Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7633–7636

TETRAHEDRON LETTERS

Regio- and stereoselective preparation of γ-alkylidenebutenolides or α-pyrones using a Stille reaction and palladium-catalysed oxacyclisation sequence

Séverine Rousset,[a] Mohamed Abarbri,[a] Jérôme Thibonnet,[a,b] Jean-Luc Parrain[b,*] and Alain Duchêne[a,*]

[a]*Laboratoire de Physicochimie des Interfaces et des Milieux Réactionnels, Faculté des Sciences de Tours, Parc de Grandmont, 37200 Tours, France*

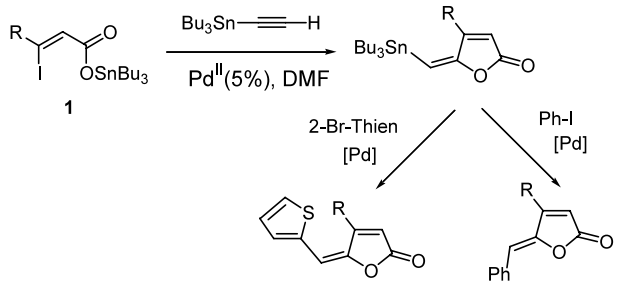
[b]*Laboratoire de Synthèse Organique, UMR 6009, Faculté des Sciences de Saint Jérôme, 13397 Marseille Cedex 20, France*

Received 27 June 2003; revised 12 August 2003; accepted 12 August 2003

Abstract—Synthesis of butenolides or α-pyrones from substituted tributylstannyl acetylides is highly dependant on the nature of the acetylide.

The heterocyclisation reaction is one of the most important reactions in organic synthesis. The synthesis of five- and six-membered ring unsaturated lactones (butenolides or α-pyrones) constitutes an important class of biologically active compounds and has been a focus of considerable attention in synthetic organic chemistry[1] and in medicinal chemistry.[2] Numerous methods reported for the synthesis of these structures in the last decade utilise transition metals (Ag, Hg, Rh, Pd) to promote intramolecular addition of carboxylic acid to alkynes.[3] In general, the lactonisation reaction of 4-alkynoic acids involves a stereoselective *trans*-addition reaction via a 5-*exo* process. In addition to the formation of γ-alkylidene butenolides, in some cases six-membered lactones have been obtained resulting from the 6-*endo* mode. In each case the synthesis suffers from a lack of selectivity. The problem of regioselectivity was recently studied by Larock et al. who demonstrated that substituted isocoumarins or α-pyrones could be prepared by treating β-halogeno α,β-unsaturated esters with internal alkynes in the presence of a palladium catalyst.[4] Nevertheless, in the case of non-symmetric alkynes two α-pyrone regioisomers were obtained. More recently Negishi et al. proposed selective conversion of (*Z*)-2-en-4-ynoic acids to α-pyranone in the presence of a catalytic amount of $ZnBr_2$ (10%) or to furanone in the presence of silver salts.[5] In order to prepare α-pyranone selectively, we recently reported two different approaches using palladium-catalysed sequences involving a functional vinylstannane and acyl chlorides[6] or β-iodovinylic acids and allenylstannanes.[7] In addition, we previously described the synthesis of dienoic acids or enynes bearing a carboxylic acid function from β-iodovinylic acids and vinyltin or alkynylzinc reagents.[8] This methodology was then applied to the synthesis of γ-tributyltinmethylidene butenolides which constitute useful intermediates in the selective synthesis of arylmethylidene butenolides (Scheme 1).[9]

To broaden our synthesis strategy and by designing a system suitable for 5- or 6-*endo* lactonisation, we



Scheme 1.

Keywords: butenolides; pyran-2-one; palladium catalyst; heteroannulation.

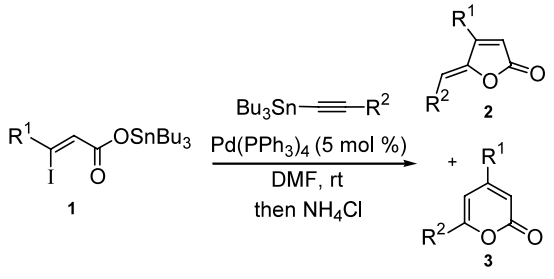
* Corresponding authors. Tel.: 33 (0)2 47 36 69 59; fax: 33 (0)2 47 36 70 40; e-mail: duchene@delphi.phys.univ-tours.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.08.043

planned to examine the reactivity of diverse substituted alkynyltin reagents with (*Z*)-β-iodoacrylic acids mediated by a palladium complex (Scheme 2).[10]

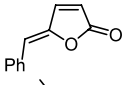
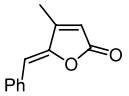
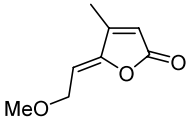
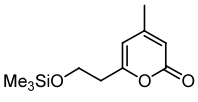
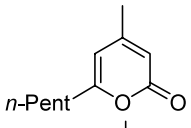
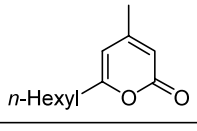
Our investigation began with the coupling of phenylalkynyltributylstannane with (*Z*)-3-iodoprop-2-enoic acid protected as tributyltinester under conditions previously defined in our group.[8e]

Compared to our initial results, no enynoic acid or its tributyltinester was recovered. Only compound **2a** was obtained as a sole isomer. Contrary to the results starting from tributyltin acetylide, we did not observe any tin metallated lactones. Moreover, the selective formation of a five- or a six-membered ring of unsaturated lactones seems to depend on the nature of the substituent on the alkynyltin reagent. Compared to other conditions reported in the literature [both in a palladium-catalysed one-pot procedure and metal salt (Zn or Ag) promoted oxacyclisation], each attempt yielded only a single lactone (Table 1).



Scheme 2.

Table 1.

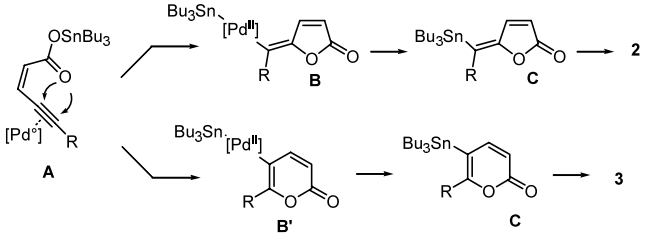
R^1	R^2	Lactone	Yield (%)	N°
H	Ph		72	**2a**
CH_3	"		68	**2b**
"	CH_2OMe		52	**2c**
"	$(CH_2)_2OSiMe_3$		62	**3a**
"	*n*-C_5H_{11}		50	**3b**
„	*n*-C_6H_{13}		49	**3c**

Compared to Sonogashira and Negishi processes, minor secondary by-products such as alkyne dimers or Michael adducts were not detected. Although the procedure described does not respond to the atom economy criteria, the clean access to only one lactone prompted us to examine the origin of the regioselectivity observed.

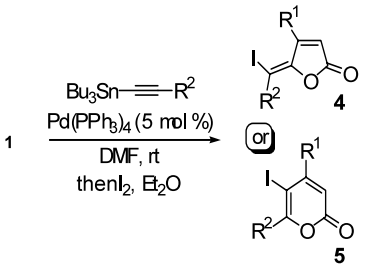
A plausible mechanism for the heteroannulation reaction is shown in Scheme 3. First, a Stille mechanism[11] would yield 3-enynoic acid by oxidative addition, transmetallation (formation of **5**) and reductive elimination. Cyclisation would then occur via an attack on the carboxylate function at the α- or β-position of the alkynyl moiety, which would give the palladium(II) intermediate. The latter would subsequently provide stannylpyrones or stannylalkylidenebutenolides and regenerate the palladium(0) catalyst.[12] At this stage the stannyllactones obtained would certainly be very sensitive to the work-up or during the silica gel purification process affording hydrolysed lactones **2** or **3**.[13]

At this point, factors affecting the pyranone/furanone ratio are not yet very clear. It is nevertheless tempting to speculate that the stereoelectronic effect of the substituent of the unsaturated bonds in tin (*Z*)-2-en-4-ynoate would lead to the formation of 2*H*-pyran-2-ones via an inductive donating effect. In contrast, aryl or potentially chelating palladium atom substituants may stereoelectronically lead to 5-*exo*-mode cyclisation.

In addition, bearing in mind the mechanism evoked in Scheme 3, we decided to trap the stannyllactones with electrophiles. The reaction of tributylstannyl acetylide reagents with a range of tributylstannyl (*Z*)-3-substituted 3-iodoprop-2-enoates followed by addition of a solution of iodine in ether, proceeded with regio- and stereocontrol to give fair yields of (*E*)-5-iodoalkylidene-5*H*-furan-2-ones or 5-iodo-2*H*-pyran-2-ones (Scheme 4, Table 2).[14] Similar regiochemical trends were again observed.

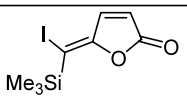
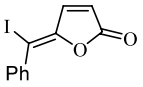
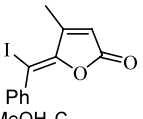
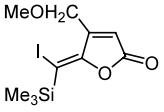
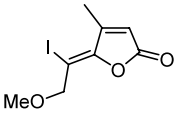
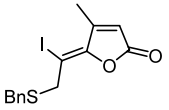
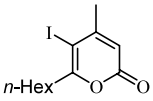
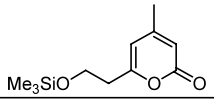


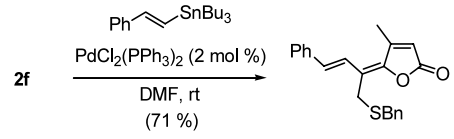
Scheme 3.



Scheme 4.

Table 2.

R^1	R^2	Iodolactone	Yield (%)	N°
H	Me_3Si		61	**4a**
"	Ph		55	**4b**
Me	"		64	**4c**
CH_2OMe	Me_3Si		61	**4d**
CH_3	CH_2OMe		55	**4e**
"	CH_2S-Bn		70	**4f**
"	*n*-C_6H_{13}		50	**5a**
"	$(CH_2)_2OSiMe_3$		59	**5b**



Scheme 5.

Finally, Stille cross-coupling of **4f** with styryltributylstannane in the presence of a catalytic amount of dichlorobis (bistriphenylphosphine)palladium(II) (5%) in DMF yielded 72% of the desired arylbutenolide (Scheme 5) but with complete retention of the configuration of the exocyclic double bond with respect to the stereochemistry of the starting iodoalkene.[15]

In conclusion, under palladium complex catalysis, we prepared by selective sequence Stille and heterocyclisation reactions butenolides or α-pyrones from alkynyltin reagents.

Acknowledgements

We thank the CNRS and MESR for providing financial support and the Service d'analyse chimique du vivant de Tours for recording NMR and mass spectra.

References

1. For reviews on butenolides, see: (a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353; (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (c) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287; (d) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; (e) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679; (f) Rossi, R.; Bellina, F. *Targets Heterocyclic Syst.* **2001**, *5*, 169; (g) Brückner, R. *Chem. Commun.* **2001**, 141. For a discussion of the chemistry of α-pyrones, see: (h) Staunton, J. In *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, England, 1979; Vol. 4, pp. 629–646. 2*H*-Pyran-2-one and its derivatives are commonly referred to as 2-pyrones or α-pyrones: (i) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72–78.
2. (a) Davies-Coleman, M. T.; Rivett, D. E. A. *Progr. Chem. Org. Nat. Prod.* **1989**, *55*, 1; (b) Kvita, V.; Fischer, W. *Chimia* **1992**, *46*, 457; (c) Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3; (d) Posner, G. H.; Nelson, T.; Kinter, C.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083.
3. For recent synthesis of butenolides using Pd or Ag catalysts, see: (a) Hanisch, I.; Brückner, R. *Synlett* **2000**, 374; (b) Brückner, R.; Ohe, F. v d. *New J. Chem.* **2000**, 659; (c) Siegel, K.; Brückner, R. *Synlett* **1999**, 1227; (d) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431; (e) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387; (f) Görth, F. C.; Umland, A.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1055; (g) Rossi, R.; Bellina, F.; Biagetti M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799; (h) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599; (i) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017; (j) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135; (k) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367; (l) Kotora, M.; Negishi, E. *Synthesis* **1997**, 201; (m) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 3238; (n) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796; (o) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587; (p) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871.
4. (a) Larock, R. C.; He, Y.; Leon, W. W.; Han, X.; Refvik, M. D.; Zenner, M. J. *J. Org. Chem.* **1998**, *63*, 2154; (b) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713 and references cited therein.
5. Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673.
6. Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *J. Org. Chem.* **2002**, *67*, 3941.
7. Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Chem. Commun.* **2000**, 1987.
8. (a) Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem.* **2000**, *65*, 7475; (b) Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **1999**, 141; (c) Prié, G.; Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **1998**, 839; (d) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771; (e) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Main Group Met. Chem.* **1997**, *20*, 195; (f) Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchêne, A. *Synthesis* **1996**, 82; (g) Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Tetrahedron Lett.* **1995**, *36*, 2469; (h) Duchêne, A.; Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R. *Synlett* **1994**, 524.

9. Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* **1999**, *1*, 701.
10. Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867 and references cited therein.
11. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813; (c) Mitchell, T. N. *Synthesis* **1992**, 803; (d) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G.; Wilkinson, G., Eds.; Elsevier: Oxford, 1995; Vol. 12, Chapter 3.4; pp. 161–241; (e) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: New York, 1996; Vol. 5, pp. 1–53; (f) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.*; Paquette, L. A., Ed.; John Wiley & Sons, 1997; Vol. 50, Chapter 1, pp. 1–652; (g) Farina, V.; Krishnamurthy, V. In *The Stille Reaction*; Wiley: New York, 1999; (h) Campagne, J.-M.; Prim, D. In *Les Complexes du palladium en synthèse organique*; CNRS Editions: Paris, 2001.
12. Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *Chem. Commun.* **1996**, 381.
13. We unambiguously established the structure and stereochemistry of these new compounds by NMR techniques. See also Ref. 6 and Ref. 7.
14. **Typical procedure**: A dry three-necked flask equipped with magnetic stirring and septum was charged with (*Z*)-tributylstannyl-3-iodobut-2-enoate (3.2 g, 3.6 mmol) in DMF (20 mL) and 5.4 mmol of 1-tributylstannyl-2-phenylethynyl. 208 mg (5% mol) of $Pd(PPh_3)_4$ were added. The resulting solution was then stirred under argon for 12 h at room temperature.
(a) The reaction mixture was then quenched with a saturated NH_4Cl solution at 0°C and Et_2O was added. After filtration over Celite, the organic layer was separated, extracted with Et_2O, washed with brine and dried over $MgSO_4$. After evaporation of solvents, the crude products **2a–c** and **3a–c** were purified by column chromatography on silica (petroleum ether/Et_2O/Et_3N; 80/18/2).
(b) Iodine (1.27 g, 5 mmol) diluted in 20 mL of Et_2O was added. Stirring was then maintained for 2 h at room temperature. The mixture was hydrolysed with 30 mL of 1 M solution of potassium fluoride and 25 mL of acetone to precipitate the tributyltin iodide formed. After strongly stirring for 1 h, the reaction mixture was filtered and extracted with diethyl ether. The organic layer was washed with a 5% solution of sodium thiosulfate. After usual work-up, **4a–f** and **5a–b** were purified by column chromatography on silica (petroleum ether/Et_2O/Et_3N; 80/18/2).
(**2a**): Mp: 82–84°C. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.02 (s, 1H), 6.20 (d, $J=5.3$ Hz, 1H), 7.31–7.42 (m, 3H), 7.49 (d, $J=5.3$ Hz, 1H), 7.74–7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 114.8, 118.7, 129.4, 129.9 (2C), 131.3 (2C), 133.4, 145.8, 149.0, 170.8. MS (70 eV): $m/z=172$ (M, 100), 144 (33), 118 (14), 116 (52), 115 (68), 90 (42), 89 (46), 86 (14), 72 (10), 64 (11), 63 (33), 62 (13), 58 (24), 57 (19), 51 (17), 50 (12), 45 (14), 39 (25), 38 (10). (**3a**): IR (neat): 2982, 2865, 1747, 1652, 1567, 1125. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.95 (s, 9H), 2.03 (s, 3H), 2.59 (t, $J=6.1$ Hz, 2H), 3.89 (t, $J=6.1$ Hz, 2H), 5.88 (bs, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 12.3, 18.3 (3C), 37.8, 60.7, 108.0, 112, 156.5, 162.5, 163.6. MS (70 eV): $m/z=226$ (M, 13), 136 (66), 184 (16), 183 (100), 155 (52), 75 (55), 45 (13). (**4f**): Mp: 103°C. IR (KBr): 2975, 2965, 2880, 1760, 1655, 1600, 1225. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.37 (s, 2H), 3.95 (s, 2H), 6.12 (q, $J=1.5$ Hz, 1H), 7.31–7.13 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 18.3, 36.6, 42.6, 88.4, 121.3, 127.0, 128.4 (2C), 129 (2C), 137.6, 149.4, 155.3, 166.3. MS (70 eV): $m/z=372$ (M, 16), 245 (97), 227 (29), 91 (100), 39 (13). (**5a**): IR (neat): 3070, 2980, 2975, 1755, 1625, 1230. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.9 (t, $J=7.3$ Hz, 3H), 1.66–1.27 (m, 8H), 2.51 (s, 3H), 2.94 (t, $J=7.1$ Hz, 2H), 6.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 14.5, 19.0, 23.0, 28.6, 29.6, 32.0, 41.5, 92.0, 121.0, 149.0, 155.7, 167.5. MS (70 eV): $m/z=320$ (M, 32), 193 (13), 175 (13), 124 (100), 55 (22), 43 (25), 41 (36), 39 (35).
15. For compounds **4** or **5**, the structure and stereochemistry were also confirmed by NMR techniques and by some Stille cross-coupling reactions; it is well known that these reactions occur always with retention of configuration. A full paper describing all these new compounds will reported in due course.