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Synthesis of β-Halobutenolides and Their Pd(0)/CuI-Catalyzed Cross-Coupling Reactions with Terminal Alkynes. A General Route to β-(1'-Alkynyl)butenolides

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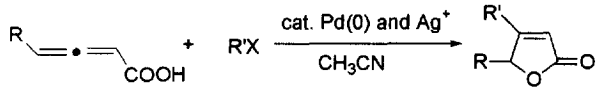
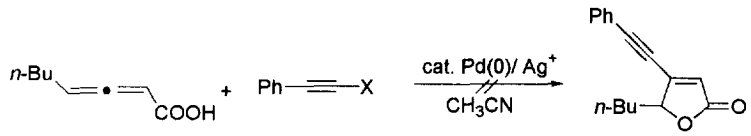
Abstract: A new procedure for the efficient synthesis of β-halobutenolides was developed. The Pd(0)-catalyzed coupling reactions of β-halobutenolides with terminal alkynes to afford β-substituted butenolides are described.

Synthesis of butenolides with different substitution patterns is an area of current interest due to their potential biological activities. Butenolide-containing compounds are considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, anti-inflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors, and phospholipase A_2 inhibitors, etc.[1] Recently, we developed a $Pd(0)/Ag^+$-cocatalyzed one-step methodology for the efficient synthesis of butenolides starting from 1,2-allenic carboxylic acids and organic halides (eq. 1).[2]



(1)

However, under these reaction conditions the $Pd(0)/Ag^+$-cocatalyzed cyclization reaction of 1-alkynyl halides with 1,2-allenic carboxylic acids did not yield the corresponding butenolides in decent yields (eq. 2). Thus, a new and general protocol was required for the efficient synthesis of β-(1-alkynyl)butenolides.



(2)

1a X = Br, I **3a**

Transition metal-catalyzed coupling reactions of terminal alkynes or organometallic reagents with organohalides have been shown to be one of the most successful pathways for the formation of C-C single

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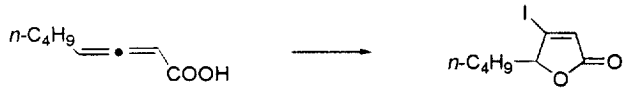
bonds. Thus, from the view point of retrosynthesis, β-halobutenolides might be an important class of building block for the synthesis of butenolides with different types of R' at the β-position. In this paper, we wish to disclose our recent study on the efficient synthesis of β-halobutenolides from 1,2-allenic acids and the corresponding Pd(0)/CuI-cocatalyzed coupling reaction of β-halobutenolides with terminal alkynes.

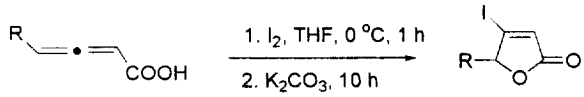
Iodolactonization reactions of 1,2-allenic carboxylic acids[3,4] to afford β-halobutenolides have been studied. Starting from 2,3-octadienoic acid (**1a**) using the procedure reported by Gill and Idvis,[3] the reaction afforded β-iodobutenolide **2a,** but only in 42% yield. In order to improve the yield of this iodolactonization reaction, several conditions were tested, and the results are summarized in **Scheme 1**. The iodolactonization reaction of **1a** with I_2/ K_2CO_3 afforded **2a** in 36% and 18% yields at 0 °C and 30 °C, respectively. *However, treatment of the acid* ***1a*** *with* I_2 *in THF at 0 °C first followed by the addition of* K_2CO_3 *afforded* ***2a*** *in 91% yield.* We prepared γ-(*n*-heptyl)-β-iodobutenolide **2b** similarly in 90% yield (**Scheme 1**).

Scheme 1



1a **2a**

Reaction conditions	yield (%)
I_2, 5% $NaHCO_3$ (aq), 6 KI, H_2O, rt, 6 h	42
I_2, K_2CO_3, THF, 0 °C, 10 h	36
I_2, K_2CO_3, THF, 30 °C, 10 h	18

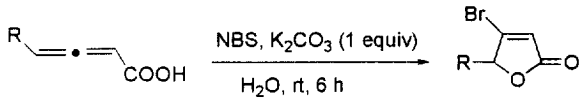


step-wise

1a (R = *n*-C_4H_9)	**2a**	91%
1b (R = *n*-C_7H_{15})	**2b**	90%

β-Bromobutenolides **2c** and **2d** were prepared by the reaction of 2,3-octadienoic acid or 2,3-undecadienoic acid with NBS and K_2CO_3 in H_2O at rt for 6 h in 84% and 81% yields, respectively (**Scheme 2**).

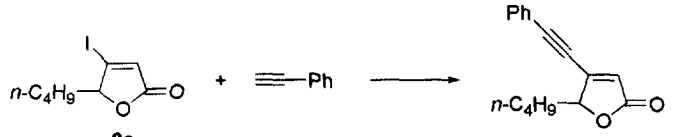
Scheme 2



1a (R = *n*-C_4H_9)	**2c**	84%
1b (R = *n*-C_7H_{15})	**2d**	81%

The results shown in **Schemes 1 and 2** indicate that the above halolactonization reaction is a novel methodology for the synthesis of β–halolobutenolides, of which the carbon-halogen bond could, in principle, be further elaborated. The Sonogashira coupling reaction[5] has been developed as one of the most powerful tools for the synthesis of disubstituted alkynes. We tested the coupling reaction of γ-(*n*-butyl)-β-iodobutenolide **2a** with phenylacetylene using Et_3N as the base and THF or CH_3CN as the solvent. Under the catalysis of $PdCl_2(PPh_3)_2$ and CuI, the coupling reaction did occur, but the yield was poor (~42%) (**Scheme 3**). Here, probably the stability of β-iodobutenolide **2a** towards Et_3N might be the reason for a low-yielding reaction. Using Et_3N as both the solvent and the base, the yield was 67%. If the coupling reaction was carried out in DMF, the yield was similar (66%) (**Scheme 3**). However, after further screening we found that when K_2CO_3 was used in place of Et_3N as the base, the coupling product **3a** was formed cleanly in CH_3CN and isolated in 99% yield (**Scheme 3**).

Scheme 3



2a **3a**

	isolated yield(%)
Et_3N, THF	43
Et_3N, CH_3CN	42
Et_3N	67
Et_3N, DMF	66
K_2CO_3, CH_3CN	99

Some typical examples are summarised in **Table 1**. Under these new reaction conditions, (1) the coupling reaction went smoothly with phenylacetylene, 1-hexyne, and trimethylsilylacetylene. Using trimethylsilylacetylene as the terminal alkyne in the reaction provides products which may be further elaborated at the C-C triple bond remote from the butenolide (entries 5 and 9, **Table 1**); (2) when propargyl alcohol was employed as the terminal alkyne, no protection of the hydroxy group was necessary (entries 4 and 8, **Table 1**); (3) the corresponding bromoanalogue **2c** also coupled with phenylacetylene smoothly to afford **3a** in 78% yield (entry 10, **Table 1**).

In conclusion, we have developed efficient methods for the synthesis of β-halo- and β-(1-alkynyl)-butenolides, and their biological activities are being studied in our laboratory.

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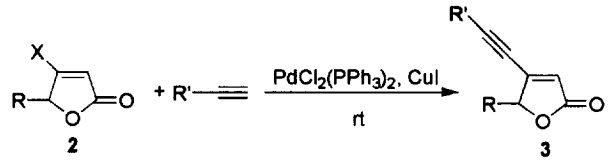
Table 1. Sonogashira Coupling Reactions of β–Halobutenolides with Terminal Alkynes[a]



Entry	2	R'	product 3	yield (%)
1	**2a**	Ph	**3a**	99
2[b]	**2a**	*n*-butyl	**3b**	<5[c]
3	**2a**	*n*-butyl	**3b**	93
4	**2a**	$HOCH_2$	**3c**	95
5	**2a**	TMS	**3d**	65
6	**2b**	Ph	**3e**	95
7	**2b**	*n*-butyl	**3f**	86
8	**2b**	$HOCH_2$	**3g**	79
9	**2b**	TMS	**3h**	70
10	**2c**	Ph	**3a**	78

[a] **2**:alkyne:K_2CO_3:CuI:$PdCl_2(PPh_3)_2$ = 1:1.02:1:0.01:0.01; [b] Et_3N and THF were used as the base and solvent, respectively; [c] Determined by ^1H NMR using CH_2Br_2 as the internal standard.

References:

1. Brima,T. S. US Pat. 4,968,817, 1990; *Chem. Abstr.* **1991**, *114*, 185246y. Tanabe, A. Jpn. Kokai Tokkyo. Koho JP. 63,211,276 [88,211,276], 1988; *Chem. Abstr.* **1989**, *110*, 94978q. Lee, G. C. M. Eur. Pat. Appl. EP. 372,940, 1990; *Chem. Abstr.* **1990**, *113*, 191137j. Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S; Therien, M. PCT Int. Appl. WO 95 00,501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y. Lee, G. C. M; Garst, M. E. PCT Int. Appl. WO 91 16,055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m.
2. Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. For the known synthetic methodologies of butenolides, see the corresponding references cited therein.
3. Gill, G. B. and Idris, M. S. H. *Tetrahedron Lett.* **1985**, *26*, 4811.
4. For the related study with esters, see: Shingu, K.; Hagishita, S.; Nakagawa, M. *Tetrahedron Lett.* **1967**, 4371 Kresze, G.; Kloimstein, L.; Runge, W. *Liebigs Ann. Chem.* **1976**, 979; Braverman, S.; Reisman, D. *Tetrahedron Lett.* **1977**, 1753.
5. Sonogashira, K.; Tohda, Y. and Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.