Communications

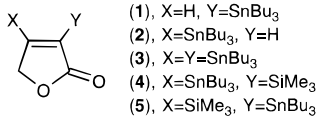
Preparation and Reactions of 3,4-Bis(tributylstannyl)-2(5*H*)-furanone

Ross Mabon, Alexandre M. E. Richecœur, and J. B. Sweeney*

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

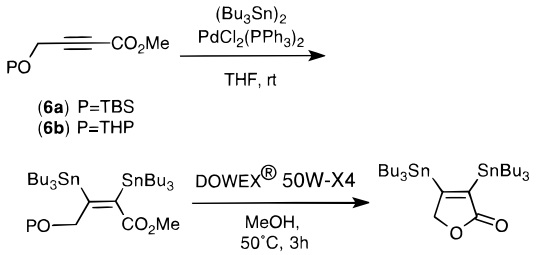
Received August 11, 1998

We have previously described the synthesis and palladium-catalyzed cross-coupling reactions ("Stille reactions") of 3- and 4-(tributylstannyl)-2(5*H*)-furanones **1** and **2**.[1] The use of these flexible synthetic species to prepare natural products containing the 2(5*H*)-furanone[2] subunit has recently occupied our attention.[3] As part of a broader synthetic strategy to facilitate preparation of, in particular, naturally occurring cardenolides[4] and their analogues,[5] we aspired also to prepare furanones **3**−**5**, which we thought would allow for greater flexibility in the selective fusion of a broad range of substituents to the furanone nucleus. We here report the preliminary results we have obtained in pursuit of this goal.

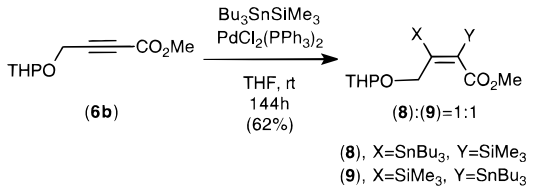


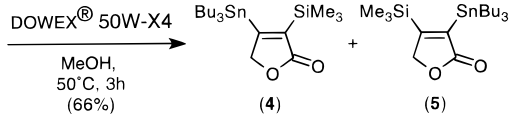
(**1**), X=H, Y=$SnBu_3$
(**2**), X=$SnBu_3$, Y=H
(**3**), X=Y=$SnBu_3$
(**4**), X=$SnBu_3$, Y=$SiMe_3$
(**5**), X=$SiMe_3$, Y=$SnBu_3$

Our program commenced with the bisstannylation of butynoate **6a**; this compound reacted with hexabutylditin in the presence of $PdCl_2(PPh_3)_2$[6] to give the 2,3-bis(tributylstannyl)acrylate **7a** in 98% yield. Unfortunately, under a variety of reaction conditions, **7a** could not be converted to **3**. To circumvent this drawback, the analogous THP-protected bis(stannane) **7b** was prepared using the same reaction conditions in 75% yield from propynoate **6b**;[7] upon reaction with acidic ion-exchange resin in methanolic solution the hydroxyl group of **7b** was unmasked and cyclization occurred to furnish lactone **3** as a colorless liquid in 74% yield. This key intermediate is stable indefinitely when stored at −30 °C.



We next attempted synthesis of mixed stannylsilylfuranones **4** and **5** by a method analogous to that used to prepare **3**. Thus, propynoate **6b** was reacted with (tributylstannyl)-trimethylsilane in the presence of $PdCl_2(PPh_3)_2$ at room temperature.[8] This rather slow reaction produced in 62% yield a 1:1 mixture of acrylates **8** and **9**, which proved to be inseparable using routine purification methods. Without further purification, **8** and **9** were deprotected and cyclized to give furanones **4** and **5** in 66% yield. Again, these materials proved to be inseparable, and our attention returned to cross-coupling reactions of **3**.





In our previous work,[1] mono(stannyl)furanones **1** and **2** displayed differing reactivities in Stille couplings with a variety of aryl iodides: in all cases, stannane **2** reacted more efficiently. We reasoned, therefore, that bis(stannane) **3** might exhibit regioselectivity in its reactions with coupling partners, and we further tentatively predicted that the C4−Sn bond would be more reactive than the neighboring C3−Sn bond. Thus, it was anticipated that **3** would react with 1 equiv of iodobenzene in THF in the presence of Pd_2dba_3, triphenylarsine, and Cu(I)I at room temperature to give 3-(tributylstannyl)-4-phenyl-2(5*H*)-furanone **10a** (R = Ph) as

(1) Hollingworth, G. J.; Perkins, G.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1913.
(2) For an excellent review of the methods available for synthesis of furanones, see: Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287.
(3) Bourguignon, J.-J.; Schoenfelder, A.; Schmitt, M.; Wermuth, C.-G.; Hechler, V.; Charlier, B.; Maitre, M. *J. Med. Chem.* **1988**, *31*, 893.
(4) For an overview, see: Marshal, P. G. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Elsevier: New York, 1970; Vol. II, Part D, p 369. For treatises describing biological activities of cardenolides, see: Florkiewicz, R. Z.; Anchin, J.; Baird, A. *J. Biol. Chem.* **1998**, *273*, 544. Luta, M.; Hensel, A.; Kreis, W. *Steroids* **1998**, *63*, 44. Braga, F. C.; deSouzo, J. D.; Howarth, O.; deOliveira, A. B. *Magn. Reson. Chem.* **1997**, *35*, 899. Carter, C. A.; Gray, E. A.; Schneider, T. L.; Lovett, C. M.; Scott, L.; Messer, A. C.; Richardson, D. P. *Tetrahedron* **1997**, *53*, 16959. Gavidia, I.; PerezBermudez, P. *Phytochemistry* **1997**, *46*, 273. Florkiewicz, R. Z.; Anchin, J.; Trudel, C.; Baird, A. *Mol. Biol. Cell* **1996**, *7*, 1080.
(5) For a pertinent example, see: Staroske, T.; Hennig, I.; Wetzel, P.; Hofmann, H. J.; Muller, D.; Hausler, T.; Sheldrick, W. S.; Zillikens, S.; Gretzer, B.; Pusch, H.; Glitsch, H. G. *Tetrahedron* **1996**, *52*, 12723.
(6) Piers, E.; Skerlj, R. T. *Can. J. Chem.* **1994**, *72*, 2468.
(7) Searle, R. A.; Townsend, L. B. *Org. Synth.* **1981**, *60*, 81.
(8) Mitchell, T. N.; Amamria, A.; Killing, H.; Wickenkamp, R. *J. Chem. Soc., Chem. Commun.* **1985**, 354.
(9) Very few monocoupling reactions of unsymmetrical bisstannanes have been reported. For an example, see: (a) Beaudet, I.; Parrain, J.; Quintard, J.; *Tetrahedron Lett.* **1991**, *32*, 6333. Several selective single coupling reaction of *symmetrical* bisstananes have been reported: (b) Haack, R. A.; Penning, T. D.; Djuric, S. W.; Dziuba, J. A. *Tetrahedron Lett.* **1988**, *29*, 2783. (c) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747. (d) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833. (e) Barrett, A. G. M.; Edmonds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238. (f) Djuric, S. W.; Huff, R. M.; Penning, T. D.; Clare, M.; Swenton, L.; Kachur, J.; Vilani-Price, D.; Krivi, G. G.; Pyla, E. Y.; Warren, T. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1367. (g) Djuric, S. W.; Huff, R. M.; Penning, T. D.; Clare, M.; Swenton, L.; Kachur, J.; Vilani-Price, D.; Krivi, G. G.; Pyla, E. Y.; Warren, T. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1367. (h) Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583.

10.1021/jo9816156 CCC: $18.00
Published on Web 01/05/1999

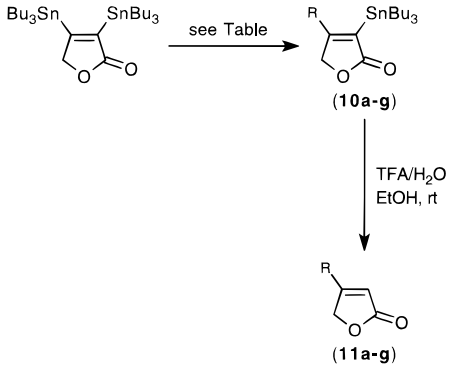
Table 1. Regioselective Stille Couplings of Bis(stannane) 3

R	condns[a]	product/yield (%)	product/yield (%)
Ph	A	(**10a**) 37	(**11a**)[c] 85
2-$MeO_2CC_6H_4$	A	(**10b**) 51	(**11b**)[c] 89
2-$CF_3C_6H_4$	A	(**10c**) 27	(**11c**)[c] 91
2-MeC_6H_4	A	(**10d**) 49	(**11d**)[c] 95
2-thienyl	A	(**10e**) 22	(**11e**)[c] 88
PhCO	B	(**10f**) 33	(**11f**)[d] 90
PhCH=CH	C	(**10g**) 35[b]	(**11g**)[d] 92

[a] (A) RI (1 equiv), Pd_2dba_3 (2 mol %), $AsPh_3$ (8 mol %), Cu(I)I (8 mol %), THF, rt; (B) PhCOCl, $BnClPd(PPh_3)_2$ (2 mol %), CO, DMF, 50 °C; (C) PhCH=CHBr, Pd_2dba_3 (2 mol %), DMF, 50 °C. [b] Only the *E*-isomer was obtained. [c] Reference 1d. Reference 10.

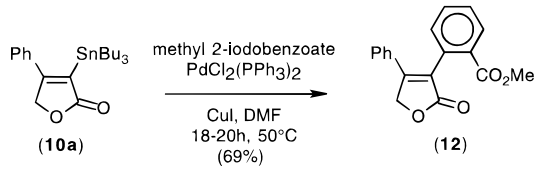
the major product of the reaction. Indeed, only one compound was produced in the reaction, in 37% yield, and chemical correlation (via protodestannylation to give **11a**, R = Ph[1]) confirmed that this product was **10a**.

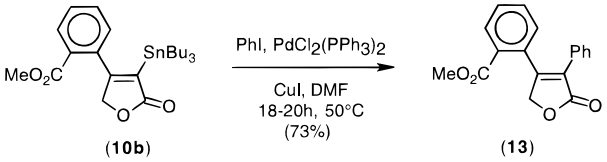
Reaction of bis(stannane) **3** with a range of coupling partners proceeded with regiocontrol to give 3-(tributylstannyl)-4-aryl-2(5*H*)-furanones **10b**−**e** in moderate yields (Table 1). Reaction with benzoyl chloride and *β*-bromostyrene proceeded with similar regiocontrol and yields to give compounds **10f** and **10g**. The reactions did not produce any trace of product in which two couplings had occurred (i.e., where both C3− and C4−Sn bonds had reacted with the coupling partner) or any product in which coupling had occurred at position 3 of the furanone. Thus, although these



reactions require optimization, the regioselectivities of the Stille couplings of furanone **3** are impressive.[9] Compounds **10a**−**g** were subsequently protodestannylated to allow chemical correlation as confirmation of the deduced substitution patterns. Furanones **11a**−**g**[1,10] were obtained in good yield.

Our preliminary experiments on couplings of the products of these reactions have so far been encouraging: thus, stannanes **10a** and **10b** reacted with, respectively, iodobenzene and methyl 2-iodobenzoate to give the isomeric 3,4-bis(aryl)furanones **12** and **13** in good yield. Once again, the C3−Sn bond is less reactive than in analogous reactions of C4-stannylfuranones, with a much higher reaction temperature required to drive the reaction to completion. The superior yield in these latter coupling reactions may indicate that there is a steric inhibition of the reaction of bis(stannane) **3** causing the lower yields in monocoupling reactions.





In summary, we have demonstrated that the regioselective Stille reaction of bis(stannane) **3** allows preparation of 4-substituted 3-stannyl-2(5*H*)furanones **10**; current research is directed toward optimizing the yields of the process and extrapolating the range of coupling reactions thus far examined.

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (EPSRC), the Nuffield Foundation, and ZENECA for financial support of this research program. We also acknowledge the contributions of Mr. K. M. Dalglish to this and previous projects.

Supporting Information Available: Experimental procedures and NMR spectra.

JO9816156

(10) Reginato, G.; Capperucci, A.; Degl'Innocenti, A.; Mordini, A.; Pecchi, S. *Tetrahedron* **1995**, *51*, 2129.