NEW ACCESS TO ETHANOISOQUINOLONES

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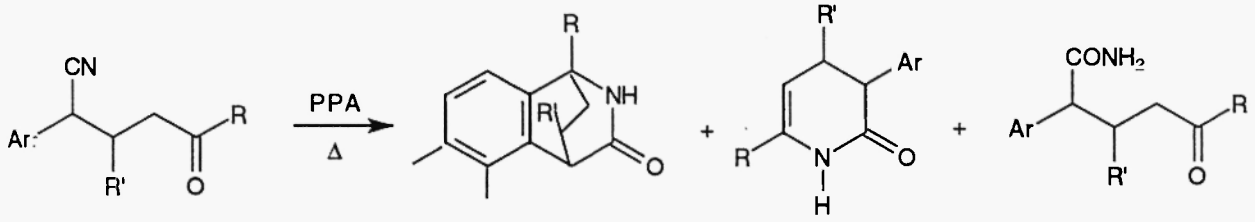
Abstract : Heating γ-aryl-γ-cyanoketones with polyphosphoric acid yields ethanoisoquinolones, dihydropyridones and δ-cetoamides depending on the structure of the starting compound. These products can be easily separated.

The ethanoisoquinoline moiety is of interest because of its pharmacologic potential (1). Only few methods have been described for the preparation of these compounds: heating of 1-amino-4-ethoxycarbonyltetralins (2) or cycloaddition of maleic anhydride or benzyne on pyridones (3,4)



1 2 3 4

In this paper, we would like to report a new method of synthesis for these derivatives. Compound 2 may be accompanied by other products but the mixture can be easily separated. The starting compounds are arylacetonitriles which react with unsaturated ketones in a Michael reaction to give γ-aryl-γ-cyanoketones 1. In the case of volatile ketones this reaction is performed in ether with sodium methanolate. For other carbonyl compounds the reaction is carried out in a two phase system (toluene/water) with potassium carbonate and a phase-transfer reagent. in this latter case, one can simplify by working with the same reagents without solvent under microwave irradiation (yield 50-80%).

When the cyanoketone 1 is heated at 140°C with fifteen times its weight of polyphosphoric acid, three main products are formed (see table1). The transformation of cyanoketone 1 into dihydropyridone 3 in acid medium has been known for a long time (5). Using hydrogen bromide in glacial acetic acid this transformation requires four days. This reaction involves the attack of the nitrogen atom on the carbenium which is generated by protonation of the carbonyl group. The resulting intermediate leads to 3 by elimination or to 2 by aromatic electrophilic substitution. Compound 4 results directly from the hydrolysis of 1.

Table 1 - Reaction of γ-aryl-γ-cyanoketones with polyphosphoric acid at 140°C.

Ar	R	R'	Time (mn)	% 2	% 3	% 4
Phenyl	Methyl	H	5	17	20	35
Phenyl	Methyl	H	15	18	20	23
Phenyl	Methyl	H	40	20	5	7
p-Methoxyphenyl	Methyl	H	10	6	5	8
Phenyl	Ethyl	H	10	13	15	43
Phenyl	Phenyl	H	15	0	50	0
Phenyl	Methyl	Phenyl	7	8	51	0
1-Naphtyl	Methyl	H	10	50	0	0

The mixture of compounds 2, 3, and 4 can be easily separated. The dihydropyridone 3 is the first to be eluted by flash chromatography (silicagel, diethylether). The two remaining compounds are treated with aqueous sodium hydroxide and δ-cetoamide 4 is the only one to yield the carboxylate ion and so is retained in the aqueous layer.

Consideration of the first three entries in table 1 shows a degradation of compounds 3 and 4 when heated in PPA. Only compound 2 resists a hot acid medium over a long time. The yields of 2 are of the order of those obtained by known methods ; but the present synthesis is much faster. This reaction can be highly selective and work is in progress to study the influence of electronic and steric effects.

References

(1) G. Grunewald, D. Sall, and J. Monn, J. Med. Chem. 31, 433 (1988).

(2) G. Walker and D. Alkalay, J. Org. Chem. 36, 491 (1971).

(3) R. Denayerr (UCB), Ger. Offen. 2.152.232, (1972) ; Chem. Abstr. 77, 48288s (1972).

(4) R. Borne, S. Law, P. Wirth and J. Murphy, J. Pharm. Sci. 66, 594 (1977).

(5) C. Allen, J. Am. Chem. Soc. 49, 1112 (1927).

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