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Palladium-catalyzed cyclocarbonylation of trifluoromethyl propargylic alcohols producing 3-trifluoromethyl-2(5*H*)-furanones (γ-lactones)

Zhong-Xing Jiang[a] and Feng-Ling Qing[a,b,*]

[a]*Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

[b]*College of Chemistry and Chemical Engineering, Donghua University, 1882 West Yanan Lu, Shanghai 200051, China*

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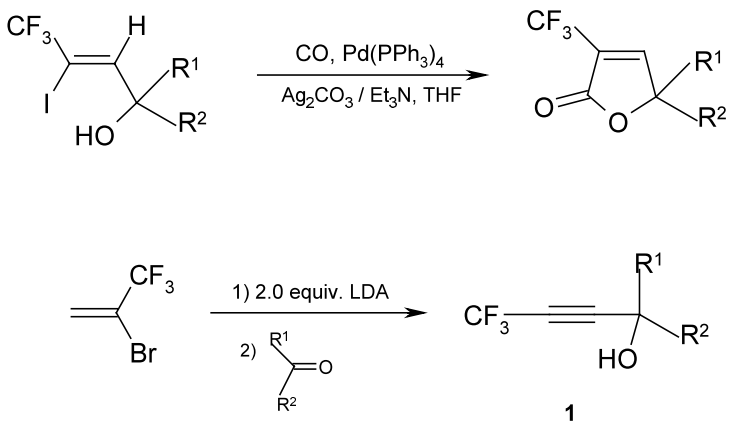
Abstract—The reaction of trifluoromethyl propargylic alcohols **1**, CO and H_2 in the presence of catalytic $Pd(OAc)_2$ and PPh_3 afforded 3-trifluoromethyl-2(5*H*)-furanones **2** in high yields. © 2001 Published by Elsevier Science Ltd.

The high electronegativity and small atomic volume of fluorine have been used to probe reactivity, especially that of biologically important molecules.[1] The development of new preparative methods and exploring the utility of specifically fluorinated compounds in biological systems are of great importance.[2] 2(5*H*)-Furanones are a class of interesting compounds that are comprised of a structural moiety frequently present in biologically active natural products and can be further transformed into other important structural moieties in organic synthesis.[3] Although a number of 2(5*H*)-furanones have been prepared, to the best of our knowledge, there is no report on the synthesis of 3-trifluoromethyl-2(5*H*)-furanones. Very recently, we developed a practical route to 3-trifluoromethyl-2(5*H*)-furanones through the palladium-catalyzed cyclocarbonylation of (*Z*)-3-iodo-3-trifluoromethyl allylic alcohols (Scheme 1).[4] Recently, Alper et al. described the transition metal-catalyzed cyclocarbonylation of alkynols to 2(5*H*)-furanones.[5] Accordingly, we were interested in testing the feasibility of the synthesis of 3-trifluoromethyl-2(5*H*)-furanones by palladium-catalyzed cyclocarbonylation of trifluoromethylated alkynols **1**.



Scheme 1.

Keywords: cyclocarbonylation; γ-lactones; trifluoromethyl-containing compounds.

* Corresponding author. Fax: 86-21-64166128; e-mail: flq@pub.sioc.ac.cn

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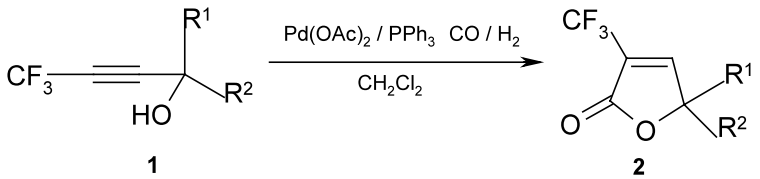
Trifluoromethyl propargylic alcohols **1** were easily prepared from 2-bromo-3,3,3-trifluoropropene and ketones (aldehydes) in the presence of 2 equiv. LDA (Scheme 1).[6] Compound 4,4,4-trifluoro-1-cyclohexyl-2-butyn-1-ol **1a** was used as a model substrate to explore the cyclocarbonylation reaction conditions (Scheme 2 and Table 1). Firstly, treatment of **1a** with 30 atm of CO and 10 atm of H_2 in the presence of 0.05 equiv. of $Pd(OAc)_2$ and 0.1 equiv. of PPh_3 in CH_2Cl_2 at 50°C for 30 h resulted in no reaction and compound **1a** was recovered (entry 1). When the reaction temperature was increased to 85°C under the conditions of entry 1, ^{19}F NMR showed that the starting material **1a** was totally converted and 3-trifluoromethyl-2(5*H*)-furanone **2a** was isolated in 65% yield. To find out the optimal reaction conditions, we studied the effect of various reaction parameters (catalyst, solvent, pressure of CO and H_2) on the outcome of the reaction. $Pd(OAc)_2/PPh_3$ was more active than $Pd(PPh_3)_4$ and $Pd(dba)_2$ in cyclocarbonylation under similar reaction conditions (entries 3, 4). Gabriele et al. reported that PdI_2/KI was an effective catalyst for the oxidative carbonylation of alkynols, producing γ-lactones.[7] However, when PdI_2/KI was used as the catalyst instead of $Pd(OAc)_2/PPh_3$ for the cyclocarbonylation of **1a** under the conditions of entry 1, **2a** was obtained in very low yield (entry 5). Fortunately, when the pressure of CO/H_2 was increased to 60/20 under the conditions of entry 1, **1a** was completely converted to **2a** in 90% isolated yield (entry 6). The nature of the solvent was an important factor. There was no reaction using THF as solvent (entry 7). The reaction conditions described in entry 6 (60 atm of CO, 20 atm of H_2, 5% mol $Pd(OAc)_2$ and 10% mol PPh_3 in CH_2Cl_2) were chosen as optimized conditions for the cyclocarbonylation of **1a**.[8]



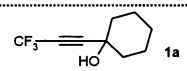
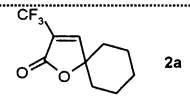
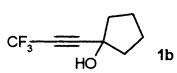
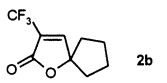
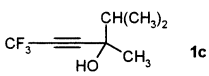
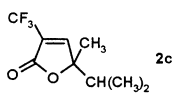
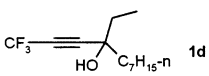
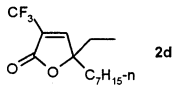
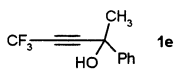
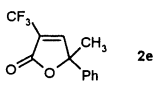
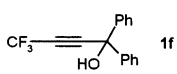
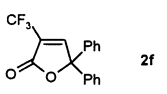
1 **2**

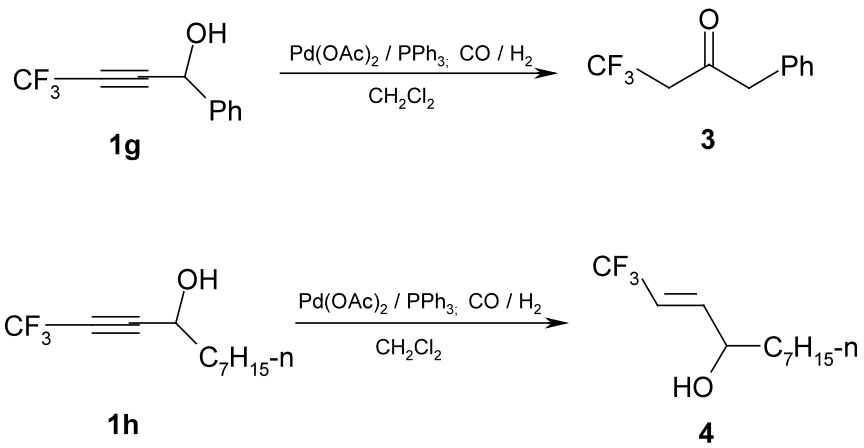
Scheme 2.

Table 1. Cyclocarbonylation optimization using **1a**

Entry	Catalyst (5 mol%)	Solvent	Temperature (0°C)	Pressure (atm) CO:H_2	Isolated yield (%)
1	$Pd(OAc)_2+PPh_3$	CH_2Cl_2	50	30:10	0
2	$Pd(OAc)_2+PPh_3$	CH_2Cl_2	85	30:10	65
3	$Pd(PPh_3)_4$	CH_2Cl_2	85	30:10	18
4	$Pd(dba)_2+PPh_3$	CH_2Cl_2	85	30:10	23
5	PdI_2+KI	CH_2Cl_2	85	30:10	21
6	$Pd(OAc)_2+PPh_3$	CH_2Cl_2	85	60:20	90
7	$Pd(OAc)_2+PPh_3$	THF	85	60:20	0

Table 2. Palladium-catalyzed cyclocarbonylation of tertiary alkynols **1** to 3-trifluoromethyl-2(5*H*)-furanones **2**

Entry	Alkynol **1**	2(5H)-furanone **2**	Isolated Yield (%)
1	 **1a**	 **2a**	90
2	 **1b**	 **2b**	81
3	 **1c**	 **2c**	70
4	 **1d**	 **2d**	77
5	 **1e**	 **2e**	43
6	 **1f**	 **2f**	61



Scheme 3.

Under the optimized conditions established for **1a**, the cyclocarbonylation of various trifluoromethyl propargylic alcohols **1** has been investigated. Tertiary alkynols can be converted to the corresponding 3-trifluoromethyl-2(5*H*)-furanone (Table 2). In contrast, when secondary phenyl substituted alkynol **1g** was treated with CO/H_2 in the presence of $Pd(OAc)_2/PPh_3$ under the typical cyclocarbonylation conditions, the product was ketone **3** which was isolated in 14% yield (Scheme 3). Interestingly, the cyclocarbonylation of secondary alkyl substituted alkynol **1h** led to the hydrogenated product **4** as a single product in 85% yield (Scheme 3).

In conclusion, we have developed a convenient route to 3-trifluoromethyl-2(5*H*)-furanone through palladium-catalyzed cyclocarbonylation of 3-trifluoromethyl alkynols.

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8. Typical cyclocarbonylation procedure: Into an autoclave with a glass liner and stirring bar was placed a mixture of **1a** (192 mg, 1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol) and CH_2Cl_2 (3 ml). The autoclave was flushed four times with hydrogen, pressurized to 20 atm, and then carbon monoxide and pressurized to 80 atm. The autoclave was placed in an oil bath at 85°C for 30 h and then allowed to cool to room temperature. The autoclave was depressurized, the reaction mixture filtered through Celite and the solvent removed by rotary evaporation. The resulting residue was purified by flash silica gel chromatography to afford **2a** (198 mg, 90% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.84 (s, 1H), 1.75 (m, 10H); ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3CO_2H as an external standard, upfield positive): δ −12.3 (s); IR: 1756, 1668, 1362, 1175 cm^{-1}; MS *m/z* 220 (M^+, 17), 122 (100); HRMS for $C_{10}H_{11}O_2F_3$: 220.07479. Found: 220.07295.