

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

Zaghloul El-Shahat Kandeel*, Fathy Mohamed Abdelrazek, and Mohamed Hilmy Elnagdi

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

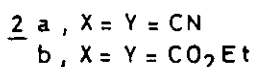
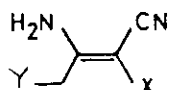
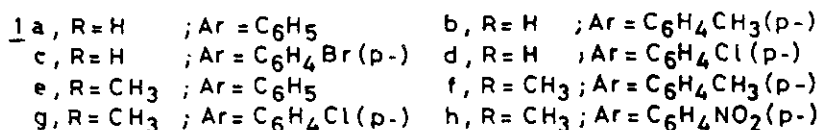
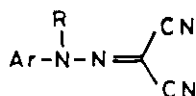
Abdel Moneim El-Torgoman

Chemistry Department, Faculty of Science, Menoufia University, Menoufia, Egypt

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

The considerable biological activities of pyridazines and their condensed derivatives have led to an intensive research on methods of their synthesis¹⁻⁵. 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 enamionitriles with trichloroacetonitrile.¹² Recently Gewald and Hain¹³ have shown that this synthetic approach affords pyridine when the enamionitrile 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 enamionitriles 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 ¹H 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



1e-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 λ_{max} . 258 and 380 nm, and proved to be completely different from those of the products of reaction of 1a-d with 2a which showed only one absorption peak (ethanol) at λ_{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 1a-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 1a-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 1e-h and therefore the final product is the monocyclic 7 without possibility of further cyclization.

Compound 2b also reacted with 1a-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 1a-d and to 10 in case of 1e-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 activity¹⁴ 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 ₉ N ₈ Br	381.194
6d	75	265	DMF	C ₁₅ H ₉ N ₈ Cl	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 ₈ Cl	350.817
7d	58	133	Ethanol	C ₁₆ H ₁₁ N ₉ O ₂	350.769
9a	78	288	Dioxane	C ₁₅ H ₈ N ₆ O ₂	304.264
9b	83	230	Ethanol/DMF	C ₁₆ H ₁₀ N ₆ O ₂	318.264
9c	76	267	Ethanol/DMF	C ₁₅ H ₇ N ₆ O ₂ Br	383.160
9d	68	263-4	DMF	C ₁₅ H ₇ N ₆ O ₂ Cl	338.709
10a	73	196	Ethanol	C ₁₈ H ₁₆ N ₆ O ₃	364.358
10b	77	178	Ethanol	C ₁₉ H ₁₈ N ₆ O ₃	378.385
10c	71	108	Ethanol	C ₁₈ H ₁₅ N ₆ O ₃ Cl	398.851

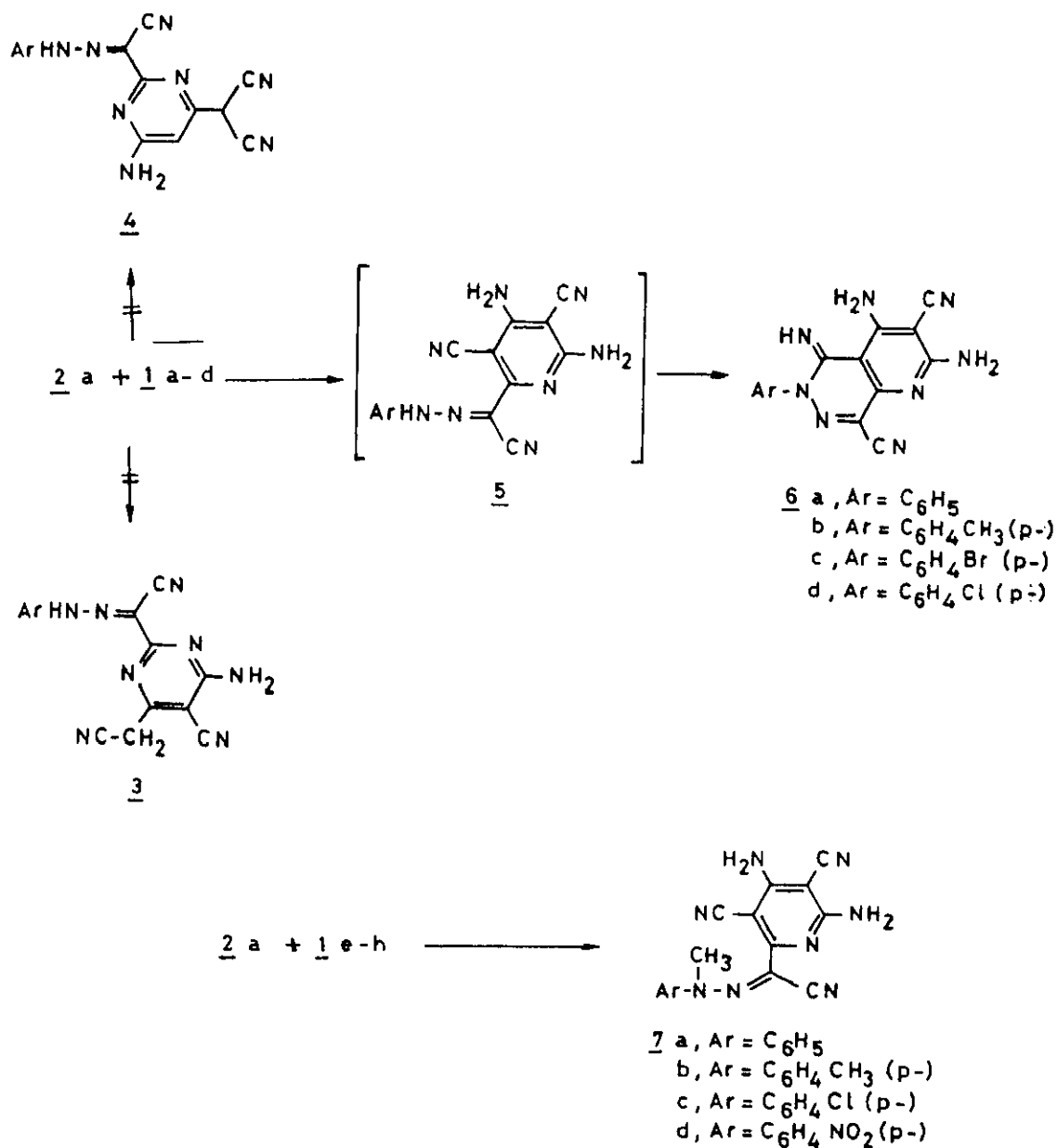
* Satisfactory elemental analyses (C ± 0.3, H ± 0.25 and N ± 0.43) have been obtained.

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

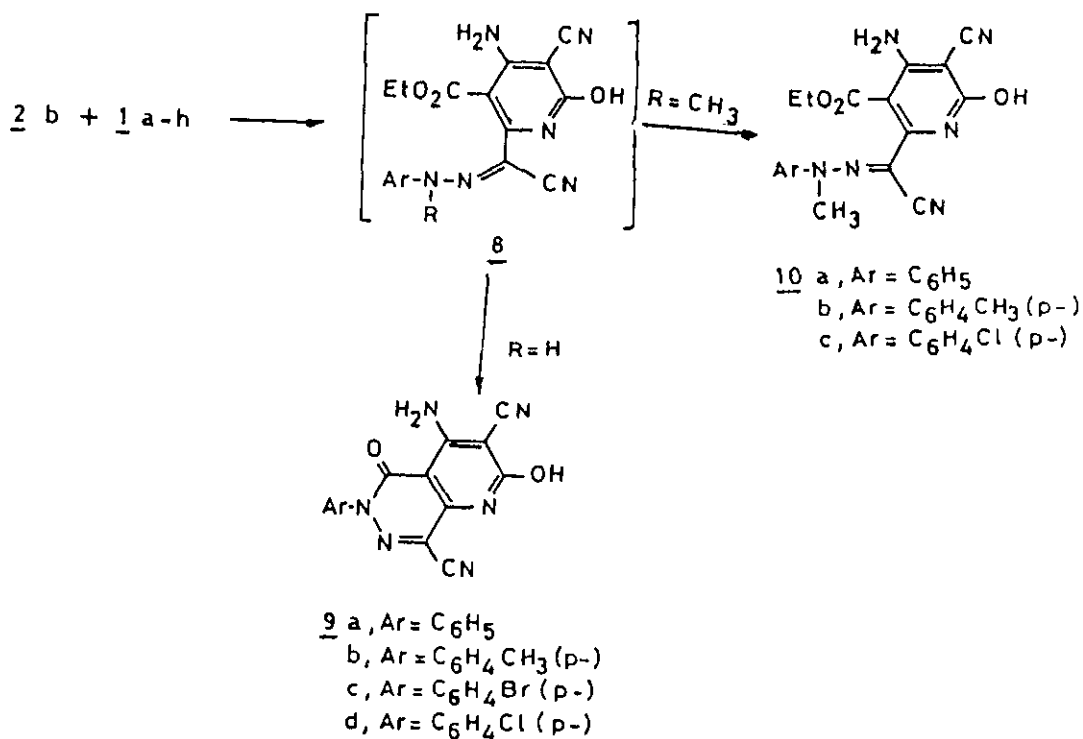
Compound number	IR, ν cm ⁻¹ (selected bands)	¹ H NMR, δ ppm (DMSO-d ₆)
6a	3400-3100 (NH ₂ and NH); 2210, 2190 (CN groups) and 1680 (C=N)	7.41-8.23 (m, 9H, aromatic and NH ₂ protons) and 12.7 (s, 1H, NH)
6b	3450-3125 (NH ₂ and NH), 2200, 2115 (CN groups)	1.38 (s, 3H, CH ₃), 7.36-8.14 (m, 8H aromatic and 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-d ₆)
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_2 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)



Scheme 1



Scheme 2

ACKNOWLEDGEMENT

The authors are greatly indebted to Dr. T. Fuchigami, Tokyo Institute of Technology, Tokyo, Japan, for his help in Spectral Measurements.

REFERENCES

1. K. Dury, Angew. Chem. Int. Ed. Engl., 1965, 4, 292.
2. H. Hori, E. Ito, T. Jakta, G. Koyama and H. Umezawa, J. Antibiot., 1964, 17A, 96.
3. G. Koyama and H. Umezawa, J. Antibiot., 1965, 18A, 175.
4. R.K. Robins, J. Het. Chem., 1963, 3, 110.
5. M.H. Elnagdi and H. Wamhoff, Chem. Lett., 1981, 419.
6. M.H. Elnagdi and H. Wamhoff, J. Het. Chem., 1981, 18, 1287.

7. Z.E. Kandeel, F.M. Abdelrazek, N.E.M. Salah Eldin and M.H. Elnagdi, J. Chem. Soc. Perkin 1, 1985, 1499.
8. F.M. Abdelrazek, N.S. Ibrahim, Z.E. Kandeel and M.H. Elnagdi, Synthesis, 1984, 432.
9. F.M. Abdelrazek, Z.E. Kandeel, K.M.H. Helmy and M.H. Elnagdi, Synthesis, 1985, 432.
10. S.E. Abdou, S.M. Fahmy, K.U. Sadek and M.H. Elnagdi, Heterocycles, 1981, 16, 2177.
11. H.A. Daboun, S.E. Abdou, M.M. Hussen and M.H. Elnagdi, Synthesis, 1982, 502.
12. M.H. Elnagdi, H.A. Elfahham, S.A. Ghazlan and G.E. Elgemeie, J. Chem. Soc. Perkin Trans. 1, 1982, 2667.
13. K. Gewald, U. Hain and M. Gruner, Chem. Ber. 1985, 118, 2198
14. A. Katritzky and C.W. Rees "Comprehensive Heterocyclic Chemistry" part 2B, Chapter 1, p. 56 (1984).

Received, 14th April, 1986