

CONJUGATE ADDITION OF (TRIMETHYLSTANNYL)COPPER REAGENTS TO α,β -ACETYLENIC
N,N-DIMETHYLAMIDES. TRAPPING OF THE INTERMEDIATES WITH ELECTROPHILES

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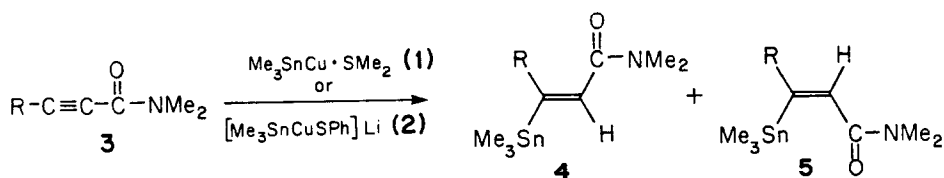
ABSTRACT: A study of the reaction of $\text{Me}_3\text{SnCu}\cdot\text{Me}_2\text{S}$ (1) and $[\text{Me}_3\text{SnCuSPh}]\text{Li}$ (2) with α,β -acetylenic N,N-dimethylamides 3 shows (a) that the overall process can be controlled experimentally so as to produce either N,N-dimethyl (E)-(4) or (Z)-3-trimethylstannyl-2-alkenamides (5), (b) that the initially formed intermediate derived from interaction of 2 and 3 is significantly more stable than that obtained by reaction of 2 and α,β -acetylenic esters, and (c) that the intermediate produced by treating 3 with 1 can be trapped with electrophiles other than proton.

Previous work^{1,2} in our laboratory showed that addition of the elements of $\text{Me}_3\text{Sn-H}$ across the triple bond of α,β -acetylenic esters by reaction of these substrates with the (trimethylstannyl)copper reagent $\text{Me}_3\text{SnCu}\cdot\text{Me}_2\text{S}$ (1) and/or the cuprate $[\text{Me}_3\text{SnCuSPh}]\text{Li}$ (2) can be controlled experimentally to provide either of the geometrically isomeric β -trimethylstannyl α,β -unsaturated esters. Subsequent investigations^{3,4} disclosed that the initial reaction of α,β -acetylenic esters with (trialkylstannyl)copper reagents is reversible and that, although protonation of the reaction intermediate(s) is efficient, it is not possible to trap the intermediate(s) with other electrophiles.

In continuing our studies of the use of (trialkylstannyl)copper reagents in organic synthesis and to assist in delineating more fully the characteristics of the reactions of these species with α,β -acetylenic carbonyl compounds, we have investigated the reaction of reagents 1 and 2 with α,β -acetylenic N,N-dimethylamides 3.^{5,6} Some of the results obtained from this study are summarized in Table I. A number of points should be made regarding these data. (a) Use of reagent 1 provides exclusively the (E)-products 4 (entries 1-3). These results, involving overall *cis* addition of the elements of $\text{Me}_3\text{Sn-H}$, are analogous to those obtained from the reaction of 1 with α,β -acetylenic esters.² (b) When ethyl 2-pentynoate is allowed to react with reagent 2 at -78°C for 3 h and the reaction mixture is then treated with a proton source, ethyl (E)- and (Z)-3-trimethylstannyl-2-pentenoate are produced in a ratio of 68:32.¹ However, if the reaction is allowed to proceed at -48°C (4 h), the (Z)-isomer is formed nearly exclusively.¹ In sharp contrast, reaction of 2 with N,N-dimethyl-2-butyneamide (3, R=Me) under either of these sets of conditions produced only the (E)-butenamide 4 (R=Me) (entries 4,5). Similar results were obtained with other substrates (entries 6-7). Thus, it appears that the initially formed intermediate obtained from reaction of 2 with 3 is significantly more stable than that derived from the analogous

reaction of **2** with acetylenic esters (*vide infra*). (c) It was not surprising to find that the reaction of **2** with **3** (R=t-Bu) was sluggish. However, interestingly, when this transformation was carried out in THF at -48°C , the major product was the (E)-isomer **4** (R=t-Bu) (entry 8). This result is in clear contrast to that observed in the reaction of **2** with ethyl 4,4-dimethyl-2-pentynoate, since attempts to find conditions to convert the latter substance into ethyl (E)-4,4-dimethyl-3-trimethylstannyl-2-pentenoate were unsuccessful. Under all conditions tried, the (Z)-product was produced predominantly.² Thus, again, it appears that the intermediate derived from **3** (R=t-Bu) is considerably more stable than that obtained from the corresponding ester. (d) Considerable effort was expended in attempts to find conditions which would effect the stereoselective conversion of **3** into the (Z)-product **5**. Eventually, it was found that addition of a less polar solvent (hexanes or ether) to the reaction medium, along with a temperature increase ($-48^{\circ}\text{C} \rightarrow 0^{\circ}\text{C}$) led to an efficient, stereoselective formation of the unsaturated amides **5** (entries 9-12). That solvent modification was crucial to the formation of **5** was shown by carrying out the reaction of **3** (R=Me) with **2** in THF at -20°C for 6 h. Under these conditions, only 7% of **5** (R=Me) was formed.

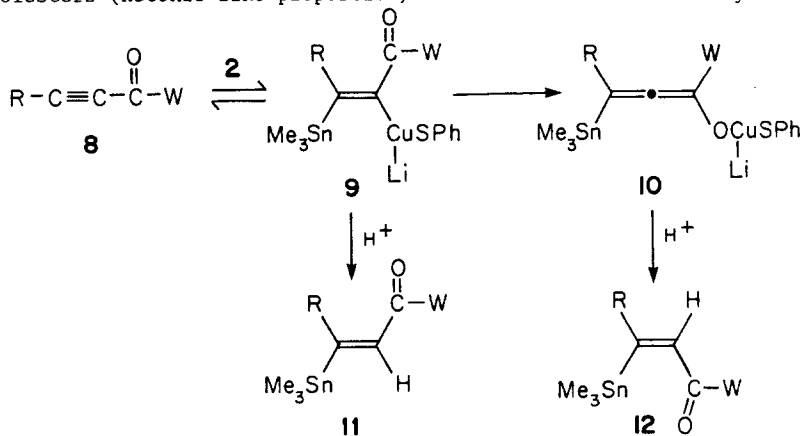
TABLE I



Entry	R	Reagent ^a	Conditions ^b	Ratio, 4 : 5 ^{c,d}	Yield (%) ^e
1	Me	1	A	>99:<1	83
2	R'O(CH ₂) ₃ ^f	1	A	>99:<1	77
3	R" ^g	1	A	>99:<1	80
4	Me	2	A	>99:<1	76
5	Me	2	B	>99:<1	80
6	R'O(CH ₂) ₃ ^f	2	A	>99:<1	76
7	R" ^g	2	A	>99:<1	76
8	<u>t</u> -Bu	2	C	88:12	69
9	Me	2	D	5:95	68
10	R'O(CH ₂) ₃ ^f	2	D	5:95	76
11	R" ^g	2	D	7:93	72
12	<u>t</u> -Bu	2	E	5:95	72

^a For entries 1-7 and 9-11, 1.5 equiv. of reagents **1** or **2** were used, while the reactions summarized by entries 8 and 12 were carried out with 3.0 equiv. of **2**. ^b A: THF, -78°C , 3 h; B: THF, -48°C , 4 h; C: THF, -48°C , 12 h; D: THF, -48°C , 1 h; add 2 volumes of Et₂O; -48°C , 1 h; -20°C , 1 h; 0°C , 2 h; E: THF, -48°C , 6 h; add 2 volumes of Et₂O; -48°C , 1 h; -20°C , 1 h; 0°C , 3 h. The reaction mixtures were quenched by addition of MeOH or aqueous NH₄Cl (pH 8). ^c As determined by gas-liquid chromatography. ^d The stereochemistry of **4** and **5** was determined conveniently by nmr spectroscopy. Thus, the α protons of **4** give rise to signals which show $|\underline{J}_{\text{Sn-H}}| \approx 70$ Hz, while for the corresponding protons of **5** $|\underline{J}_{\text{Sn-H}}| \approx 120$ Hz (see ref. 2). ^e Yield of the major isomer after chromatography and distillation. ^f R' = SiBu^tMe₂. ^g R" = 2-(2-cyclopentenyl)ethyl.

On the basis of earlier work,^{1,2} that discussed above, and some unpublished studies involving the reaction of **2** with α,β -acetylenic thioesters,⁷ it seems reasonable to propose that the course of the reaction of **2** with functional derivatives of α,β -acetylenic carboxylic acids may be rationalized as follows. Addition (*cis* stereochemistry) of **2** to **8** provides initially the vinylcuprate species **9** (the "kinetic intermediate") which, depending on a number of factors, may rearrange to the copper allenoate **10**.⁸ Protonation of **9** would provide **11** while, apparently, protonation of **10** gives, stereoselectively, the geometric isomer **12**. The stability of **9** depends upon a number of factors, including the nature of the reaction medium (solvent), the size of R, and/or the constitution of W. Apparently, less polar (or less coordinating) solvents (e.g. Et₂O-THF vs. pure THF) and, as one might expect, bulky R groups (e.g. *t*-Bu) tend to destabilize **9**. With respect to the nature of W, **9** is most stable when W=NMe₂, of intermediate stability when W=OR', and is quite unstable (if it is formed at all) when W=SR'. This order of stability is not entirely unexpected since one would anticipate that the likelihood of forming the allenoate species **10** would be greatest with thioesters (ketonic-like properties) and lowest with the dimethylamide substrates.

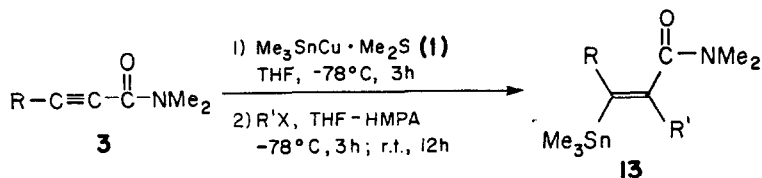


In contrast to similar attempts with α,β -acetylenic esters,^{3,4} experimentation directed towards electrophilic trapping of the intermediate(s) derived by reaction of (trimethylstannyl)copper reagents with α,β -acetylenic *N,N*-dimethylamides eventually proved to be successful. Thus, treatment of **3** (R=Me) with reagent **1**, followed by addition of HMPA and MeI, gave (87%) the unsaturated amide **13** (R=R'=Me)⁹ (see Table II, entry 1). Results obtained from experiments involving other substrates and/or alkylating agents are summarized in Table II.

Although the reactions summarized in Table II were efficient, it should be pointed out that the use of less reactive alkylating agents (even primary alkyl iodides) failed to produce the trapped products **13**. In these cases, only protonated materials (**13**, R'=H) were formed. However, we have shown¹¹ that the methylated products (entries 1, 5, 8, 9) can be alkylated at the β' position and, thus, a wide spectrum of compounds of general structure **13** are readily prepared.

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TABLE II



Entry	R	R'X	Yield (%) ^a
1	Me	MeI	87
2	Me	allyl bromide	82
3	Me	methallyl iodide	81
4	Me	dimethallyl bromide	78
5	Et	MeI	77
6	Et	allyl bromide	79
7	Et	methallyl iodide	77
8	R ^b	MeI	78
9	R ^c O(CH ₂) ₃ ^c	MeI	76

^a Yield of distilled product after purification by chromatography. ^b R^b=2-(2-cyclopentenyl)ethyl. ^c R^c=SiBu^tMe₂.

REFERENCES AND NOTES

1. E. Piers and H.E. Morton, *J. Org. Chem.*, **45**, 4263 (1980). 2. E. Piers, J.M. Chong, and H.E. Morton, *Tetrahedron Lett.*, **22**, 4905 (1981). 3. S.D. Cox and F. Wudl, *Organometallics*, **2**, 184 (1983). 4. E. Piers and J.M. Chong, *J. Org. Chem.*, **47**, 1602 (1982). 5. The substrates **3** were prepared (77-95%) by successive treatment of the appropriate 1-alkyne with MeLi (THF, -78°C → -20°C) and N,N-dimethylcarbamoyl chloride (THF, -20°C → r.t.). 6. All compounds reported herein exhibited spectra in accord with structural assignments. New compounds gave satisfactory high resolution mass spectrometric molecular mass determinations. 7. Reaction of substrates **6** with reagent **2** in THF under a variety of conditions (even at -78°C in the presence of acetic acid) gave very largely (>90%) the (Z)-product **7**. We were unable to find conditions which would provide, stereoselectively, the corresponding (E)-isomer (E. Piers and R. Urech, unpublished work). 8. Both vinylcopper and allenolate species have been proposed as intermediates in the addition of alkyl- and/or vinylcuprate reagents to α,β-acetylenic esters. For some pertinent reports, see J.P. Marino and R.J. Linderman, *J. Org. Chem.*, **48**, 4621 (1983); **46**, 3696 (1981); R.J. Anderson, V.L. Corbin, G. Cotterrell, G.R. Cox, C.A. Henrick, F. Schaub, and J.B. Siddall, *J. Am. Chem. Soc.*, **97**, 1197 (1975); J. Klein and R. Levene, *J. Chem. Soc., Perkin Trans. II*, 1971 (1973). 9. The stereochemistry of this material was shown as follows. Treatment of ethyl (Z)-2-methyl-3-trimethylstannyl-2-butenate⁴ with MeAl(Cl)NMe₂ in refluxing benzene (18 h)¹⁰ gave (58%) N,N-dimethyl (Z)-2-methyl-3-trimethylstannyl-2-butenamide, which was clearly geometrically isomeric with **13** (R=R'=Me). 10. J.I. Levin, E. Turos, and S.M. Weinreb, *Synth. Commun.*, **12**, 989 (1982). 11. E. Piers and B.A. Keay, unpublished work.

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