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Dearomatization−Bis-alkylation of Aromatic and Heteroaromatic Diesters Promoted by Me_3SnLi via a Stanna−Brook Rearrangement

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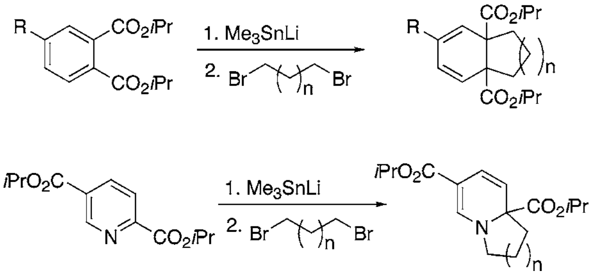
ABSTRACT



Reaction of Me_3SnLi with aromatic and heteroaromatic diesters proceeds through a fast stanna-Brook rearrangement that generates an stable bis-enolate which can be regioselectively alkylated and cyclized, in one step, to bicyclic compounds containing 6,5-, 6,6-, and 6,7-fused ring systems.

Trialkylstannyllithium reagents (R_3SnLi) have found numerous applications in organic synthesis.[1] They are easily prepared and react as nucleophiles to give stannanes of high synthetic value[2,3] upon reaction with carbonyl compounds, α,β-unsaturated carbonyl compounds, alkyl or aryl chlorides, benzotriazoles, or epoxides. In contrast, only a few examples of the addition of anionic tin nucleophiles to carboxylic acid derivatives have been reported,[4] although direct acylation of R_3SnLi with thioesters, or with esters in the presence of $BF_3{\cdot}OEt_2$, has allowed the preparation of acylstannanes in moderate yields.[5] We have recently reported[6] that R_3SnLi reagents add to carboxylic acid derivatives (esters, amides, and Weinreb amides) to give an α-alkoxystannyl adduct that suffers a stanna-Brook rearrangement where the stannyl group migrates from carbon to oxygen to give a carbanion, which then evolves differently depending on the structure of the substrate.

In this paper, we report a novel dearomatization−alkylation procedure resulting from the addition of trimethylstannyllithium to aromatic and heteroaromatic diesters, a process that does not occur by nucleophilic addition to the electron-deficient aromatic ring but instead by 1,2-addition to one of the carboxylic ester groups followed by Sn−Brook rearrangement of the initial stannyl adduct to give an stable bis-enolate. This bis-enolate can be alkylated with bis-electrophiles to provide bicyclic compounds containing 6,5-,

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[1] (a) Davies, A. G. *Organotin Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) Sato, T. *Synthesis* **1990**, 259.

[2] Marshall, J. A. *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2002.

[3] (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

[4] Wyatt, P. B. *Sci. Synth.* **2003**, *5*, 423.

[5] Capperucci, A.; Degl'Innocenti, A.; Faggi, C.; Reginato, G.; Ricci, A.; Dembech, P.; Seconi, G. *J. Org. Chem.* **1989**, *54*, 2966.

[6] Paleo, M. R.; Calaza, M. I.; Graña, P.; Sardina, F. J. *Org. Lett.* **2004**, *6*, 1061.

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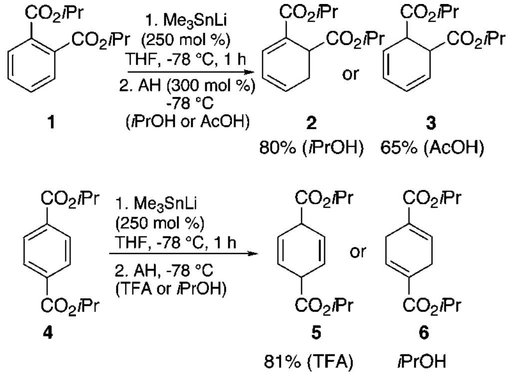
6,6-, and 6,7-fused ring systems in one step. Dearomatization of aromatic rings has been achieved by Birch reduction[7,8] or by nucleophilic addition to an electron-deficient arene that possesses groups which are either not electrophilic[9] or whose reactivity at the carbonyl group has been blocked by using hindered derivatives[10] or Lewis acids.[11]

Addition of excess Me_3SnLi (300 mol %) to phthalate **1** in THF gave, after quenching with pH 7.0 buffer, a mixture of dienes **2** and **3**. When the reaction was quenched with *i*PrOH, only **2** was observed in the ^1H NMR of the crude product (80% isolated yield). A very clean reaction was also observed when AcOH was used as the quench: **3** was the only product present in the reaction mixture (isolated in 65% yield as a 2.2:1 mixture of stereoisomers). Diene **3** proved to be quite unstable on standing and during chromatography, and it slowly underwent isomerization to the more stable isomer **2**.

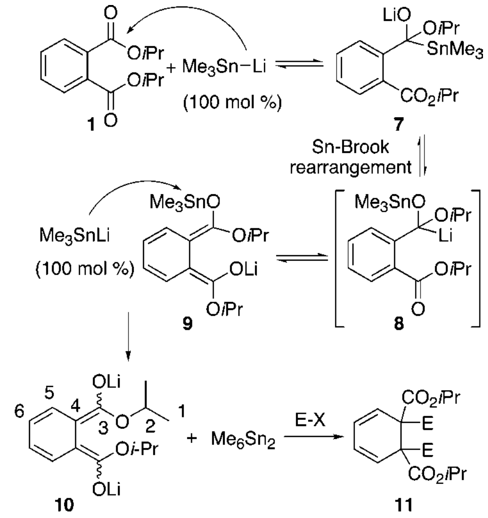
Scheme 1. Dearomatization Reactions of Aromatic Diesters



The effect of the ester group (Me, Et, Bu, *i*Pr, *t*Bu) was investigated, and it was found that the isopropyl group showed cleaner reactions. Regarding the amount of Me_3SnLi, at least 200 mol % is necessary for complete conversion as starting material was recovered when the reactions were performed using 100 or 150 mol % of Me_3SnLi. The use of 300 or 500 mol % did not lead to higher yields.[12]

A similar behavior was observed when terephthalate **4** was used as a substrate. Treatment of **4** with Me_3SnLi at −78 °C for 1 h followed by quenching with TFA allowed the isolation of the unconjugated diene **5** in 81% yield. The α,β-unsaturated diester **6** was formed when the reaction was quenched with *i*PrOH.

To explain these results, we propose the mechanism depicted in Figure 1. Addition of 100 mol % of Me_3SnLi to one of the carboxylate groups of **1** should give the stannyl alkoxyde **7**, which would then suffer a rapid Sn-Brook rearrangement to formally give α-oxy-carbanion **8** which is, actually, enolate **9**. This rearrangement should be fast due to the very stable nature of the resulting enolate. Nucleophilic displacement at tin by Me_3SnLi (second equivalent) in intermediate **9** would give the lithium bis-enolate **10** and hexamethyldistannane. Bis-enolate **10** would then undergo kinetically (AcOH or TFA) or thermodynamically (*i*PrOH) controlled protonation to provide the observed reaction products, dienes **2** or **3**, respectively.[13]



atom	1	2	3	4	5	6
^1H-NMR	1.08	4.57	-	-	6.53	5.02
^{13}C-NMR	22.8	65.2	151.2	92.5	113.2	130.0
^{119}Sn-NMR	0 and -112.5					

Figure 1. Mechanism for the partial reduction reaction and representative NMR data for intermediate bisenolate **10**. All chemical shifts in ppm.

The presence of *dilithium* bis-enolate **10** as an intermediate in this reaction was substantiated by analysis of the ^1H, ^{13}C, and ^{119}Sn NMR spectra of several reaction mixtures. When a mixture of MeLi (250 mol %) and Me_6Sn_2 (250 mol %) in THF-d_8 was treated with diester **1** (100 mol %) at −78 °C and the subsequent reaction followed by NMR, we observed the complete disappearance of starting material and the appearance of a new product which showed signals consistent with the structure of bis-enolate **10** (Figure 1).

The presence of only four signals in the ^1H NMR spectrum and of six signals in the ^{13}C NMR spectrum of the reaction mixture before quenching in THF-d_8, taken together with the upfield chemical shifts displayed by H-5 and H-6, and by C-4 and C-5, strongly suggest the formation of a symmetric bis-enolate intermediate, such as **10**. The ^{119}Sn NMR spectrum showed only two signals that can be assigned

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(8) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1.

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(10) (a) Clayden, J.; Foricher, Y. J. Y.; Lam, H. K. *Chem. Commun.* **2002**, 2138. (b) Clayden, J.; Foricher, Y. J. Y.; Lam, H. K. *Eur. J. Org. Chem.* **2002**, 3558.

(11) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091.

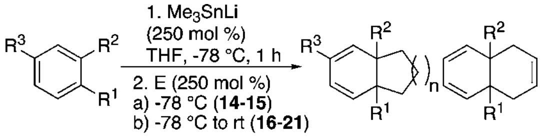
(12) For convenience, 250 mol % of Me_3SnLi (obtained by reaction of Me_6Sn_2 with MeLi at 0 °C for 15 min) was used in most of the experiments.

(13) Leading references on lithium bis-enolates in synthesis: (a) Bilyard, K. G.; Garratt, P. J.; Hunter, R.; Lete, E. *J. Org. Chem.* **1982**, *47*, 4731. (b) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125 and references therein.

to Me_4Sn (δ 0 ppm) and Me_6Sn_2 (δ -112 ppm), no other stannyl-containing product, such as a stannyl enolate like **9**, is present in the reaction mixture[14] which is supportive of the proposed mechanism. The corresponding bisenolate intermediates were also observed in the reactions of diesters **4** and **23** with Me_3SnLi (vide infra).

Since the proposed intermediate bis-enolates should be powerful nucleophiles we decided to study their reaction with bis-electrophiles, in the hope of developing straightforward access to highly functionalized bicyclic systems of great synthetic potential. Thus, treatment of diester **1** with Me_3SnLi in THF at -78 °C for 1 h, followed by addition of 1,3-diiodopropane or 1,3-propanediol di-*p*-toluensulfonate (300 mol %) afforded hydrindane diene **14** in 99% and 90% yields, respectively (see Scheme 2). When 1,4-diiodobutane was used as electrophile, unsaturated decalin **15** was obtained in 85% yield. The ring-forming dialkylation of bis-enolate **10** with 1,5-diiodopentane to build a seven-membered ring was not as straightforward as the previous examples, and the main product obtained under the usual conditions was diene **11** (E = $(CH_2)_5I$, Figure 1), which had incorporated *two* molecules of electrophile. A successful way of constructing the seven-membered ring was found, nevertheless. Thus, treatment of the reaction intermediate with only 100 mol % of 1,5-diiodopentane at -78 °C for 3 h, followed by warming up to 35 °C, afforded **16** in 71% yield. When using a functionalized bis-electrophile such as *cis*-1,4-dichloro-2-butene, the corresponding bicycle **17** was isolated in 60% yield. All bicyclic compounds were obtained with complete stereoselectivity, as only one stereoisomer was detected in the crude reaction mixtures. The products were shown to be the *cis*-fused stereoisomers by reduction of hydrindane **14** and decalin **15** to the corresponding diols (excess $LiAlH_4$ in THF at 0 °C) and X-ray diffraction analysis of these compounds (see the Supporting Information). The close similarities of the NMR chemical shifts of compounds **14**−**16** lead us to believe that the stereochemistry of the ring junction in the 6,7-fused system **16** is also cis.

Scheme 2. Dearomatizing Anionic Cyclizations of Aromatic Di- and Triesters



1, 4, 12-13 **14-16, 18-21** **17**

starting material	E	product (yield %)
1, R^3 = H	$I(CH_2)_3I$	**14**, n = 1 (99%)
$R^1 = R^2 = CO_2iPr$	$I(CH_2)_4I$	**15**, n = 2 (85%)
	$I(CH_2)_5I$	**16**, n = 3 (71%)
		**17** (60%)
4, R^2 = H	$Br(CH_2)_3Br$	**18**, n = 1 (89%)
$R^1 = R^3 = CO_2iPr$		
12, R^3 = Me	$I(CH_2)_3I$	**19**, n = 1 (60%)
$R^1 = R^2 = CO_2iPr$		
13, $R^1 = CO_2Me$	$I(CH_2)_3I$	**20**, n = 1 (99%)
$R^2 = R^3 = CO_2Me$	$I(CH_2)_4I$	**21**, n = 2 (99%)

The bis-enolate derived from the reaction of *p*-diester **4** with Me_3SnLi proved to be less reactive than its ortho analogue, and starting material was often recovered from the reaction mixture. Thus reaction of terephthalate **4** with the tin nucleophile, followed by 1,3-diiodopropane provided hydrindane **18** as a 2:1 nonseparable mixture with starting ester **4**. NMR analysis of the reaction showed the complete consumption of starting material before the addition of the electrophile, and the reformation of the starting ester and *cyclopropane*, along with the expected alkylation product **18**, afterward. These observations indicate that 1,3-diiodopropane acts partially as an iodinating agent and not only as a C-electrophile. When 1,3-dibromopropane was used as electrophile the desired bicycle **18** was isolated in 89% yield. No bicyclic products were isolated when excess 1,4-diiodobutane or 1,5-diiodopentane were used as electrophiles, the products being dialkylated compounds incorporating two molecules of the electrophile. The cis-fused nature of hydrindane **18** was tentatively established by NOE studies.

A cursory exploration of the effects of the presence of further substituents on the starting ester on the outcome of the dearomatization−cyclization sequence was carried out. The presence of alkyl substituents on the ring does not appear to adversely affect the process, since methyl-substituted phthalate **12** provided the expected bicycle **19** (isolated in 60% yield) when reacted with Me_3SnLi and 1,3-diiodopropane.

The incorporation of a third ester group into the aromatic ring of the substrate allowed us to explore the regioselectivity of the reaction. Thus, when triester **13** was submitted to the usual reaction conditions using 1,3-diiodopropane and 1,4-diiodobutane as electrophiles, the only products formed were those arising from the alkylation of the ortho-diester system, hydrindan **20** and decalin **21**, which were isolated in excellent yields.

This dearomatization−bisalkylation methodology was then applied to electron-deficient pyridines **22** and **23**, obtained from the corresponding commercially available diacids (*i*PrOH, DCC, DMAP, 70%). As can be seen from the data presented in Scheme 3, fused 6,5-, 6,6-, and 6,7-ring systems (**24**−**29**) were prepared in one step and isolated in high yields by reaction of Me_3SnLi with diesters **22** or **23** followed by addition of the appropriate diiodoalkane. Treatment of 2,3-disubstituted pyridine **22** with Me_3SnLi followed by 1,3-diiodopropane afforded a mixture of regioisomers **24** and the nitrogen analogue to **14** in approximately 1:1 ratio, this ratio increased to 9.3:1 when the harder electrophile 1,3-dibromopentane was used, and indolizidine **24** was thus

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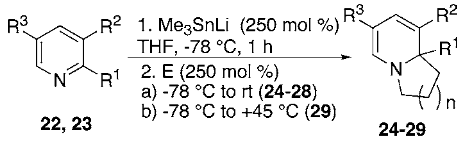
[14] It has been described that a mixture of Me_3SnLi and $Me_3SnSnMe_3$ shows a single ^{119}Sn NMR signal at a position depending on the ratio of the two compounds, as a result of rapid exchange through nucleophillic attack of tin on tin: Kobayashi, K.; Kawanisi, M.; Kozima, S.; Hitomi, T.; Iwamura, H.; Sugawara, T. *J. Organomet. Chem.* **1981**, *217*, 315. Me_4Sn is formed as a side product of the generation of Me_3SnLi.

Scheme 3. Dearomatizing Anionic Cyclizations of Heteroaromatic Diesters



starting material	E	product (yield%)
22, R^3 = H	$Br(CH_2)_3Br$	**24**, n = 1 (86%)
$R^1 = R^2 = CO_2i\text{Pr}$	$I(CH_2)_4I$	**25**, n = 2 (86%)
	$I(CH_2)_5I$	**26**, n = 3 (81%)
23, R^2 = H	$I(CH_2)_3I$	**27**, n = 1 (96%)
$R^1 = R^3 = CO_2i\text{Pr}$	$I(CH_2)_4I$	**28**, n = 2 (77%)
	$I(CH_2)_5I$	**29**, n = 3 (73%)

isolated in 86% yield. Only the indolizidine isomer was detected in the reactions with 1,4-diiodobutane (**25**, 86%) and 1,5-diiodopentane (**26**, 81%). It is surprising that the cyclization to give the seven-membered ring occurs now uneventfully to give the bicyclo 6,7-ring system in very good yield.

The same set of reactions was performed starting from 2,5-disubstituted pyridine **23** (see Scheme 3) to prepare compounds **27**−**29** in good to excellent yields. The preparation of **27**−**29** had already been accomplished[15] by partial reduction of electron deficient pyridine **23** by using Birch or sodium naphthalenide, followed by quenching with chloroiodoalkanes and then cyclization in the presence of DBU in a two-steps sequence.

We are currently extending this methodology to different aromatic and heteroaromatic systems and investigating the viability of the asymmetric version of this dearomatization-cyclization process.

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Supporting Information Available: Complete experimental procedures, spectroscopic and analytical data of all new compounds, and ORTEP projections of diols **30** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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