Tetrahedron Letters 50 (2009) 5326–5328

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 3-aryl-4-chalcogen-2*H*-benzopyrans from 3-iodo-4-chalcogen-2*H*-benzopyrans using a Suzuki cross-coupling

Benhur Godoi, José S. S. Neto, Adriane Sperança, Carmine Ines Acker, Cristina W. Nogueira, Gilson Zeni *

Laboratório de Síntese, Reatividade, Avaliação Farmacológica e Toxicidade de Organocalcogênios, CCNE, UFSM, Santa Maria, Rio Grande do Sul CEP 97105-900, Brazil

ARTICLE INFO

Article history:
Received 20 April 2009
Revised 30 June 2009
Accepted 1 July 2009
Available online 8 July 2009

ABSTRACT

The Suzuki cross-coupling reaction of 3-iodo-4-chalcogen-2*H*-benzopyran derivatives with a variety of organoboron compounds in the presence of catalytic amount of palladium salt is described. This cross-coupling reaction proceeded cleanly and was performed with aryl boronic acids bearing electron-withdrawing, electron-donating, and neutral substituents, furnishing the corresponding products in moderate to good yields.

The synthesis of heterocycles has attracted much attention in recent years due to their interesting biological properties.[1] Substituted six-membered oxygenated heterocycles or pyrans play key pharmacophore functions in many pharmaceuticals.[2] In addition to the diverse biological activity of the naturally occurring compounds, synthetically derived benzopyrans also exhibit significant bioactivity.[3]

The most used strategies for the synthesis of multiple substituted 2*H*-benzopyran involve: (a) the construction of the 2*H*-benzopyran nucleus after the substituents have been installed and properly functionalized; (b) a preformed 2*H*-benzopyran to which carbon substituents are attached in successive order.

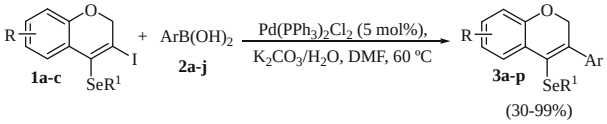
In connection with a project directed at the preparation of novel 3,4-disubstituted benzopyran derivatives, we reasoned that 3-iodo-4-chalcogen-2*H*-benzopyran **1**, easily prepared from organochalcogen propargyl aryl ethers, via electrophilic cyclization protocol,[4] could become a valuable starting material on Suzuki cross-coupling reactions (Scheme 1).

Suzuki cross-coupling reactions of various heteroaryl derivatives have been well documented.[5] However, the application of this protocol to 3-iodo-4-chalcogen-2*H*-benzopyran remains largely unexplored,[6] consequently it is necessary to design a simple, efficient, and versatile method for the construction of benzopyran rings having two different groups at 3- and 4-positions.

For preliminary optimization of the cross-coupling reaction conditions, 3-iodo-6-methyl-4-(1-butylselenyl)-2*H*-benzopyran **1a** and phenylboronic acid **2a** were chosen as standard substrates. Thus, the reaction of **1a** (0.25 mmol) and arylboronic acid **2a** (0.5 mmol) was performed under 60 °C, using different palladium catalysts, solvents, and bases (Table 1).

As shown in Table 1, both Pd(0) and Pd(II) catalysts with different ligands were tested, the best result was obtained using $Pd(PPh_3)_2Cl_2$ 10 mol % which gave the desired product **3a** in 91% yield (Table 1; entry 1). It is important to note that when the amount of catalyst was reduced from 10 to 5 mol %, an increase in the yield was observed and the product **3a** was obtained quantitatively (Table 1, entry 8). However, using less than 5 mol % of $Pd(PPh_3)_2Cl_2$ a decrease in the yield of the coupling product was observed. Our experiments also showed that in the absence of catalysts the formation of the product was not detected, in this case the starting material was recovered (Table 1, entry 7).

Regarding the influence of the solvent, the best results were achieved using a mixture of DMF/H_2O, which furnished the desired product **3a** in 99% yield (Table 1, entry 8). By using DMSO, MeOH, dioxane, hexane, and THF moderate to good yields were also obtained (Table 1, entries 9–13). The presence of base was crucial for a clean, high-yielding reaction. For this reason, in our experiments we investigated the influence of organic and inorganic bases. As listed in Table 1, when the reaction was carried out using K_3PO_4, Cs_2CO_3, NaOH, and pyrrolidine the target product was obtained in moderate yields (Table 1, entries 15–18). The best result was obtained using K_2CO_3, which gave the desired product **3a** in 99% yield (Table 1, entry 8). When the amount of K_2CO_3 was reduced from 2 to 1 equiv a significant decrease in the yield was observed (Table 1, entry 20). When the Suzuki reaction was carried out in the absence of base the coupling product was not obtained (Table 1, entry 19). Careful analysis of the optimized reactions revealed that the optimum conditions for this coupling reaction were the use of $Pd(PPh_3)_2Cl_2$ (5 mol %), 3-iodo-6-methyl-4-(1-butylselenyl)-2*H*-benzopyran **1a** (0.25 mmol), phenylboronic acid **2a**

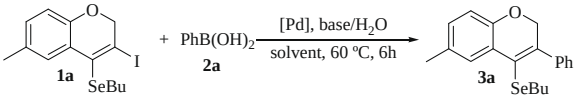


Scheme 1. General scheme.

* Corresponding author.
E-mail address: gzeni@pq.cnpq.br (G. Zeni).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.07.008

Table 1
Optimization of reaction conditions for the formation of **3a**



#	[Pd] (mol %)	Solvent	Base (equiv)	Yield[a] (%)
1	$PdCl_2(PPh_3)_2$ (10)	DMF	K_2CO_3 (2)	91
2	$PdCl_2(PhCN)_2$ (10)	DMF	K_2CO_3 (2)	83
3	$PdCl_2$ (10)	DMF	K_2CO_3 (2)	71
4	$Pd(Oac)_2$ (10)	DMF	K_2CO_3 (2)	73
5	$Pd(acac)_2$ (10)	DMF	K_2CO_3 (2)	71
6	$Pd(PPh_3)_4$ (10)	DMF	K_2CO_3 (2)	86
7	—	DMF	K_2CO_3 (2)	—
8	$PdCl_2(PPh_3)_2$ (5)	DMF	K_2CO_3 (2)	>99
9	$PdCl_2(PPh_3)_2$ (5)	DMSO	K_2CO_3 (2)	69
10	$PdCl_2(PPh_3)_2$ (5)	Dioxane	K_2CO_3 (2)	51
11	$PdCl_2(PPh_3)_2$ (5)	MeOH	K_2CO_3 (2)	80
12	$PdCl_2(PPh_3)_2$ (5)	THF	K_2CO_3 (2)	72
13	$PdCl_2(PPh_3)_2$ (5)	Hexane	K_2CO_3 (2)	96
14	$PdCl_2(PPh_3)_2$ (5)	DMF	K_2CO_3 (2)	16[b]
15	$PdCl_2(PPh_3)_2$ (5)	DMF	K_3PO_4 (2)	80
16	$PdCl_2(PPh_3)_2$ (5)	DMF	Cs_2CO_3 (2)	48
17	$PdCl_2(PPh_3)_2$ (5)	DMF	NaOH (2)	64
18	$PdCl_2(PPh_3)_2$ (5)	DMF	Pyrrolidine (2)	21
19	$PdCl_2(PPh_3)_2$ (5)	DMF	—	—
20	$PdCl_2(PPh_3)_2$ (5)	DMF	K_2CO_3 (1)	43
21	$PdCl_2(PPh_3)_2$ (5)	DMF	K_2CO_3 (2)	23[c]

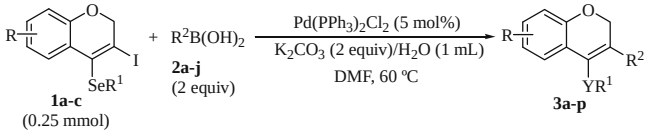
[a] Yields are given by GC analysis.
[b] Reaction carried out in the absence of water.
[c] Reaction carried out under room temperature.

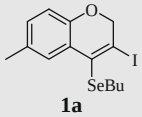
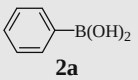
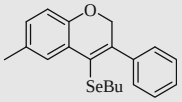
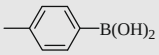
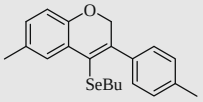
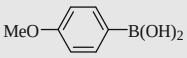
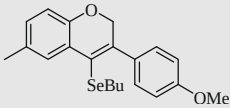
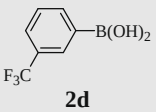
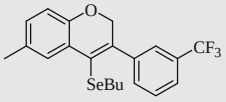
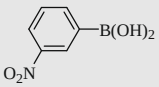
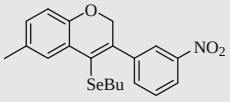
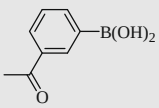
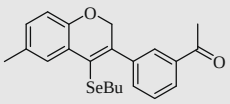
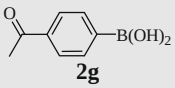
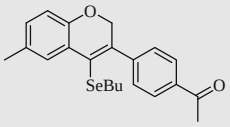
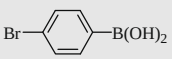
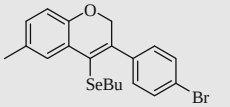
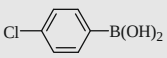
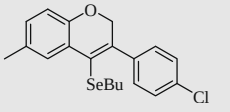
(2 equiv) in DMF (5.0 mL), and H_2O (1.0 mL) at room temperature. After that, the base K_2CO_3 (2 equiv) was added and the mixture was heated at 60 °C for 6 h. Using this reaction condition we were able to prepare 3-aryl-4-chalcogen-2*H*-benzopyran **3a** in quantitative yield. In order to demonstrate the efficiency of this protocol, we explored the generality of our method extending the conditions to other 3-iodo-4-chalcogen-2*H*-benzopyran compounds **1a–c** with different arylboronic acids **2a–j** and the results are summarized in Table 2.[7]

First, to determine the real influence of the substituent at aromatic ring of boronic acids, we kept the substrate **1a** invariable. The results revealed that the reaction is not sensitive to the electronic effect of the aromatic ring attached in the boron atom. For example, arylboronic acid bearing an electron-donating group methoxyl at the *para* position gave a very similar yield than the arylboronic acid bearing an electron-withdrawing group CF_3 (Table 2; entry 3 vs entry 4). Differentiation in the reactivity between halogen and boron atoms can be seen by coupling shown in the experiments described in table 1, entries 8 and 9, which provide only the Suzuki product, without any homo-coupling product. To the best of our knowledge, aryl halogen could react with boronic acids in the presence of palladium catalysts to afford biaryl products.[8] In our case, the halogen substituent was not affected. In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with other 3-iodo-4-chalcogen-2*H*-benzopyran was also investigated. Then the substrates **1b** and **1c**, which have a selenophenyl group in the 4-position of the benzopyran ring, were also cross-coupled efficiently, under the same reaction conditions (Table 2; entries 12–16).

More recently, significant advances have been made in the use of organoboron reagents as coupling partners in a number of palladium-mediated carbon–carbon bond formations. Among them, the use of potassium organotrifluoroborates, as the organoboron coupling partner, has some advantages in comparison to boronic acids and boronic esters, such as being more nucleophilic, stable in the air, crystalline as solids, and easily prepared.[9]

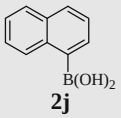
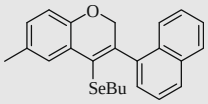
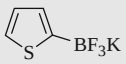
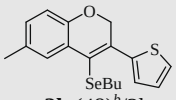
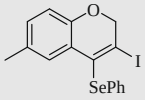
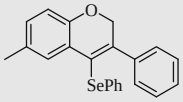
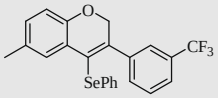
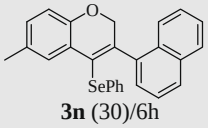
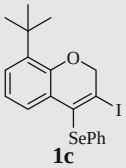
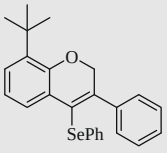
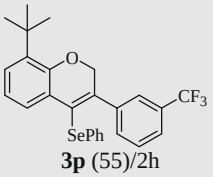
Table 2
Palladium-catalyzed formation of 3-aryl-4-chalcogen-2*H*-benzopyrans **3a–p**



#	Substrate	Organoboron	Product yield (%)[a]/time
1	 **1a**	 **2a**	 **3a** (99)/1.5h
2	**1a**	 **2b**	 **3b** (73)/1.5h
3	**1a**	 **2c**	 **3c** (64)/2h
4	**1a**	 **2d**	 **3d** (65)/3h
5	**1a**	 **2e**	 **3e** (74)/3h
6	**1a**	 **2f**	 **3f** (70)/2h
7	**1a**	 **2g**	 **3g** (77)/2h
8	**1a**	 **2h**	 **3h** (96)/2h
9	**1a**	 **2i**	 **3i** (93)/2h

(*continued on next page*)

Table 2 (*continued*)

#	Substrate	Organoboron	Product yield (%)[a]/time
10	**1a**	 **2j**	 **3j** (85)/2h
11	**1a**	 **2k**	 **3k** (48)[b]/2h
12	 **1b**	**2a**	 **3l** (82)/1.5h
13	**1b**	**2d**	 **3m** (55)/6h
14	**1b**	**2j**	 **3n** (30)/6h
15	 **1c**	**2a**	 **3o** (70)/2h
16	**1c**	**2d**	 **3p** (55)/2h

[a] Yields are given for isolated products.
[b] Reaction carried out at 100 °C.

In this way, substrate **1a** underwent palladium cross-coupling with thienyl trifluoroborates furnishing the corresponding 3-thienyl-4-butylselenyl-2*H*-benzopyran **3k** in moderate yield (Table 2, entry 11).

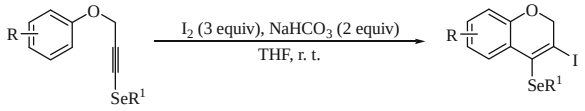
In summary, we have explored the Suzuki cross-coupling reaction of arylboronic acids with 3-iodo-4-chalcogen-2*H*-benzopyran derivatives using a catalytic amount of $PdCl_2(PPh_3)_2$. The reaction proceeded cleanly under mild reaction conditions, short reaction time, and was performed with aryl boronic acids bearing electron-withdrawing, electron-donating, and neutral substituents. It is important to point out that this route permits an easy and efficient access to highly substituted benzopyran. The pharmacological activity of these compounds is in progress and will appear in a specialized journal soon.

Acknowledgments

We are grateful to CNPq/INCT-catalise, CAPES (SAUX), and FAPERGS, for financial support. CNPq is also acknowledged for the fellowships (to G.Z. and B.G.).

References and notes

1. (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409; (c) Masters, K. S.; Flynn, B. L. *J. Org. Chem.* **2008**, *73*, 8081; (d) Halim, R.; Scarnmells, P. J.; Flynn, B. L. *Org. Lett.* **2008**, *10*, 1967; (e) Bui, C. T.; Flynn, B. L. *J. Comb. Chem.* **2006**, *8*, 163; (f) Sebille, S.; Gall, D.; de Tullio, P.; Florence, X.; Lebrun, P.; Pirotte, B. *J. Med. Chem.* **2006**, *49*, 4690; (g) Madrid, P. B.; Liou, A. P.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2006**, *49*, 4535; (h) Heinrich, T.; Böttcher, H.; Schiemann, K.; Holzemann, G.; Schwarz, M.; Bartoszyk, G. D.; Amsterdam, C.; Greiner, H. E.; Seyfried, C. A. *Bioorg. Med. Chem.* **2004**, *12*, 4843; (i) Tang, L.; Yu, J.; Leng, Y.; Feng, Y.; Yang, Y.; Ji, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3437.
2. (a) Jin, Z.; Kang, Y. Total synthesis of daurichromenic acid. PCT Int. Appl. WO 2004058738, 2004.; (b) Iwata, N.; Wang, N.; Yao, X.; Kitanaka, S. *J. Nat. Prod.* **2004**, *67*, 1106; (c) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.
3. Korec, R.; Sensch, K. H.; Zoukas, T. *Arzneim. Forsch.* **2000**, *50*, 122.
4. (a) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347; (b) Godoi, B.; Speranca, A.; Back, D. F.; Brandao, R.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 3469; (c) The best condition for the I_2 cyclization reactions was the addition of $NaHCO_3$ (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 I_2 in 2 mL of THF was gradually added at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h.



5. (a) Schroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245; (b)*Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; (c)*Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (d)*Cross-coupling Reactions: A Practical Guide*; Miyaura, N., Ed.Topics in Current Chemistry Series 219; Springer: New York, 2002; (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
6. Frigoli, M.; Moustrou, C.; Samat, A.; Guglielmetti, R. *Eur. J. Org. Chem.* **2003**, 2799.
7. General procedure for the cross-coupling reaction: To a solution of appropriate 3-iodo-4-chalcogen-2H-benzopyran (0.25 mmol) in DMF (5 mL) were added the $Pd(PPh_3)_2Cl_2$ (0.003 g, 5 mol %) and boronic acid (0.5 mmol) under argon. The resulting solution was stirred for 30 min at room temperature. After this time, a solution of K_2CO_3 (0.5 mmol, 0.254 g) in H_2O (1 mL) was added. The mixture was then heated at 60 °C for the time indicated in Table 2, cooled to room temperature, diluted with dichloromethane (20 mL), and washed with brine (2×20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography. Selected spectral and analytical data for 3-phenyl-6-methyl-4-butylselenyl-2*H*-benzopyran (**6a**): Yield: 0.087 g (99%). ^1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.57 (s, 1H), 7.42–7.29 (m, 5H), 6.98–6.95 (m, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.39 (quint, J = 7.6 Hz, 2H), 1.16 (sext, J = 7.6 Hz, 2H), 0.74 (s, 3H). ^{13}C NMR: $CDCl_3$, 50 MHz, δ (ppm): 151.7, 140.7, 139.2, 131.0, 129.4, 128.9, 128.8, 128.0, 124.1, 122.7, 115.7, 70.3, 31.6, 27.2, 22.4, 20.8, 13.4. MS (EI, 70 eV) m/z (relative intensity): 357 (4), 354 (51), 298 (100), 252 (3), 218 (90), 189 (14), 176 (37), 163 (14), 150 (10), 114 (14), 101 (6), 57 (3). Anal. (%) Calcd for $C_{20}H_{22}OSe$: C 67.22, H 6.21. Found: C 67.45, H 6.47.
8. (a) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101; (b) LeBlond, C. R.; Andrews, A. T.; Sowa, J. R.; Sun, Y. *Org. Lett.* **2001**, *3*, 1555.
9. (a) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973; (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (c) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. *Synlett* **2005**, 1763; (d) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49; (e) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950; (f) Molander, G. A.; Yun, C. S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534; (g) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302; (h) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416; (i) Molander, G. A.; Reviro, M. R. *Org. Lett.* **2002**, *4*, 107.