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SYNTHESIS OF HETEROCYCLIC COMPOUNDS XXXVI*
PREPARATION OF ALKYL SUBSTITUTED PYRANCARBONITRILES.

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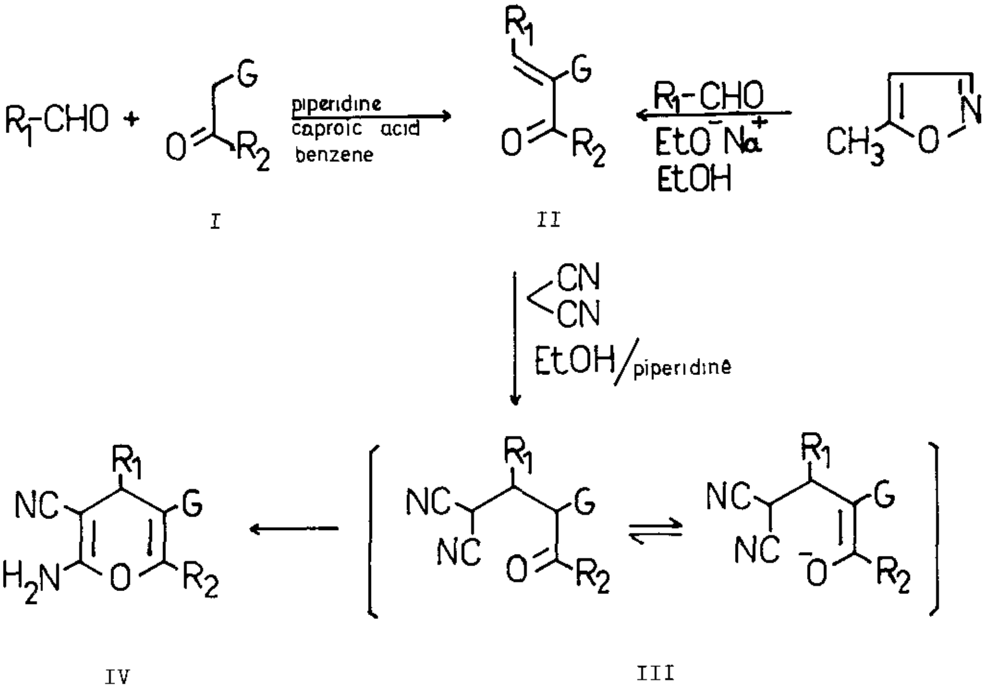
Abstract - The cyclization of the ketonitriles obtained from the reaction of suitably substituted propenones with propanedinitrile leads to alkyl substituted 4H-pyrans. Some of the starting propenones had to be prepared by base promoted opening of an isoxazole ring in the presence of an aldehyde. An exception to the general synthesis is also reported.

The synthesis of alkyl-substituted 4H-pyrans by cyclization of α,ω-difunctionalized compounds is usually prevented by the occurrence of aldol-type intramolecular cyclizations[1-3], unless suitable structural features do not allow the formation of a carbocyclic ring[4-9].

In previous papers[10] we reported the synthesis of 2-amino-3-cyano-4H-pyrans by means of the heterocyclization of aryl-substituted δ-ketonitriles. Since an aldol or Thorpe-type homocyclization is possible as an alternative reaction, we study in this communication whether the above mentioned shortcomings are also present in our synthesis when alkyl groups are substituted for the aryl groups.

Ketonitriles III result from the reaction of propanedinitrile with suitably substituted propenones (II) which are in turn prepared by a piperidine or piperidinium caproate catalyzed Knoevenagel condensation between an aldehyde and a β-ketoester ($I,G=CO_2Et$)[11], a 1,3-diketone (I,G=CO-R)[11] or an aromatic ketone (I,G=Ph)[12]. When G is a cyano group, the preparation of the corresponding propenones II by the same procedure is not possible because of the instability of acetylacetonitrile (I,G=CN)[13]. Thus, this compound was generated in situ in the presence of an aldehyde by a base promoted ring opening of 5-methylisoxazole[14].

Reaction of propanedinitrile with propenones II in a basic medium, results in the conjugate addition of the anion of propanedinitrile, followed by the spontaneous cyclization of the resulting ketonitrile by a nucleophilic attack by the enolic oxygen at the cyano group (Scheme 1).



Scheme 1

The reaction is carried out at room temperature in alcoholic solution and pyrans IV are easily isolated as crystalline solids in medium to good yields (Table I). As an exception, addition of propanedinitrile to 3,4-diphenylbutenone (II,R_1=G=Ph, R_2=Me) brings about the Michael addition, but no cyclization occurs and the open chain ketonitrile (III,R_1=G=Ph,R_2=Me) is isolated as the final, stable compound. The same result is achieved if a stronger base such as sodium ethoxide is used as the catalyst. A lesser degree of stabilization of the enolic form in ketonitrile III_k when G is a phenyl group rather than a cyano or ethoxycarbonyl is probably responsible for the lack of cyclization in this case. However, if both substituents on the enolic double bond are phenyl groups, cyclization does take place and the corresponding pyran is obtained[10].

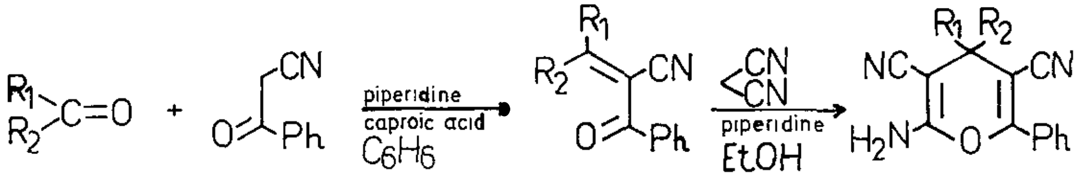
Table I

Compound	R_1	G	R_2	M.P. (ºC)	Yield (%)
IVa	C_6H_5	CO_2Et	CH_3	184-186 (ethanol)	87
IVb	p-Me-C_6H_4	CO_2Et	CH_3	180-182 (ethanol)	77
IVc	p-MeO-C_6H_4	CO_2Et	CH_3	137-139 (ethanol)	55
IVd	p-Cl-C_6H_4	CO_2Et	CH_3	182-184 (ethanol)	78
IVe	p-NO_2-C_6H_4	CO_2Et	CH_3	181-183 (ethanol)	76
IVf	p-CN-C_6H_4	CO_2Et	CH_3	154-156 (ethanol)	37
IVg	m-NO_2-C_6H_4	CO_2Et	CH_3	183-185 (ethanol)	80
IVh	3,4-Cl_2-C_6H_3	CO_2Et	CH_3	184-186 (ethanol)	71
IVi	Isopropyl	CO_2Et	CH_3	192-194 (ethanol)	49
IVj	Sec-butyl	CO_2Et	CH_3	142-144 (ethanol)	49
IIIk	C_6H_5	C_6H_5	CH_3	no cyclization[a]	
IVl	C_6H_5	CN	CH_3	215-217 (ethanol)	19
IVm	p-MeO-C_6H_4	CN	CH_3	141-142 (ethanol)	55
IVn	Isopropyl	CN	CH_3	197-199 (ethanol)	30
IVo	Sec-butyl	CN	CH_3	163-165 (ethanol)	12
IVp	Isopropyl	CN	C_6H_5	166-168 (ethanol)	58
IVq	Sec-butyl	CN	C_6H_5	149-151 (ethanol)	76
IVr	Terc-butyl	CN	C_6H_5	232-234 (ethanol)	74
IVs	C_6H_5	CO-CH_3	CH_3	162-164 (ethanol)	66

a: The open chain intermediate was isolated as a stable, crystalline solid, mp 176-178 ºC (ethanol) in 10% yield. See text.

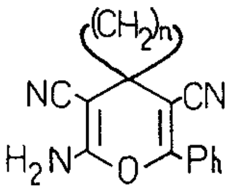
The structure of the new pyrans obtained was ascertained on the basis of analytical and spectral data. As in previously reported 2-amino-4H-pyrans[10], the amino group gives rise to the stretching bands at 3310-3410 cm^{-1} and bending bands at 1600-1670 cm^{-1} which appear together with the bands due to the carbon-carbon double bond in the IR spectra and a broad band at 6.8-7 ppm in the ^1H-NMR spectra. Cyano groups appear as a sharp band at 2180-2200 cm^{-1} (compounds IVa-j,s) or two bands at 2190-2210 and 2210-2230 cm^{-1} (compounds IVl-r). The hydrogen at position 4 of the pyran ring appears as a singlet at 4.0-4.4 ppm but is a doublet at about 3 ppm if R_1 is an isopropyl or sec-butyl group (IVi,j,n-q).

The preparation of 4,4-dialkyl-substituted 4H-pyrans (VII) was also possible by means of addition of propanedinitrile to propenones VI, obtained by condensation of ketones with ω-cyanoacetophenone (V) (Scheme 2, Table II).



V VI VII

Scheme 2



VIII

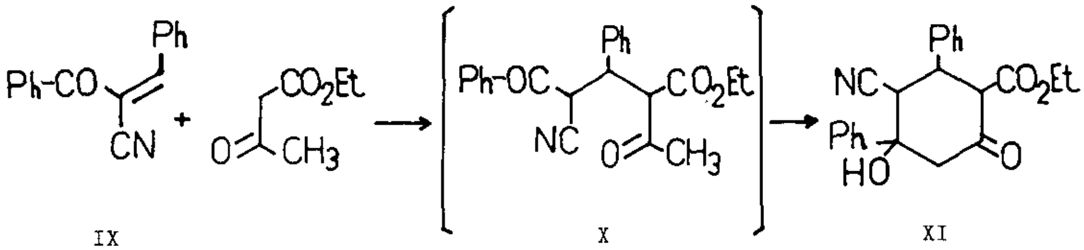
n= 3,4,5

Attempts to prepare 4,4-disubstituted pyrans of this kind with an ethoxycarbonyl group at position 5 by using ethyl acetoacetate or ethyl benzoylacetate rather than ω-cyanoacetophenone failed, but the latter compound condensed with cyclic ketones allowing the synthesis of spiropyrans VIII.

Table II

Compound	R_1	R_2	M.P. (ºC)	Yield (%)
VIIa	CH_3	CH_3	182-184 (ethanol)	72
VIIb	CH_3	CH_3-CH_2	162-164 (ethanol)	32
VIIIa	-CH_2-$(CH_2)_3$-CH_2-		165-167 (ethanol)	52
VIIIb	-CH_2-$(CH_2)_2$-CH_2-		176-178 (ethanol)	71
VIIIc	-CH_2-CH_2-CH_2-		177-179 (ethanol)	45

There is a particular case in our reaction where a δ-ketonitrile cyclizes to a carbocyclic ring. When α-benzoylcinnamonitrile *(IX) is treated with ethyl aceto*acetate, Michael addition takes place but the resulting δ-ketonitrile (X) under*goes a spontaneous* aldol-cyclization to a 3-hydroxycyclohexanone (XI) (mp 240-241 ºC)[15] which is obtained in 87% yield.



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