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Palladium-Catalyzed One-Pot Synthesis of Highly Substituted Furans by a Three-Component Annulation Reaction

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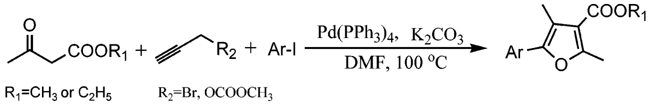

A new three-component cyclization−coupling reaction catalyzed by palladium was developed, producing polysubstituted furans in good yields from readily available substrates. The reaction conditions and the scope of the process were examined, and a possible mechanism is proposed.

Highly substituted furans are structural features of many natural products and important pharmaceuticals.[1] They are also important reaction intermediates in organic synthesis by virtue of their specific chemistry and latent functionality.[2] For these reasons, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic chemists.[3] Thus, efficient and general methodologies for the synthesis of furans with substituents at some or all of the four positions are still of current interest.

Several Pd-mediated strategies for the preparation of furans have been developed.[4] Among them, a one-pot furan annelation reaction by a Pd-catalyzed reaction of propargyl carbonates with β-keto esters was reported by Tsuji,[5] and Cacchi and Larock reported another palladium-catalyzed reaction of 2-propargyl-1,3-dicarbonyl compounds with vinylic or aryl triflates or halides giving 2,3,5-trisubstituted furans.[6] During the same period, multicomponent condensations have gained considerable interest in the field of heterocycle synthesis due to their potential of generating molecular diversity in a single synthetic step from simple, readily available starting materials.[7] In this area, methodologies based on palladium-catalyzed cascade reactions are of particular importance owing to the diversity of bond-forming processes available, the mildness of reaction conditions, the high levels of chemo-, regio-, and stereoselectivities, and the excellent functional group tolerance.[8] There are some methods have been devised for the synthesis of the multiply substituted furans by multicomponent reaction.[9] Herein, we wish to report a one-pot three-component coupling−cyclization reaction based on palladium-mediated that combines three readily available and inexpensive materials, β-keto esters, propargyl carbonate, and aryl iodide, to yield polysubstituted furans.

Initially, we employed methyl acetoacetate **1a**, propargyl bromide **2a**, and iodobenzene **3a** as substrates to afford trisubstituted furan **4a**[6] in 20% yield in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ (5 mol %) and KO-*t*-Bu (2.0 equiv) in DMF at 100 °C for 12 h (Table 1, entry 1).[10]

Then, we investigated the reaction under other palladium-catalyzed cyclization conditions. To our surprise, in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ in DMF

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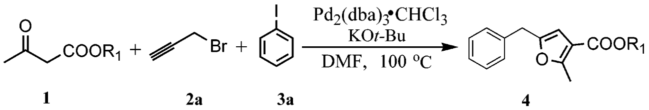
10.1021/jo050908d CCC: $30.25

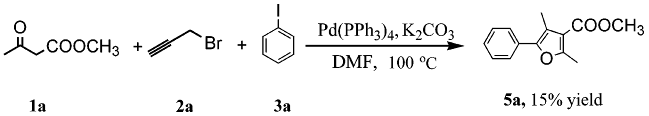
TABLE 1. Palladium-Catalyzed Synthesis of 2,3,5-Trisubstituted Furans[a]



entry	**1**, R_1 =	time (h)	product (yield, %)
1	CH_3	12	**4a** (20)[b]
2	C_2H_5	12	**4b** (22)[b]

[a] The reaction was carried out at 100 °C using **2a** (0.2 mmol), nucleophile (0.2 mmol), aryl halide (0.2 mmol), KO-*t*-Bu (0.4 mmol), and $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) in DMF (2 mL). [b] Isolated yields.

SCHEME 1

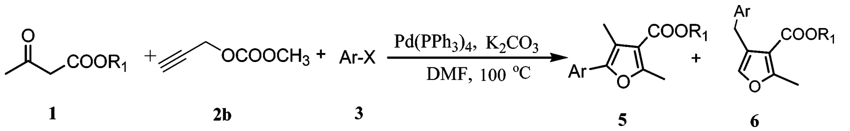


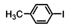
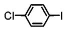
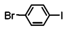
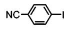
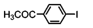
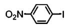
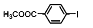
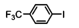
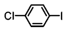
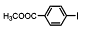
at 100 °C for 12 h, with K_2CO_3 as a base, the product was identified as tetrasubstituted furan **5a** by NMR and MS, which was dramatically different from **4a** (Scheme 1).

The reaction, when conducted with methyl propargyl carbonate **2b**, resulted in the obvious increase in the yield to 40%. We then screened various bases using **1a**, **2b**, and **3a** as the reactants and $Pd(PPh_3)_4$ as the catalyst in DMF. We found that K_2CO_3 was the most effective base. Other bases such as K_3PO_4, Cs_2CO_3, NaOAc, and KO-*t*-Bu were less effective, and Et_3N was ineffective. We sought to investigate various combinations of aryl halides, propargyl carbonates, and β-keto esters. The generality of the methodology was firmly demonstrated by the variety of furans that could be produced. The results are summarized in Table 2. Almost all aryl iodides gave satisfactory results (entries 1−9). Importantly, the reactions afforded the corresponding multiply substituted furans products **5a**−**m** in moderate to good yields with excellent regioselectivities, except entry 5.

Treatment of methyl acetoacetate, **2b**, and iodobenzene in a 1:1:1 ratio at 100 °C in DMF with 5 mol % of $Pd(PPh_3)_4$ and 2.0 equiv of K_2CO_3 for 12 h afford **5a** in 40% yield, but the Sonogashira-coupling product was isolated in 5% yield. For 4-methyliodobenzene, a similar result was observed. Fortunately, when the reaction was run in the presence of 1.0 equiv of KI, only the desired tetrasubstituted furan was formed (entry 1). However, when 1-iodo-4-methoxybenzene was used, only a trace amount of the desired product was isolated. We next examined several aryl iodides to clarify the scope and limitations of this reaction (entries 3−9). Electron-deficient aryl halides performed much better than their

TABLE 2. Palladium-Catalyzed Synthesis of Polysubstituted Furans[a]



entry	**1** R_1	Ar-X	time (h)	yield (%)[b]	ratio of 5/6[c]
1	CH_3		12	**5a**[e] (50)	99:1
2	CH_3		10	**5b**[e] (47)	99:1
3	CH_3		10	**5c** (57)	>99:1
4	CH_3		10	**5d** (62)	>99:1
5	CH_3		13	**5e** (68[d])	86:14
6	CH_3		11	**5f** (63)	>99:1
7	CH_3		10	**5g** (60)	>99:1
8	CH_3		12	**5h** (65)	99:1
9	CH_3		14	**5i** (73)	>99:1
10	CH_3		13	**5j** (63)	>99:1
11	CH_3		11	**5j** (20)	>99:1
12	C_2H_5		14	**5k** (60)	98:2
13	C_2H_5		8	**5l** (65)	>99:1
14	C_2H_5		11	**5m** (67)	98:2

[a] The reaction was carried out at 100 °C using **2b** (0.2 mmol), nucleophile (0.2 mmol), aryl halide (0.2 mmol), K_2CO_3 (0.4 mmol), and $Pd(PPh_3)_4$ (5 mol %) in DMF (2 mL). [b] Isolated yields of the major isomer. [c] The ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Isolated yields of the two isomers. [e] Added 0.2 mmol of KI.

SCHEME 2

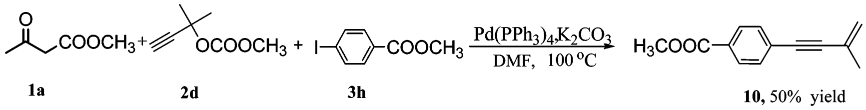
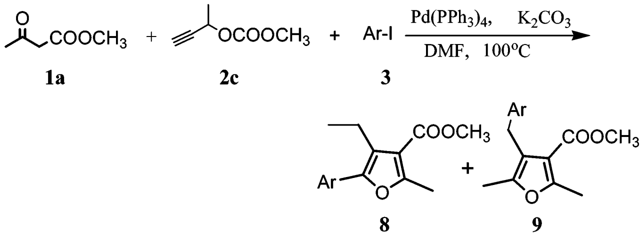
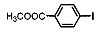
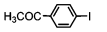
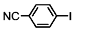


TABLE 3. Palladium-Catalyzed Synthesis of 2,3,4,5-Tetrasubstituted Furans[a]



entry	Ar-I	time (h)	8 yield (%)[b]	9 yield (%)[b]
1		12	**8a** (28)	**9a** (29)
2		14	**8b** (17)	**9b** (33)
3		14	**8c** (16)	**9c** (34)

[a] The reaction was carried out at 100 °C using **2c** (0.2 mmol), nucleophile (0.2 mmol), aryl halide (0.2 mmol), K_2CO_3 (0.4 mmol), and $Pd(PPh_3)_4$ (5 mol %) in DMF (2 mL). [b] Isolated yields.

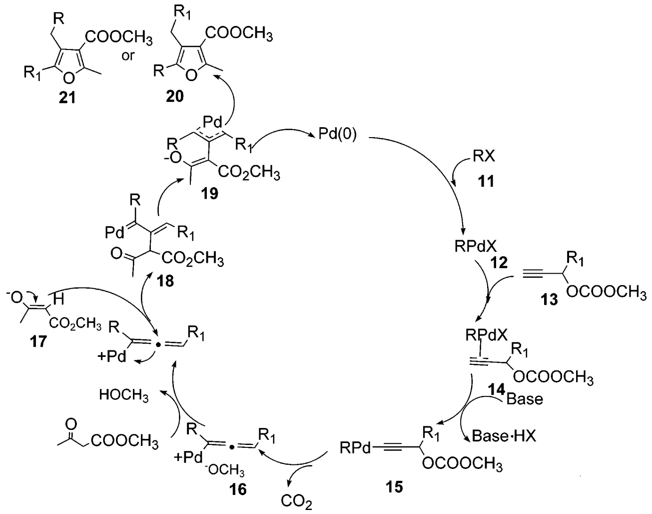
electron-rich counterparts, and 4-chloroiodobenzene with an electron-withdrawing group on the benzene ring worked equally well to provide **5c** in better yields than 4-methyliodobenzene (entry 3). In addition, 2-iodothiophene also can give the furan **5j** (entry 10). The use of 2- bromothiophene instead of 2-iodothiophene produced **5j** in a lower yield (entry 11). Another β-keto ester, ethyl acetoacetate, also effected the three-component cyclization–coupling reaction, yielding the corresponding product **5k–m** (entries 12–14). Unfortunately, the use of other β-keto esters and β-diketones afforded only a minute amount of the desired product under the same reaction conditions.

We then turned our attention to the cyclization reaction using secondary carbonate **2c.** However, substitution of the hydrogen group by methyl gave a mixture of the two annulated regioisomers **8** and **9,** which can be isolated on silica gel column (Table 3). In addition, we established the structures of **5h** and **9c** by gHMBC experiments.

Furthermore, condensation of propargylic tertiary carbonate **2d**, methyl acetoacetate and methyl 4- iodobenzoate **3h** afforded none of the desired three- component cyclization products and an identified product **10** was isolated (Scheme 2).

A tentative mechanism was proposed in Scheme 3. Oxidative addition of the organic halide to the Pd^0 catalyst generates a σ-arylPd^{II}X complex **12**. The propargyl carbonate reacts with palladium complex **12** to give the π-palladium complex **14**,[11] upon coordination, the C–H bond is weakened, and HX is removed from **14** in the presence of a base to form arylalkynylpalladium

SCHEME 3



species **15**. Complex **15** then undergoes decarboxylation to give a methoxide anion,[12] which picks up an acidic hydrogen from the active methylene compound to give the enolate complex **17**. Then the enolate anion attacks the sp carbon of the 1,2-propadienyl moiety to form the palladium complex **18**, which isomerizes to (π-allyl)-palladium complex **19** by intramolecular proton transfer. In the case of propargylic carbonates **2b**, the π-allyl complex **19** undergoes the intramolecular O-alkylation with the carbonyl oxygen at the more substituted side of the π-allyl system, leading predominantly to the regioisomer **5a–m** (Table 2, entries 1–14).[5] While, for the propargylic carbonates **2c** the attack occur on the less-substituted side, the regioisomer **9a–c** (Table 3, entries 1–3) being the predominant products.[13]

In conclusion, we have developed a palladium-catalyzed novel three-component cyclization-coupling reaction of propargyl carbonate, β-keto esters, and aryl iodide. This three-component cyclization–coupling protocol provides an efficient access to a variety of polysubsituted furans and shows some advantages in terms of its simple operation, easily availability, and diversity of the starting material.

Experimental Section

Methyl 2,4-Dimethyl-5-phenylfuran-3-carboxylate 5a. To a solution of $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) in 2.0 mL of anhydrous DMF under argon were added **2b** (22.8 mg, 0.2

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(10) For the detailed experimental procedure see the Supporting Information.

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mmol), iodobenzene (40.8 mg, 0.2 mmol), methyl acetoacetate (23.2 mg, 0.2 mmol), and K_2CO_3 (55.2 mg, 0.4 mmol). The mixture was stirred at 100 °C for 12 h.The reaction was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with Et_2O. The combined organic extracts were washed with water and saturated brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford **5a**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.57 (d, 2H), 7.44−7.39 (t, 2H) 7.32−7.29 (t, 1H) 3.86 (s, 3H), 2.61 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 158.6, 147.7, 130.9, 128.5 (2C), 127.2, 126.1 (2C), 116.8, 115.1, 51.1, 14.5, 10.9; IR (KBr, cm^{-1}) 2952, 2926, 1715, 1441, 1325, 1237, 1097, 765, 697; EI-MS *m/z* 230 (M^+), 215, 198,170, 141, 128, 105, 77, 43. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.25; H, 6.38. For characterization data of other compounds see the Supporting Information.

Acknowledgment. We thank the NSF (NSF-20021001, NSF-20172024) and the “Hundred Scientist Program” from the Chinese Academy of Sciences for financial support.

Supporting Information Available: Typical experimental procedure and characterization for all products and gHMBC experimental data of **5h** and **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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