FORMATION OF DIMETHYL CYCLOHEXANONEDICARBOXYLATES ON ADDITION OF LITHIUM DIORGANOCUPRATES TO METHYL CROTONATE IN THF

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The addition of lithium diorganocuprates, $(LiR_2Cu)_2$, to α,β-unsaturated carbonyl compounds in diethyl ether generally gives high yields of 1,4-addition products.[1] We are presently studying the possibility of asymmetric induction in the 1,4-addition of chiral organocuprates, $(LiRR*Cu)_2$,[2] to α,β-unsaturated carbonyl compounds, R being alkyl or phenyl, R* being 2(1-dimethylaminoethyl)-phenyl obtained from (-)$\underline{N},\underline{N}$-dimethyl-1-phenylethylamine. From these chiral mixed cuprates high chemical yields are obtained of the 1,4-addition products from transfer of the R group selectively, if diethyl ether is used as the solvent.[3,4] So far, the specific rotation of the products has been low, however.

$$(LiRR*Cu)_2 + CH_3\text{-}CH{=}CH\text{-}COOCH_3 \xrightarrow{\text{ether}} CH_3\text{-}\underset{R}{CH}\text{-}CH_2\text{-}COOCH_3$$

When chiral lithium 2(1-dimethylaminoethyl)phenyl phenylcuprate is reacted with methyl trans-crotonate in tetrahydrofuran, THF, instead of ether the main product is no longer methyl 2-phenylbutanoate but a high-boiling compound identified as a derivative of dimethyl cyclohexanonedicarboxylate.
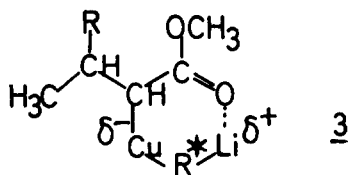
This unexpected product has been compared with that obtained by adding lithium dimethylcuprate, $(LiMe_2Cu)_2$,[5] to methyl crotonate. The analogous reaction product has been isolated in high yield.

Chiral 2(1-dimethylaminoethyl)phenyllithium[6] (prepared from 20 mmol each of (-)N,N-dimethyl-1-phenylethylamine and butyllithium in 30 ml of diethyl ether) was added to phenylcopper[7] (prepared from 20 mmol each of phenyllithium and copper(I) iodide in ether-THF) and the mixture was stirred at 0 to 5 °C until Gilman Test I[8] was negative. Most of the ether and THF was then removed under a stream of dry nitrogen at 0 °C and then 50 ml of THF was added. The mixture was slowly warmed to room temperature and methyl crotonate (0.50 g, 5 mmol) was added all at once to the slightly greenish brown solution of chiral lithium 2(1-dimethylaminoethyl)phenyl phenylcuprate. The crotonate was completely consumed within 15 min (GLC). After about 45 min a copious green precipitate appeared. The mixture was stirred for a total of 1 h and then hydrolysed with NH_3/NH_4Cl solution. The organic products were extracted in ether and from the ether extract the basic components were removed by extraction with 2 M HCl (3x30 ml). The crude product mixture was separated on silica gel with petroleum ether (b.p. 60-80 °C) and then methanol giving 0.31 g of biphenyl (probably from the preparation of phenylcopper), methyl 3-phenylbutanoate, 0.03 g after distillation, 3 % based on methyl crotonate, and a solid, identified as dimethyl 5(1-phenylethyl)-2,6-dimethyl-4-oxo-1,3-cyclohexanedicarboxylate, (structure 1) 0.22 g after recrystallisation from methanol, 38 %, m.p. 209-212 °C. Abs. mass 346.176 $\pm$ 0.003, calc. for $C_{20}H_{26}O_5$ 346.178. IR (KBr): carbonyl absorptions at 1740 and 1710 cm^{-1}. UV (methanol): λ_{max} = 258 nm (log ε = 2.7). ^{1}H-NMR (270 MHz, CDCl$_3$) δ = 0.85 (3H, d) H_1, 1.03 (3H, d) H_g, 1.15 (3H, d) H_k, 2.68-3.24 (6H, m) H_a-H_e, H_i, 3.67 (3H, s) H_h, 3.76 (3H, s) H_f, 7.0-7.3 (5H, m) R=C_6H_5.

Coupling constants were determined from spectra recorded on a solution of 2 mg of the sample and 12.6 mg of Eu(Fod)$_3$ using decoupling technique: J_{ab}=11.8, J_{bc}=12.0, J_{bg}=5.9, J_{de}=3.6, J_{di}=10.5, J_{ae}≈3.6, J_{el}=7.0, and J_{ki}=7.0. On addition of the shift reagent H_c was the most shifted proton followed by H_b, H_d, H_i, and H_a.

When lithium dimethylcuprate was used in the above reaction at 10 °C for 1.8 h in an analogous way, there was obtained, subsequent to work-up and recrystallisation from benzene-petroleum ether (b.p. 60-80 °C), 0.23 g, 49 % of dimethyl 5(1-methylethyl)-2,6-dimethyl-4-oxo-1,3-cyclohexanedicarboxylate (structure 2), m.p. 152-155 °C. Abs. mass 284.163 $\pm$0.003, calc. for $C_{15}H_{24}O_5$ 284.162. IR (KBr): 1740 and 1710 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ = 0.72 (3H, d) H_1, 0.85, 0.91 (3H, d; 3H, d) H_k, R=CH$_3$, 1.02 (3H, d) H_g, 2.04 (1H, d of sept) H_i, 2.25 (1H, dd) H_d, ~2.7 (2H, m) H_a, H_e, 2.84 (1H, tq), H_b, 3.08 (1H, dd) H_c, 3.73 (3H, s) H_f, 3.78 (3H, s) H_h. Coupling constants were determined using decoupling technique: J_{ab}=11.8, J_{bc}=11.8, J_{bg}=5.7, J_{cd}~0.5, J_{de}=4.0,

$J_{di}=10.8$, $J_{el}=7.3$, and $J_{Ri}=J_{ik}=6.5$.

The formation of dimethyl cyclohexanonedicarboxylates could be explained by the following sequence of 1,4-additions and a final ring closure:

$$(LiRR^*Cu)_2 + CH_3-CH=CH-COOCH_3 \xrightarrow[1]{THF} CH_3-\underset{\underset{R}{|}}{CH}-CH=\underset{\underset{OCH_3}{|}}{C}-OLi \longrightarrow$$

$$\xrightarrow[2]{CH_3CH=CHCOOCH_3} CH_3-\underset{\underset{R}{|}}{CH}-\underset{\underset{CH_3}{|}}{CH}-CH-CH=\underset{\underset{OCH_3}{|}}{\overset{\overset{COOCH_3}{|}}{C}}-OLi \xrightarrow[3]{CH_3CH=CHCOOCH_3}$$

$\underline{1}$ R=C_6H_5 $\underline{2}$ R=CH_3

Protons H_a, H_c, and H_d have carbonyl groups as neighbours, which make them acidic. It is assumed that both compounds $\underline{1}$ and $\underline{2}$ will rearrange to the thermodynamically most stable isomer during work-up. The NMR spectra indicates that in these structures H_a, H_b, H_c, and H_d assume axial positions. H_e is found to be equatorial. Methyl groups g and l thus are trans to each other. The absence of an isomer with methyl groups cis to one another indicates a high degree of stereoselectivity in step 3.

THF is generally not used as a solvent for conjugate additions of cuprates to α,β-ethylenic enones and enoates.[1] Only a few comparisons are available of THF and diethyl ether concerning their effect on reaction rates, product distribution, and yields. However, the conjugate addition of cuprates to α,β-acetylenic enones and enoates in THF and diethylether has been studied. With these substrates the reaction rate is ca. ten times faster in diethyl ether than in THF.[1] Still, THF is the solvent of choice for additions to α,β-acetylenic carbonyl compounds because the most stereoselective conjugate addition occurs due to the effect of THF on the configurational stability of the vinylcopper species formed.

In the present case it is not clear whether copper has any influence on steps 2 and 3 in the proposed reaction sequence. The formation of a α-carbon-copper σ-bond can not be excluded in the first step. This copper compound, $\underline{3}$, could then add to another molecule of methyl crotonate.

$$\underline{3}$$

Generally, the initial products from addition of lithium diorganocuprates to enones and enoates are lithium enolates and an organocopper compound, RCu.[9]

Since lithium enolates are known to add 1,4 to α,β-unsaturated carbonyl compounds, Michael reaction,[10] it can be assumed that steps 2 and 3 proceed without the involvement of copper. However, recently published results indicate the possible formation of copper compounds analogous to $\underline{3}$.[11]

There are a few observations of the formation of ring compounds similar to compounds $\underline{1}$ and $\underline{2}$ as side reactions in anionic polymerisation (e.g. with $LiPh_2N$) of methyl methacrylate.[12]

The present work is the first example of the use of lithium diorgano-cuprates in oligomerisation of an α,β-unsaturated ester, it also provides a simple synthesis of cyclohexanonedicarboxylates.

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