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Pd/C-catalyzed cyclization/isomerization: A new route to 2-aroyl-3-vinyl benzo[*b*]furans *via* carbon–carbon bond formation

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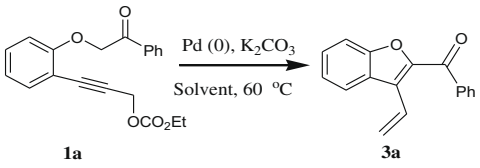
ABSTRACT



1a 3a

A variety of 2-aroyl(acyl, or carboxyl)-3-vinyl benzo[*b*]furans have been prepared *via* C–C bond formation in good to excellent yields by Pd/C-catalyzed cyclization/isomerization of propargylic compounds. The reaction proceeded with easily accessible starting materials and inexpensive catalyst under mild conditions. Furthermore, a number of benzo[*b*]furan derivatives including an allene functional group have been prepared too.

1. Introduction

Benzo[*b*]furan, are widely presented in many naturally occurring and biologically active compounds, which display various pharmacological activities [1–6]. Consequently, great efforts have been devoted to the development of general methods for the assembly of substituted benzo[*b*]furans on the basis of C–O cyclization [7–22]. However, there have been few reports on benzo[*b*]furans syntheses from alkynylbenzene derivations *via* carbon–carbon bond (C–C) cyclization [23–26]. In particular there have been only a few limited studies on the synthesis of 3-vinyl benzo[*b*]furan [27]. The terminal olefins not only can further be converted to methyl ketones with Pd(II) catalysts, which was usually referred to as the Wacker reaction [28,29]; but also can directly be converted into the corresponding α-hydroxy ketones by potassium permanganate oxidation [30]. And the synthesis of α-hydroxy carbonyl compounds is a topic of interest because of their use in organic synthesis and their widespread occurrence in numerous important natural products [31]. Besides, many methods for selectively constructing benzo[*b*]furans through the transition metal-catalyzed transformations exhibits some disadvantages: (1) require harsh conditions and (2) cost the catalytic system. In this paper, we describe our efforts toward the synthesis of such 2-aroyl(acyl, or carboxyl)-3-vinyl benzo[*b*]furans by a phosphine-free Pd/C catalysis system in good to excellent yields (Scheme 1).

Recently, we described a convenient approach to the synthesis of 2,3-dihydro-benzo[*b*]furan derivatives *via* Pd-catalyzed carboannulation of propargylic carbonates with nucleophiles [32], as well as the synthesis of indene derivatives including an allene functional group *via* a palladium catalyzed transformation [33]. So we envisaged that **1a** might enable the formation of benzo[*b*]-furan derivatives **2a** including an allene functional group *via* a palladium catalyzed transformation (Scheme 2).

2. Results and discussion

Treatment of propargylic carbonate **1a** with 5 mol% of $Pd(PPh_3)_4$ and 2.0 equiv. of K_2CO_3 in DMF at 60 °C for 1 h affords the single product 3-vinyl-benzo[*b*]furan **3a** with 86% yield. This result indicated that the isomerization product **3a** was more stable than **2a** which can be explained by the higher delocalization of the double bonds after formation of the aromatic ring and encouraged us to further investigate this reaction. Various solvents and catalysts have been tested on substrate **1a**. For solvents, as shown in Table

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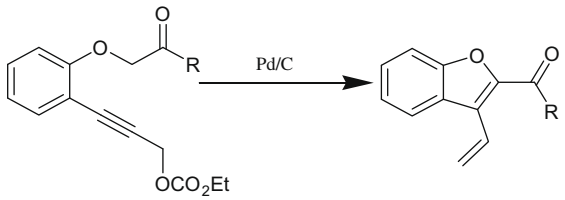
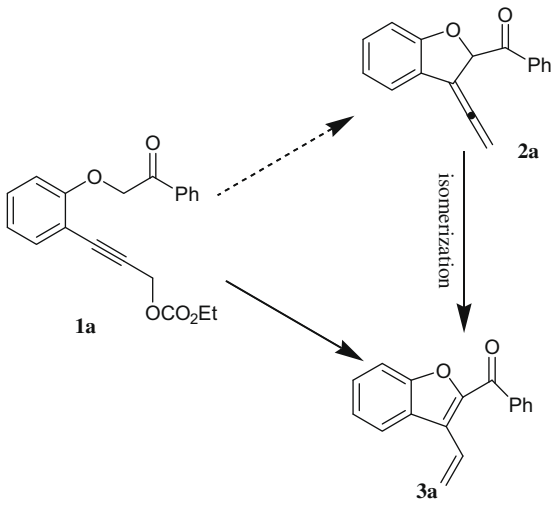


Scheme 1.

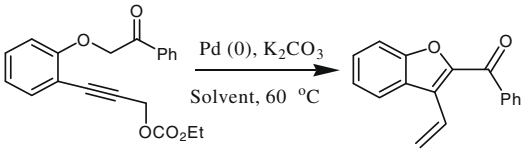


Scheme 2.

1, DMF was found to be the best, while THF gave no reaction at all (entries 1–4). The catalytic activity of palladium catalysts was also examined. $Pd_2(dba)_3{\cdot}CHCl_3$ gave a little lower yield and $Pd_2(dba)_3$ was less effective (Table 1, entries 5 and 6). To our delight, using Pd/C as catalyst in the absence of phosphine ligand, the yield was comparable to the corresponding reaction using $Pd(PPh_3)_4$ (entry 7). Finally, the amount of Pd/C was examined (entries 8 and 9). We found that 10% of Pd/C (0.02 equiv.) also afforded product in an excellent yield. It should be pointed out that no reaction occurs without the base or Pd catalyst (entries 10 and 11). Thus, the optimal procedure described in entry 8 has been employed to study the scope of this reaction.

Under the optimized reaction conditions above, the scope of this methodology was investigated, and the results are summarized in Table 2. Initially we focused our attention on the reaction of primary propargylic carbonate. First, when R^3 = aryl, the influence of the substituents R^1 and R^2 on the aromatic moiety was

Table 1
Optimization of the Pd-catalyzed cyclization of propargylic carbonate **1a.**[a]

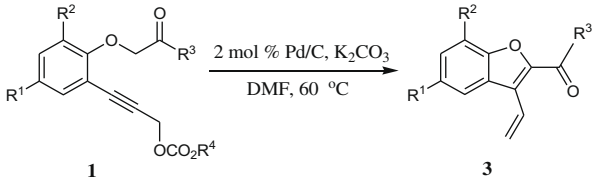


1a **3a**

Entry	Catalyst	Pd mol (%)	Solvent	Time (h)	Yield (%)[b]
1	$Pd(PPh_3)_4$	5	DMF	1	86
2	$Pd(PPh_3)_4$	5	CH_3CN	1	70
3	$Pd(PPh_3)_4$	5	DMSO	1	74
4	$Pd(PPh_3)_4$	5	THF	8	n.r.[c]
5	$Pd_2(dba)_3{\cdot}CHCl_3$	5	DMF	1	79
6	$Pd_2(dba)_3$	5	DMF	1	56
7	Pd/C	5	DMF	1	86[d]
8	**Pd/C**	**2**	**DMF**	**1**	**86**[d]
9	Pd/C	0.5	DMF	3	60[d]
10	Pd/C	2	DMF	8	n.r.[c,d,e]
11	None		DMF	10	n.r.[c,d]

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent at 60 °C for the specified period of time with 1.0 equiv. of **1a**, 2.0 equiv. of K_2CO_3, and [Pd].
[b] Isolated yields.
[c] n.r. = No reaction.
[d] The reactions were run under air.
[e] The reaction was run without K_2CO_3.

Table 2
Synthesis of 3-vinyl benzo[*b*]furans.[a]



1 **3**

Entry	R^1	R^2	R^3	R^4	**1**	Time (h)	**3**	Yield[c]
1	H	H	Ph	Et	**1a**	1	**3a**	86
2	CH_3	H	Ph	CH_3	**1b**	1	**3b**	89
3	CH_3	CH_3	Ph	Et	**1c**	1	**3c**	95
4	Cl	H	Ph	CH_3	**1d**	1	**3d**	90
5	*t*-Bu	H	Ph	CH_3	**1e**	2	**3e**	90
6	H	H	*p*-BrC_6H_4	Et	**1f**	1	**3f**	96
7	Cl	H	2,4-Dimethylphenyl	CH_3	**1g**	1	**3g**	93
8	H	H	CH_3	Et	**1h**	6	**3h**	76
9	*t*-Bu	H	CH_3	Et	**1i**	8	**3i**	70
10	H	H	OEt	Et	**1j**	3	**3j**	82[b]
11	CH_3	H	OEt	Et	**1k**	3	**3k**	95[b]
12	CH_3	CH_3	OEt	Et	**1l**	3	**3l**	89[b]
13	Cl	H	OEt	Et	**1m**	3	**3m**	80[b]

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of DMF at 60 °C using l.0 equiv. of **1**, 2.0 equiv. of base, and 0.02 equiv. of Pd/C.
[b] Using Cs_2CO_3 instead of K_2CO_3 as base.
[c] Isolated yields.

studied (Table 2, entries 1–7). To our delight, no matter the substituent is an electron-withdrawing group or an electron-donating group in the para positions, the corresponding substituted benzo[*b*]furans **3** were obtained in excellent yields (entries 2, 4 and 5). And also we got desired product in a very good yield using disubstituted groups (entry 3). When **1f** and **1g** were employed in the reaction, the desired products were isolated in 96% and 93% yields, respectively (entries 6 and 7). Furthermore, with substitution of phenyl by methyl or ethoxyl at the carbonyl position, the reaction continued to proceed smoothly to the corresponding cyclization/isomerization products in good to excellent yields (Table 2, entries 8–13). To the best of our knowledge, there is no report about the synthesis of 2-aroyl(acyl, or carboxyl)-3-vinyl benzo[*b*]furans and these derivatives probably have antimicrobial activity [34].

For secondary propargylic carbonate **4a**, a good yield was given in the Pd/C catalysts system, but a mixture product (*E*/*Z* = 50:50) was obtained (Table 3, entry 1). For tertiary propargylic esters **4b** and **4c**, the desired products were also afforded in the presence of $Pd_2(dba)_3$ in moderate yields, while Pd/C showed poor results (entries 2 and 3).

In light of the product **3a** from the substrate **1a**, we believe that introducing a substituent in the α-position of carbonyl compounds can inhibit the isomerization and allenyl benzo[*b*]furan derivatives can also be obtained. As far as we know, there is no report about the synthesis of allenyl benzo[*b*]furan derivatives. So we prepared **6a** and as we expected, the desired 3-allenyl benzo[*b*]furan derivatives **7a** was obtained in a good yield in the presence of $Pd_2(dba)_3$, NaOAc in DMSO at 60 °C. We then examined the scope of the reaction with the optimal condition (Table 4, entries 1–5).

From Table 4, we can see that primary propargylic **6a** and **6b** gave the good yields while the secondary carbonates afforded the mixture products. Tertiary acetate **6e** can also give the desired product in 62% with a longer time.

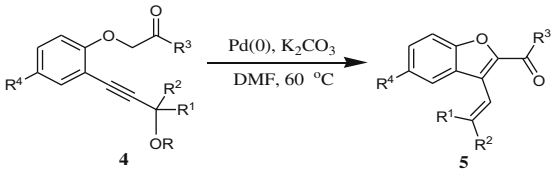
3. Reaction mechanism

A plausible mechanism is proposed in Scheme 3. It consists of the following key steps: (a) palladium(0) attack at propargylic carbonate through S_N2' substitution to form an allenylpalladium complex [35] and (b) regioselective intarmolecular nucleophilic attack of the carbanion forms the allenyl product **2a.** When the R = H, the vinyl product **3a** was obtained after isomerization; when the R = CH_3, the product was **7a.**

4. Conclusion

In conclusion, we have developed an efficient and versatile route to 2-aroyl-3-vinyl benzo[*b*]furans and 2-aroyl-3-allenyl ben-

Table 3
Synthesis of 3-vinyl benzo[*b*]furans.[a]

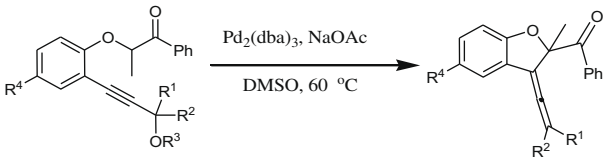


4 5

Entry	R^1	R^2	R^3	R^4	R	4	5	Yield (%)
1	H	*p*-$CH_3C_6H_5$	Ph	Cl	CO_2Et	**4a**	**5a**	80[b]
2	CH_3	CH_3	Ph	Cl	CO_2Et	**4b**	**5b**	60[c]
3		R^1–R^2 = $(CH_2)_4$	OEt	H	Ac	**4c**	**5c**	64[d]

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of DMF at 60 °C using l.0 equiv. of **4**, 2.0 equiv. of base, and 0.02 equiv. of [Pd]; all reactions were run for 2–3 h.
[b] The product was isolated as a 50:50 *E*/*Z* mixture.
[c] Using $Pd_2(dba)_3$ (5 mol%) as catalyst.
[d] Using Cs_2CO_3 and $Pd_2(dba)_3$ (5 mol%) instead of K_2CO_3 and Pd/C.

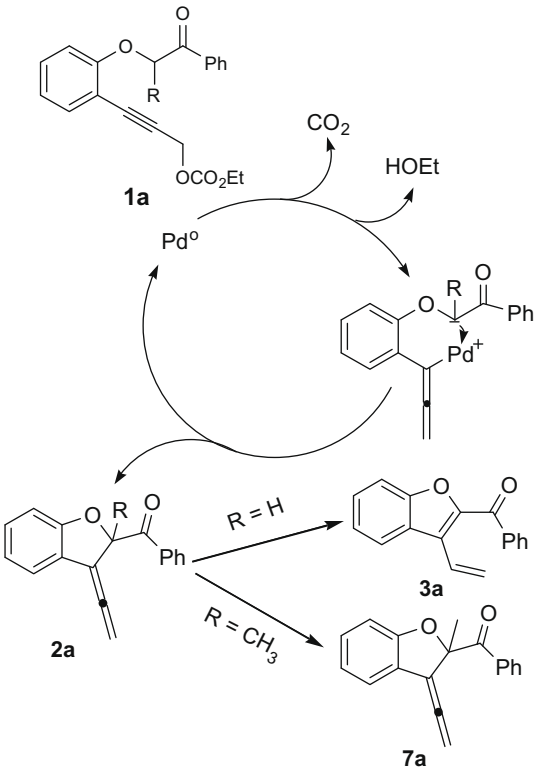
Table 4
Synthesis of 2-aroyl-3-allenyl benzo[*b*]furans derivatives.[a]



6 7

Entry	R^1	R^2	R^3	R^4	6	Time (h)	7	Yield (%)[c]
1	H	H	CO_2Et	H	**6a**	1.5	**7a**	84
2	H	H	CO_2Et	CH_3	**6b**	1.5	**7b**	80
3	H	Ph	CO_2Et	H	**6c**	4	**7c**	75[b]
4	H	*m*-$OCH_3C_6H_5$	CO_2Et	H	**6d**	4	**7d**	74[b]
5	CH_3	CH_3	Ac	H	**6e**	6	**7e**	62

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of DMSO at 60 °C for the specified period of time with 1.0 equiv. of **6**, 2.0 equiv. of NaOAc, and 5 mol% $Pd_2(dba)_3$.
[b] The products were isolated as a 50:50 mixture.
[c] Isolated yields.



Scheme 3.

zo[*b*]furans derivatives *via* Pd-catalyzed cyclization of propargylic compound. A wide scope of substrates undergoes this process in good to excellent yields. Further studies on the application of the products are underway.

5. Experimental

*5.1. General procedure for the preparation of 3-vinyl benzo[b]furans **3a–i***

To a solution of propargylic compound **1** (0.20 mmol) in DMF (2.0 mL) was added K_2CO_3 (0.40 mmol). The mixture was stirred for 1 min and 10% Pd/C (4.2 mg, 0.004 mmol, 2 mol%) was added. The resulting mixture was then heated under air at 60 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na_2SO_4, filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford substituted benzo[*b*]furan derivatives **3a–i**.

The **3j–3m** were prepared as the similar way above, but using Cs_2CO_3 instead of K_2CO_3.

3a: Yellow solid: mp 58–60 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.06–8.03 (q, 2H), 7.99–7.96 (d, J = 6.9 Hz, 1H), 7.61–7.22 (m, 7H), 6.15–6.08 (d, J = 18.3 Hz, 1H), 5.69–5.65 (d, J = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 154.6, 147.9, 137.6, 132.7, 129.8, 128.2, 128.1, 128.0, 126.5, 126.0, 124.0, 122.9, 120.6, 112.4; IR (neat, cm^{-1}) 1646, 1532, 961, 727; Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.30; H, 4.75.

5.2. General procedure for the preparation of 2-aroyl-3-allenyl benzo[b]furan derivatives 7

To a solution of propargylic compound **6** (0.20 mmol) in DMSO (2.0 mL) was added anhydrous NaOAc (32.8 mg, 0.40 mmol). The mixture was stirred for 1 min and $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 5 mol%) was added. The resulting mixture was then heated under an argon atmosphere at 60 °C. The work–up procedure was the same as that described for 3-vinyl benzo[*b*]furan derivatives.

7a: Yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.72 (d, J = 8.1 Hz, 2H), 7.41–7.38 (t, 1H), 7.28–7.13 (m, 4H), 6.95–6.90 (t, 1H), 6.80–6.77 (d, J = 8.4 Hz, 1H), 5.39–5.26 (q, 2H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 197.5, 158.0, 134.3, 132.5, 129.8, 128.9, 128.0, 123.0, 122.5, 121.9, 110.6, 108.1, 92.1, 84.4, 24.9; IR (neat, cm^{-1}) 1688, 1460, 1084, 750, 690; Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.30; H, 5.50.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2009.10.028.

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