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Palladium-mediated synthesis of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones☆

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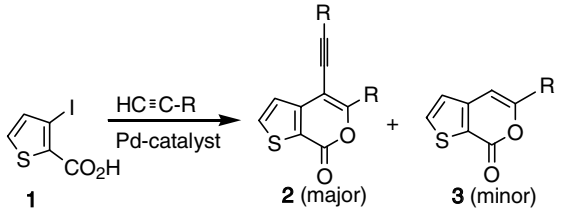
Abstract—We describe here, the first palladium-mediated tandem C–C bond forming reaction between 3-iodothiophene-2-carboxylic acid and terminal alkynes to afford the unexpected 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones in good yields.

Isocoumarins[1a] are of considerable synthetic and pharmacological interest because of their wide range of activities[1b–d] such as antifungal, antimicrobial, phytotoxic and other effects. The angiogenesis inhibitor NM-3,[1e] which belongs to this class is presently undergoing Phase-I clinical trials. On the other hand, the thiophene moiety is common in many bioactive agents and drugs[2a] and is considered as a bioisostere of the benzene ring.[2a] Thus, one can anticipate that replacing the benzene ring of isocoumarin with a thiophene ring would afford compounds (i.e., thieno[2,3-*c*]pyran-7-ones) of potential pharmacological interest.[2b] However, thienopyranones are a different class of heterocycles and only a few methods are known for their synthesis.[2c–e] Moreover, the synthesis of 4-alkynylthieno[2,3-*c*]pyran-7-ones has not been reported thus far. These derivatives are attractive due to the synthetic potential of C-4 alkynyl fragments for use in library construction. Therefore, to enrich the chemistry of thiophenes and more importantly, to synthesize a library of isocoumarins[3] for biological screening we became interested in the synthesis of thieno[2,3-*c*]pyran-7-ones.

Among the many methods reported for the synthesis of isocoumarins one widely used process is the Sonogashira-type coupling followed by electrophilic or transition metal mediated cyclization of the resulting alkynes possessing a carboxylate or an equivalent group in proximity to the triple bond.[4] Attractive features of this process include its versatility and functional group tolerance. Thus, isocoumarins have been prepared by reacting *o*-iodobenzoic acid with terminal alkynes in the presence of $Pd(PPh_3)_4$, Et_3N and a stoichiometric amount of $ZnCl_2$.[5a] The use of $ZnCl_2$ in place of CuI[5b,c] was found to be responsible for the predominant formation of isocoumarins over phthalides. Nevertheless, we have noted that 3-iodothiophene-2-carboxylic acid (**1**) reacts smoothly with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$–Et_3N–CuI as a catalyst system affording 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones (**2**) in good yields (Scheme 1). To the best of our knowledge this demonstration represents the first example of a mild, single-step, Pd-catalyzed approach to substituted thieno[2,3-*c*]pyran-7-ones.[6]



Scheme 1. Pd-catalyzed reaction of 3-iodothiophene-2-carboxylic acid **1** with terminal alkynes.

Keywords: 4-Alkynylthieno[2,3-*c*]pyran-7-one; Palladium catalyst; Terminal alkynes; 3-Iodothiophene-2-carboxylic acid.
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Table 1. Pd-mediated synthesis of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones[a]

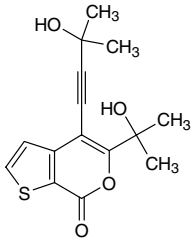
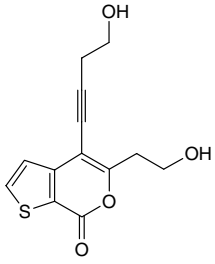
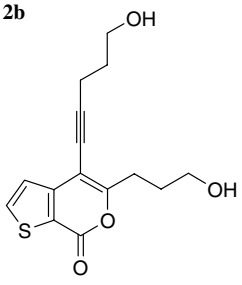
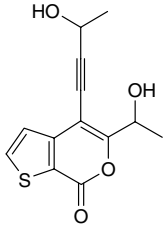
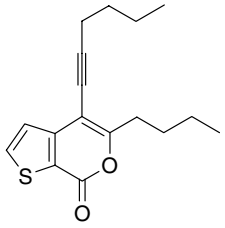
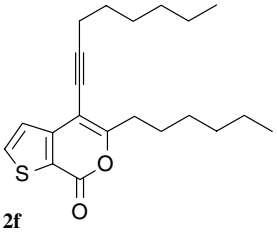
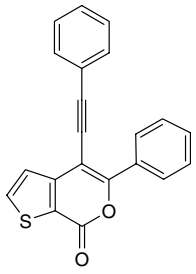
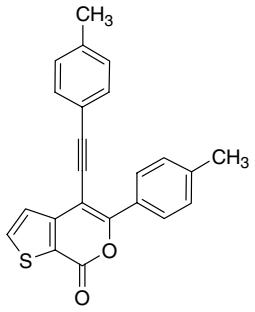
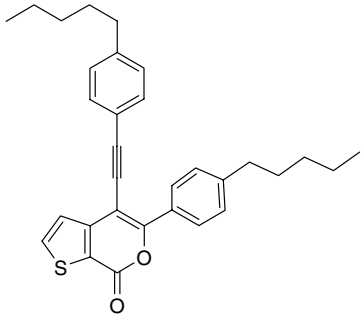
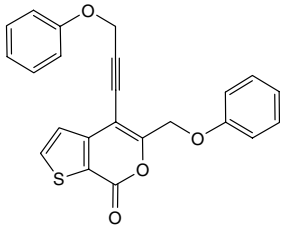
Entry	Alkyne (HC≡C–R)	Solvent; time (h)	Product (**2**)	Yield (%)	
				2	**3**
1	–$C(CH_3)_2OH$	EtOH; 12	 **2a**	50	24
2	–$C(CH_3)_2OH$	1,4-dioxane; 12	**2a**	30	0
3	–$C(CH_3)_2OH$	DMA; 12	**2a**	55	0
4	–$C(CH_3)_2OH$	DMF; 8	**2a**	80	0
5	–$(CH_2)_2OH$	DMF; 12	 **2b**	53	0
6	–$(CH_2)_3OH$	DMF; 12	 **2c**	61	0
7	–$CH(OH)CH_3$	DMF; 10	 **2d**	82	0
8	–$(CH_2)_3CH_3$	DMF; 12	 **2e**	65	15
9	–$(CH_2)_5CH_3$	DMF; 12	 **2f**	62	35

Table 1 (*continued*)

Entry	Alkyne (HC≡C–R)	Solvent; time (h)	Product (**2**)	Yield (%)	
				2	**3**
10	$-C_6H_5$	DMF; 12	 **2g**	57	0
11	$-C_6H_4CH_3$-*p*	DMF; 12	 **2h**	62	0
12	$-C_6H_4C_5H_{11}$-*p*	DMF; 8	 **2i**	73	0
13	$-CH_2OC_6H_5$	DMF; 8	 **2j**	75	0

[a] All reactions were carried out using **1** (1.0 equiv), terminal alkyne (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.048 equiv), CuI (0.06 equiv) and Et_3N (5 equiv) at 70–80 °C under nitrogen.

While preparing 5-substituted thieno[2,3-*c*]pyran-7-ones (**3**) under Sonogashira conditions,[7] we observed that Pd-catalyzed coupling of **1**[8a] with 2-methyl-3-butyn-2-ol in ethanol afforded 5-alkylthieno[2,3-*c*]pyran-7-ones (**3a**, R = $-C(CH_3)_2OH$, Scheme 1) in 24% yield and the unexpected 4-(3-hydroxy-3-methylbut-1-ynyl)-5-(1-hydroxy-1-methylethyl)thieno[2,3-*c*]pyran-7-one (**2a**) in 50% purified yield (2:1 ratio of **2a** and **3a**) (Table 1, entry 1). Compound **2a** was isolated as a light brown gum (λ_{max}(MeOH) at 312.0, 252.8, 238.4 for **2a** versus 360.0, 353.8, 310.4, 282.0, 230.8 for **3a**) and was characterized by ^1H and ^{13}C NMR and other spectroscopic methods. The mass spectra showed an intense molecular ion peak at *m*/*z* 293 (M^+, 100%) that was higher than the *m*/*z* of **3a** [211 (M^+)]. In the ^1H NMR spectra, compound **3a** demonstrated a signal at δ 6.8 due to

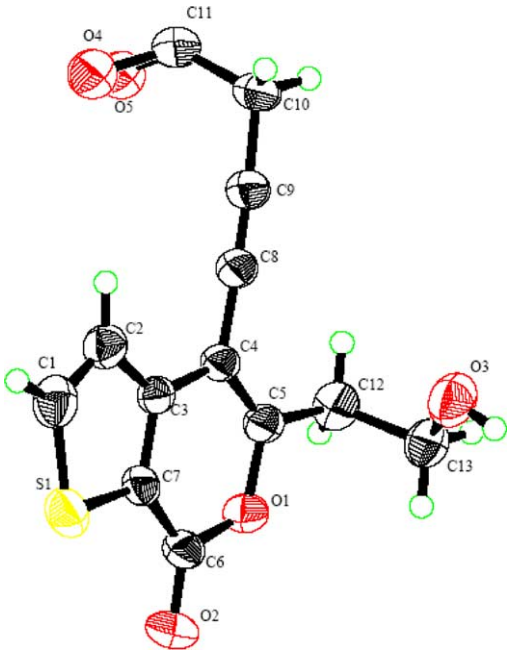


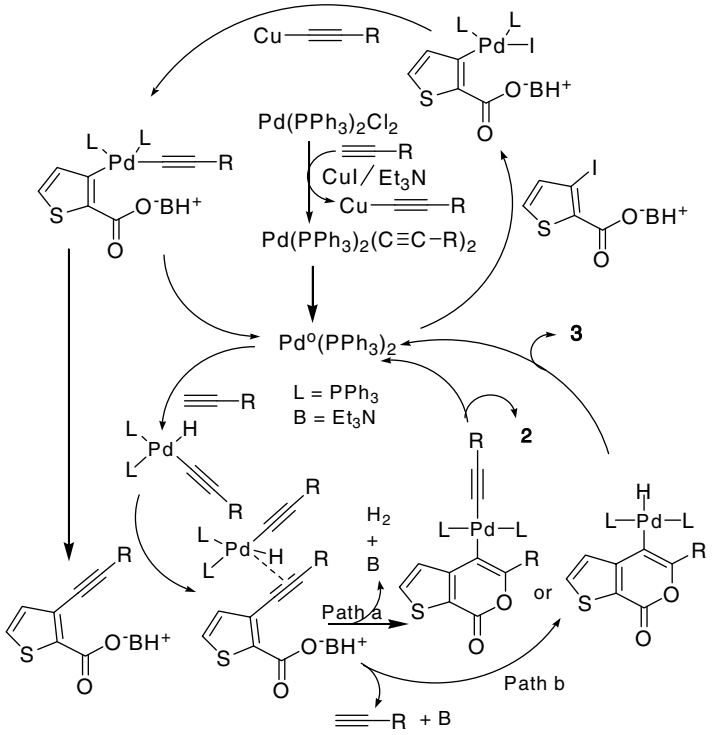
Figure 1. X-ray crystal structure of **2b** (ORTEP diagram).

the vinylic proton, which was not observed in the case of **2a**. Moreover, **2a** gave a signal at δ 1.61 accounting for the four methyl groups.

The spectral data thus identified **2a** as an alkyne possessing the thieno[2,3-*c*]pyran-7-one ring at one end. This was supported by the molecular structure of **2b** (R = $-CH_2CH_2OH$), which was confirmed by X-ray analysis.[8b] The ORTEP diagram of **2b** (Fig. 1) shows a planar thieno[2,3-*c*]pyran-7-one core with a disordered hydroxyl group due to the alkynyl side chain along with the other hydroxy group oriented in the opposite direction. The unexpected formation of **2a** thus prompted us to investigate this reaction in a more systematic manner.

The reaction was originally carried out in ethanol in the presence of $PdCl_2(PPh_3)_2$ (0.048 equiv), CuI (0.06 equiv), Et_3N (5.0 equiv) and 2.0 equiv of the terminal alkyne at 75 °C. Keeping the molar ratio of Pd:Cu at 1:1.3, we carried out a series of optimization experiments on the reaction of **1** with 2-methyl-3-butyn-2-ol. We found that changing the solvent from ethanol to a non-protic solvent such as 1,4-dioxane or dimethylacetamide (DMA) suppressed the formation of **3a** completely (Table 1, entries 2 and 3) and **2a** was isolated in 30% and 55% yields, respectively. The best result was obtained using DMF where **2a** was isolated exclusively in 80% yield (Table 1, entry 4). In a separate study we carried out this reaction using a smaller amount of terminal alkyne (1.0 equiv); **2a** was isolated in 28% yield and the reaction did not reach completion. Both Pd and Cu catalysts played crucial roles as no reaction was observed when either was omitted. The use of other Pd catalysts, for example, $Pd(PPh_3)_4$, $Pd(OAc)_2$ or $PdCl_2(dppf)_2$ was investigated where **2a** was isolated as major product albeit in low yield (35–40%). Originally, we speculated that the formation of **2a** might first involve the formation of **3a**, which subsequently reacted with another mole of the terminal alkyne under Pd–Cu catalysis. However, formation of **2a** was not observed when **3a** was subjected to the same Pd-catalyzed reaction conditions.

We then tested the optimized reaction conditions[9] with other terminal alkynes (Table 1, entries 5–13). Various functional groups including aryl, alkyl, hydroxyl, ether,



Scheme 2. A plausible mechanism for Pd-catalyzed formation of **2** and **3**.

etc. present in the terminal alkyne were well tolerated. Generally, compounds **2** were isolated as the sole products in all cases except when 1-hexyne and 1-octyne were used (Table 1, entries 8 and 9). The reaction shows very high regioselectivity as no isomeric thieno[2,3-*c*]furan-6-ones resulting from 5-'*exo-dig*' cyclization were detected under the reaction conditions studied. This is in sharp contrast to earlier observations[5] where the coupling-cyclization followed 5-*exo-dig* ring closure, predominantly under Pd–Cu catalysis in DMF.

Mechanistically, the reaction seems to proceed via in situ generation of 3-(1-alkynyl)thiophene-2-carboxylic acid according to the typical Sonogashira pathway (Scheme 2).[5b] Once formed this acid then undergoes intramolecular cyclization aided by the Pd(II) complex[4a] or copper salt[3] to give **2** or **3**. However, formation of **2** clearly suggests that this is a Pd(II)-mediated process and presumably, proceeds via insertion of the Pd(0) complex into the acetylenic C–H bond of the terminal alkyne leading to a Pd(II) intermediate[10] that catalyzes the '*6-endo-dig*' ring closure via path a or b (Scheme 2). A '5-*exo-dig*' ring closure, although allowed by Baldwin's rule, was not observed in the present case because of the favourable geometry associated with the 5–6 ring formation rather than the 5–5 ring.

In summary, a novel catalytic approach to 4-alkynylthieno[2,3-*c*]pyran-7-ones has been developed through the coupling of 3-iodothiophene-2-carboxylic acid with terminal alkynes under palladium–copper catalysis. The process was found to be quite general and highly regioselective, placing the alkynyl moiety at the C-4 position of the thieno[2,3-*c*]pyran-7-one ring. We are presently investigating the scope of this novel palladium-catalyzed transformation.

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8. For the synthesis of 3-iodo-thiophene-2-carboxylic acid (**1**), see: (a) Duffault, J.-M.; Tellier, F. *Synth. Commun.* **1998**, *28*, 2467; (b) Single crystals suitable for X-ray diffraction of **2b** were grown from chloroform. Crystals were obtained as colourless plates in the triclinic space group $P\bar{1}$ with cell dimensions $a = 7.565\ (2)$, $b = 7.938\ (1)$, $c = 11.083\ (2)$, $\alpha = 98.525\ (3)$, $\beta = 105.020\ (6)$, $\gamma = 101.606\ (6)$ and $V = 615.4\ (2)$ containing 2 molecules in the unit cell. The intensity data have been collected on a Rigaku AFC-7S single crystal diffractometer using Mo Kα ($\lambda = 0.7107$ Å). The structure was solved by direct methods, and was refined using least squares procedures using the Crystal Structure software. The present *R* factors of **2b** are: $R\ (Rw) = 0.099$ (0.15, with 1687 reflections). Crystallographic data (excluding structure factors) for **2b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 280767.
9. *General procedure for the preparation of 5-substituted 4-alkynylthieno[2,3-c]pyran-7-ones* (**2**): A mixture of 3-iodo thiophene-2-carboxylic acid (0.787 mmol), $PdCl_2(PPh_3)_2$ (0.038 mmol), CuI (0.047 mmol) and Et_3N (4 mmol) in DMF (10 mL) was stirred for 1 h under nitrogen. The acetylenic compound (1.57 mmol) was added and the mixture was stirred at room temperature for 1 h and then at 70–80 °C for 8–12 h. After completion of the reaction,

DMF was removed under reduced pressure and the residue was extracted with ethyl acetate (3×50 mL). The organic layers were collected, combined, washed with saturated aq $NaHCO_3$ (2×25 mL) followed by water (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography on silica gel using light petroleum ether (60–80 °C)–ethyl acetate. Spectral data for **2a**: Light brown gum; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85 (d, $J = 5.0$ Hz, 1H), 7.34 (d, $J = 5.0$ Hz, 1H), 2.24 (br s, 2H, –OH), 1.61 (s, 12H, CH_3); IR (cm^{-1}, $CHCl_3$) 3391, 2981, 1715 (C=O), 1626; *m/z* (ES Mass) 293 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4 (C=O), 148.3, 144.0, 138.8 (2C), 124.7, 105.6, 104.0, 74.1, 73.6, 65.6, 31.1 (2C, CH_3), 28.5 (2C, CH_3); UV (nm, MeOH) 312.0, 252.8, 238.4, 214.2; HPLC 96.3%, column Zorbax Eclipse XDB C-18 (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B) 0/30, 13/70, 15/100, 25/100, flow rate 1.5 mL/min, UV 254 nm, retention time 11.3 min. Spectral data for **2j**: white solid; mp 115.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, $J = 7.5$ Hz, 1H), 7.34–7.23 (m, 6H), 7.22–7.00 (m, 5H), 4.93 (s, 2H, CH_2), 5.03 (s, 2H, CH_2); IR (cm^{-1}, KBr) 2925, 1733 (C=O), 1598, 1240; *m/z* (CI Mass) 389 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 157.9 (C=O), 156.9, 154.5, 153.8, 152.7, 137.0, 129.6 (2C), 129.5 (2C), 126.6, 124.7, 121.8, 121.7, 115.0 (2C), 114.9 (2C), 101.2, 92.7, 78.1, 65.0, 56.2; UV (nm, MeOH) 313.0, 255.8, 202.8; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate 1.0 mL/min, UV 254 nm, retention time 17.4 min.

10. Insertion of the Pd(0) complex into the acetylenic C–H bond has been suggested earlier, see: Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.