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LITHIUM DIORGANOCUPRATE REACTIONS WITH L-SERINE DERIVATIVES

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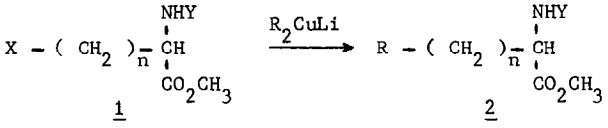
SUMMARY : The lithium diorganocuprate reactions with L-serine derivatives are studied. Retention of configuration, or at least a high enantiomeric excess (>80%) of the formed α-amino esters is observed in all cases. Attempts are made to restrict side-reactions.

Recently we have developed a synthetic method of carbon-carbon σ bond formation in the γ position of α-amino esters 2 (n = 2) which proceeds with retention of the α-carbon configuration due to the smooth reaction of organocuprates with the γ halogeno precursors (1)[1].



Here we report the results of our attempts to further generalize this method and synthesise amino esters of type 2 (n = 1), thus allowing chain modifications nearer to the chirality center.

To this effect, we start with β-tosyl-L-serine and β-iodo-L-alanine, inexpensive and much more easily available starting materials (also as D enantiomers), than the homoserine analogues, necessary in the case of n = 2.

Despite the pronounced tendency of such compounds to undergo β-elimination[2,3], O-tosyl serine derivatives were found to react with sodium thiolacetate or with sodium benzyl selenide without loss of optical activity[4,5]. Taking into account the poor basicity and the strong nucleophilic character of organocuprate reagents, it seemed likely that substitution products, with retention of optical purity, would be obtained.

In the preceding papers[1,6], we have shown that the use of N-tert-butyloxycarbonyl derivatives (1 ; Y = Boc) affords the best yield and selectivity in products 2 (n = 2) ; the methyl ester protection for the carboxyl group was selected to ensure the best precision of spectral evaluation of any possible racemisation. Therefore the reactions were realised with methyl-N-Boc-O-tosyl-L-serinate (1a)[7,8] $[\alpha]_D$-5°(c 2,MeOH) and the iodo derivative (1b) $[\alpha]_D$-4°(c 3,MeOH) obtained from 1a by action of NaI[9].

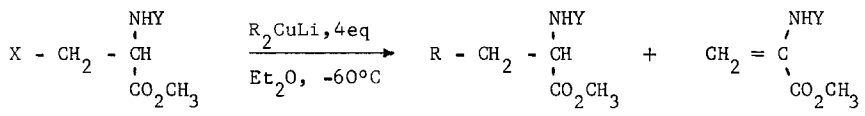
We choose to carry out the present experiments in diethyl ether, because in the first reactions run with dimethylcuprate, the substitution products were formed only if this solvent was employed ; THF or ether-hexane mixture gave exclusively a dehydroalanine derivative 3a (Y = Boc). Additives (e.g. Bu_2S, HMPA) designed to favour displacement reactions had a negligible or deleterious effect.

Numerous studies[2] carried out with 1a showed a correlation between the percentage of the competitive dehydrohalogenation product (3) and the reagent basicity. According to this, our results indicate that lithium dipropyl and dibutylcuprates are significantly the less basic among those used.
In fact, in the reactions with 1a and 1b, some quantity of dehydroalanine 3 (easily separable by column chromatography on silicagel) is formed along with the substitution product (Table I). The substitution : elimination ratio depends not only on the cuprate nature, but also on the leaving group X ; iodide is more efficient in promoting the displacement reaction than tosylate, except in the case of the propyl and butylcuprates.
To avoid any ambiguity in the interpretation of these results, we investigated the reaction of organocuprates on 3a (Y = Boc) under similar reaction conditions. They do not give any 1,4-addition (whatever organocuprate used) ; therefore 2 results from a substitution reaction rather than the elimination-addition sequence.

The enantiomeric excess analysis shows that total retention of the amino ester configuration (ee $>$95%) is always accompanied with a relatively large ($>$20%) yield of the elimination product. When the latter diminishes, slight racemisation of 2 (84$<$ ee$<$ 95) is observed. It is probably induced by the cuprate acting as a base.

Trying to restrict the side reactions (β-elimination, racemisation) we have also investigated the reactions with N-tosyl-β-iodo-L-alanine methyl ester (1c) $[\alpha]_D$+4°(c 6,EtOH) prepared[9] from the corresponding ditosyl derivative[10]. Use of this N-protecting group excludes β-elimination, with the exception of dimethylcuprate (Table I), but results in some racemisation of 2. The elimination product 3b (Y = Ts) does not react with organocuprates, thus proving that, as in the preceding reactions, the racemisation is not due to a consecutive 1,4-addition.

Table I - Organocopper substitution reaction[a]



1 2 3

X	Y	R	Time hr	Yield % 2	$[\alpha]_D^{20°}$ (c, solvent) found	reported	ee[b] 2	Yield % 3
OTs	Boc	Me	5	42	-39(2, MeOH)		>95	45
I	Boc	Me	5	27	-39(2, MeOH)		>95	63
OTs	Boc	Et	3	0				90
I	Boc	Et	3	48	-30(2, MeOH)	-30(1, MeOH)[12]	>95	42
OTs	Boc	n-Pr	3	72	-22(2, MeOH)	-26(2, MeOH)[1]	85	6
I	Boc	n-Pr	3	64	-23(3, MeOH)	-26(2, MeOH)[1]	90	10
OTs	Boc	n-Bu	3	75	-17(3, MeCH)	-18(3, MeOH)[1]	88	2
I	Boc	n-Bu	3	68	-16(3, MeOH)	-18(3, MeOH)[1]	84	9
I	Boc	t-Bu	3	34	-26(2, MeOH)		>95	48
I	Boc	Ø[c]	5	16	-3 (2, MeOH)	-3,1(2, MeOH)[13]	>95	70
I	Boc	=	18	60	-9 (2, MeOH)		>95	21
I	Ts	Me	3	62	-18(1, EtOH)	-22(1, EtOH)[d]	82	12
I	Ts	Et	3	70	-13(2, EtOH)	-15(3, EtOH)[d]	87	0
I	Ts	n-Pr	3	74	-11(2, EtOH)	-12(2, EtOH)[d]	92	0
I	Ts	=	3	69	-6 (4, EtOH)			0
I	Ts	Ø[c]	5	65	+3 (1, MeOH)	+3,1(1, MeOH)[14]		0

[a] general procedure[1,6]

[b] ee of 2a (Y = Boc) calculated from ^{1}H-nmr spectra with d-Eu(hfc)$_3$, after removal of the amine protection ; for 2b (Y = Ts) it is based on specific rotation data

[c] reaction temperature -10°C

[d] prepared by N-tosylation[10] of the corresponding amino ester

The interest of the method described is best illustrated by the preparation of neopentylglycine which has been recently obtained[11] by a multi-step synthesis, followed by a fastidious resolution ; the organocuprate procedure allowa a one step access to this compound with ee>95% (by action of ditert-butylcuprate on 1a).

Were are continuing to explore the scope of the method.

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