1,4-ACYLATION REACTIONS BY ALLYLIC CUPRATES IN THE PRESENCE OF CARBON MONOXIDE

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Summary: Exposure of higher order mixed allylic cyanocuprates to an atmosphere of CO at low temperatures followed by an enone leads to products of 1,4-acylation which contain the unit "allyl-CO".

A few years ago, Seyferth and Hui made the impressive finding that higher order cyanocuprates derived from *n*-BuLi, *s*-BuLi, and *t*-BuLi (plus 0.5 equiv CuCN),¹ as well as certain lower order analogs (*s*-BuCu(CN)Li and *t*-BuCu(CN)Li),² when exposed to excess CO at -110° undergo "direct nucleophilic 1,4-acylation" reactions with enones and enals. In light of the recent insight gained³ and applied⁴ toward the development of novel allylic cyanocuprates, reagents which we find are among the most reactive cuprates yet observed,⁵ the potential was recognized for delivering an allylic ligand as part of an acyl moiety. We now report that by choosing the appropriate mixed alkyl allylic cyanocuprate (i.e., 1), 1,4-acylations are indeed realizable which result in transfer of the "allyl-CO" moiety to $\alpha_n\beta$ -unsaturated ketones.



Results from initial attempts using a dimethallylcuprate were seriously compromised by competing 1,2-addition of the over-reactive reagent 2 leading to tertiary alcohols, isolated in addition to low yields of the desired diketone (Scheme 1). By switching to the less robust mixed 2-thienyl⁶ species 3, the situation improved somewhat, although yields only in the 40-50% range were still obtained. Ultimately, it was found that use of a methyl group as a second "dummy" ligand (i.e., 1, R = Me) provided a reagent possessing the correct balance of reactivity and selectively of transfer.⁷



Table I, therefore, contains our results concerning which the following salient points can be made: (1) good yields can be expected employing allyl, methallyl, and crotyl mixed cyanocuprates;⁸ (2) highly hindered enones are not amenable to this process, with or without additives such as Me₃ SiCl⁹; (3) crotyl ligands react predominantly at the γ -site to afford a diastereomeric mix of products, an observation contrary to the 1,4-addition of crotylcopper TMS-Cl to α,β -unsaturated ketones which add with virtually complete α -selectivity.^{4 a}

A representative procedure for the conjugate allylic acylation of an α , β -unsaturated ketone¹⁰ (Table 1, entry 2) is as follows: In a 10 mL pear bottom flask, allyltributyltin (1.41 g, 4.0 mmol, 94% pure) was degassed in vacuo for 5 min, purged with Ar, dissolved in freshly distilled THF (4.0 mL), and cooled to -78°. The solution was treated with methyllithium (2.35 mL, 4.0 mmol, 1.7 M in Et, O) and the resulting golden solution was stirred for 20 min at -78°. During this time, two reaction vessels were prepared, the first being a three-necked 250 mL flask cooled under a stream of CO (the CO was first passed through a -78° trap and then a course-porosity gas dispersion tube) at a pressure of 5-6 psi and then charged with anhydrous Et, O (40 mL), anhydrous THF (30 mL), and dry pentane (10 mL). This solvent system was sparged for 10 min with vigorous stirring and then cooled to -110° (liquid N₂/Et₂O). The second vessel, a 25 mL pear bottom flask, was charged with cuprous cyanide (360 mg, 4.0 mmol), gently flame-dried in vacuo, cooled under Ar, and charged with anhydrous THF (3.0 mL). The resulting slurry was cooled to -78°, treated with methyllithium (1.77 mL, 3.0 mmol, 1.7 M in Et, O) and allyllithium (vide supra). A tan solution resulted after a brief warming to ca. -40° which was immediately recooled to -78° and added via cannula to the sparging solution of CO (maintained at -110°) over 5 min. The bright yellow solution was sparged for an additional 5 min at which time the reagent was treated with the bromo enone (297 mg, 0.947 mmol) in dry Et₂O (2.0 mL). An orange/red color immediately ensued and the reaction mixture was quenched after 3-4 min with 5 mL of an aqueous solution of 10% NH, OH/sat'd NH, Cl, and upon warming to room temperature was extracted with ethyl acetate (4 x 15 mL). The combined organic extract was washed with brine and dried over Na_2SO_4 . Flash chromatography

Cuprate⁷ Yield(%)^a Substrate Product(s) Entry 0 Me 73^b(93)^c 1 Cu(CN)Li₂ A С 74 2 Α Bı Br 45^d 3 Me 81-89^b =0 4 . Cu(CN)Li2 B 5 B 75 Me₃SiO, Me₃SiO O Ĥ 63^f(84)^c 6 В Me 62^g 7 u(CN)Li₂ C 0 0 0 59^g 8 n

Table I.1,4-Acylations of Enones by Mixed Allylic Cyanocuprates Under a CO
Atmosphere in THF/Et2O/pentane at -110° for <5 minutes.</th>

^aIsolated, fully characterized products. ⁵A 12:1 mix of *trans:cis* isomers by VPC. ^cBased on recovered educt. ^dThe 3° alcohol resulting from 1,2-allylation was isolated in 43% yield. ^eReaction time: 30 min. ^fA 1.7:1 mix of diastereomers. ^gThe products from γ -acylation predominated, $\gamma/\alpha > 30:1$ by VPC. (silica gel, eluted with 15:85 ethyl acetate/hexanes) afforded the desired 1,4-dicarbonyl compound (266 mg, 74%) as a colorless oil: R_f (15:85 ethyl acetate/hexanes) 0.33; IR (NaCl, thin film) 3090, 3030, 2970, 2940, 2880, 1710, 1640, 1590, 1390, 1370, 1240, 1035, 825 cm⁻¹, ¹H NMR (500 MHz, CDCl_s) & 7.35 (d, J=9.0 Hz, 2H), 6.38 (d, J=9.0 Hz, 2H) 5.98-5.91 (m, 1H), 5.15 (dd, J=1.0, 10.0 Hz, 1H), 5.08 (dd, J=1.0, 17.0 Hz, 1H), 3.93-3.86 (m, 2H) 3.46-3.26 (m, 3H), 2.96 (dd, J=9.5, 18.0 Hz, 1H), 2.50 (dd, J=4.5, 18.0 Hz, 1H), 2.31-2.21 (m, 2H), 2.11-2.01 (m, 2H), 1.88-1.81 (m, 1H), 0.85 (dd, J=1.5, 7.0 Hz, 6H); ^{1 3} C NMR (125 MHz, CDCl_s) & 210.7, 208.8, 157.5, 132.3, 130.7, 118.6, 116.2, 113.1, 65.5, 51.6, 47.4, 44.9, 42.9, 30.8, 24.6, 22.5, 22.45; HRCIMS (CH₄) calculated for (M⁺ + 1 with ^{8 1}Br) C_{1 9} H_{2 6} BrO₈ 383.1045, found 383.1069.

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References and Notes

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- (a) Lipshutz, B.H., Ellsworth, E.L., Dimock, S.H., Smith, R.A.J., <u>J Am. Chem Soc.</u>, in press (1,4-allylations); (b) Lipshutz, B.H., Elworthy, T.R., <u>J. Org. Chem.</u>, in press (couplings with vinyl triflates).
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- 7. The nature of the reagent responsible for the 1,4-acylations is unknown; hence, the cuprate drawn in Table I is simply a stoichiometric representation as shown.
- 8. Prenyl-containing reagents are surprisingly less efficient, mainly due to their subsequent 1,2-addition to the initially formed keto enolates, as illustrated below.



- Interestingly, use of TMS-Cl in these reactions led predominantly to the non-acylated materials of 1,4-addition; see also Lipshutz, B.H., Ellsworth, E.L., Siahaan, T.J., Shirazi, A., <u>Tetrahedron Lett.</u>, 1988, 29, 6677; Johnson, C.R., Marren, T.J., <u>ibid.</u>, 1987, 28, 27; Alexakis, J.A., Berlan, J., Besace, Y., <u>ibid.</u>, 1986, 27, 1047; Nakamura, E., Matsuzawa, S., Horiguchi, Y., Kuwajima, I., <u>ibid.</u>, 1986, 27, 4029; Corey, E.J., Boaz, N.W., <u>ibid.</u>, 1985, 26, 6015, 6019; Lindstedt, E-L., Nilsson, M., Olsson, T., <u>J. Organomet. Chem.</u>, 1987, <u>334</u>, 255. Matsuzawa, S., Horiguchi, Y., Nakamura, E., Kuwajima, I., <u>Tetrahedron</u>, 1989, <u>45</u>, 349. Bergdahl, M., Lindstedt, E-L., Nilsson, M., Olsson, T., <u>ibid.</u>, 1989, <u>45</u>, 535.
- 10. An attempt to acylate a β -substituted, $\alpha_{,\beta}$ -unsaturated aldehyde was not successful due to predominant 1,2-allylation.