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REACTION OF SCHIFF BASES ANIONS WITH α,ω-DIHALOALKANES : SYNTHETIC ROUTE TO CYCLIC α-AMINOACID DERIVATIVES(1).

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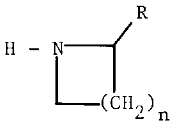
Imine anions of α-aminoesters, obtained from LDA/THF, undergo copper-catalyzed substitution reactions with α,ω-dihaloalkanes to lead to ω-haloalkylimines which are converted to cyclic α-aminoacid derivatives under anionic and thermal conditions.

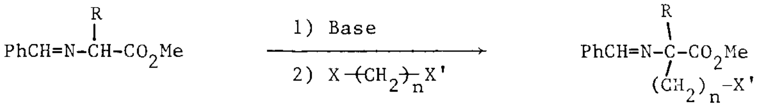
We have shown that imine anions undergo addition-elimination as well as substitution reactions with 4-halo-2-butenoates(2). These anions react with α,ω-dihaloalkanes to lead to substituted α-haloalkyl(3) α-cycloalkyl(4-7) α-aminoacid derivatives depending on the substitution at the carbon α to the nitrogen. Base-induced cyclization from ω-haloaminophosphonates(8) and isocyanoacetates(9) leading to compounds 1 are known.



1 : R = $P(O)(OR^1)_2$, $COOR^1$

We report the synthesis of ω-haloalkylimines 4-6 from imines 2 and α,ω-dihaloalkanes 3 with LDA and copper salts as catalysts. Further transformation to cyclic α-aminoacid derivatives has been achieved by thermal and base induced reactions.

Under usual alkylation conditions, either NaH, THF, HMPA, 0° to room temperature or LDA, THF, HMPA, -78° to room temperature, reactions were never complete after 16 h. even with large excess of alkylating reagent. Increased reaction times did not improve yields but favored by-product formation.



2 a : R = H	3	4 R = H (n = 3, 4 ; X' = C, Br)
b : R = Me	n = 1-6	5 R = Me (n = 1-6 ; X' = Cl)
c : R = Ph	X, X' = Cl, Br	6 R = Ph (n = 3-5 ; X' = Cl)

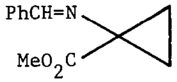
As good yield of alkylation was of importance to use ω-haloalkylimines 4-6 to further transformations without purification(10) we succeeded in with copper(II) salts as catalysts.

The catalytic effect of copper derivatives for coupling reactions has been well established(11-13). Yield of alkylation was improved when the reactions were performed with catalytic amounts of Li_2CuCl_4 in the absence of HMPA. Thus, by-products were avoided even for prolonged reaction times (up to 60 h.).

Other copper salts have been found effective to catalyze alkylation reaction (table I) nevertheless Li_2CuCl_4 gave best results to avoid by-products.

Table I. Yields of imine 5 after 16 h. at r.t.

5	HMPA	CuI	$CuCl_2$	$Cu(OAc)_2$	Li_2CuCl_4
n = 1	52	-	40	40	40
n = 2	25	50	90	10	70
n = 3	10	55	90	60	90



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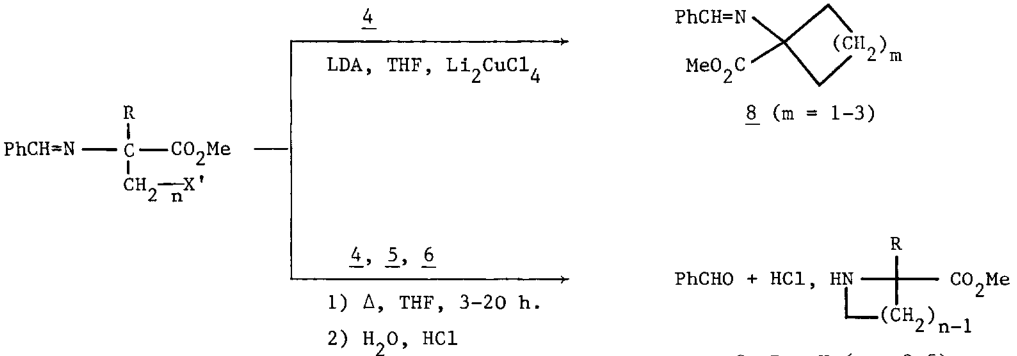
ω-Haloalkylimines 4 with n = 1 or n = 2 could not be prepared from imine 2a. With 1,1-dihalomethanes untractable material was always obtained. In all attempts, only cyclopropane 7 was recovered from the reaction of imine 2a and 1,2-dihaloethanes(14).

With LDA and copper catalysts, imine 4 were cyclized to derivatives 8 (m = 1, 66 % ; m = 2, 90 % ; m = 3, 72 %) which gave satisfactory spectroscopic data. Direct dialkylation from 2a and 3 to cycloalkyl compounds 8 was previously reported(6) with better yields than our two-step transformation.



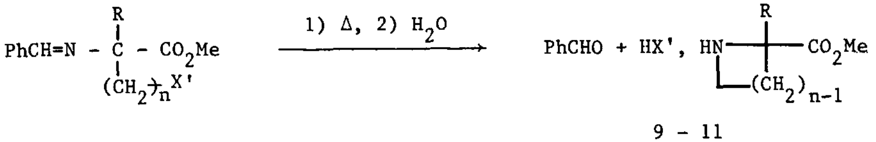
8 (m = 1-3)

9 R = H (n = 3-5)
10 R = Me (n = 3-5)
11 R = Ph (n = 3)

When 5 (n = 3, X' = Cl), 1 g (3.8 mmole) and NaI, 0.1 g (0.6 mmole) were refluxed in dry THF under nitrogen atmospher for 16 h., work-up as usual led to 416 mg of 10 (n = 3, 60 %). In the same manner cyclic α-aminoesters 9, 10, 11 were obtained.

Thermal cyclization to aziridines and azetidines from the corresponding α- and β-haloalkylimines 5 did not occur.

Such a cyclisation may proceed through the intermediate iminium 12(15) which gives after hydrolysis cyclic α-aminoesters with nitrogen incorporated in the ring.



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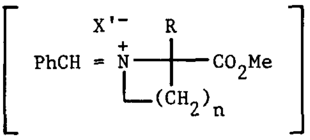

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The use of ω-haloalkyliminoesters for the synthesis of other cyclic and alicyclic α-aminoacid derivatives is under active investigation.

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