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INTRAMOLECULAR CYCLISATION-N-DEALKYLATION OF AZETIDINE-3-ACETIC ACIDS

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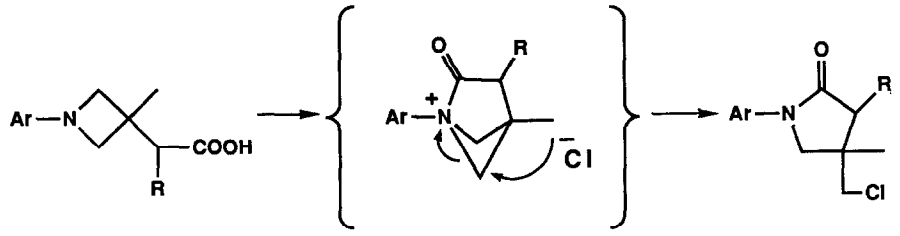
Summary. *N-Aryl-azetidine-3-acetic acids are converted to pyrrolidinones when treated with oxalyl chloride. The intramolecular cyclisation-N-dealkylation reaction occurs via an azabicyclic intermediate. N-Aryl-azetidine-3-acetic acids are prepared from N-aryl-3-(chloromethyl)azetidin-2-ones.*

Intramolecular cyclisation-N-dealkylation reactions occur if an acyl chloride moeity is formed within a molecule which contains a tertiary amine.[1] In this way, novel N-aryl-azetidine-3-acetic acids 1 on attempted conversion into acid chlorides with oxalyl chloride give 4-(chloromethyl)pyrrolidine-2-ones 3 via the azabicyclic intermediate 2. (Scheme 1.)

Intramolecular cyclisation-N-dealkylation reactions, via an azabicylic intermediate, have not, to our knowledge, been previously described with azetidines. However, it is known that pyrrolidinones are obtained, via azabicyclic intermediates, when piperidine-4-carboxylic acids[2] and also pyrrolidine-3-acetic acids[3] react with thionyl chloride.

SCHEME 1[4]



1 2 3

a. Ar = $3,5Cl_2C_6H_3$-, R = H. a. 60% (mp. 78-79°C)

b. Ar = $3CF_3C_6H_4$-, R = H. b. 59% (mp. 59-60°C)

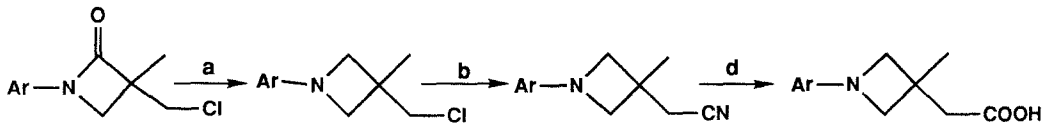
c. Ar = $3CF_3C_6H_4$-, R = Me. c. 40% (mp. 68-69°C)

The N-aryl-azetidine-3-acetic acids 1 are prepared (Scheme 2) from N-aryl-3-(chloromethyl)-3-methylazetidin-2-ones 4[5] by reduction with hydrolane[6] to give 5. Nucleophilic substitution with cyanide anion gives 6 followed by alkaline hydrolysis to azetidines 1a and 1b. Azetidine-3-acetic acid 1c is obtained by methylation of 6b, followed by alkaline hydrolysis.

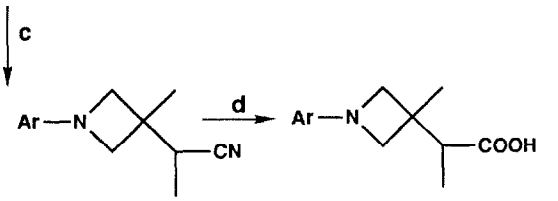
Typical reaction conditions for conversion of 1 to 3 are as follows:- To a stirred solution of 1 (1 eq.) in dichloromethane (20ml) and dimethylformamide (4 drops) is added oxalyl chloride (1 eq.), dropwise at room temperature. The reaction mixture is stirred at room temperature for 3 hours and then left to stand overnight. The solvent is removed by evaporation and the residue purified by flash column

chromatography (ether : hexane; 1:1). 1a and 1b are isolated as R/S mixtures and 6c is an 8 : 1 mixture in which the 3S,4R; 3R,4S pair is the major product and the 3S,4S; 3R,4R pair the minor product.

Scheme 2[4]



4	5a. 76% (oil)	6a. 86% (mp. 70°C)	1a. 65% (mp. 138°C)
	5b. 88% (oil)	6b. 91% (oil)	1b. 44% (mp. 79°C)



6c. 70% (oil) 1c. 36% (mp. 96°C)

Reagents. a) $AlCl_3$, $LiAlH_4$, ether. b) KCN (1eq), DMSO, 100°C. c) $Li(SiMe_3)_2$, MeI, THF. d) NaOH (4eq.) aq. EtOH.

The synthesis of the N-aryl-azetidine-3-acetic acids, described here, is limited. Further studies are in hand to develop a new route to these acids to enable further investigation of cyclisation-N-dealkylation reactions of azetidines which will be reported shortly.

References and footnotes.

1. J.H. Cooley and E.J. Evain. *Synthesis*, 1 - 7, (1989).
2. R.L. Clarke, A. Mooradian, P. Lucas and T.J. Slauson. *J. Amer. Chem. Soc.*, 71, 2821 (1949).
3. C.D. Lumsford, A.D. Cale Jr., J.W. Ward, B.V. Franco and H. Jenkins. *J. Med. Chem.*, 7, 302 (1964).
4. All quoted yields are pure and isolated. All products give satisfactory microanalytical (M.F. Jamieson, ICI Agrochemicals) and NMR data (P. Stanley, ICI Agrochemicals)
5. D. Bartholomew and M.J. Stocks. *Tet. Lett.*, (1991).
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N-Alkyl-3-(chloromethyl)-3-methylazetidin-2-ones are not reduced to the corresponding azetidines. Ring opening and decomposition are thought to occur.

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