An Improved Synthesis of 2-Substituted-Pyrrolines

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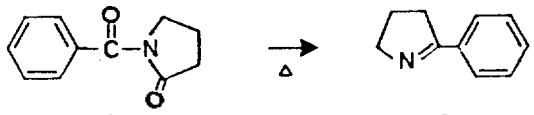
In the course of our extensive research toward the development of new antibiotics, we were interested in the synthesis of 2-substituted pyrrolines, since the pyrrolidine derivative, the reduction product of a pyrroline could be a potential substituent for cephalosporin antibiotics[1] or quinolone antibacterial agents[2].

The pyrolysis of N-acylated-2-pyrrolidone with a free flame in the presence of calcium oxide is known to yield a 2-pyrroline by molecular rearrangement[3]. This reaction is particulary valuable for the simplicity of the procedure. But the reaction is not practical for the synthetic purpose due to a low yield. Also the reaction residue is not easy to be removed from a reaction vessel.

For improving a reaction yield and reaction conditions for the rearrangement, N-benzoyl-2-pyrrolidone (1) as a model compound was subjected to pyrolysis using several oxides and hydroxides. The results of our study are shown in Table 1.

Table 1. Rearrangement of N-Benzoyl-2-pyrrolidone

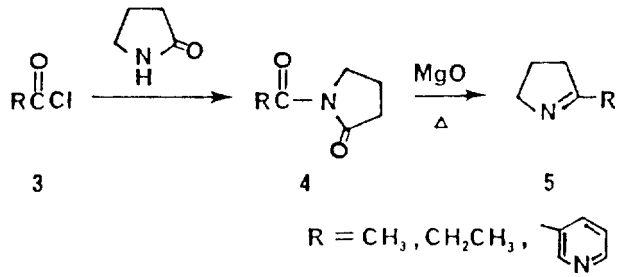


1 2

conditions	product yield
CaO	20%[a]
MgO	58%[a]
BaO	10%[a]
Al_2O_3	a trace[b]
ZnO	a trace[b]
KOH	
$Ca(OH)_2$	

[a]isolated yield by distillation. [b]detected by TLC.

Of particular interest was the observation that the reaction with magnesium oxide gave 2-phenylpyrroline (2) in a much improved yield and a clean residue. The reaction using aluminum oxide or zinc oxide gave a trace of the rearranged product accompanied with a large amount of the starting material and 2-pyrrolidone. Attempted rearrangement reaction with hydroxides resulted in the cleavage of only the amide bond. Several pyrrolines were prepared by heating N-acylated-2-pyrrolidones in the presence of magnesium oxide in over 60% yields[4].



3 4 5

R = CH_3, CH_2CH_3,

N-Acylated-2-pyrrolidones (4) were easily prepared from 2-pyrrolidone and acid chlorides in excess amounts of pyridine at 80°C for 6-8hr. The general procedure for a rearrangement reaction is the following. The N-acylated-2-pyrrolidone was mixed thoroughly with an equal weight or a half weight of magnesium oxide. The mixture was gently heated until all of the crdue product distilled with the flame from a micro burner. The crude product was purified by a chromatographic method or reduced pressure distillation.

The mechanistic course of this reaction and the synthesis of natural products[5] using this methodology are under study in this lab.

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References

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