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Improved method for the synthesis of (*E*)-cyclic-β-alkoxyacrylates under mild conditions

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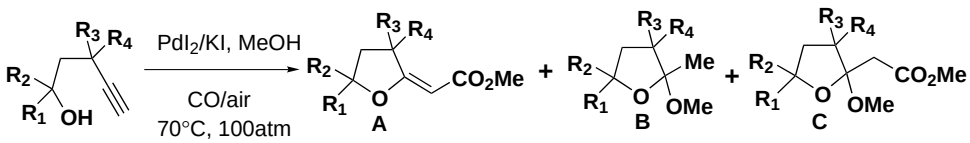
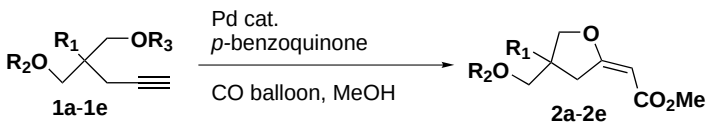
Abstract—The oxidative cyclization–methoxycarbonylation of cyclic- and acyclic-4-yn-1-ols **1** in the presence of Pd(II)/*p*-benzoquinone in methanol at 0°C under a carbon monoxide atmosphere (balloon) afforded (*E*)-cyclic-β-alkoxyacrylates **2** in good to excellent yields. The present reaction is applicable to the above-mentioned substrates bearing the additional functional groups such as acetate, hydroxyl, ketone, ester, terminal acetylene and the acid-sensitive protecting groups (TBDPS, TBDMS, MOM and THP). A new synthesis of the left part of the cystothiazoles is presented. © 2001 Elsevier Science Ltd. All rights reserved.

A β-alkoxyacrylate system is a common structure which is present in antifungal antibiotics such as cystothiazoles,[1] myxothiazoles,[2] meithiazoles,[3] strobilurins[4] and oudemansins.[5] The practical construction of the β-alkoxyacrylate system is attractive for the synthesis of β-methoxyacrylate antibiotics. Palladium-catalyzed carbonylation of alkynes is one of the useful methods for the synthesis of acetylene carboxylate,[6] γ-lactones[7] and benzofurans.[8] Recently, Okumoto et al.[9] and Gabriele et al.[10] reported the palladium-mediated synthesis of γ-acetoxy-β-methoxyacrylates and (*E*)-cyclic-β-alkoxyacrylates, respectively. A 1,1-disubstituted propargylic acetate in the substrate is indispensable for the former reaction. The latter reaction was performed under high pressure and temperature using a PdI_2/KI catalyst, and afforded a mixture of the acetal products **B** and **C** by the generated acid-catalyzed addition of MeOH along with β-alkoxyacrylate **A** (Scheme 1). In order to overcome this disadvantage, we focused our attention on trapping the acid, which is co-produced from the reaction. *p*-Benzoquinone was found to be a very efficient reagent for trapping a proton of hydrochloric acid arising from a catalytic cycle and oxidative transfer of the generated Pd(0) species to a Pd(II) species.[11] Now we wish to report here an improved method for the synthesis of (*E*)-cyclic-β-alkoxyacrylates **2** using a Pd(II)/*p*-benzoquinone catalytic system under mild conditions and a new approach to the synthesis of the left part of the cystothiazoles (Scheme 2).[12]



Scheme 1.



Scheme 2.

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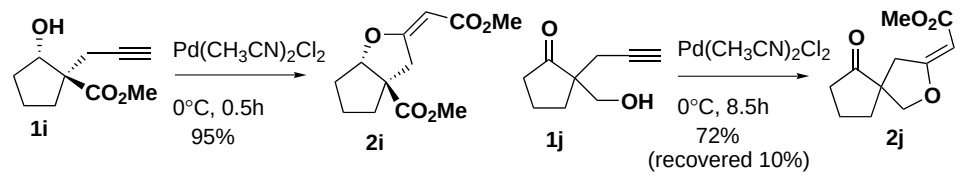
As shown in Table 1 (entries 1–5), five kinds of palladium catalysts were examined in oxidative cyclization of the mono-protected diol derivative **1a**. Among them, palladium(II)chloride and bis(acetonitrile)-dichloropalladium(II) gave good results (entries 4 and 5). The oxidative cyclization–methoxycarbonylation of **1a** in the presence of Pd(II)/*p*-benzoquinone in methanol at 0°C under a carbon monoxide atmosphere (balloon) afforded (*E*)-cyclic-β-alkoxyacrylates **2a** in good yields.[13] The use of a diacetate **1b** possessing no hydroxyl group gave the starting material **1b** quantitatively (entry 6). These results suggested that the presence of a free hydroxyl group in the substrate is indispensable for initiating the reaction. The influence of the present reaction on some typical protecting groups in the substrates was investigated. The substrates **1c–e** bearing a protecting group such as TBDMS, MOM and THP reacted smoothly to afford **2c–e** in good yields, respectively (entries 7–9). These protecting groups tolerated the present reaction condition. The reactions of diol substrate **1f** and bis-propargyl substrate **1g**, **1h** also afforded the corresponding products **2f** (79%), **2g** (87%) and **2h** (91%), respectively (entries 10, 11 and 12).

The present reaction is applicable to the cyclic substrates **1i** and **1j** to afford the bicyclo acrylate **2i** and the spiro cyclic product **2j** in good to excellent yields (Scheme 3).

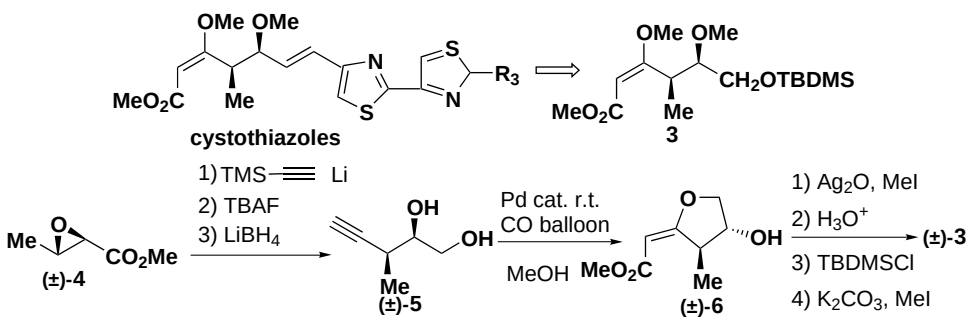
As a synthetic application, silyl ether **3** corresponding to the left part of the cystothiazoles[12] was synthesized (Scheme 4). The nucleophilic ring-opening of the epoxy ester **4**[14] followed by desilylation and subsequent reduction of the ester afforded 4-yn-1-ol derivative **5** (73%, three steps). The oxidative cyclization–methoxycarbonylation of **5** catalyzed by $PdCl_2$ gave the tetrahydro-2-furylidene acetate derivative **6** in 76% yield. Compound **6** was converted into the silyl ether **3** by the following four-step sequence in 31% overall yield. Methylation of the hydroxyl group in **6** followed by acid-catalyzed hydrolysis of cyclic enol ether and subsequent silyl protection of the hydroxyl group afforded

Table 1. Methoxycarbonylative cyclization of **1**

Entry	Pd cat. (5 mol%)	Substrate	R_1	R_2	R_3	Product	Yield (%)	Condition	
1	$Pd_2(dba)_3$	**1a**	Bn	Ac	H	**2a**	20	rt	20 h
2	$(Ph_3P)_2PdCl_2$	**1a**	Bn	Ac	H	**2a**	28	rt	20 h
3	$Pd(OAc)_2$	**1a**	Bn	Ac	H	**2a**	20	rt	20 h
4	$PdCl_2$	**1a**	Bn	Ac	H	**2a**	80	rt	15 h
5	$(CH_3CN)_2PdCl_2$	**1a**	Bn	Ac	H	**2a**	88	0°C	5 h
6	$(CH_3CN)_2PdCl_2$	**1b**	Bn	Ac	Ac	–	Recovery	rt	20 h
7	$(CH_3CN)_2PdCl_2$	**1c**	Bn	TBDMS	H	**2c**	87	0°C	4 h
8	$(CH_3CN)_2PdCl_2$	**1d**	Bn	MOM	H	**2d**	88	0°C	5 h
9	$(CH_3CN)_2PdCl_2$	**1e**	Bn	THP	H	**2e**	69	0°C	4 h
10	$(CH_3CN)_2PdCl_2$	**1f**	Bn	H	H	**2f**	79	0°C	1 h
11	$(CH_3CN)_2PdCl_2$	**1g**	Propargyl	Ac	H	**2g**	87	0°C	4 h
12	$(CH_3CN)_2PdCl_2$	**1h**	Propargyl	TBDPS	H	**2h**	91	0°C	4 h



Scheme 3.



Scheme 4.

β-keto ester, which was treated with MeI to provide the desired compound **3**.

In summary, we have presented an oxidative cyclization–methoxycarbonylation of cyclic- and acyclic-4-yn-1-ols using a Pd(II)/*p*-benzoquinone catalytic system under mild conditions. The present reaction is considered to be efficient for the construction of bicyclic and spiro cyclic compounds and for the synthesis of β-methoxyacrylate antibiotics such as cystothiazoles.

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13. The substrates **1** (except **1b**) are all racemic compounds. General procedure: A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.01 mmol), *p*-benzoquinone (0.22 mmol) and MeOH (4 mL), was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping-filling via the three-way stopcock. A solution of the substrate **1** (0.2 mmol) in MeOH (2 mL) was added dropwise to the stirred mixture via a syringe at 0°C. After being stirred for the period of time, the mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% NaOH aq (40 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (20/1–10/1) afforded **2** as a colorless oil. Satisfactory analytical data were obtained for all new compounds. **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.83 (2H, s), 3.07 (2H, d, $J=1.6$ Hz), 3.66 (3H, s), 3.92 (2H, s), 4.05 (1H, d, $J=9.2$ Hz), 4.08 (1H, d, $J=9.2$ Hz), 5.31 (1H, t, $J=1.6$ Hz), 7.09–7.32 (5H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.9, 38.7, 39.6, 45.8, 50.8, 65.8, 76.5, 90.7, 126.9, 128.5, 129.8, 135.9, 168.5, 170.4, 174.9; FAB-MS *m*/*z*: 305 (M^++1); anal. found: C, 67.41; H, 6.99. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62%. The (*E*)-stereochemistry of **2a** was confirmed by the following isomerization experiment. Treatment of **2a** with excess of *p*-TsOH gave (*Z*)-**2a** in 2.8% together with unchanged **2a**. The stereochemistry of (*Z*)-**2a** was confirmed by an NOE experiment. (*Z*)-**2a** was converted to **2a** again in $CDCl_3$. **2j**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.07 (4H, m), 2.26–2.44 (2H, m), 3.15 (1H, dd, $J=17.0$, 1.8 Hz), 3.21 (1H, dd, $J=17.0$, 1.8 Hz), 3.66 (3H, s), 4.06 (1H, d, $J=8.8$ Hz), 4.23 (1H, d, $J=8.8$ Hz), 5.34 (1H, t, $J=1.8$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 19.6, 35.2, 37.4, 40.8, 50.8, 54.7, 78.0, 90.5, 168.7, 174.4, 217.8; FAB-MS *m*/*z*: 211 (M^++1); anal. found: C, 62.79; H, 6.71. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%.
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