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REGIO AND STEREOSPECIFIC SYNTHESIS OF CIS AND TRANS 3-METHYL-6-METHYLETHYL CYCLOHEXENES AND 3-METHYL-4-METHYLETHYLCYCLOHEXENES. REACTIONS OF ALLYLIC ACETATES AND CARBAMATES WITH $Li_2Cu_3Me_5$ AND $LiCuMe_2$

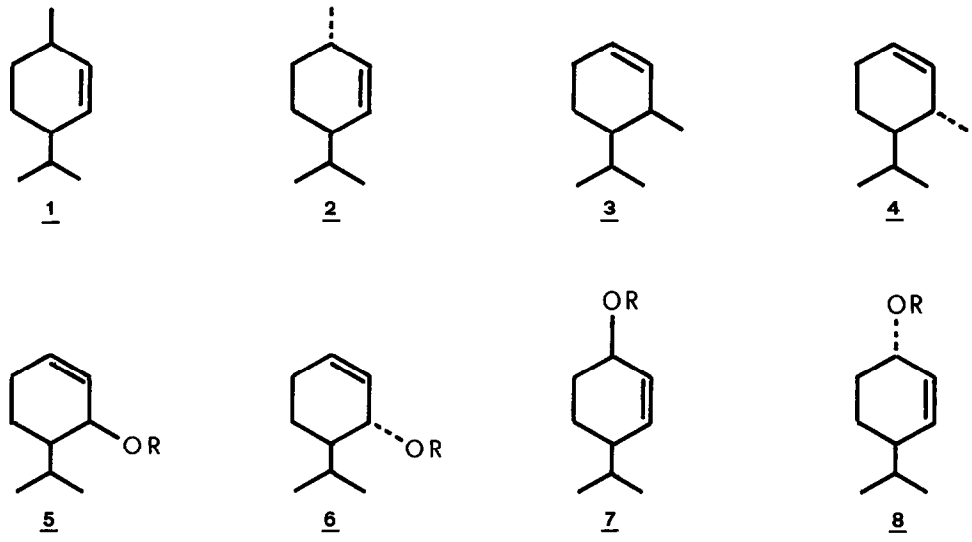
C. Gallina
Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica Farmaceutica dell'Università, P.le A. Moro, I-00185 Roma (Italy)

Abstract. The isomeric alkenes 1-4 have been obtained by syn, γ substitution of the appropriate allylic carbamates with $Li_2Cu_3Me_5$. The behaviour of carbamates is deeply affected by the nature of the copper reagent.

Cis-p-menth-2-ene (1) was recently obtained by Kreft[1] by regioselective coupling of 6a and 8a mesitoates with $LiCuMe_2$; the trans isomer 2 can be obtained from readily available materials by elimination pathways;[2] the cis and trans o-isomers 3 and 4 have been only prepared[1] as a 75/25 mixture by catalytic reduction of the corresponding exo-methylene compound. We report that all four isomers 1-4 have been obtained by regio and stereospecific coupling[3] of the carbamates 5b-8b with $Li_2Cu_3Me_5$.

Carbamates 5b-8b[4] were prepared from the corresponding alcohols[2,5] and further purified by crystallisation. For preparative purposes the reactions were carried out as follows on a 4 mmoles scale: to a stirred suspension of the carbamate in diethylether (5 ml), at 0°C, under nitrogen, one molar equivalent of a 0.065 M solution of $Li_2Cu_3Me_5$, prepared according to Ashby,[6] was added. An abundant yellow precipitate formed immediately. After 15 hr at 15°C, the reaction was quenched with aqueous NH_4Cl, the organic layer washed with aqueous HCl and $NaHCO_3$, and dried over Na_2SO_4. Hexane was substituted for ether by distillation, and the solution filtered through a short pad of silica gel saturated with NH_3. Removal of the solvent and distillation of the residue at 20 mm Hg and 60°C (bath temp.) gave the pure alkenes 1-4 (1 from 5b, 79%; 2 from 6b, 81%; 3 from 7b, 82%; 4 from 8b, 68% isolated yields).[7] Contamination by unwanted isomers could be checked directly by GLC[8] and was, if any, less than 1% (see Table).

Since some preliminary trial runs employing $LiCuMe_2$ disappointingly



a, R = H; b, R = OCONHPh; c, R = $COCH_3$. One enantiomer only shown.

showed a not so good control of regio and stereochemistry, we suspected that the results could be influenced by the nature[6] of the copper reagent. The generalised procedure outlined above was therefore employed to evaluate the behaviour of carbamates 5b-8b and of the corresponding acetates 5c-8c[9] against $Li_2Cu_3Me_5$, $LiCuMe_2$ and Li_2CuMe_3[10] in diethylether. Reactions were carried out on a 0.5 mmole scale in the presence of n-undecane as internal standard; further experimental details are reported in the Table; pentane solutions of the products were analysed by GLC[8] for yield and composition.

The results reported in the Table show that the behaviour of allylic acetates, except 8c, is little affected by the nature of the copper reagent and is essentially in accordance with the findings of Kreft.[1]

In order to rationalise the course of the reaction of an allylic carbamate with $LiCuMe_2$ some further experimental data will be useful. Addition of one molar equivalent of $LiCuMe_2$ to an ethereal solution of 7b at 0°C immediately afforded a yellow precipitate: MeCu and the lithium carbamate were formed probably. In fact, the starting carbamate could be completely recovered after 15 hr at 15°C, while conversion into the alkene could not be observed. When three equivalents of $LiCuMe_2$ were used, the yellow precipitate that was produced first, immediately disappeared after completion of the addition. The reaction stoichiometry suggests that $Li_2Cu_3Me_5$ and the lithium carbamate

Table. Reaction of Allylic Carbamates and Acetates with $Li_2Cu_3Me_5$ (A) and $LiCuMe_2$ (B) in diethylether

Allylic derivative	Reagent	Molar ratio[a]	Reaction temp.(°C)	Product composition (%)[b] 1	2	3	4	Yield (%)[b]
5b	A	1	15	>99	<1	-	-	92
5b[c]	B	3	15	57	27	-	16	79
6b	A	1	15	<1	>99	-	-	95
6b[c]	B	3	15	30	69	-	<1	88
7b	A	1	15	-	-	>99	<1	97
7b[c]	B	3	15	-	25	62	13	88
8b	A	1	15	-	-	<1	>99	79
8b[c]	B	3	15	4	2	-	94	73
5c	A	0.5	0	<1	66	-	33	89
5c	B	3	0	-	65	-	35	87
6c	A	0.5	0	>99	<1	-	<1	85
6c	B	3	0	>99	<1	-	<1	78
7c	A	0.5	0	-	65	-	35	90
7c	B	3	0	-	65	-	35	83
8c	A	0.5	0	>99	<1	-	<1	73
8c	B	3	0	61	22	<1	16	32

a) Copper reagent/allylic derivative molar ratio; b) determined by GLC analysis using internal standard; c) previously converted into its lithium salt by addition of one equivalent of MeLi at -78°C.

were formed probably. Prompt quenching allowed the starting carbamate to be recovered again, while warming at 15°C for 15 hr mainly gave the product of *syn*, γ substitution.

These findings strongly suggest that the course of the reaction should be governed by three processes: (i) fast conversion of the carbamate into its lithium salt, (ii) fast equilibration of the organocopper species, (iii) slow reaction of the lithium carbamate with $Li_2Cu_3Me_5$. Thus, the actual situation appears to be similar to that obtained by direct addition of $Li_2Cu_3Me_5$, where formation of the lithium salt again preceeds substitution. Of course, this last technique avoids the danger of stoichiometric and/or local excess of $LiCuMe_2$.

The behaviour of an allylic lithium carbamate in the presence of $LiCuMe_2$ can be observed by addition of more than three equivalents of the reagent to the corresponding carbamate. Otherwise the lithium salt can be generated previously by addition of one equivalent of MeLi at -78°C. Both methods gave similar

results.

Under these circumstances (see Table) the product of syn, γ substitution is accompanied by substantial amounts of other isomers; this behaviour should be regarded as the consequence of two competing reactions: the attack of the lithium carbamate by both $LiCuMe_2$, added at the beginning, and $Li_2Cu_3Me_5$, which is formed during the course of the reaction. On the contrary, the reaction proceeds exclusively by syn, γ attack when $Li_2Cu_3Me_5$ is used, even in the case of 7b, where this path appears to be severely hindered by steric factors.

From a mechanistic point of view, $Li_2Cu_3Me_5$ rather than $LiCuMe_2$, appears to be the reagent actually involved in this regio and stereospecific reaction. This finding is in accordance with our hypothesis of a concerted process with a cyclic transition state where $Li_2Cu_3Me_5$, which is expected to be more electrophilic than $LiCuMe_2$, could better cohordinate the negatively charged lithium carbamate leaving group.

REFERENCES AND NOTES

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7. Satisfactory elemental analyses, IR, ^1H NMR and MS spectra were obtained; 1, n_D^{20} 1.4542; 2, n_D^{20} 1.4509; 3, n_D^{20} 1.4600; 4, n_D^{20} 1.4532.
8. 10 m, 2 mm i. d., 15% OV 275 on 100-120 mesh Chromosorb (Supelco); retention times: 1, 32.65; 2, 31.15; 3, 40.50; 4, 35.15 min. at 110°C, and 5 ml/min nitrogen flow rate.
9. Prepared by Ac_2O/pyridine acetylation of the alcohols obtained from the purified carbamates.
10. Both carbamates and acetates react with respectively three and two molar equivalents of Li_2CuMe_3 to give mainly the corresponding alcohols and mixtures of the alkenes in poor yield as a consequence of prevailing attack of the reagent on the ester carbonyl group.

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