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Note

Pd/C-Catalyzed coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes leading to alkylidenefuranones

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ABSTRACT

Palladium-catalyzed coupling of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes and subsequent regioselective 5-*exo-dig* cyclization produces (*Z*)-alkylidenefuranones in good yields.

1. Introduction

Palladium-catalyzed carbon–carbon bond formation by the cross-coupling of terminal alkynes with organo-electrophiles such as aryl- and vinyl-halides and triflates is known as Sonogashira coupling reaction [1,2]. This protocol has been recognized as an attractive tool in synthetic organic chemistry and effectively applied to the synthesis of conjugated acetylenic compounds. Among them, the coupling reaction followed by intramolecular cyclization has been used for the construction of various heterocyclic compounds [2]. In connection with this report, several groups have reported that 2-iodobenzoic acids are coupled and cyclized with terminal alkynes in the presence of a palladium catalyst to give 5-*exo-dig* cyclized phthalides or 6-*endo-dig* cyclized isocoumarins and the product yield and distribution are varied by reaction conditions (Scheme 1) [3,4]. For example, the reactions under the conditions of Pd/CNTs-NaOAc-DABCO-DMF-H_2O and Pd/C-PPh_3-CuI-Et_3N-EtOH preferentially afforded 5-*exo-dig* cyclized phthalides and 6-*endo-dig* cyclized isocoumarins, respectively. On the other hand, β-bromo-α,β-unsaturated aldehydes and their derivatives, which are readily prepared from the corresponding ketones by Vilsmeier–Haack reaction [5] and subsequent transformation, have been introduced for the synthesis of versatile cyclic compounds [6–25]. It has been reported by us that several carbo- and heterocyclic compounds can be synthesized from β-bromo-α,β-unsaturated aldehydes and their derivatives in the presence of a palladium catalyst [26–32]. The present work was disclosed during the course of the extension of the palladium-catalyzed Sonogashira coupling and cyclization protocol to the reaction with β-bromo-α,β-unsaturated carboxylic acids. This report describes a palladium-catalyzed tandem coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes leading to alkylidenefuranones.

2. Results and discussion

The starting materials **3** were synthesized by initial conversion of the corresponding α-methylene containing ketones **1** into β-bromovinyl aldehydes **2** under bromination conditions of Vilsmeier–Haack reaction (PBr_3/DMF/$CHCl_3$) [5] followed by oxidation of **2** into β-bromo-α,β-unsaturated carboxylic acids **3** by treating with $NaClO_2$–H_2O_2 [33] (Scheme 2).

The results of several attempted coupling and cyclization of 2-bromocyclohex-1-enecarboxylic acid (**3a**) with 1-octyne (**4a**) under various reaction conditions are listed in Table 1. Treatment of **3a** with two equivalents of **4a** in 1-propanol in the presence of 10% Pd/C (5 mol% based on **3a**) and CuI (10 mol% based on **3a**) along with Bu_3N afforded (3*Z*)-4,5,6,7-tetrahydro-3-heptylideneisobenzofuran-1(3*H*)-one (**5a**) in 50% isolated yield (entry 1). The

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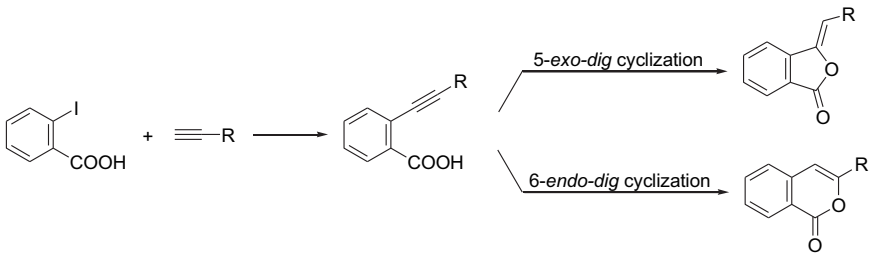
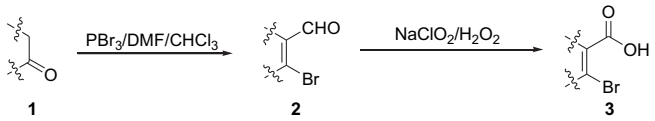


Scheme 1. 5-*Exo-dig* and 6-*endo-dig* cyclizations.



Scheme 2. Synthesis of β-Bromo-α,β-unsaturated carboxylic acids.

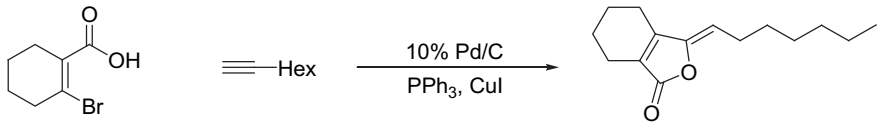
reaction seems to proceed via initial Sonogashira coupling between **3a** and **4a** to form usual sp^2-carbon-*sp*-carbon coupled product and subsequent regioselective 5-*exo-dig* cyclization of the coupling product. No 6-*endo-dig* cyclized product was formed at all. The stereochemistry of **5a** was unequivocally assigned by comparing the chemical shift of vinyl proton signal in ^{1}H NMR with that of known (3*Z*)-4,5,6,7-tetrahydro-3-butylideneisobenzofuran-1(3*H*)-one [34,35]. As will be shown later, the configuration was also identified by the direct comparison of ^{1}H and ^{13}C NMR spectrum and GC retention time of **5b** with the authentic sample prepared by our recent report [32]. Performing the reaction for a longer reaction time (40 h) gave no significant improvement in the yield of **5a** (entry 2). The reaction carried out at higher temperature in a stainless autoclave also resulted in similar yield of **5a** (entry 3). Among solvent examined under the employment of Bu_3N as base, 1-propanol and dioxane revealed to be the solvent of choice in terms of product **5a** yield (entries 1, 4–6). When the reaction was carried out with other bases such as K_2CO_3, NaOAc and DBU combined with 1-propanol, the synthesis of **5a** did not occur effectively (entries 7–9).

After the reaction conditions had been optimized, various β-bromo-α,β-unsaturated carboxylic acids **3** were subjected to the reaction with terminal alkynes **4** in order to investigate the reaction scope, and several representative results are summarized in Table 2. The β-bromo-α,β-unsaturated carboxylic acid **3a** was readily coupled and cyclized with several terminal alkynes (**4a**–**d**) having linear and branched alkyl chains and phenyl group. Here again no 6-*endo-dig* cyclized products were formed at all. Methyl and phenyl substituted six-membered β-bromo-α,β-unsaturated carboxylic acids (**3b** and **3c**) were also coupled and cyclized with 1-hexyne (**4b**) to give the corresponding alkylidenefuranones (**5e** and **5f**) in similar yields. With β-bromo-α,β-unsaturated carboxylic acids (**3d**–**g**) having various ring sizes, the coupled and cyclized alkylidenefuranones (**5g**–**j**) were formed in the range of 48–68% yields without any identifiable side product, and the product yield was not significantly affected by the ring size of **3d**–**g**. Regioisomers (**3h** and **3i**) exhibited different rates, and the reaction of **3h** proceeded more slowly to result in 24% yield of **5k** in 40 h reaction time. The low reactivity of **3h** is ascribable to slow Sonogashira coupling reaction because the corresponding carboxylic acid was not observed in the crude mixture.

3. Conclusion

In summary, we have demonstrated that β-bromo-α,β-unsaturated carboxylic acids undergo coupling with terminal alkynes and subsequent regioselective 5-*exo-dig* cyclization in the presence of Pd/C and CuI to give (*Z*)-alkylidenefuranones in good yields. The present reaction provides a new route for (*Z*)-alkylidenefuranones from readily available starting ketones. Further study of synthetic applications to heterocycles by using this ketone as starting compound is in progress.

Table 1
Optimization of conditions for the reaction of **3a** with **4a**.[a]

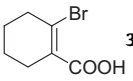
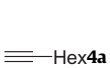
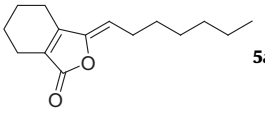
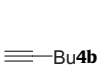
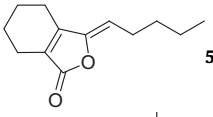
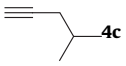
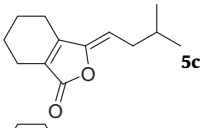
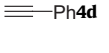
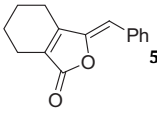
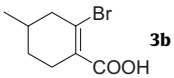
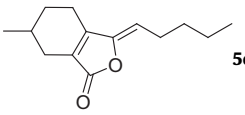
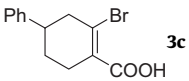
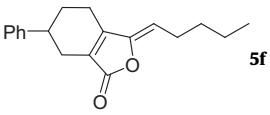
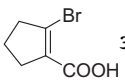
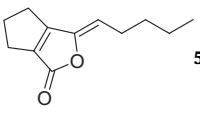
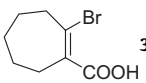
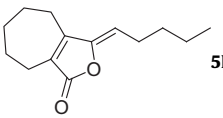
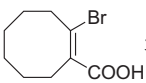
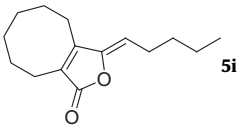
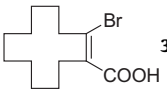
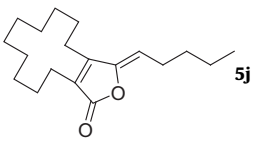
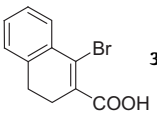
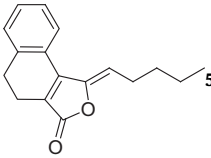
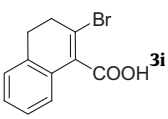
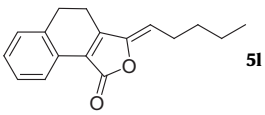


3a **4a** **5a**

Entry	Base	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	Bu_3N	1-propanol	110	20	50
2	Bu_3N	1-propanol	110	40	51
3[b]	Bu_3N	1-propanol	135	20	52
4	Bu_3N	DMF	110	20	40
5	Bu_3N	$HOCH_2CH_2OH$	110	20	0
6	Bu_3N	dioxane	110	20	51
7	NaOAc	1-propanol	110	20	18
8	K_2CO_3	1-propanol	110	20	0
9	DBU	1-propanol	110	20	0

[a] Reaction conditions: **3a** (0.5 mmol), **4a** (1 mmol), 10% Pd/C (0.25 mmol), PPh_3 (0.1 mmol), CuI (0.05 mmol), base (2.5 mmol), solvent (8 mL).
[b] The reaction was carried out in autoclave.

Table 2
Palladium-catalyzed coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids **3** with 1-alkynes **4**.[a]

β-Bromo-α,β-unsaturated carboxylic acids **3**	1-Alkynes **4**	Alkylidenefuranones **5**	Yield (%)
 **3a**	 Hex **4a**	 **5a**	51
	 Bu **4b**	 **5b**	57
	 **4c**	 **5c**	43
	 Ph **4d**	 **5d**	52
 **3b**	**4b**	 **5e**	68
 **3c**	**4b**	 **5f**	51
 **3d**	**4b**	 **5g**	57
 **3e**	**4b**	 **5h**	53
 **3f**	**4b**	 **5i**	50
 **3g**	**4b**	 **5j**	48
 **3h**	**4b**	 **5k**	24[b]
 **3i**	**4b**	 **5l**	42

[a] Reaction conditions: **3** (0.5 mmol), **4** (1 mmol), 10% Pd/C (0.25 mmol), PPh_3 (0.1 mmol), CuI (0.05 mmol), Bu_3N (2.5 mmol), dioxane (8 mL), 110 °C, 20 h.
[b] For 40 h.

4. Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. IR spectra were measured on a Shimadzu FT IR-8400S spectrophotometer. Melting points were determined on a Stanford Research Inc. MPA100 automated melting point apparatus. GLC analyses were carried out with Shimadzu GC-17A (FID) equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using N_2 as carrier gas. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). β-Bromo-α,β-unsaturated carboxylic acids **3** were synthesized by two steps, initial treatment of ketones **1** with PBr_3/DMF/$CHCl_3$ [5] to produce β-bromovinyl aldehydes **2** and oxidation of **2** under $NaClO_2$–H_2O_2 [33]. Commercially available organic and inorganic compounds were used without further purification.

4.1. General experimental procedure

To a 50 mL stainless steel autoclave were added β-bromo-α,β-unsaturated carboxylic acid (0.5 mmol), terminal alkyne (1 mmol), 10% Pd/C (0.027 g, 0.025 mmol), PPh_3 (0.026 g, 0.1 mmol), CuI (0.010 g, 0.05 mmol), Bu_3N (0.463 g, 2.5 mmol) and dioxane (8 mL). The reaction mixture was allowed to react at 110 °C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate black precipitate. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give (*Z*)-alkylidenefuranones **5**. Except for **5a**, **5c**–**f**, **5l**, all products prepared by the above procedure were characterized by GLC and spectroscopic comparison with authentic samples synthesized by our recent report [32].

4.1.1. (3Z)-4,5,6,7-Tetrahydro-3-heptylideneisobenzofuran-1(3H)-one (**5a**)

Oil; IR (neat) 2924, 2855, 1759, 1674, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.26–1.35 (m, 6H), 1.41–1.48 (m, 2H), 1.72–1.79 (m, 4H), 2.30–2.39 (m, 6H), 5.11 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.28, 20.19, 21.24, 21.64, 21.91, 22.79, 26.07, 29.19, 29.40, 31.81, 110.98, 127.00, 149.28, 151.32, 170.27; HRMS (EI) Anal. Calc. for $C_{15}H_{22}O_2$ (M^+): 234.1620. Found: 234.1618.

4.1.2. (3Z)-4,5,6,7-Tetrahydro-3-(3-methylbutylidene)isobenzofuran-1(3H)-one (**5c**)

Oil; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 6H), 1.71–1.80 (m, 5H), 2.24–2.32 (m, 4H), 2.37–2.40 (m, 2H), 5.13 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.15, 21.24, 21.61, 21.88, 22.56, 28.85, 34.90, 109.70, 127.04, 149.75, 151.26, 170.32; HRMS (FAB) Anal. Calc. for $C_{13}H_{19}O_2$ ($[M + H]^+$): 207.1385. Found: 207.1382.

4.1.3. (3Z)-4,5,6,7-Tetrahydro-3-benzylideneisobenzofuran-1(3H)-one (**5d**)

Solid, m.p. 116–117 °C (from hexane) (lit [36]. 123–125 °C); ^{1}H NMR ($CDCl_3$): δ 1.75–1.86 (m, 4H), 2.35–2.38 (m, 2H), 2.48–2.52 (m, 2H), 5.87 (s, 1H), 7.27–7.32 (m, 1H), 7.36–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.34, 21.36, 21.69, 21.83, 108.03, 126.84, 128.71, 128.92, 130.50, 133.33, 148.19, 152.76, 170.19.

4.1.4. (3Z)-4,5,6,7-Tetrahydro-6-methyl-3-pentylideneisobenzofuran-1(3H)-one (**5e**)

Oil; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.31–1.48 (m, 5H), 1.76–1.89 (m, 3H), 2.32–2.40 (m, 3H), 2.44–2.51 (m, 2H), 5.11 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.06, 21.00, 21.34, 22.57, 25.75, 28.26, 28.55, 29.86; HRMS (FAB) Anal. Calc. for $C_{14}H_{21}O_2$ ($[M + H]^+$): 221.1542. Found: 221.1544.

4.1.5. (3Z)-4,5,6,7-Tetrahydro-6-phenyl-3-pentylideneisobenzofuran-1(3H)-one (**5f**)

Solid, m.p. 113–114 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.32–1.49 (m, 4H), 1.83–1.93 (m, 1H), 2.12–2.16 (m, 1H), 2.36–2.61 (m, 5H), 2.68–2.73 (m, 1H), 2.87–2.94 (m, 1H), 5.16 (t, *J* = 7.8 Hz, 1H), 7.22–7.26 (m, 3H), 7.32–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.07, 21.69, 22.59, 25.83, 27.79, 29.28, 31.51, 39.85, 111.56, 126.86, 126.98, 127.00, 128.87, 144.94, 149.00, 151.08, 169.77; HRMS (FAB) Anal. Calc. for $C_{19}H_{23}O_2$ ($[M + H]^+$): 283.1698. Found: 283.1696.

4.1.6. (3Z)-4,5-Dihydro-3-pentylidenenaphtho [1,2-c]furan-1(3H)-one (**5l**)

Solid, m.p. 63–65 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.34–1.53 (m, 4H), 2.45 (q, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 8.1 Hz, 2H), 3.02 (t, *J* = 8.1 Hz, 2H), 5.35 (t, *J* = 8.0 Hz, 1H), 7.20–7.30 (m, 3H), 8.06–8.08 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.06, 19.98, 22.63, 26.21, 27.65, 31.48, 114.05, 123.59, 124.51, 127.35, 127.62, 128.08, 128.89, 135.06, 148.15, 149.28, 167.56; HRMS (EI) Anal. Calc. for $C_{17}H_{18}O_2$ (M^+): 254.1307. Found: 254.1307.

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