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CONJUGATE ADDITION REACTIONS OF α,β- UNSATURATED ESTERS WITH HIGHER ORDER CUPRATES $R_2Cu(CN)Li_2$

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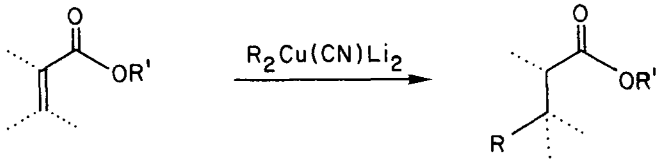
SUMMARY: *Higher order, mixed cuprates $R_2Cu(CN)Li_2$ react rapidly and in high yields with β-substituted enoates. α,β-Disubstituted systems afford moderate yields of product in certain cases whereas β,β-disubstituted unsaturated esters lead to 1,2-followed by 1,4-addition.*

While α,β-unsaturated ketones are used extensively as Michael acceptors in reactions with Gilman reagents, R_2CuLi, similar chemistry involving enoates is generally not considered a synthetically useful process.[2] The relative reactivity of α,β-unsaturated esters, compared to their ketone counterparts, is such that alternative modes of reaction (e.g., 1,2-addition) are oftentimes preferred. Yamamoto and co-workers[3] have described an alternative approach <u>via</u> an alkyl copper reagent (i.e., $RCu{\cdot}BF_3$) which relies on the action of a Lewis acid to successfully mediate the coupling.

More recently higher order, mixed cuprates $R_2Cu(CN)Li_2$ (<u>1</u>), have been shown to be quite reactive toward a variety of organic substrates.[4] Stabilizing, solubilizing, and/or activating ligands such as phosphorus derivatives, Lewis acids, etc. are not required even where sensitive cuprates normally prone to decomposition are being used. In this Letter we now report that β-substituted enoates react rapidly and efficiently with reagents <u>1</u> at low temperatures attesting to the remarkable differences between <u>1</u> and more traditional lower order organocuprates.[2]



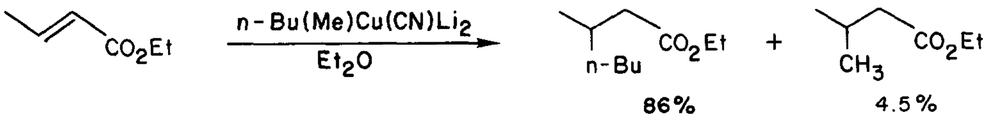
As illustrated in Table I, entries 1-6, cuprates <u>1</u> and β-substituted enoates are excellent reaction partners. Unlike earlier work[3] where only n-BuLi-derived species were investigated, in this study several ligands (alkyl, vinyl, aryl) have been transferred, providing further evidence as to the scope of the method. There was no apparent dependence of efficiency on the nature of the alkyl ester (methyl vs. ethyl). It is noteworthy that a $t\text{-}BuMe_2Si$ ester (entry 2) can also serve in the same capacity thereby permitting the subsequent mild and selective fluoride ion induced cleavage to the corresponding acid under essentially neutral conditions.[5] Interestingly, the bulkier yet softer t-BuPh$_2$Si ester (entry 3)[6] afforded noticeably lower yields of desired product. The geometrical orientation of the appendage at the β-carbon was of little consequence as both the E (entry 4) and Z (entry 5) isomers reacted with similar rates and overall yields, in contrast to the *cisoid* array preferred in reactions of BuCu·BF$_3$.[3] Although *1* effects opening of trisubstituted oxiranes,[7] an epoxy enoate (entry 6) reacted exclusively with n-Bu$_2$Cu(CN)Li$_2$ in a Michael fashion.

In general, β-substituted enoates require just over 1 equiv of cuprate for complete consumption of starting material. Moreover, short reaction times (usually $<$ 1h) and low temperatures ($\leq$ -25°C) suffice, observations which are, again, quite contrary to literature reports involving R$_2$CuLi on similar types of substrates.[2] To amplify these dissimilarities, side by side reactions of ethyl crotonate with both Ph$_2$CuLi and Ph$_2$Cu(CN)Li$_2$ were performed leading to (by VPC) 38% product in the former case while *1*, R=Ph afforded a 75% yield. More unexpected was the finding that *1*, R=n-Bu reacted (at -78°, 5h) to the extent of 61%, while n-BuCu(CN)Li gave <1% of the same product under otherwise identical conditions.

A brief study on the effects of solvent was made as this parameter can oftentimes play a crucial role in deciding the outcome of the coupling process.[8] Treatment of ethyl crotonate *in route* to ethyl 3-methylheptanoate with *1*, R=n-Bu (-78°, 30 min; -25°, 15 min) led to the following observations: Et$_2$O, 81-94%, THF, 17-18%; DME; 3-5%; Et$_2$O/PhCH$_3$(1:1), 91%; Et$_2$O/PhCH$_3$ (1:2), 91%. These results are in line with the apparent preference for solvents of poorer Lewis basicity and presumably reflect decreased competition by the solvent for metal complexation with the enoate carbonyl oxygen.[8]

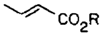
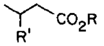
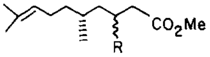
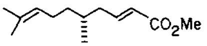
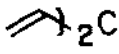
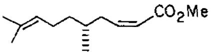
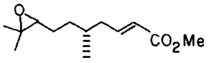
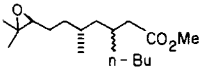
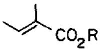
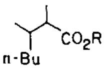
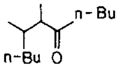
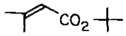
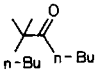
An effort was made to extend this procedure[9] to α,β-disubstituted systems with only marginal success being realized. Using esters of tiglic acid (entries 7-11), moderate yields were obtained only with a hindered t-BuPh$_2$Si ester. These findings were unexpected in light of Yamamoto's results which led to the conclusion that α-substitution enhances conjugate addition by providing additional steric shielding for the carbonyl group.[3] All attempts to add an n-Bu ligand to β,β-dimethylacrylic acid ester (entry 12) led to the product derived from a 1,2-addition-conjugate addition sequence.[10]

Lastly, so as to establish the feasibility of conserving potentially valuable lithium reagents, the more highly mixed species Me(n-Bu)Cu(CN)Li$_2$ was prepared and reacted with ethyl crotonate. As analyzed by VPC, a 93% yield of products was obtained composed of 86% the product of n-Bu transfer and 4.5% from Me transfer. Thus, this *ca*. 19:1 ratio for the selectivity of transfer suggests that a simple methyl group may function as a second 'dummy' ligand.[11]



Further studies on the reactions and properties of these reagents and their applications in synthesis will be reported in due course.

Table I. Reactions of Unsaturated Esters with $R_2Cu(CN)Li_2$ in Et_2O

Entry	Ester	Reagent	(equiv)	Conditions	Product(s)[a]		Yield (%)[b]
							
1	R = Et	$n\text{-}Bu_2Cu(CN)Li_2$ **3**	(1.11)	−78°, 30 min −25°, 15 min	R = Et, R' = n-Bu		94[c]
		$Ph_2Cu(CN)Li_2$	(1.05)	−78°, 6 h	R = Et, R' = Ph		75[c]
2	R = $SiMe_2$(t-Bu)	**3**	(1.25)	−78°, 5 min −50°, 2 h −25°, 15 min	R = $SiMe_2$(t-Bu), R' = n-Bu		92[c]
3	R = $SiPh_2$(t-Bu)	**3**	(2.00)	−78°, 5 min −25°, 15 min	R = $SiPh_2$(t-Bu), R' = n-Bu		61
			(1.25)	−78°, 30 min −25°, 15 min			23
							
4		**3**	(1.02)	− 78°, 30 min − 25°, 30 min − 10°, 30 min	R = n-Bu		88
		 $_2Cu(CN)Li_2$	(1.02)	− 78°, 15 min − 25°, 30 min − 10°, 30 min	R = vinyl		65
		$n\text{-}Pr_2Cu(CN)Li$	(1.10)	− 78°, 30 min − 25°, 60 min	R = n-Pr		87
5		**3**	(1.02)	− 78°, 30 min warm to − 10°, 20 min	R = n-Bu		92
6		**3**	(1.10)	− 78°, 15 min − 25°, 45 min			95
					 :		
7	R = Et	**3**	(1.00)	− 78°, 1-3 h 0°, 5 min	0	1	d
8	R = t-Bu	**3**	(1.11)	−78°, 4 h	3 − 4	1	d
9	R = $SiMe_2$(t-Bu)	**3**	(3.12)	−78°, 3 h	1	2	d
10	R = $SiPh_2$(t-Bu)	**3**	(3.11)	−78°, 1 h		—	50-65
11	R = Si(i-Pr)$_3$	**3**	(1.10)	−78°, 30 min −25°, 30 min 0°, 5 min		—	e
12		**3**	(2.94)	− 78 → 0°, 1 h			d

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[a] All products gave satisfactory IR, NMR, and Mass spectral data. [b] Isolated yields unless indicated otherwise. [c] Determined by quantitative VPC. [d] Not determined. [e] At least five products detected, by vpc.

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References and Notes

1. Recipient of an American Cancer Society Junior Faculty Research Award, 1981-1983.
2. Posner, G. H., Org. React., 1972, 19, 1.
3. Yamamoto, Y., Yamamoto, S., Yatagai, H., Ishihara, Y., Maruyama, K., J. Org. Chem., 1982, 47, 119.
4. Lipshutz, B. H., Wilhelm, R. S., Kozlowski, J., Tetrahedron Letters, 1982, 23, 3755 and references therein.
5. Corey, E. J., Venkateswarlu, A., J. Am. Chem. Soc., 1972, 94, 6190.
6. Use of this silyl ester in synthesis, to our knowledge, has not been studied.
7. Lipshutz, B. H., Kozlowski, J., Wilhelm, R. S., J. Am. Chem. Soc., 1982, 104, 2305.
8. House, H. O., Wilkins, J. M., J. Org. Chem., 1978, 43, 2443.
9. The method calls for the preparation of $R_2Cu(CN)Li_2$ as described previously[4,7] followed by introduction of the enoate (neat or in Et_2O) at -78°. Stirring at this temperature for 30 min with subsequent warming to -25° for an additional 15 min was generally sufficient to drive the reaction to completion. Quenching with NH_4Cl/NH_4OH followed by a standard extractive workup gave the product, purified by filtration through silica gel.
10. Kindt-Larsen, T., Bitsch, V., Andersen, I. G. K., Jart, A., Munch-Petersen, J., Acta Chem. Scand., 1963, 17, 1426.
11. This methodology takes on added significance in light of a recent report by Oppolzer and Loher which demonstrated that reactions of copper reagents with trans-8-phenylmethyl enoates occur with significant chiral induction; Cf. Oppolzer, W., Loher, H. J., Helv. Chim. Acta, 1981, 64, 2808.

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