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NOVEL SYNTHESIS OF N-ALKYLATED LACTAMS /1/

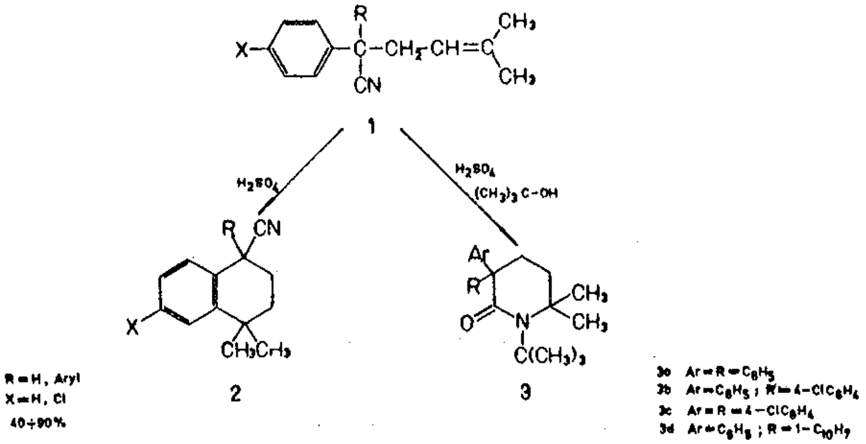
Edward Grochowski* and Teresa Bolesławska

Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw, Poland

A novel synthesis of γ- and δ-lactams from hydroxy and olefinic nitriles was described. The mechanism of this double two steps alkylation is discussed.

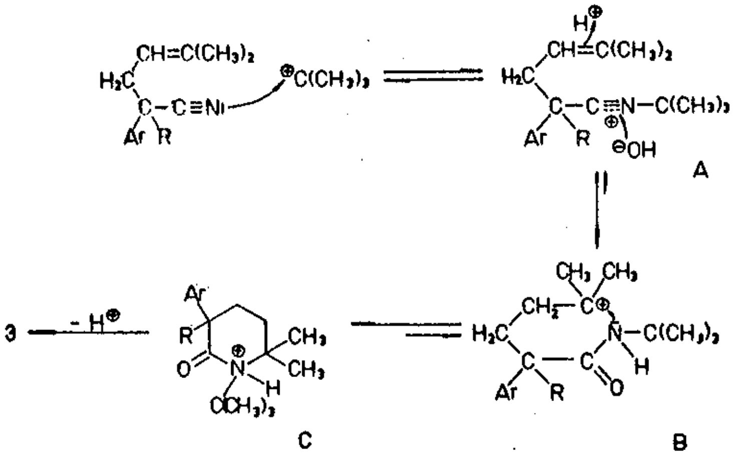
The electrophilic addition of carbonium ions, generated with alkenes or alcohols in the presence od concentrated sulfuric acid, to nitrile group is a very important method for obtaining the **N**-substituted amides /2/. However, there are only few cases known of the intramolecular cyclisation of olefinic nitriles or hydroxynitriles giving rise to γ- and δ-lactams /3/. The steric hinderance existing in such compounds causes that the cyano group is rather a good electrophile with respect to the hydroxyl group or the double bond leading in the consequence to the creation of a new C-O or C -C bond. Thus, the hydroxynitriles produce on subsequent action of concentrated sulfuric acid and water γ-and δ-lactones, and the unsaturated nitriles the corresponding ketones. The δ-ketonitriles give under the same conditions dihydropyridones - the yields of all these reactions are rather moderate.

We reported in our previous papers /4/, that in concentrated sulfuric acid the carbonium ions generated from alkenonitriles 1 do not attack the nitrile group /Ritter reaction/ but the aromatic ring /Friedel-Crafts reaction/ giving the tetralins 2.



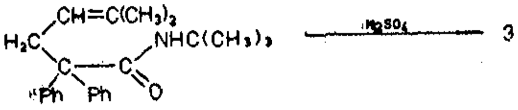
Scheme 1

The subject of our present communication is the same reaction carried out in the presence of tert.-butyl alcohol. We found that this modification leads - probably via subsequent inter- and intramolecular addition of carbonium ions to the nitrile group - to the derivatives of N-tert.-butylpiperidones 3 as the sole reaction products. The possible mechanism of this new synthesis of piperidones is presentend on Scheme 2.



Scheme 2

Some evidence of such a course of this double two step alkylation of nitrogen yielded the result of the cyclisation of N-tert.-butyl-- α - /3,3-dimethylallyl/-diphenylacetamide 4, obtained on an independent way, under the conditions which normally led to the tetralin 2,



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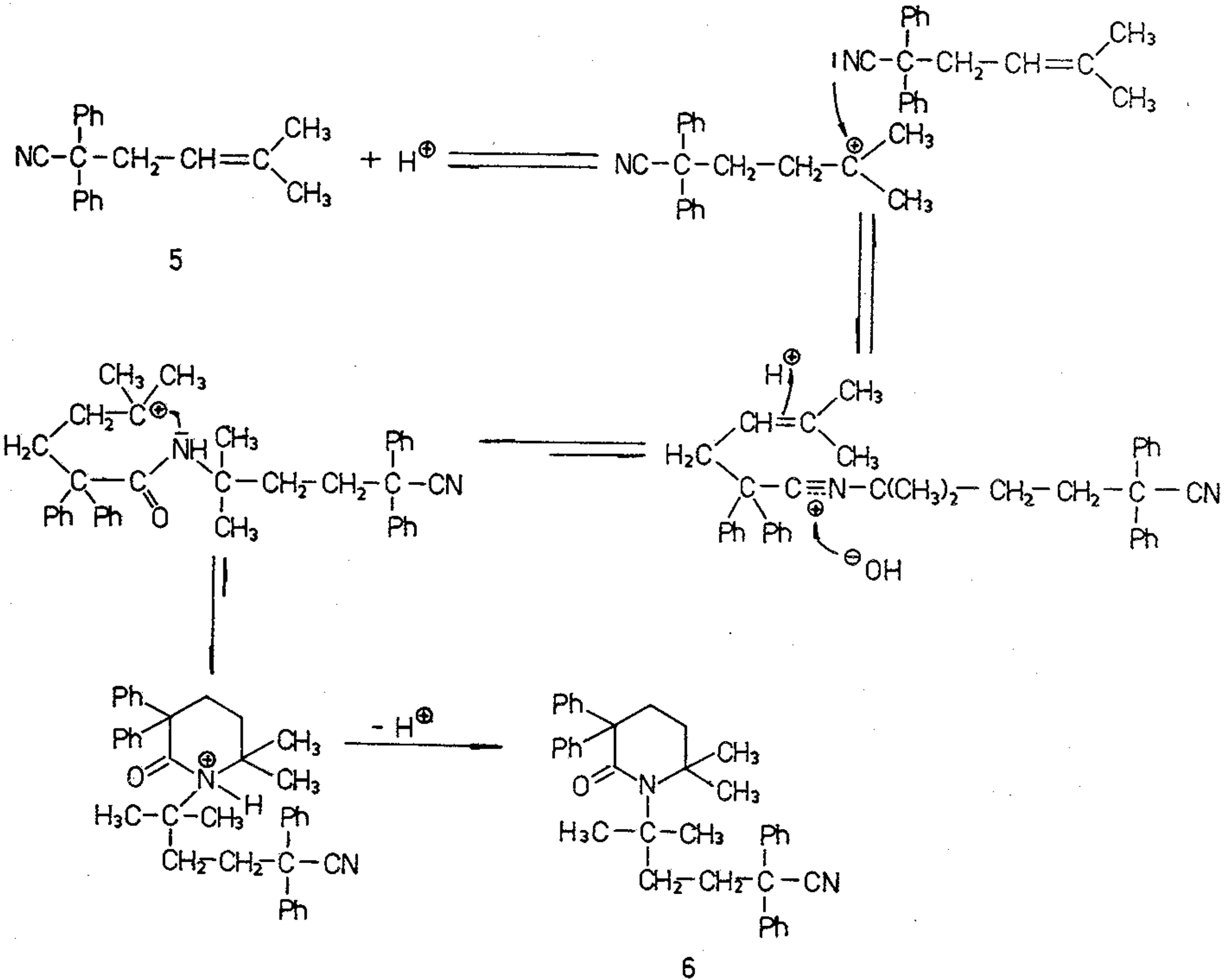
Scheme 3

The latter one was not formed, instead the same N-tert.-butyl-piperidone 3 was obtained in very good yield as the sole reaction product.

We have to point out that in the intermolecular reaction the amides do not undergo N-alkylation under Ritter reaction conditions with the exeption of urea /5/ and urethanes /6/, which are alkylated by tertiary alcohols and alkanes. We suppose that the presence /or absence/ of water in the reaction medium is very essential for direction of carbonium ion attack- water as only nucleophile present in the reaction medium stabilizes the nitrilium ion A and consequently promotes its conversion to the amide grouping followed by the next phase i.e. the formation of the carbonium ion to give B, and the intramolecular alkylation of the latter produces C and at the end 3.

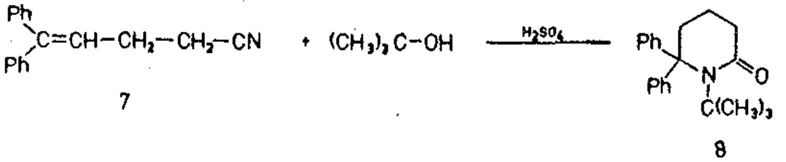


Scheme 4

This suggestion was confirmed by the reaction of the nitrile 5 under the conditions of Friedel-Crafts alkylation /4/ but in the presence of two equivalents of water for one equivalent of nitrile i.e. with approximately 90% sulfuric acid. No trace of ring alkylation was observed, instead we obtained again piperidone 6. We assume that this product is formed as in the previous case by two step reaction as illustrated in the Scheme 4.

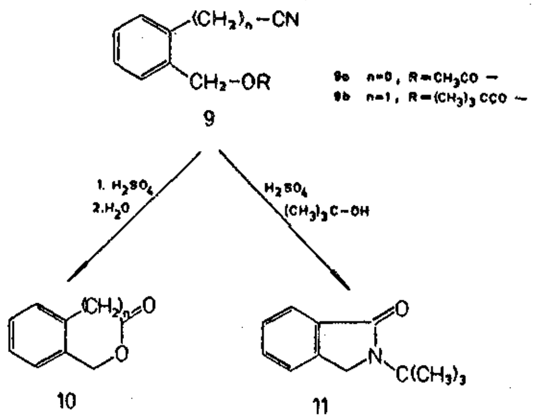
Butyl carbonium ion from the preceeding reaction is now replaced by the cation created by protonation of the double bond of the substrate 5, which is acting as alkylating species on the nitrile group intermolecularly. The presence of water facilitates then the intramolecular alkylation in the "dimeric" intermediate.

The above described synthesis can be further extended for systems containing double bonds able to form tert.-carbonium ions, located in γ, δ -position with respect to the nitrile group e.g. as in 7. In that case as illustrated by Scheme 5 similarly built 6-membered lactams 8 are formed.



Scheme 5

Further application of this new synthetic method is shown by the reaction of compounds 9. The "normal" cyclisation /7/ of these compounds in concentrated sulfuric acid solution followed by water treatment yields the lactones 10. However, compound 9a treated with concentrated sulfuric acid in the presence of tert.-butyl alcohol gives as the single reaction product the γ-lactam 11. The only difference between this reaction and the above described ones is that the carbonium ion of the second phase is a primary one, but the reactivity of benzylic cations in Ritter reaction is a very well known fact.



Scheme 6

Table 1 contains a list of some newly obtained lactams. All new compounds presented therein gave satisfactory microanalyses, and their spectral data /IR, NMR, MS/ confirmed the proposed structures.

TABLE 1

Compound	Yield %	m.p. °C
3 a	59	83 - 84
3 b	60	138 -140
3 c	63	206 -208
3 d	54	181 - 183
6	72	149 - 150
8	49	87 - 89
11	73	71 - 72

The above presented method can be applied for the synthesis of γ- and δ-lactams from hydroxy and olefinic nitriles, in which the double bond and the alcoholic carbon atom form readily the corresponding carbonium ion.

Preparation of N-Alkylated Lactams

General method

To the solution of hydroxy or olefinic nitrile /0.01 m/ and tert.-butyl alcohol /0.01 m/ in ether /4 cm^3/, concentrated sulfuric acid /1.5 cm^3/ was added dropwise with vigorous stirring. The stirring was continued for 6 h at 40-45°C. The reaction mixture was poured on ice and extracted with benzene. The reaction products were separated and purified by crystallization.

Acknowledgement

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References

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