THE USE OF SOME ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESES

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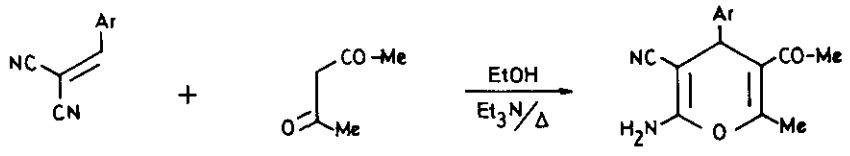
Abstract - The recently reported synthesis of a variety of 4H-pyrans from cinnamonitriles is reinvestigated and revised structures are given. New reaction products are also described.

In a paper recently published in this journal,[1] the synthesis of several 4H-pyrans was described. Significant discrepancies with our own extensive work on the synthesis of 4H-pyrans[2-8] were apparent in this paper, which led us to reinvestigate the work reported by Ibrahim.[1] Our results confirm that some of his proposed structures must be amended.

The reactions described below are reported in reference 1. They have all been reexamined by us and each is discussed separately.

Reaction of acetylacetone with α-cyanocinnamonitriles

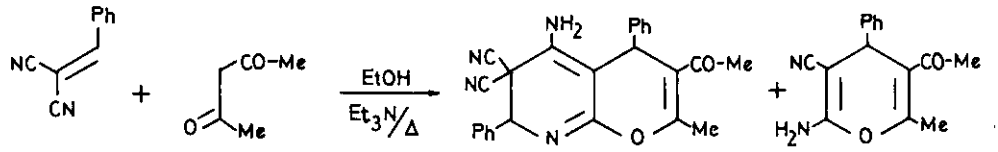
The following reaction is reported in reference 1:



Ar= Ph; p-MeO-C_6H_4; 2-Furfuryl

When we carried out this reaction, (Ar=Ph) two compounds were obtained, which were isolated by fractional precipitation. The compound that precipitated first (20%) showed mp 292-296°C (decomp.), while the second product (40%) melted at 158-160°C. Ibrahim gives an intermediate mp 210°C for his reaction product.

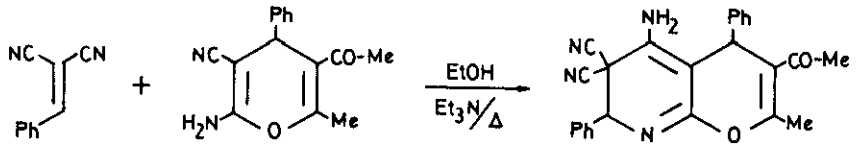
The compound melting at 292-296°C has analytical and mass spectral data (M^+ 408) which indicate a molecular formula $C_{25}H_{20}N_4O_2$. On the basis of the data given below, a structure of pyranopyridine (I), resulting from two molecules of α-cyanocinnamonitrile and one molecule of acetylacetone, is assigned to this compound. The second product (mp 158-160°C) was identified as the 2-amino-4H-pyran II by comparison with an authentic sample prepared as previously described:[6,8]



I II

The ^1H nmr spectrum (DMSO-d_6, 300 MHz, 50°C) of I showed the following signals: δ 1.90 (3H, s), 2.09 (3H, d, J= 2.0 Hz), 4.48 (1H, s), 4.94 (1H, q, J= 2.0 Hz), 7.1-7.4 (10H, m) and a very broad signal at approx. δ 8.0 (2H), which disappeared on the addition of a trace of deuterated trifluoroacetic acid. A double resonance experiment indicated that the proton at δ 4.94 was coupled to the methyl group at δ 2.09 (J= 2.0 Hz). The ^{13}C nmr spectrum of I confirmed the proposed pyranopyridine structure. It showed the following signals (SFORD multiplicities): δ17.2 (q), 29.7 (q), 48.1 (s), 50.1 (d), 50.8 (d), 52.1 (s) 116.0 (s), 117.8 (s), 128.4 (d, 2C), 128.5 (d, 2C), 129.4 (d,5C), 129.6 (d), 130.6 (s), 134.6 (s), 135.2 (s), 139.5 (s), 163.5 (s), 168.3 (s) and 201.6 (s).

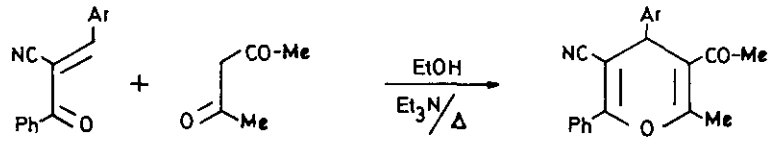
The formation of the pyranopyridine ring by a reaction with two molecules of α-cyanocinnamonitrile could involve the 2-amino-4H-pyran II as an intermediate. To prove this point, we carried out a separate reaction by treating the pyran with α-cyanocinnamonitrile. As expected, the same pyranopyridine I was obtained as the reaction product (60% yield).



Reaction of acetylacetone with α-benzoylcinnamonitriles

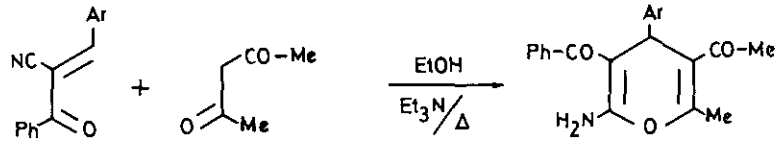
Although little structural discussion was entered into, the author in reference 1 proposed two different routes for this reaction, depending upon the aryl group: formation of (a) a 2-phenyl-4H-pyran, when Ar= p-MeO-C_6H_4, or (b) a 2-amino-4H-pyran, when Ar=Ph. The first reaction involves cyclization with two carbonyl groups[9] and the second cyclization with one carbonyl group and the cyano group.

a)



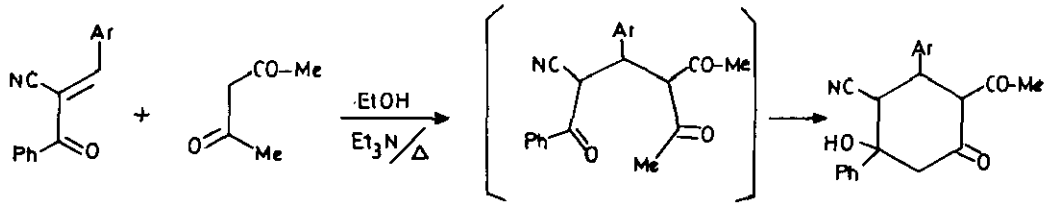
Ar=p-MeO-C_6H_4

b)



Ar=Ph

As regards reaction (a), we carried it out using the same conditions as reported, and obtained a crystalline solid (30%) with mp 207-209°C. Its spectroscopic data do not agree with a 4H-pyran structure. The analytical and mass spectral data (M^+ 363) indicate the molecular formula $C_{22}H_{21}NO_4$. The ir spectrum (KBr) shows an OH band at 3330 cm^{-1}, a CN band at 2240 cm^{-1} (very weak, as expected for an unconjugated nitrile[10]) and two C=O bands at 1720 and 1700 cm^{-1}. The ^1H nmr spectrum (DMSO-d_6)[11] shows two sharp singlets at δ 1.97 (CH_3) and 3.60 (CH_3O), a singlet at δ 6.40 (1H, OH; it disappears on the addition of TFA), aromatic protons at δ 6.6-7.0 (9H) and aliphatic ring protons at δ 2.4 (CH_2) and 3.05-4.3 (3H, m). On the basis of these data, a structure of 3-hydroxycyclohexanone resulting from intramolecular aldol condensation should be assigned to this compound.

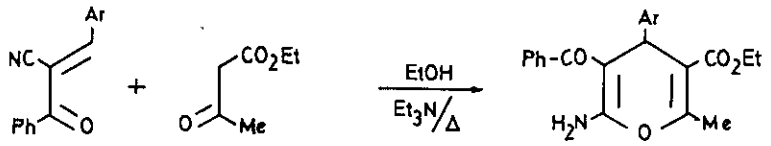


Ar= p-MeO-C_6H_4; Ph

Similarly, repetition of reaction (b) afforded a compound in clear disagreement with the proposed 2-amino-4H-pyran. A compound with mp 204-206°C and molecular formula $C_{21}H_{19}NO_3$ was obtained (21%). The spectral data are in every way analogous to those of the compound with a p-MeO-C_6H_4 group. (ir: 3340, 2240, 1720, 1700 cm^{-1}. ^1H nmr[11]: δ 1.97 (s, CH_3), 6.45 (1H, OH), 2.5 (CH_2), 3.3-4.5 (m, 3H) and 7.0-7.6 (10 H). These results lead to the expected conclusion that the reaction course is the same whether there is a phenyl or a p-methoxyphenyl group in the starting material, a 3-hydroxycyclohexanone being obtained in both cases.

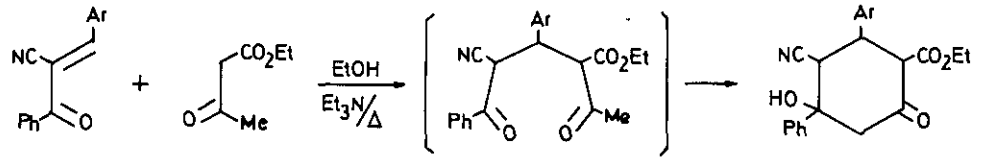
Reaction of ethyl acetoacetate with α-benzoylcinnamonitriles

In reference 1, cyclization involving the acetyl and the cyano groups, leading to a 2-amino-4H-pyran structures is proposed:



Ar=Ph; p-MeO-C_6H_4

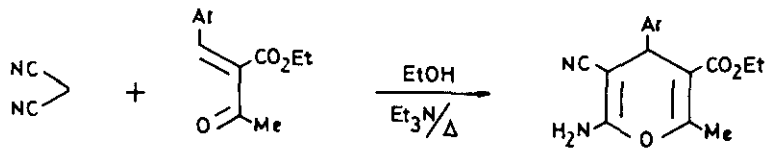
This reaction has recently been reported by other authors (Ar=Ph) as giving the open chain Michael adduct[12]. Our own results in this reaction have led us to the conclusion that the cyclization of the Michael adduct takes place through intramolecular aldol cyclization, affording a 3-hydroxycyclohexanone ring[6], the structure of which is discussed in reference 13:



Reaction of α-cyanocinnamonitrile with ethyl acetoacetate

A structure of 2-amino-4H-pyran is proposed in reference 1 for the product resulting from this reaction. Reinvestigation of this compound (Ar=Ph) proved the structure to be correct, the reaction product being the same compound we obtained by

using either piperidine/ethanol or triethylamine/ethanol in the reaction of malononitrile with ethyl α-acetylcinnamates[6]:



Ar=Ph; p-MeO-C_6H_4

However, the assignement of the ^{13}C nmr signals of the compound (Ar=Ph) made in reference 1 is wrong. As discussed in our general study of ^{13}C nmr spectra of 2-amino-4H-pyrans[14], C-3 actually resonates at a very high field (δ 57.4), C-4 appears at δ 38.8 and C-5 at δ 107.3. The CH_2 in the substituent at C-5 appears at δ 60.1 because it is an ethoxycarbonyl group and not a propionyl group as mistakenly drawn in chart 1 of reference 1.

ACKNOWLEDGEMENT

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