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Palladium-Catalyzed Synthesis of Trimethylsilyl Substituted Benzopyran Derivatives

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Abstract: Palladium catalysis is an efficient way to obtain trimethylsilyl substituted benzopyran derivatives. After screening a series of reactions , we found optimized conditions.

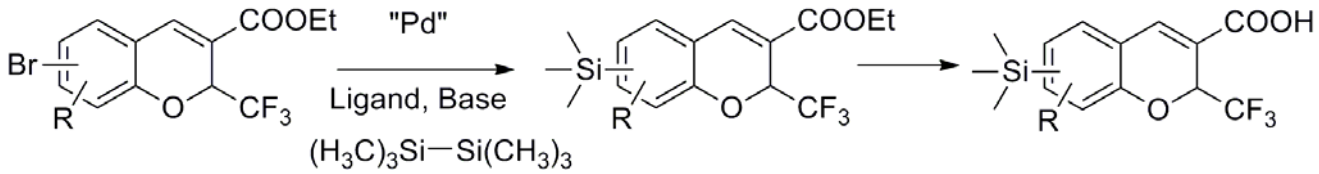
Keywords: Palladium-catalyzed, benzopyran, trimethyl silylation, selective COX-2 inhibitors.

INTRODUCTION

A number of benzopyran derivatives possess biological and pharmacological applications [1]. Studies show that benzopyrans have many biological activities such as anti-estrogenic, insulin-sensitizing, selective thrombin inhibition, antimicrobial, antibacterial, hypoglycemic and so on [2-6]. Selected substituted 2*H*-chromene-3-carboxylates were recently reported to possess anti-inflammatory and analgesic activities by selective inhibition of the inducible form of cyclooxygenase (COX-2) [7-9]. Among this series of compounds, the t-Bu substituted 2*H*-chromene-3-carboxylates showed excellent selective inhibition of COX-2. Therefore there exists strong interest to develop trimethylsilyl substituted 2*H*-chromene-3-carboxylates as COX-2 inhibitors as a new chemical entity. In this study, we detail the preparation of trimethylsilyl substituted 2*H*-chromene-3-carboxylates for evaluation as selective COX-2 inhibitors.

The most common method for synthesis of arylsilanes is the reaction of an aryllithium or magnesium reagent with halosilanes [10,11]. The discordancy of organometallic reagents with a number of aromatic substituents often dictate departure from this synthesis approach. To solve this problem, we sought a general synthesis method of arylsilanes compatible with a wide variety of functional groups, which was a strategy based on transition metal-catalyzed reaction of aryl halides with disilanes. Such a transformation was first described in a patent by Atwell and Bokermann in 1973 [12]. Subsequently, Matsumoto and co-workers prepared various arylsilanes from aryl bromides and selected electron-deficient aryl chlorides with hexamethyldisilane using $Pd(PPh_3)_4$ as catalyst [13-15]. Gooßen and co-workers disclosed a mild and efficient procedure for the catalytic silylation of aryl bromides in 2000 [16]. In spite of the aforementioned advancements, there remains considerable interest in the development of a robust general method for metal-catalyzed synthesis of arylsilanes.

In connection with our interest in the synthesis of 2*H*-chromene-3-carboxylate derivatives, we became interested in the synthesis of certain trimethylsilyl-2*H*-chromene-3-carboxylates from their more readily available bromo-2*H*-chromene-3-carboxylate analogs by palladium catalysis (Scheme **1**).



Scheme (1). Palladium-catalyzed synthesis of trimethylsilyl-2H-chromene-3-carboxylate.

RESULTS AND DISCUSSION

Initially, we studied the reaction of aryl bromide (**3a)** with hexamethyldisilane as the model reaction for screening reaction conditions (Scheme **2**, Table **1**). To our delight, the desired product (**4a**) was isolated in high yield by employing

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the combination of Pd_2dba_3, [1,1'-biphenyl]-2-yldi-tert-butylphosphine, water and KF in tetrahydro-1,3-dimethyl-2(1H) pyrimidone (DMPU) at 100 ºC under argon (Table **1**, entry 1). After screening other palladium catalysts, we found that $PdCl_2(dppf)CH_2Cl_2$ in the presence of [1,1'-biphenyl]-2-yldi-tert-butylphosphine was a superior catalyst/ligand combination, producing **4a** in even higher yield (Table **1**, entries 1-4). The importance of added [1,1'-biphenyl]-2-yldi-tert-butylphosphine was illustrated in Table **1**, entry 5. No product was observed in the absence of [1,1'-biphenyl]-2-yldi-tert-butylphosphine. Encouraged by these results, we further optimized the reaction conditions by examination of experimental parameters including bases, solvents, ligands and reaction temperature (Table **1**, entries 8-18). No product (**4a**) was observed in the absence of bases (Table **1**, entry 8). Of the bases tested: KF, K_2CO_3, K_3PO_4, Cs_2CO_3 (Table **1**, entries 2, 9-11), KF consistently provided the most favorable yield of desired product. Among the solvents examined: DMPU, DMF, DMSO, and EtOH (Table **1**, entries 2, 12-14), DMPU was uniformly superior. Using our optimized catalyst system, solvent and base, we found that 100-120 ºC was optimal (Table **1**, entries 16-18). We also examined the effect of the amount of $PdCl_2(dppf)CH_2Cl_2$, and found the amount of $PdCl_2(dppf)CH_2Cl_2$ was reduced in accordance with the decrease of target product yield (**4a**) (Table **1**, entries 19-20). The yield of **4a** significantly decreased when only 1.0 equiv of hexamethyldisilane was used (Table **1**, entry 21) and the yield was also reduced when the amount of [1,1'-biphenyl]-2-yldi-tert-butylphosphine was reduced (Table **1**, entry 22). The yield of **4a** decreased under anhydrous conditions (Table **1**, entry 23 versus entry 2). The optimum conditions were identified (Table **1**, entry 2) affording **4a** in 87% yield.

With optimized conditions in hand, the scope and limitations of this new methodology were evaluated as shown in Table **2**. A variety of aryl bromides, possessing both electron-donating and electron-withdrawing substituents, were reacted with hexamethyldisilane to generate the arylsilanes

Table 1. Selected Results of Screening for Optimal Conditions

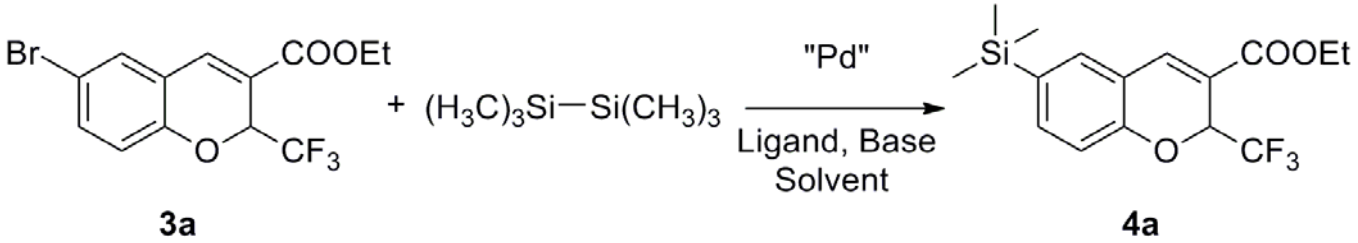
Entry	Catalyst	Solvent	Base	Ligand	Yield (%)[a]
1	Pd_2dba_3	DMPU	KF	2-(di-t-butylphosphino)biphenyl	78
2	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	87
3	$Pd(PPh_3)_4$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	80
4	$PdCl_2(PPh_3)_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	56
5	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	none	NR
6	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	tricyclohexyl phosphine	28
7	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	PPh_3	<5
8	$PdCl_2(dppf)CH_2Cl_2$	DMPU	none	2-(di-t-butylphosphino)biphenyl	NR
9	$PdCl_2(dppf)CH_2Cl_2$	DMPU	K_2CO_3	2-(di-t-butylphosphino)biphenyl	35
10	$PdCl_2(dppf)CH_2Cl_2$	DMPU	K_3PO_4	2-(di-t-butylphosphino)biphenyl	<5
11	$PdCl_2(dppf)CH_2Cl_2$	DMPU	Cs_2CO_3	2-(di-t-butylphosphino)biphenyl	<5
12	$PdCl_2(dppf)CH_2Cl_2$	DMF	KF	2-(di-t-butylphosphino)biphenyl	79
13	$PdCl_2(dppf)CH_2Cl_2$	DMSO	KF	2-(di-t-butylphosphino)biphenyl	47
14	$PdCl_2(dppf)CH_2Cl_2$	CH_3CH_2OH	KF	2-(di-t-butylphosphino)biphenyl	NR
15	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	NR[b]
16	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	28[c]
17	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	45[d]
18	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	86[e]
19	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	35[f]
20	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	62[g]
21	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	33[h]
22	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	48[i]
23	$PdCl_2(dppf)CH_2Cl_2$	DMPU	KF	2-(di-t-butylphosphino)biphenyl	70[j]

[a] All reactions were run with aryl bromide (**3a)**, hexamethyldisilane (2.0 equiv), Pd source (4.0 mol %), ligand (15.0 mol %), base (5.0 equiv), water(2.0 equiv), solvent (10 mL), 100 ºC under argon for 5 hours. Isolated yield. [b] at room temperature. [c] at 50 ºC. [d] at 80 ºC. [e] at 120º C. [f] $PdCl_2(dppf)CH_2Cl_2$ (2.0 mol %). [g] $PdCl_2(dppf)CH_2Cl_2$ (3.0 mol %). [h] hexamethyldisilane(1.0 equiv). [i]2-(di-t-butylphosphino)biphenyl (10.0 mol%). [j] no water.

(**4,** Scheme **3**). In general, we found substrates bearing electron donating substituent(s) afforded higher yields of desired silylated product, (Table **2**, entries 8-14), whereas the yields were diminished slightly when electron- deficient aryl bromides were substrates, (Table **2**, entries 4-7). Generally, 8-aryl substituted derivatives gave higher yields than those substrates bearing an 8-position aliphatic moiety (Table **2**, entries 15, 16, 17 vs 8, 9, 10, 11, 12, 14). The steric effect the reaction system was further examined (Table **2**, entries 1, 2, 3 vs 18) and found there was no silylation of aryl bromide (3r) with hexamethyldisilane due to methyl group at the o-position of reacting bromide.

Finally, the optimum conditions for saponification of the present trimethylsilyl substituted esters was found to be lithium hydroxide in mixture of methanol and water (CH_3OH:H_2O=10:1). All of the esters (**4**) were converted to the corresponding acids (**5**) in excellent yield under these conditions. With an ample supply of the desired compounds in hand their activity against cyclooxygenase-2 was evaluated and will be reported upon in due course as further optimizations are made.

In summary, we have developed a general and efficient palladium-catalyzed silylation reaction of aryl C–Br bonds, providing arylsilanes products in moderate to good yields.



3a **4a**

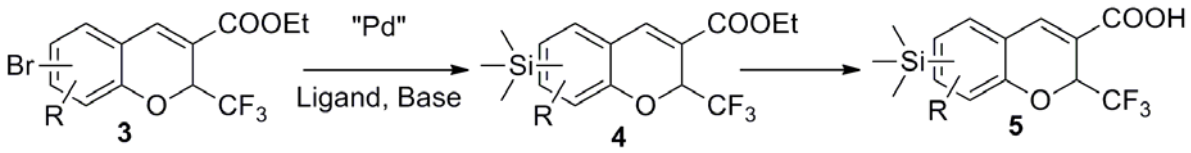
Scheme (2). The synthesis of ethyl 2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3 –carboxylate.

Table 2. Pd-Catalyzed Silylation of Aryl Bromides with Hexamethyldisilane

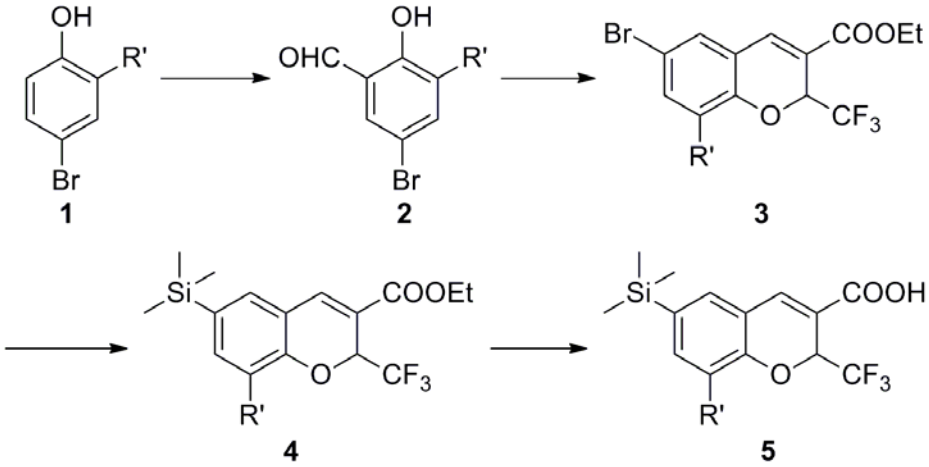
Entry	Aryl bromide (3)		Product (4)	Product (5)
	Br	R	Yield[%][a]	Yield[%][b]
1	6-Br	H	87(4a)	98(5a)
2	7-Br	H	85(4b)	98(5b)
3	5-Br	H	80(4c)	97(5c)
4	6-Br	8-F	82(4d)	94(5d)
5	6-Br	8-Cl	42(4e)	95(5e)
6	6-Br	8-Br	37(4f)	92(5f)
7	6-Br	8-CF_3	31(4g)	90(5g)
8	6-Br	8-CH_3	80(4h)	98(5h)
9	6-Br	8-CH_2CH_3	78(4i)	97(5i)
10	6-Br	8-$CH_2CH_2CH_3$	76(4j)	96(5j)
11	6-Br	8-$CH(CH_3)_2$	75(4k)	98(5k)
12	6-Br	8-$C(CH_3)_3$	72(4l)	95(5l)
13	6-Br	8-OCH_3	80(4m)	93(5m)
14	6-Br	8-cyclohexyl	70(4n)	94(5n)
15	6-Br	8-C_6H_5	83(4o)	99(5o)
16	6-Br	8-(p-FC_6H_4)	81(4p)	99(5p)
17	6-Br	8-(p-$CH_3C_6H_4$)	84(4q)	97(5q)
18	7-Br	8-CH_3	0(4r)	0(5r)

[a] Reaction conditions: aryl bromide (**3**), hexamethyldisilane (2.0 equiv), $PdCl_2(dppf)CH_2Cl_2$ (4.0 mol %), 2-(di-t-butylphosphino)biphenyl (15.0 mol %), KF (5.0 equiv), water (2.0 equiv), DMPU (10 mL), 100 °C under argon for 5-8 hours. Isolated yield.

[b] Reaction conditions: arylsilanes (**4**), LiOH (10 equiv), solvent (H_2O:EtOH=1:10), room temperature ,overnight, dilution hydrochloric acid; isolated yield.



Scheme (3). Pd-Catalyzed Silylation of Aryl Bromides with hexamethyldisilane.



Scheme (4). The design of compound synthesis.

Particularly noteworthy is the ability to conduct the silylation procedure without harm to the ethyl 2*H*-chromene-3-carboxylate ring.

Procedure for Synthesis of Trimethylsilyl Substituted Benzopyran Derivatives Synthesis of 5-bromo-2-hydroxybenzaldehyde (2a, Scheme 4)

A stirred solution of 4-bromophenol (3.81 g, 22.0 mmol) in trifluoroacetic acid (50 mL), was added hexamethylenetetramine (3.70 g, 26.4 mmol) and maintained at 70° C for 2 h. After completion of the reaction (TLC), the mixture was quenched with water (70 mL) whereupon a solid precipitated. The mixture was stirred for 20 min and allowed to stand for 1 h. The solid was isolated by filtration and washed with water. The solid was purified by column chromatography (petroleum ether/ethyl acetate, 100:1) to give title compound (1.59 g, 36 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.91 (d, *J*=8.8Hz, 1H), 7.60(dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H), 7.67 (d, *J*=2.4Hz, 1H), 9.84 (s 1H), 10.92 (s, 1H).

MS (MM-ES+APCI), m/z: 200 (M - 1).

Synthesis of ethyl 6-bromo-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3a).

To a stirred solution of 5-bromo-2-hydroxybenzaldehyde (1.59 g, 7.9 mmol), cesium carbonate (2.61 g, 7.9 mmol) in dry *N, N*-dimethylformamide (15 mL), was added ethyl 4,4,4-trifluorocrotonate (2.66 g, 15.8 mmol). The solution was warmed to 120° C for 4 h, after completion of the reaction (MS), the mixture was quenched with water (50 mL), and extracted with ethyl acetate. The extract was dried over Na_2SO_4, concentrated *in* vacuo, and purified by column chromatography (petroleum ether/ethyl acetate, 20:1) to give title compound (1.57 g, 57%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s 1H), 7.40 (dd, *J*=1.6, 8.4 Hz, 1H), 7.35 (d, *J*=1.6 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 1H), 5.70 (q, *J*=6.8 Hz, 1H), 4.32 (q, *J*=7.2 Hz, 2H), 1.35 (t, *J*=7.2 Hz, 3H).

MS (MM-ES+APCI), m/z: 350 (M - 1).

Synthesis of ethyl 2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylate (4a).

To a solution of ethyl 6-bromo-2-(trifluoromethyl)-2H-chromene-3-carboxylate (0.99 g, 2.8 mmol), dba_3Pd_2 (95.5 mg, 0.11 mmol), 2-(di-t-butylphosphino)biphenyl (121.6 mg, 0.42 mmol), KF (0.82 g, 14.0 mmol) in tetrahydro-1,3-dimethyl-2(1H)pyrimidone (10 mL) under argon was added water (100.8 mg, 5.6 mmol), hexamethyldisilane (0.68 g.5.6 mmol) and the mixture was warmed at 100 °C for 4 h. After completion of the reaction (MS), the mixture was quenched with water (30 mL), extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by the column chromatography (petroleum ether/ethyl acetate, 30:1) to get the title compound (0.84 g, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s 1H), 7.46 (dd, *J*=1.6, *J*=8.0 Hz, 1H), 7.36 (d, *J*=1.6 Hz, 1H), 6.96 (d, *J*=8.0 Hz, 1H), 5.73 (q, *J*=6.8 Hz, 1H), 4.32 (q, *J*=7.2Hz, 2H), 1.35 (t, *J*=7.2 Hz, 3H), 0.26 (s, 9H).

MS (MM-ES+APCI), m/z: 344 (M - 1).

Synthesis of 2-(trifluoromethyl)-6-(trimethylsilyl)-2*H*-chromene-3-carboxylic acid (5a).

A mixture of ethyl 2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylate (0.75g, 2.4 mmol), lithium hydroxide (1.01 g, 24.0 mmol) was dissolved in methanol (20 mL), water (2 mL), and then the mixture was stirred over-

night at room temperature. After completion of the reaction (TLC), the mixture was concentrated *in vacuo*. The residue was stirred with dilute hydrochloric acid (0.1 mol/L,pH 3) , and then a white solid was formed, isolated washed and concentrated *in vacuo*, affording 743 mg, 98% of compound **5a.**

White solid; mp 124-126 ºC; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 7.62 (d, *J*=1.6 Hz, 1H), 7.85 (s, 1H), 7.50 (dd, *J*=1.2, 8.0 Hz, 1H), 7.02 (d, *J*=8.0 Hz, 1H), 5.89 (q, *J*=7.2 Hz, 1H), 0.23 (s, 9H); HRMS calcd for $C_{14}H_{15}F_3O_3Si$ m/z 317.08153, found 317.08194.

2-(trifluoromethyl)-7-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5b): Yield 98%; white solid; mp 102-104 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 5.89 (q, J=7.2Hz, 1H), 7.10(s, 1H), 7.18 (d, J=7.2Hz, 1H), 7.44 (t, J=7.2Hz, 1H), 7.84 (s, 1H); HRMS calcd for $C_{14}H_{15}F_3O_3Si$ m/z 317.08153, found 317.08182.

2-(trifluoromethyl)-5-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5c): Yield 97%; white solid; mp 202-203 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.33 (s, 9H), 5.89 (q, J=7.2Hz, 1H), 7.06 (d, J=8.0Hz, 1H), 7.19 (d, J=7.2Hz, 1H), 7.37 (t, J=7.6Hz, 1H), 7.91 (s, 1H), 13.37 (brs, 1H); HRMS calcd for $C_{14}H_{15}F_3O_3Si$ m/z 317.08153, found 317.08165.

8-fluoro-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5d): Yield 94%; white solid; mp 186-187 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.24 (s, 9H), 6.06 (q, J=7.2Hz, 1H), 7.43-7.48 (m, 2H), 7.94 (s, 1H), 13.41 (brs, 1H); HRMS calcd for $C_{14}H_{14}F_4O_3Si$ m/z 335.07211, found 335.07230.

8-chloro-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5e): Yield 95%; white solid; mp 199-201 ºC; 1H NMR (d6-DMSO, 400 MHz) δ0.24 (s, 9H), 6.09 (q, J=7.2Hz, 1H), 7.56(s, 1H), 7.61 (s, 1H), 7.90 (s, 1H); HRMS calcd for $C_{14}H_{14}ClF_3O_3Si$ m/z 351.04256, found 351.04279.

8-bromo-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5f): Yield 92%; white solid; mp 204-206 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.25 (s, 9H), 6.09 (q, J=7.2Hz, 1H), 7.65-7.69 (m, 2H), 7.90 (s, 1H), 13.38 (brs, 1H); HRMS calcd for $C_{14}H_{14}BrF_3O_3Si$ m/z 394.99204, found 394.99218.

2,8-bis(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5g): Yield 90%; pale yellow solid; mp 166-167 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.27 (s, 9H), 6.12 (q, J=7.2Hz, 1H), 7.71 (s, 1H), 7.97-7.98 (m, 2H); HRMS calcd for $C_{15}H_{14}F_6O_3Si$ m/z 385.06891, found 385.06765.

8-methyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5h): Yield 98%; white solid; mp 163-165 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 2.19 (s, 3H), 5.94 (q, J=7.2Hz, 1H), 7.38 (s, 1H), 7.45 (s, 1H), 7.85 (s, 1H) ; HRMS calcd for $C_{15}H_{17}F_3O_3Si$ m/z 331.09718, found 331.09727.

8-ethyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5i): Yield 97%; white solid; mp 130-132 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 1.14 (t, 3H), 2.54-2.67 (m, 2H), 5.94 (q, J=7.2Hz, 1H), 7.36 (s, 1H), 7.44-7.45 (m, 1H), 7.82 (s, 1H) ; HRMS calcd for $C_{16}H_{19}F_3O_3Si$ m/z 345.11283, found 345.11323.

8-propyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5j): Yield 96%; white solid; mp 175-177 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 0.89 (t, J=7.2Hz, 3H), 1.51-1.60 (m, 2H), 2.57-2.64 (m, 2H), 5.92 (q, J=7.2Hz, 1H), 7.35 (m, 1H), 7.45 (s, 1H), 7.85 (s, 1H) ; HRMS calcd for $C_{17}H_{21}F_3O_3Si$ m/z 359.12880, found 359.12848.

8-isopropyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5k): Yield 98%; white solid; mp 140-142 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.22 (s, 9H), 1.19 (dd, J1=2.4Hz, J2=6.8Hz, 6H), 3.17-3.24 (m, 1H), 5.92 (q, J=7.2Hz, 1H), 7.38-7.43 (m, 2H), 7.83 (s, 1H) ; HRMS calcd for $C_{17}H_{21}F_3O_3Si$ m/z 359.12874, found 359.12848.

8-(tert-butyl)-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5l): Yield 95%; white solid; mp 174-175 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 1.36 (s, 9H), 6.01 (q, J=7.2Hz, 1H), 7.43 (d, J=1.2Hz, 1H), 7.49 (d, J=1.2Hz, 1H), 7.84 (s, 1H) ; HRMS calcd for $C_{18}H_{23}F_3O_3Si$ m/z 373.14413, found 373.14440.

8-methoxy-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5m): Yield 93%; white solid; mp 181-183 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.25 (s, 9H), 3.84 (s, 3H), 5.93 (q, J=7.2Hz, 1H), 7.17 (s, 1H), 7.21 (s, 1H), 7.85 (s, 1H), 13.24 (brs, 1H) ; HRMS calcd for $C_{15}H_{17}F_3O_4Si$ m/z 347.09210, found 347.09234.

8-cyclohexyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5n): Yield 94%; white solid; mp 203-205 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.23 (s, 9H), 1.23-1.53 (m, 5H), 1.71-1.81 (m, 5H), 5.93-5.94 (m, 1H), 7.39 (s, 1H), 7.44 (s, 1H), 7.85 (s, 1H) ; HRMS calcd for $C_{20}H_{25}F_3O_3Si$ m/z 399.15978, found 399.15989.

8-phenyl-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5o): Yield 99%; white solid; mp 194-194 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.27 (s, 9H), 5.91 (q, J=7.2Hz, 1H), 7.34-7.39 (m, 1H), 7.43-7.49 (m, 5H), 7.66 (d, J=0.8Hz, 1H), 7.85 (s, 1H), 7.94 (s, 1H) ; HRMS calcd for $C_{20}H_{19}F_3O_3Si$ m/z 393.11283, found 393.11322.

8-(4-fluorophenyl)-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5p): Yield 99%; white solid; mp 227-229 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.26 (s, 9H), 5.92 (q, J=7.2Hz, 1H), 7.26-7.30 (m, 2H), 7.45 (d, J=1.6Hz, 1H), 7.50-7.53 (m, 2H), 7.65 (d, J=1.6Hz, 1H), 7.93 (s, 1H) ; HRMS calcd for $C_{20}H_{18}F_4O_3Si$ m/z 411.10341, found 411.10356.

8-(p-tolyl)-2-(trifluoromethyl)-6-(trimethylsilyl)-2H-chromene-3-carboxylic acid (5q): Yield 97%; white solid; mp 166-168 ºC; 1H NMR (d6-DMSO, 400 MHz) δ 0.26 (s, 9H), 2.35 (s, 3H), 5.87 (q, J=7.2Hz, 1H), 7.24-7.26 (m, 2H), 7.36-7.38 (m, 3H), 7.53 (s, 1H), 7.70 (s, 1H) ; HRMS calcd for $C_{21}H_{21}F_3O_3Si$ m/z 407.12848, found 407.12885.

CONFLICT OF INTERESTS

The author(s) confirm that this article content has no conflicts of interest.

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