

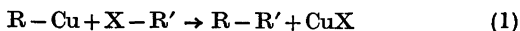
Lithium Methyl-, Butyl- and Phenyl-[(±)-2-(1-dimethylaminoethyl)phenyl]cuprate Reagents and their Conjugate Addition to Methyl Cinnamate

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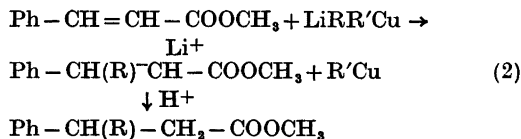
Lithium methyl-, butyl- and phenyl-[(±)-2-(1-dimethylaminoethyl)phenyl]cuprate reagents have been obtained from 2-(1-dimethylaminoethyl)phenyllithium and the appropriate organocopper compounds or from 2-(1-dimethylaminoethyl)-phenylcopper and the organolithium compounds. Methyl cinnamate on treatment with these reagents in ether gives methyl 3-phenylbutyrate, methyl 3-phenylheptanoate and methyl 3,3-diphenylpropionate, respectively, in 50 to 70 % yields.

Organocopper reagents are finding increasing use in organic synthesis since they are selective and react preferentially with "soft" groups in organic substrates.¹⁻⁴ Common examples are reactions with organic halides to form substitution products (eqn. 1) and 1,4-addition to α,β -unsaturated carbonyl compounds (eqn. 2).



The formation of Meisenheimer compounds from organocopper reagents and 1,3,5-trinitrobenzene^{5,6} can also be looked upon as 1,4-addition reactions.

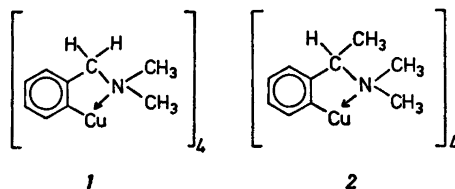
Special interest has been devoted to the lithium diorganocuprates (LiRR'Cu). The homocuprates have been widely used in conjugate addition (eqn. 2), and lithium dimethylcuprate is a standard reagent. With more precious groups an inexpensive or re-usable R' group can be used, e.g. acetylde.^{4,7}



The reaction of lithium diorganocuprates may be facilitated by soft complexing agents.^{7,8}

Thermally stable, chelated arylcopper compounds such as 2-(dimethylaminomethyl)phenylcopper (*1*) have been described by van Koten and Noltes.^{9,10} Such compounds appear to be interesting components in mixed lithium diorganocuprates. The organocopper compound *1* could be expected to be regenerated or retained in a cuprate when a mixed lithium diorganocuprate is added to an α,β -unsaturated carbonyl compound. Also, simple modifications of compound *1* could give chiral organocopper compounds, such as 2-(1-dimethylaminoethyl)-phenylcopper (R*Cu, *2*) for preparation of chiral mixed organocuprates. We are therefore investigating lithium diorganocuprate reagents containing this component and their addition to α,β -unsaturated carbonyl compounds.

In the course of the work we learned about research on the optically active 2-(1-dimethylaminoethyl)phenylcopper.¹¹



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RESULTS

Organocuprate reagents. Treatment of (\pm)-*N,N*-dimethyl-1-phenylethylamine with butyllithium gives 2-(1-dimethylaminoethyl)phenyllithium, characterized by deuteration and by trimethylsilylation, in at least 87 % yield. Further reaction of the lithium compound with copper(I) iodide in ether gave a 2-(1-dimethylaminoethyl)phenylcopper (2). Compound 2 was thermally stable and was only slowly hydrolyzed by water. It was more sensitive to water and oxygen in the presence of organic solvents. Compound 2 reacted with allyl bromide and with iodine to give the expected products.

Addition of slightly less than an equimolar amount of methylolithium to a preparation of 2 gave a black product which was not very soluble in ether. We used this reagent *in situ* assuming it to be a lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate. The reagent was more conveniently obtained from 2-(1-dimethylaminoethyl)phenyllithium and methylcopper. In analogous ways we obtained the corresponding mixed butyl- and phenylcuprates. These mixed cuprate reagents seem to be thermally more stable than lithium dimethylcuprate and lithium dibutylcuprate, respectively.

Conjugate addition. Preliminary experiments confirmed^a that an excess of the dimeric¹² lithium dimethylcuprate is necessary to obtain good yields in conjugate additions to α,β -un-

saturated esters in ether, and accordingly 4 mol of cuprate (calc. as a monomer) was used per mol of cinnamate in the subsequent reactions.

Methyl cinnamate added to an excess of lithium (\pm)-methyl[2-(1-dimethylaminoethyl)phenyl]cuprate in ether at 0 to -5°C , was rapidly consumed (GLC). A greenish-yellow precipitate, characteristic of compound 2, appeared. Hydrolysis and separation gave the conjugate addition product, methyl 3-phenylbutanoate, in a fair yield. Pure *N,N*-dimethyl-1-phenylethylamine could be recovered in ca. 65 % yield.

The results for various cuprates prepared in different ways are summarized in Table 1. The yields of the 1,4-addition products obtained from the mixed cuprates are somewhat lower than those obtained from lithium dimethyl-, dibutyl- and diphenylcuprates. The table also shows that the yield is higher if the reagent is prepared from 2-(1-dimethylaminoethyl)phenyllithium and methylcopper. GLC measurements indicate that the actual yields of the conjugate addition products before distillation are in the order of 85 %. According to GLC, some high-boiling (nonbasic) material is also formed, which so far has not been further investigated. All reagents contain lithium bromide or iodide from the preparation of lithium compounds or from the reactions with copper(I) iodide. This may be important for the course and rate of the reactions (cf. Ref. 13).

Table 1. 1,4-Addition of racemic lithium diorganocuprates, $\text{LiRR}'\text{Cu}$, to methyl *trans*-cinnamate (molar ratio 4:1) in diethyl ether. Yields refer to distilled and isolated products. R^* stands for the 2-(1-dimethylaminoethyl)phenyl group.

| $\text{LiRR}'\text{Cu}$ | $\text{LiRR}'\text{Cu}$ prepared from | Reaction time/min | Reaction temp./ $^\circ\text{C}$ | Main product | Isolated yield/% |
|---------------------------|---------------------------------------|-------------------|----------------------------------|---|------------------|
| LiMe_2Cu | $\text{MeLi} + \text{CuI}$ | 40 | -5 to $+5$ | $\text{PhCH}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{CH}_3$ | 79 ^a |
| LiMeR^*Cu | $\text{R}^*\text{Cu} + \text{MeLi}$ | 45 | -5 to 0 | $\text{PhCH}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{CH}_3$ | 55 |
| LiMeR^*Cu | $\text{R}^*\text{Li} + \text{MeCu}$ | 50 | -5 to 0 | $\text{PhCH}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{CH}_3$ | 68 |
| LiBu_2Cu | $\text{BuLi} + \text{CuI}$ | 45 | -20 | $\text{CH}_3(\text{CH}_2)_3\text{CH}(\text{Ph})\text{CH}_2\text{CO}_2\text{CH}_3$ | 77 |
| LiBuR^*Cu | $\text{R}^*\text{Li} + \text{BuCu}$ | 312 | -45 | | ^b |
| | and | 60 | -20 | $\text{CH}_3(\text{CH}_2)_3\text{CH}(\text{Ph})\text{CH}_2\text{CO}_2\text{CH}_3$ | 56 |
| LiPh_2Cu | $\text{PhLi} + \text{CuI}$ | 30 | -5 to 0 | $\text{Ph}_2\text{CHCH}_2\text{CO}_2\text{CH}_3$ | 70 |
| LiPhR^*Li | $\text{R}^*\text{Li} + \text{PhCu}$ | | -5 to 0 | $\text{Ph}_2\text{CHCH}_2\text{CO}_2\text{CH}_3$ | 60 |

^a Ref. 24. ^b GLC indicated ca. 45 % yield of methyl diphenylpropionate after 312 min at -45°C . After additional stirring at -20°C for 60 min the yield was $>90\%$ according to GLC.

DISCUSSION

The main observation in the present work is that the methyl, butyl and phenyl groups are selectively transferred from the organocopper reagents to the α,β -unsaturated esters in fair yields. 2-(1-Dimethylaminoethyl)phenylcopper, R^*Cu , is regenerated in the reaction mixture, and no product from the transfer of the 2-(1-dimethylaminoethyl)phenyl group has been observed.

Although we have assumed the presence of the dimeric lithium alkyl[2-(1-dimethylaminoethyl)phenyl]cuprate, $(LiRR^*Cu)_2$, this may not be the main organocopper cluster in the reaction mixture. Equilibria between several different organocopper clusters can be expected. Such equilibria are being studied by van Koten *et al.*, using NMR spectroscopy.¹⁴

In earlier work² it has been assumed that the mixed cuprate, $LiRR^*Cu$, is the main organocopper cluster present after mixing RLi and R^*Cu . Some experimental support for this assumption has been published by Posner *et al.*¹⁵

In the reactions of the mixed cuprates one group is transferred to the substrate regenerating the more stable or less reactive organocopper compound.⁷ The thermal stability and low reactivity of the 2-(1-dimethylaminoethyl)phenylcopper tetramer probably reflect its thermodynamic stability. The low reactivity of this copper compound, R^*Cu , was well established during the attempts to prepare derivatives of R^*Cu and R^*Li . Relatively low yields of derivatives were obtained after long reaction periods. This may reflect a high thermodynamic stability but also a kinetic stability due to steric hindrance at the position next to the bulky 1-dimethylaminoethyl group.

EXPERIMENTAL

Organometallic reactions were carried out under dry, oxygen-free nitrogen. Dry diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl, and toluene from $LiAlH_4$. Commercial butyllithium in hexane and methylithium in ether were used at the strength determined by the supplier. All organometallic reagents contained lithium halides from their preparation. Infrared spectra were recorded on a Beckman IR 9 spectrometer, NMR spectra on a Bruker WH 270 or a

Varian A 60 spectrometer, mass spectra on an AEI MS 902 or a Varian 1200 GC-AEI MS 20 combination, and gas chromatograms on a Perkin Elmer 900 instrument using SE 30, OV 17 or OV 225 on Chromosorb W.

(\pm) -2-(Dimethylaminoethyl)phenyllithium. N,N -Dimethyl-1-phenylethylamine¹⁶ (10 mmol) was lithiated^{10,17} with butyllithium (10 mmol) in ether (50 ml) by stirring the components together for about 50 h at room temperature. The solution became pale yellow and gave a positive response to Gilman test I.¹⁶ (Gilman test II remained positive for about 44 h.¹⁹)

2-(1-Dimethylaminoethyl)phenyllithium and deuterium oxide. Deuterium oxide (2 ml) was added to the lithium reagent thus prepared. The yellow colour of the lithium reagent disappeared within 1 min. After stirring overnight at room temperature, the ether layer was separated and extracted with 1 M HCl. The acidic extract was made alkaline, the free amine collected in ether, and the ether layer dried over anhydrous sodium sulfate. After removal of the ether at reduced pressure 2-(1-dimethylaminoethyl)deuteriobenzene (1.3 g, 87 %) was isolated. NMR data: δ 7.15–7.35 (3.94 H, m), 3.20 (1 H, q), 2.15 (6 H, s) and 1.34 (3 H, d).

When methylithium was used in place of butyllithium in the above lithiation reaction, the yield of the lithium reagent was about 5 % after 6 h as determined by derivatizing with chlorotrimethylsilane (see below).

2-(1-Dimethylaminoethyl)phenyllithium and chlorotrimethylsilane. An excess of trichlorotrimethylsilane (ca. 10 mmol) was added to 2-(1-dimethylaminoethyl)phenyllithium (prepared from 6.66 mmol of N,N -dimethyl-1-phenylethylamine in 50 ml of ether) and the mixture was stirred for 4 h at room temperature, followed by 1 h at 34 °C. The mixture was hydrolysed with aqueous ammonia/ammonium chloride solution and worked up in the usual way to give a yellowish oil. This oil, when purified by column chromatography and cup-distillation, gave 0.9 g (60 %) of 2-(1-dimethylaminoethyl)phenyltrimethylsilane. (Found: C 70.9, H 10.7. Calc. for $C_{13}H_{23}NSi$: C 70.5; H 10.5. The IR spectrum showed a strong absorption at 763 cm^{-1} indicating 4 adjacent hydrogens. NMR data: δ 7.59 (1 H, d), 7.46 (1 H, d), 7.35 (1 H, t), 7.19 (1 H, t), 3.39 (1 H, q), 2.22 (6 H, s), 1.30 (3 H, d), 0.35 (9 H, s). MS: m/e 221 (M^+ , 4 %); 206 (87 %); 72 (100 %). The measured mass at m/e 221 was 221.160; calc. for $C_{13}H_{23}NSi$ 221.160.

General procedure for the preparation of 2-(1-dimethylaminoethyl)phenylcopper reagent. Copper(I) iodide (3.4 mmol) was added to a cold (-20 °C) ether solution of 2-(1-dimethylaminoethyl)phenyllithium reagent (prepared from 3.3 mmol of N,N -dimethyl-1-phenylethylamine in 50 ml of ether) over a period of 2 h (with the help of a solid addition tube). With the addition of the first portion of copper(I) iodide,

a black precipitate appeared which rapidly disappeared to give a white precipitate with subsequent additions of CuI. When approximately half of the CuI had been added, a green precipitate began to appear. The mixture was stirred at -20°C for 1 h after the addition of CuI, and then at room temperature for 2 h during which period Gilman test I became negative. This copper reagent was used without isolation for subsequent reactions. In one instance it was isolated by filtration under nitrogen. The green precipitates were washed with 3×30 ml of dry ether and subsequently recrystallised from ether. This procedure gave lemon-green crystals which were stable in the presence of air or water. Several weeks of exposure to air at room temperature changed the colour to dark green. The copper compound, however, reacted much faster with both water and oxygen in the presence of an organic solvent. The solid copper compound started to decompose without melting at 228°C and the decomposition was complete at 260°C as determined visually.

2-(1-Dimethylaminoethyl)phenylcopper and deuterium oxide. Deuterium oxide (0.7 ml) was added to the green slurry of 2-(1-dimethylaminoethyl)phenylcopper (prepared from 3.33 mmol of *N,N*-dimethyl-1-phenylethylamine), and the mixture was stirred at room temperature. No immediate reaction took place. Some green precipitates of the copper compound could be seen even after 24 h. The mixture was worked up after 66 h of stirring to give 2-(1-dimethylaminoethyl)deuteriobenzene (0.45 g, 89 %). This deuterio compound was identical to that obtained on deuteriolysis of 2-(1-dimethylaminoethyl)phenyllithium.

2-(1-Dimethylaminoethyl)phenylcopper and iodine. Solid iodine (20 mmol) was added to a cold (-78°C) slurry of 2-(1-dimethylaminoethyl)phenylcopper (prepared from 20 mmol of *N,N*-dimethyl-1-phenylethylamine in 50 ml of ether) and the mixture was stirred overnight at this temperature.³ After warming to room temperature the mixture was worked up in the usual way to give a brown liquid (2.4 g). TLC showed three components. Separation by preparative TLC gave 2-(1-dimethylaminoethyl)iodobenzene (2.05 g, 37 %). The IR spectrum was as expected. NMR data: δ 7.8 (1 H, d), 7.5 (1 H, d), 7.3 (1 H, t), 6.9 (1 H, t), 3.55 (1 H, q), 2.25 (6 H, s), 1.27 (3 H, d). MS: $m/e=275$, (M^+ , 11 %); 260 (100 %); 132 (37 %); 104 (20 %); 72 (83 %).

2-(1-Dimethylaminoethyl)phenylcopper and allyl bromide. Allyl bromide (10 mmol) was added to 2-(1-dimethylaminoethyl)phenylcopper (prepared from 10 mmol of *N,N*-dimethyl-1-phenylethylamine in 50 ml of ether) at -20°C and the mixture was stirred for 0.5 h. The mixture was then stirred overnight at room temperature. Usual work-up gave 0.95 g of a liquid which was a 1:3 mixture (GLC area ratio) of *N,N*-dimethyl-1-phenylethylamine and *N,N*-

dimethyl-1-(2-allylphenyl)ethylamine. The mixture was separated on an SE 30 column and the MS was obtained for the latter component. MS: $m/e=189$ (M^+).

Preparation of mixed cuprates

Lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate was prepared by gradually adding 2-(1-dimethylaminoethyl)phenyllithium (20 mmol) to methylcopper (prepared by adding 20 mmol of methylolithium to 21 mmol of copper(I) iodide in ether) at -5°C and stirring the mixture until Gilman Test I was negative.

Lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate was prepared by using phenylcopper in place of the methylcopper. Phenylcopper was prepared as described previously.²¹

Lithium butyl[2-(1-dimethylaminoethyl)phenyl]cuprate was prepared by using butylcopper and the temperature was kept at -40°C . Butylcopper was prepared as described before.²²

Lithium dibutylcuprate and lithium diphenylcuprate were prepared from copper(I) iodide and butyllithium and phenyllithium, respectively, as described before.²³

1,4-Addition reactions to methyl cinnamate

Solid methyl cinnamate (5 mmol) was added all at once to the cuprate, $\text{LiRR}'\text{Cu}$, (20 mmol) in 50 ml of ether. For $\text{LiRR}'\text{Cu}$ =lithium diphenylcuprate, lithium methyl[2-(1-dimethylaminoethyl)phenyl]cuprate and lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate the reaction temperature was 0 to -5°C . For $\text{LiRR}'\text{Cu}$ =lithium butyl[2-(1-dimethylaminoethyl)phenyl]cuprate and lithium dibutylcuprate the reaction temperature was -20°C . After stirring for 1 h the mixture was poured into a saturated solution of aqueous ammonia and ammonium chloride (pH 8), shaken well and the organic material extracted into ether. The ether extract was washed with 3×50 ml portions of $\text{NH}_3/\text{NH}_4\text{Cl}$ solution or until all the copper(I) halide was removed, and then once with 50 ml of a dilute sodium thiosulfate solution. The basic compounds were removed from this ether solution by extracting with 2 M HCl (3×50 ml). From the acid extract the starting amine, *N,N*-dimethyl-1-phenylethylamine, was recovered in about 65 % yield. The ether extract was dried over sodium sulfate and the ether removed under reduced pressure. The 1,4-addition products were isolated after distillation of the crude oil. Small amounts of high-boiling by-products were observed.²⁴ Main products, yields, and reaction conditions are summarised in Table 1.

Products

Methyl 3-phenylbutyrate, b.p. 133–135 °C/22 mm, lit.²⁴ b.p. 74–78 °C/0.5 mm, identical with an authentic sample by comparison of NMR spectra.

Methyl 3-phenylheptanoate, b.p. 67–68 °C/0.06 mm. Mol. weight determined by exact mass measurement 220.1456, calc. for C₁₄H₂₀O₂ 220.1463. NMR data: δ 7.25 (2 H, m), 7.18 (3 H, m), 3.56 (3 H, s), 3.07 (1 H, quin.), 2.60 (2 H, dd), 1.56–1.69 (2 H, m), 1.04–1.35 (4 H, m) and 0.82 (3 H, t).

Methyl 3,3-diphenylpropionate, m.p. 42–45 °C, lit.²⁵ m.p. 48 °C, b.p. 144 °C/0.15 mm. Mol. weight determined by exact mass measurements was 240.1123, calc. for C₁₆H₁₆O₂ 240.1150. NMR data: δ 7.13–7.27 (10 H, m), 4.56 (1 H, t), 3.54 (3 H, s), 3.05 (2 H, d).

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