

Conjugate Addition of Lithium Dimethylcuprate, Lithium Diphenylcuprate and a Chiral Lithium Phenyl(aryl)cuprate Reagent to Methyl 3-(2-Furyl)acrylate

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Addition of LiMe_2Cu or LiPh_2Cu containing lithium halides to methyl *trans*-3-(2-furyl)acrylate gave methyl 3-(2-furyl)-butanoate and methyl 3-(2-furyl)-3-phenylpropanoate, respectively. Addition of the cuprates essentially free from lithium halides required longer reaction times, higher temperature, or a large excess of the cuprate. Addition of the mixed chiral cuprate, lithium phenyl[2-(1-dimethylaminoethyl)-phenyl]cuprate, prepared from (–)-*N,N*-dimethyl-1-phenylethylamine, to methyl 3-(2-furyl)acrylate gave methyl 3-(2-furyl)-3-phenylpropanoate with a small negative rotation.

In the search for a stable, chiral ligand to copper we have chosen to study the (–)-2-(1-dimethylaminoethyl)phenyl group. Addition of an organolithium reagent to such an organo-copper compound should give a chiral cuprate which could transfer one ligand in 1,4-addition reactions with α,β -unsaturated carbonyl compounds and induce optical activity at the β carbon.

Addition of such mixed, racemic lithium diorganocuprates, LiRR^*Cu , to methyl *trans*-cinnamate [R being methyl, butyl and phenyl, R^* being 2-(1-dimethylaminoethyl)phenyl] gives good yields of the 1,4-addition product when diethyl ether is used as a solvent.¹ When tetrahydrofuran is used as a solvent, other reactions compete with the conjugate addition.²

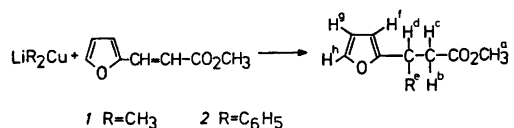
We have now investigated the conjugate addition to methyl *trans*-3-(2-furyl)acrylate of some common organocuprates and of the chiral

lithium phenyl [2-(1-dimethylaminoethyl)phenyl]cuprate prepared from (–)-*N,N*-dimethyl-1-phenylethylamine. We have also studied the effect of lithium salts on the reactivity of the cuprates. It has previously been shown that some Grignard and lithium reagents undergo conjugate addition to 3-(2-furyl)acrolein.³

RESULTS

The influence of the method of preparation of the cuprates, the temperature and the solvent on the conjugate addition of lithium dimethylcuprate and lithium diphenylcuprate to methyl 3-(2-furyl)acrylate are summarised in Table 1.

Methyl and phenyl groups are transferred selectively and in high yields by the cuprates to the β carbon of the enoate.



We have observed a substantial difference in reactivity of cuprates from different preparations. When care was taken to exclude the lithium halides in the preparation of lithium diphenylcuprate, the relatively salt-free cuprate was less reactive towards the methyl furylacrylate than the "ordinary" cuprate reagent containing stoichiometric amounts of lithium bromide and iodide (see experiments 4 and 5 in Table 1).

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Table 1. 1,4-Addition of lithium diorganocuprates, LiRR'Cu, to methyl *trans*-3-(2-furyl)acrylate. Reactions were run in diethyl ether at 0 °C unless indicated otherwise. R* = (-)-2-(dimethylaminoethyl)phenyl.

Exp. No.	LiRR'Cu	Method of preparation	Cuprate: substrate molar ratio	Re-action time/h	Main product	GLC yield/%	Isolated yield/%
1	LiMe ₂ Cu	MeLi(LiBr) + CuI	1.1:1	1.5	1 ^a	90	63.5
2	LiMe ₂ Cu	MeLi(com) ^b + CuI	2.0:1	12 ^c	1	90	
3	LiMe ₂ Cu	MeLi(com) + CuI	12.0:1	1	1	80	
4	LiPh ₂ Cu	PhLi(LiBr) + CuI	1.3:1	1	2 ^d	97	64.5
5	LiPh ₂ Cu	PhLi(LiBr) + PhCu	1.5:1	1	2	10	
6	LiPhR*Cu	R*Li + PhCu(LiBr + LiI)	1.4:1	1	2 ^e	97	64.5

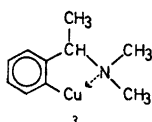
^a 1 is methyl 3-(2-furyl)butanoate. ^b Commercial methyllithium (Fluka). ^c Reaction temp. 20 °C. ^d 2 is methyl 3-(2-furyl)-3-phenylpropanoate. ^e Specific rotation of isolated ester: $[\alpha]_{D}^{20} = -0.67^\circ$ (c 0.159, chloroform).

When methyllithium, prepared from bromomethane and lithium, was used to prepare the cuprate, the resulting solution contained Li(CH₃)₂Cu, LiBr and LiI in molar ratios of 1:2:1. This reagent was very reactive.

Commercial methyllithium (Fluka) and copper(I) iodide gave a cuprate, which required longer reaction times and higher temperatures or alternatively a large excess of the cuprate (see expts. 1, 2, and 3 in Table 1). With cuprates containing stoichiometric amounts of lithium halides only a small excess of the cuprate was necessary to give high yields of 1,4-addition products within one hour (experiments 1 and 4 in Table 1).

When tetrahydrofuran, THF, was used as a solvent, the reaction rate drastically decreased, and most of the substrate (ca. 80 %) remained unchanged after 48 h.

Reaction of a small excess of chiral lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate with methyl 3-(2-furyl)acrylate in ether (in the presence of lithium halides) gave the 1,4-addition product at a rate comparable to that of lithium diphenylcuprate. The phenyl group was selectively transferred with the simultaneous formation of chiral 2-(1-dimethylaminoethyl)phenylcopper, 3. The specific rotation of the product was small but reproducible. The optical yield did, however, not exceed 2.2 %.



DISCUSSION

The asymmetric induction obtained so far is small. Further work on other systems is under way.

It has been suggested that copper in a lithium diorganocuprate is the attacking nucleophile in reactions with organic halides,⁶ and it is reasonable to assume that this could be the case in conjugate additions to enones and enoates as well. If copper were the attacking nucleophile there would have to be vacant sites to allow attack on the enoate. Exchange of ether for the more strongly complexing THF would lead to the observed solvent effect. A similar effect of solvent change on the reactivity of cuprates has been observed previously² and is opposite to what is observed for organolithium reagents.⁵

The salt effect has mostly been discussed for the reactions of lithium diorganocuprates with organic halides.⁷ The observed difference in reaction rates (compare expts. 1, 2, 3, 4 and 5 in Table 1) probably is the result of different concentrations of lithium halides. It could be assumed that more reactive species than clusters of lithium diorganocuprates are formed in the presence of lithium halides.⁸

The effect of lithium salts on the addition of CH₃Li–Li(CH₃)₂Cu to 4-*t*-butylcyclohexanone has recently been discussed.⁹ It was suggested that lithium forms a complex with the carbonyl oxygen when ether is used as a solvent, while no complex is formed in THF. It can be assumed that a similar complexation of

lithium to the carbonyl oxygen of the α,β -unsaturated ester would increase the reactivity of the β -carbon. This would account for both the salt effect and the solvent effect observed.

EXPERIMENTAL

All handling and reactions of organometallic reagents were carried out under dry, oxygen-free nitrogen. Dry diethyl ether and tetrahydrofuran, THF, were distilled from sodium benzophenone ketyl. Commercial butyllithium (Merck) in hexane and methylithium (Fluka) in ether were used after their strength had been determined by titration.

*Lithium dimethylcuprate and methyl 3-(2-furyl)acrylate.*⁹ Lithium dimethylcuprate was prepared by addition of 55.5 ml of a 1.42 M solution of methylithium (79 mmol, prepared from bromomethane and lithium) to copper(I) iodide (7.6 g, 40 mmol) in 20 ml of ether at 0 °C. After stirring for 30 min, Gilman Test I¹⁰ was negative, and methyl 3-(2-furyl)acrylate (4.56 g, 30 mmol), in 30 ml of ether was added. The mixture was stirred for 1.5 h at 0 °C and then poured into aqueous NH₄Cl, extracted with ether, washed with water, and dried over MgSO₄. GLC analysis showed methyl 3-(2-furyl)butanoate as the major component (> 90 %) and a small amount of a high-boiling product. After evaporation of the ether and distillation, 3.2 g of methyl 3-(2-furyl)butanoate [63.5 %, based on methyl 3-(2-furyl)acrylate] was isolated, b.p. 85 °C/0.05 mmHg. ¹H NMR (270 MHz, CDCl₃): δ 3.63 (3 H, s) H_a, 2.43 (1 H, dd, J_{bc} 15.3 Hz) H_b, 2.70 (1 H, dd, J_{cd} 6.4 Hz) H_c, 3.34 (1 H, qdd, J_{bd} 8.1 Hz) H_d, 1.28 (3 H, d, J_{de} 7.0 Hz) R_e = CH₃, 5.98 (1 H, ddd, J_{fg} 3.2 Hz, J_{df} 0.5 Hz) H_f, 6.23 (1 H, dd, J_{gh} 1.8 Hz) H_g, 7.27 (1 H, dd, J_{fh} 0.8 Hz) H_h.

When this experiment was repeated with commercial methylithium for the preparation of lithium dimethylcuprate, it was necessary to raise the reaction temperature to 20 °C and leave the reaction with stirring overnight to get the same high yield of the 1,4-addition product. Lithium dimethylcuprate was present in 100 % excess. When a 12-fold excess of this cuprate was used at 0 °C, 80 % of the methyl furylacrylate was consumed after 1 h (GLC).

With THF as a solvent instead of diethyl ether for the addition of lithium dimethylcuprate (methylithium prepared from bromomethane and lithium), most of the methyl furylacrylate (~80 %) remained unchanged after 48 h.

Lithium diphenylcuprate and methyl 3-(2-furyl)acrylate. Lithium diphenylcuprate was prepared by addition of 89 ml of a 0.89 M ether solution of phenyllithium (79 mmol, prepared from bromobenzene and lithium in ether) to copper(I) iodide (7.6 g, 40 mmol) in 20 ml of ether. After stirring for 30 min, methyl

3-(2-furyl)acrylate (4.56 g, 30 mmol) in 30 ml of ether was added dropwise. After stirring for 1 h at 0 °C, the reaction mixture was poured into aqueous NH₄Cl, extracted with ether, washed with water, and dried. GLC analysis indicated two products, methyl 3-(2-furyl)-3-phenylpropanoate, ca. 97 %, and a small amount of a high-boiling product. After evaporation of the ether and distillation, 4.45 g of methyl 3-(2-furyl)-3-phenylpropanoate, 64.5 %, was isolated, b.p. 92 °C/0.03 mmHg. ¹H NMR (270 MHz, CDCl₃): δ 3.47 (3 H, s) H_a, 2.86 (1 H, dd, J_{bc} 15.6 Hz, J_{bd} 7.9 Hz) H_b, 3.05 (1 H, dd, J_{bc} 7.6 Hz) H_c, 4.55 (1 H, dd, J_{df} 0.9 Hz) H_d, 7.11–7.21 (5 H, m) R_e = C₆H₅, 5.99 (1 H, ddd, J_{fg} 3.2 Hz) H_f, 6.18 (1 H, dd, J_{gh} 1.9 Hz) H_g, 7.21 (1 H, dd, J_{fh} 0.9 Hz) H_h.

Hydrolysis (ethanol/KOH) of the ester afforded 3-(2-furyl)-3-phenylpropanoic acid, m.p. 104.5–105 °C. Anal. C₁₃H₁₂O₃: C, H. ¹H NMR (270 MHz, CDCl₃): δ 2.90 (1 H, dd, J_{bc} 16.0 Hz) H_b, 3.00 (1 H, dd, J_{cd} 7.9 Hz) H_c, 4.51 (1 H, dd, J_{bd} 7.5 Hz) H_d, 6.01 (1 H, ddd, J_{df} 0.5 Hz, J_{fh} 0.5 Hz) H_f, 6.23 (1 H, dd, J_{fg} 3.3 Hz) H_g, 7.27 (1 H, dd, J_{gh} 1.7 Hz) H_h, 7.19–7.26 (5 H, m) R_e = C₆H₅, 11.5 (1 H, s).

(+)- and (-)-3-(2-furyl)-3-phenylpropanoic acid. Racemic 3-(2-furyl)-3-phenylpropanoic acid (4.0 g) was dissolved by heating in 40 ml of an ethanol-water solution (3:1). (-)-1-Phenylethylamine (1.8 g) was added. Needle shaped crystals precipitated. After recrystallisation and hydrolysis (+)-3-(2-furyl)-3-phenylpropanoic acid was obtained, $[\alpha]_{D}^{20} = +41.51^\circ$ (c 0.01573; CHCl₃). When the procedure was repeated with (+)-1-phenylethylamine and racemic acid (-)-3-(2-furyl)-3-phenylpropanoic acid was obtained, $[\alpha]_{D}^{20} = -39.5^\circ$ (c = 0.00710; CHCl₃).

(-)-Methyl 3-(2-furyl)butanoate. (-)-3-(2-Furyl)-3-phenylpropanoic acid (132 mg) was treated with an excess of CH₃I (800 mg) in CH₂Cl₂ (30 ml) (ion-pair alkylation with tetrabutylammonium hydrogensulfate, 510 mg, dissolved in 0.1 M NaOH, 30 ml). After boiling for 30 min conventional workup resulted in (-)-methyl 3-(2-furyl)butanoate (122 mg) $[\alpha]_{D}^{20} = -30.5^\circ$ (c 0.0244; CHCl₃).

Preparation of salt-free lithium diphenylcuprate and its addition to methyl 3-(2-furyl)acrylate. Phenylcopper was prepared by addition of an ether solution of phenyllithium (10.7 mmol, 0.92 M, prepared from bromobenzene and lithium) to copper(I) iodide (2.09 g, 11 mmol) in 10 ml of ether at 0 °C. A white precipitate of phenylcopper appeared. The precipitate was allowed to settle. The solids were washed three times with ether so as to remove the soluble lithium halides. Phenyllithium (9.3 ml) was then added. The white colour of phenylcopper disappeared, and a black solution of lithium diphenylcuprate was obtained. Methyl 3-(2-furyl)acrylate (1.0 g, 6.6 mmol) was added, and the reaction mixture was stirred for 1 h at 0 °C. Less than 10 % of

methyl 3-(2-furyl)-3-phenylpropanoate was formed, and most of the methyl furylacrylate remained unchanged (GLC).

Chiral lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate and methyl 3-(2-furyl)acrylate. Lithium phenyl[2-(1-dimethylaminoethyl)phenyl]cuprate was prepared by addition of an ether solution of chiral 2-(1-dimethylaminoethyl)phenyllithium (prepared by stirring (-)-*N,N*-dimethyl-1-phenylethylamine, 16.2 mmol, with butyllithium, 14.6 mmol, in ether, 20 ml, at room temperature for 48 h¹¹) to a suspension of phenylcopper in ether (prepared by adding phenyllithium, 0.89 M, 14.6 mmol, in ether to copper(I) iodide, 14.6 mmol, in ether, 20 ml, at 0 °C). After stirring for 30 min, a solution of methyl 3-(2-furyl)acrylate (1.65 g, 10.8 mmol) in 30 ml of ether was added dropwise and the mixture was left with stirring for 1 h. After the reaction mixture had been poured into aqueous NH₄Cl, the organic components were extracted in ether and the basic compounds were removed by extraction with 2 × 30 ml of dilute HCl. The ether fraction was washed with a saturated solution of NaHCO₃, and water and then dried. According to GLC there was no *N,N*-dimethyl-1-phenylethylamine left. Methyl 3-(2-furyl)-3-phenylpropanoate was present in ca. 97%. The product was isolated after evaporation of the ether and distillation. The specific rotation was $[\alpha]_{D}^{20} = -0.67^{\circ}$ (c 0.159, chloroform) and the optical yield correspondingly 2.2%.

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