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NEW APPROACH TO THE SYNTHESIS OF α-HALOGENOMETHYL-α-AMINO ACIDS

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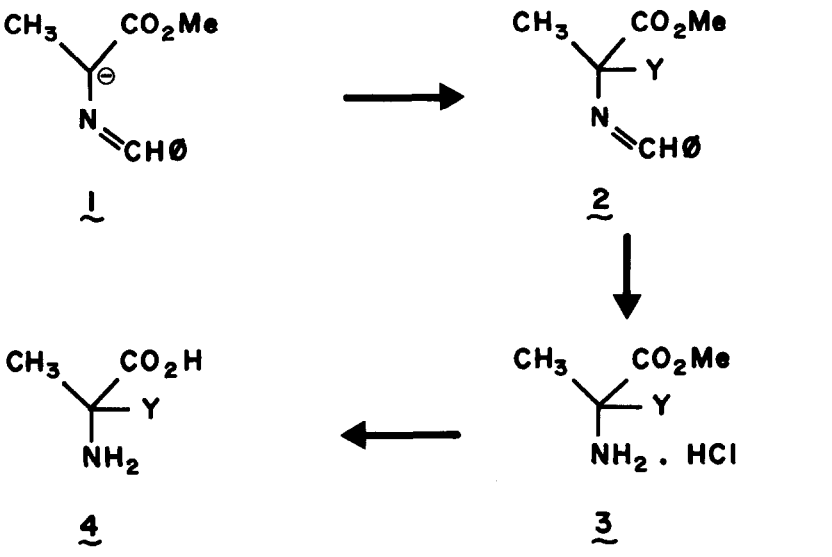
α-Halogenomethyl-α-amino acids represent a class of compounds which is generally not readily available from the Bucherer or Strecker reactions classically employed for the preparation of α-amino acid analogs [1]. In the past years, the synthesis of α-substituted-α-amino acids via direct alkylation at the α-carbon atom of a derivative of the parent α-amino acids has received considerable attention [2]. In line with this strategy, we showed that Schiff base esters of α-amino acids were useful and practical synthons for the preparation of α-functionalized methyl-α-amino acids [3]. The utilization of these synthons to approach the synthesis of α-halogenomethyl-α-amino acid was an attractive possibility. We report now our exploratory work along these lines using the benzylidene alanine methyl ester as a model synthon.

The reactivity of the anion 1 derived from the alanine synthon [lithium diisopropylamide (LDA), 1 equiv, THF] towards polyhalogenomethane derivatives was investigated first with chlorobromomethane (1.1 equiv, room temp.) and chlorodifluoromethane (excess, 45°). The chloromethyl and difluoromethyl adducts 2a and 2b were obtained respectively with excellent yield in both cases. Judging by pmr spectra of the crude reaction mixture [($CDCl_3$), ppm (ref TMS): 1.56 (3H, s, C-CH_3), 3.66 (3H, s, OCH_3), 3.86 (2H, AB syst, J = 10 Hz, δ = 6Hz, CH_2Cl), 7.0-7.8 (5H, m, H aromatic), 8.13 (1H, s, ØCH = N -) for 2a and 1.53 (3H, m long distance coupling with fluorine, C-CH_3) 3.73 (3H, s, OCH_3), 6.16 (1H, t, J_{HF} = 55 Hz, CHF_2), 7.1-7.8 (5H, m, H aromatic), 8.20 (1H, s, ØCH = N) for 2b], the alkylation appears to occur regiospecifically at the α-carbon atom. Selective removal of the benzylidene group of 2a and 2b under mild acidic conditions (HCl, M, room temp. 4 hr) gave the hygroscopic methyl ester hydrochlorides 3a and 3b which were hydrolyzed (HCl, 6M, reflux, overnight) to the corresponding α-halogenomethyl alanine derivatives in good yield (Scheme I); the α-chloromethyl analog 4a was isolated as its monohydrochloride salt [4] [mp: 244°; nmr δ(D_2O) ppm: 1.57 (3H, s, C-CH_3), 3.70 (2H, AB syst, J = 12 Hz δ = 8 Hz, CH_2Cl)] and the α-difluoromethyl analog 4b was crystallized as the free amino acid upon neutralization of a solution of its hydrochloride in ethanol with propylene oxide [mp: 220° subl.; nmr: δ(D_2O) ppm: 1.56 (3H, m,

C-CH_3), 6.10 (1H, t, J_{HF} = 53 Hz, CHF_2)].

SCHEME I



a: Y = CH_2Cl b: Y = CHF_2 c: Y = CF_2Br

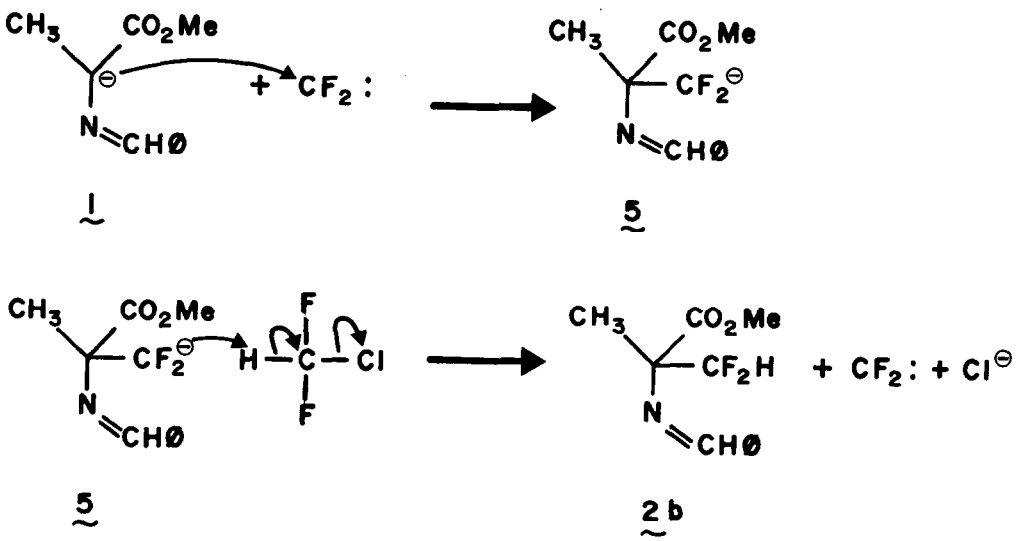
d: Y = CH_2F e: Y = CF_3

The rate of formation of adducts 2a and 2b from the anion 1 under the above conditions differed dramatically. With chlorobromomethane, the alkylation reaction proceeded slowly and required 12 hr to go to completion whereas, with difluorochloromethane it was completed almost instantaneously. This difference in reactivity alludes to the existence of at least two mechanisms for the alkylation process. Considering that polyhalogenomethane derivatives in presence of nucleophilic reagents can undergo either direct displacement of one halogen atom [5] or α-elimination [6] depending on their substitution patterns, it seems reasonable to propose that chlorobromomethane reacts by an S_N2 type mechanism to give the adduct 2a and that chlorodifluoromethane is transformed first to the electrophilic difluoromethylene [7] which then alkylates the anion 1 as depicted in Scheme II. The intermediate 5 by reacting with a new molecule of difluorochloromethane affords 2b and difluorocarbene.

This hypothesis is supported by the following observations: 1) Addition of HMPA to the reaction medium (15 % v/v) increases the rate of formation of adduct 2a (reaction completed in less than 2 hr). This is consistent with the known influence of dipolar solvents on the rate of S_N2 reaction [8]. 2) A slow addition of difluorochloromethane to the anion 1 or the presence of HMPA in the medium results in an important recovery of the starting Schiff base together with the adduct 2b which can be explained by an arrest under these conditions of the carbene chain reaction.

Further evidence in favor of the respective S_N2 and carbene mechanisms came from the alkylation of the model synthon with dichloromethane and dibromodifluoromethane. Thus, dichloromethane (1.1 equiv, THF) was found to alkylate the sodium salt of 1 (generated with NaH) slowly at room temperature to give 2a quantitatively whereas under the same conditions the lithium salt of 1 (generated with LDA) was not alkylated. In the latter case for the reaction to proceed it was necessary to add HMPA to the medium. This dependency of the reactivity of the methylene halides in the alkylation process on the countercation of the carbanion 1 and on the halogen atom displaced (chlorine versus bromine) is in agreement with a S_N2 mechanism [5,9].

SCHEME II



Difluorodibromomethane was found to react almost instantaneously with either the sodium or the potassium salt of 1 (generated with NaH or KH in THF) even at -78° to afford the adduct 2c [bp: 85°/0.02 mm (bulb to bulb evaporative distillation); nmr: $\delta(CDCl_3)$ ppm (ref TMS): 1.73 (3H, m, C-CH_3), 3.77 (3H, s, OCH_3), 7.1-7.9 (5H, m, aromatic) 8.20 (1H, s, ØHC = N)]. Interestingly, the adduct 2b was always present as a side product and its relative proportion was dependent upon the rate of addition of difluorodibromomethane to the anion 1. Only the carbene mechanism, with the intermediary generation of carbanion 5 (Scheme II) can account for the formation of 2b.

Preliminary experiments indicate that the monofluoromethyl and trifluoromethyl analogs 2d and 2e can be obtained by reacting 1 with respectively chlorofluoromethane[10] and bromotrifluoromethane. Particularly attractive is the fact that these alkylation reactions allow the synthesis of fluorinated α-amino acid analogs without resorting to the use of toxic fluorinating agents [11]. Extension of the work to the alkylation of various carbanions with mixed fluorohalogenomethane derivatives as a potential route to the direct introduction of fluoro substituted methyl group is currently under investigation.

Acknowledgement

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