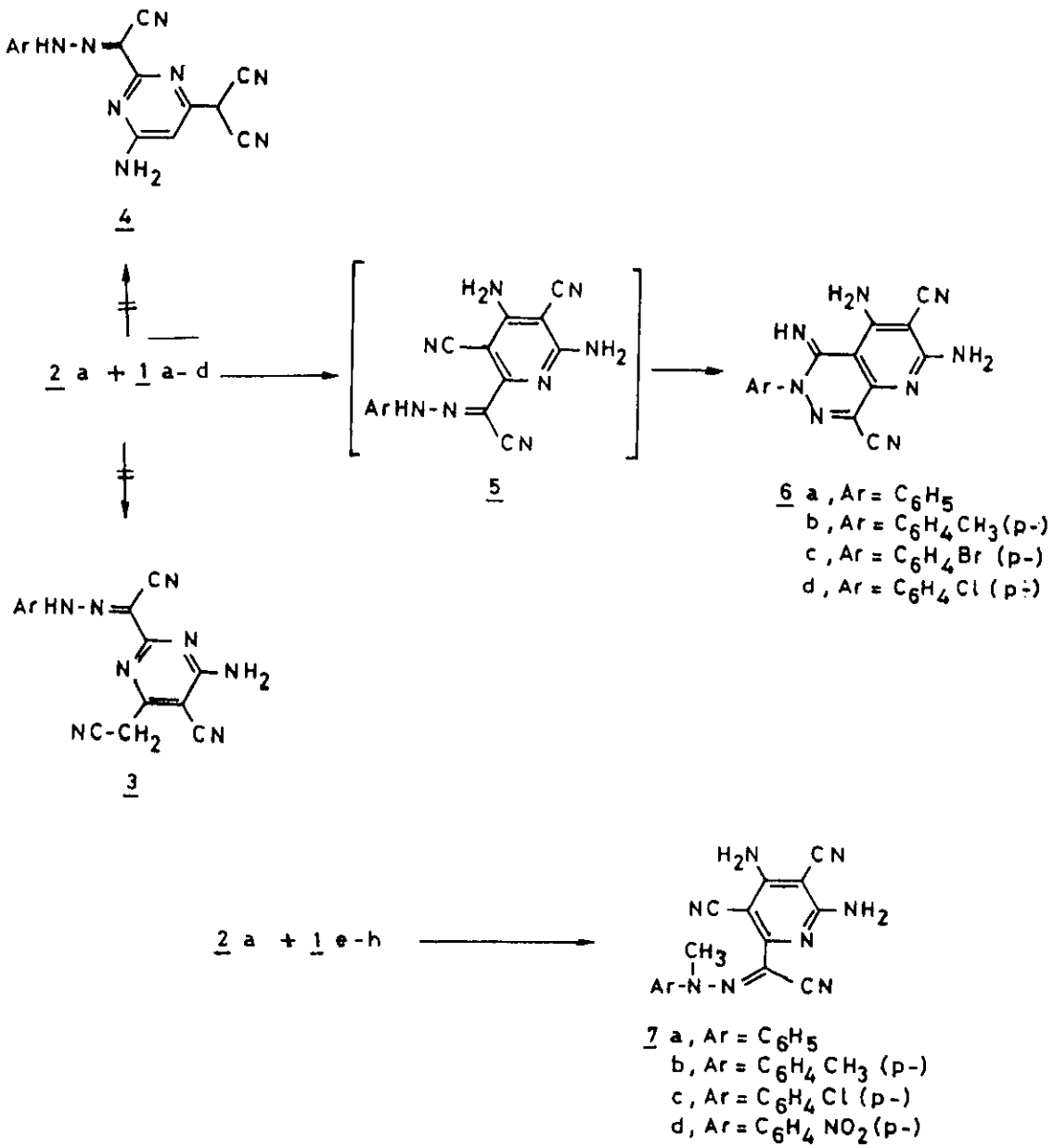
* Satisfactory elemental analyses (C ± 0.3, H ± 0.25 and N ± 0.43) have been obtained.

Table 2: IR and ^{1}H NMR data of some of the newly synthesized compounds

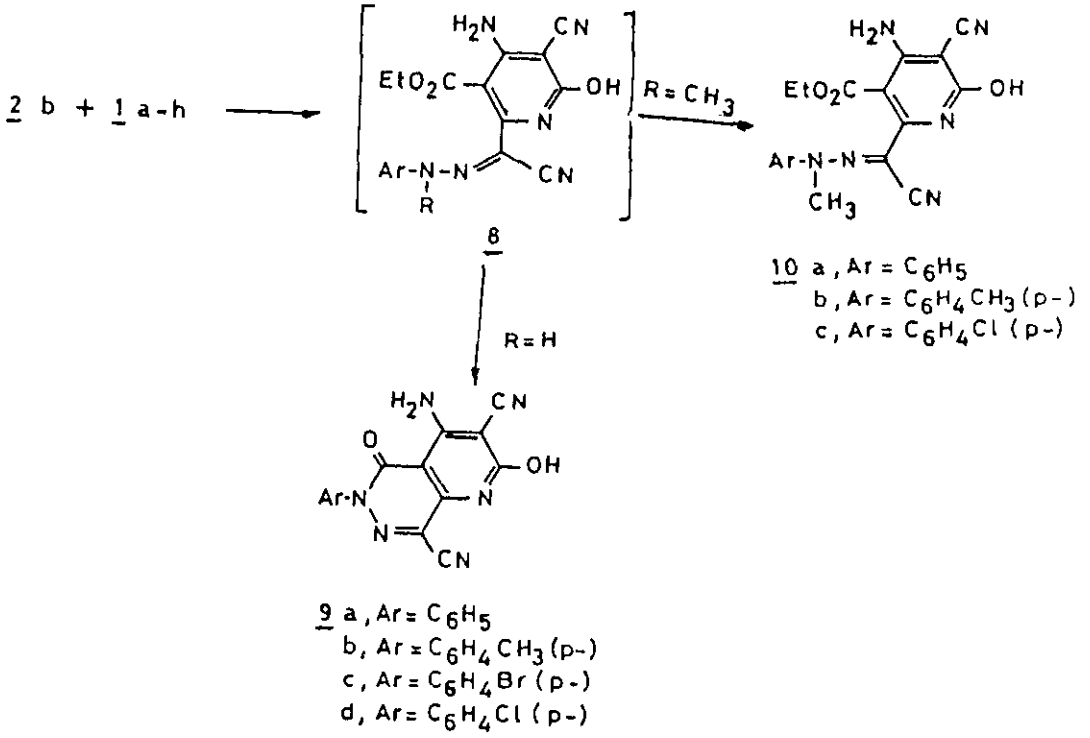
Compound number	IR, ν cm^{-1} (selected bands)	^{1}H NMR, δ ppm (DMSO-d6)
6a	3400-3100 (NH_2 and NH); 2210, 2190 (CN groups) and 1680 (C=N)	7.41-8.23 (m, 9H, aromatic and NH_2 protons) and 12.7 (s, 1H, NH)
6b	3450-3125 (NH_2 and NH), 2200, 2115 (CN groups)	1.38 (s, 3H, CH_3), 7.36-8.14 (m, 8H aromatic and NH_2 protons) and 12.5 (s, 1H, NH)

Table (2) Contd.

Compound number	IR, $\bar{\nu}$ cm^{-1} (selected bands)	^1H NMR, δ ppm (DMSO-d6)
6c	3410-3200 (br, NH_2 and NH) and 2210, 2200 (CN groups)	Insoluble in common NMR solvents
6d	3430-3095 (NH_2 and NH), 2218, 2210 (CN groups) and 1680 (C=N)	Insoluble in common NMR solvents
7a	3490-3220 (NH_2), 2210 (CN groups)	4.15 (s, 3H, N-CH_3), 7.4-7.7 (m, 5H, aromatic protons)
7b	3400-3100 (NH_2); 2200 (CN groups)	———
7c	3490-3220 (NH_2 groups), 2210 (CN groups)	4.13 (s, 3H, N-CH_3), 7.11-7.82 (m, 8H, arom. protons and NH_2)
7d	3500-3100 (br., NH_2); 2210, 2205 (s, CN groups); 1570, 1366 (NO_2 groups)	4.02 (s, 3H, N-CH_3), 7.36-7.46 (m, 4H, aromatic protons)
9a	3550-3200 (br., NH_2 and OH); 2218, 2190 (CN groups), 1680 (ring C=O)	———
9b	3560-3200 (br., OH and NH_2) 2220, 2200 (CN groups) and 1680 (ring C=O)	1.3 (s, 3H, CH_3); 4.5 (s, 1H, OH) and 7.58-7.85 (m, aromatic and NH_2 protons)
9c	3600-3220 (OH and NH_2) 2220, 2205 (CN groups) and 1685 (ring C=O)	4.45 (s, 1H, OH); 7.6-7.9 (m, 6H aromatic and NH_7 protons)
10a	3500-3100 (OH and NH_2) 2220, 2210 (CN groups) and 1700 (C=O)	———
10b	3540-3200 (br., OH and NH_2); 2220, 2210 (CN groups) and 1690 (Ester C=O)	1.45 (s, 6H, two CH_3); 4.16 (s, 3H, N-CH_3) 4.45 (q, 2H, CH_2) and 7.4-7.7 (m, 4H, aromatic protons)
10c	3550-3100 (br., NH_2 and OH) 2215, 2200 (s, CN groups) and 1705 (Ester C=O)	1.41 (t, 3H, CH_3); 4.13 (s, 3H, N-CH_3); 4.45 (q, 2H, CH_2) and 7.66-8.33 (m, 4H, aromatic protons)


ArHN-N
CN
N
N
CN
CN
NH2
4
2 a + 1 a-d
H2N
CN
NC
NH2
N
ArHN-N
CN
5
HN
Ar-N
N
6 a, Ar = C6H5
b, Ar = C6H4CH3(p-)
c, Ar = C6H4Br (p-)
d, Ar = C6H4Cl (p-)
NC-CH2
3
2 a + 1 e-h
CH3
Ar-N-N
7 a, Ar = C6H5
b, Ar = C6H4CH3 (p-)
c, Ar = C6H4Cl (p-)
d, Ar = C6H4NO2(p-)

Scheme 1



Scheme 2

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