ON THE RING CLEAVAGE OF ISOXAZOLES: A NOTE

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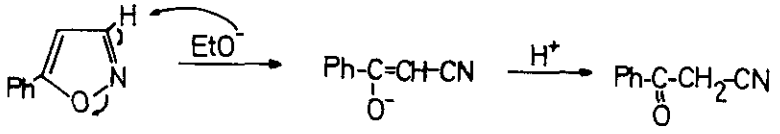
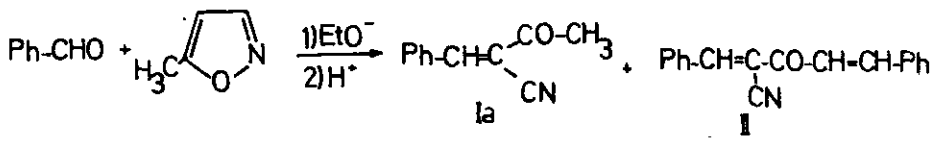
Abstract- A new heterocyclic compound is obtained from the basic cleavage of an isoxazole ring in the presence of an aldehyde.

The cleavage of an isoxazole ring by a basic reagent is a well known reaction[1]. The ring opening is specially facile in 5-substituted derivatives with no substituent at position 3[2], where abstraction of the proton at position 3 prompts the N-O bond cleavage.



If the resulting β-ketonitrile is an stable compound it can be prepared in excellent yields using this reaction. It has been utilized as a convenient means of changing a ketone into an α-cyanoketone via an isoxazole, even in the synthesis of some natural products such as equilenin[3].

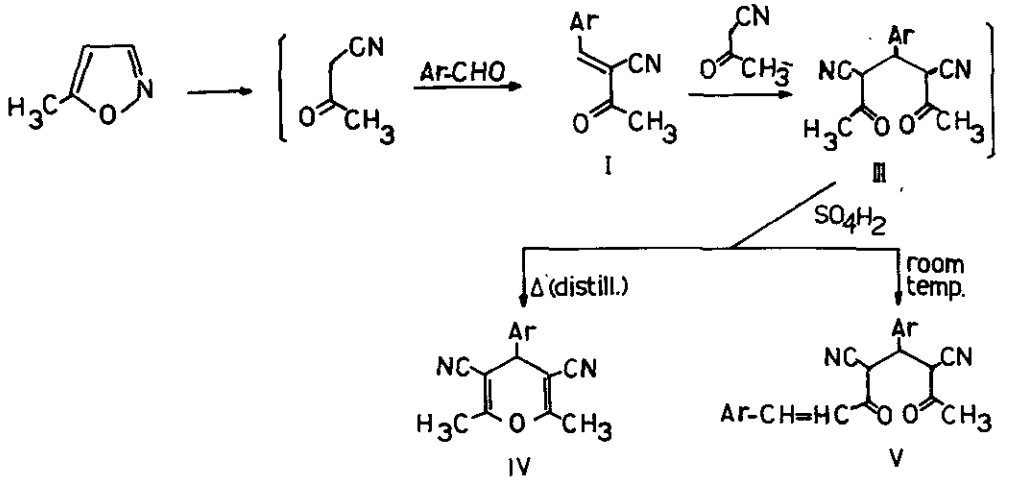
When 5-alkyl-substituted isoxazoles are used, the resulting, easily polimerizable ketonitrile is usually too unstable to be isolated and complex mixtures are obtained[4,5]. However, Eugster et al. have reported[5] that when the ring cleavage of 5-methylisoxazole is carried out in the presence of benzaldehyde, the unstable ketonitrile is isolated in the form of benzylidenecyanoacetone (Ia) and the double condensation product (II) (Scheme I). These compounds were of interest to us in connection with the synthesis of some furan compounds[6] and we prepared them using the above mentioned reaction.



SCHEME I

We found that, together with the reported compounds, another product is also obtained from the reaction. Tipycally, 5-methylisoxazole (16.6 g) and benzaldehyde (21.2 g) were allowed to react with sodium ethoxide in dry ethanol for 24 hours at room temperature followed by acid treatment. Compound IVa is obtained upon vacuum distillation (160-170°C/0.01 mm Hg) as an oil which solidifies after a few hours and is recrystallized twice from methanol (0.9 g; m.p. 137-138°C).

Structure IVa is confirmed by the following data: the molecular formula $C_{15}H_{12}N_2O$ is inferred for this compound from the analytical (C, 76.41%; H, 5.35%; N, 12.20%) and mass spectral data (M^+, 236). The cyano group (2220 cm^{-1}) and the C=C double bond (1670 cm^{-1})[7] give rise to the appropriate bands in the IR spectrum. The five aromatic protons appear as a multiplet at 7.2-7.4 ppm in the ^{1}H-NMR spectrum (Cl_3CD) and the methyl group appear at 2.2 ppm. The hydrogen located at position 4 of the ring is responsible for the peak at 4.1 ppm[8]. The values of the chemical shifts in the ^{13}C-NMR spectrum (DMSO-d_6) are also in agreement with the calculated values[9]. The γ carbon of the heterocyclic ring appears at 38.52 ppm, the α carbons



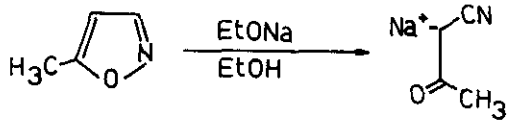
SCHEME II

peaks appear at 159.79 ppm and the β carbons at 89.15 ppm. A peak at 116.57 ppm due to the cyano carbon and a peak at 18.31 ppm for the methyl groups are also in the spectrum, together with the aromatic carbons.

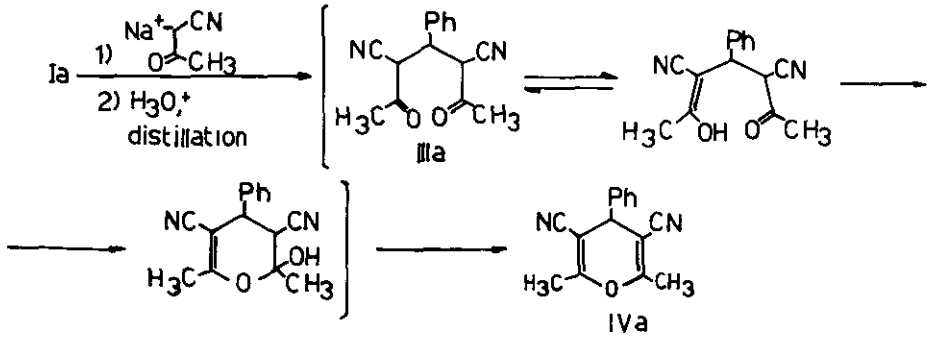
Scheme II summarizes a likely mechanism for the formation of IV. It involves the ring opening of isoxazole to give cyanoacetone, which is converted by the aldehyde into benzylidenecyanoacetone (Ia). Addition of another unit of cyanoacetone to I affords diketone III which, upon cyclization by nucleophilic attack of an oxygen to a carbonyl group, gives rise to IVa.

If no distillation is involved, compound V, resulting from a double condensation of aldehyde, is obtained instead of pyran IV. Furthermore, attempts to obtain substituted derivatives of pyran IV by using different aldehydes were unsuccesful. Thus, when p-methylbenzaldehyde was used, compound Ib (Ar=p-CH_3-C_6H_4) was the only product isolated from distillation.

As a confirmation for the proposed mechanism, the sodium salt of cyanoacetone was obtained, as a stable solid, by ring cleavage of 5-methylisoxazole:

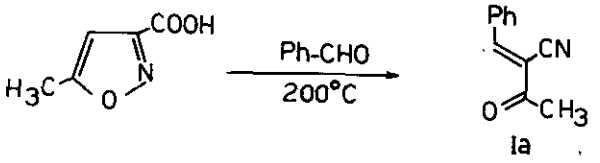


Treatment of Ia, obtained from 5-methylisoxazole, with the sodium salt of cyanoacetone followed by acid treatment and distillation, leads to pyran IVa. (Scheme III)



SCHEME III

Moreover, compound Ia could be obtained as a pure compound by melting together benzaldehyde and 5-methylisoxazole-3-carboxilyc acid[10], in the abscence of any solvent, at 200°C.



Ia

The acid treatment is responsible for the heterocyclization between the two carbonyl groups. Cyclization of similar intermediates in basic medium involves the reaction between a carbonyl and a cyano group, leading to 2-amino-4H-pyran[11]. It must be pointed out that the formation of pyran IV is an unusual reaction, because cyclization of an alkyl substituted 1,5-diketone to a pyran ring is usually prevented by the occurrence of an intramolecular aldol cyclization to a cyclohexanone ring[12]. The pyran ring is only obtained when it is somehow stabilized[13].

ACKNOWLEDGEMENTS

Support of this work by the Comisión Asesora de Investigación Científica y Técnica de la Presidencia del Gobierno of Spain is gratefully acknowledged.

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Received, 17th January, 1984