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Stereoselective synthesis of α-alkylidene- and substituted alkylidene-γ-lactones

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Abstract

Cross-coupling reactions of (*E*)- and (*Z*)-tosylates of α-hydroxymethylene-γ-butyrolactone with aryl, heteroaryl, alkyl, and alkynylzinc chlorides under $Pd(PPh_3)_4$ catalysis were found to be a suitable synthetic method for stereoselective preparation of α-alkylidene- and substituted alkylidene-γ-lactones. The reactions, conducted under mild conditions, proceed with high stereoselectivity and moderate yields.

Keywords: methylene lactones; coupling reactions; palladium; zinc compounds.

The α-methylene-γ-lactone moiety is an integral building block of many natural products exhibiting a wide range of important biological activities, such as cytotoxicity,[1] phytotoxicity,[2] or antitumor activity.[3,4] However, possible application of such compounds is strongly limited by their high cytotoxicity.[5] One way to modify chemical and physical properties as well as the biological activity of methylene lactones is alkylation and arylation of their exocyclic double bond.[6] Such substituted α-methylene-γ-lactones also occur in many natural compounds;[7] normally, they can be synthesized via two general ways. One, represented by a classical Claisen condensation, is based on introduction of the alkylidene group on to the α-position of the lactone ring,[8] the second yields α-alkylidene lactones by ring closure reactions from acyclic, olefinic or acetylenic, precursors containing suitable functional groups.[9] Although a number of methods have been reported, only a few of them can control the configuration of the exocyclic double bond.[10,11]

Recently, a stereoselective preparation of sulfonates and carboxylates of α-hydroxymethylene lactones has been developed in our department.[12] Since it is well-known that vinylic sulfonates are suitable substrates for coupling reactions with a variety of organometallic reagents, forming new C–C bonds with outstanding stereoselectivity,[13] we decided to investigate the potential of such reactions for stereoselective synthesis of the title lactones. Organozinc compounds were chosen as coupling reagents because of their easy accessibility and tolerance to many reactive groups including ester and lactone functionalities.[14]

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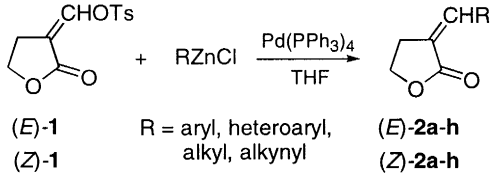
In this paper we report a novel, general method of stereoselective synthesis of α-alkylidene- and substituted alkylidene-γ-butyrolactones by cross-coupling reactions of (*E*)- and (*Z*)-3-(tosyloxymethylene)dihydro-2(3*H*)-furanones ((*E*)- and (*Z*)-**1**) with various aryl, heteroaryl, alkyl, and alkynylzinc chlorides (Scheme 1). The reaction was catalyzed by 3–5 mol% of tetrakis(triphenylphosphine)palladium(0). The starting organozinc compounds were prepared from the corresponding Grignard (phenyl, naphthyl, and octyl) or organolithium (furyl, thienyl, butyl, phenylethynyl, and trimethylsilylethynyl) reagents. With (*E*)-**1**, reactions have been carried out in THF at 70°C, but with (*Z*)-**1**, the temperature has to be kept between 0–5°C in order to get satisfactory stereoselectivity.[15,16]



Scheme 1.

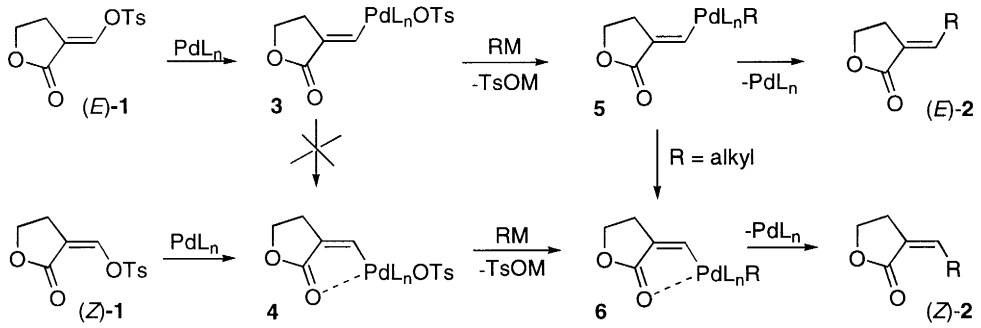
Table 1 shows that the coupling gave the best results with arylzinc chlorides, entries 1, 2, 9, and 10, where excellent stereoselectivity was obtained for both isomers of **1**. Also very good stereoselectivity was achieved in the reactions of heteroarylzinc chlorides. In the case of (*E*)-**1**, total retention of configuration was observed (entries 3 and 4), whereas tosylate (*Z*)-**1** gave small amounts of the thermodynamically more stable[8] (*E*)-products (5% entry 11, 7% entry 12). Similarly, the coupling of (*Z*)-**1** with alkylzinc chlorides, entries 13 and 14, gave only 4 and 5% of (*E*)-products, respectively. The amount of (*E*)-product increased with reaction time in the order aryl<heteroaryl<alkyl<alkynyl. The largest extent of stereochemical leakage, about 20%, was obtained in coupling of alkynylzinc chlorides with (*Z*)-**1**, entries 15 and 16. The reason for thus could again lie in the higher thermodynamic stability of the (*E*)-isomers of **2g** and **2h** and in a more facile isomerization of enyne lactone system in the presence of Pd(II)-complexes. The only enyne lactone of this type in the literature was prepared by Ji et al.[17] by Heck coupling of phenylacetylene with 3-bromomethylene-4-hydroxymethyl-5-pentyldihydro-2(3*H*)-furanone. The starting lactone as well as the product had an (*E*)-configuration.

Table 1
Results of cross-coupling reactions of (*E*)-**1**, entries 1–8, and (*Z*)-**1**, entries 9–16, with organozinc chlorides (Scheme 1)

Entry	RZnCl	Main prod.	R.time [h]	% *E*[a]	Yield[b] [%]	Entry	RZnCl	Main prod.	R.time [h]	% *Z*[a]	Yield [%][b]
1	Ph	(*E*)-**2a**	1.0	>99	73	9	Ph	(*Z*)-**2a**	1.0	>99	71
2	2-naphthyl	(*E*)-**2b**	1.5	>99	50	10	2-naphthyl	(*Z*)-**2b**	1.0	>99	82
3	2-furyl	(*E*)-**2c**	5.0	>99	68	11	2-furyl	(*Z*)-**2c**	8.0	95	70
4	2-thienyl	(*E*)-**2d**	3.5	>99	69	12	2-thienyl	(*Z*)-**2d**	7.5	93	69
5	*n*-C_4H_9	(*E*)-**2e**	3.0	88	76	13	*n*-C_4H_9	(*Z*)-**2e**	8.0	96	70
6	*n*-C_8H_{17}	(*E*)-**2f**	3.6	90	74	14	*n*-C_8H_{17}	(*Z*)-**2f**	7.6	95	71
7	C≡CPh	(*E*)-**2g**	3.5	>99	58	15	C≡CPh	(*Z*)-**2g**	96	80	61
8	C≡CTMS	(*E*)-**2h**	4.0	>99	62	16	C≡CTMS	(*Z*)-**2h**	96	81	62

[a] Determined by ^{1}H NMR. [b] Isolated yield of the main product.

Quite surprisingly, reactions of (*E*)-**1** with alkylzinc chlorides gave mixtures of isomers with about 10% of (*Z*)-products. Within the generally accepted mechanism of Pd-catalyzed cross-coupling reactions, these results could be rationalized according to Scheme 2. Obviously, isomerization during the oxidative addition step can be ruled out, because this reaction step does not involve RZnCl and is the same as that which occurs in the reactions yielding complete retention of configuration. The reason for the *E–Z* isomerization can, however, lie in the different character of Pd(II)-complex **5** formed after transmetallation by RZnCl. Compared to other R substituents, alkyls are pure σ-donors without possibility of π-interaction with orbitals on the palladium. Therefore, these orbitals can take part in some kind of push–pull interaction with the methylene lactone system weakening the exocyclic double bond and facilitating its rotation to the (*Z*)-configuration, which is stabilized by an additional, though weak, chelating interaction of Pd with the lactone carbonyl oxygen. Reductive elimination of **6** would then result in formation of the (*Z*)-isomer.



Scheme 2.

Our efforts to couple tosylates **1** with some vinyl- or allylzinc chlorides failed due to product decomposition.

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15. Typical procedure for coupling of **1** was as follows: A solution of (*E*)-**1** (0.53 g, 2 mmol) and $Pd(PPh_3)_4$ (0.115 g, 0.1mmol) in the THF (10 ml) was added via syringe to a solution of phenylethynylzinc chloride (4 mmol), prepared by the reaction of phenylacetylene (0.4 ml, 4 mmol) and *n*-BuLi (4 mmol) in THF (10 ml) at 0–5°C and subsequent transmetallation with THF solution of $ZnCl_2$ (0.7 g, 5 mmol) at room temperature. The reaction mixture was then refluxed until (*E*)-**1** was consumed. Usual work-up with aqueous NH_4Cl gave crude product that was chromatographed on silica gel (petroleum ether:ether, 3:2). Recrystallization from petroleum ether gave 0.23 g (58 %) of (*E*)-**2g**: m.p. 109.5–110.2°C; ^{1}H NMR: 7.50 (m, 2 H, arom); 7.39 (m, 3H, arom), 6.82 (t, *J*=3.2 Hz, 1H), 4.45 (t, *J*=7.3 Hz, 2H), 3.16 (dt, *J*=3.2 Hz, 7.3 Hz, 2H); ^{13}C NMR: 170.2, 135.7, 131.8, 129.5, 128.5, 122.1, 116.9, 102.0, 85.7, 65.4, 27.3, IR: 2067, 1741, 1645, cm^{-1}. Anal. calcd for $C_{13}H_{10}O_2$: C, 78.8%; H, 5.1%; found: C, 78.6%; H, 5.5%.
16. Selected physical and spectroscopic data of newly synthesized compounds: (*E*)-**2d**: m.p. 130.3–131.2°C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.76 (s, 1H), 7.56 (d, *J*=4.9 Hz, 1H), 7.33 (d, *J*=3.3 Hz, 1H), 7.16 (m, 1H), 4.49 (t, *J*=7.3 Hz, 2H), 3.15 (dt, *J*=2.7 Hz, 7.3 Hz, 2H); ^{13}C NMR: 172.1, 139.1, 132.3, 130.2, 129.1, 128.1, 121.1, 65.3, 27.4; IR: 1736, 1641 cm^{-1}. Anal. calcd for $C_9H_8O_2S$: C, 60 %; H, 4.5 %; found: C, 60.3%; H, 4.3%. (*E*)-**2h**: m.p. 44.2–45.1°C; ^{1}H NMR ($CDCl_3$, 500 MHz): 6.57 (t, *J*=3.1 Hz, 1H), 4.41 (t, *J*=7.2 Hz, 2H), 3.07 (dt, *J*=3.1 Hz, 7.2 Hz, 2H), 0.23 (s, 9H); ^{13}C NMR: 170.1, 137.1, 116.7, 108.9, 100.6, 65.4, 27.3, −0.2; IR: 2197, 1751, 1646 cm^{-1}. Anal. calcd for $C_{10}H_{14}O_2Si$: C, 61.8%; H, 7.3%; found: C, 61.5%; H, 7.3%. (*Z*)-**2c**: m.p. 88–89°C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.78 (d, *J*=3.6 Hz, 1H), 7.45 (d, *J*=1.3 Hz, 1H), 6.85 (t, *J*=2.3 Hz, 1H), 6.50 (m, 1H), 4.39 (t, *J*=7.4 Hz, 2H), 3.15 (dt, *J*=2.3 Hz, 7.4 Hz, 2H); ^{13}C NMR: 169.9, 157.0, 143.9, 121.9, 120.9, 117.5, 106.7, 65.3, 28.4; IR: 1729, 1642 cm^{-1}. Anal. calcd for $C_9H_8O_3$: C, 65.8%; H, 4.9%; found: C, 65.5%; H, 5.0%. (*Z*)-**2d**: m.p. 96.5–97.3°C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.57 (d, *J*=3.5 Hz, 1H), 7.33 (d, *J*=5.1 Hz, 1H), 7.12 (s, 1H), 7.07 (m, 1H), 4.41 (t, *J*=7.4 Hz, 2H), 3.12 (dt, *J*=2.0 Hz, 7.4 Hz, 2H); ^{13}C NMR: 169.5, 139.1, 136.9, 134.6, 131.1, 126.8, 119.1, 65.3, 30.5; IR: 1726, 1633 cm^{-1}. Anal. calcd for $C_9H_8O_2S$: C, 60%; H, 4.5%; found C, 60.3%; H, 4.3%. (*Z*)-**2g**: m.p. 75.4–76.5°C; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.57 (m, 2H), 7.35 (m, 3H), 6.35 (t, *J*=2.6 Hz, 1H), 4.37 (t, *J*=7.3 Hz, 2H), 3.10 (dt, *J*=2.3 Hz, 7.3 Hz, 2H); ^{13}C NMR: 167.3, 134.7, 130.8, 128.9, 128.4, 121.2, 115.9, 101.9, 84.7, 64.8, 26.6; IR: 2198, 1745, 1635 cm^{-1}. Anal. calcd for $C_{13}H_{10}O_2$: C, 78.8 %; H, 5.1%; found: C, 78.8%; H, 5.5%. (*Z*)-**2h**: m.p. 64.2–65.0°C; ^{1}H NMR ($CDCl_3$, 500 MHz): 6.14 (t, *J*=2.7 Hz, 1H), 4.32 (t, *J*=7.2 Hz, 2H), 3.03 (dt, *J*=2.7 Hz, 7.3 Hz, 2H), 0.20 (s, 9H); ^{13}C NMR: 167.6, 135.5, 116.5, 108.9, 99.6, 64.7, 28.9, −0.2; IR: 2113, 1742, 1638 cm^{-1}. Anal. calcd for $C_{10}H_{14}O_2Si$: C, 61.8%; H, 7.3%; found: C, 61.5%; H, 7.3%.
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