

Pd(II)-Catalyzed Coupling Cyclization of 2,3-Allenic Acids with Allylic Halides. An Efficient Methodology for the Synthesis of β -Allylic Butenolides

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Received April 22, 2003

An effective method for the synthesis of β -allyl polysubstituted butenolides from the easily available allylic halides and 2,3-allenic acids is described. By using this method optically active butenolides can be obtained. According to the results presented in this paper, the reaction may proceed via three consecutive steps: cyclic oxypalladation of the allene, insertion of the C=C bond in allylic halides, and β -dehalopalladation.

Introduction

Butenolides, a structural unit in many natural products, are important intermediates in organic synthesis.¹ Butenolide-containing compounds are considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors, phospholipase A₂ inhibitors, etc.² Thus, much attention has been paid to the development of new methods for the synthesis of these interesting compounds.³

Transition metal-catalyzed methodology has been proven to be one of the most powerful pathways for the formation of carbon-carbon bonds as well as carbon-heteroatom bonds.⁴ Recently, we have applied the transition metal-promoted or -catalyzed cyclization reactions of 2,3-allenic acids/esters or salts with organic halides for the synthesis of several kinds of substituted butenolides.⁵ In those reactions, the sp²-hybridized carbon atom

could be easily introduced to the β -position of butenolides.^{5e-j} Nevertheless, under those established reaction conditions the sp³-hybridized carbon atom could not be introduced into the products via the direct reaction of 2,3-allenic acids and sp³-carbon halides due to the potential stability problem of alkyl palladium species. Although we have successfully developed an alternative two-step protocol for the synthesis of the β -alkyl-substituted butenolides,^{5k-1} efficient and general routes for the direct synthesis of the β -sp³-hybridized carbon atom substituted butenolides from 2,3-allenic acids are still challenging. On the other hand, palladium-catalyzed allylation is a

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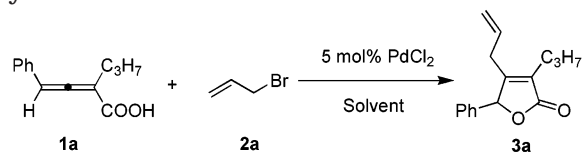
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TABLE 1. Pd(II)-Catalyzed Coupling Cyclization Reaction of 4-Phenyl-2-propyl-2,3-butadienoic Acid and Allyl Bromide

entry	equiv of 2a	solvent	<i>T</i> (°C)	time (h)	yield (%)
1	5	DMA	rt	38	68 ^a
2	5	DMA	rt	96	65 ^b
3	5	DMA	rt	24	0 ^c
4	5	CH ₃ CN	50	61	47
5	5	THF	50	84	63
6	5	DMA	50	17	88
7	1.1	DMA	50	38	40
8	2	DMA	50	38	77
9	10	DMA	50	24.5	90

^a **1a** was recovered in 20% yield. ^b 5 mol % of Pd(OAc)₂ was used. ^c 1 equiv of K₂CO₃ was added and allyl 4-phenyl-2-propyl-2,3-butadienoate (**6**) was obtained in 95% yield.

practical tool for introducing the allylic group into the products.^{6,7} In this paper, we wish to disclose an efficient way to prepare β -allylic-substituted butenolides by the Pd(II)-catalyzed coupling cyclization of 2,3-allenoic acids with allylic halides.

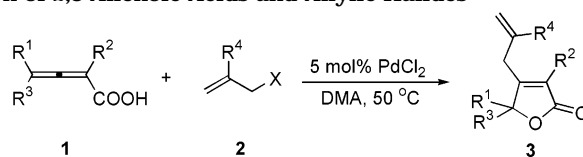
Results and Discussions

The reaction of 4-phenyl-2-propyl-2,3-butadienoic acid (**1a**) and allyl bromide **2a** was used to optimize the reaction conditions and some representative results are listed in Table 1. In most cases, the reaction proceeds smoothly in the presence of a large excess of allyl bromide (Table 1, entries 1–6). The fewer the equivalents of allyl bromide used, the lower the yields (Table 1, entries 6–9). In this reaction, the use of a base should be avoided since the reaction afforded the corresponding ester, i.e., allyl

4-phenyl-2-propyl-2,3-butadienoate **6**, in the presence of 1 equiv of potassium carbonate (Table 1, entry 3). Palladium acetate was less effective than palladium chloride (Table 1, entries 1 and 2). The best results were obtained when 5 mol % of PdCl₂ and 5 equiv of allyl bromide **2a** in DMA were used, leading to a 88% yield of **3a**.

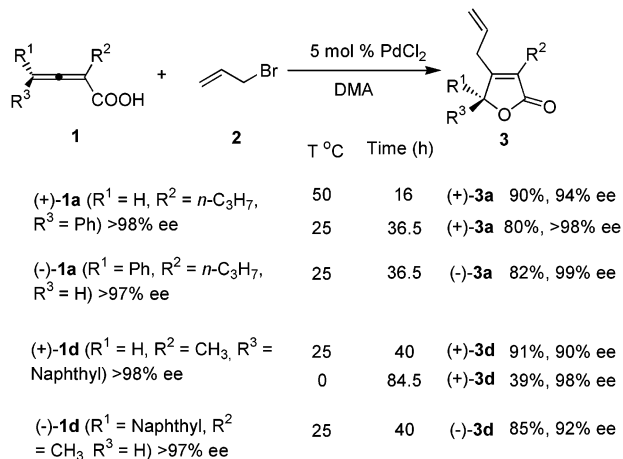
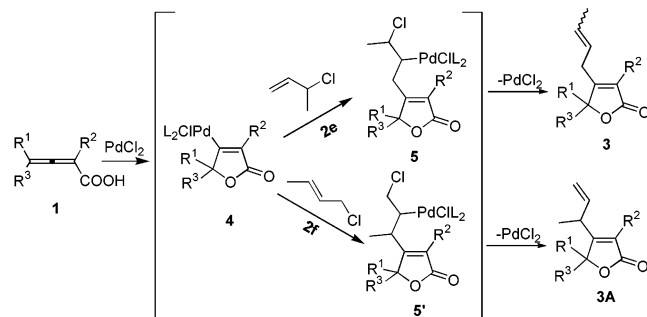
Some typical results under the established conditions are shown in Table 2. From Table 2 it should be pointed out that the yields range from moderate to excellent. Allylic chloride is equally active (Table 2, entries 7, 8, and 13). The substituents of the 2,3-allenoic acids may be aryl, allyl, benzyl, or alkyl. The reaction of 4-alkyl (methyl)-substituted 2,3-allenoic acid **1g** and 5 equiv of allyl bromide **2a** afforded the corresponding product **3n** in 52% yield (Table 2, entry 14). By increasing the amount of allyl bromide to 10 equiv, a higher yield was observed (Table 2, entry 15). On the other hand, a range of substituted allylic halides that bear a phenyl group, a bromine atom, or a methyl group can be successfully coupled (Table 2, entries 6–13). With the fully substituted 2,3-allenoic acid **1h**, the reaction also afforded **3o** in 83% yield (Table 2, entry 16).

Furthermore, the syntheses of optically active butenolides were realized from the optically active 2,3-allenoic acids, which could be easily obtained by resolution of the racemic allenoic acids.^{5d} Under the standard conditions, the chirality transfer is less effective (Scheme 1) probably due to the relatively high reaction temperature. When the reaction was carried out at 25 °C, the chirality of the starting material was transferred into the product efficiently. Under the new conditions, we easily obtained four optically active butenolides. The chirality transfer is less effective when optically active 2,3-allenoic acid **1d** was used. When the reaction temperature was further decreased to 0 °C, the reaction gave the product **3d** in a higher ee but a lower yield. The absolute configurations

TABLE 2. The Coupling Reaction of 2,3-Allenoic Acids and Allylic Halides^a

entry	1			2		time (h)	3	yield (%)
	R ¹	R ²	R ³	R ⁴	X			
1	Ph	<i>n</i> -C ₃ H ₇	H (1a)	H	Br (2a)	17	3a	88
2	Ph	CH ₃	H (1b)	H	Br (2a)	17.5	3b	83
3	1-naphthyl	<i>n</i> -C ₃ H ₇	H (1c)	H	Br (2a)	21	3c	78
4	1-naphthyl	CH ₃	H (1d)	H	Br (2a)	16	3d	81
5	Ph	PhCH ₂	H (1e)	H	Br (2a)	16	3e	71
6	1-naphthyl	<i>n</i> -C ₃ H ₇	H (1c)	Ph	Br (2b)	24	3f	93
7	Ph	<i>n</i> -C ₃ H ₇	H (1a)	CH ₃	Cl (2c)	24	3g	89
8	1-naphthyl	<i>n</i> -C ₃ H ₇	H (1c)	CH ₃	Cl (2c)	15.5	3h	95
9	Ph	<i>n</i> -C ₃ H ₇	H (1a)	Br	Br (2d)	21	3i	77
10	1-naphthyl	<i>n</i> -C ₃ H ₇	H (1c)	Br	Br (2d)	23	3j	79
11	1-naphthyl	CH ₃	H (1d)	Br	Br (2d)	23.5	3k	69
12	Ph	Allyl	H (1f)	H	Br (2a)	17	3l	72
13	1-naphthyl	CH ₃	H (1d)	CH ₃	Cl (2c)	24	3m	76
14	CH ₃	PhCH ₂	H (1g)	H	Br (2a)	17	3n	52
15	CH ₃	PhCH ₂	H (1g)	H	Br (2a)	17.5	3n	73 ^b
16	Ph	CH ₃	Et (1h)	H	Br (2a)	19	3o	83
17	4-Br-C ₆ H ₅	<i>n</i> -C ₃ H ₇	H (1i)	H	Br (2a)	11.5	3p	75

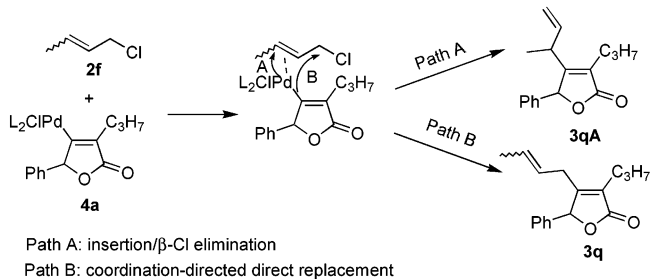
^a The reaction was carried out with 2,3-allenoic acids (0.5 mmol), allylic halide (2.5 mmol), and PdCl₂ (0.022 mmol). ^b 10 equiv of allyl bromide was used.

SCHEME 1. Four Optically Active Products Obtained by Chirality Transfer**SCHEME 2. Pd(II)-Catalyzed Pathway**

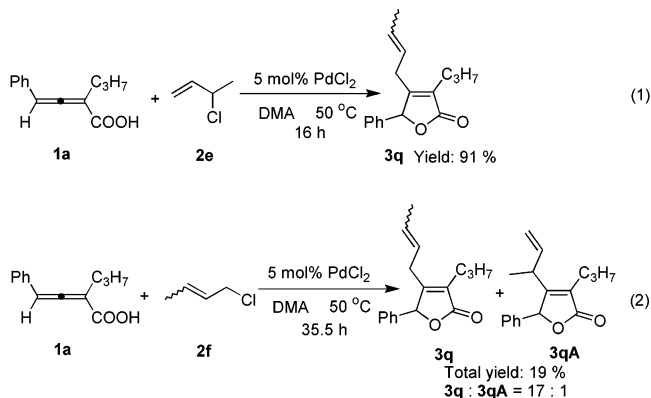
of butenolides were tentatively assigned based on the stereochemical outcome of oxypalladation.^{5j}

The mechanism of the palladium-catalyzed allylation is obscure for there are two possible pathways in the reaction,⁷ i.e., the Pd(0)-catalyzed pathway and the Pd(II)-catalyzed pathway. In the reaction of 1,2-allenyl ketones with allylic halides, we observed both the Pd(0)-catalyzed pathway and the Pd(II)-catalyzed pathway.^{7a} However, only the Pd(II)-catalyzed pathway was possible in the reaction of 2,3-allenols with allylic halides.^{7c} Thus, 3-chloro-1-butene (**2e**) and 1-chloro-2-butene (**2f**) were used as the probe to study the mechanism. If this Pd(0)-catalyzed reaction pathway is operative,^{7c} the same results should be observed for the reaction with **2e** or **2f** since the same π -allyl palladium species may be formed from either **2e** or **2f**. In the Pd(II)-catalyzed mechanism (Scheme 2), PdCl₂ coordinates with the double bond remote from the carboxylic group in 2,3-allenol acids **1**. Subsequent cyclic oxypalladation affords palladium intermediate **4**, which reacts with allylic halide to give a new intermediate **5** or **5'** followed by dehalopalladation to provide the final product **3** or **3A** while regenerating the Pd(II) species. If the reaction occurs by this pathway, different products would be expected for allylic chlorides **2e** and **2f**.

Actually the reaction of substrate **1a** and 3-chloro-1-butene (**2e**) gave 91% of the product **3q** (eq 1) while the reaction of substrate **1a** with 1-chloro-2-butene (**2f**) was relatively slow leading to a 17:1 mixture of **3q** and **3qA**

SCHEME 3. The Possible Reaction Pathway of Producing Unusual Product 3q

in a combined yield of 19% (eq 2).



On the basis of the results outlined in eqs 1 and 2, the reaction more possibly proceeded through the Pd(II)-catalyzed pathway rather than the Pd(0)-catalyzed mechanism. Moreover, it was in accordance with the facts that Pd(PPh₃)₄ could not promote the reaction to yield **3q** in an inert atmosphere and the reaction catalyzed by 5 mol % Pd₂(dba)₃·CHCl₃ gave product **3a** in only 15% yield together with 82% yield of allyl 2-propyl-4-phenyl-2,3-butadienoate **6**.

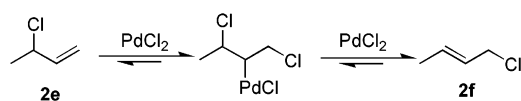
But there is still one problem: why the reaction shown in eq 2 also gave **3q** as the major product. To explain this phenomenon, we propose that the major regioisomer in eq 2 may be formed via a coordination-directed direct replacement of the chlorine atom by the corresponding palladium species **4a** (Scheme 3) or the reductive elimination of the palladium(IV) species, which may be formed by the oxidative addition of **4a** with **2f**.⁸

However, further study showed that both 3-chloro-1-butene (**2e**) and 1-chloro-2-butene (**2f**) existed in the reaction of **1a** with either **2e** or **2f**, while the main component was the more stable isomer **2f** as monitored

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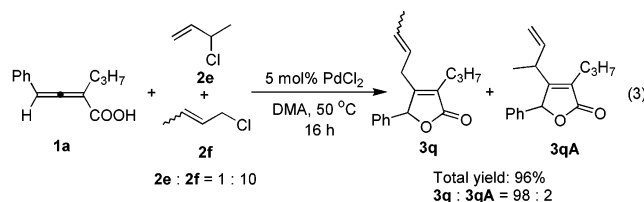
(7) For the Pd-catalyzed coupling cyclization reaction of allenyl ketones or alcohols with allylic halides, see: (a) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941. (b) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (c) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104.

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SCHEME 4. The Interconversion of 2e and 2f

by gas chromatography. This phenomenon indicated that the allylic halides could isomerize in the reaction media (Scheme 4).

Furthermore, the reaction of 2,3-allenoic acid **1a** with the 1:10 mixture of **2e** and **2f** gave a 98:2 mixture of product **3q** and **3qA** in a combined yield of 96% (eq 3).



This fact shows that the reaction of 2,3-allenoic acid **1a** with **2e** is much faster than that with **2f**. The product **3q** in eq 2 may be formed via the fast reaction of **1a** with the in situ formed **2e**.

Conclusion

We have developed an effective method for the synthesis of β -allyl-polysubstituted butenolides from the easily available allylic halides and 2,3-allenoic acids. As a result of introducing an allylic group into the products, further elaboration of the C=C bond would provide an efficient access to other butenolide derivatives. By using this method optically active butenolides can be obtained. According to the results presented in this paper, the reaction may proceed via three consecutive steps: cyclic oxypalladation of the allene moiety, insertion of the C=C bond in allylic halides, and β -dehalopalladation. Further study in this area is underway in our laboratory.

Experimental Section

Starting Materials. 2,3-Allenoic acids were prepared according to the known method by treatment of the acid chlorides

with ethyl 2-(triphenylphoranylidene)propionate and subsequent hydrolysis of the 2,3-allenoic esters with 1.5 equiv of NaOH.⁹

General Procedure for the Pd(II)-Catalyzed Coupling Cyclization of 2,3-Allenoic Acids with Allylic Halides. A mixture of **1** (0.5 mmol), allylic halide **2** (2.5 mmol), and palladium chloride (0.025 mmol) in DMA (3 mL) was stirred at 50 °C for the stated time. Then the mixture was diluted with ether, washed with water, and dried over MgSO₄. After evaporation, the residue was purified via flash chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to afford butenolides **3**. All solid products were recrystallized from ethyl acetate and petroleum ether.

4-Allyl-5-phenyl-3-propyl-2(5H)-furanone (3a): A mixture of **1a** (50 mg, 0.25 mmol), allyl bromide (**2a**; 0.11 mL, 153 mg, 1.25 mmol), and PdCl₂ (2 mg, 0.011 mmol) in DMA (2 mL) was stirred for 17 h to afford 53 mg (88%) of **3a** (petroleum ether/ethyl acetate 20:1). Oil; ¹H NMR (300 MHz, CDCl₃) δ 7.26–7.34 (m, 3 H), 7.08–7.15 (m, 2 H), 5.63 (s, 1 H), 5.48–5.62 (m, 1 H), 5.02 (d, J = 10.06 Hz, 1 H), 4.94 (d, J = 15.62 Hz, 1 H), 3.09 (dd, J = 5.40, 15.32 Hz, 1 H), 2.62 (dd, J = 7.55, 15.32 Hz, 1 H), 2.26 (t, J = 7.51 Hz, 2 H), 1.49–1.59 (m, 2 H), 0.89 (t, J = 7.41 Hz, 3 H); ¹³C NMR (75.4 MHz, CDCl₃) δ 13.9, 21.5, 25.5, 30.8, 83.6, 118.2, 126.9, 127.7, 128.9, 129.2, 132.3, 134.7, 160.7, 174.3; EIMS m/z 243 (M^+ + 1, 54.30), 242 (M^+ , 20.74), 105 (100); IR (neat) 1709, 1626, 1594 cm⁻¹; HRMS calcd for C₁₆H₁₈O₂ 242.13068, found 242.12617.

(+)-4-Allyl-5-phenyl-3-propyl-2(5H)-furanone (3a): A mixture of (+)-**1a** (50 mg, >98% ee, 0.25 mmol), allyl bromide (**2a**; 0.11 mL, 153 mg, 1.25 mmol), and PdCl₂ (2 mg, 0.011 mmol) in DMA (2 mL) was stirred at 25 °C for 36.5 h to afford 48 mg (80%, >99% ee) of **3a**. HPLC conditions: AS column; rate, 0.7 mL/min; eluent, hexane/*i*-PrOH 85/15. [α]_D²⁰ +191 (c 1.15, EtOH).

Acknowledgment. Financial support from the National Natural Science Foundation of China and the Major State Basic Research Development Program (Grant No. G2000077500) is greatly appreciated. Sheng-ming Ma is the recipient of a 1999 Qiu Shi Award for Young Scientific Workers issued by Hong Kong Qiu Shi Foundation of Science and Technology (1999–2003).

Supporting Information Available: Analytical data for compounds **3** and **6**, ¹H NMR and ¹³C NMR spectra of those compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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