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HMPA-MEDIATED CONJUGATE ADDITION OF ALKYL- AND PHENYLTHIOALLYL ANIONS TO CYCLOPENTENONE

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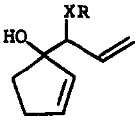
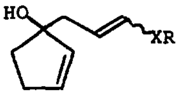
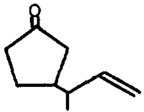
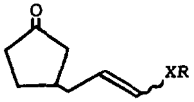
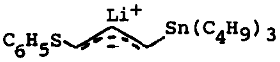
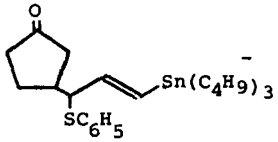
Abstract: One equivalent of HMPA induces 1,4-addition of the title anions predominantly through the α-position to cyclopentenone in THF at -78°. In THF alone irreversible addition takes place to give mixtures comprising largely α- and γ-1,2 products.

Vicinal dialkylation of conjugated enones employing conjugate (1,4- or Michael) addition of an organocuprate or other "ate" complex and direct alkylation of the resulting enolate has limited synthetic utility, due to low reactivity of the latter intermediate towards alkylating agents.[1a] Although this limitation may be rather unsatisfactorily overcome by trapping the enolate as its trimethylsilyl enol ether, and generating a more reactive lithium enolate therefrom,[1b] most "conjugate-addition" routes to products containing the 2,3-dialkylcyclopentanone nucleus as a consequence of the foregoing require use of 2-cyclopentenones already bearing the appropriate substituent at C-2.[2] Current developments in the chemistry of α-sulfur and α-selenium stabilized carbanions,[3] and in particular, a growing appreciation of their reactivity towards conjugated enones[4] suggested to us that the synthetically useful alkylthioallyllithium and related reagents could be made to function as Michael donors towards 2-cyclopentenones under aprotic conditions, and thus directly generate a lithium enolate suitable for further alkylation.[5] This reaction in yielding products of defined stereochemistry and which are easily converted into the corresponding sulfoxides, and thence into the allylically transposed alcohols (see below), would considerably expedite syntheses of prostaglandin derivatives. As preliminary work in this area, we have examined the reactions of a series of the above reagents with cyclopentenone, and herewith report our results.

Addition of cyclopentenone to the anions **1a**-**1e**[6] in the THF at -78° results in immediate disappearance of the orange colour of the anion, and formation of the products indicated in the Table,[7a] which were isolated by preparative t.l.c. from reaction mixtures quenched with aqueous NH_4Cl after 5 min. at -78°.[7b] While anions **1a** and **1e** show some propensity towards α and γ-1,4-addition, in most cases, α- and γ-1,2-addition predominates. However, generation of the anion in the presence of one equivalent of hexamethylphosphoric triamide (HMPA) followed by addition of the cyclopentenone results in exclusive (and predominantly α-) 1,4-addition (Table). The α- and γ-1,2-products were not formed in detectable amounts, and the corresponding lithium alkoxides did not rearrange to the 1,4- products in THF containing HMPA, either at -78° or at 0°. All products are thus obtained under conditions of kinetic control, which contrasts with previously reported cases involving addition of α-sulfur stabilized carbanions to conjugated enones.[4b,8,9] Use of TMEDA or hexamethylphosphorus triamide in place of HMPA yielded products of 1,2-addition only.

The α-1,4-addition product **2** was quantitatively converted by *m*-chloroperbenzoic acid in dichloromethane at -78° into sulfoxide **3**[7b] and thence into the allylic alcohol **4** (75%).[10,11] An attempt to prepare **3** directly from cyclopentenone and **5** in the THF containing HMPA (1-2.5 eq.) at -78° yielded the isomeric sulfoxide **6**.[7b] This regiochemistry was also displayed by the anion **7**[12] which yielded **8**[7b] (45%). As the anion **1f**[6] undergoes α-1,4-addition in the presence of HMPA, it is clear that electronic and steric effects exerted by the tri-n-butylstannyl substituent on the regiochemistry of **1f** and **7** are negligible. The disparity in reactivities of **1a** and **5** is noteworthy.

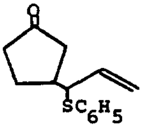
TABLE. REACTION OF ALKYLTHIOALLYLLITHIUM AND RELATED ANIONS WITH CYCLOPENTENONE

 **1**	 α-1,2[b]	 γ-1,2 (E:Z)	 α-1,4[b]	 γ-1,4 (E:Z)	OVERALL YIELD[a]
a					
R=C$_6$H$_5$,X=S in THF	60	18 (1:1.1)	12	8 (1:4.2)	85
+ 1 eq HMPA	0	0	95	5[c]	89
b					
R=(C$_6$H$_5$)$_3$C,X=S in THF	∿30[d]	∿70[d]	-	-	∿30[e]
+ 1 eq HMPA	-	-	90	10	∿30[e]
c					
R=CH$_3$,X=S in THF	64	36 (1:0.6)	0	0	87
+ 1 eq HMPA	0	0	95	5[c]	89
d					
R=t-C$_4$H$_9$,X=S in THF	42	58 (1:0.25)	0	0	78
+ 0.2 eq HMPA	27	35 (1:0.25)	38	0	85
+ 1 eq HMPA	0	0	95	5[c]	85
+ 3 eq TMEDA	41	59	0	0	80
+ 1 eq CuI	0	0	100	0	75
e					
R=C$_6$H$_5$,X=Se in THF	58	20	12	10 (1:1.9)	79
+ 1 eq HMPA	0	0	95	5[c]	81
 **1f** in THF + 2 eq HMPA	-	-		-	38

[a] Ratios of products determined by ^{1}H nmr spectroscopy. [b] Mixtures of diastereomers. [c] E:Z ratios not determined. [d] Approx. values (±10%). [e] Other unidentifed products also formed.

5 R=H

7 R=Sn(C$_4$H$_9$)$_3$



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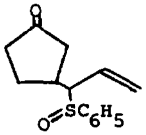

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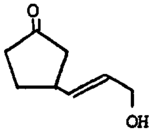

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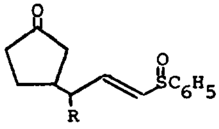

6 R=H

8 R=Sn(C$_4$H$_9$)$_3$

The sulfoxide **3** in THF containing HMPA (2.5 eq) and LDA (1.0 eq) at -78° during 10 hr did not undergo detectable conversion into **6**. Quenching reaction mixtures of **5** and cyclopentenone in THF containing HMPA (2.5 eq) at -78° after 1, 4 or 18 hr did not yield any other addition product apart from **6**, which is thus a kinetic product.

The essentially specific *α*-1,4-directing effect exerted by HMPA on the reaction of the ambident nucleophiles **1a**-**1e** with the ambident electrophile, cyclopentenone, has considerable synthetic importance. As only one equivalent of HMPA is required, it provides a more attractive alternative to the use of traditional organocopper reagents, and additionally, it is likely to enhance the reactivity of the lithium enolate resulting from the addition. It should be noted that HMPA also induces *α*-addition of related anions to saturated aldehydes and ketones.[3b,13] Replacement of the Li^+ by less electropositive counterions,[14] in particular, Cu^{+}[15] in the absence of HMPA, also results in predominantly *α*-addition to these substrates. In the present case, replacement of Li^+ in **1d** by Cu^+ using one equivalent of cuprous iodide in THF at -40°, followed by addition of cyclopentenone at -78° results in exclusive formation of the corresponding *α*-1,4-product (Table).[16] Current theory on 1,2- and 1,4-additions of anions to conjugated enones suggests that efficient solvation of Li^+ by HMPA enables frontier orbital control to operate in the 1,4-addition of the anion with conjugated enones.[8,17] In the present case insufficient literature data does not allow a prediction on the reactivity of an ambident anion, such as **1**, to be made, although the pronounced *α*-regiospecificity would require the larger atomic coefficient in the HOMO to be *α*- to the sulfur substituent.[17] A rationale for the parallel behaviour exerted by Cu^+ on the reactivity of alkylthioallyl anions towards both saturated ketones and conjugated enones is, however, less obvious.[18]

Reactions of *γ*-substituted thioallyl anions with substituted cyclopentenones and enolate trapping experiments are currently under examination.

References and Notes

1. (a) Boeckmann, R.K., *J. Org. Chem.*, 1973, **38**, 4450; Coates, R.M., and Sandefur, L.O., *ibid.*, 1974, **39**, 275; Posner, G.H., Sterling, J.J., Whitten, C.E., Lentz, C.M., and Brunelle, D.J., *J. Amer. Chem. Soc.*, 1975, **97**, 107; Greene, A.E., and Crabbé, P., *Tet. Letters*, 1976, 4867; Monteiro, H.J., *J. Org. Chem.*, 1977, **42**, 2324. (b) Patterson, J.W., and Fried, J.H., *ibid.*, 1974, **39**, 2506; Binkley, E.S., and Heathcock, C.H., *ibid.*, 1975, **40**, 2156.

2. Examples of prostaglandin syntheses employing organocuprates are summarized in "Prostaglandin Research" (Ed. P. Crabbé) (Academic Press: New York 1977); Bindra, J.S., and Bindra, R., "Prostaglandin Synthesis" (Academic Press: New York 1977). See also Trost, B.M., Timko, J.M., and Stanton, J.L., *Chem. Comm.*, 1978, 436; Buckler, R.T., and Garling, D.L., *Tet. Letters*, 1978, 2257; Chen, S-M.L., Schaub, R.E., and Grudzinskas, C.V., *J. Org. Chem.*, 1978, **43**, 3450; Hart, T.W., Metcalfe, D.A., and Scheinmann, F., *Chem. Comm.*, 1979, 156; Chen, S.M., Grudzinskas, C.V., and Dessy, F., *Prostaglandins*, 1979, **17**, 707. For conjugate addition of alanates, see Floyd, M.B., and Weiss, M.J., *J. Org. Chem.*, 1979, **44**, 71; Bernady, K.F., Floyd, M.B., Poletto, J.F., and Weiss, M.J., *ibid.*, 1979, **44**, 1438.

3. (a) Evans, D.A., and Andrews, G.C., *Accounts Chem. Res.*, 1974, **7**, 147. (b) Gröbel, B-T., and Seebach, D., *Synthesis*, 1977, 357; Warren, S., *Accounts Chem. Res.*, 1978, **11**, 401. (c) Reich, H.J., *ibid.*, 1979, **12**, 22.

4. (a) Hermann, J.L., Richmann, J.E., and Schlessinger, R.H., *Tet. Letters*, 1973, 3271, 3275; Schultz, A.G., and Yee, Y.K., *J. Org. Chem.*, 1976, **41**, 4044; Ostrowski, P.C., and Kane, V.V. *Tet. Letters*, 1977, 3549. (b) Luchetti, J., and Krief, A., *Tet. Letters*, 1978, 2697; Wilson, S.R., and Misra, R.N., *J. Org. Chem.*, 1978, **43**, 4903.

5. For an example of this sequence using lithiated trialkylstannyl- and silyl dithioacetals see Bürstinghaus, R., and Seebach, D., *Chem. Ber.*, 1977, **110**, 841.

6. These were generated from the parent sulfide or selenide (0.01 mole in THF, 40 ml) using lithium di-isopropylamide (LDA) (1.1 eq) for **1**a and **1**e, and sec-C_4H_9Li for **1**a-**1**d in THF at -78° under N_2. **1**f was generated by treatment with LDA (1.1 eq) in THF -78° of (E)-3-(tri-n-butylstannyl)-1-phenylthio-1-propene **9**,[7b] prepared in 79% yield from **1**a and $(n\text{-}C_4H_9)_3$ SnCl (1.0 eq) in THF at -78°.

7. (a) Composition of product mixtures in the Table were estimated by 100 MHz ^1H nmr spectroscopy. (b) Products were isolated from reaction mixtures by preparative t.l.c. All new compounds except for the unstable allyl trityl sulfide addition products, gave satisfactory spectral, microanalytical and/or accurate mass data.

8. For examples involving HMPA - mediated 1,4-addition of other stabilized carbanions, see Sauvetre, R., and Seyden-Penne, J., Tet. Letters, 1976, 3949; Sauvetre, R., Roux-Schmitt, M-C., and Seyden-Penne, J., Tetrahedron, 1978, 2135; Deschamps, B., Roux-Schmitt, M-C., and Wartski, L., Tet. Letters, 1979, 1377.

9. Kinetic 1,4-addition induced by HMPA has also been reported for other α-sulfur stabilized carbanions during the course of this work: Brown, C.A., and Yamaichi, A., Chem. Comm., 1979, 100; Wartski, L., El Bouz, M., Seyden-Penne, J., Dumont, W., and Krief, A., Tet. Letters, 1979, 1543. The first example is undoubtedly the HMPA-mediated conjugate addition of Grignard reagents to 2,4,6-cyclooctatrien-1-one: Ogawa, M., Takagi, M., and Matsuda, T., Tetrahedron, **29**, 3813.

10. Cleavage of the sulfenate precursor of **4** was effected using either $(C_6H_5)_3P$ or $(CH_3O)_3P$ (2 eq) in methanol during 24 hr. Yields from sulfoxides analogous to **3** but bearing a γ-alkyl substituent are higher: Lüthy, C., Konstantin, P., and Untch, K.G., J. Amer. Chem. Soc., 1978, **100**, 6211; Kondo, K., Unemoto, T., Yako, K., and Tunemoto, D., Tet. Letters, 1978, 3927.

11. Corey, E.J., and Wollenberg, R.H., J. Org. Chem., 1975, **40**, 2265.

12. This was prepared in situ from **5** and $(n\text{-}C_4H_9)_3$ SnCl (1.0 eq) in THF at -78°, followed by addition of LDA (1.1 eq). The presumed intermediate, (E)-3-(tri-n-butylstannyl)-1-phenylsulfinyl-1-propene (**10**) is unstable at 0°.

13. Atlani, P.M., Biellmann, J.-F., Dube, S., and Vicens, J.J., Tet. Letters, 1974, 2665; Still, W.C., and MacDonald, T.L., J. Org. Chem., 1976, **41**, 3620. Brownbridge, P., and Warren, S., J.C.S. Perkin 1, 1977, 2272.

14. (a) Brownbridge, P., and Warren, S., J.C.S. Perkin 1, 1977, 1131; Biellmann, J.-F., and Schirlin, D., Synth. Comm., 1978, **8**, 409; Pomatkohr, M., Geiss, K-H, and Seebach, D., Chem. Ber., 1979, **112**, 1420. (b) Ericson, B.W., Ph.D. Thesis, Harvard University, 1970.

15. Oshima, K., Yamamoto, H., and Nozaki, H., J. Amer. Chem. Soc., 1973, **95**, 7926.

16. With 2-cyclohexenone, **1**a and **1**c with Mg,Zn or Cd derived counterions yield primarily α-1,2-products only.[14b]

17. Lefour, J-M., and Loupy, A., Tetrahedron, 1978, 2597.

18. Cu^+ is unlikely to complex with the carbonyl oxygen of cyclopentenone in the reaction of the organocopper reagent derived from **1**d.[17] However, one equivalent of LiI is also present in the reaction mixture; this is presumably associated initially with the organocopper reagent, and thence with the Cu(1) species produced after addition.

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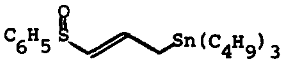

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