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

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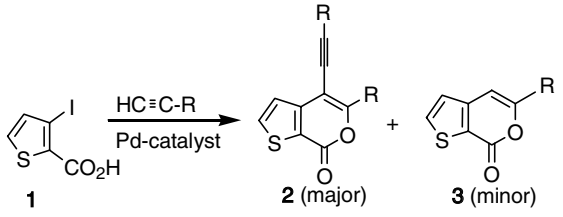
Abstract—We describe here, the first palladium-mediated tandem C–C bond forming reaction between 3-iodothiophene-2-carboxylic acid and terminal alkynes to afford the unexpected 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones in good yields.

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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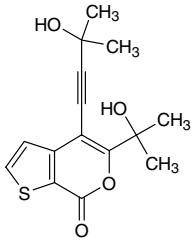
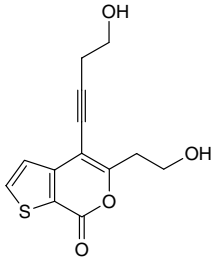
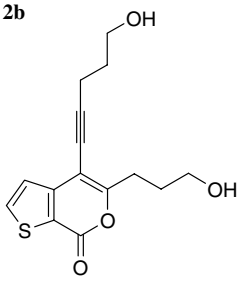
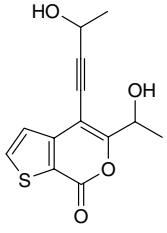
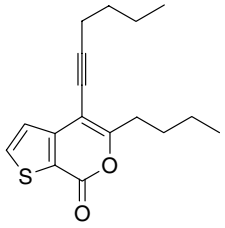
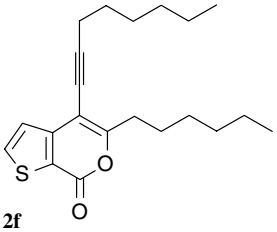
Table 1. Pd-mediated synthesis of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones[a]

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