



3-Iodo-4-chalcogen-2H-benzopyran as a convenient precursor for the sonogashira cross-coupling: synthesis of 3-alkynyl-4-chalcogen-2H-benzopyrans

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ABSTRACT

3-Iodo-4-chalcogen-2H-benzopyran derivatives underwent a direct Sonogashira cross-coupling reaction with several terminal alkynes in the presence of a catalytic amount of Pd(PPh₃)₂Cl₂ with CuI as a co-catalyst, using Et₃N as base and solvent. This cross-coupling reaction proceeded cleanly under mild conditions and was performed with propargylic alcohols, propargylic ethers, as well as alkyl and aryl alkynes, furnishing the correspondent 3-alkynyl-4-chalcogen-2H-benzopyrans in good yields.

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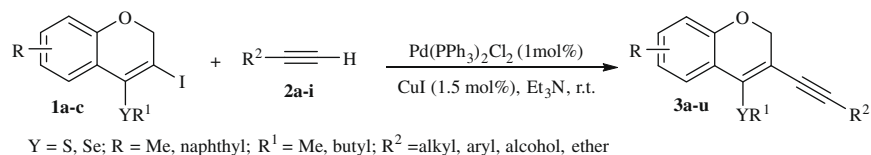
Transition-metal-catalyzed cross-coupling reactions between Csp²-centers have been extensively used for selective construction of carbon–carbon bonds, in particular, for the formation of structural units found in natural products, pharmaceuticals, and electrical conductors.¹ In this context, palladium-catalyzed coupling systems have been developed as a consequence of the great interest in the increase of coupling substrates that are more economic, more easily accessible, and reactive even under mild conditions. In this way, the palladium-catalyzed cross-coupling reactions of aryl halides or triflates with terminal alkynes, commonly referred to as Sonogashira reactions, are powerful, versatile, and popular tools for selective construction of the new carbon–carbon bonds.² To this reaction that is generally co-catalyzed by copper salts, an amine as a base and a phosphine as a ligand for palladium are also typically included. Recent advances of Sonogashira reactions, including the development of conditions with metals other than palladium³ and a copper-free protocol⁴ have been described. Of the variety of reactions that fall in this category, the preparation of conjugated enyne, and enediyne systems as well as heterocycles represent a great area of investigation.⁵ Among heterocycles, the six-membered oxygenated heterocycles, or pyrans, are probably one of the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites present in the structure of several biologically interesting compounds. In particular, 2H-benzopyrans are present in a variety of compounds that possess important pharmaceutical and biological

applications, such as daurichromenic acid that exhibits anti-HIV activity,⁶ and coutareagenin that is known to present antidiabetic property.⁷ To the best of our knowledge, there is no protocol describing the introduction of alkyne and chalcogen at 3 and 4-positions of benzopyran, respectively, using 3-iodo-4-chalcogen-2H-benzopyrans as a substrate in the Sonogashira cross-coupling. The applicability of the selectivity of these two functionalities can constitute as a synthetic approach to the preparation of biological active benzopyran compounds. Combining the knowledge that our group has accumulated in the synthesis of heterocycles containing a chalcogen⁸ with the opportunity for further functionalization in these compounds, herein we suggest an entirely new approach that focuses on the application of 3-iodo-4-chalcogen-2H-benzopyrans **1a–c** as substrates in the Sonogashira cross-coupling to give 3-alkynyl-4-chalcogen-2H-benzopyrans (Scheme 1).

Initially, to optimize the reaction conditions, we examined the reaction between 3-iodo-4-(1-buthylselenyl)-2H-benzopyran **1a**⁹ and phenyl acetylene **2a** in the presence of a variety of Pd(II) or Pd(0) catalysts with various solvents, using bases and CuI (1.5 mol %).

A comparison of the effectiveness of catalysts showed that Pd(PPh₃)₂Cl₂ and Pd(PPh₃)₄ were effective (Table 1, entries 1 and 5), whereas Pd(PhCN)₂Cl₂, PdCl₂, and Pd(OAc)₂ were less active (Table 1, entries 2–4). It is important to note that when the amount of catalyst was reduced from 2 to 0.5 mol % there was no change in the catalytic effect (Table 1, entries 7 and 8). However when the reaction was carried out in the absence of CuI the coupling product was not observed (Table 1, entry 9). In addition to using Et₃N as base and solvent, we tried other solvents and bases. The reaction

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Scheme 1.

Table 1
Influence of reaction conditions on the formation of 3-alkynyl-4-chalcogen-2H-benzopyran **3a**

S. No.	[Pd] (mol %)	Solvent (mL)	Base (equiv)	Yield ^a (%)
1	PdCl ₂ (PPh ₃) ₂ (2)	Et ₃ N (2)	—	99
2	PdCl ₂ (PhCN) ₂ (2)	Et ₃ N (2)	—	49
3	PdCl ₂ (2)	Et ₃ N (2)	—	54
4	Pd(Oac) ₂ (2)	Et ₃ N (2)	—	67
5	Pd(PPh ₃) ₄ (2)	Et ₃ N (2)	—	87
6	—	Et ₃ N (2)	—	—
7	PdCl ₂ (PPh ₃) ₂ (1)	Et ₃ N (2)	—	98
8	PdCl ₂ (PPh ₃) ₂ (0.5)	Et ₃ N (2)	—	97
9	PdCl ₂ (PPh ₃) ₂ (1)	Et ₃ N (2)	—	— ^b
10	PdCl ₂ (PPh ₃) ₂ (1)	Dioxane (1.5)	Et ₃ N	45
11	PdCl ₂ (PPh ₃) ₂ (1)	MeOH (1.5)	Et ₃ N	95
12	PdCl ₂ (PPh ₃) ₂ (1)	CH ₃ CN (1.5)	Et ₃ N	86
13	PdCl ₂ (PPh ₃) ₂ (1)	DMF (1.5)	Et ₃ N	32
14	PdCl ₂ (PPh ₃) ₂ (1)	MeOH (2)	Pyrrolidone (2)	60
15	PdCl ₂ (PPh ₃) ₂ (1)	MeOH (2)	Cs ₂ CO ₃ (2)	95
16	PdCl ₂ (PPh ₃) ₂ (1)	MeOH (2)	NaOH (2)	76
17	PdCl ₂ (PPh ₃) ₂ (1)	MeOH (2)	K ₂ CO ₃ (2)	83

^a Yields are given by GC analysis.

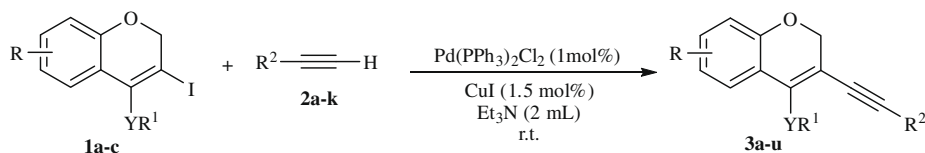
^b Reaction was performed in the absence of CuI.

in dioxane and DMF formed not only **3a** in 45% and 32% yields, respectively, but also side products, while in that reaction involving MeOH and CH₃CN, **3a** was found almost exclusively (Table 1, entries 10–13). Replacement of Et₃N with other bases such as pyrrolidone, Cs₂CO₃, NaOH, and K₂CO₃ went equally well or worse (Table 1, entries 14–17).

Good to excellent yields could be obtained from the Sonogashira coupling reactions across a wide range of alkynes and 3-iodo-4-chalcogen-2H-benzopyran derivatives using the established reaction conditions¹⁰ (Table 2).

Studies defining the scope and limitations of this reaction led us to a good understanding of this process. First, to determine the real influence of the terminal alkynes, we keep the chalcogen-2H-benzopyran **1a** invariable. The cross-coupling worked well with respect to alkynes having aryl, aryl substituted and alkyl groups (Table 2, entries 1–4). Both hindered and nonhindered propargyl alcohols gave the desired 3-alkynyl-4-2H-benzopyrans in moderated to good yields (Table 2, entries 5–9). In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with other 3-iodo-4-chalcogen-2H-benzopyrans was also investigated. Then the substrates **1b** and **1c**, which have a methylthio group in the 4-position of the benzopyran ring, were also cross-coupled efficiently, under the same reaction conditions (Table 2, entries 10–21).

Table 2
Synthesis of 3-alkynyl-4-chalcogen-2H-benzopyrans **3a–u**^a



S. No.	Substrate	Alkyne (equiv)	Product yield ^b (%) / time
1		2a (1.2)	3a (99)/12h
2	1a	2b (1.2)	R ² = C ₆ H ₄ -Me- <i>p</i> 3b (57)/12 h
3	1a	2c (3)	R ² = <i>n</i> -Bu 3c (55)/12 h
4	1a	2d (1.2)	R ² = <i>t</i> -Bu 3d (60)/10 h

(continued on next page)

Table 2 (continued)

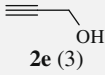
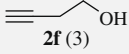
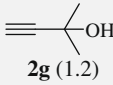
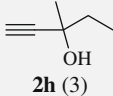
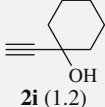
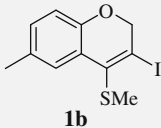
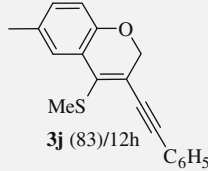
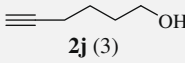
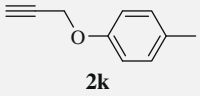
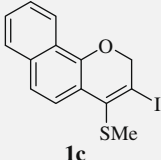
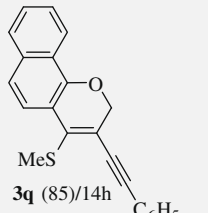
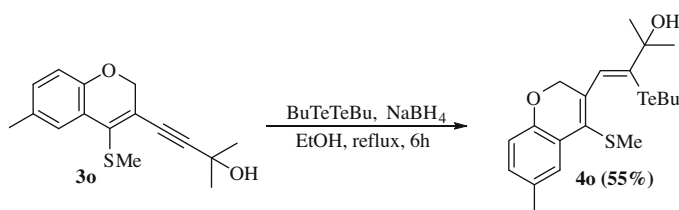
S. No.	Substrate	Alkyne (equiv)	Product yield ^b (%) / time
5	1a	 2e (3)	R ² = CH ₂ OH 3e (52)/14 h
6	1a	 2f (3)	R ² = (CH ₂) ₂ OH 3f (47)/14 h
7	1a	 2g (1.2)	R ² = C(CH ₃) ₂ OH 3g (73)/13 h
8	1a	 2h (3)	R ² = C(CH ₂)OHCH ₂ CH ₃ 3h (33)/13 h
9	1a	 2i (1.2)	R ² = OH- <i>c</i> -C ₆ H ₁₀ 3u (91)/15 h
10	 1b	2a (1.2)	 3j (83)/12h C ₆ H ₅
11	1b	2c (3)	R ² = <i>n</i> -Bu 3k (82)/16 h
12	1b	2e (3)	R ² = CH ₂ OH 3l (72)/15 h
13	1b	2f (3)	R ² = (CH ₂) ₂ OH 3m (81)/16 h
14	1b	 2j (3)	R ² = (CH ₂) ₄ OH 3n (71)/15 h
15	1b	2g (3)	R ² = C(CH ₃) ₂ OH 3o (82)/16 h
16	1b	 2k	R ² = CH ₂ O- <i>t</i> -tolyl- <i>p</i> 3p (75)/15 h
17	 1c	2a (1.2)	 3q (85)/14h C ₆ H ₅
18	1c	2c (3)	R ² = <i>n</i> -Bu 3r (80)/15 h

Table 2 (continued)

S. No.	Substrate	Alkyne (equiv)	Product yield ^b (%) / time
19	1c	2e (3)	R ² = CH ₂ OH 3s (67)/15 h
20	1c	2f (3)	R ² = (CH ₂) ₂ OH 3t (84)/16 h
21	1c	2g (3)	R ² = C(CH ₃) ₂ OH 3u (91)/15 h

^a Reactions were performed by using **1a–c** (0.25 mmol), alkyne **a–k**, Pd(PPh₃)₂Cl₂ (1 mol %), and CuI (1.5 mol %) in Et₃N (2 mL), under room temperature.

^b Yields of **3a–u** are given for isolated products.



We believe that this approach to 3-alkynyl-4-chalcogen-2H-benzopyrans should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting functionalities into other substituents. In view of this, the potential of these products as precursors for increasing molecular complexity via hydrotelluration reaction has been briefly investigated.¹¹ For example, the compound **3o** was reacted with BuTeTeBu and NaBH₄ in ethanol under reflux temperature for 6 h, affording, the corresponding vinylic telluride **4o**, in 55% yield (Scheme 2). Vinyl tellurides are useful intermediates in organic synthesis,¹² including the synthesis of natural products by using cross-coupling reactions.¹³

We have described that 3-iodo-4-chalcogen-2H-benzopyrans were versatile units for the Sonogashira cross-coupling in the preparation of 3-alkynyl-4-chalcogen-2H-benzopyrans. This cross-coupling reaction proceeded cleanly under mild conditions and was performed with propargylic alcohols, propargylic ethers, as well as alkyl and aryl alkynes. The product obtained was effective for subsequent hydrotelluration reaction at triple bond giving the vinylic telluride in moderate yield. The studies in the structure–activity relationship and pharmacological activity of these compounds are in progress and will appear in a specialized journal soon.

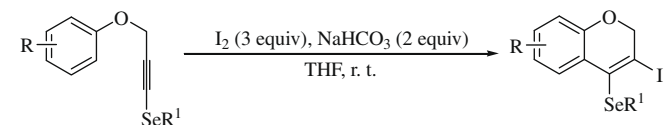
Acknowledgments

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- (a) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347; (b) The best condition for the I₂ cyclization reactions was the addition of NaHCO₃ (0.5 mmol), at room temperature, to a solution of 0.25 mmol of selenophenyl propargyl aryl ethers in 3 mL of THF. After that, 3 equiv of I₂ in 2 mL of THF was gradually added at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h



- General procedure for the cross-coupling reaction: To a Schlenk tube, under argon, containing an appropriate 3-iodo-4-chalcogen-2H-benzopyran (0.25 mmol) in Et₃N (1.5 mL) was added Pd(PPh₃)₂Cl₂ (0.0017 g, 0.0025 mmol). The resulting solution was stirred for 5 min at room temperature. After this time the CuI (0.0007 g, 0.0036 mmol) was added and the solution was stirred for an additional 20 min. After that, appropriate terminal alkyne (0.3 mmol) dissolved in 0.5 mL of Et₃N was then added dropwise, and the reaction mixture was stirred at room temperature for the required time. After this the mixture was diluted with dichloromethane (20 mL), and washed with brine (3 × 20 mL). The organic phase was separated, dried over MgSO₄, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral and analytical data for: *3-p-tolylethynyl-6-methyl-4-butylselenyl-2H-benzopyran (3b)*. Yield: 0.056 g (57%). ¹H NMR: (CDCl₃, 400 MHz) δ (ppm): 7.50 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.96–6.94 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 4.73 (s, 2H), 2.91 (t, J = 7.1 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 1.66 (quint, J = 7.3 Hz, 2H), 1.41 (sext, J = 7.3 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H). ¹³C NMR: (CDCl₃, 100 MHz), δ (ppm): 151.6, 138.8, 131.3, 131.1, 130.2, 129.9, 129.1, 128.7, 123.9, 121.2, 120.0, 115.8, 98.8, 68.6, 32.3, 27.9, 22.7, 21.5, 20.7, 13.5. MS (EI, 70 eV) m/z (relative intensity): 395 (6), 392 (64), 335 (85), 256 (100), 212 (26), 187 (4), 114 (13), 57 (2). Anal. Calcd for C₂₃H₂₄OSe: C, 69.65; H, 5.93. Found: C, 69.87; H, 6.12.
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