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A Novel Protocol for the Stereoselective Synthesis of Variously Substituted (Z)-5-Ylidene-5*H*-furan-2-ones

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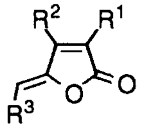
***Abstract*:** The Pd(II)- or Ag(I)-catalyzed lactonization of easily available (*E*)-4-(1-alkynyl)-2-bromopropenoic acids provides (Z)-3-bromo-5-ylidene-5*H*-furan-2-ones, **5**. These compounds, which represent an unpreviously reported class of (Z)-alkylidenebutenolides, are able to undergo Pd-catalyzed cross-coupling reactions with arylzinc halides, tetraalkylstannanes or alkenylstannanes to provide the corresponding 3-substituted (Z)-5-ylidene-5*H*-furan-2-ones, **1**. The new procedure for the preparation of compounds **1** has been employed in a new synthesis of the butter flavour component bovolide.

3-Substituted and 3,4-disubstituted (Z)-5-ylidene-5*H*-furan-2-ones, **1**, are synthetic targets for which there is a continuous interest because they include a number of natural products which display a wide range of biological activities.[1] Very simple examples of these naturally-occurring substances include tetrenolin, which displays antibiotic activity,[2] the furanosesquiterpenoid freelingyne,[3] the butter flavour component bovolide,[4] and nostoclides I and II, which display cytotoxic activity.[5]



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Since most of the methods developed earlier for the synthesis of compounds **1** produce *Z* and *E* mixtures,[6] in recent years several highly selective organometallic methods have been developed.[1a] Among these those which have proven to be very synthetically useful are based either on the Ag- ot the Pd-catalyzed lactonization of suitable substituted (Z)-2-en-4-ynoic acids, **2**,[7] or a tandem process involving a Pd-catalyzed cross-coupling between 1-alkynes, **3**, and suitable substituted (Z)-3-halopropenoic acids, **4**, under the Sonogashira conditions,[8] and a subsequent Pd-catalyzed lactonization of the resulting (Z)-2-en-4-ynoic acids (Scheme 1).[9] Obviously, these synthetic strategies afford compounds **1** characterized by a number of carbon atoms identical to that of compounds **2** which are used as starting materials or are formed *in situ* from **3** and **4**.

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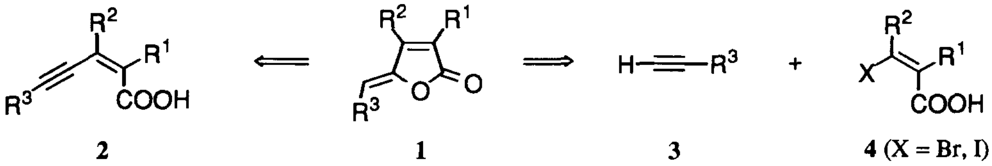
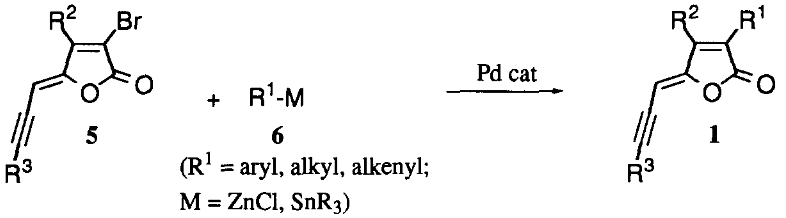
Unfortunately, in the case of compounds **1** characterized by a functionalized carbon chain in their 3-position (*e.g.* the (*E*)-3-hydroxy-1-propenyl unit), these strategies require the use of not easily available starting materials.

Scheme 1



We surmised that a solution to this problem might be represented by a convenient synthesis of (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones, **5**, and the subsequent use of these new derivatives as electrophiles in Pd-catalyzed reactions with alkenyl-, aryl or alkylmetal derivatives which could contain a functional group (Scheme 2). We now wish to report some preliminary results obtained in the study on the synthesis of compounds **5** and the reactions of these versatile new reagents.

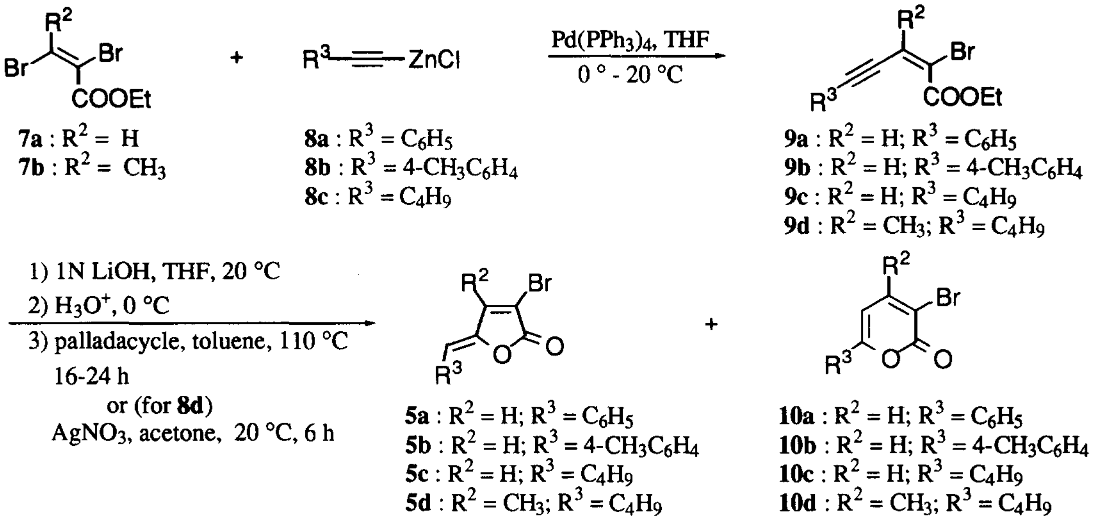
Scheme 2



Thus, according to a general procedure which we had previously developed for the regioselective and stereospecific monoarylation, monoalkynylation and monoalkylation of stereodefined 2,3-dibromo-2-alkenoates,[10] we prepared stereoisomerically pure compounds **9a**, **9b**, **9c** and **9d** in 64, 68, 80 and 49 % yield, respectively, by reaction of the corresponding (*E*)-2,3-dibromo-2-alkenoates, **7a**[10b] and **7b**[10c], respectively, with 1.3 equiv of **6a**, **6b** and **6c**, respectively, in THF at 0-20 °C for 24-36 h in the presence of 5 mol % $Pd(PPh_3)_4$. (Scheme 3).

Compounds **9a-d** were then converted into the desired (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones, **5a-d**, by saponification with 1N LiOH in THF at 20 °C followed by acidification and lactonization of the crude carboxylic acids so obtained by heating their deareated toluene solutions under argon at 110 °C for 16-24 h in the presence of 5 mol % *trans*-di(μ-acetato)-bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II).[11] Compounds **5a**, **5b**, **5c** and **5d** were so obtained in 45, 36, 50 and 25 % yield, respectively (Scheme 3).[12] It is interesting to note that, analogously to what observed by Kotora and Negishi[7b] for the synthesis of γ-alkylidenebutenolides by lactonization of 3-aryl substituted (*Z*)-2-en-4-ynoic acids in the presence of $Pd(PPh_3)_4$, the new protocol that we used for the cyclization of the crude (*E*)-2-bromo-2-en-4-ynoic acids which derived from **9a-c**, afforded compounds **5a-c** contaminated by *ca.* 3-6 % of the corresponding 3-bromo-2*H*-pyran-2-ones, **10a-c**. However, quite surprisingly, the cyclization of the crude carboxylic acid derived from **9d** provided a mixture of **5d** and **10d** in a 38.5 : 61.5 ratio, respectively. Purification of this mixture by MPLC on silica gel allowed to isolate **5d** and **10d** in 25 and 45 % yield, respectively. Nevertheless, when the crude carboxylic acid derived from **9d** was reacted in acetone at 20 °C for 6 h in the presence of 20 mol % $AgNO_3$, a mixture of **5d** and **10d** in a *ca.* 79 : 21 ratio, respectively, was obtained and pure **5d** could be isolated in 52 % yield (Scheme 3).

Scheme 3



7a : R^2 = H
7b : R^2 = CH_3

8a : R^3 = C_6H_5
8b : R^3 = 4-$CH_3C_6H_4$
8c : R^3 = C_4H_9

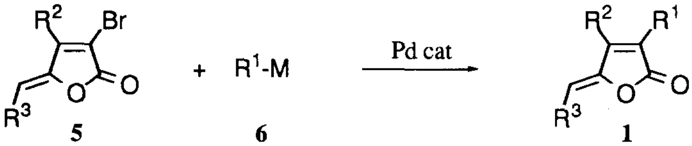
9a : R^2 = H; R^3 = C_6H_5
9b : R^2 = H; R^3 = 4-$CH_3C_6H_4$
9c : R^2 = H; R^3 = C_4H_9
9d : R^2 = CH_3; R^3 = C_4H_9

5a : R^2 = H; R^3 = C_6H_5
5b : R^2 = H; R^3 = 4-$CH_3C_6H_4$
5c : R^2 = H; R^3 = C_4H_9
5d : R^2 = CH_3; R^3 = C_4H_9

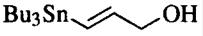
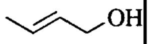
10a : R^2 = H; R^3 = C_6H_5
10b : R^2 = H; R^3 = 4-$CH_3C_6H_4$
10c : R^2 = H; R^3 = C_4H_9
10d : R^2 = CH_3; R^3 = C_4H_9

With compounds **5** now readily available on a multigram scale, some their uses as synthetic equivalents for incorporation of a (*Z*)-5-ylidene-5*H*-furan-2-one unit were investigated. It was so found that reaction of **5a** with 1.5 equiv of 4-fluorophenylzinc chloride, **6a**, in THF at 65 °C for 6h provided **1a** in 67 % yield (entry 1, Table).

Table. Palladium-catalyzed cross-coupling reaction between compounds **5** and organometallic reagents.



5 **6** **1**

Entry	Compound **5**	Organometallic reagent **6**	Catalyst system	Solvent	Reaction conditions (h / °C)	Product				Yield (%)
						1	R^1	R^2	R^3	
1	**5a**	4-F-C_6H_4ZnCl **6a**	$Pd(PPh_3)_4$	THF	6 / 65	**1a**	4-F-C_6H_4	H	C_6H_5	67
2	**5b**	 **6b**	$PdCl_2(PhCN)_2$ $AsPh_3$, CuI	NMP	40 / 70	**1b**		H	C_4H_9	36
3	**5c**	Me_4Sn **6c**	$PdCl_2(PhCN)_2$ $AsPh_3$, CuI	NMP	23 / 80	**1c**	CH_3	H	CH_3	92
4	**5d**	Me_4Sn **6c**	$PdCl_2(PhCN)_2$ $AsPh_3$, CuI	NMP	72/80	**1d**	CH_3	CH_3	C_4H_9	54

Moreover, treatment of **5b** with 1.5 equiv of (*E*)-3-hydroxy-1-propenyltributyltin, **6b**, in NMP at 70 °C for 40 h, in the presence of 5 mol % $PdCl_2(PhCN)_2$, 10 mol % $AsPh_3$ and 10 mol % CuI provided **1b** in 36 % yield (entry 2, Table). Interestingly, a much better yield into the desired cross-coupled product was obtained in a similar Pd-catalyzed reaction between **5c** and 3 equiv of tetramethyltin, **6c**. In fact, this reaction provided **1c** in 92 % yield (entry 3, Table). Finally, treatment of **5d** with **6c** under experimental conditions simlar to those employed for the synthesis of **1c**, allowed to obtain bovolide, **1d**,[14] in 54 % yield (entry 4, Table).

In conclusion, it has been shown that the Pd(II)- or Ag(I)-catalyzed lactonization of easily available (*E*)-4-(1-alkynyl)-2-bromopropenoic acids provides (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones, **5**. These compounds, which represent an unpreviously reported class of (*Z*)-γ-ylidenebutenolides, have been shown to be able to undergo Pd-catalyzed cross-coupling reactions with organozinc or organotin derivatives to provide 3-aryl, 3-(1-alkenyl) and 3-methyl substituted (*Z*)-5-ylidene-5*H*-furan-2-ones, **1**. Moreover, the new procedure for the synthesis of compounds **1** has been used in a new synthesis of bovolide.

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11. Recently, we successfully used this complex described by Herrmann et al. [Herrmann, W. A.; Brossner, C.; Öfele, K.; Reisinger, C-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844-1848] for the cyclization of (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids to the corresponding (*E*)-3-ylidene-3*H*-furan-2-ones (see: Ref 10d).
12. All the new products in this study gave satisfactory spectral and microanalytical data. Some characteristic data for compounds **5a**, **5b**, **5c** and **5d** are as follows. **5a**: orange liquid; MS, *m/z* (%): 252 (26), 250 (24), 115 (100), 105 (18), 77 (39); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.77 (br d, J = 7.7 Hz, 2H), 7.57 (br s, J = 1.5 Hz, 1H), 7.39 ((m, 2H), 7.37 (m, 1H), 6.07 (br s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.58, 146.94, 142.90, 132.43; 130.87; 129.75, 128.99, 114.91, 111.13 .**5b**: m.p. 159-161 °C; MS, *m/z* (%): 266 (72), 264 (72), 157 (51), 129 (100), 104 (74). IR (KBr): 1756, 987, 930, 903 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.67 (br s, 2H), 7.56 (br s, 1H), 7.21 (br s, 2H), 6.05 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 165.78, 146.37, 142.91, 140.38, 130.91, 129.91, 129.70, 115.17, 110.42, 21.56. **5c**: yellow liquid; MS, *m/z* (%): 232 (29), 230 (31), 123 (71), 81 (58), 41 (100); ^{1}H NMR ($CDCl_3$, 600 MHz): 7.43 (s, 1H), 5.38 (t, J = 7.9 Hz, 1H), 2.35 (dt, J = 7.9 and 7.9 Hz, 2H), 1.44 (quint, J = 7.9 Hz, 2H), 1.33 (sext, J = 7.9 Hz, 2H), 0.89 (t, J = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 165.61, 147.96, 141.51, 118.79, 111.63, 30.79, 25.93, 22.26, 13.65. **5d**: yellow liquid; MS, *m/z* (%): 246 (26), 244 (27), 190 (1007, 67 (96), 55 (73). IR (neat): 1780, 996, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.46 (t, J = 7.9 Hz, 1H), 2.37 (dt, J = 7.9 and 7.9 Hz, 2H), 2.14 (s, 3H), 1.60-1.50 (br m, 4H), 0.92 (t, J = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.34, 151.18, 149.28, 114.78, 110.12, 30.98, 25.67, 22.47, 13.79, 17.68.
13. We also attempted the synthesis of **5a** from (*E*)-2,3-dibromopropenoic acid and phenylacetylene using $PdCl_2(PPh_3)_2$, PPh_3, CuI and Et_3N according to the general procedure described by Lu et al. for the synthesis of (*Z*)-γ-ylidenebutenolides [Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963-5966]. Unfortunately, this reaction did not provide **5a** but afforded 1,4-diphenylbutadiyne and a compound to which, on the basis of its MS spectrum, we tentatively assigned the structure of 1,2,4-triphenylbenzene.
14. For previous syntheses of bovolide, see: *(a)* Ref 4; *(b)* Coperét, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422-3431; *(c)* Wulff, W. D.; Gilbertson, S. R.; Springer, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 520-522.