# TIN ANALOGS OF THE VINYLOGOUS REFORMATSKY REACTION. REGIO- AND STEREOCHEMICAL CONSIDERATIONS

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Abstract: Ethyl-4-(tri-n-butyltin)-3-methyl crotonate and ethyl 4-(tri-n-butyltin)-3-methoxycrotonate were condensed with benzaldehyde and cyclohexanone. The regio- and stereochemical profiles were determined in an effort to control the course of dienolate additions to carbonyl compounds under acid-catalyzed conditions.

Additions of ester dienolates or ester dienolate anions to carbonyl compounds remain important issues in organic synthesis. The interactions of functionalized crotonate units with carbonyls pose stereo- and regiochemical problems that are more complex than those associated with the corresponding ketone or ester enolate anion additions. Several investigations in this area have appeared in the recent years. The regiochemistry of the vinylogous Reformatsky reaction with aldehydes,[2] ketones,[2] and enones[3] has been addressed; the intramolecular version of this reaction has also been reported.[4] The reactions of dienolate anions of crotonates with carbonyl compounds have been investigated by Heathcock,[5] and Oppolzer has shown that an ester dienolate addition to enones can be controlled.[6] Silicon equivalents of processes such as the vinylogous Reformatsky reaction have also been reported,[7] and an example of a tin crotonate addition to several carbonyl compounds has recently appeared.[8]
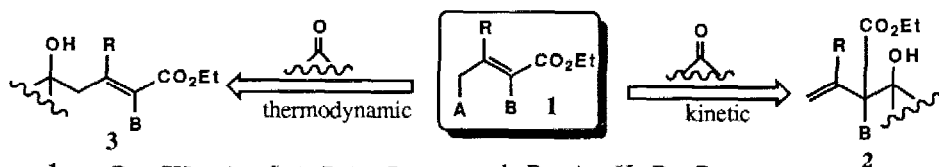

1 a. R = CH₃, A = Sn(n-Bu)₃, B = H   d. R = A = H, B = Br
   b. R = OCH₃, A = Sn(n-Bu)₃, B = H   e. R = B = H, A = Sn(n-Bu)₃ or Si(n-Bu)₃
   c. R = H, A = B = Br   f. R = H, CH₃, OCH₃, A = Sn(n-Bu)₃, B = Br

A new vinylcyclopropanation methodology based on the kinetic 1,4-α-adduct resulting from the addition of the dienolate anion of 2-bromocrotonate 1d to unsaturated carbonyl compounds was recently developed in our laboratory.[9] We wish to report on the regiochemical control in the addition of two such reagents to simple aldehydes and ketones in order to assess the potential of using more highly substituted analogs of reagent 1 in future carbon-carbon bond forming reactions. In this manuscript we examine regiochemical control in the production of adducts 2 and 3 resulting from the addition of crotonates 1a and 1b to aldehyde and ketone carbonyls.

We examined the addition of ethyl 3-methyl- and 3-methoxy(tri-n-butyltin)crotonates to benzaldehyde and cyclohexanone in anticipation that their acid-catalyzed reactions would be governed by kinetic and thermodynamic parameters observed during our study of vinylogous Reformatsky reactions.[3] The results of our study are summarized in Table 1.

Table 1. Acid-catalyzed additions of tin crotonates to carbonyls.

Carbonyl substrate	Crotonate	Conditions	Product ratios[1]			Total yield[2] (%)
			α	γ	other	
CHO (benzaldehyde)	Me⁀Bu₃Sn, E; 1a[4]; E=CO₂Et	BF₃·Et₂O, CH₂Cl₂ 2h, -78°	2a (threo) (100)			91
		BF₃·Et₂O, CH₂Cl₂ 2h at -78°, 5.5h →14° (22h)	2a (threo) (10)	4a (90)		85
		TiCl₄, CH₂Cl₂ 1h at -78°, 0.5h → -45°	2a (erythro) (45) 2a (threo) (5)		5a-Z (50)	64
		TiCl₄, CH₂Cl₂ 1h at -78°, 1.5h → -5°[3]	2a (erythro) (41) 2a (threo) (5)	3a-Z (4)	5a-Z (50)	72
	MeO⁀Bu₃Sn, E; 1b[5]; E=CO₂Et	BF₃·Et₂O, CH₂Cl₂ 2h at -78°, 2.5h → 2°	3b (85) 4b (14)		7b (1)	75
		BF₃·Et₂O, CH₂Cl₂ 2h at -78°, 4h →20°	3b (29) 4b (60)	6b (5)	7b (6)	75
O (cyclohexanone)	Me⁀Bu₃Sn, E; 1a	BF₃·Et₂O, CH₂Cl₂ 2h at -78°, 1h → -50°	8a (20)	9a (60) 10a (12)	11a (8)	80
	MeO⁀Bu₃Sn, E; 1b	BF₃·Et₂O, CH₂Cl₂ 2h at -78°, 3h → 7°		9b (94)	12b (6)	70

Notes: 1. Determined from ^{1}H-NMR analysis of aliquots. 2. Isolated yield. 3. After this point the content of α-threo began to increase. If the temperature was raised to 24 °C within one more hour, the resulting ratio of α-threo/α-erythro/3a-Z/5a-Z was 20:34:3:43. The total yield was only 45%. 4. 1a is a known compound. Dr. Yamamoto sent us its NMR spectrum, which matched ours. 5. 1b is previously unknown and is made from ethyl-3-methoxy crotonate (E isomer). The two isomers of this reagent have been separated by fractional distillation. The yields were 80% for the E isomer and 5% for the Z isomer. The stereochemical assignments were made on the basis of their ^{1}H-NMR spectra and NOE experiments.

In the reaction of **1a** with benzaldehyde in the presence of BF$_3 \cdot$Et$_2$O, only α addition occurred at -78 °C to give **2a** exclusively in the threo configuration, confirming the observation made by Yamamoto.[8] This compound was transformed to γ-lactone **4a** as a function of both time and temperature of the reaction. When pure **2a** was subjected to the conditions of the reaction, quantitative isomerization to **4a** occurred, indicating that acid-catalyzed crotonate additions may subscribe to the same principles of α/γ reversibility as the zinc-mediated Reformatsky reactions.[3] In contrast, the use of TiCl$_4$ at low temperature

2a, threo, R = Me, with BF$_3$ **3a** **4a**
2a, erythro, R= Me, with TiCL$_4$ **3b** **4b**
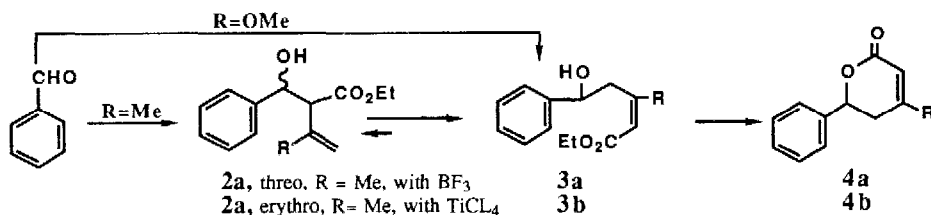
produced a mixture of threo and erythro isomers of **2a** (with the erythro isomer predominating) and the γ-hydroxy ester **3a**, which did not lactonize to **4a** under the reaction conditions. At higher temperatures the content of the threo isomer increased because of apparent equilibration. (See note 3, Table 1.) The chloro ester **5a** was produced during the reaction, presumably by simple chlorination of **3a**.

The addition of reagent **1b** to benzaldehyde proceeded via γ-addition only, leading to γ-hydroxy ester **3b** and lactone **4b**. The α-product was not intercepted even at extremely short reaction times at -78 °C. Minor products in these reaction, diene **6b** and keto ester **7b**, may have resulted from work-up.

The additions of **1a** and **1b** to cyclohexanone followed a similar course, although the selectivity was not as clear cut as in the case of benzaldehyde. The reaction profiles were determined by quenching aliquots and analyzing the product mixtures by ^{1}H-NMR, after the chemical shift parameters for each product had been made available from the spectra of pure standards. The major products were the γ-hydroxy esters **9a** and **9b** in addition to a small amount of γ-lactone **10a** and some minor products. (See Table 1.) The BF$_3$-catalyzed reaction also gave 20% of α-adduct **8a**. From careful monitoring of these reactions it appeared that, in the case of benzaldehyde, all of the starting material was channeled into the kinetic α product prior to other transformations, whereas in the case of cyclohexanone the rates for the formation of the α and the γ adducts were similar.

and / or

9a, R=Me **9b**, R=OMe **10a**, R=Me
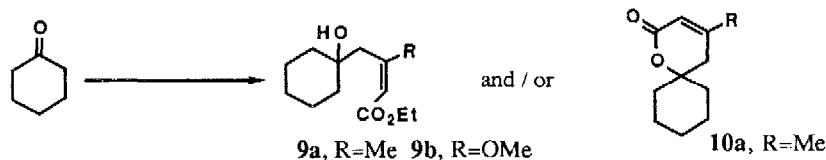
The steric integrity of reagents **1a** and **1b** under acid-catalyzed conditions has been addressed. Thus **1a** (Z isomer) was subjected to BF$_3 \cdot$Et$_2$O at -78°C without the carbonyl acceptor in an effort to detect isomerization of the reactive species. NMR analysis of aliquots indicated no changes in stereochemistry with the reagent recovered upon quenching as the original Z isomer. (Seventy percent of the material is recovered unchanged after 30 min at -78°C with complete decomposition occurring in 2 hours.) With TiCl$_4$ 70% of the material is unchanged after up to 15 min, but complete decomposition occurs in 30 min at -78 °C. Reagent **1b** (E isomer) decomposes within 30 min on exposure to TiCl$_4$ at -78 °C, but with BF$_3 \cdot$Et$_2$O

decomposition is slower (30% of material is recovered in 15 min) and isomerization of E to Z is seen (E:Z = 1:9 after 15 min, 1:20 after 30 min).

The results in Table 1 show promise with respect to the potential synthetic utility of reagents **1a** and **1b**. The α/γ selectivity, well researched for the vinylogous Reformatsky reaction,[2,3] is also possible for stannyl crotonate **1a**, whereas only γ-selectivity exists for the methoxy derivative **1b**. Although it would be premature to attempt to explain these results in detail at this time, some preliminary interpretations can be attempted. In order to assess these reagents and their behavior under acid-catalyzed conditions, several known parameters must be combined. First, the reacting species is composed of a dienolate and an allyl stannane. Thus Heathcock's explanations of selectivity based on dienolate geometry and charge density at the α versus the γ carbon must be taken into account.[5] The interpretations of Yamamoto[10] and Keck[11] regarding additions of crotyl stannanes to carbonyls under acid-catalyzed conditions must then be combined with explanations of ester dienolate behavior to arrive at a working model. For example, the stereochemistry of allylstannane addition to carbonyl compounds has been shown to be controlled by inverse additions.[11,12] As reagents **1a** and **1b** are more complex than any of their known component entities, further investigation of their chemistry is in order. A detailed mechanistic study will be conducted as a prelude to investigations aimed at the use of reagents such as **1f** for acid-catalyzed cyclopropanations.

References:

1. Recipient of the NIH Research Career Development Award (AI-00564), 1984-1989.
2. Hudlicky, T.; Rice, L.; Boston, M. C.; Finklea, H. O.; Suder, B. J. *J. Org. Chem.* **1984**, *49*, 1845.
3. Hudlicky, T.; Natchus, M. G.; Kwart, L. D.; Colwell, B. *J. Org Chem.* **1985**, *50*, 4300.
4. Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745; Hudlicky, T.; Sinai-Zingde, G.; unpublished observations.
5. Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181.
6. Oppolzer, W.; Pitteloud, R. *J. Am. Chem. Soc.* **1982**, *104*, 6478.
7. Bellassoued, M.; Gaudemar, M. *C. R. Acad. Sci. Paris* **1986**, Ser B, 199; Cunico, R. F.; Lee, H. M. *J. Am. Chem. Soc.* **1977**, *99*, 7613, Weber, W. P.; Felix, R. A. *Tetrahedron Lett.* **1971**, 1445; Cunico, F. R.; Lee, H. M.; Herbach, J. *J. Organomet. Chem.* **1973**, *52*, C7.
8. Yamamoto, Y.; Hatsuya, S,; Yamada, J. *J. Chem. Soc., Chem. Commun.* **1987**, 561.
9. Hudlicky, T.; Radesca, L.; Luna, H.; Anderson, F. E., III. *J. Org. Chem.* **1986**, *51*, 4746.
10. Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maroyama, K. *Tetrahedron*, **1984**, *40*, 2239.
11. Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927.
12. The inverse addition of benzaldehyde to a mixture of **1a** and $BF_3 \cdot Et_2O$ resulted in 20% of **3a** and decomposition of the reagent. No α product was observed.