

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

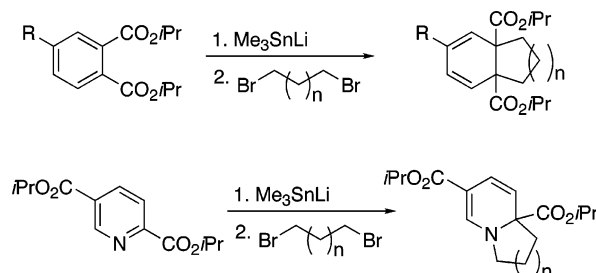
Pablo Monje, Paula Graña, M. Rita Paleo, and F. Javier Sardina*

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

qojksd@usc.es

Received December 26, 2005

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.

Trialkylstannyl lithium 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 $\text{BF}_3\cdot\text{OEt}_2$, has allowed the preparation of acylstannanes in moderate yields.⁵ We have recently reported⁶ 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 trimethylstannyl lithium 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-,

(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.

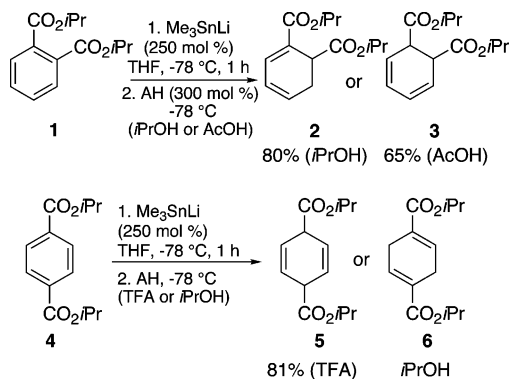
(5) Capperucci, A.; Degl'Innocenti, A.; Faggi, C.; Reginato, G.; Ricci, A.; Dembech, P.; Seconi, G. *J. Org. Chem.* **1989**, *54*, 2966.

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

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 electrophilic⁹ or whose reactivity at the carbonyl group has been blocked by using hindered derivatives¹⁰ or Lewis acids.¹¹

Addition of excess Me₃SnLi (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**.

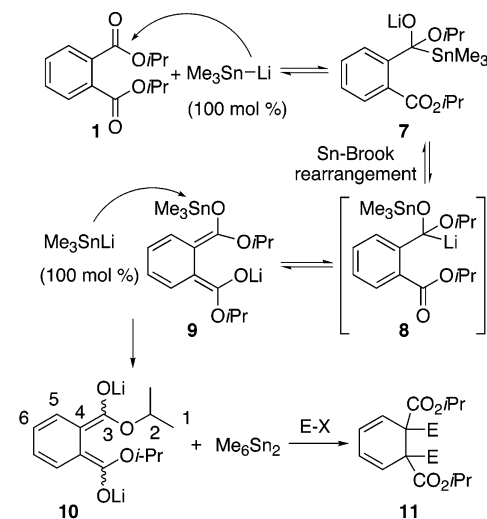
Scheme 1. Dearomatization Reactions of Aromatic Diesters



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 Me₃SnLi, 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 Me₃SnLi. 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 Me₃SnLi 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 Me₃SnLi to



atom	1	2	3	4	5	6
¹ H-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.

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 Me₃SnLi (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

The presence of *dilithium* bis-enolate **10** as an intermediate in this reaction was substantiated by analysis of the ¹H, ¹³C, and ¹¹⁹Sn NMR spectra of several reaction mixtures. When a mixture of MeLi (250 mol %) and Me₆Sn₂ (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 ¹³C 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 ¹¹⁹Sn NMR spectrum showed only two signals that can be assigned

(7) Schultz, A. G. *Chem. Commun.* **1999**, 1263.

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

(9) (a) Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, 4, 1611. (b) Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, 4, 787. (c) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **2000**, 65, 3018.

(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.

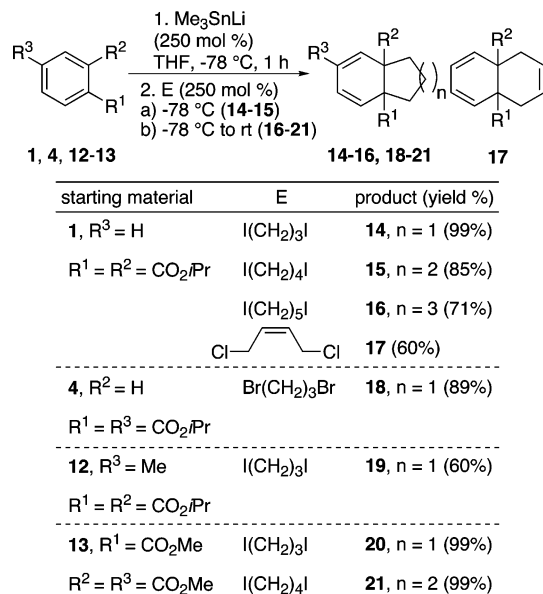
(12) For convenience, 250 mol % of Me₃SnLi (obtained by reaction of Me₆Sn₂ with MeLi at 0 °C for 15 min) was used in most of the experiments.

(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 mixture¹⁴ 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

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



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** ($\text{E} = (\text{CH}_2)_5\text{I}$, 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%

(14) It has been described that a mixture of Me_3SnLi and $\text{Me}_3\text{SnSnMe}_3$ 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 nucleophilic attack of tin on tin: Kobayashi, K.; Kawanishi, 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 .

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*.

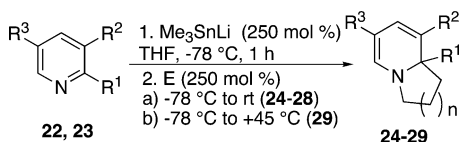
The bis-enolate derived from the reaction of *p*-diester **4** with Me_3SnLi proved to be less reactive than its ortho analogue, and starting material was often recovered from the reaction mixture. Thus reaction of terephthalate **4** with the tin nucleophile, followed by 1,3-diiodopropane provided hydrindane **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, hydrindane **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

Scheme 3. Dearomatizing Anionic Cyclizations of Heteroaromatic Diesters



starting material	E	product (yield%)
22 , R ³ = H	Br(CH ₂) ₃ Br	24 , n = 1 (86%)
R ¹ = R ² = CO ₂ iPr	I(CH ₂) ₄ I	25 , n = 2 (86%)
	I(CH ₂) ₅ I	26 , n = 3 (81%)
23 , R ² = H	I(CH ₂) ₃ I	27 , n = 1 (96%)
R ¹ = R ³ = CO ₂ iPr	I(CH ₂) ₄ I	28 , n = 2 (77%)
	I(CH ₂) ₅ I	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 prepara-

tion of **27–29** had already been accomplished¹⁵ by partial reduction of electron deficient pyridine **23** by using Birch or sodium naphthalenide, followed by quenching with chloriodoalkanes 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.

Acknowledgment. Financial support from the MCYT and MECN (Spain, Grant No. BQU2002-01368 and fellowships to P.M. and P.G.) and the Xunta de Galicia (Grant No. PGIDIT03PXIC20910PN) are gratefully acknowledged.

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>.

OL053130R

(15) (a) Donohoe, T. J.; McRiner, A. J.; Sheldrake, P. *Org. Lett.* **2000**, 2, 3861. (b) Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.