Tetrahedron Letters No. 36, pp 3171 - 3174, 1977. Pergamon Press. Printed in Great Britain.

ASYMMETRIC INDUCTION IN THE CONJUGATE ADDITION OF LITHIUM DIORGANOCUPRATES TO (-)MENTHYL 3-(2-FURANYL)ACRYLATE

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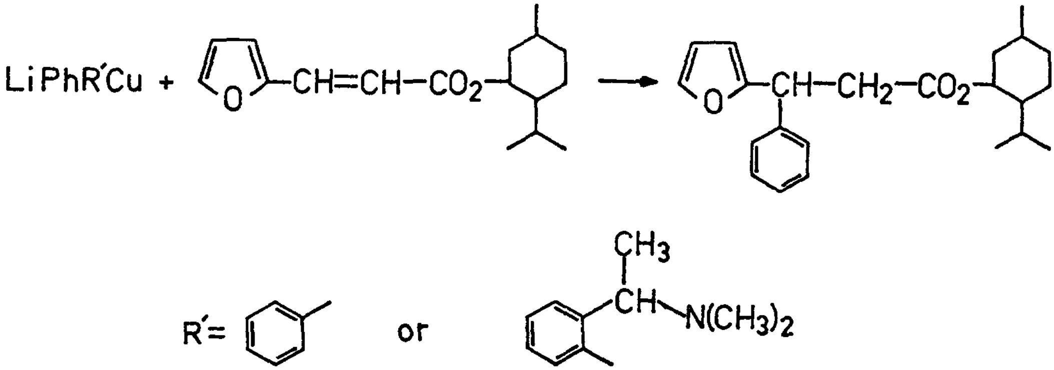
(Received in UK 27 June 1977; accepted for publication 14 July 1977)

We have recently investigated the addition of racemic and chiral, mixed lithium diorganocuprates, LiRR´Cu, to methyl trans-cinnamate[1] and methyl trans-3-(2-furanyl)acrylate.[2] With R being an alkyl or phenyl group and R´ being a chiral 2-(1-dimethylaminoethyl)phenyl group a small optical rotation can be observed in the conjugate addition product.

Asymmetric induction in the conjugate addition of Grignard reagents to (-)menthyl crotonate has been reported. 1,4-Addition of phenylmagnesium bromide and subsequent hydrolysis gave an excess of (+)3-phenylbutanoic acid (7%), while the copper catalysed addition resulted in an excess of (-)3-phenylbutanoic acid (5-10%).[3,4]

It is known that the size of the alkoxy group of an α,β-unsaturated ester will influence the rate of formation and the yield of the 1,4-addition products in the reaction with lithium diorganocuprates.[5] The addition of chiral and achiral cuprates to (-)menthyl trans-3-(2-furanyl)acrylate[6] should increase the knowledge about the reagent behaviour and composition and thereby also the possibilities to obtain asymmetric induction.



The reactions of lithium diphenylcuprate, the racemic and the two chiral lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprates[2,7] (30 mmol in diethyl ether) with (-)menthyl 3-(2-furanyl)acrylate (20 mmol) proved to be slower than the corresponding additions to methyl 3-(2-furanyl)acrylate (GLC). (See Table 1). The normal 1,4-addition product was no longer the main product. Instead, products of higher molecular weight were formed. Addition of lithium diphenylcuprate to (-)menthyl 3-(2-furanyl)acrylate afforded 11.3% of the normal 1,4-addition product menthyl 3-(2-furanyl)-3-phenylpropanoate (b.p. 120 °C/5 Pa) and 46% of another product probably menthyl 4-menthoxycarbonyl-3,5-di-(2-furanyl)-5-phenylpentanoate[8] (b.p. *ca*. 300 °C/4 Pa; abs. mass 630.385±0.006). The optical rotation of 3-(2-furanyl)-3-phenylpropanoic acid[2] was determined after distillation and hydrolysis of the 1,4-adduct.

Table 1. 1,4-Addition of lithium diorganocuprates, LiPhR´Cu (R´= 2-(1-dimethylaminoethyl)phenyl), to (-)menthyl 3-(2-furanyl)acrylate at 0 °C in diethyl ether. The isolated yields of the 1,4-adduct were determined by weighing after distillation.

Exp. nr	LiPhR´Cu	Reaction time (h)	Isolated yield (%)	$[\alpha]^{20}_{578}$ of isol. acid (*c*, $CHCl_3$)	Optical yield (%)
1	$LiPh_2Cu$	3	11.3	+0.8° (0.0344)	2
2	LiPh(-R´)Cu	8	10.2	+0.4° (0.0622)	1
3	LiPh(±R´)Cu	8	9.2	+1.2° (0.0488)	3
4	LiPh(+R´)Cu	8	7.5	+4.3° (0.0338)	10

The low chemical yields of the 1,4-addition of cuprates to (-)menthyl 3-(2-furanyl)acrylate must be improved in order to make this approach to asymmetric synthesis valuable. However, there are several interesting features of these reactions.

It can be concluded that some asymmetric induction occurs in the reactions of chiral cuprates with α,β-unsaturated esters. The optical yields depend on the alkoxy group in the ester as well as on the cuprate. Exp. 1 in Table 1 shows that the (-)menthyl group induces some optical activity in the addition of lithium diphenylcuprate to the ester. When one of the phenyl groups in the cuprate is changed into the racemic 2-(1-dimethylaminoethyl)phenyl group (Table 1, exp. 3) the steric hindrance become more severe. The rate of 1,4-addition is substantially decreased with the bulkier cuprate. This obviously increases the possibilities to obtain asymmetric induction.

In exp. 2 the result of two competing effects can be observed. The (-)menthyl group directs the reaction towards an excess of one enantiomer while the (-)2-(1-dimethylaminoethyl)phenyl group will induce the formation of the other enantiomer. Finally, exp. 4 shows the combined effects of the (-)menthyl group and the (+)2-(1-dimethylaminoethyl)phenyl group. The optical yield is increased to a degree suggesting a synergistic interaction of the two groups.

The optical yields and the reaction rates, in the addition of the cuprates to (-)menthyl 3-(2-furanyl)acrylate, strongly indicate that a mixed cuprate has been formed initially and that there is no fast equilibrium giving homogenous cuprates[9] or mixed halide-containing cuprates of the form LiRXCu,[10] which should react faster and not be able to give any optical induction. It is,

$$2\ R'Li\ +\ 2\ PhCu \longrightarrow (LiPhR'Cu)_2 \not\rightleftharpoons LiPh_2Cu\ +\ LiR'_2Cu$$

however, possible that the reagent is dimeric in analogy with lithium dimethylcuprate[11] and lithium di-[2-(1-dimethylaminoethyl)phenyl]cuprate.[12] In the latter cuprate the amino groups bond to the lithium atoms leaving the copper atoms open for complexation with solvent molecules. It should also be possible for an essentially dimeric reagent to react <u>via</u> a small amount of a more reactive monomeric cuprate in equilibrium with the dimeric form.

The initial steps in the reaction of a lithium diorganocuprate with an α,β-unsaturated carbonyl compound could tentatively be formulated in the following way: The cuprate cluster carries solvent molecules as ligands to the copper atoms. One of these solvent molecules has to leave the cluster to create an active site. The cuprate will approach the α,β-unsaturated carbonyl substrate with the copper acting as a nucleophile. The formation of a copper-carbon bond to the β-carbon atom can be followed by a collapse of this reactive intermediate with transfer of an organic group from the cuprate to the β-carbon (or side reactions can occur when steric hindrances are severe). The products are then an enolate and a smaller copper-lithium cluster or lithium ion in solution while one equivalent of RCu is precipitated.

Acknowledgements: This work has been supported by grants to B.G. from the Finnish Oil Industry, Neste Oy, and from the Research Institute of the Åbo Akademi Foundation (Åbo, Finland), and by a grant from the Swedish Board of Technical Development.

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