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NEW SYNTHESIS OF PIPECOLIC ACID AND ANALOGS

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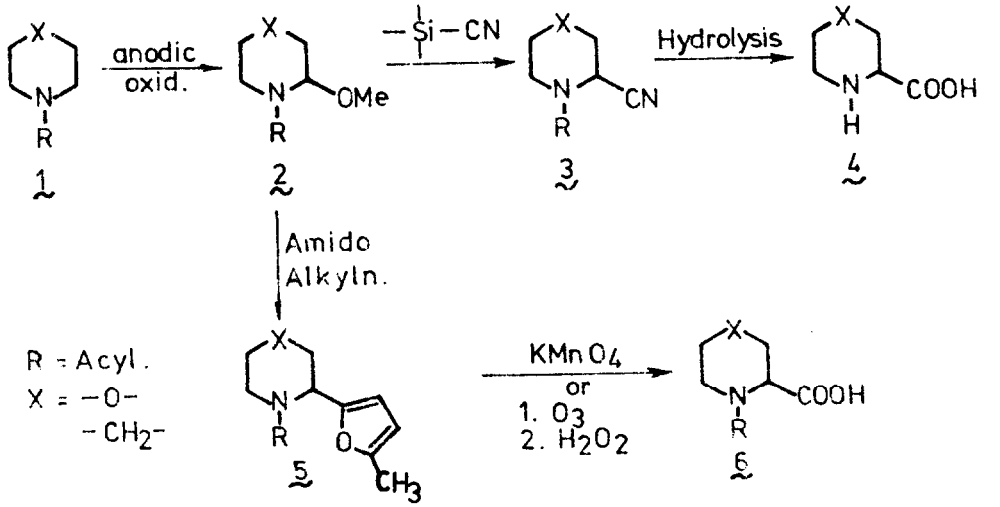
ABSTRACT. Pipecolic acid congeners are synthesised from α-cyanoamides, obtained by substitution of α-methoxyamides with trimethylsilyl cyanide and in an alternative route via oxidation of amidoalkylationproducts of the α-methoxyamides.

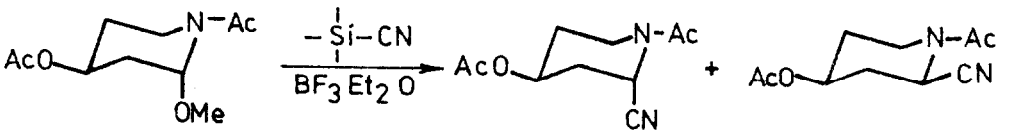
We have found that α-methoxy amides (2), obtained by anodic oxidation [1] of nitrogen protected amines such as piperidine, piperazine, or morpholine (1), represent easily accessible synthons for the economical preparation of racemic α-amino acids (4). This conversion can be realised by substitution of the methoxy grouping for cyanide using trimethylsilyl cyanide followed by acid hydrolysis.

Alternatively, amidoalkylation, [2] via N-acyl carbenium ions as the transient intermediates, results in the corresponding 5 substituted 2 methyl furan derivatives of the amides (5). Subsequent ozonolysis or oxidation following the method of Terent'ev and Gracheva[3] is also possible but represents a less attractive route.



Experiments have been tested in order (a) to optimise the conditions for substitution of the α-methoxy group by cyanide, and (b) to search for the best NH protecting group R in respect with its influence on substitution of the methoxy derivative by cyanide or amidoalkylation and, in the light of selective hydrolysis, for the conversion of 3 to 6.

SUBSTITUTION OF α-METHOXY GROUP BY CYANIDE.



7 8 9

Substitution of α-methoxy group by cyanide using hydrogen cyanide under a variety of acidic conditions gave poor yields. Excellent yields are obtained with trimethylsilyl cyanide as the reagent (now cheaply available)[4] in the presence of catalytic amounts of Lewis acids.

A solution of 0.01 mole of α-methoxy amide (2) with 0.02 mole of trimethylsilyl cyanide and catalytic amount of stannic tetrachloride results in 95% yield of the nitrile 3, 85% with borontrifluoride diethyl etherate as the catalyst. Zinc iodide did not catalyse the reaction (R = CH_3.CO).

Starting from trans-N-acetyl-2-methoxy-4-O-acetyl piperidine 7 an equimolecular mixture of trans and cis N-acetyl piperidine nitriles 8 and 9 are obtained. This is an indication that the reaction is not stereospecific.

None of the N-protecting groups were found to be ideal in order to meet all conditions. Among the protecting groups studied so far, the formyl, acetyl and benzene sulphonyl groups prove best when synthesising N-unprotected pipecolic acids via the α-cyano-derivatives.

Table 1.

$\underset{\sim}{2}$	$\underset{\sim}{3}$	Yield (%)	$\underset{\sim}{4}$	Yield (%)
N-Acetyl-2-methoxypiperidine	N-Acetyl-2-cyanopiperidine	95	Pipecolic acid	55
N-Acetyl-3-methoxymorpholine	N-Acetyl-3-cyanomorpholine	95	4-oxapipecolic acid	55
N-N-Diacetyl-2-methoxypiperazine	N-N-Diacetyl-2-cyanopiperazine	>90	Piperazic acid	40

AMIDOALKYLATION is carried out in ether or in methylene chloride with an excess of 2-methylfuran an equimolar ratio of the methoxy compound and borontrifluoride diethyl etherate resulting in 70% yield of the furyl derivative $\underset{\sim}{5}$ for different acyl groups.

OZONOLYSIS at -70 °C in methanol or ethyl acetate and subsequent oxidation with H_2O_2 resulted in only 30% yield of the amino acids.

A benzoyl group offers the best alternative for the oxidation with potassium permanganate of the α-furyl N-benzoylated piperidines $\underset{\sim}{5}$. The inconveniance however is that a α-furyl N-benzoyl piperidine must be prepared via amidoalkylation of an intermediately prepared α-furyl N-trifluoroacetyl piperidine because the α-methoxy N-benzoyl piperidines tend to eliminate chiefly to enamides under the circumstances of amidoalkylation. The furyl derivatives are oxidised to the amino acids with cold potassium permanganate solution as described by A.P. Terent'ev and co-workers,[3] with 50% yield of pipecolic acid hydrochloride.

References

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