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BIS-β,β′-CONJUGATE ADDITION

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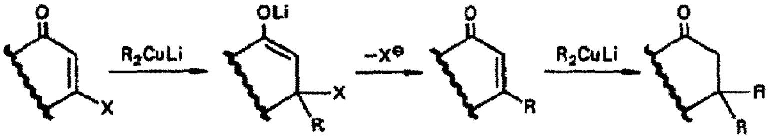
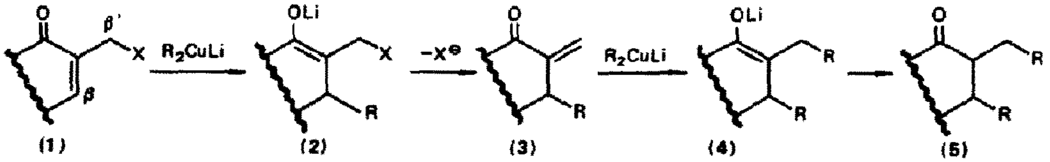
Summary: Addition of organocuprates to α,β-enones which possess on the β'-carbon a heteroatom substituent leads in good to excellent yield to β,β'-dialkylated ketones. This process is termed bis-β,β'-conjugate addition.

In the early 1970's a number of research groups lead by Coates, Posner, Casey, Piers and Mis explored 1,4-conjugate addition of dialkyl and diaryl organocuprates to enones possessing on the carbon a variety of heteroatom substituents (i.e. OAc[2a], OCH$_3$[2b,c], SPh[2b], and halide[2d]). Depend upon the specific reaction conditions including stoichiometry, these investigators demonstrated i several cases that one could isolate either the mono- or dialkylated ketone. The overall reactio sequence was suggested to involve initial 1,4-conjugate addition to generate an enolate which und the reaction conditions expels the β-heteroatom substituent; 1,4-conjugate addition of a second equivalent of cuprate then affords the dialkylated product.



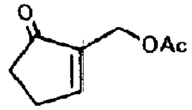
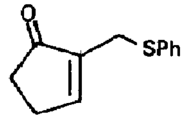
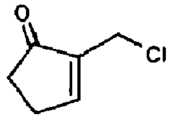
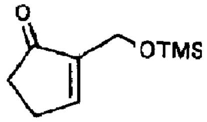
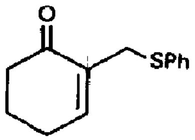
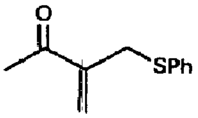
In connection with our study of the novel synthons available through application of the α-ke vinyl anion equivalent methodology recently developed in our[3] and other laboratories,[4-6] we have covered a new, albeit related conjugate addition reaction process. Consider for example, 1,4-conjugate addition of a nucleophile to the β-carbon of enone 1. The initial result would be enolate subsequent collapse of this enolate via expulsion of the β'-substituent would then generate a new enone system α,β' to the original enone (i.e. 3); 1,4-addition of a second nucleophile, possibly ferent from the first, would then lead to a β,β'-dialkylated product. We term this process bis-β conjugate addition.[7]



To explore the generality of this reaction process we subjected several enones, possessing on the β'-carbon a heteroatom substituent, to readily available organocuprate reagents;[8] in each case an excess (ca. 2.2-3.3 equivalents) of cuprate was employed. Our results are illustrated in Tabl

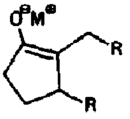
(1) (5)

Table I. Bis-β,β'-conjugate Additions

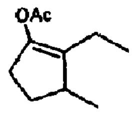
Entry	*Enone* (1)	*R*	*Yield*[9] (*percent*)	*Product ratio* (*trans:cis*)
a		Me	66	4:1
b		*n*-Bu	62	5:1
c		Ph	80	>20:1
d		Me	76	4:1
e		*n*-Bu	60	5:1
f		Ph	80	>20:1
g		Me	52	4:1
h		Me	72	3:1
i		*n*-Bu	63	5:1
j		Me	77	8:1
k		*n*-Bu	61	ND
l		Me	64	—
m		*n*-Bu	90	—

ND = ratio not determined.

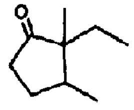
Several comments concerning these and related observations are in order. First, bis-β,β'-conjugate addition is both an efficient and general process resulting in the generation of new carbon carbon bonds at the β and β'-centers.[9a] Yields of isolated products,[9] while not maximized, were good. Furthermore, both cyclic and acyclic systems participate equally well. Second, with one exception (vide infra) the process appears to be independent of the nature of the β'-heteroatom su stituent. Third, when protonation of the penultimate intermediate (i.e. enolate 4) can take place to afford a diastereomeric mixture, the trans isomer was found in every case either to be the exclusive product, or at the very least, to greatly predominate the product mixture (ca. > 4:1). In tial stereochemical assignments here were based on ^1H and/or ^{13}C NMR observations,[10] in conjunctio with the generally accepted principle that the relative stability of transition states leading to product formation via protonation of epimerizable carbanions usually reflects the stabilities of t products.[11] To confirm these assignments in the case of 5a and 5j we subjected pure samples of bo the cis and trans isomers to base catalyzed equilibration (NaOAc/MeOH). The equilibrium mixture f 5a was 7:1 trans:cis while that for 5j was 2:1. Fourth, given that the penultimate intermediate o the bis-β,β'-conjugate addition reaction coordinate is an enolate (e.g. 4), we explored the feasib lity of generating a third bond either at oxygen or carbon. The site of bond formation would, of course, depend on the nature of the electrophile. To this end, we subjected the enolate derived v addition of $LiMe_2Cu$ to 1a to the electrophiles Ac_2O and MeI. Treatment with Ac_2O resulted in 50% yield[12] of enol acetate 6, while methyl iodide afforded 2,3-dimethyl-2-ethyl cyclopentanone (7) al beit in only poor yield (ca. 5%).[12]



(4)

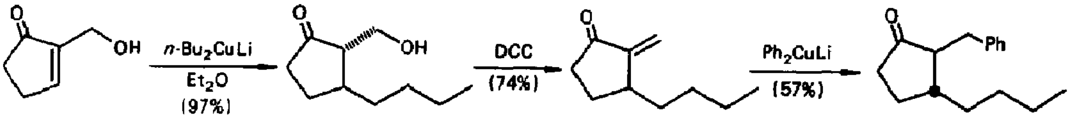


(6)



(7)

Finally, although to date we have not been successful in devising reaction conditions which would allow a "one-pot" sequential introduction of two different substituents at the β and β'-cent respectively, we have developed an alternative efficient protocol. This strategy is illustrated b low with the synthesis of trans-2-benzyl-3-n-butylcyclopentanone (11). Specifically, treatment of 8 with 2.2 eq. of $(nBu)_2CuLi$ affords monoadduct 9 in near quantitative yield (ca. 97%). Dehydration employing the conditions of Rouessac $(DCC/CuCl/Et_2O)$[13] then yields exo-methylene ketone 10, whic in turn affords the desired product (11) upon 1,4-conjugate addition of Ph_2CuLi.



(8) (9) (10) (11)

Although we illustrated here the bis-β,β'-conjugate addition reaction sequence with organocuprate reagents, there is no reason to believe that this overall process should not be general for a wide variety of nucleophiles. Studies directed to this end are currently in progress in our laboratory.

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References and Footnotes

1. Camille and Henry Dreyfus Teacher Scholar, 1978-1983; Recipient of a National Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985.

2. a) C. R. Casey, D. F. Marten and R. A. Boggs, Tetrahedron Letters, 2071 (1973); see also C. P. Casey and D. F. Marten, Syn. Commun., 3, 321 (1973); b) R.M. Coates and R. L. Sowerby, J. Am. Chem. Soc., 93, 1027 (1971); G. H. Posner and D. J. Brunelle, Chem. Commun., 907 (1973); see also R. M. Coates and L. O. Sandefur, J. Org. Chem., 39, 275 (1974),; c) S. Casshi A. Caputo and D. Misiti, Ind. J. Chem., 12, 325 (1974); d) E. Piers and I. Nagakura, J. Org. Chem., 40, 2694 (1975); E. Piers, C. K. Lau and I. Nagakura, Tetrahedron Letters, 3233 (1976)

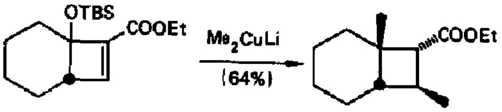
3. M. A. Guaciaro, P. M. Wovkulich and A. B. Smith, III, Tetrahedron Letters, 4661 (1978); also see S. J. Branca and A. B. Smith, III, J. Amer. Chem. Soc., 100, 7767 (1978).

4. J. Ficini and J.-C. Depezay, Tetrahedron Letters, 4797 (1969).

5. H. O. House and W. C. McDaniel, J. Org. Chem., 42, 2155 (1977).

6. M. J. Manning, P. W. Raynolds and J. S. Swenton, J. Am. Chem. Soc., 98, 5008 (1976); also see P. W. Raynolds, M. J. Manning and J. S. Swenton, Chem. Commun., 499 (1977).

7. To our knowledge the only previous example of bis-β,β'-conjugate addition, illustrated below, was reported by R. D. Clark, Syn. Commun., 325 (1979).



8. For a review of organocuprate conjugate addition reactions see: G. H. Posner, Org. Reactions, 19, 1 (1972).

9. a) The structure assigned to each new compound was in accord with its infrared and 220, 250 or 360 MHz NMR spectra. Analytical samples of all new compounds, obtained by recrystallization or chromatography (VPC, LC or TLC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high resolution mass spectrometry. b) All yields recorded here are based upon isolated material which was > 97% pure.

10. Evident here is the generalization observed by Pfeffer and Osman [J. Org. Chem., 37, 2425 (1972)] that C(3)-methyl substituents in the cis isomers of 2,3-dialkyl cycloalkanones appear upfield ($\Delta\delta$ 0.22-0.26) relative to that of the corresponding methyl in the trans isomer [eg. cis-5a: δ_{3CH_3} = 0.87; trans-5a: δ_{3CH_3} = 1.15; cis-5j: δ_{3H} = 0.82; trans-5j: $3CH_4$ = 1.04]

11. M. J. Robinson, Tetrahedron, 21, 2475 (1965). For example Vandewalle has demonstrated that kinetic protonation of the thermodynamic lithium enolate of 2,3-dimethylcyclopentanone derived via lithium in liquid ammonia reduction of 2,3-dimethylcyclopentenone affords a 3:1 mixture with the trans isomer predominating over the cis; see: M. Samson, P. DeClerq and M. Vandewalle, Tetrahedron, 31, 1233 (1975).

12. Although extremely attractive from the synthetic point of view, the capture of cuprate generated enolates is not in general an efficient process; for a discussion of this problem see: R. Davis and K. G. Untch, J. Org. Chem., 44, 3755 (1979).

13. C. Alexandre and F. Rouessac, Bull. Chem. Soc. Fr., 1837 (1971).

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