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(18) This work was supported by National Institutes of Health Grant GM-HL 19882.
(19) Postdoctoral Fellow on leave from the Department of Biochemistry of Warsaw University, Poland.
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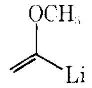
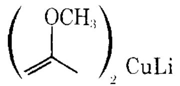
Preparation and Synthetic Applications of Lithium Di(α-methoxyvinyl)cuprate

Sir:

Acyl anion equivalents have been rigorously investigated within the last 5 years, as evidenced by the vast number of papers since 1969.[1] Baldwin and coworkers[1] have recently prepared α-methoxyvinyllithium (MVL) (**1**) and demonstrated its usefulness in 1,2-additions to various carbonyl moieties and alkylations with halides. We now wish to report the preparation of lithium di(α-methoxyvinyl)cuprate (**2**) from MVL and its synthetic utility in conjugate additions[2] and alkylations.


1


2

As shown in Scheme I, reaction of **2** with an α,β-unsaturated ketone **3** would result in a 3-(α-methoxyvinyl) ketone (**4**) which, when either hydrolyzed or ozonized, would produce a 1,4-diketone (**5**) or γ-ketoester (**6**), respectively.

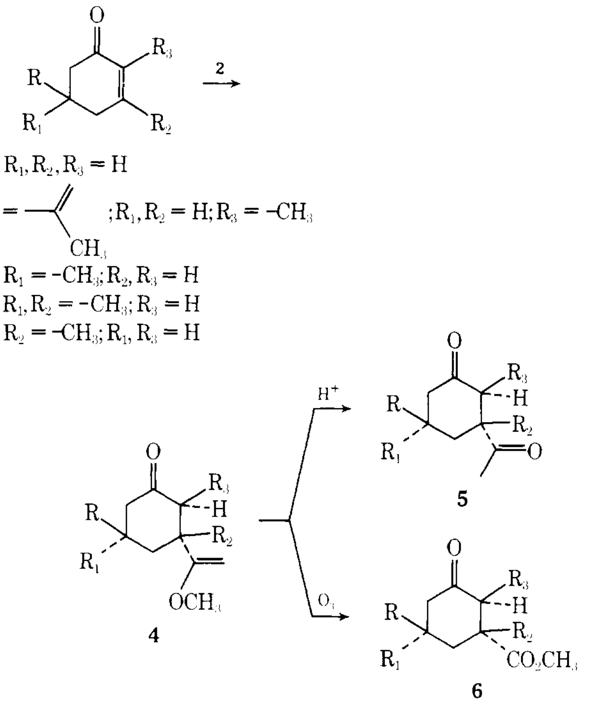
When purified cuprous iodide[3] was added to a stirred solution of MVL at −65°, the mixture gradually turned black, implying that the cuprate (**2**) had indeed formed (since the color of lithium divinylcuprate appears black[4]). However, this was not the case, as addition of 2-cyclohexen-1-one (**3a**) and work-up resulted in a nearly quantitative yield of 1,2-adduct, with no more than a few per cent of the conjugate addition product **4**. This problem was circumvented. Addition of MVL to a solution of cuprous iodide, dimethyl sulfide,[5] and freshly distilled THF at −40° initially produces a deep red-brown mixture which turns yellow near the end of the addition. After stirring for 30 min at −40°, the enone in THF is added and stirring continued at −40° for 10 min and then raised to −10 or −5°, where the red mixture is then stirred for 45–75 min, depending on the unsaturated ketone involved. Work-up is accomplished by quenching with 20% aqueous ammonium chloride, followed by routine ether extraction and isolation. The results are provided in Table I.

Table I. Reactions of Lithium Di(α-methoxyvinyl)cuprate (2) with α, β-Unsaturated Ketones

Electrophile	Adduct (% yield)
2-Cyclohexen-1-one (3a)[a]	4a (66)[d,h]
d-Carvone (96%) (3b)[b]	4b (50)[d,e,h]
5,5-Dimethyl-2-cyclohexen-1-one (3c)[c]	4c (67)[d,h]
Isophorone (3d)[c]	3d (80) + (4d + 1,2-adduct) (20)[f]
3,5-Dimethyl-2-cyclohexen-1-one (3e)[c]	3e (80) + (4e + 1,2-adduct) (20)[g]

[a] Stirred with 2 at −10° for 30 min. [b] Stirred with 2 at −10° for 30 min and −5° for 75 min. [c] Stirred with 2 at −10° for 45 min. [d] Distilled yield. [e] ^{1}H NMR reveals essentially one stereoisomer. [f] The crude recovery is quantitative and the per cent ratios are determined by ^{1}H NMR and ir analyses. [g] The crude recovery is quantitative, and the per cent ratios are determined by ^{1}H NMR, ir, and GLC analyses. [h] Satisfactory ^{1}H NMR, ir, and elemental analyses.

Scheme I

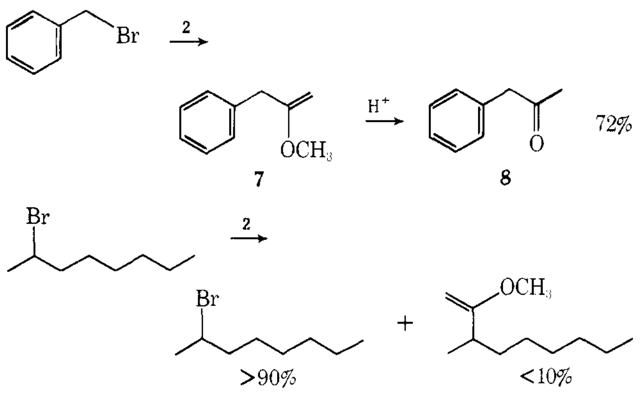


The red mixture, formed on initial addition of MVL to the cuprous iodide-dimethyl sulfide complex and again after addition of the enone, is apparently the intermediate α-methoxyvinylcopper(I), and the yellow mixture is lithium di(α-methoxyvinyl)cuprate (**2**).[6]

Cuprate (**2**) is sensitive to the steric environment at the C-5 position of the cyclohexenones studied, as demonstrated with *d*-carvone (**3b**). The adduct (**4b**) is assumed to have the geometry shown, based on the fact that ^{1}H NMR reveals essentially one isomer and on the previous observation that 5-alkyl-2-cyclohexenones react with dialkylcuprates to give primarily trans products.[7] Conjugate addition appears to be inhibited by further alkyl substitution at the 3-position, but not at the 5-position (see the adducts of **3b** and **3c** in comparison to **3d** and **3e**).

The 1,4-addition products (**4a–c**) can be efficiently converted to diketones or ketoesters as demonstrated with **4c.** Hydrolysis of **4c** at room temperature for 30 min with di-

Scheme II



lute acid (0.025 *N* HCl) in methanol-water (4:1) afforded the 1,4-diketone, 5,5-dimethyl-3-acetylcyclohexanone (**5c**) (see Scheme I) in 80% distilled yield.[8,9] Ozonolysis of **4c** in dichloromethane-methanol (9:1) at −60°,[10] followed by addition of dimethyl sulfide,[11] resulted in a 73% distilled yield of the γ-ketoester,[12] 5,5-dimethyl-3-carbomethoxycyclohexanone (**6c**)[8] (see Scheme I).

Concerning alkylations of the cuprate (**2**) with halides, we noted that Baldwin[1] was unsuccessful in alkylating MVL (**1**) with benzyl bromide (presumably due to trans metalation) nor was any mention made of alkylations with secondary halides. Addition of benzyl bromide to the cuprate (**2**) at −40° followed by stirring at 0° for 5 hr yielded the desired crude α-(α-methoxyvinyl)toluene (**7**). The enol ether was then hydrolyzed in the same manner as **4c** to product 1-phenyl-2-propanone (**8**)[8] in 72% distilled yield (based on benzyl bromide). Attempted distillation of the crude enol ether (**7**) afforded a 2:3 mixture of **7** and its double bond isomer. Treatment of 2-bromooctane in the same fashion, with the cuprate, followed by stirring at 0° for 4 hr and room temperature for 15 hr, however, resulted in a greater than 90% recovery of the starting alkyl bromide. These results are summarized in Scheme II.

A typical procedure for the generation and reaction of lithium di(α-methoxyvinyl)cuprate with electrophiles is demonstrated with 5,5-dimethyl-2-cyclohexen-1-one (**3c**). A solution of MVL prepared according to Baldwin[1] from 5.24 ml (69.6 mol) of methyl vinyl ether and 54.4 ml (43.5 mmol) of 0.8 *M t*-BuLi in 30 ml of THF was cooled to below −40° and added over 15 min via a glass-jacketed dropping funnel containing Dry Ice-isopropyl alcohol to a solution of 4.17 g (21.9 mmol) of purified cuprous iodide[3] and 6.30 ml (85.8 mmol) of dimethyl sulfide[5] in 30 ml THF at −40° (mole ratio $CH_2{=}CHOCH_3$-*t*-BuLi-CuI-$CH_3SCH_3 \approx 3{:}2{:}1{:}4$). After stirring for 30 min, 1.80 g of 5,5-dimethyl-2-cyclohexen-1-one (**3c**) (14.5 mmol) in 15 ml of THF was added over 10 min to the yellow mixture and stirred at −40° for 10 min and then at −10° for 45 min. The red mixture was then quenched with 20% NH_4Cl and extracted with ether and the crude product isolated and distilled, affording 1.76 g (67%) of 5,5-dimethyl-3-(α-methoxyvinyl)-2-cyclohexen-1-one (**4c**); bp 73-76° (0.25 mm): ^1H NMR (CCl_4) δ 3.87 (d, 1, J = 2.5 Hz), 3.80 (d, 1, J = 2.5 Hz), 3.57 (s, 3), 1.4-2.8 (m, 7), 1.1 (s, 3), 0.92 (s, 3); ir (film) 1724, 1661, 1631 cm^{-1}. High resolution mass spectrum gave an M^+ 182.1327 ($C_{11}H_{18}O_2$).

In summary, lithium di(α-methoxyvinyl)cuprate provides an efficient route to γ-diketones and γ-ketoesters from α,β-unsaturated ketones and complements MVL with regard to alkylations of halides.[13]

Acknowledgments. We thank the United States Public Health Service (CA-12617) for financial support.

References and Notes

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(4) We have observed the black color of lithium divinyl cuprate in our laboratory; vinylcuprates: (a) E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7318 (1971); (b) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970); (c) H. O. House, R. A. Latham, and C. D. Slater, *J. Org. Chem.*, **31**, 2667 (1966).
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(8) Satisfactory ^1H NMR, ir, and elemental analyses.
(9) The conjugate addition of lithium di(phenylthio)methylcopper reagents to α,β-unsaturated ketones, followed by $CuCl_2$-CuO/aqueous acetone hydrolysis, also provides 1,4-diketones; see T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
(10) Use of methanol as solvent resulted in hydrolysis of the enol ether prior to ozonolysis. The methanol is added to a solution of the enol ether (e.g., **4c**) in dichloromethane at −60° just before ozonolysis; for another example utilizing these conditions, see R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 2027 (1974).
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(12) For another recent approach to the synthesis of γ-ketoesters, see P. A. Wehrli and V. Chu, *J. Org. Chem.*, **38**, 3436 (1973).
(13) NOTE ADDED IN PROOF. Professor R. K. Boeckman has informed us that he and Professor J. E. Baldwin have independently synthesized lithium di(α-ethoxyvinyl)cuprate and shown that it enters into conjugate additions with ketones. We thank Professors Boeckman and Baldwin for informing us of their results prior to publication.

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Lanthanum-139 as a Nuclear Magnetic Resonance Probe of Macromolecular Dynamics

Sir:

Nuclear relaxation rates reflect in principle the molecular dynamics in solution. Particularly sensitive in this regard are nuclei possessing a quadrupole moment (spin $I > \frac{1}{2}$), for which the molecular motion modulates the interaction between the nuclear quadrupole moment and intramolecular electric field gradients. The longitudinal relaxation rates of such nuclei are related (to a good approximation[1]) to the correlation time, τ_c, characteristic of the molecular motion by[2]

$$1/T_1 = C\left(\frac{\tau_c}{1 + \omega^2\tau_c^2} + \frac{4\tau_c}{1 + \omega^2\tau_c^2}\right) \qquad (1)$$

where ω is the nuclear resonance frequency and C is a constant for a given nucleus and chemical environment. Thus measurements of longitudinal relaxation rates at several frequencies should permit an unequivocal determination of the correlation time. Attempts to study macromolecular dynamics via the above relationship using quadrupole nuclei such as ^2H, ^{23}Na, and ^{35}Cl have met with difficulties in the interpretation, the main reason being the little specificity and the weakness of the chemical interactions leading to rapid local motions.[3-5]

Recent spectroscopic and magnetic resonance studies (for a review cf. ref 6) have shown that the lanthanide ions form strong and specific complexes with a number of proteins and nucleic acids. Among the trivalent rare-earth ions, only lanthanum and lutetium are diamagnetic, and it appears