Palladium Dihalide Catalysed Stereoselective Synthesis of α-(*Z*)-Halomethylene-γ-butyrolactone Derivatives

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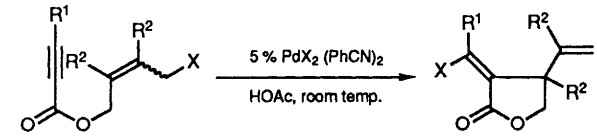
α-Methylene-γ-butyrolactone rings have been constructed by a palladium dihalide catalysed intramolecular cyclization reaction of allylic propiolates.

There has been much recent interest in α-methylene-γ-butyrolactones due to the discovery of several naturally occurring cytotoxic or antitumor agents (*e.g.*, euparotin, elephantin, vernolepin, *etc.*) which possess this characteristic α-methylene lactone ring.[1,2] There have been several reports on the synthesis of α-methylene lactones.[3—5] Generally, the α-methylene lactones are synthesized either by α-methylenation of preformed lactones or from functionalised acyclic precursors. In the latter case, several methods such as the lactonization of the corresponding acids or esters have been reported, but intramolecular cyclization of a corresponding propiolate to construct an α-methylene lactone ring directly has not been studied.

There are reports in the literature of palladium-catalysed cyclocarbonylations of hydroxysubstituted vinyl halides and cyclizations of homoallylic carbonochloridates.[6—8] Recently, much attention has been focused on the transition metal(0) complex catalysed intramolecular Heck reaction,[9] intramolecular allylation of alkenes or alkynes,[10] and the cyclization reaction of dienes, enynes, and diynes,[11] but the transition metal(0) complex catalysed cyclization reaction of allylic unsaturated esters has not been described, probably due to predicted allylic carbon–oxygen bond cleavage by the transition metal(0) catalyst. Thus, it is interesting to study the cyclization reaction of allylic unsaturated esters which would lead to a lactone ring. Kaneda *et al.* have studied the palladium dihalide catalysed codimerization of alkynes and allylic halides in which the allylic halides were used in large excess both as a reactant and as a solvent.[12] It occurred to us that it might be possible to construct the important α-methylene-γ-butyrolactone structural unit from a molecule which incorporates both the carbon–carbon triple bond and the allylic halide moiety, using as a catalyst a divalent palladium complex which will not cleave the allylic C–O bond. Based on these considerations, we attempted the bisbenzonitrile palladium dichloride complex catalysed cyclization reaction of (4-chlorobut-2-enyl)propiolate, which can be synthesized conveniently from propiolic acid and 1,4-dichlorobut-2-ene. The α-(*Z*)-chloromethylene-β-vinyl-γ-butyrolactone (**2a**) was obtained stereoselectively in high yield, Scheme 1, Table 1.

This reaction did not proceed well in MeCN, C_6H_6, EtOH, tetrahydrofuran (THF), and $MeNO_2$; HOAc was the most suitable solvent. With both chloro- and bromo-derivatives, the α-(*Z*)-halomethylene-β-vinyl-γ-butyrolactones (**2**) were obtained stereoselectively in high yield.† The ratios of *Z*/*E* isomers referred to the *exo* carbon–carbon double bonds were determined from 90 MHz ^{1}H NMR spectra and GC. The configuration of the allylic double bond does not influence the reaction (compare Table 1, entries 1 and 2). Only a small amount of cyclized product was formed from an ester with a tetrasubstituted allylic double bond (entry 6). No cyclic product was isolated when the allylic double bond moiety in ester (**1**) was displaced by two conjugated double bonds, *e.g.*, ester (**3**).



(1) **a**; $R^1 = R^2 = H$, X = Cl
b; $R^1 = R^2 = H$, X = Cl
c; $R^1 = R^2 = H$, X = Br
d; $R^1 = R^2 = H$, X = I
e; R^1 = n-C_5H_{11}, $R^2 = H$, X = Br
f; $R^1 = H$, R^2 = Me, X = Br

(2)

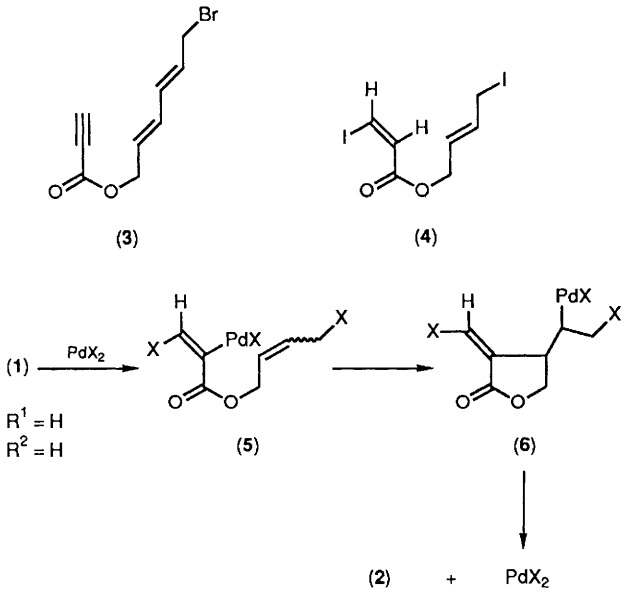
Scheme 1

Table 1. Cyclization reaction of (4-halobut-2-enyl)propiolate catalysed by bisbenzonitrile palladium dihalide in acetic acid.[a]

Entry	(1)[b]	Reaction time	(2)	Yield of (2)[c] /%
1	(**1a**)	1 h	(**2a**)	81 (>97/3)
2	(**1b**)	1 h	(**2b** = **2a**)	75 (>97/3)
3	(**1c**)	3 h	(**2c**)	86 (97/3)
4	(**1d**)	6 days	(**2d**)	53 (88/12)
5	(**1e**)	24 h	(**2e**)	71 (55/45)
6	(**1f**)	6 days	(**2f**)	<5

[a] All products gave satisfactory IR, MS, and ^{1}H NMR spectroscopic data, and the new compounds gave satisfactory elemental analyses. [b] The allylic double bonds in (**1**) are in the *E* configuration except in (**1a**), which is in the *Z* configuration. [c] The numbers in parentheses are ratios of *Z*/*E* isomers referred to the *exo* double bonds, the configuration of which was assigned on the basis of the higher field ^{1}H NMR resonance for the *Z* isomer.[14] For (**2a**) or (**2b**), only one isomer could be detected by ^{1}H NMR spectra. The stereochemistry of the two isomers of (**2e**) was determined by comparison of the chemical shifts of the allylic methylene protons on the pentyl group.[14]

† *Spectroscopic data* for (**2a**)/(**2b**): IR (neat) 1760, 1640, 1160 cm^{-1}; ^{1}H NMR [$CDCl_3$, 90 MHz, tetramethylsilane (TMS)] δ 6.57 (d, 1H, *J* 2.7 Hz), 5.90—5.04 (m, 3H), 4.45 (t, 1H, *J* 7.6 Hz), 3.95 (t, 1H, *J* 7.6 Hz), 3.73 (m, 1H, *J* 7.6, 2.7 Hz); MS (*m*/*z*) 161 [M^+ +1 (^{37}Cl)], 160 [M^+ (^{37}Cl)], 159 [M^+ +1 (^{35}Cl)], 158 [M^+ (^{35}Cl)], 130, 128, 102, 100, 93, 65. For (**2c**): IR (neat) 1760, 1630, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz, TMS) δ [7.60 (d, *J* 2.7 Hz), 6.80 (d, *J* 2.7 Hz), 1H], 5.91—5.06 (m, 3H), 4.45 (t, 1H, *J* 7.6 Hz), 3.95 (t, 1H, *J* 7.6 Hz), 3.75 (m, 1H, *J* 2.7, 7.6 Hz); MS (*m*/*z*) 205 [M^+ +1 (^{81}Br)], 204 [M^+ (^{81}Br)], 203 [M^+ +1 (^{79}Br)], 202 [M^+ (^{79}Br)], 174, 172, 146, 144, 93, 65. For (**2d**): IR (neat) 1760, 1630, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz, TMS) δ [7.85 (d, *J* 2.7 Hz), 7.20 (d, *J* 2.7 Hz), 1H], 5.84 (m, 3H), 4.40 (t, 1H, *J* 7.6 Hz), 3.90 (t, 1H, *J* 7.6 Hz), 3.70 (m, 1H, *J* 2.7, 7.6 Hz); MS (*m*/*z*) 251 (M^+ +1), 250 (M^+), 220, 123, 93, 65. For (**2e**) *Z* isomer: IR (neat) 1760, 1640, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz, TMS) δ 6.20—5.60 (m, 2H), 5.40—5.00 (m, 1H), 4.80—3.60 (m, 3H), 2.45 (m, 2H), 1.30 (m, 6H), 0.90 (t, 3H); MS (*m*/*z*) 275 [M^+ +1 (^{81}Br)], 274 [M^+ (^{81}Br)], 273 [M^+ +1 (^{79}Br)], 272 [M^+ (^{79}Br)], 193, 163, 149, 147, 133, 121, 119, 107, 105, 93, 91, 55. For (**2e**) *E* isomer: IR (neat) 1760, 1650, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz, TMS) δ 6.20—5.60 (m, 2H), 5.40—5.00 (m, 1H), 4.80—3.60 (m, 3H), 3.20 (m, 2H), 1.30 (m, 6H), 0.90 (t, 3H); MS (*m*/*z*) 275 [M^+ +1 (^{81}Br)], 274 [M^+ (^{81}Br)], 273 [M^+ +1 (^{79}Br)], 272 [M^+ (^{79}Br)], 193, 163, 149, 147, 123, 107, 105, 93, 91, 55.



Scheme 2

In the case of (4-iodobut-2-enyl)propiolate (**1d**), an equimolar amount of lithium iodide was added to dissolve the insoluble palladium di-iodide and the reaction was carried out at 20—60 °C. In addition to the lactone (**2d**), another product characterized as (4′-iodobut-2′-enyl)-3-iodopropenoate (**4**) was isolated. Thus, it is proposed that the present reaction probably occurs *via trans*-halopalladation of the triple bond,[13] followed by insertion of the double bond in ester (**1**) to the newly formed carbon–palladium bond to form (**6**), and finally dehalopalladation to form a new double bond and regenerate the catalyst PdX_2 (Scheme 2). The mechanism of the formation of the by-product (**4**) is not clear. Here the carbonyl group acts as a directing group to control the regiochemistry of the halopalladation of the triple bond. The *trans*-halopalladation determines the stereochemistry of the *exo* double bond in product (**2**).

A typical procedure is as follows. Glacial acetic acid (2.5 ml), [4-chloro-(*E*)-but-2-enyl]propiolate (**1b**) (80 mg, 0.05 mmol), and bisbenzonitrile palladium dichloride (10 mg, 0.0026 mmol) were added to a reaction tube under nitrogen. The reaction was stirred at room temperature for 1 h, then ether was added. The mixture was washed with water then saturated $NaHCO_3$ solution and the combined aqueous layers were extracted with ether. The combined organic layers were then washed with saturated NaCl solution and dried over $MgSO_4$. After evaporation of the solvent, (**2b**) was obtained by preparative TLC (eluent, light petroleum : ethyl acetate 10 : 1) in 75% yield (60 mg).

This reaction offers a convenient route for preparing α-methylene-γ-butyrolactone derivatives under mild conditions and in high yield. In particular, it can simultaneously introduce the *exo* cyclic (*Z*)-halomethylene and vinyl groups as useful functionalities for further synthetic studies.

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