Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A convenient Synthesis of 6-Substituted-2,2-Dimethyl-2H-1-Benzopyrans

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Published online: 19 Aug 2006.

To cite this article: Charles Z. Ding (1996) A convenient Synthesis of 6-Substituted-2,2-Dimethyl-2H-1-Benzopyrans, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:22, 4267-4273, DOI: 10.1080/00397919608004664

To link to this article: http://dx.doi.org/10.1080/00397919608004664

SYNTHETIC COMMUNICATIONS, 26(22), 4267-4273 (1996)

A CONVENIENT SYNTHESIS OF 6-SUBSTITUTED-2,2-DIMETHYL-2*H*-1-BENZOPYRANS

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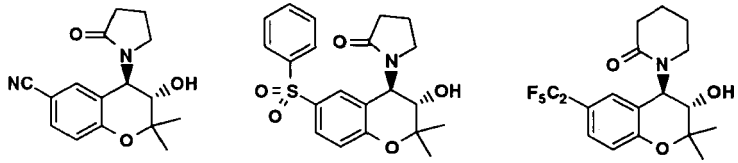
Abstract: Various 2,2-dimethyl-6-functional-2*H*-1-benzopyrans were prepared *via* a halogen-metal exchange reaction followed by treatment with electrophiles. These 6-functionalized chromenes are important synthetic intermediates for preparation of benzopyran-based potassium channel openers.

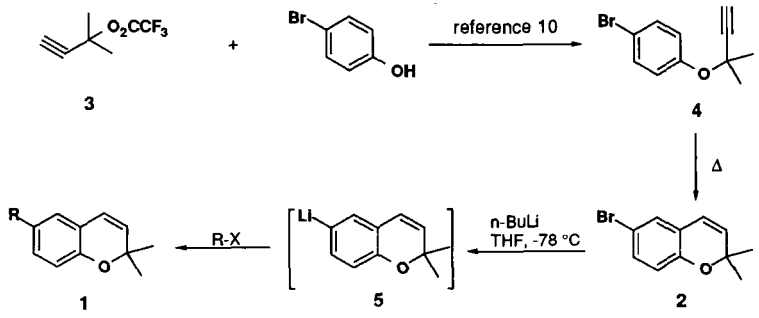
Benzopyran-based ATP-sensitive potassium channel openers (PCO) are a class of agents with diverse pharmacological properties.[1] Levcromakalim is representative of the first-generation antihypertensive potassium channel openers (Scheme 1).[2] Modifications of the benzopyran ring of levcromakalim have led to some second-generation potassium channel openers with better tissue-selectivity and potency relative to levcromakalim.[3] For example, substitution of the 6-cyano group of levcromakalim by a phenylsulfonyl group produced HOE 234 (rilmakalim, Scheme 1) with potent and selective bronchodilatory properties.[4] Potassium channel opener BRL 55834 (Scheme 1) is another tissue-selective antiasthmatic agent.[5] The obvious difference between levcromakalim and BRL 55834 is at the 6-position of the benzopyran ring. Preparation of these benzopyran-based potassium channel openers requires an efficient synthesis of 6-substituted chromenes (**1**, Scheme 2). In our ongoing tissue-selective cardioprotective potassium channel opener program,[6] we needed an efficient synthesis of various 6-substituted chromenes (**1**). Chromenes are generally prepared *via* the Claisen rearrangement of aryl propargyl ethers.[7] However,

preparation of a series of 6-substituted chromenes *via* the Claisen rearrangement would be repetitive and laborious.[8] We report here a convenient method for the synthesis of various 6-substituted chromenes. This methodology involves a halogen-metal exchange reaction of 6-bromochromene (**2**) followed by treatment with electrophiles (Scheme 2).[5,9]

Scheme 1

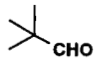
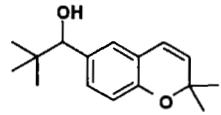
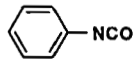
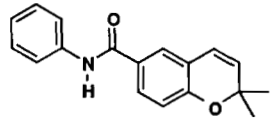
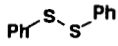
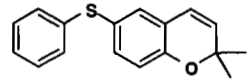
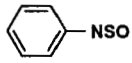
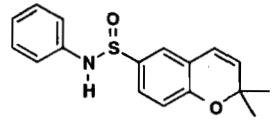
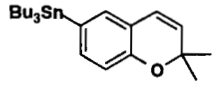
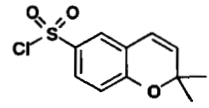


Scheme 2



Following the Godfrey protocol,[10] 4-bromophenol was reacted with 2-methyl-3-butynyl trifluoroacetate (**3**) in acetonitrile in the presence of DBU and a catalytic amount of $CuCl_2$ at 0 °C for 5 h. The resulting 4-bromophenyl propargyl ether (**4**, 83% yield) underwent the Claisen rearrangement in N, N-diethylaniline at 190 °C to give 6-bromochromene (**2**) in excellent yield. The halogen-metal exchanging reaction was performed by addition of n-butyl lithium (1.1 eq.) to a solution of 6-bromochromene (**2**) in anhydrous THF at -78 °C. The putative lithiochromene (**5**) was reacted with trimethylacetaldehyde at -78 °C to provide *tert*-butyl chromenylmethanol in 77% yield (entry 1, Table 1). The results of the reaction of intermediate **5** with other electrophiles are summarized in

Table 1

Entry	Electrophile	Product	Yield[a]	mp (°C)
1			77%	79-81
2			90%	152-153
3			92%	-
4			69%	132-133
5	Bu_3SnCl		91%	-
6	SO_2, then SO_2Cl_2		63%	80-81

a. The yields are isolated overall yields.

Table 1. Generally, the overall yields are good to excellent. In addition to carbon-carbon bond formations (entries 1, and 2),[9] the reaction is widely applicable for generation of carbon-heteroatom bonds. For examples, reaction of **5** with diphenyldisulfide generated phenylsulfide (92%, entry 3); reaction with N-thionylaniline gave chromenesulfinamide (69%, entry 4) and reaction with tributyltin chloride produced tributylstannochromene (91%, entry 5). When **5** was reacted with sulfur dioxide, chromenesulfinic acid was formed, which could be oxidized by SO_2Cl_2 to generate chromenesulfonyl chloride (entry 6). No oxidation of the double bond was observed under these conditions.

In summary, treatment of the readily available 6-bromochromene (**2**)[10] with n-butyllithium followed by reaction with electrophiles gives various 6-

functionalized chromenes. These chromenes are versatile precursors for the synthesis of benzopyran-based potassium channel openers.

Experimental:

1-Bromo-4-[(1,1-dimethyl-2-propynyl)oxy]benzene (**4**): To a solution of 2-methyl-3-butyn-2-ol (22.3 mL, 0.23 mol) in acetonitrile (100 mL) at 0 °C was added 1,8-diazabicyclo[5,4,0]undec-7-ene (40 mL, 0.26 mol), followed by dropwise addition of trifluoroacetic acid anhydride (32 mL, 0.23 mol) *via* a syringe over 30 min. The resultant yellow solution was stirred at 0°C for 40 min. In a separate flask, a solution of 4-bromophenol (34.6 g, 0.2 mol) in acetonitrile (150 mL) at 0°C was treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (39 mL, 0.26 mol), followed by addition of 100 mg of $CuCl_2 \cdot 2H_2O$. To this mixture at 0°C was added the above prepared solution of 2-methyl-3-butyn-2-yl trifluoroacetate (**3**) dropwise *via* a cannula in 40 min. The resultant reaction mixture was stirred at 0°C for 5 h, concentrated *in vacuo* and the residue was poured into water (300 mL). The aqueous solution was extracted with hexanes (300 mL); combined organic extracts were washed successively with 1N HCl (200 mL), 1N KOH (2 x 100 mL) and brine. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil [40 g, 83%]. This material was used directly for the next reaction.

6-Bromo-2,2-dimethyl-2*H*-1-benzopyran (**2**): To 40 mL of N,N-diethylaniline at 185°C was added 1-bromo-4-[(1,1-dimethyl-2-propynyl)oxy]-benzene (**4**, 40 g) dropwise at such a rate that the internal temperature does not exceed 195°C. The resultant solution was stirred at 190°C for 3 hours and poured into a mixture of hexanes (200 mL) and chilled 5% HCl (200 mL). The organic layer was separated, washed with 5% HCl (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give an oil (40 g, 100%). The product was used directly for the next reaction. Anal. calc'd for $C_{11}H_{11}BrO$: C, 55.98; H, 4.92; Br, 32.58. Found: C, 55.95; H, 4.61; Br, 32.44.

A representative procedure for halogen-metal exchange reaction followed by reaction with electrophiles is illustrated by the preparation of 2,2-dimethyl-N-phenyl-2*H*-1-benzopyran-6-sulfinamide (entry 4): A solution of 6-bromo-2,2-dimethyl-2*H*-1-benzopyran (2.4 g, 10.0 mmol) in 50 mL of anhydrous THF at - 78 °C under argon was treated with n-BuLi (2.5 M, 4.5 mL, 11.3 mmol) via a syringe. The resultant reaction mixture was stirred at - 78 °C for 15 min and

reacted with a solution of N-thionylaniline in anhydrous THF (1.3 g, 9.0 mmol) rapidly. The resultant reaction mixture was stirred at - 78 °C for 10 min, and quenched with 40 mL of saturated NH_4Cl solution at - 78 °C. The mixture was poured into ether (150 mL); organic layer was washed successively with water, brine (50 mL each), and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellowish solid which was triturated with hexane-ether give a white solid [1.85 g, 69%, mp: 132-133 °C]. TLC *Rf*: 0.50 (EtOAc,hexane; 1:1). ^1H NMR (270 MHz, $CDCl_3$) δ 7.42 (dd, J = 2.3, 8.8 Hz, 1 H), 7.37 (d, J = 2.3 Hz, 1 H), 7.25 (m, 2 H), 7.05 (m, 3 H), 6.85 (d, J = 8.8 Hz, 1 H), 6.47 (s, 1H), 6.30 (d, J = 9.4 Hz, 1 H), 5.68 (d, J = 9.4 Hz, 1 H), 1.45 (s, 6 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 156.25, 141.36, 136.29, 132.33, 130.00, 127.03, 124.12, 123.91, 122.18, 122.06, 119.24, 117.51, 77.85, 28.79. MS (eletrospray): 300 (M+H). Anal cal'd for $C_{17}H_{17}NSO_2$: C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.20; H, 5.64; N, 4.61; S, 10.49. IR (KBr) 3453, 3183, 1605, 1499, 1265, 1113, 1080, 1055, 883, 756.

2,2-Dimethyl-6-(1-hydroxy-2,2-dimethylpropyl)-2*H*-1-benzopyran (entry 1): mp: 79-81 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.01 (d, J = 8.2 Hz, 1 H), 6.91 (s, 1 H), 6.71 (d, J = 8.2 Hz, 1 H), 6.30 (d, J = 9.6 Hz, 1 H), 5.60 (d, J = 9.6 Hz, 1 H), 4.27 (s, 1 H), 3.40 (bs, 1 H), 1.42 (s, 6 H), 0.90 (s, 9 H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 152.13, 134.65, 130.79, 128.38, 125.50, 122.53, 120.37, 115.36, 82.07, 76.28, 35.71, 28.02, 26.03. MS (CI) 247 (M+1). Anal. cal'd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.11; H, 9.06.

2,2-Dimethyl-N-phenyl-2*H*-1-benzopyran-6-carboxamide (entry 2): mp: 152-153 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.95 (bs, 1 H), 7.60 (m, 3 H), 7.52 (s, 1 H), 7.35 (m, 2 H), 7.13 (m, 1 H), 6.79 (dd, J = 2.3, 8.2 Hz, 1 H), 6.32 (dd, J = 2.3, 8.8 Hz, 1 H), 5.65 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.32, 156.16, 138.13, 131.43, 128.97, 128.00, 127.16, 125.70, 124.25, 121.61, 121.05, 120.20, 116.29, 28.21.

2,2-Dimethyl-6-phenylthio-2*H*-1-benzopyran (entry 3): ^1H NMR (270 MHz, $CDCl_3$) δ 7.20 (m, 7 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.25 (d, J = 9.5 Hz, 1 H), 5.60 (d, J = 9.5 Hz, 1 H), 1.43 (s, 6 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 153.77, 139.03 135.35, 132.36, 131.70, 129.36, 128.56, 126.13, 124.49, 122.64, 122.12, 117.86, 28.56. Anal. cal'd for $C_{17}H_{16}SO$: C, 76.08; H, 6.01; S, 11.95. MS (CI): 269 (M+H). Found: C, 75.86; H, 5.92; S, 11.60.

2,2-Dimethyl-6-tributylstannyl-2*H*-1-benzopyran (entry 5): ^1H NMR (270 MHz, $CDCl_3$) δ 7.20 (d, J = 8.2 Hz, 1 H), 7.05 (s, 1 H), 6.75 (d, J = 8.2 Hz, 1 H),

6.30 (d, J = 10 Hz, 1 H), 5.60 (d, J = 10 Hz, 1 H), 0.90-1.60 (m, 42 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 153.60, 137.21, 134.16, 132.30, 130.33, 122.44, 121.05, 116.11, 29.08, 28.13, 27.38, 13.59, 9.53. Anal. calc'd for $C_{23}H_{38}OSn$: C, 61.49; H, 8.53. Found: C, 61.60; H, 8.62.

2,2-Dimethyl-2*H*-1-benzopyran-6-sulfonyl chloride (entry 6): mp: 80-81 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.85 (dd, J = 2.3 , 8.8 Hz, 1 H), 7.73 (d, J = 2.3 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 1 H), 6.45 (d, J = 10 Hz, 1 H), 5.85 (d, J = 10 Hz, 1 H), 1.60 (s, 6 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 158.99, 135.83, 132.67, 128.66, 125.47, 121.44, 120.37, 117.09, 78.76, 28.57; MS (CI): 258 (M). Anal calc'd for $C_{11}H_{11}ClSO_3$: C, 50.61; H, 4.35; Cl, 13.58; S, 12.28. Found: C, 50.61; H, 4.19; Cl, 13.80; S, 11.99.

Acknowledgment: The author thanks Dr. Karnail S. Atwal for stimulating discussions during this work. The author also acknowledges Mr. Arthur V. Miller for technical assistance.

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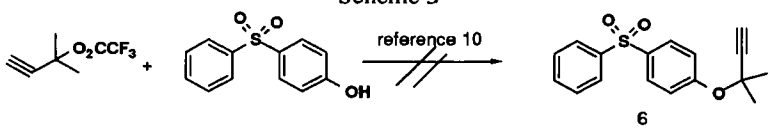
8. In attempt to prepare 6-phenylsulfonylchromene via Claisen rearrangement, we could not synthesize the required aryl propargyl ether (**6**) under Godfrey's conditions (Scheme 3). The chromene can be prepared by selective oxidation of 6-phenylthiochromene (product in entry 3, Table 1) with mCPBA.

Scheme 3



6

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(Received in the USA 12 June 1996)