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Stanna-Brook Rearrangement of Carboxylic Acid Derivatives. Synthetic Utility and Mechanistic Studies

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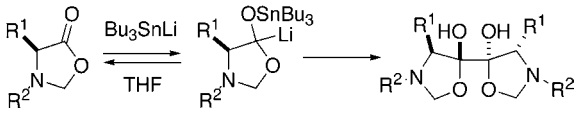
ABSTRACT



The reaction of R_3SnLi with carboxylic acid derivatives proceeds through a novel, very fast stanna-Brook rearrangement that generates α-alkoxyorganolithium compounds as intermediates. The outcome of these reactions depends on the nature of the carboxyl derivatives. Reaction of R_3SnLi with ester derivatives gives rise to coupled products through a novel C−C bond formation reaction. Experimental evidence of the detailed reaction mechanism is provided.

The reaction of organotin anions with carbonyl derivatives has found an increasing number of applications in organic synthesis.[1] Stable α-alkoxy- and α-aminostannanes have been prepared by addition of R_3SnLi to aldehydes or ketones followed by protection or displacement of the α-hydroxystannane intermediate.[1] These α-heterosubstituted stannanes are convenient precursors to α-oxy- and α-aminoorganolithium compounds, which are valuable nucleophiles.[2] Surprisingly, only a few studies on the reactions of R_3SnLi with carboxylic acid derivatives have appeared, despite the fact that these additions could provide expedient access to acylstannanes,[3] important reagents for C−C bond formation.[4] The reaction of R_3SnLi with acyl chlorides[5] is usually very low-yielding and limited to the preparation of the acyltriphenyltin derivatives.[6] Moderate yields of acylstannanes[7] have also been obtained by reaction of trialkyltinlithium reagents with esters,[8] in the presence of excess $BF_3{\cdot}Et_2O$ or with thioesters.[9] We wish to report that carboxylic acid derivatives react with Bu_3SnLi to form a new C−C bond through a novel stanna-Brook rearrangement.

We were interested in preparing enantiomerically pure α-amino-acylstannanes by an extension of our previously reported method for the synthesis of α-amino ketones,[10] which would involve the addition of Bu_3SnLi to α-amino acid-derived oxazolidinones **1**.

Treatment of *N*-phenylfluorenyl-alanine-oxazolidinone (**1a**) with Bu_3SnLi (from Bu_3SnH and LDA) in THF at −55 °C, led to a product that did not show any Bu_3Sn signals in its ^1H NMR spectrum.[11] Analysis of its spectroscopic data suggested a dimeric structure **2a** for the reaction product, which was confirmed by X-ray crystallographic analysis. No

(1) (a) Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997. (b) Sato, T. *Synthesis* **1990**, 259.

(2) (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(3) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

(4) Wyatt, P. B. *Sci. Synth.* **2003**, *5*, 423.

(5) (a) Shirakawa, E.; Yamamoto, Y.; Nakao, Y.; Tsuchimoto, T.; Hiyama, T. *Chem. Commun.* **2001**, 1926 and references therein. (b) Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 9030.

(6) Acyltins can be alternatively prepared by a Pd-catalyzed reaction from acyl chlorides and hexaalkylditin compounds: (a) Mitchell, T. N.; Kwetkat, K. *Synthesis* **1990**, 1001. (b) Mitchell, T. N.; Kwetkat, K. *J. Organomet. Chem.* **1992**, *439*, 127.

(7) Peddle, G. J. D. *J. Organomet. Chem.* **1968**, *14*, 139.

(8) Acylstannanes can also be prepared by reaction of excess aldehyde with $R_3SnMgCl$ or with R_3SnLi and an oxidant: (a) Quintard, J.-P.; Elissondo, B.; Mouko-Mpegna, D. *J. Organomet. Chem.* **1983**, *251*, 175. (b) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

(9) Capperucci, A.; Degl'Innocenti, A.; Faggi, C.; Reginato, G.; Ricci, A.; Dembech, P.; Seconi, G. *J. Org. Chem.* **1989**, *54*, 2966.

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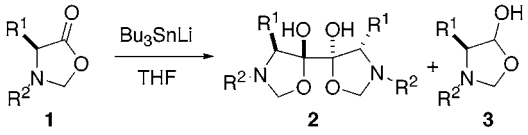
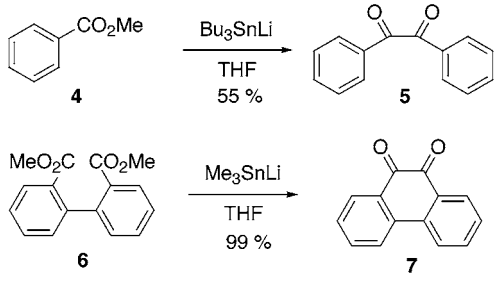
other diastereomer was observed in the crude reaction mixture. With the structure of the product firmly established, we studied the generality of this surprising C−C bond-forming process. After some experimentation we found that when Boc-protected oxazolidinones **1b**−**e** were reacted with Bu_3SnLi, dimers **2** were always obtained as the main products (Scheme 1), along with small amounts of alcohols **3** (6−8%

Scheme 1. Reactions of Carboxylic Acid Derivatives with Bu_3SnLi



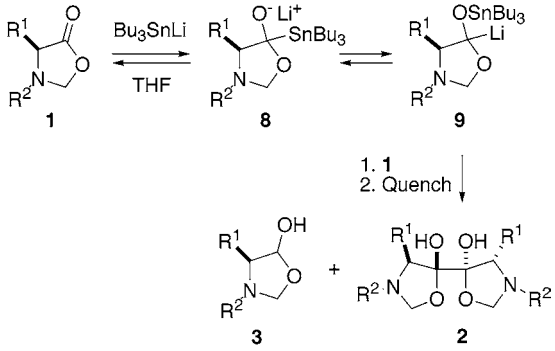
entry	product	R^1	R^2	yield
1	**2a**	CH_3	Pf	54%
2	**2b**	CH_3	Boc	63%
3	**2c**	$(CH_3)_2CH$	Boc	82%
4	**2d**	$PhCH_2$	Boc	65%
5	**2e**	$MeS(CH_2)_2$	Boc	63%



yield).[12] The reactions were very stereoselective, and mainly, or exclusively, one diastereoisomer of dimer **2** was obtained. *N*-Boc-Alanine derivative **1b** led to the corresponding product as an 8:1 ratio of diastereoisomers. *N*-Boc-Valine-derived oxazolidinone (**1c**) led to the C_2-symmetric diastereoisomer **2c** in 72% yield, whose structure was unambiguously established by X-ray crystallography. The dimer **2c** was obtained in an improved 82% yield when Bu_3SnLi prepared from hexabutylditin and *n*BuLi was reacted with **1c**. Phenylalanine derivative **1d** led to an inseparable mixture of diastereoisomers, which was equilibrated at 330 K in $CDCl_3$, to provide only the symmetrical stereoisomer **2d**. We checked that an equilibration was indeed taking place by warming a $CDCl_3$ solution of the pure unsymmetrical isomer (obtained by precipitation of the mixture from CH_2Cl_2−hexane) at 50 °C for 24 h, a procedure that yielded the symmetric isomer **2d** quantitatively. Reaction of **1e** gave a mixture of two methionine-derived dimers (63% yield) that was quantitatively transformed into pure **2e** by warming at 50 °C for 6 h. It thus appears that the dimerization is very stereoselective, and even in the less selective cases the thermodynamically favored isomer can be obtained as the sole product after equilibration of the crude reaction mixture.

Other types of esters underwent this C−C bond-forming reaction as well, both in inter- and intramolecular fashion (Scheme 1). We propose that these coupling reactions proceed via rearrangement of the initially formed stannyl adduct **8** to give α-oxy-carbanion **9** (Scheme 2). To our

Scheme 2. Proposed Mechanism

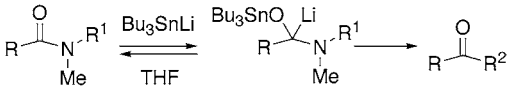


knowledge, this is the first example of a rearrangement where the stannyl group migrates from carbon to oxygen[13] in what constitutes a tin analogue of the Brook rearrangement.[14]

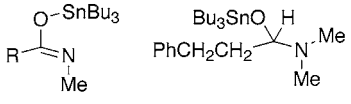
The reaction takes a different course when *silyl*-lithium reagents are used as nucleophiles. Thus, reaction of oxazolidinones **1a**,**b** with $PhMe_2SiLi$ in THF led to the corresponding acylsilanes in 69 and 72% yield, respectively. No dimers were detected in the crude reaction mixtures.

Valuable mechanistic information was derived from a series of experiments on *amide* substrates. Reaction of Bu_3SnLi with *N*-methoxyamides **10a**−**c** gave primary amides **13a**−**c** in good to excellent yields,[15] with loss of the *N*-methoxy group (Scheme 3, entries 1−3). This supports

Scheme 3. Reaction of Bu_3SnLi with Amides



entry	compound	R	R^1	R^2	product
1	**10a**	Ph	OMe	NHMe	**13a** (90%)
2	**10b**	$Ph(CH_2)_2$-	OMe	NHMe	**13b** (88%)
3	**10c**	CycloPr	OMe	NHMe	**13c** (60%)
4	**11a**	Ph	Me	H	**14a** (30%)
5	**11b**	$Ph(CH_2)_2$-	Me	H	**14b** (54%)



the intermediacy of carbanion **12**, the product of the Sn-Brook rearrangement, in the reaction, since such a species should undergo fast elimination of the β-methoxy group to give imidate **15**, which should yield the observed products upon aqueous workup. In fact, the presence of a benzimidate as an intermediate in this reaction was substantiated by

analysis of the ^{119}Sn and ^{13}C NMR spectra of the reaction mixture of **10a** and Me_3SnLi in deuterated THF before quenching (^{13}C NMR of the imidate carbon, δ 168.0 ppm; ^{119}Sn NMR of the Sn−O moiety, δ 103.2 ppm).[16]

We did not detect any ring-opened products from the reaction of cyclopropylamide **10c** with Bu_3SnLi, a result that strongly argues against the intermediacy of free radicals in this transformation, since cyclopropyl-substituted methyl radicals readily experience ring opening.[17]

This N-demethoxylation process should produce methoxide anion as a byproduct. That this is in fact the case was shown by quenching the reaction of **10a** and Bu_3SnLi with benzoyl chloride: ^{1}H NMR analysis of the crude reaction mixture showed the formation of an equimolar amount of methyl benzoate. This result rules out an alternative mechanism for this reaction, namely, the abstraction of one of the *N*-methoxy hydrogens by a base, followed by expulsion of a benzimidate anion, since formaldehyde should be formed in this process instead of methoxide.[18]

A very different outcome, but also supportive of the stanna-Brook rearrangement mechanism, was obtained from the reactions of *N*,*N*-dialkylamides. Treatment of *N*,*N*-dimethylbenzamide (**11a**) with Bu_3SnLi at 0 °C for 6 h led mainly to recovered amide when carefully dried amide **11a** was used; however, when moisture was not removed from the starting material, we observed the presence of approximately 5% benzaldehyde in the crude reaction mixture, presumably due to protonation of the small amount of anion **12** (R = phenyl, R^1 = Me) present at equilibrium. When the reaction was repeated with thoroughly dried **11a**, but now slowly adding a solution of THF−H_2O for 3 h as a quench, benzaldehyde was isolated in 30% yield.[19] Deuterated benzaldehyde (**14a**, R^2 = D) was obtained when THF−D_2O was slowly added as a quench, proving that the protonation of the carbanionic intermediate was happening during the quench and that all the steps leading to anion **12** are equilibria faster than the protonation of the stannyl-lithium nucleophile.

When the reaction was conducted with the aliphatic amide **11b**, the corresponding aldehyde was formed in good yield without the need to resort to a slow aqueous quench, since *i*Pr_2NH, present in the reaction medium as a byproduct from Bu_3SnLi generation, is acidic enough to protonate the intermediate anion **12** (R = $Ph(CH_2)_2$−, a more basic anion than its benzylic counterpart). Thus, treatment of **11b** with Bu_3SnLi (320 mol %) at 0 °C to room temperature for 48 h provided aldehyde **14b** in 54% yield.[19] When the reaction was run in deuterated THF and followed by ^{1}H and ^{13}C NMR, the formation of aminal **16**, derived from protonation of intermediate anion **12** (R = phenethyl, R^1 = Me), was assessed by the presence of a triplet at δ 4.51 ppm in the ^{1}H NMR spectrum (which disappeared after aqueous quenching) and a CH signal at δ 93.5 ppm in the ^{13}C NMR spectrum.[20]

All these observations taken together point to a common mechanism for the reaction of R_3SnLi with carboxylic acid derivatives: an initial nucleophilic addition to the carbonyl carbon followed by a fast, reversible stanna-Brook rearrangement that generates an α-oxycarbanion whose fate depends on the structure of the substrate and the reaction conditions.

In summary, we report a new and very fast stanna-Brook rearrangement of carboxylic acid derivatives upon reaction with R_3SnLi. This addition−rearrangement pathway seems to be quite common since we have observed it in reactions of several types of esters and amides with trialkyltinlithium reagents. We are currently further exploring the synthetic applications of these transformations, in particular for the preparation of the core part of a series of HIV-protease[21] inhibitors from amino-diols **2**.

Acknowledgment. Financial support from the CICYT (Grant BQU2002-01368 and a fellowship to P.G.) and the Xunta de Galicia (Grant PGIDIT03PXIC20910PN and a fellowship to M.I.C.) is gratefully acknowledged.

Supporting Information Available: Complete experimental procedures, spectroscopic and analytical data, and X-ray crystal structure data for **2a** and **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3462.

(12) For characterization purposes, the reduced products **3** were independently prepared by treatment of the corresponding oxazolidinones with $LiAlH(tBuO)_3$ in THF.

(13) (a) A different kind of anionic 1,2-stannyl rearrangement was reported: Iwamoto, K.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1999**, *574*, 171. (b) We have suggested that a similar rearrangement may be taking place in the reaction of α-aminoaldehydes and 3-oxo-azepines with Bu_3SnLi, although we could not provide any experimental mechanistic evidence: Calaza, M. I.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc.* **2001**, *123*, 2095.

(14) (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(15) Addition of $PhMe_2SiLi$ to amides **10a**,**b** led to the corresponding secondary amides **13a**,**b**, indicating that Weinreb amides undergo Brook rearrangement on reaction with Si anions.

(16) (a) A similar compound, 4,5-dihydro-4,4-dimethyl-2-phenyloxazole, showed a signal at δ 162.2 ppm in ^{13}C NMR: Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 3076. (b) See ref 1a, p 21.

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(19) Material balance is composed of starting amide.

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(21) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.