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SYNTHESIS OF α-ALKYL AND α-FUNCTIONALIZED METHYL-α-AMINO ACIDS

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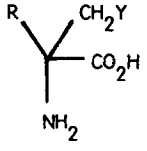
As part of our program aimed at the design of specific enzyme inhibitors, we have been interested in the synthesis of α-alkyl substituted-α-amino acids of type 1 (Y = H or heteroatom functions).



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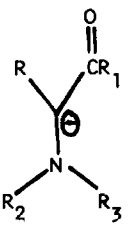

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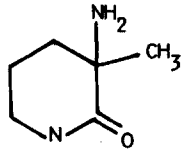

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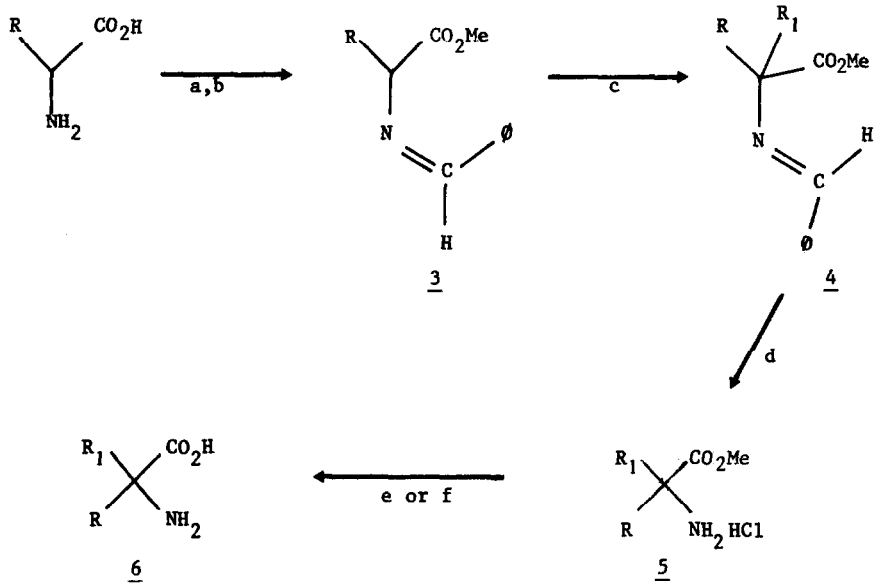
The classical route to α-alkyl substituted-α-amino acids consists of a Bucherer or a Strecker reaction on the corresponding ketones[1]. These methods which imply hydrolyses of hydantoin or α-amino nitrile intermediates to the corresponding α-amino acids, suffer from requiring drastic conditions that are not always compatible with sensitive functionalities[2]. More recently, new procedures based on alkylation of anions of type 2 derived from various protected forms of α-amino acids have been developed. The protecting groups on the carboxyl and on the amine functions serve at the same time the purpose of activating the α position. Anions from α-isocyano carboxylate (R_1=OEt, R_2, R_3= =C)[3], azlactone (R_1, R_2, R_3= =C–Ø)[4], α-nitro carboxylate (R_1=OEt, R_2=R_3=O)[5], α-[Bis(alkylthio)methylenamino] carboxylate (R_1=OEt, R_2, R_3= =C(-SR)$_2$ and α-benzylidene amino lactam (R_1=N<; R_2, R_3= =CHØ)[7] have been used successfully. In line with this approach, we have investigated the use of Schiff base ester 3 of α-amino acids as a general synthon for the synthesis of α-alkyl and α-functionalized methyl-α-amino acids. A recent report by Stork[8] describing a similar synthon prompts us to disclose our results.

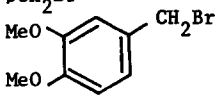
The Schiff base methyl esters 3 are readily available in two steps from the corresponding α-amino acids in almost quantitative yield[9]. Lithium diisopropyl amide (1 equivalent) in THF at -78° or sodium hydride (1 equivalent) in THF at room temperature convert the Schiff base esters 3 to the anions 2 (R_1:OMe, R_2, R_3= =CHØ) which react smoothly with various alkyl iodides to give the corresponding α-substituted derivatives 4.



a: $SOCl_2$/MeOH or MeOH/HCl; b: ØCHO (1 eq), NEt_3; c: DIA (1 eq), BuLi (1 eq)/THF, R_1X;
d: HCl(N), r.t., 1 hr; e: NEt_3 (2 eq)/H_2O, r.t., 24 hr; f: HCl(3N), reflux, 12 hr.

SCHEME I

Judging by n.m.r. spectra of crude reaction mixtures, the alkylation appears to be regiospecific. Only products alkylated on the carbon atom α to the ester can be detected. Non-activated bromides and chlorides do not react. Table I lists examples of alkylation products obtained with the Schiff base ester 3 from alanine (R=CH_3). Hydrolysis of the α-alkylated Schiff base esters 4 to the α-substituted-α-amino acids 6 can be effected smoothly and stepwise (see Scheme I). The mildness of the deprotection procedure is attested by the retention of the cyano group in the conversion of 4 (R=CH_3, R_1=CH_2CN) to the corresponding 6. The Schiff base methyl ester anion 2 of 3 (R=CH_3) also undergoes rapid Michael addition to acrylonitrile and methyl acrylate in equilibrating conditions (catalytic amount of triton B in MeOH/C_6H_6, r.t., 1 hr) to yield quantitatively the adducts 4 (R=CH_3 and R_1=CH_2CH_2CN or $CH_2CH_2CO_2Me$).

R_1X	4* Yield***	4* bp/mmHg**	5* Yield***	5* m.p.
CH_3I	94 %	77°/0.06		
$(CH_3)_2CHI$	95 %	120°/0.1		
Pht $N(CH_2)_3I$			77 %	243°
$CH_2=CHCH_2Br$	90 %	87°/0.03		
$\emptyset CH_2Br$	90 %	170°/0.07		
	80 %	190°/0.01		
$N\equiv CCH_2Cl$	76 %	160°/0.01		
MeO_2CCH_2Br	85 %	130°/0.03		
CH_3OCH_2Cl	87 %	115°/0.01		
CH_3SCH_2Cl	87 %	130°/0.02		

* All new compounds gave acceptable elemental analyses. N.m.r. and i.r. spectra were consistent with the proposed structure.

** Evaporative bulb to bulb distillation using a Buchi Kugelrohrofen.

*** Yield of distilled or crystallized product.

TABLE I

The synthetic utility of this new alkylation procedure is illustrated by the preparation of α-methyl ornithine[10]. Two strategies can be envisaged for the obtention of this potent reversible inhibitor of ornithine decarboxylase (E.C.4.1.1.17)[7a,11], the rate-limiting enzyme of the polyamine biosynthetic pathways in mammals. They consist in introducing either the side chain of ornithine onto the synthon 3 derived from alanine or a methyl group onto the synthon 3 derived from ornithine [R= $(CH_2)_3N=CH\emptyset$].

Both strategies were successful, the former having been implemented either through alkylation with a protected form of 3-iodopropyl amine (phthaloyl group) or through Michael addition to acrylonitrile followed by catalytic hydrogenation ($PtO_2/AcOH/H_2$, 3 Atm, 2hr) of the corresponding cyano amino ester 5 (R=CH_3, $R_1=CH_2CH_2CN$). Hydrolysis of the various protecting groups in concentrated hydrochloride acid gives in each case an excellent yield of D,L-α-methyl ornithine. More interestingly, selective removal of amine protecting groups (dilute HCl for the benzylidene group and hydrazine for the phthaloyl group)allows the obtention of the piperidone 7 in quantitative yield, which can then easily be resolved via its (+) or (-) binaphthyl phosphoric salt[12], thus giving after hydrolysis a convenient access to both enantiomers of α-methyl ornithine. Preliminary results indicate that Schiff base methyl ester anions react also with alkyl and aryl acid chlorides to yield the corresponding α-C-acyl-α-amino acid derivatives[13]. The scope of these versatile alkylations is currently under investigation.

Acknowledgements

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