SYNTHESIS OF HETEROCYCLIC COMPOUNDS XIX[1] PREPARATION OF 4,6-DIARYL-3,5-DICYANO-2-PYRIDONES

C. Seoane, J. L. Soto* and M. P. Zamorano
Departamento de Química Orgánica. Facultad de Química.
Universidad Complutense. Madrid-3. Spain.

Reaction of cyanoacetamide with α-benzoylcinnamonitriles (I) leads to a new series of 4,6-diaryl-3,5-dicyano-2-pyridones (IV). The initial Michael's addition is followed by a cyclization to a 6-hydroxy-2-piperidone ring (II), whose acid dehydration gives rise to 3,4-dihydro-2-pyridones (III). The latter are easily aromatized to 4,6-diaryl-3,5-dicyano-2-pyridones (IV) by treatment with sodium nitrite in sulfuric acid.

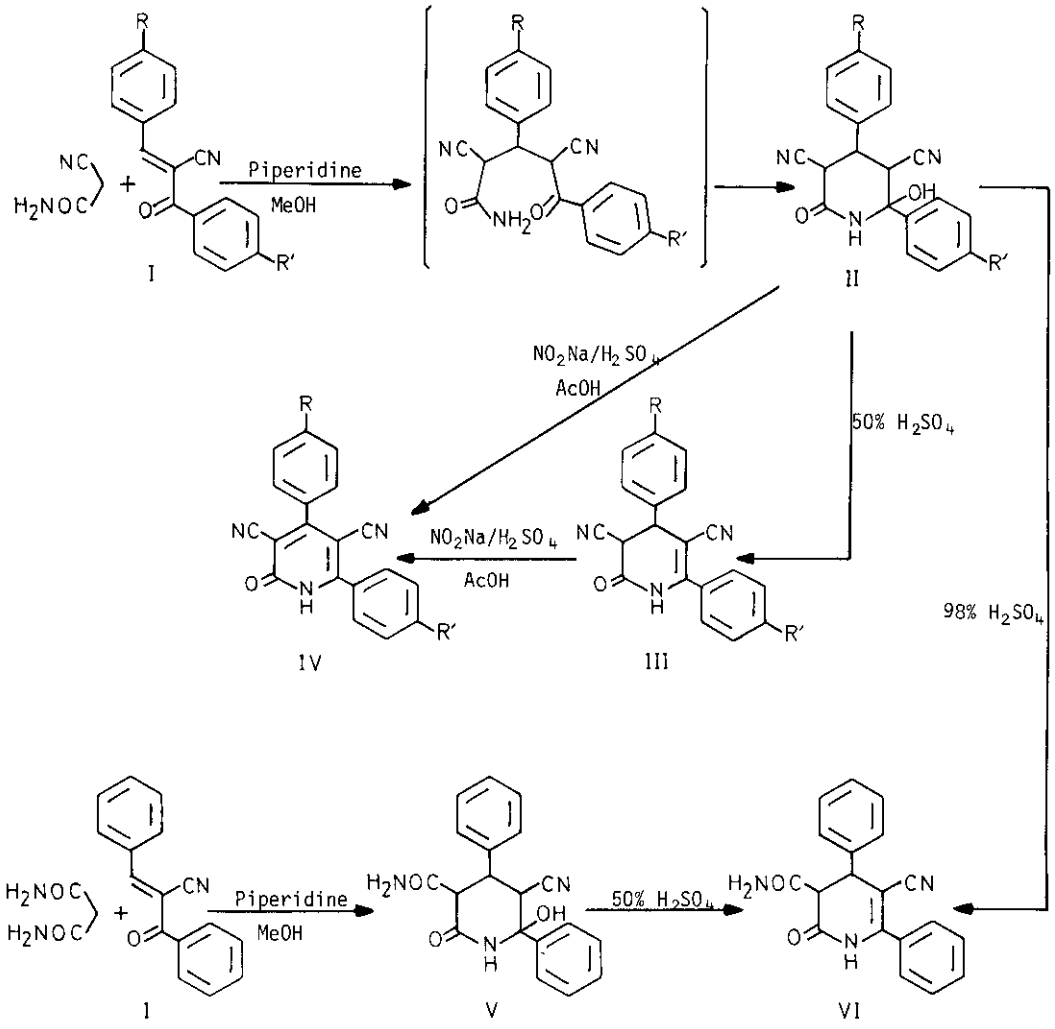
The reactions of α-benzoylcinnamonitriles (I) with either malononitrile or ethyl cyanoacetate have been described in previous papers[2,3] and lead to a new synthesis of 2-amino-4H-pyrans, through the cyclization of the corresponding Michael adduct by nucleophilic attack of the carbonyl oxygen at the cyano group of the malononitrile or ethyl cyanoacetate. In a similar way, 2-aminofurans are obtained from the reaction of cyanide anion with α-benzoylcinnamonitriles[4].

We report here the results obtained with the use of cyanoacetamide as the active methylene compound.

Cyanoacetamide reacts by Michael's addition with a series of α-benzoylcinnamonitriles (Ia-f), which are easily prepared through a Knoevenagel condensation of an aromatic aldehyde and ω-cyanoacetophenones[5-8]. The resulting adducts cyclize in situ (Scheme I) by attack of the amidic nitrogen to the carbonyl group to give the novel 6-hydroxy-2-piperidones (II) shown in Table I. The reaction is carried out in methanol at room temperature with a few drops of piperidine as the basic catalyst. Compounds II precipitate from the reaction medium in high yield and can be purified by recrystallization in an appropriate solvent (Note 1). Their NMR spectra (in DMSO-d_6) show a multiplet at 6,8-7,9 ppm corresponding to the aromatic protons and a complex multiplet (mixture of stereoisomers) at 3,7-4,8 ppm due to the three protons of the ring. The peak due to the hydroxyl group appears within the aromatic multiplet and can be identified with TFA. The NH of the ring appears as a singlet at 9-9,1 ppm.

This reaction doesn't take place with α-benzoyl-p-nitrocinnamonitrile (Ie). In this case, α-cyano-p-nitrocinnamamide (VII), formed through a retro-Michael decomposition of the adduct, is isolated instead of the 6-hydroxy-2-piperidone (Scheme II).

Treatment of hydroxypiperidones II with sodium nitrite/sulfuric acid in acetic



SCHEME I

acid results in their transformation into a new series of 4,6-diaryl-3,5-dicyano-2-pyridones (IV) through dehydration and aromatization in almost quantitative yield (Scheme I, Table I). The preparation of IV starting from II can also be achieved in two steps: dehydration of compounds II with 50% sulfuric acid giving a high yield of 4,6-diaryl-3,5-dicyano-3,4-dihydro-2-pyridones (III) and subsequent aromatization to IV by treatment with sodium nitrite/sulfuric acid (Note 2). It should be pointed out that dihydropyridones III are obtained as a cis-trans mixture, as revealed by the NMR spectra. The signals due to the hydrogens located at positions 3 and 4 appear as two pairs of doublets betwen 4,3 and 5,3 ppm (J=7 Hz and J=12Hz). From integration of these signals formation of equal amounts of cis and trans isomers is inferred.

If the acid dehydration of II is performed with 98% sulfuric acid, the reaction is accompanied by hydrolisis of a cyano group, to give 4,6-diphenyl-3-carboxamido-

TABLE I*

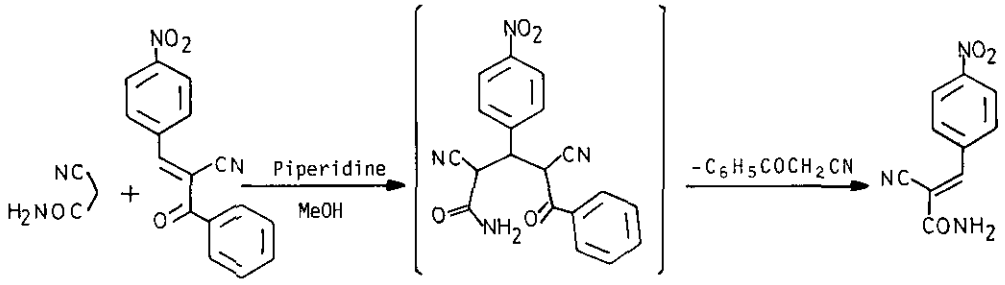
			II		III		IV	
	R	R'	M.P.(°C)	Yield (%)	M.P.(°C)	Yield (%)	M.P.(°C)	Yield (%)**
a	H	H	147-8 (methanol)	91	183-4 (methanol)	80	252-3 (et.acetate)	81
b	CH_3	H	133-4 (methanol)	91	141-3 (benzene)	93	308-10 (acetone)	100
c	Cl	H	201-2 (methanol)	98	171-3 (methanol)	94	338-9 (methanol)	90
d	CH_3O	H	133-4 (methanol)	71	170-2 (methanol)	91	325-6 (methanol)	100
e	NO_2	H	----	--	----	--	----	--
f	H	CH_3	124-5 (methanol)	60	216-8 (ethanol)	89	289-91 (benzene)	100

*All melting points were determined by the capillary method and are uncorrected

**Yields obtained in the preparation of IV from III

5-cyano-3,4-dihydro-2-pyridone (VI). The cyano group that undergoes hydrolysis is the one at the position 3, because dihydropyridone VI can be obtained in two steps by reaction of malonamide with α-benzoylcinnamonitriles (Ia) followed by dehydration of the resulting 6-hydroxy-2-pyperidone (V) with 50% sulfuric acid.

Work in progress indicates that the synthesis reported can be applied to the reaction of ethyl α-benzoylcinnamates with either cyanoacetamide or malonamide.



I VII

SCHEME II

Acknowledgements

The authors are indebted to Miss María Jesús Rubio for her assistance. One of us (M.P.Z.) would like to thank the Ministerio de Educación y Ciencia of Spain

for a grant within the Plan de Formación de Personal Investigador.

REFERENCES AND NOTES

1. Previous paper: J.L. Soto, C. Seoane and J.A. Ciller, An. Quim., in press.
2. M. Quinteiro, C. Seoane and J.L. Soto, Tetrahedron Letters, 1977, 1835.
3. M. Quinteiro, C. Seoane and J.L. Soto, J. Heterocyclic Chem., 1978, 15, 57
4. V. Arán and J.L. Soto, Communication to the 1st European Symposium on Organic Chemistry. Cologne, August 1979.
5. H. Kaufman, Ber., 1917, 50, 5150.
6. D. Drapkina, V. Brudz and B. Bolotin, Tr. Vses. Nauch. Isled Inst. Khim. Reactiv. Osobo Chist. Khim. Veshehestr., 1967, (30), 333. C.A. 1967, 69, 6727p.
7. E.V. Meyer, J. Prakt. Chem., 1915, 92, 183.
8. R. Long, J. Am. Chem. Soc., 1947, 69, 990.

Note 1. Hydroxypyperidones II are rather unstable compounds and decompose partially during normal purification procedures. In order to achieve correct microanalyses, recrystallization of II must be carried out by dissolving them in the appropiate solvent at room temperature and cooling the solution at -20°C.

Note 2. In certain cases, aromatization takes place to some extent during recrystallization.

Received, 10th March, 1980