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A NOVEL REARRANGEMENT REACTION CONVERSION OF 3-(CHLOROMETHYL)AZETIDIN-2-ONES TO AZETIDINE-3-CARBOXYLIC ACID ESTERS

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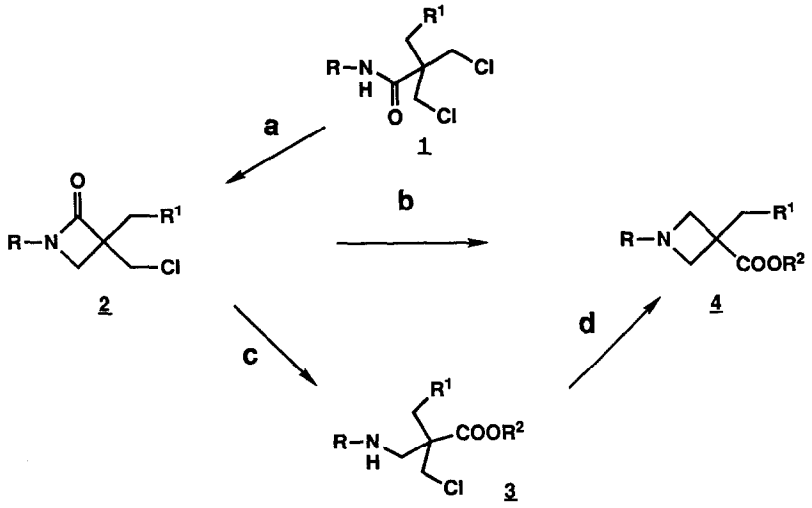
Summary: *Transformation of 3-(chloromethyl)azetidin-2-ones to azetidine-3-carboxylic acid esters is described. The readily available 3-(chloromethyl)azetidin-2-ones rearranged in good yields to azetidine-3-carboxylic acid esters on treatment with alkoxides. An alternative ring opening - ring closure procedure is also identified.*

Efficient syntheses of azetidines from azetidin-2-ones previously described in the literature are by direct and selective reduction with hydroalanes[1] or a two step procedure where the azetidin-2-one is first reduced to a β-aminoalcohol with diborane followed by a modified Mitsunobo[2] reaction to effect ring closure. We now wish to describe a non-reductive synthesis via a rearrangement reaction in which the azetidin-2-ones are converted directly to azetidines without isolation of the intermediate β-aminoacid ester. However, a two step sequence via the β-aminoacid ester intermediates can also be applied.



Reagents.

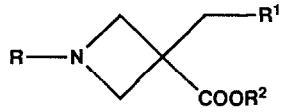
a) 40% aq.NaOH, CH_2Cl_2, Bu_4NBr.

b) $NaOR^2$, R^2OH for R = alkyl; $NaOR^2$, DMF for R = aryl.

c) $NaOR^2$, R^2OH. d) Bu_4NI, NEt_3, 100 - 160°C.

Investigation of this transformation is performed with N-substituted 3-(chloromethyl)azetidin-2-ones and N-substituted 3,3-bis(chloromethyl)azetidin-2-ones. The N-substituents are alkyl or aryl. The required azetidin-2-ones 2 are prepared by established phase transfer catalysed[3] ring closure reactions of 3-chloropivaloylamides. The 3-chloropivaloylamides 1 are prepared by the reaction of various amines with 3,3'-dichloropivaloyl chloride[4] or 3-chloro-2,2-bis(chloromethyl)propionyl chloride.[5]

TABLE 1[6]



4

4	R	R^1	R^2	%Yield (isolated and purified)
a	n-Bu	H	Et	47
b	n-Bu	Cl	Et	41
c	$-(CH_2)_5-$	H	Et	49
d	$-(CH_2)_5-$	Cl	Et	58
e	$C_6H_5CH_2-$	H	Et	80
f	$C_6H_5CH_2-$	Cl	Et	54
g	n-Pr	H	Me	58
h	$2-CF_3C_6H_4-$	H	Et	60
i	$2-CF_3C_6H_4-$	H	n-Pr	58
j	$2,3-Cl_2C_6H_3-$	H	n-Pr	82
k	$2,4-Cl_2C_6H_3-$	H	n-Pr	78
l	$3,5-Me_2C_6H_3-$	H	Et	88
m	C_6H_5-	H	Et	85
n	$3-ClC_6H_4-$	H	Et	71
o	$4-ClC_6H_4-$	H	Et	70
p	$3-CF_3C_6H_4-$	H	n-Pr	80
q	$3,5-F_2C_6H_3-$	H	Et	50
r	$3,5-Cl_2C_6H_3-$	Cl	Et	87
s	$3,5-(CF_3)_2C_6H_3-$	Cl	Et	85
t	$3,5-Cl_2C_6H_3-$	Cl	n-Pr	67
u	$3,5-Cl_2C_6H_3-$	Cl	iso-Pr	70

All products isolated as oils except 4q, mp 48°C.

N-Alkyl-substituted 2 (R^1 = H or Cl) rearranged directly to 4 when heated to reflux temperature with sodium alkoxide in dry alcohol solvent (examples 4a - 4 g). N-Aryl-substituted 2 (R^1 = H but not R^1 = Cl) give 4 with sodium alkoxide in dimethylformamide at room temperature (examples 4h - 4k). A ring opening - ring closure sequence via 3 can also be applied to N-aryl-substituted 2 (R = Ar, R^1= H). Thus 2 (R = Ar, R^1 = H) with sodium alkoxide in alcohol gives only 3, even after prolonged reaction times at reflux temperature. 3 (R = Ar, R^1 = H) when heated with tetrabutylammonium iodide and triethylamine readily cyclise to 4 (examples 4l - 4q). N-Aryl-substituted 2 (R^1 = Cl) with sodium alkoxide in dimethylformamide or alcohol at room temperature or above, do not give the azetidine 4 and only the β-aminoacid ester 3 (R = Ar, R^1 = Cl) is seen. Therefore to convert N-aryl-substituted 2 (R^1 = Cl) to azetidine 4, the two step sequence via ring opening to 3 followed by ring closure to 4 must be applied (examples 4r - 4u).

This rearrangement reaction presents a general and versatile route to various 3,3-disubstituted azetidines in that the ester and chloromethyl groups can be further derivatised as desired by common synthetic transformations. For example, the esters are readily hydrolysed to acids;[7] the chloromethyl group is easily substituted with nitrile[8] and sulphur[9] nucleophiles. Azetidine 4e is hydrogenated in the presence of 20% palladium hydroxide on carbon at 100 - 150°C at approximately 10 bar to give azetidine 4 (R = R^1 = H, R^2 = Et. 83% yield).[10] Hydrolysis of 4e (saturated barium hydroxide solution, reflux temperature, 3 hours) gives 4 (R = Benzyl, R^1 = R^2 = H, 88% yield) which on hydrogenation under the above conditions gives 4 (R = R^1 = R^2 = H, 84% yield) as a hygroscopic solid.[11]

Typical reaction conditions used in this work given for 4 are as follows:- Azetidin-2-one 2 (R = alkyl, R^1 = H or Cl, 1eq.) is added to sodium alkoxide (2eq.) in dry alcohol and the solution heated to reflux temperature until reaction complete, as judged by GLC. Evaporation of the solvent, addition of water and extraction with chloroform gives the product. Azetidin-2-one 2 (R = aryl, R^1 = H, 1eq.) is added dropwise to a solution of sodium alkoxide (1eq.) in dimethylformamide. When no starting material remains, as judged by GLC, water is added and extraction with ether gives the product. Azetidin-2-one 2 (R =aryl, R^1 = H or Cl, 1eq.) is added to sodium alkoxide (1eq.) in alcohol and the solution heated at reflux temperature for 2 hours. Evaporation of the solvent, addition of water to the residue and extraction with chloroform gives 3. 3 (R = aryl, R^1 = H or Cl, 1eq.) is heated with tetrabutylammonium iodide (0.2eq.) and triethylamine (1eq.) at 100 - 160°C until reaction is complete as judged by GLC. Addition of water and extraction with chloroform gives the product. Purification is by flash column chromatography or bulb-tube distillation.

References and footnotes.

1. M.Yamashita and I.Ojima, *J. Amer. Chem. Soc. 105*, 6339 (1983).
2. P.G.Sammes and S.Smith, *J. Chem. Soc. Perkin Trans.*, 2415 (1984).
3. T.Okawara, T.Matsuda, Y.Noguchi and M.Furukawa, *Chem. Pharm. Bull., 30*, 1574 (1982). S.R.Fletcher and I.T.Kay, *J. Chem. Soc. Chem. Comm., 903* (1984).
4. 3,3'-Dichloropivaloyl chloride was prepared from commercially supplied 3,3'-dichloropivalic acid (Aldrich Chemical Co. Ltd.) and thionyl chloride.

5. 3-Chloro-2,2-bis(chloromethyl)propionyl chloride was prepared from pentaerythritol. Thionyl chloride with pentaerythritol in pyridine gives 3-chloro-2,2-bis(chloromethyl)propan-1-ol which is oxidised with concentrated nitric acid to 3-chloro-2,2-bis(chloromethyl)propanoic acid. Treatment with thionyl chloride gives the acid chloride.
A.Mooridan and J.B.Cloke, *J. Amer. Chem. Soc., 67*, 942 (1945).

6. All products give satisfactory microanalytical (M.F.Jamieson, ICI Agrochemicals.) and N.M.R. data (P.Stanley, ICI Agrochemicals).

7. Easily converted to acids by hydrolysis with aqueous ethanolic sodium hydroxide; eg. 4l (R^2 = H), 58% yield, mp. 132 - 133°C. 4m (R^2 = H),60% yield, mp. 92 - 94°C. Azetidines 4 (R^1 = Cl) when hydrolysed with aqueous sodium hydroxide are converted to 4 (R^1 = OH, R^2 = H), eg. 4o gives 4 (R = $3,5Cl_2C_6H_3$-, R^1 = OH, R^2 = H), 59% yield, mp. 137 - 138°C.

8. 4o with potassium cyanide in dimethylsulphoxide at 100 - 120°C. 10 hours gives 4 (R = $3,5Cl_2C_6H_3$-, R^1 = CN, R^2 = isopropyl) 95% yield, obtained as an oil; I.R. ν C≡N 2260cm^{-1}, C=O 1730cm^{-1} , N.M.R. ($CDCl_3$) δ, 1.20, d, 6H, J = 6Hz; 2.92, s, 2H; 3.70, d, 2H, J = 9Hz; 4.04, d, 2H, J = 9Hz; 5.00, m, 1H; J = 6Hz; 6.20, s, 2H; 6.68, s, 1H.

9. 4o with sodium thiomethoxide in dimethylformamide at room temperature overnight gives 4 (R = $3,5Cl_2C_6H_3$-, R^1 = SMe, R^2 = isopropyl), 70% yield, mp. 55 - 56°C.

10. Azetidine 4 (R = R^1 = H, R^2 = Et) is obtained as an oil. Purification by distillation is difficult (bp. 92 - 94°C / 28mm.) and product losses are observed due to polymerisation. I.R. ν NH 3320cm^{-1}; C=O 1750 cm^{-1}. N.M.R. ($CDCl_3$) δ, 1.25, t, 3H, J = 7Hz; 1.60, s, 3H; 1.90, broad NH; 3.54, d, 2H, J = 9Hz; 4.00, d, 2H, J = 9Hz; 4.20, q, 2H, J = 7Hz; Derivatisation with 3,4-dichlorophenyl isocyanate gives 4 (R = $3,4\text{-}Cl_2C_6H_3NHCO$-, R^1 = H, R^2 = Et) 50% yield, mp. 121 - 122°C.

11. Azetidine 4 (R = R^1 = R^2 = H) is readily derivatised by acylation; eg. with 2,6-dichlorobenzoyl chloride to give 4 (R = $2,6Cl_2C_6H_3CO$-, R^1 = R_2 = H), 60% yield, mp. 172 - 173°C.

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