

SYNTHESIS OF HETEROCYCLIC COMPOUNDS XXXVI*

PREPARATION OF ALKYL SUBSTITUTED PYRANCARBONITRILES.

José L. Soto*, Carlos Seoane, Nazario Martín and Margarita Quinteiro†
 Departamento de Química Orgánica, Facultad de Química,
 Universidad Complutense, Madrid-3, SPAIN

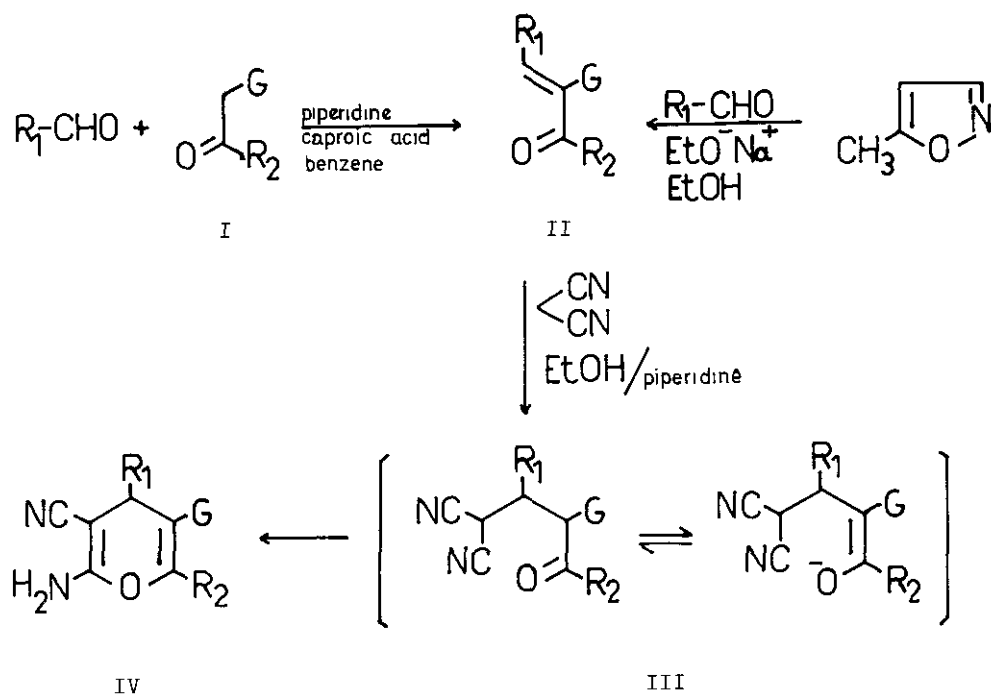
Abstract - The cyclization of the ketonitriles obtained from the reaction of suitably substituted propenones with propanedinitrile leads to alkyl substituted 4H-pyrans. Some of the starting propenones had to be prepared by base promoted opening of an isoxazole ring in the presence of an aldehyde. An 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 cyclizations¹⁻³, unless suitable structural features do not allow the formation of a carbocyclic ring⁴⁻⁹.

In previous papers¹⁰ 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=CO₂Et)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-methylisoxazole¹⁴.

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, $\text{R}_1=\text{G}=\text{Ph}$, $\text{R}_2=\text{Me}$) brings about the Michael addition, but no cyclization occurs and the open chain ketonitrile (III, $\text{R}_1=\text{G}=\text{Ph}$, $\text{R}_2=\text{Me}$) 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 obtained¹⁰.

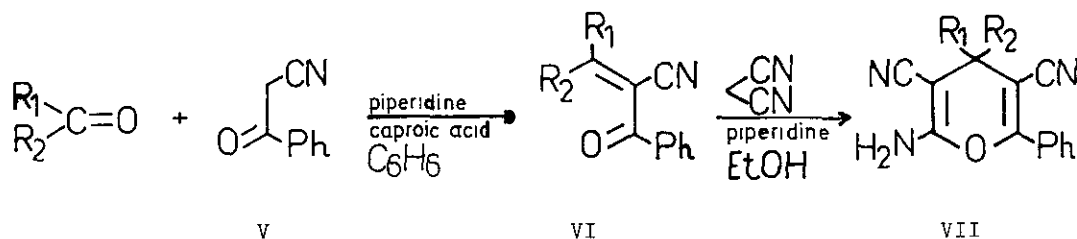
Table I

Compound	R ₁	G	R ₂	M.P. (°C)	Yield (%)
IVa	C ₆ H ₅	CO ₂ Et	CH ₃	184-186 (ethanol)	87
IVb	p-Me-C ₆ H ₄	CO ₂ Et	CH ₃	180-182 (ethanol)	77
IVc	p-MeO-C ₆ H ₄	CO ₂ Et	CH ₃	137-139 (ethanol)	55
IVd	p-Cl-C ₆ H ₄	CO ₂ Et	CH ₃	182-184 (ethanol)	78
IVe	p-NO ₂ -C ₆ H ₄	CO ₂ Et	CH ₃	181-183 (ethanol)	76
IVf	p-CN-C ₆ H ₄	CO ₂ Et	CH ₃	154-156 (ethanol)	37
IVg	m-NO ₂ -C ₆ H ₄	CO ₂ Et	CH ₃	183-185 (ethanol)	80
IVh	3,4-Cl ₂ -C ₆ H ₃	CO ₂ Et	CH ₃	184-186 (ethanol)	71
IVi	Isopropyl	CO ₂ Et	CH ₃	192-194 (ethanol)	49
IVj	Sec-butyl	CO ₂ Et	CH ₃	142-144 (ethanol)	49
IIIk	C ₆ H ₅	C ₆ H ₅	CH ₃	no cyclization ^a	
IVl	C ₆ H ₅	CN	CH ₃	215-217 (ethanol)	19
IVm	p-MeO-C ₆ H 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 ₆ H ₅	166-168 (ethanol)	58
IVq	Sec-butyl	CN	C ₆ H ₅	149-151 (ethanol)	76
IVr	Terc-butyl	CN	C ₆ H ₅	232-234 (ethanol)	74
IVs	C ₆ H 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 °C (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-pyrans¹⁰, 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 R₁ 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).



Scheme 2



VIII

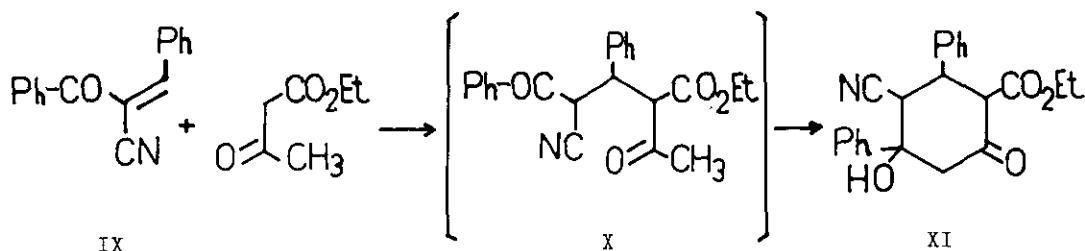
$n = 3, 4, 5$

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. (°C)	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 -benzoylcinnamonnitrile (IX) is treated with ethyl acetoacetate, Michael addition takes place but the resulting δ -ketonitrile (X) undergoes a spontaneous aldol-cyclization to a 3-hydroxycyclohexanone (XI) (mp 240-241 °C)¹⁵ which is obtained in 87% yield.



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REFERENCES

- * Previous paper: M.J. Rubio, C. Seoane and J.L. Soto, Heterocycles, 1983, 20, 783.
- + Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alcalá de Henares, Madrid, Spain.
- 1. For reviews on this topic, see: C. Seoane, "La Química de los 4H-piranos". Monografía de la Real Academia de Ciencias. Madrid, 1982.
- M. Quinteiro, C. Seoane and J.L. Soto, Heterocycles, 1980, 14, 337.
- 2. E. Knoevenagel, Ann., 1894, 281, 97.
- 3. R.E. Forgher and W.H. Perkin, J. Chem. Soc., 1914, 105, 1353.
- 4. A. Peres de Carvalho, Compt. Rend., 1934, 199, 1430.
- 5. E. Blaise and H. Gault, Bull. Soc. Chim. France, 1907, 19.
- 6. I. Degani and C. Vicenzi, Boll. Sci. Fac. Chim. Ind. Bologna, 1967, 25, 51; C.A., 1968, 68, 29543u.
- 7. V. Feofilaktov, J. Russ. Phys. Chem. Soc., 1929, 61, 1145; C.A., 1930, 24, 832.
- 8. H.S. Hauer, Doctoral Thesis, Purdue University, 1969; C.A., 1970, 73, 3740j.
- 9. J. Wolinsky and H.S. Hauer, J. Org. Chem., 1969, 34, 380; 1969, 34, 3169.
- 10. J.L. Soto, C. Seoane, N. Martín and L.A. Blanco, Heterocycles, 1983, 20, 803 and references cited therein.
- 11. E.F. Pratt and E. Werble, J. Am. Chem. Soc., 1950, 72, 4638; E.C. Horning, J. Koo, M.S. Fish and G.N. Walker, Org. Synth., 1951, 31, 56.

12. H.E. Zimmerman, L. Singer and B.S. Thyagarajan, J. Am. Chem. Soc., 1959, 81
108.
13. C.J. Eby and C.R. Hauser, J. Am. Chem. Soc., 1957, 79, 723.
14. C.H. Eugster, L. Leichner und E. Jenny, Helv. Chim. Acta, 1963, 46, 551.
15. J. Chicharro, Trabajo de Licenciatura, Universidad de Alcalá, in progress.

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