Tetrahedron Letters,Vol.27,No.37,pp 4435-4436,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ALKYLATION OF SCHIFF BASE ANIONS WITH ω-HALOGENO ESTERS : A LACTAM SYNTHESIS.

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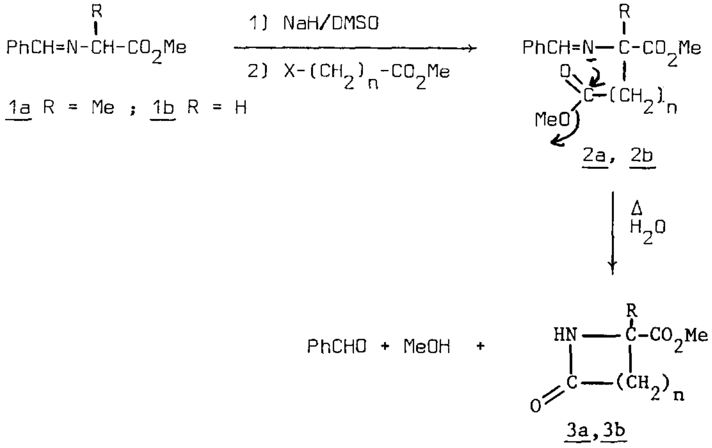
Summary : Imine anions of α-aminoesters, obtained from NaH/DMSO are alkylated with ω-halogenoesters. Thermolysis of the alkylated compounds lead to functionnalized lactams.

Lactam synthesis by cyclodehydration of amino acids and esters using various catalysts is well documented (1-6), but these reactions do not allow the straightforward introduction of a functionnal group α to the nitrogen. We report now an easy access to this type of compounds starting from imine derivatives of α aminoesters. It has been shown in this laboratory (7) that the nitrogen atom of alkylated imines was nucleophilic enough to promote an intramolecular substitution. We have use this ability to acheive lactam synthesis according to the following scheme.



The first step is the alkylation of the imine. For 1a the reaction leads to 2a with good yields after short path distillation ($n = 1$, 72% ; $n = 2$, 80% ; $n = 3$, 72% ; $n = 4$,58%). For 1b owing to the presence of two hydrogens we observed a competition between mono (major product) and dialkylation (2b,R =H and 2b, $R = -(CH_2)_nCO_2Me$) but these compouds were separated by short path distillation (2b,R =H ; $n = 2$,60% ; $n = 3$, 45%; $n = 4$, 43%).

The alkylated imines 2 are characterized by H^1 NMR for instance :
2a, n = 2 : 1.58 (s, 3H) ; 2.0 to 2.7 (m, 4H) ; 3.68 (s, 3H) ; 3.75 (s, 3H) ; 7.23 to 7.5 (m, 3H) ; 7.68 to 7.85 (m, 2H) ; 8.28 (s, 1H).
2b, R = H, n = 2 : 2.25 to 2.45 (m, 4H) ; 3.63 (s, 3H) ; 3.75 (s, 3H) ; 4.2 (t, 1H) ; 7.25 to 7.5 (m, 3H) ; 7.68 to 7.88 (m, 2H) ; 8.33 (s, 1H).

The second step in the thermolysis of 2 which is realized by heating the neat product at 180°. The resulting lactams are purified by short path distillation (3a, n = 2, F = 60°, 70 % ; n = 3, F = 102°, 60 % ; n = 4, F = 128°, 47 % ; 3b, n = 2, $Eb_{0.05}$ = 150° ; n = 3, $Eb_{0.03}$ = 120°, 22 %)(8). These lactams are characterized by NMR spectroscopy, mass spectroscopy and elemental analysis, for instance :
3a, n = 4 (H^1 NMR) : 1.53 (s, 3H) ; 1.63 to 2.0 (m, 6H) ; 2.28 to 2.58 (m, 2H) ; 3.80 (s, 3H) ; 6.35 (s, wide, D_2O exchange). Mass spectrometry : $C_9H_{15}NO_3$ (calculated : 185.1051 ; found : 185.1052).
3b, n = 2 (H^1 NMR) : 2.15 to 2.65 (m, 4H) ; 3.78 (s, 3H) ; 4.3 (t, 1H) ; 7.53 (s, wide, D_2O exchange). Mass spectrometry : $C_6H_9NO_3$ (calculated : 143.059 ; found : 143.0582).

The yields are lower for 3b and this may be due to the presence of an hydrogen α to the nitrogen which allows the thermal equilibrium with the azomethine ylid moiety (9-10) and reduces the nucleophilicity.

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(Received in France 16 June 1986)