ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS : THE REACTION OF CYANOACETHYDRAZIDE WITH ∝-SUBSTITUTED CINNAMONITRILE DERIVATIVES

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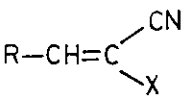
Abstract - The cinnamonitrile derivatives reacted with cyanoacethydrazide at room temperature to yield N-aminopyridones. The latter underwent a rearrangement reaction on refluxing in ethanolic triethylamine. The same rearrangement products could be directly obtained from the reaction of cinnamonitrile derivatives and cyanoacethydrazide in refluxing ethanol-triethylamine. The mechanism of the reactions involved is suggested.

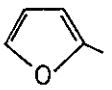
Functionally substituted nitriles are synthetically useful compounds which have been extensively utilized for the synthesis of heterocyclic derivatives.[1-3] We report in this paper the reaction of the cinnamonitrile derivatives 1a-d with cyanoacethydrazide 2 . The work resulted in development of a new approach for the synthesis of 1-aminopyridone derivatives. Furthermore a pyridine ring opening and recyclization reactions could be observed. Thus , in a typical procedure it has been found that when a mixture of 1a (20 m moles) and 2 (20 m moles) in absolute ethanol (30 ml) was stirred at room temperature for 1 h in the presence of catalytic amount of triethylamine a 1 : 1 adduct is formed. Five theoretically possible isomeric structures were considered for the reaction product (cf. structures 3-7). Structures 3-5 could be , however , eliminated based on IR and ^{1}HNMR spectra. Thus , the IR spectrum of the reaction product showed only a signal for one cyano group. For structures 3-5 , it is anticipatable that the IR spectrum

should show two cyano group signals . Moreover , ^{1}HNMR of the reaction product did not show any signal for either pyrazoline H-3 or tetrahydropyridine H-3 and H-4 thus structure 5 was ruled out . Structure 6 was also considered least likely based on the stability of the reaction product under conditions reported to effect ready rearrangement or deacylation of N-acylpyrazole.[4] Thus , structure 7 was established for the reaction product . The formation of 7 in this reaction is assumed to proceed via addition of the active methylene group in 2 to the cyano function in 1a and cyclization via attack of the hydrazide nitrogen on the electron deficient CN carbon . This is in contrast to the previously reported behaviour of active methylene reagents toward 1a where usually addition to the activated double bond system has been observed.[5] However , similar anamolous behaviour have been recently observed in the reaction of 1-phenyl-3-methyl-2-pyrazolin-5-ones with 1a,b.[6]

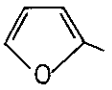
On the other hand , when the reaction of 1a with 2 was conducted in 95% ethanol in the presence of triethylamine and the reaction mixture was refluxed for 3 h a product of molecular formula $C_{14}H_{14}N_4O_4$ is formed. The same product was formed on refluxing 7 in 95% ethanol for 3 h in the presence of catalytic amount of triethylamine. This product was assigned structure 8 based on ^{1}HNMR data which revealed two multiplets at δ 4.22-4.66 for 2-oxo-tetrahydropyridone H-2 and H-3. The formation of 8 from 1a and 2 or from 7 is assumed to proceed via hydrolysis of 7 into the dione 9 which then undergoes further ring opening and recyclization reaction.

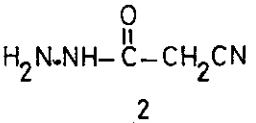


1a, R= C_6H_4·OCH_3(p) ; X = CN

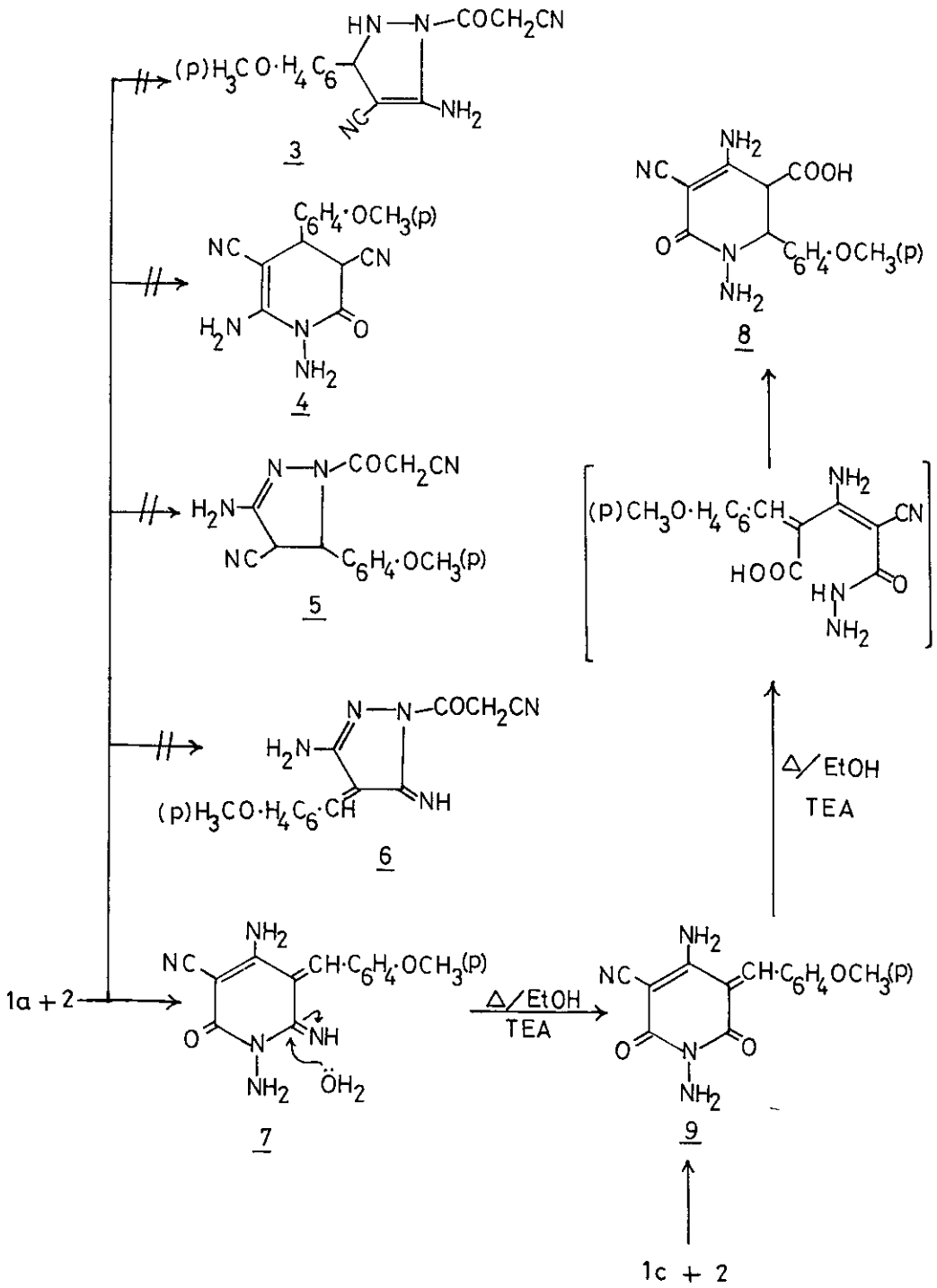
b, R=  , X = CN

c, R= C_6H_4·OCH_3(p) ; X = $CO_2C_2H_5$

d, R=  ; X = $CO_2C_2H_5$



2


3
4
5
6
7
8
9
1a + 2
1c + 2
Δ/EtOH
TEA
Δ/EtOH
TEA

Similar to the behaviour of 1a toward 2 , compound 1b reacted with 2 to yield either the pyridine derivative 10 or 11 depending on the applied reaction conditions. Thus , at room temperature compound 10 was formed whereas under reflux 11 was the isolable product. Compound 10 could be also converted into 11 under the same conditions utilized to effect rearrangement of 7 into 8. The formation of 11 is assumed to proceed via sequence similar to that previously suggested to effect rearrangement of 7 into 8. However , the resulting product undergoes ready oxidation into the pyridone 11 perhaps by the action of unreacted 1b. Ready oxidation of tetrahydropyridone into dihydropyridine derivatives was previously observed.[7] The stability of 8 toward oxidation under the reaction conditions may be attributed to the electron donating effect of the methoxy group which makes the change in ΔG on oxidation less important. In support of this view is the ready oxidation of 10 and also the tetrahydropyridines obtained from the reaction of benzal- and p-nitrobenzalmalononitrile with 2 which has been recently observed.[8]

Compound 1c reacted with 2 in ethanolic triethylamine at room temperature to yield compound 9 (mp and mixed mp). Moreover , compound 9 readily rearranged into 8 on refluxing for 3 h in ethanolic triethylamine. Formation of 9 is assumed to proceed via addition of 2 to the cyano group in 1c and ethanol elimination. In support of this view is the isolation of compound 12 from the reaction of 1d and 2. Compound 12 rearranged readily into the acid 11 on treatment with ethanolic triethylamine perhaps via intermediacy of the dione 13 in a way similar to that discussed above.

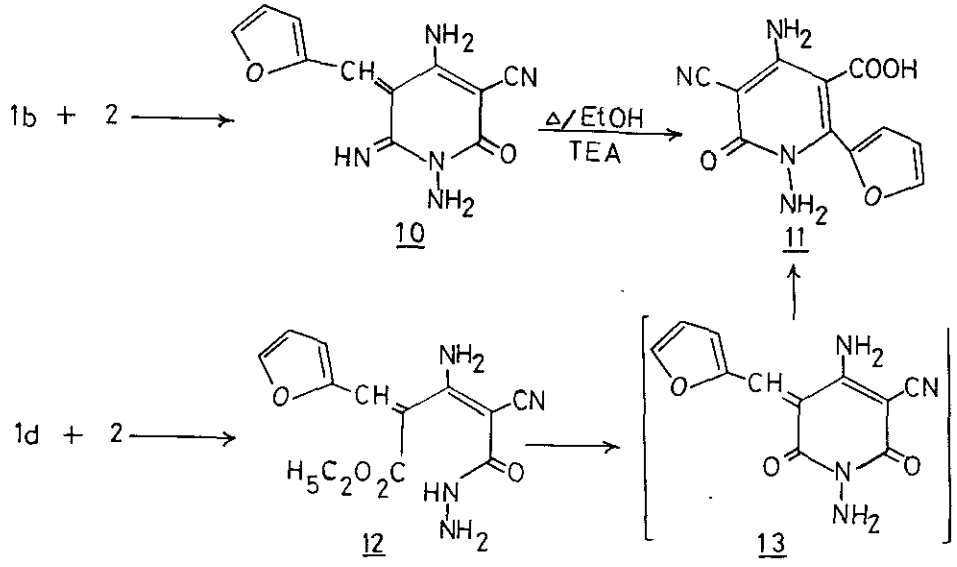


Table 1 : Analysis of the newly synthesized compounds

Compound* (Colour)	MP (°C)	Cryst. Solvent	Yield (%)	Compound* (Colour)	MP (°C)	Cryst. Solvent	yield (%)
7 (Colourless)	212	dioxan	80	8 (Yellow)	195	dioxan	70
9 (Yellow)	108	dioxan	75	10 (Yellow)	>300	DMF/H_2O	75
11 (Reddish)	>300	DMF/H_2O	73	12 (Reddish)	198	Ethanol	65

* Satisfactory elemental analyses for all the newly synthesized compounds were obtained .

Table 2 : Spectroscopic data of the newly synthesized compounds

Compound	IR (cm^{-1})	^{1}HNMR (ppm)
7	1670 (CO) , 2210 (CN) , 3100-3210 (NH_2)	4.0(s , 3H , OCH_3) ; 7.06-8.1(m , 5H , arom. and ylidene CH)
8	1665 (CO) , 2200 (CN) , 3100-3220(NH_2) ,3410 (OH)	4.0(s , 3H , OCH_3) ; 4.22-4.66(m , 2H, pyridone H-2 & H-3 ; 7.1-8.06(m,4H, arom. H)
9	1670 (CO) , 2260 (CN) , 3100,3200 (NH_2)	3.9-4.0(m,7H,$2NH_2$ and OCH_3); 7.06-8.22 (m,4H,arom.H) and 8.66(m,1H, ylidene CH(cis and trans)
10	1650 (CO) , 2210 (CN) , 3100-3300 (NH_2)	4.0(s,5H,NH protons); 6.85(m,1H,furan H-4); 7.56-7.9(m,3H,furan H-3,H-5 and ylidene CH)
11	1650 (CO) , 2210 (CN) , 3110-3310 (NH_2) ,3410 (OH)	6.66-7.66 (furan protons)
12	1670 (CO) , 2260 (CN) , 3090-3110 (NH_2)	1.3(t,3H,CH_3); 2.22 and 3.9(NH,NH_2 , 5 protons); 4.22(m,2H,CH_2); 7.06(furan protons); 8.0(m,2H,furan H-2 and H-5), 8.16 ylidene CH)

REFERENCES

1 . J. Sepiol, Synthesis, 1983, 559.

2 . H. A. A. F. Daboun, S. E. Abdou, M. M. Hussein and M. H. Elnagdi, Synthesis, 1982, 502.

3 . M. R. H. Elmoghayar, M. A. E. Khalifa, M. K. A. Ibraheim and M. H. Elnagdi, Monatshefte, 1982, 113,53.

4 . M. H. Elnagdi and M. Ohta, Bull. Chem. Soc. Japan, 1973, 46, 1830.

5 . M. A. E. Khalifa, A. A. Elbanany and G. H. Tammam, Curr. Sci., 1982, 51, 1112.

6 . S. Abdou, S. M. Fahmy, K. U. Sadek and M. H. Elnagdi, Heterocycles, 1981, 16, 2177.

7 . S. Kambf, K. Saito, A. Sakurai and H. Midorikawa, Synthesis, 1981, 531.

8 . M. Y. A. Nasr, Ph.D. Thesis, Cairo University, 1984.

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