

A NOVEL SYNTHESIS OF 4-H-THIOPYRANS: UNEXPECTED PRODUCTS OF REACTION OF CYANTHIOACETAMIDE WITH CINNAMONITRILE DERIVATIVES

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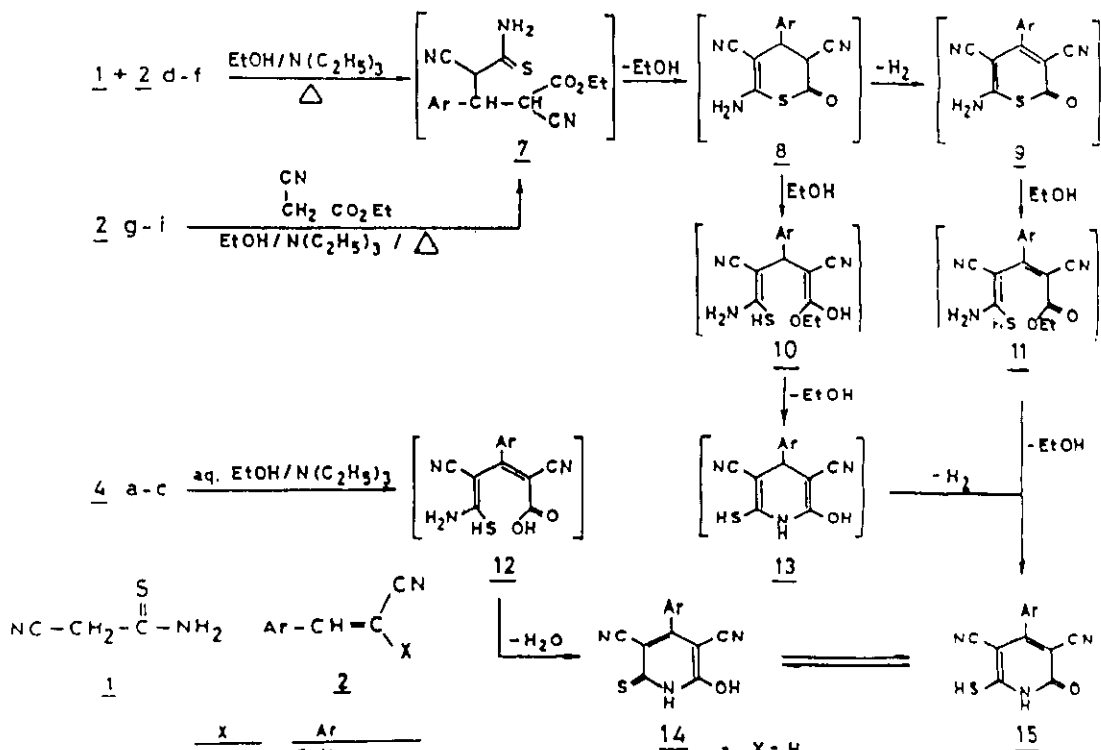
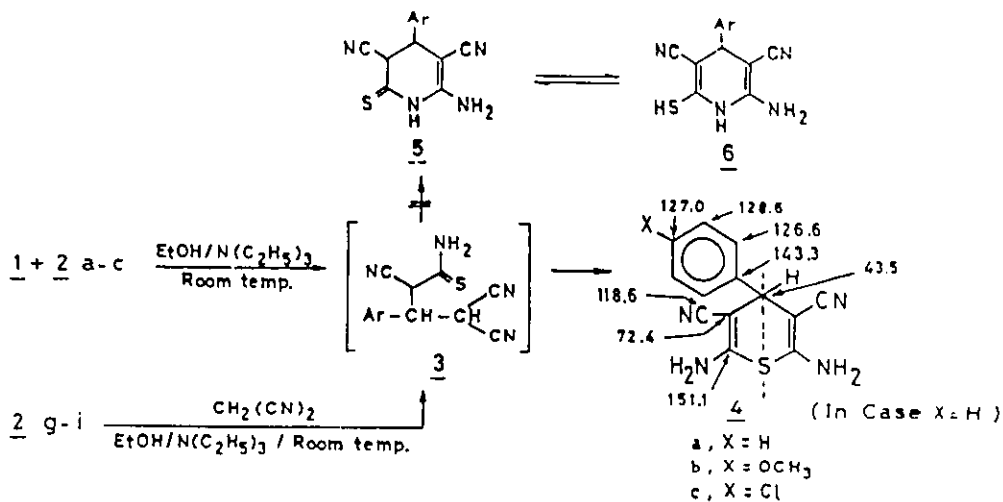
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Abstract - The reaction of arylidenemalononitrile with cyanothioacetamide afforded either thiopyrans or pyridine derivatives depending on reaction conditions. ¹³C NMR was utilised to elucidate the proposed structures of the reaction products.

In the last few years we were involved in a program aiming to develop synthetic approaches for polyfunctionally substituted heterocycles utilising readily obtainable nitriles as starting materials^{1,2}. In conjunction to this work we investigated the reaction of cyanothioacetamide (1) with cinnamitrile derivatives 2a-f. Literature contains plenty of reactions of active methylene reagents with 2 that lead to 1,2-dihydropyridine or pyran derivatives^{3,4}. In our laboratories 1 reacted with 2a-c in cold ethanolic triethylamine to yield 1:1 adducts. The same products were obtained, in 60-70% yields, from reaction of 2g-i with malononitrile which excluded several possible structures as it indicates that the reaction occurred through addition to the activated double bond to yield either acyclic derivatives resulting from addition of active methylene, amide or thioimidic form of 1 or their cyclisation products. Dihydropyridine forms seemed to us unlikely as one would expect that the products would be readily oxidised under the reaction conditions in a way similar to that reported for their oxo counter analogues⁵. ¹³C NMR of the product of reaction of 1 with 2a revealed, in addition to signals due to aromatic ring carbons at 126.6, 128.5 and 131.6 ppm and one CN signal at 118.6 ppm, signals at 72.4 ppm (C-3 and C-5), 43.5 ppm (C-4) and 151.1 ppm (C-2 and C-6). It is clear that such spectrum can only be

rationalized in terms of a thiopyran form 4 in which carbons C-2; C-6 and C-3; C-5 are identical as the molecule exhibits a plane of symmetry. Compounds 4 are believed to be formed via intermediacy of acyclic 3 which affords the end product 4 on cyclisation. Cyclisation of 3 to yield the dihydropyridine form 5 or tautomeric 6, in a way similar to that observed recently⁵ on reaction of 1 with α -cyanochalcones, did not occur. It is of value to report that the formation of thiopyrans from reaction of 1 with 2a-c constitutes a novel synthesis of the not readily accessible thiopyran ring system.

Trials to effect reaction of 2d-f with 1 under the same conditions failed to produce isolable products. The reaction in refluxing ethanolic triethylamine afforded compounds 14a-c, which correspond to the addition of 1 to 2d-f followed by ethanol and hydrogen molecule elimination. When the reaction of 1 with 2a-c was conducted under reflux in ethanolic aqueous triethylamine, the same compounds, 14a-c, were obtained, in 55-60% yields. Compounds 14a-c were also formed in 60-65% yields on refluxing 4a-c in ethanolic aqueous triethylamine. Thus, it seemed most likely that 14a-c are formed via intermediacy of a thiopyran form. Again these compounds were obtained by reaction of 2d-f with ethyl cyanoacetate. The ¹³C NMR spectra of the products revealed absence of any sp³ carbons or -CH in the molecules. Thus the reaction products should exist either in the enol or the keto forms 14 and 15. ¹³C NMR showed that in DMSO the thione form 14 predominates as it revealed a signal at 179.4 ppm, comparable to the signal at 176.4 ppm for pyridine thione. Pyridine thiols are expected to reveal signals at 160 ppm. The signal at 162 ppm can be assigned to C-6 as it can be correlated to the signal at 164.9 ppm observed for 2-methoxypyridine⁶. Moreover IR spectrum of the products revealed the absences of absorption for ring CO. The results show that the reaction of 1 with 2a-f can lead either to thiopyrans, kinetically or to the dihydropyridines thermodynamically. Reactions of similar molecules reported earlier are now being reinvestigated to see if the products of reaction are also dependent on reaction conditions.



X	Ar
a, CN	C ₆ H ₅
b, CN	C ₆ H ₄ -OCH ₃ -p
c, CN	C ₆ H ₄ -Cl-p
d, CO ₂ Et	C ₆ H ₅
e, CO ₂ Et	C ₆ H ₄ -OCH ₃ -p
f, CO ₂ Et	C ₆ H ₄ -Cl-p
g, C-NH ₂	C ₆ H ₅
h, C-NH ₂	C ₆ H ₄ -OCH ₃ -p
i, C-NH ₂	C ₆ H ₄ -Cl-p

a, X = H
 b, X = OCH₃
 c, X = Cl

Table (1): List of compounds 4a-c and 14a-c

Compound Colour	Cryst. Solvent	Mp. (°C)	Yield (%)	Mol. Formula ³ Mol. Weight	M ⁺
<u>4a</u> (Colourless)	EtOH	184	72 ¹	C ₁₃ H ₁₀ N ₄ S (254)	254
<u>4b</u> (colourless)	EtOH	300	70 ¹	C ₁₄ H ₁₂ N ₄ OS (284)	284
<u>4c</u> (colourless)	EtOH	250-252	65 ¹	C ₁₃ H ₉ N ₄ SCl (288.5)	288, 290
<u>14a</u> (yellow)	EtOH	195	68 ²	C ₁₃ H ₇ N ₃ OS (253)	253
<u>14b</u> (Yellow)	EtOH	295-296	72 ²	C ₁₄ H ₉ N ₃ O ₂ S (283)	283
<u>14c</u> (Yellow)	EtOH	280-281	70 ²	C ₁₃ H ₆ N ₃ OSCl (287.5)	287, 289

1- Yields based on reaction of 1 with 2a-c. 2- Yields based on reaction of 2d-f with 1. 3- All compounds reported were obtained in analytically pure state and give spectral data (IR, ¹H NMR and ¹³C NMR) in agreement with their structures.

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