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ORGANOCUPRATES MEDIATED CARBON-CARBON BOND FORMATION IN ϑ POSITION OF α-AMINO ESTERS WITHOUT RACEMISATION

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SUMMARY : A new general method of synthesis of optically pure α-amino esters by action of organocuprates on t-butyloxycarbonyl-L-α-amino-ϑ-bromobutyric acid methyl ester is described.

Growing interest in enantiomerically pure non-proteinogenic amino acids is due to their documented or potential biological activity. Their syntheses are most often based on asymmetric induction reactions which rarely give the products with a satisfactory enantiomeric excess and therefore require fastidious resolution procedures to obtain sufficiently pure amino acids.
Thus, any general synthetic method, giving access to these compounds via simple amino acids (inexpensive and available in both enantiomeric forms) without affecting the starting material asymmetric center, could prove to be of great value.

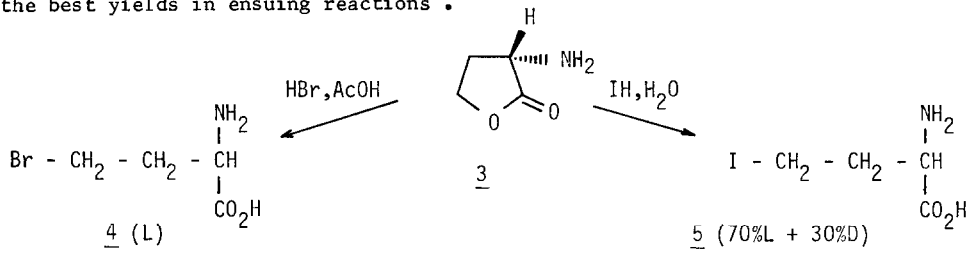
Recently, we reported[1] on the action of organocuprates on racemic ϑ-halogeno α-amino esters (1 ; X = I, Y = Boc, Z, Bz) affording the substitution products (2) in good yields.

1 2

Here we describe our attempts to generalize this method for the synthesis of optically pure amino acids. Although it does not imply directly the substrate center of chirality, we could not exclude a priori a possible racemisation by organocuprates ;

they are less basic[2-4] than the corresponding lithium and magnesium derivatives, but give dimerisation[5,6], enolisation[6-8] or dehydrohalogenation[4,9] by-products, while acting on compounds containing activated protons.

Tert-Butyloxycarbonyl-L-α-amino-γ-bromobutyric acid methyl ester (1 ; X = Br, Y = Boc) - $[\alpha]_D$-46° (c 3, MeOH) ; lit.[10] $[\alpha]_D$-37°(c 0.5, same solvent) - a synthon in our investigations - was easily prepared by hydrogen bromide cleavage of L-γ-butyrolactone[11](3); We chose a methyl ester protection for the carbonyl group in order to ensure the best detection of any possible racemisation (based on ^{1}H-nmr spectra in presence of d-Eu(hfc)$_3$ as chiral shift reagent) and that of Boc for the amino group[12] : it is removed easily and gives the best yields in ensuing reactions[1].



The iodo equivalent (5) would be more useful, iodine being a better leaving group in the organocuprates reactions[2], but the same ring opening mode with hydrogen iodide (56% aqueous solution)[13] proceeds with partial racemisation.

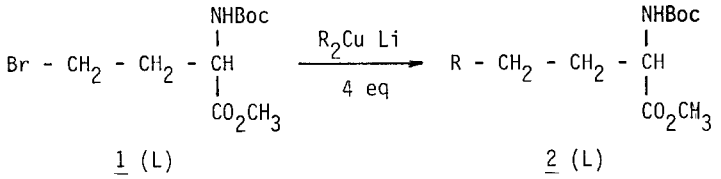
Despite more "drastic" reaction conditions (longer reaction time and higher temperature), yields of the alkyl cuprates substitutions products (2) (Table I) are comparable with those obtained if X = I ; as expected, THF brings about a better reactivity than diethyl ether[14].
The specific rotation values of 2, compared with literature, as well as enantiomeric excess, measured (nmr spectra) after having removed the amine protecting group, proved the reaction to occur without any mesurable (e.e. >95%) loss of optical purity.

This new, efficient synthetic method, allowing a carbon-carbon σ-bond formation with total retention of configuration, will be applied to synthesise uncommon amino acids, of interest in organic and biorganic chemistry.

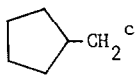
Experimental :

A solution of copper iodide (11,5 mmol) in 50 ml of solvent (see Table 1) at -60°C (-10°C for $(C_6H_5)_2CuLi$), under nitrogen, is treated with 23 mmol of n-butyllithium and if necessary 23 mmol of dibutylsulfide - in 50 ml of the same solvent. After 30 min, amino ester 1 (2,88 mmol in 20 ml of the solvent) is added and stirring continued for the time and at the temperature indicated in table 1.

Table I - Organocopper substitution reaction with tert-butyloxycarbonyl-L-α-amino-γ-bromobutyric acid methyl ester



1 (L) 2 (L)

R	Solvent	Temp. °C	Time hr	Yield %	$[\alpha]_D^{20°}$ (c, MeOH) found	reported	ee[a] %
Me	THF	-10	9	78	-30 (c 1,7)	-30[15] (c 1)	>95
	Et_2O	0	18	52[d]	-30 (c 1,9)	-30[15] (c 1)	>95
Et	THF	-10	7	75	-26 (c 1,9)	-26[b] (c 1,7)	>95
n-Pr	THF	-10	7	72	-18 (c 3,4)	-	>95
n-Bu	THF	-10	7	74	-18 (c 2,6)	-	>95
	Et_2O	0	14	51[d]	-17 (c 2,4)	-	>95
	Et_2O	-5	14	44[d]	-16 (c 2,2)	-	>95
Ø	Et_2O	-5	14	71	-15 (c 1,6)	-	>95
=	Et_2O	-5	14	42[d]	-17 (c 1,2)	-	>95

[a] Only one enantiomer detectable in the ^{1}H-nmr spectrum (HA 100) using Eu(hfc)$_3$ as shift reagent

[b] Prepared from $(Boc)_2O$ and HCl-L-norleucine methyl ester[12]

[c] Prepared from bromo-6 hexene-1[16]

[d] With recovery of starting material

The reaction mixture is quenched with saturated ammonium chloride solution and the aqueous layer extracted with 3 x 30 ml of ether. After drying over magnesium sulfate, the combined organic extracts are concentrated in vacuo and chromatographed on silica gel with 3 : 1 ether -light petrol ether. The amino esters obtained (oils) were characterised by their nmr, mass spectrometry, microanalysis and specific rotation data.

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