Archiv der Pharmazie

317. Band April 1984 Heft 4

Arch. Pharm. (Weinheim) *317*, 289–293 (1984)

Activated Nitriles in Heterocyclic Synthesis: Studies on the Chemistry of Antipyrin-4-ylacetonitrile

Abdel-Ghani A. El-Agamey*)+), Ibrahim El-Sakka++, Zaghloul El-Shahat+++ and Mohamed H. Elnagdi+++

+ Faculty of Education (Damietta), Mansoura University; ++ Faculty of Education, Menofia University; and +++ Chemistry Department, Faculty of Science, Cairo University, Giza, A.R. Egypt

Eingegangen am 20. Januar 1983

Several new pyrazoles, isoxazoles and coumarin derivatives have been synthesized by the reaction of 4-antipyrinylacetonitrile with a variety of bidentate nucleophilic reagents.

Aktivierte Nitrile in der Synthese von Heterocyclen: Studien der Chemie von 4-Antipyrinylacetonitril

Einige neue Pyrazol-, Isoxazol- und Coumarin-Derivate werden durch Umsetzung von 4-Antipyrinylacetonitril mit nucleophilen Reagenzien hergestellt.

3-Oxonitriles are highly reactive multifunctional reagents which undergo a wide range of condensation and cyclization reactions[1,2]. Inspite of the enormous number of reports on the chemistry of acyl and aroylacetonitriles, very little attention has been paid to the chemistry of azoloylketonitrile[2]. In continuation to our interest in this class of compounds[1-4], we report on the chemistry of antipyrin-4-ylacetonitrile.

The work has resulted in synthesis of several new pyrazoles, isoxazoles and coumarin derivatives having antipyrin-4-yl substituents. As diverse biological activities has been reported for antipyrine derivatives[5], the obtained compounds appear interesting for biological evaluation studies.

Thus, 4-antipyrinylacetonitrile **(1)**, prepared *via* the action of potassium cyanide on 4-chloroacetylantipyrine **(2)** as has been reported[6], reacted with hydrazine hydrate to yield the aminopyrazole **3**. **1** also reacted with phenylhydrazine to yield a product which may be formulated as **4** or its isomer **5**. The formation of **4** is assumed to proceed *via* condensation of the unsubstituted nitrogen atom with the oxo function in **1** and cyclization. Structure **5** was considered for the product based on similarity to the well established behaviour of acyl and aroylacetonitrile[7] on reaction with aryl hydrazines.

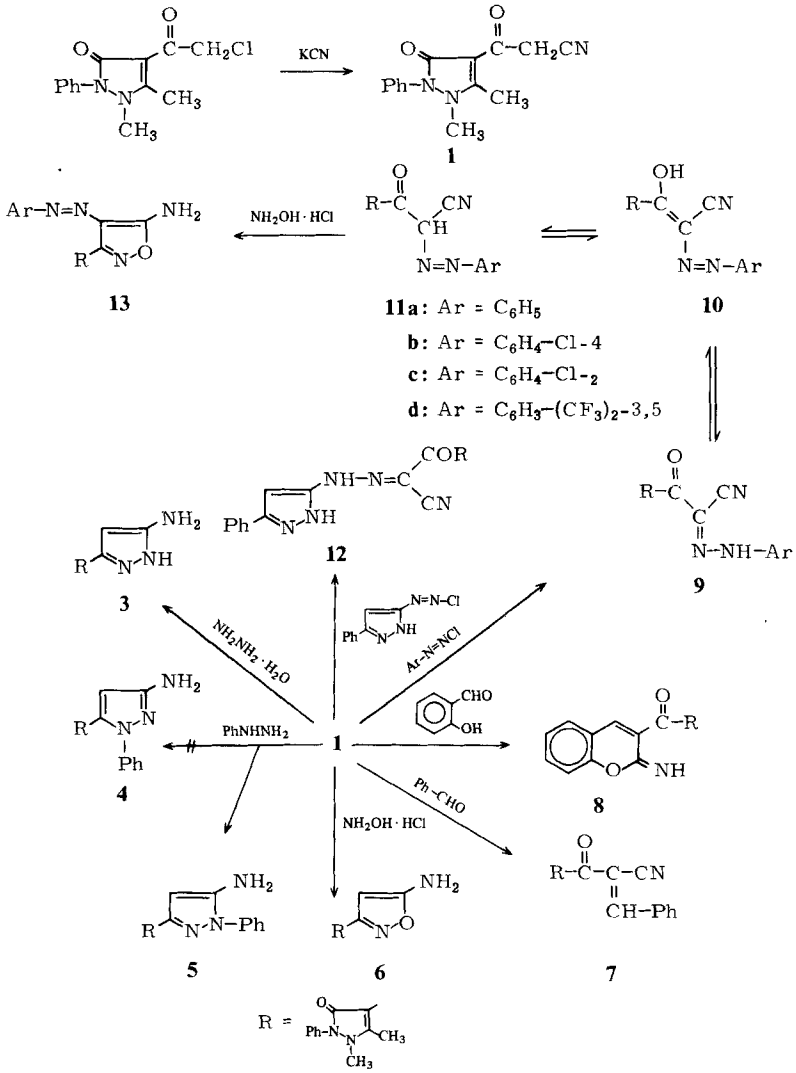
Similar to its behaviour towards hydrazine, **1**, reacted with hydroxylamine to yield the corresponding aminoisoxazole derivative **6**. This is similar to the reported formation of aminoisoxazoles on treatment of aroylacetonitriles with hydroxylamine[8].

0365-6233/84/0404-0289 $ 02.50/0

Compound **1** condensed with benzaldehyde to form the benzylidene derivative **7**. On the other hand the coumarin derivative **8** was formed on treatment of **1** with salicylaldehyde.

Compound **1** also coupled with aromatic diazonium salts to yield coupling products for which structures **9–11** seemed possible. The aryl azo structures **9, 10** could be ruled out based on the presence of a conjugated –CN group in the IR spectra of the coupling products and the absence of absorption due to enols. Thus the hydrazone structure **11** was established for the reaction product.

In contrast to the reported formation of pyrazole[1,5-c]-as-triazines on coupling diazotised 5-amino-3-phenylpyrazole with benzoylacetonitrile via cyclocondensation



reaction that takes place under coupling conditions[9,10], **1** coupled with 3-phenyl-5-diazonium chloride to yield the hydrazone **12** which could not be cyclised under a variety of conditions.

The arylhydrazone **11** reacted with hydroxylamine to yield the aminoisoxazoles **13.** This is in contrast to the reported formation of amidoximes on treatment of the aryl counter analogues with the same reagent under the same conditions[11]. This preferential attack of the nucleophile at the CO and not CN indicates that CO in **13** is more reactive than that in the aryl counter analogues.

Table 1: *Newly synthesized products*

Comp. No.	M.P.	Yield %	Cryst. Solvent	Formula (M.W.)	Found Calcd.	Analysis C	H	N
3	208	90	Ethanol	$C_{14}H_{15}N_5O$ (269)		62.3 62.5	5.8 6.0	26.0 26.0
5	245	72	Ethanol/ Chloroform	$C_{20}H_{19}N_5O$ (345)		69.4 69.6	5.7 5.5	20.0 20.3
6	275	25	Chloroform	$C_{14}H_{14}N_4O_2$ (270)		61.5 62.2	5.7 5.1	20.5 20.7
7	165	40	Ethanol	$C_{21}H_{17}N_3O_2$ (343)		73.2 73.5	5.1 4.9	12.0 12.2
8	232	60	Ethanol/ Chloroform	$C_{21}H_{17}N_3O_3$ (359)		69.7 70.2	4.9 4.7	11.8 11.7
11a	215	95	Ethanol	$C_{20}H_{17}N_5O_2$ (359)		66.8 66.9	4.9 4.7	19.7 19.5
11b*	210	90	Ethanol	$C_{20}H_{16}N_5O_2Cl$ (393.5)		61.0 61.0	3.7 4.1	17.9 17.8
11c**	234	91	Ethanol	$C_{20}H_{16}N_5O_2Cl$ (393.5)		61.2 61.0	3.9 4.1	18.0 17.8
11d***	222	92	Ethanol	$C_{22}H_{15}N_5O_2F_6$ (495)		53.8 53.3	2.8 3.0	14.0 14.1
12	200	85	Ethanol	$C_{23}H_{19}N_7O_2$ (425)		64.9 64.9	4.5 4.5	23.5 23.6
13	185	80	Ethanol	$C_{20}H_{18}N_6O_2$ (374)		64.4 64.2	5.0 4.8	22.5 22.5

* Cl Calcd 9.1 Found 9.0
** Cl Calcd 9.2 Found 9.0
*** F Calcd 23.3 Found 23.0

Table 2: *IR and ^{1}H-NMR data of the newly prepared compounds*

Compd. No.	IR; cm^{-1}	^{1}H-NMR; δ (ppm)
3	3500–3700 (NH_2 and NH); 1650 (CO) and 1620 (C=C).	2.33 (s, 3H, CH_3); 3.10 (s, 3H, N–CH_3); 5.5 (s, 1H; pyrazole H-4) 6.9 (s, 2H; NH_2) and 7.0–7.21 m, 5H; C_6H_5) and 12.0 (s, br; 1H; NH).
5	3500–3250 (NH_2); 1620–1630 (CO and C=C)	Insoluble in the common ^{1}H–NMR solvents
6	3420 and 3220 (NH_2); 1700–1660 (exocyclic of antipyrinyl CO) and 1640 (C=N)	Insoluble in the common ^{1}H–NMR solvents
7	2200 (CN) and 1700–1660 (ring and azoloyl CO)	Insoluble in the common ^{1}H–NMR solvents
8	3500–3300 (NH); 1700–1660 (exocyclic of antipyrinyl CO) and 1640 (C=N).	2.58 (s, 3H, CH_3–C); 3.30 (s, 3H; N–CH_3); 5.10 (s, 1H coumarin H-4) and 7.00–7.16 (m, br, 9H; arom. protons).
11a	3500–3400 (NH); 2210 (conjugated CN); 1660–1640 (ring and azoloyl CO) and 1620 (C=N)	2.55 (s, 3H, CH_3–C); 3.28 (s, 3H, N–CH_3) and 7.00–7.30 (m, 11H; arom. protons and NH).
12	3440 (NH); 2230 (CN) and 1670–1630 (ring and aroyl CO and C=N)	Insoluble in Common ^{1}H–NMR solvents
13	3420 and 3220 (NH_2); 1700–1675 (CO and NH_2) 1650 and 1625 (N=N and C=N)	2.33 (s, 3H, CH_3–C); 3.15 (s, 3H, N–CH_3); 5.18 (s, 1H, isoxazole H-4); 6.9 (s, 2H, NH_2) and 7.00–7.08 (m, 5H, C_6H_5).

Experimental Part

MP: uncorr. *Infrared spectra:* (KBr disc) Pye-Unicam SP-1100 spectrophotometer. *^{1}H-NMR spectra:* varian A-60 spectrophotometer using Me_4Si as int. stand., chem. shifts: δ (ppm). Satisfactory *analytical data* (± 0.3 %) were performed by the Microanalytical Center at Cairo University.

Reaction of **1** *with:*

a) *Hydrazine hydrate:* 2.6 ml (0.05 mole) (98 %) hydrazine hydrate was added to 5.1 g (0.02 mole) of **1**. The mixture was heated in water bath 15 min. Upon cooling an orange crystalline solid is formed. The solid product was triturated with ethanol, and recrystallized from ethanol.

b) *Phenylhydrazine:* To 5.1 g (0.02 mole) of **1**, 2.7 ml (0.025 mole) phenylhydrazine were added. The reaction mixture was heated at 110°C bath temp. for 3 h and then triturated with icewater. The obtained solid was washed several times with water and then recrystallized from ethanol/chloroform mixture.

c) *Hydroxylamine hydrochloride:* To 2.55 g (0.01 mole) **1** in 50 ml ethanol, 0.7 g (0.01 mole) hydroxylamine hydrochloride and 1 g sodium acetate were added, the reaction mixture was refluxed for 4 h. The excess solvent removed i. vac. and the remaining product triturated with water. The formed solid was washed several times with water, dried and crystallized from chloroform. Compound **6** was obtained in 30 % yield.

d) *Benzaldehyde:* Equimolar amounts of **1** and benzaldehyde (0.02 mole of each) were fused in presence of anhydrous sodium acetate in an oil bath at 110–120 °C for 1 h. The reaction mixture was triturated with water, the solid product was washed several times with cold water and then crystallized from ethanol.

e) *Salicylaldehyde*: To 1 ml (8 mmole) Salicylaldehyde and 2 g (7,8 mmole) **1** in 10 ml absol. ethanol few drops of piperidine were added and refluxed for 3 h, upon cooling a crystalline solid was formed and recrystallized from ethanol/chloroform.

f) *Aryl diazonium salts*: To a solution of 2.55 g (0.01 mole) **1** in 100 ml ethanol and 5 g anhydrous sodium acetate 0.01 mole of the appropriate aryl diazonium salt (prepared from 0.01 mole of the amine and the required quantities of sodium nitrite and hydrochloric acid) was added slowely with contineous stirring. The solid product so formed was washed with cold water and then recrystallized (cf. table 1).

g) *3-Phenylpyrazole-5-diazonium chloride*: To a solution of (0.01 mole) **1** in 80 ml ethanol 5.0 g anhydrous sodium acetate and a solution of diazotised 3-phenyl-5-aminopyrazole (prepared from 3-phenyl-5-aminopyrazole as has been described previously[12]) was added with stirring. The solid product, so formed, was recrystallized (cf. table 1).

Reaction of **11a** *with hydroxylamine hydrochloride*: To 3.59 g (0.01 mole) of **11a** in 100 ml ethanol were treated with 0.7 g (0.01 mole) of hydroxylamine hydrochloride and 1 g sodium acetate. The reaction mixture was refluxed for 4 h. The solvent was then removed i. vac. and the remaining was poured in cold H_2O. The solid product, so formed, was crystallized from ethanol.

References

1 M.H. Elnagdi, N.A.L. Kassab, M.E.E. Sobhy, M.R. Hamza and M.U. Wahby, J. Prakt. Chem. *314*, 815 (1972).

2 M.H. Elnagdi, D.H. Fleita and R.H. Elmoghayar, Tetrahedron *31*, 63 (1975).

3 M.H. Elnagdi, E.A.A. Hafez and H.A. Elfahham, J. Heterocycl. Chem. *17*, 73 (1980).

4 M.H. Elnagdi, S.M. Fahmy, E.A.A. Hafez, M.R.H. Elmoghayar and S.A.R. Amer, J. Heterocycl. Chem. *16*, 1109 (1979).

5 M.H. Elnagdi, H.A. Elfahham, M.R.H. Elmoghayar, K.U. Sadek and G.E.H. Elgemeie, J. Chem. Soc. Perkin Trans. 1, *1982*, 989.

6 H.P. Kaufmann und L.S. Huang, Chem. Ber. *75*, 1214 (1942).

7 M.H. Elnagdi, M.R.H. Elmoghayar and D.H. Fleita, J. Prakt. Chem. *316*, 975 (1974).

8 S. Yamada and C. Kowaki, J. Pharm. Soc. Jpn. *71*, 1356 (1951).

9 M.H. Elnagdi, E.M. Zayed and S. Abdou, Heterocycles *19*, 3, 1982.

10 M.H. Elnagdi, E.M. Zayed, M.A.E. Khalifa and S.A. Ghozlan, Monatsh. Chem. *112*, 245 (1981).

11 M.H. Elnagdi, M.R.H. Elmoghayar, E.A.A. Hafez and H.H. Alnima, J. Org. Chem. *40*, 2604 (1975).

12 M.H. Elnagdi, M.R.H. Elmoghayar, D.H. Fleita, E.A. Hafez and S.M. Fahmy, J. Org. Chem. *41*, 3781 (1976).