Tetrahedron Letters,Vol.23,No.37,pp 3755-3758,1982 0040-4039/82/373755-04$03.00/0
Printed in Great Britain

CHEMISTRY OF HIGHER ORDER, MIXED ORGANOCUPRATES. 3.[1] REACTIONS OF α,β-UNSATURATED KETONES.

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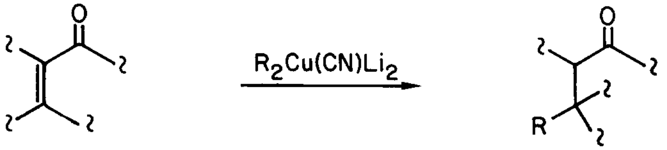
SUMMARY: *Organocuprates of general formula $R_2Cu(CN)Li_2$ react rapidly with α,β-unsaturated ketones at low temperatures and in high yields to deliver ligands in a conjugate manner. These reagents apparently do not require the use of additives for stabilizing or solubilizing purposes.*

One of the fundamental contributions of organocopper chemistry to organic synthesis is the ability of Gilman reagents, R_2CuLi, 1, or modified Gilman reagents, to deliver a variety of ligands in a 1,4-sense to α,β-unsaturated ketones.[3] In many situations where reagent solubility and/or stability is a potential problem, additives such as Me_2S,[4] LiBr,[5] and perhaps more commonly, phosphorous derivatives (e.g. HMPA,[6] $(EtO)_3P$,[7] $n\text{-}Bu_3P$[8]) must be employed. In light of our previous studies on the reactions of organocopper reagents of general formula $R_2Cu(CN)Li_2$(2),[1,9] we were aware of the dissimilarity in chemical properties of 2 relative to the more traditional reagents 1. Hence, we decided to examine the reactions of higher order cuprates 2 with enones so as to compare and contrast them with their lower order counterparts 1.



Herin we report on our findings which suggest that this new methodology is among the mildest and most efficient for effecting conjugate addition to substrates of this type.

Initially there was good reason to be skeptical about the outcome of such a study. Ashby had shown that the higher order species Me_3CuLi_2 exists to an appreciable degree in equilibrium with Me_2CuLi and free MeLi.[10] This complex (i.e., $Me_2CuLi{\cdot}MeLi$) is well-known to react extremely rapidly with ketones.[11] In many cases it delivers 'CH_3^-' in a 1,2-sense upon reactions with enones.[12] In our own chemical and spectroscopic studies on 2,[9b] the NMR spectrum of 2, R=Me in THF showed no visible signs of an equilibrium. However, the same experiment on the more highly mixed species Me(n-Bu)Cu(CN)Li_2(3) in Et_2O revealed free MeLi at low temperatures, along with MeCu(CN)Li. Hence, the key question remained as to whether 2 and/or 3 would be sufficiently reactive toward enones so as to compete with any free RLi which would be expected to add in a 1,2 fashion.

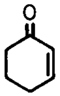
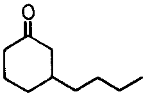
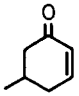
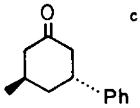
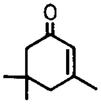
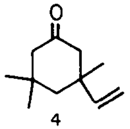
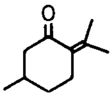
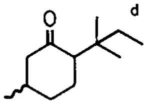
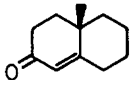
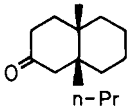
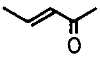
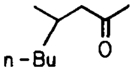
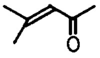
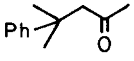
In the event, additon of an enone (neat or in Et_2O) to a cold solution of 2 and monitoring the reaction by tlc or vpc, led cleanly to the desired product of conjugate addition. A variety of mixed cuprates can be employed and considerable structural variation is tolerated in the substrate. The results are summarized in Table I. Most enones reacted readily at -78°. Relatively unhindered systems such as cyclohexenone and 3-penten-2-one (entries 1 and 6) react readily with 2, R=n-Bu to afford the desired ketones in 86 and 84% isolated yields, respectively. Acyclic β,β-disubstituted compounds typified by mesityl oxide (entry 7) accept an aryl group leading to a β-trisubstituted ketone (83%). 5-Methylcyclohexen-2-one (entry 2) gave a 98.5 : 1.5 mixture of trans:cis isomers upon treatment with $Ph_2Cu(CN)Li_2$ in a combined yield of 82%. This ratio of products compares quite favorably with that observed previously on the same enone under the influences of the lower order reagent Ph_2CuLi.[14]

Somewhat more challenging cases are exemplified by entries 3, 4, and 5. Addition of divinylcopperlithium in the presence of n-Bu_3P to isophorone according to the Hooz procedure[8] requires conditions of 0° over 1 h and gives the desired product 4 in 60% isolated yield. By comparison, reaction of 2, R = vinyl, with this enone in Et_2O at -50° for 2 h, without an additive gave 4 in 88% isolated yield (entry 3). Similarly, $Et_2Cu(CN)Li_2$ very efficiently delivered an ethyl group to pulegone in 99% (vpc) yield (81% isolated), albeit at a somewhat higher temperature (entry 4). The material was obtained as a 3.5:1 mixture of isomers as determined by vpc. Hindered octalone 5[15] (entry 5) smoothly accepts an n-propyl moiety presumably from the less congested convex face affording the cis-fused bicyclic network[16] to the extent of 85%. That a single product was obtained in this case was indicated by capillary VPC and ^{13}C NMR spectroscopy.

In conclusion, the reactions of higher order, mixed organocuprates derived from CuCN with α,β-unsaturated ketones take place under very mild conditions and result in good to excellent yields of the corresponding ketones. Mono-, di-, and trisubstituted enones all participate in the coupling process. A variety of alkyl, vinyl, and aryl ligands are efficiently transferred at low temperature in Et_2O without competing 1,2-addition to the carbonyl group. Moreover, from a practical standpoint, in addition to the other inherent benefits of CuCN- over CuI-based cuprates,[9a] there is no apparent need for modification of the reagent via additives which simplifies the overall reaction, workup and isolation procedures.[17]

Acknowledgment. We are pleased to acknowledge the financial support provided by the National Institutes of Health (GM 28128), the American Cancer Society (JFRA #37 to B. H. L.) and (in part) the Committee on Research, UCSB.

TABLE I. Reactions of $R_2Cu(CN)Li_2$ with α, β-Unsaturated Ketones

Entry	Substrate	Cuprate	Conditions	Product[a]	Yield[b]
1		n-$Bu_2Cu(CN)Li_2$	Et_2O −78°, .5h		86
2		$Ph_2Cu(CN)Li_2$	Et_2O −78°, 1 h	 [c]	82
3		 $_2Cu(CN)Li_2$	Et_2O −50°, 2 h	 4	88
4		$Et_2Cu(CN)Li_2$	Et_2O −25°, 3 h	 [d]	81(99)[e]
5	 [f] 5	n-$Pr_2Cu(CN)Li_2$	Et_2O −25°, 2 h	 [g]	85
6		n-$Bu_2Cu(CN)Li_2$	Et_2O −78°, 1 h		84
7		$Ph_2Cu(CN)Li_2$	Et_2O −78°, 1 h		83

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[a] All products gave satisfactory IR, NMR, and Mass Spectral data. [b] Yields refer to isolated, chromatographically pure materials, unless stated otherwise. [c] Major isomer, see text. [d] 3.5 : 1 ratio of isomers; see text. [e] By quant. VPC using cyclohexanone as standard. [f] Prepared according to Ref. 15. [g] Product has mp 52−54°.

References and Notes

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   (b) Yamamoto, Y., Yamamoto, S., Yatagai, H., Ishihara, Y., and Marauma, K., J. Org. Chem., 1982, 47, 119, and references therein.
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13. Analyzed by capillary vpc using a 50 m x 0.21 mm (int. diam.) OV-101 column purchased from Hewlett-Packard.
14. Spectral data on the products were compared with that in the literature; House, H. O., Giese, R. W., Kronberger, K., Kaplan, J. P., Simeone, J. F., J. Am. Chem. Soc., 1966, 31, 1016.
15. Marshall, J. A., Fanta, W. I., J. Org. Chem., 1964, 29, 2501.
16. A similar result is reported using MeMgI/Cu(OAc); Marshall, J. A., Fanta, W. I., Roebke, H. J. Org. Chem., 1966, 31, 1016.
17. A typical experimental procedure for the preparation of 4 (Table I) is as follows. CuCN (89 mg, 1 mmol) was placed in a dry two-necked flask and azeotropically dried with toluene (1.5 mL) at room temperature under vacuum. The dry CuCN was placed under argon and dry Et$_2$O (1.0 mL) was introduced. The slurry was cooled to -78°C and vinyllithium (2.07 M, 0.95 mL, 1.97 mmol) was added *via* syringe. The mixture was allowed to warm to 0° C at which point it became a homogeneous light tan solution. After 1-2 min at 0°C the flask was recooled to -78° C. Isophorone (69 mg, 0.5 mmol) was added and the reaction mixture was warmed to -50°C and stirred for 3.5 h. The mixture was quenched at -50°C with 10% NH$_4$OH/90% saturated NH$_4$Cl solution followed by extractive work-up (Et$_2$O), and drying (MgSO$_4$). Chromatography on silica gel with Et$_2$O:pentane (15/85) gave 3,5,5-trimethyl-3-vinylcyclohexanone (68.3 mg, 88%); TLC: R$_f$= 0.32(Et$_2$O:pentane 15/85); IR(neat) cm^{-1} 1710, 1635, 913; NMR (CDCl$_3$) δ 5.95-5.60, 5.10-4.85 (3H, m, vinyl CH), 2.58, 2.14 (2H, AB, J = 25 Hz), 2.15 (2H, s), 1.67 (2H, s), 1.14 (3H, s), 1.07 (3H, s), 1.00 (3H, s); MS:m/e (relative intensity, %) 166 (M$^+$, 37.9), 151 (18.8), 124 (2.4), 123 (9.6), 109 (33.5).

(Received in USA 21 June 1982)