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CHEMOSELECTIVE AND STEREOSELECTIVE ADDITION OF ORGANOCUPRATES TO α-OXOKETENE DITHIOACETALS

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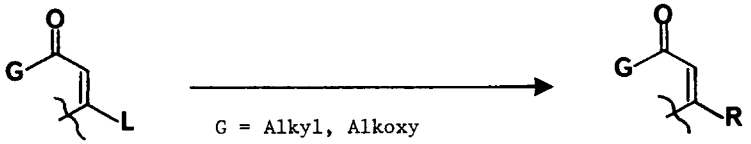
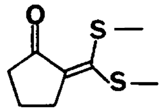
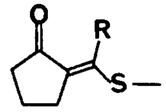
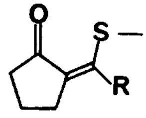
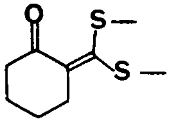
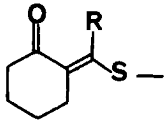
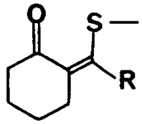
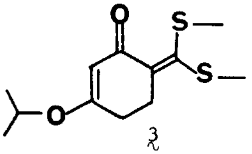
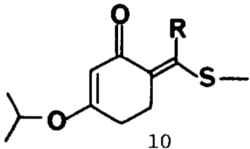
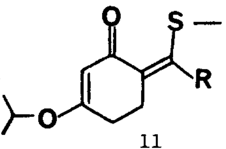
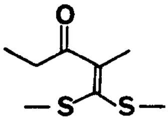
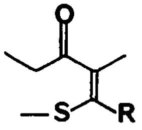
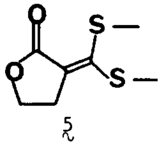
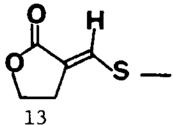
Abstract: The chemoselective and stereoselective addition of organocuprates to cyclic α-oxoketene dithioacetals affords predominately the *E* vinylogous thioesters. An acyclic α-oxoketene dithioacetal affords the *Z* vinylogous thioester stereoselectively. The observed selectivities are dependent upon substrate structure and the organocopper reagent.

The chemoselective conjugate addition of organocuprates to α,β-unsaturated ketones and esters containing a good leaving group at the β-carbon atom constitutes a versatile synthetic route to β-substituted α,β-unsaturated ketones and esters. The reaction has been observed for substrates containing halide,[1] acetate,[2] phosphate,[3] alkoxy,[4,5e] and alkylthio[5] substituents as the leaving group. Generally, the substitution occurs stereoselectively in acyclic substrates[1f,2,3,5b-d] and the procedure has been exploited for the stereoselective synthesis of trisubstituted olefins.[2,3,5b-d] Similarly, α-oxoketene dithioacetals have been reported to undergo organocopper conjugate addition reactions in a relatively non-selective process to afford α-alkylidene or α-tertiary alkyl ketones.[6] We report our observations detailing the chemoselective and stereoselective addition of organocuprates to α-oxoketene dithioacetals to afford vinylogous thioesters. This represents, to our knowledge, the first study of an efficient and selective addition of organocuprates to enones containing two good leaving groups at the β-carbon atom. The chemoselective conjugate addition of a single alkyl group permits the efficient utilization of the α-oxoketene dithioacetal functionality for sequential carbon-carbon bond formation.



Ketene dithioacetals 1 - 5 were readily prepared according to an established procedure.[7] Initially, it was observed that some degree of chemoselectivity could be achieved by control of the reaction temperature. Treatment of enone 1 with 1.5 equivalents of lithium dimethylcuprate in ether at -50°C and -78°C afforded vinylogous thioester 6 in 46% and 65% yield respectively. It was anticipated that higher yields and greater chemoselectivity might be obtained by utilizing a more stable less reactive mixed cuprate. In the event, treatment of 1 with lithium phenylthiomethylcopper[8] in THF[9] (entry 1, Table 1) afforded 6 in 70% yield. Large scale experiments afforded the diastereomer 7 in less than 2% yield. Ketene dithioacetals 1 - 3 similarly underwent conjugate addition of lithium phenylthiomethyl (entries 4,5) or *n*-butylcopper (entry 2) to afford the *E* vinylogous thioesters as the predominate diastereomers.

Table 1. Conjugate Addition of Organocuprates to Conjugated Ketene Dithioacetals

Entry	Substrate	R[a]	Product(s)[b] (% Yield)[c]	
	 1		 6	 7
1		a. CH_3	70	2
2		b. n-Bu	65	——
3		c. $(CH_3)_3C$	72 (1:1)[d]	
4	 2	CH_3	 8 58	 9 17
5	 3	CH_3	 10 78	 11 6
6	 4	CH_3	 12 70	
7	 5	CH_3	 13 60	

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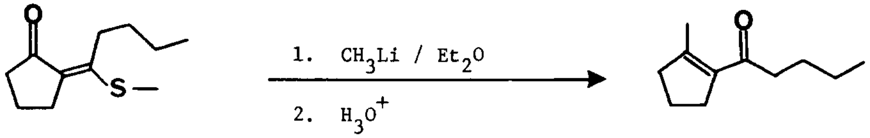
[a] The mixed cuprates [RCuSPh]Li were employed. Reactions were run in THF between -78°C and 0°C. [b] See reference 14. [c] All yields are based upon isolated products purified by column chromatography on silica gel. [d] This mixture of diastereomers was not separated.

Reaction of **1** with lithium phenylthio-tert-butylcopper afforded an equimolar mixture of diastereomers **6c**:**7c** (entry 3). Entries 1-3 reveal that the stereoselectivity of the reaction is affected by the steric bulk of the organocopper alkyl group. Treatment of the acyclic substrate **4** with lithium phenylthiomethylcopper (entry 6) afforded a single vinylogous thioester which proved to be the Z isomer (**12**). Lactone **5** (entry 7) afforded the reduction product **13**.

Diastereomers **6a**, **7a** and **8** - **11** were individually isolated and the geometry about the double bond initially determined from the proton magnetic resonance (pmr) spectra. The E vinylogous thioesters **6a**, **8**, and **10** displayed downfield vinyl methyl absorptions (δ 2.50, 2.38 and 2.45 respectively) compared to the Z vinylogous thioesters **7a**, **9**, and **11** (δ 2.15, 2.14 and 2.10 respectively). These chemical shift trends are in accord with the vinyl methyl absorptions reported for pulegone[10] and α-isopropylidinecyclopentanone.[11] The assignments were consistent with a study of the lanthanide induced shifts in the pmr spectra of **8** and **9**. Additional evidence for the assignments was obtained from the UV spectra. The E diastereomers **6a**, **8**, and **10** gave more intense absorption bands at shorter wavelengths [$\lambda_{max}^{ethanol}$ (ε): 311 (24,000), 307 (18,000), and 321 (18,500) respectively] than the corresponding Z diastereomers **7a**, **9**, and **11** [$\lambda_{max}^{ethanol}$ (ε): 322 (16,000), 320 (12,000), and 332 (12,500) respectively] in accord with previous observations.[12] Structural assignments for vinylogous thioesters **6b** and **7b** were determined from the UV spectra [$\lambda_{max}^{ethanol}$ (ε): 312 (18,500) and 322 (13,500) respectively]. Vinylogous thioester **12** displayed a UV [$\lambda_{max}^{ethanol}$ (ε): 298 (12,000)] absorption suggestive of the Z isomer.

The pure vinylogous thioesters displayed a tendency to undergo isomerization upon standing as CCl_4 solutions or neat samples. Isomer **9** was observed to isomerize quantitatively to **8** upon standing in CCl_4 for several days, whereas **6b** afforded a 96:4 mixture of **6b**:**7b**. Similarly, the E/Z mixture of **6c**:**7c** was slowly converted to the Z isomer [$\lambda_{max}^{ethanol}$ (ε): 318 (6,600)].



6b **14**

The chemoselective addition of organocuprates to α-oxoketene dithioacetals may be exploited as a key step in a 1,3-carbonyl transposition methodology that permits sequential regioselective carbon-carbon bond construction. Treatment of vinylogous thioester **6b** with methyllithium followed by acid catalyzed hydrolysis[13] affords transposed enone **14**[14] (60% yield). Consequently, a three step procedure is available for converting a ketone to a homologous β-substituted α,β-unsaturated ketone. The chemoselective and stereoselective addition of organocuprates to α-oxoketene dithioacetals, as described above, provides a versatile method for carbon-carbon bond constructions. Currently, investigations into other kinds of synthetic applications of this methodology are underway in our laboratory.[15]

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15. We are currently exploring the potential of this reaction as a method for effecting diastereoselective aldol condensations.

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