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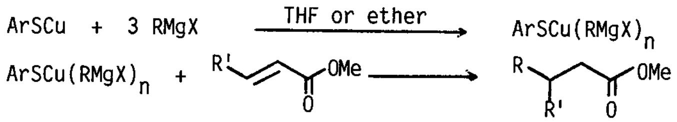
REGIOSPECIFIC ADDITION OF ORGANOCOPPER REAGENTS TO α,β-UNSATURATED ESTERS[1]

Mohammad Behforouz,* Timothy T. Curran[2] and Joseph L. Bolan
Department of Chemistry, Ball State University, Muncie, IN 47306

Abstract: Mixed cuprates ArSCu(RMgX)$_n$ add rapidly to crotonates and cinnamates to give high yields of Michael adducts. Cuprates of methyl, ethyl, isopropyl, t-butyl, phenyl and vinyl were used. Crotonates give much higher yields of adducts with cuprates using 2-methoxythiophenoxide as a ligand than with those using thiophenoxide.

In the past three decades the conjugate addition of organocopper reagents to unsaturated ketones or esters has been widely used in the synthesis of organic compounds.[3] While cuprate 1,4-additions to enones have been extensively studied, only a few investigators have reported such studies with the less reactive enoates.[4-7] Munch-Petersen and his co-workers were the first to extend the copper catalyzed addition of Grignard reagents to the α,β-unsaturated esters.[4] However, the yields were generally low; and in order to prevent 1,2-additions, either esters of hindered alcohols or bulky Grignard reagents were used. Efficient Michael additions of boron trifluoride n-butyl copper complex, n-$C_4H_9Cu{\cdot}BF_3$, to different α,β-unsaturated carbonyl systems have been reported by Yamamoto and his co-workers.[5] Higher order cuprates, $R_2Cu(CN)Li_2$ of primary, phenyl or vinyl reagents have been used successfully by Lipshutz in the conjugate additions to α,β-unsaturated esters.[6] Oppolzer has reported[7] the 1,4-addition of tri-n-butylphosphide or cyanide stabilized $RCu{\cdot}BF_3$ (R = Me, 1° and Ph) to the α,β-unsaturated esters of such optically active hindered alcohols as (-)-8-phenylmethol and in an enantioselective manner has obtained high yields of 1,4-adducts. To our knowledge, with one possible exception,[4] studies on the conjugate additions of hindered alkyl groups to enoates have not been reported.

In this communication we report the conjugate addition of both hindered and unhindered organocuprates of thiophenoxides to α,β-unsaturated esters. Organocuprates using thiophenoxide ligand were first reported by Posner to be efficient reagents for 1,4-additions to enones.[8] A similar reaction of this type was used by us for the addition of an isopropyl group to a cinnamate derivative in the total synthesis of marine allomone 9-isocyanopupukeanane.[9] Equation 1 shows the formation of organocopper reagents and their subsequent additions to cinnamates and crotonates.



Eq. 1

MgX = MgCl, MgBr; Ar = C_6H_5, o-$MeOC_6H_4$

R' = CH_3, C_6H_5; R = Me, Et, i-pr, *t*-Bu, C_6H_5, Vinyl

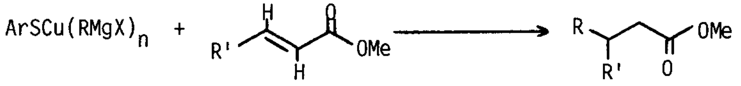
In a typical reaction procedure, 12 mmol of the Grignard reagent was dropwise added to a slurry of 4 mmol of cuprous thiophenoxide in 15 ml of dry THF or 50 ml of dry ether under an inert atmosphere at -40°. The mixture was allowed to warm until a color change indicating the formation of the complex was observed ($\sim$-15°). To this, a solution of 4 mmol of enoate in 5 ml of THF or ether was added dropwise and the reaction mixture was monitored by GC or TLC. Upon completion, the reaction mixture was added slowly with stirring to 100 ml of a cold solution of saturated ammonium chloride. The cuprous thiophenoxide precipitate was filtered off and the product was isolated from the filtrate by extraction with ether, drying, and evaporation of solvent. Based on their nmr spectra, the cinnamate products obtained were relatively pure.[10] The yields of crotonate products are based on GC analyses of ether extracts in the presence of appropriate internal standards. The cuprous thiophenoxides were prepared by the reactions of the corresponding thiols with cuprous oxide in refluxing ethanol.[8b] For efficient conjugate addition to esters three equivalents of Grignard reagent were necessary for one equivalent of ester. Under similar reaction conditions unreacted ester was obtained when lesser amounts of isopropyl magnesium chloride were used in the addition to methyl cinnamate. At this time the exact nature of the copper complex is not clear to us.

Unlike previously reported methods that were applied only to less hindered reagents[5-7] or generally gave lower yields of adducts[4], this method appears to be more general and specifically gives high yields of adducts for secondary and tertiary reagents. As illustrated in Table I, additions to cinnamates with a range of heterocuprates derived from cuprous thiophenoxide can be carried out efficiently and in high yields. However, in the crotonate reactions, 2-methoxythiophenoxide was shown to be superior and gave much higher yields than those of thiophenoxide reactions (compare numbers 7, 9 and 11 with 8, 10 and 12 in Table I).[11] Although THF was an excellent solvent for the cinnamate system, the crotonate reactions in this medium gave impure products in low yields. In line with the previous studies[6,12] we found that ether was the preferred solvent in these reactions. An ether-pentane mixture did not improve the yields of crotonate reactions. We also found that Lewis acids such as BF_3 did not have a catalytic effect on these additions.[13]

It appears that the difference in behavior between the two thiophenoxide copper reagents is due to the methoxide group. The methoxy oxygen unshared pair of electrons may bind with the metals and consequently may affect the structure and aggregation states of the complexes.[14] It may also change the stability and the structure of the original π complex between the heterocuprate and the enoate system.[15] To expand the theoretical basis for understanding these observations, our future studies will focus on the nature of copper complexes of this type. Further studies on the effects of other substituents, specifically those promoting enantioselective conjugate additions, will be reported in due course.

TABLE I

$$\mathrm{ArSCu} + 3\ \mathrm{RMgX}^{a} \longrightarrow \mathrm{ArSCu(RMgX)}_n$$ **(Step 1)**



(Step 2)

					Step 1 Conditions		Step 2 Conditions		
No.	R	R'	Ar	Sol.	Addition min (°C)	Stirring min (°C)	Addition min (°C)	Stirring min (°C)	% Yield
1	Me	Ph	Ph	T[b]	10 (-40)	20 (-15)	20 (-15)	90 (-10 to -5)	84
2	Et	Ph	Ph	T	10 (-40)	20 (-15)	30 (-5 to 0°)	15 (-5 to 0)	92
3	i-Pr	Ph	Ph	T	10 (-40)	20 (-15)	20 (-15)	60 (-10 to -5)	86
4	*t*-Bu	Ph	Ph	T	10 (-40)	20 (-15)	20 (-15)	90 (-10 to -5)	87
5	V[c]	Ph	*o*-MeOPh	E[d]	20 (-40)	5 (-40)	20 (-40)	180 (-40)	100
6	V	Ph	Ph	E	25 (-40)	5 (-40 to -25)	20 (-40)	150 (-40)	90
7	Me	Me	*o*-MeOPh	E	20 (-40)	10 (-10)	20 (-70)	40 (-70) 60 (-20 to -10)	67[e]
8	Me	Me	Ph	E	same		same		33[e]
9	Et	Me	*o*-MeOPh	E	15 (-40)	20 (-25)	25 (-70)	60 (-70) 60 (-40) Warmed to 0	94
10	Et	Me	Ph	E	same		same		41[e]
11	i-Pr	Me	*o*-MeOPh	E	20 (-40)	15 (-15)	20 (-70 to -60)	75 (-40 to -35)	95
12	i-Pr	Me	Ph	E	same		same		60[e]
13	Ph	Me	*o*-MeOPh	E	20 (-40)	20 (-40)	20 (-40)	120 (-40) Warmed to -25	100

a) For R = i-Pr and Ph X = Cl, otherwise bromide Grignard reagents were used.

b) T = THF c) V = vinyl d) E = ether

e) GC showed no starting materials but some higher boiling by-products were observed.

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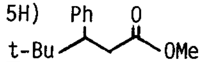
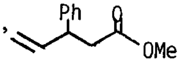
References and Notes:

1. Presented in part at the 190th ACS National Meeting, Chicago, IL, September 8-13, 1985, Org. Sect. Abstract 117.
2. A Ball State University Honors College Undergraduate Fellow.
3. (a) G. H. Posner, *Org. React.*, **19**, (1972)
   (b) G. H. Posner, "An Introduction to Synthesis Using Organocopper Reagents," Wiley: New York (1980)
   (c) H. O. House, *Acct. Chem. Res.*, **9**, 59 (1976)
   (d) E. Erdik, *Tetrahedron*, **40**, 641 (1984)
4. J. Munch-Petersen, *Bull. Soc. Chim.*, 471 (1966) and references therein.
5. (a) Y. Yamamoto and K. Marayuma, *J. Amer. Chem. Soc.*, **100**, 3240 (1978)
   (b) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Marayuma, *J. Org. Chem.*, **47**, 119 (1982)
6. B. H. Lipshutz, *Tetrahedron Letters*, 127 (1983)
7. (a) W. Oppolzer and H. J. Loher, *Helv. Chim. Acta*, **64**, 2808 (1981)
   (b) W. Oppolzer, R. Moretti, T. Godel, A. Meunier and H. Loher, *Tetrahedron Letters*, 4971 (1983)
8. (a) G. H. Posner, C. E. Whitten and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 7788 (1973)
   (b) G. H. Posner, D. J. Brunelle and L. Sinoway, *Synthesis*, 662 (1974)
9. E. J. Corey, M. Behforouz and M. Ishiguro, *J. Amer. Chem. Soc.*, **101**, 1608 (1979)
10. All products gave satisfactory spectral data. Except for methyl 4,4-dimethyl-3-phenylpentanoate (no. 4) and methyl 3-phenyl-4-pentenoate (no. 5), the remaining products are known. Methyl 4,4-dimethyl-3-phenylpentanoate; bp 95-100°/1.2 mm.
    ^{1}H nmr ($CDCl_3$) 0.85 (s, 9H), 2.6-3 (m, 3H), 3.4 (s, 3H), 7.1 (s, 5H)
    ms m/z 220 ($M^{\cdot+}$), 164, 121, 104, 91, 77

    Methyl 3-phenyl-4-pentenoate; bp 80-90°/0.5 mm.
    ^{1}H nmr ($CDCl_3$) 2.67 (d, 2H), 3.55 (s, 3H), 3.81 (m, 1H), 4.86 (m, 1H), 5.1 (m, 1H), 5.6-6.2 (m, 1H), 7.15 (s, 5H)
    ms m/z 190 ($M^{\cdot+}$), 130, 117, 115, 91, 77

11. While phenyl cuprate was added in a 1,4-fashion to methyl crotonate (Table I, number 13) methyl cinnamate with this reagent gave high yields of 1,3,3-triphenyl-1-propanone (1,2 and 1,4-additions) in the presence of either thiophenoxides and in ether or in THF.
12. H. O. House and J. M. Wilkins, *J. Org. Chem.*, **43**, 2443 (1978)
13. A. B. Smith, III and P. J. Jerris, *J. Amer. Chem. Soc.*, **103**, 194 (1981)
14. (a) B. H. Lipshutz, J. A. Kozolowski and C. M. Breneman, *J. Amer. Chem. Soc.*, **107**, 3197 (1985)
    (b) K. R. Stewart, J. R. Lever and M.-H. Whangbo, *J. Org. Chem.*, **47**, 1472 (1982)
15. (a) S. R. Krauss and S. G. Smith, *J. Amer. Chem. Soc.*, **103**, 141 (1981)
    (b) E. J. Corey and N. W. Boaz, *Tetrahedron Letters*, 3063 (1984)
    (c) G. Hallnemo and C. Ullenius, *Tetrahedron Letters*, 395 (1986)

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