HETEROCYCLES, Vol. 24, No. 8, 1986

NITRILES IN HETEROCYCLIC SYNTHESIS: NEW APPROACHES FOR SYNTHESIS OF PYRAZOLES, ISOXAZOLES AND PYRIMIDINES

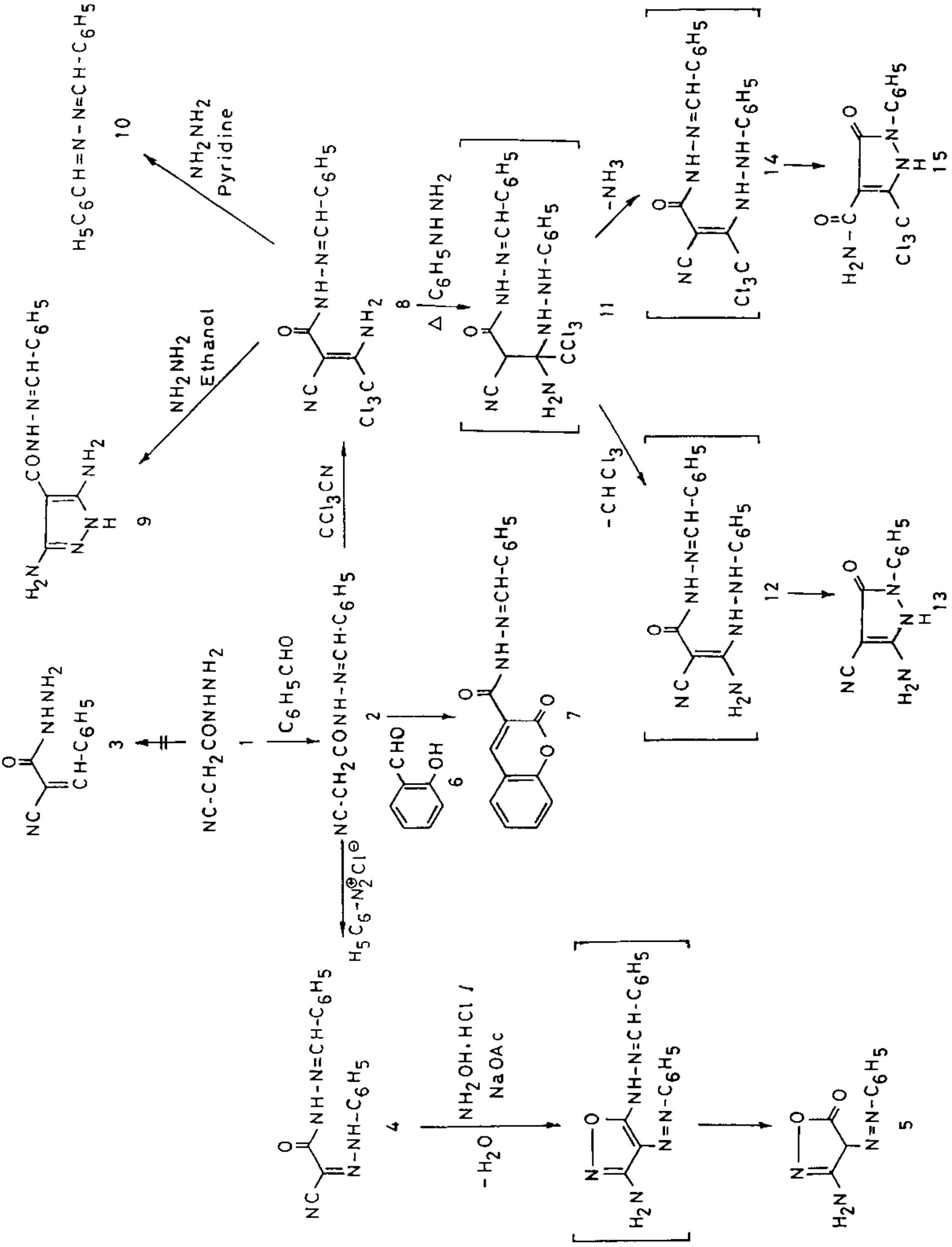
Nadia S. Ibrahim, Ebtisam A.A. Hafez, and Raafat M. Mohareb

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

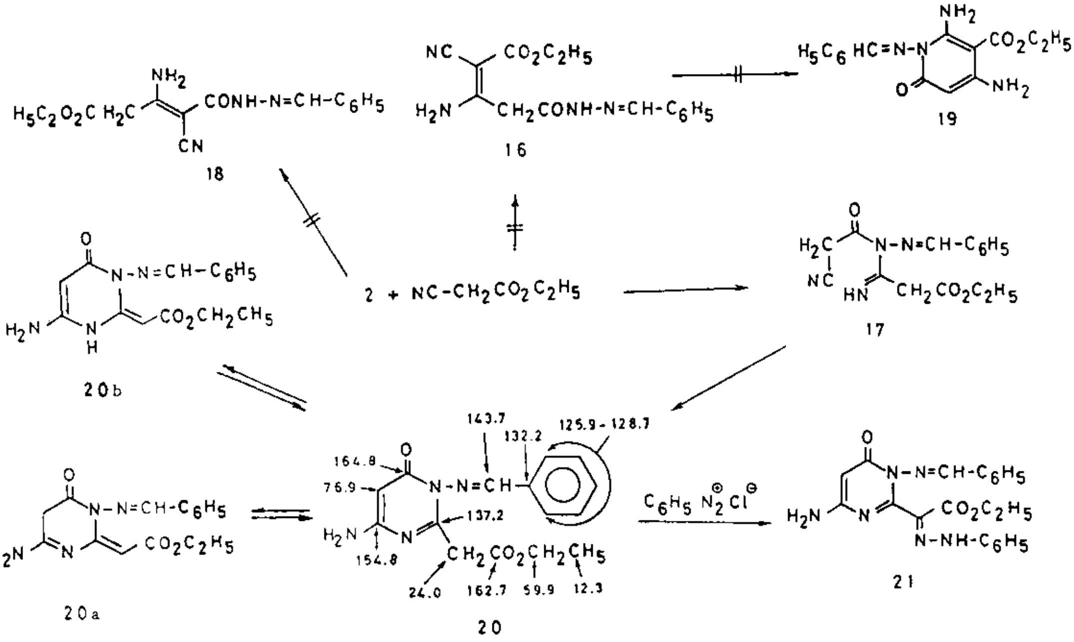
Abstract - A variety of pyrazoles and aminoisoxazole were prepared from reaction of *N-benzylidene cyanoethanoic* hydrazide derivatives with hydrazines and hydroxylamine. A novel pyrimidine synthesis from reaction of ethyl cyanoacetate with the hydrazide is reported.

In the last few years, we have been involved in a program directed for developing new approaches for the synthesis of functionally substituted azoles and azolines utilising readily obtainable nitrile derivatives as starting materials.[1-3] In conjunction of this work, we report here on the utility of N-benzylidene-cyanoethanoic hydrazide (2). Compound 2 was obtained via condensation of equimolecular amounts of cyanoethanoic hydrazide (1) and benzaldehyde (0.01 mole) in refluxing ethanol (30 ml) catalyzed by a few drops of piperidine for 2 h. The structure of this compound was established for the reaction product based on ^{1}H-NMR which revealed a signal for CH_2 protons at δ 4.6 ppm. Thus, the hydrazide 2 (0.01 mole) coupled with benzenediazonium chloride (prepared from 0.01 mole of aniline and the appropiate amount of hydrochloric acid and sodium nitrite) in pyridine (10 ml) to yield phenylhydrazone 4. Compound 4 (0.01 mole) could be converted into the known 3-amino-5-hydroxy-4-phenylazoisoxazole[4] (5) (identity was made by mp and mixed mp) on treatment with 0.01 mole of hydroxylamine hydrochloride in refluxing ethanol (30 ml) containing sodium acetate (3 g) for 4 h. Moreover the compound 2 condensed with o-hydroxybenzaldehyde (6) to yield the coumarine derivative 7.

Similarly to the reported[5] behaviour of other active methylene reagents with trichloroacetonitrile. 2 (0.01 mole) reacted with trichloroacetonitrile (0.01 mole) in ethanol (30 ml) containing 3 g of sodium acetate (left-overnight) to yield the adduct 8 in good yield. Compound 8 (0.01 mole) was refluxed with hydrazine hydrate (0.01 mole) in ethanol (30 ml) for 2 h to yield the pyrazole derivative 9, while in refluxing pyridine (2 h), the azine 10 was the only isolable product. Attempt to effect similar reaction by heating 8 (0.01 mole) at 160°C with phenylhydrazine (0.01 mole) for 2 h resulted in the formation of a mixture of the pyrazoles 13 and 15 which were separated by fractional crystallization. The formation of 13 and 15 is assumed to proceed through the common intermediate 11 formed via addition of the more basic and less hindered hydrazine nitrogen moiety to the activated double bond in 8. This intermediate


NC-CH$_2$CONHNH$_2$
1
3
NC
CH-C$_6$H$_5$
NHNH$_2$
C$_6$H$_5$CHO
NC-CH$_2$CONH-N=CH-C$_6$H$_5$
2
CCl$_3$CN
NC
Cl$_3$C
NH$_2$
NH-N=CH-C$_6$H$_5$
8
NH$_2$NH$_2$
Ethanol
9
H$_2$N
CONH-N=CH-C$_6$H$_5$
NH$_2$
NH$_2$NH$_2$
Pyridine
10
H$_5$C$_6$CH=N-N=CH-C$_6$H$_5$
Δ
C$_6$H$_5$NHNH$_2$
11
H$_2$N
CCl$_3$
NH-NH-C$_6$H$_5$
NH-N=CH-C$_6$H$_5$
-NH$_3$
14
Cl$_3$C
NH-NH-C$_6$H$_5$
15
H$_2$N-C
N-C$_6$H$_5$
-CHCl$_3$
12
13
NC
H$_2$N
CHO
OH
6
7
NH-N=CH-C$_6$H$_5$
H$_5$C$_6$-N$_2^{\oplus}$Cl$^{\ominus}$
4
N-NH-C$_6$H$_5$
NH$_2$OH.HCl /
NaOAc
-H$_2$O
N=N-C$_6$H$_5$
5

either looses chloroform affording 12 which then cyclizes to the final isolable 13 or ammonia to yield 14 which affords the other isolable pyrazole 15.



Recently Gewald et al.[6] have reported that activated nitriles react with active methylene nitriles to yield addition products that cyclized readily into pyridines. In our hands, 2 (0.01 mole) reacted with ethyl cyanoacetate (0.01 mole) in refluxing ethanol (30 ml) catalyzed with a few drops of piperidine (4 h) to yield a 1:1 adduct.

IR spectrum of the reaction product revealed the absence of cyano absorption. Thus acyclic structures like 16-18 were ruled out. Two isomeric structures (19 and 20) were thus considered. ^{13}C-NMR could be successfully utilized to establish the structure 20 for the reaction product as it revealed a methylene triplet at δ 24.0 ppm. If the reaction product was 19, the triplet should have not appeared. Moreover, the existence of this triplet indicated that 20 exists as such in CDCl$_3$ solution. Thus, other potentially tautomeric forms e.g. 20a or 20b were ruled out. In 20a the methylene triplet is expected at higher field[7] ~ δ 42.5 ppm. In 20b the methylene triplet is absent and a new doublet for exocyclic CH at ~ δ 60 ppm

Moreover, structure 20 was confirmed by ready coupling with benzenediazonium chloride giving the phenylhydrazone 21.

The formation of 20 from 2 and ethyl cyanoacetate may be considered as a novel route for synthesis of N-aminopyrimidines. Derivatives of this type are comparatively few.

Table: List of compounds newly synthesized.

Compound*	Solvent	Mp(^{o}C)	Yield (%)	Mol Formula	IR, selected bands (cm^{-1})
2	ethanol	165	90	$C_{10}H_9N_3O$	3300(NH); 2200(CN); 1710(CO).
4	acetic acid	190	80	$C_{16}H_{13}N_5O$	3350(NH); 2200(CN); 1700(CO)
5	ethanol	208	75	$C_9H_8N_4O_2$	3400(NH_2); 1700(CO)
7	ethanol	242	60	$C_{17}H_{12}N_2O_3$	3300(NH); 1700, 1690(CO)
8	DMF/H_2O	185	85	$C_{12}H_9N_4OCl_3$	3400, 3300 (NH_2 and NH); 2200(CN); 1690(CO).
9	DMF/H_2O	>300	50	$C_{11}H_{12}N_6O$	3450, 3350 (NH_2 and NH); 1690(CO)
13	acetic acid	>300	50	$C_{10}H_7N_4O$	3400 (NH_2 and NH); 2200(CN); 1700(CO)
15	DMF/H_2O	>300	40	$C_{11}H_7N_3O_2Cl_3$	3300 (NH_2 and NH), 1700, 1690 (CO)
20	ethanol	196	75	$C_{15}H_{16}N_4O_3$	3450(NH_2); 1700, 1690(CO)
21	ethanol	178	80	$C_{21}H_{20}N_4O_3$	3400, 3300 (NH_2 and NH); 1710, 1690(CO)

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

ACKNOWLEDGEMENT

We are deeply indebted to Prof. G. Pitacco, Dipartimento Di Scienze Chimiche, Universita Degli Studi Di Trieste, Italy, for facilities that enabled measurements of ^{1}H and ^{13}C-NMR.

REFERENCES

1. N.S. Ibrahim, N.M. Abed and Z.E. Kandeel, Heterocycles, 1984, 22, 1677.
2. N.M. Abed, N.S. Ibrahim, S.M. Fahmy and M.H. Elnagdi, Org. Preparations and Procedures Int., 1985, 17, 107.
3. F.M. Abdelrazek, N.S. Ibrahim, Z.E. Kandeel and M.H. Elnagdi, Synthesis, 1984, 970.
4. M.H. Elnagdi, M.R.H. Elmoghayar, E.A.A. Hafez and H.H. Alnima, J. Org. Chem., 1975, 2604.
5. N.S. Ibrahim, F.M. Abdelrazek, S.I. Aziz and M.H. Elnagdi, Monatsh. Chem., 1985, 116, 551.
6. K. Gewald, U. Hain and M. Gruner, Chem. Ber., 1985, 2198.
7. E. Breitmayer and W. Voelter, ^{13}C-NMR Spectroscopy, 2nd. Edition, Verlag Chemie, Weinheim, New York, 1978, 240.

Received, 24th March, 1986