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CONJUGATE ADDITION REACTIONS OF SOME MAGNESIUM-BASED ORGANOCUPRATES WITH α-ETHYLENIC CARBONYL COMPOUNDS

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Summary

Bromomagnesium diphenylcuprate and the iodomagnesium dimethylcuprate reagent (prepared from 2 RMgX + CuI) react with methyl or ethyl 3-phenylpropenoate and methyl 2-butenoate to give 25—70% yields of the corresponding conjugate addition products. The reactions of these cuprates with 4-methylpent-3-en-2-one, 4-(4-methoxyphenyl)but-3-en-2-one or 1,3-diphenylprop-2-en-1-one give the corresponding conjugate adducts in 49—70% yields. In general, the yields are lower when the phenylcopper reagent (prepared from PhMgBr + CuI) is employed.

Introduction

Grignard reagents undergo conjugate addition reactions with α-ethylenic carbonyl compounds in the presence of copper(I) salts as catalysts [1—3]. Recently, it has been discovered that lithium diorganocuprates * and other types of "stoichiometric" ** organocoppers are also capable of giving conjugate addition to the same or similar substrates [2,3,5—7]. This indicated that organocoppers might be the reactive intermediates in copper-catalysed conjugate addition of Grignard reagents [3]. Although the synthetic usefulness of the copper-catalysed conjugate addition is well documented, "stoichiometric" organocoppers appear to be much better as conjugate addition reagents. These latter

* For the nomenclature of "ate" complexes see ref. 4.

** In accordance with Posner's definition [2], by "stoichiometric" organocoppers, will be meant organocopper reagents prepared from one equivalent of RMgX and one or one-half equivalent of CuI (*i.e.*, $XMgR_2Cu$ or ($RCu + MgX_2$) type). They are to be distinguished from "catalytic" organocoppers, prepared from Grignard reagents and a catalytic amount of copper(I) salt.

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reagents, particularly the lithium diorganocuprates, generally give better yields of the conjugate adducts with greater stereoselectivity than the "catalytic" organocoppers [2]. Furthermore, they are effective in addition to a wide variety of α-ethylenic carbonyl substrates [2]. However, the effectiveness in these reactions of "stoichiometric" magnesium-based organocuprates of the type XMgYRCu (where X = halogen and Y = organic group or halogen) has not been investigated extensively *, even though they appear to be less expensive than their lithium counterparts.

We report below that halomagnesium diorganocuprates, derived from Grignard reagents and one-half equivalent of copper(I) iodide, are also effective in conjugate addition reactions, and appear to be useful alternative reagents to the lithium diorganocuprates.

Results and discussion

Bromomagnesium diphenylcuprate and iodomagnesium dimethylcuprate react with α-ethylenic ketones and esters (Scheme 1) to give 25—70% isolated yields of the corresponding conjugate adducts (Table 1). The yield is lower when an organocopper of the type ($RCu + MgX_2$) is employed instead of the corresponding diorganocuprate. The best yield is obtained when the molar ratio of the cuprate (on the basis of the monomeric formula, $XMgR_2Cu$) to substrate is 3 or 4 to 1. The table further indicates that the yield of the conjugate adduct decreases whenever an electron-donating group is attached to the β-carbon atom. In other words, as the positive character of the β-carbon of the α,β-unsaturated carbonyl systems decreases, the yield decreases. This may point to a nucleophilic type of attack by the cuprate reagent on the β-carbon **.

The conjugate addition reactions of the "stoichiometric" organomagnesium copper reagents are considerably slower than those of the "catalytic" organocoppers. For example, the former reactions require at least 2.5 h for completion, whereas the latter are normally complete within seconds [3]. This is primarily because the "stoichiometric" organomagnesium copper reagents form heterogeneous reaction mixtures in ether [10] but the copper-catalysed Grignard addition involves a homogeneous dark green solution. However, it is also possible that "stoichiometric" organocoppers as such are not involved in the rate-determining step of the copper-catalysed conjugate additions. One possibility is the participation in the rate-determining step of a "higher" cuprate species which could be formed from one equivalent of copper(I) halide and more than two equivalents of a Grignard reagent.

It is clear that halomagnesium diorganocuprates, which are less expensive than their lithium analogues, undergo conjugate addition reactions with α-ethylenic ketones and esters and give synthetically useful yields of the conjugate adducts.

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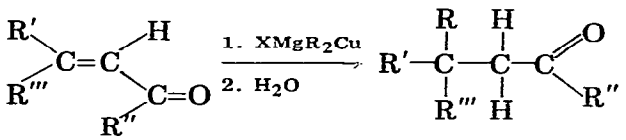
* For conjugate addition reactions involving some "stoichiometric" magnesium cuprates see ref. 8.

** For probable mechanisms of conjugate addition of lithium diorganocuprates see ref. 9.

SCHEME 1



Experimental

General

The reactions were carried out under a positive pressure of dry, oxygen-free nitrogen. Diethyl ether was dried over sodium and distilled from sodium-benzophenone ketyl before use. Copper(I) iodide was obtained commercially (E. Merck) and used without further purification. The IR spectra were recorded either as Nujol mull or as liquid film on a Pye Unicam SP 1025 Infrared Spectrophotometer and NMR spectra in $CDCl_3$ using TMS as an internal standard, on a Bruker WH 270 MHz spectrometer.

Preparation of halomagnesium diorganocuprates

Bromomagnesium diphenylcuprate reagent was prepared as described pre-

TABLE 1

CONJUGATE ADDITION REACTIONS OF SOME MAGNESIUM-BASED ORGANOCUPRATES WITH α-ETHYLENIC KETONES AND ESTERS

α-Ethylenic carbonyl substrate (0.01 mol)	Organocopper reagent [a]	mol [b]	Product	Yield [c] (%)
PhCH=CHCOOMe	$BrMgPh_2Cu$	0.02	Ph_2CHCH_2COOMe	52
PhCH=CHCOOMe	$BrMgPh_2Cu$	0.03	Ph_2CHCH_2COOMe	58
PhCH=CHCOOMe	$BrMgPh_2Cu$	0.04	Ph_2CHCH_2COOMe	56
PhCH=CHCOOMe	$IMgMe_2Cu$	0.03	$PhMeCHCH_2COOMe$	46
PhCH=CHCOOMe	$IMgMe_2Cu$	0.04	$PhMeCHCH_2COOMe$	58
PhCH=CHCOOMe	PhCu (+ MgBrI)	0.03	Ph_2CHCH_2COOMe	2
PhCH=CHCOOEt	$BrMgPh_2Cu$	0.03	Ph_2CHCH_2COOEt	60
MeCH=CHCOOMe	$BrMgPh_2Cu$	0.03	$PhMeCHCH_2COOMe$	70
MeCH=CHCOOMe	$BrMgPh_2Cu$	0.015	$PhMeCHCH_2COOH$ [d]	60
MeCH=CHCOOMe	PhCu (+ MgBrI)	0.015	$PhMeCHCH_2COOH$ [d]	64
MeCH=CHCOOMe	$IMgMe_2Cu$	0.04	Me_2CHCH_2COOMe	25
Me_2C=CHCOMe	$BrMgPh_2Cu$	0.015	$PhMe_2CCH_2COMe$	45
Me_2C=CHCOMe	$BrMgPh_2Cu$	0.02	$PhMe_2CCH_2COMe$	61
Me_2C=CHCOMe	$BrMgPh_2Cu$	0.03	$PhMe_2CCH_2COMe$	70
4-$MeOC_6H_4$CH=CHCOMe	$BrMgPh_2Cu$	0.03	(4-$MeOC_6H_4$)$CHPhCH_2COMe$	50
PhCH=CHCOMe	$BrMgPh_2Cu$	0.03	Ph_2CHCH_2COMe	64
PhCH=CHCOMe	$IMgMe_2Cu$	0.04	$PhMeCHCH_2COMe$	50
PhCH=CHCOPh	$BrMgPh_2Cu$	0.03	Ph_2CHCH_2COPh	66
PhCH=CHCOPh	PhCu (+ MgBrI)	0.03	Ph_2CHCH_2COPh	49
PhCH=CHCOPh	$IMgMe_2Cu$	0.04	$PhMeCHCH_2COPh$	51

[a] The notations used have no structural implications. [b] Calculated on the basis of the monomeric formula. [c] Based on the unsaturated substrate used. [d] Isolated as carboxylic acid subsequent to alkali hydrolysis (with a 10% KOH solution in aqueous ethanol at reflux temperature for 4 h) followed by customary work-up.

viously [10,11] by stirring phenylmagnesium bromide (2x mol) with copper(I) iodide (x mol) in diethyl ether (100 ml) at —10 to —15°C for 5 h or until Gilman Test I [12] was negative.

Iodomagnesium dimethylcuprate [10] was prepared as described above except that methylmagnesium iodide was used instead of phenylmagnesium bromide.

Preparation of phenylcopper reagent

Phenylcopper was prepared by the previously published [13—15] procedure by stirring phenylmagnesium bromide (x mol) and copper(I) iodide (x mol) in diethyl ether at —5°C for 2 h or until Colour Test I [12] was negative.

General procedure for conjugate addition reactions

To a preparation of a halomagnesium diorganocuprate (3x or 4x mol) or phenylcopper reagent (3x mol) at —8 to —10°C an α-ethylenic ketone or ester (x mol) was added all in one portion. The mixture was stirred at —8 to —10°C for 2.5 h and then hydrolysed with a saturated solution of aqueous ammonia and ammonium chloride (pH ~8). The organic material was extracted three times with ether (3 × 50 ml), and the combined ether extracts were washed several times with the aq. NH_3/NH_4Cl solution (or until the blue colour of the copper complex disappeared). The ether extract was dried overnight over anhydrous magnesium sulphate and filtered. Removal of ether (and benzene formed during hydrolytic work-up when excess bromomagnesium diphenylcuprate or phenylcopper was used) gave a crude oil (or solid). Purification of this crude product either by fractional distillation or by column chromatography (followed by a further distillation) gave the pure conjugate adduct (along with biphenyl (3—10%) if the copper reagent was $BrMgPh_2Cu$ or (PhCu + MgX_2)). Further details are given in Table 1.

The conjugate addition products were identified from m.p.'s or b.p.'s and by their spectral properties.

Methyl 3,3-diphenylpropionate: b.p. 142—143°C/0.2 mmHg, m.p. 44—46°C (lit. [16] 48°C); IR, 1737 cm^{-1} (ester C=O); NMR, δ 7.10—7.26 (10 H, m, aryl CH), 4.57 (1 H, t, benzal CH), 3.55 (3 H, s, OCH_3) and 3.06 (2 H, d, CH_2CO).

Methyl 3-phenylbutanoate: b.p. 98°C/5 mmHg (lit. [6] 133—135°C/22 mmHg); IR, 1741 cm^{-1} (ester C=O); NMR, δ 7.35—7.20 (5 H, m, aryl CH), 3.61 (3 H, s, OCH_3), 3.27 (1 H, m, benzylic CH), 2.58 (2 H, d, CH_2CO) and 1.29 (3 H, d, CH_3).

Ethyl 3,3-diphenylpropionate: b.p. 138—140°C/0.25 mmHg (lit. [16] 190—193°C/12 mmHg); IR, 1740 cm^{-1} (ester C=O); NMR, δ 7.02—7.33 (10 H, m, aryl CH), 4.55 (1 H, t, benzal CH), 3.96 (2 H, q, OCH_2), 3.00 (2 H, d, CH_2CO) and 1.01 (3 H, t, CH_3).

Methyl 3-methylbutanoate: b.p. 116—117°C (lit. [17] 115—116°C); IR, 1740 cm^{-1} (ester C=O); NMR, δ 3.61 (3 H, s, OCH_3), 2.10 (3 H, m, isopropylic CH and CH_2CO) and 0.81—1.20 (6 H, m, CH_3).

4-(4-Methoxyphenyl)-4-phenyl-2-butanone: b.p. 171—172°C/1 mmHg; m.p. 82.5—83.5°C (lit. [18] 83.5—84°C); IR, 1707 cm^{-1} (C=O); NMR, δ 7.28—

6.70 (9 H, m, aryl CH), 4.54 (1 H, t, benzal CH), 3.68 (3 H, s, OCH_3), 3.13 (2 H, d, CH_2CO) and 2.02 (3 H, s, $COCH_3$).

4,4-Diphenyl-2-butanone: b.p. 168—169°C/1 mmHg; IR, 1725 cm^{-1} (C=O); NMR, δ 7.36—7.07 (10 H, M, aryl CH), 4.60 (1 H, t, benzal CH), 3.13 (2 H, d, CH_2CO) and 2.01 (3 H, s, $COCH_3$) (*cf.* [19]).

4-Phenyl-2-pentanone: m.p. 71—73°C (lit. [20] 74°C), b.p. 90—92°C/3.5 mmHg (lit. [5] 64—66°C/0.45 mmHg; IR, 1720 cm^{-1} (C=O); NMR, δ 7.18 (5 H, m, aryl CH), 3.24 (1 H, m, benzylic CH), 2.48—2.82 (2 H, m, CH_2CO), 1.97 (3 H, s, $COCH_3$) and 1.24 (3 H, d, CH_3).

1,3,3,-Triphenyl-1-propanone: m.p. 95°C (lit. [21] 96°C); IR, 1680 cm^{-1} (conjugated C=O); NMR, δ 7.49—7.16 (15 H, m, aryl CH), 4.83 (1 H, t, benzal CH) and 3.75 (2 H, d, CH_2CO).

1,3-Diphenyl-1-butanone: m.p. 71—72°C (lit. [5] 70.5—71°C); IR, 1681 cm^{-1} (conjugated C=O); NMR, δ 7.02—8.47 (10 H, m, aryl CH), 3.01—4.02 (3 H, m, aliphatic CH) and 1.48 (3 H, d, CH_3).

4-Phenyl-4-methyl-2-pentanone: b.p. 100—101°C/4 mmHg (lit. [22] 252°C); IR, 1715 cm^{-1} (C=O); NMR, δ 7.19—7.10 (5 H, m, aryl CH), 2.71 (2 H, s, CH_2CO), 1.75 (3 H, s, $COCH_3$) and 1.42 (6 H, s, $C(CH_3)_2$).

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