HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 474-486. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 23rd August, 2016, Accepted, 25th November, 2016, Published online, 20th January, 2017
DOI: 10.3987/COM-16-S(S)38

A DIRECT SYNTHESIS OF 2,2-DISUBSTITUTED 3-SILYLCHROMENES BY [4+2] CYCLOADDITION OF *IN SITU* GENERATED *o*-QUINONEMETHIDES WITH ELECTRON-RICH ALKYNES

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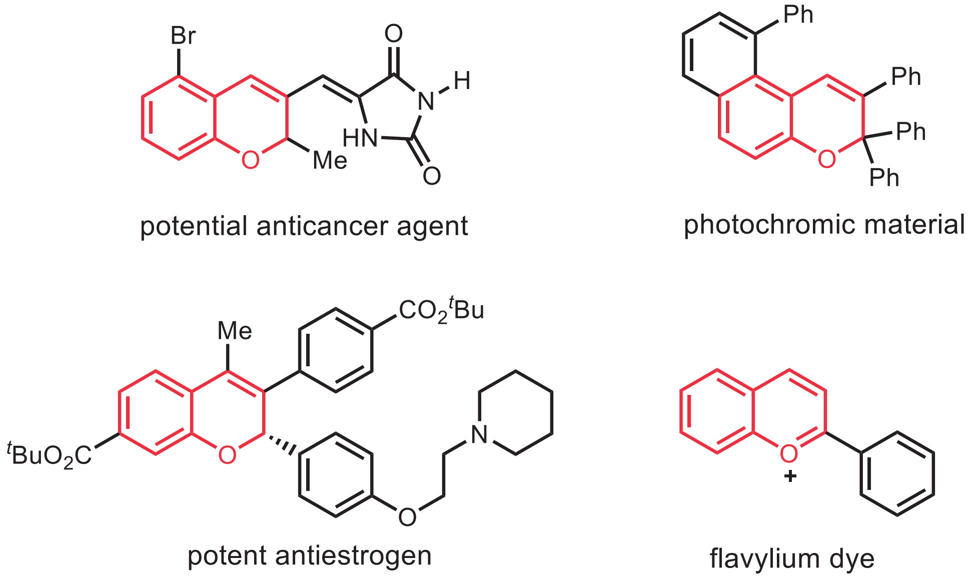
Abstract – A direct synthesis of 2,2-disubstituted 3-silylchromenes by [4+2] cycloaddition of *in situ* generated *o*-quinonemethides with electron-rich alkynes has been developed. The procedure is applicable for easily available starting materials like various substituted alkynylsilanes and salicylaldehydes. The present reaction provides versatile access to functionalized 2*H*-chromenes that would be a useful tool for the synthesis of biologically and photochemically active molecules.

INTRODUCTION

2*H*-Chromenes are present in a vast number of natural products and represent important structural motifs in medicinal chemistry and materials science. 2*H*-Chromene is an important skeleton that appears in interesting compounds such as anticancer,[1] antiestrogen,[2] photochromic materials[3] and a precursor of flavylium dyes[4] (Figure 1). Based on the importance of these compounds, a number of research groups have developed methodologies to synthesize these compounds. The approaches include three-component coupling reaction of arynes, ketene *N,S*-acetals, and DMF,[5] $BF_3 \cdot OEt_2$-$AgSCF_3$ mediated trifluoromethylthiolation/cascade cyclization of propynols,[6] palladium(0)-catalyzed annulations of alkynyl aryl ethers with alkynes,[7] microwave-assisted reaction of salicylaldehydes with enamines,[8] ring-closing olefin metathesis,[9] the tandem ylide annulation reaction,[10] electrocyclic ring closure of vinylquinone derivatives,[11] catalytic Petasis reaction of salicylaldehydes,[12] cobalt(II)-based metalloradical reaction,[13] simultaneous synthesis of both rings of chromenes via a benzannulation/*o*-quinonemethide formation/electrocyclization cascade,[14] electrophile-induced cyclization of aryl propargyl ethers,[15] palladium-catalyzed intramolecular cyclization,[16] and *L*-proline catalyzed three-component reaction of salicylaldehydes with diketone in alcohol.[17] Recently, a few research groups reported the synthesis of the 2*H*-chromene ring system via intermolecular cycloaddition reaction with alkynes.[18] However, most of previous methods utilized alkynes only having electron-withdrawing substituents like dimethyl acetylenedicarboxylate (Scheme 1a).



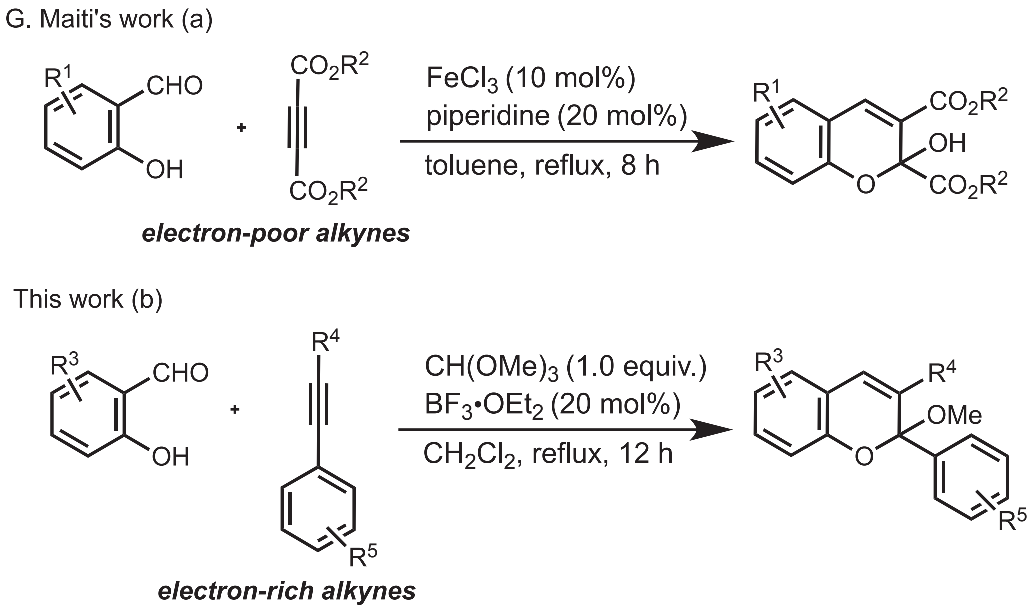
potential anticancer agent

photochromic material

potent antiestrogen

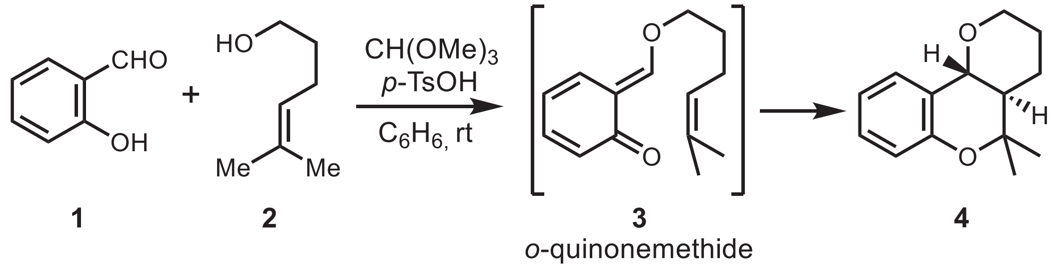
flavylium dye

Figure 1. Selected examples of 2*H*-chromenes



Scheme 1. Synthesis of 2*H*-chromenes with alkynes

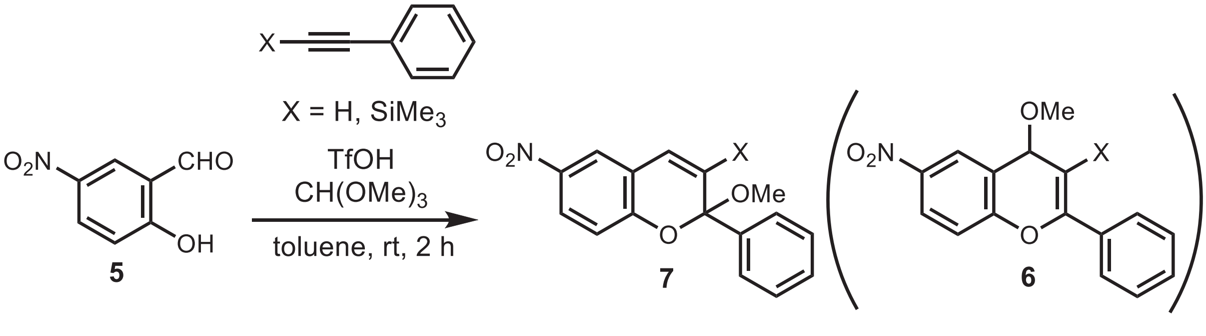
Unfortunately these methods for the synthesis of chromene derivatives suffer from limitations, including a limited kind of substrate, *e.g.* withdrawing group-substituted alkynes and requiring multi-steps for preparation of starting materials as well as expensive noble transition metals. Since natural products and bioactive compounds containing 2*H*-chromenes have a variety of substituent patterns, there remains a demand for general strategies that can more efficiently provide variously substituted chromene systems. Recently, we have investigated the generation of *o*-quinonemethide under mild conditions.[19] In the course of this study we reported that salicylaldehyde **1** reacted with alcohol **2** in benzene in the presence of *p*-TsOH and trimethyl orthoformate at room temperature to give *trans*-**4** in high yield as a single stereoisomer (Scheme 2).[20] Herein we report the novel synthesis of polysubstituted chromenes via regioselective intermolecular cycloaddition reaction of easily available electron-rich alkynes like silyl substituted arylalkynes with substituted salicylaldehydes (Scheme 1b).



Scheme 2. Previous work

RESULTS AND DISCUSSION

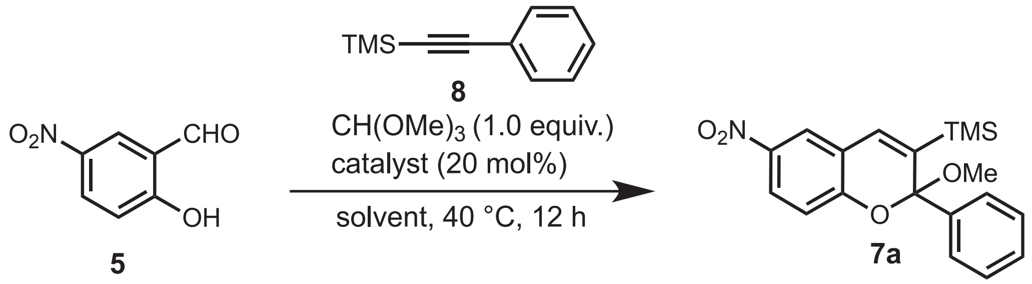
We initially examined the reaction of 5-nitrosalicylaldehyde with phenylacetylene in the presence of TfOH (20 mol%) and $CH(OMe)_3$ (1.0 equiv.) in toluene (Scheme 3). Contrary to expectation, the reaction gave the complex mixture (checked by TLC), and no Diels–Alder cycloadduct **6** was obtained. Unknown polymerized compound was obtained as a major product mainly due to the instability of unprotected terminal alkynes. Therefore the terminal methyne carbon of phenylacetylene was protected by trimethylsilyl group. Interestingly, when trimethylsilylethynylbenzene was subjected to the reaction conditions, the isomerized 2*H*-chromene product **7** was obtained in 14% yield instead of 4*H*-chromene **6**. Because vinyl silanes are useful building blocks, which are readily transformed to a variety of functional groups such as ketone, alcohol, nitro, and chloride,[21] we decided to further explore this cycloaddition reaction.



Scheme 3. Cycloaddition of 5-nitrosalicylaldehyde with phenylacetylenes in the presence of a catalytic amount of TfOH and $CH(OMe)_3$ in toluene

Thus we investigated the reaction of 5-nitrosalicylaldehyde with trimethylsilylethynylbenzene in the presence of acid catalysts in various solvents (Table 1). When high polar solvents like acetonitrile, DMF, and MeOH were used, no desired product was obtained (entries 1-3). On the other hand several common medium polar solvents such as toluene and dichloromethane led to the formation of 3-trimethylsilylchromene **7** (entries 5-6). When the reaction was used toluene and 1,2-dichloroethane instead of dichloromethane under refluxing, the yield of chromene **7** was not increased (entries 7-8). Next we examined some Lewis acid catalysts. A catalytic amount of $Yb(OTf)_3$, $Sn(OTf)_3$, which are known as hard Lewis acids, afforded the desired product in moderate yields (entries 9-10). However, when a soft Lewis acid $Pd(OAc)_2$ was used, cycloaddition did not proceed (entry 11). On the other hand, some Brønstead acid such as p-$TsOH \cdot H_2O$, TfOH, $HBF_4 \cdot OEt_2$ were used, the reaction was proceed and the corresponding product was obtained in medium yields (entries 12-14). Finally, because $BF_3 \cdot OEt_2$ was not expensive compared with $HBF_4 \cdot OEt_2$, it was suggested that the best reaction condition could be obtained by using 5-nitrosalicylaldehyde (1.0 equiv.), trimethylsilylethynylbenzene (4.0 equiv.), $CH(OMe)_3$ (1.0 equiv.), and $BF_3 \cdot OEt_2$ (20 mol%) in refluxing dichloromethane (entry 6).

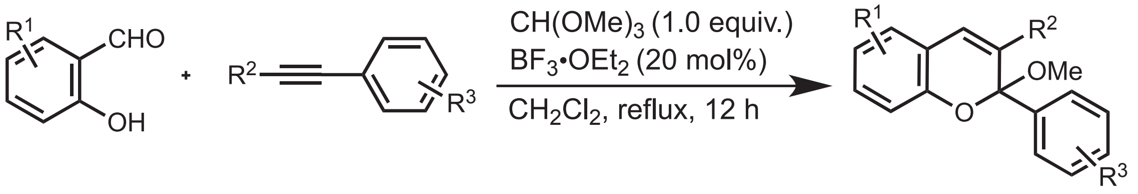
Table 1. Optimization of reaction conditions[a]

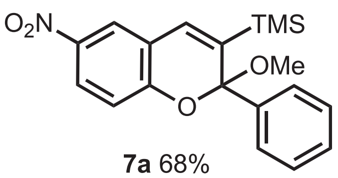


entry	catalyst	solvent	yield (%)
1	$BF_3 \cdot OEt_2$	DMF	N.R.
2	$BF_3 \cdot OEt_2$	MeCN	N.R.
3	$BF_3 \cdot OEt_2$	MeOH	N.R.
4	$BF_3 \cdot OEt_2$	THF	N.R.
5	$BF_3 \cdot OEt_2$	toluene	32
6	$BF_3 \cdot OEt_2$	CH_2Cl_2	**68**
7[b]	$BF_3 \cdot OEt_2$	toluene	32
8[b]	$BF_3 \cdot OEt_2$	CH_2ClCH_2Cl	55
9	$Yb(OTf)_3$	CH_2Cl_2	39
10	$Sn(OTf)_3$	CH_2Cl_2	60
11	$Pd(OAc)_2$	CH_2Cl_2	N.R.
12	p-$TsOH \cdot H_2O$	CH_2Cl_2	32
13	TfOH	CH_2Cl_2	52
14	$HBF_4 \cdot OEt_2$	CH_2Cl_2	**70**

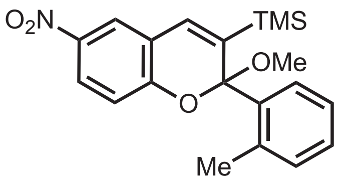
[a] All reactions were carried out with **5** (1.0 mmol), **8** (4.0 mmol), $CH(OMe)_3$ (1.0 equiv.), and catalyst (20 mol%) in solvent (5.0 mL) under nitrogen. [b] reflux

Table 2. Reaction of salicylaldehydes with alkynes

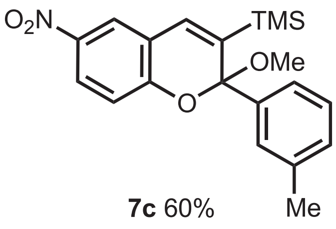




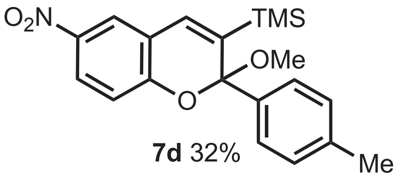
7a 68%



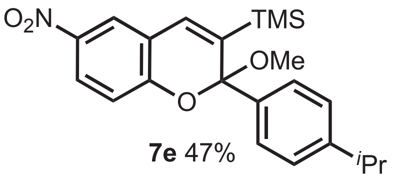
7b 40%



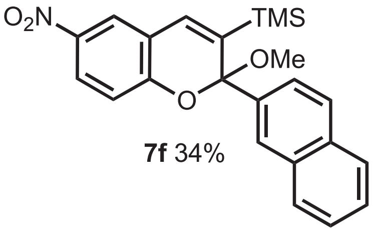
7c 60%



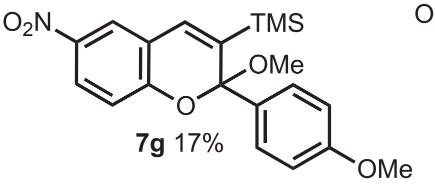
7d 32%



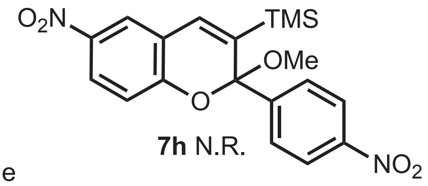
7e 47%



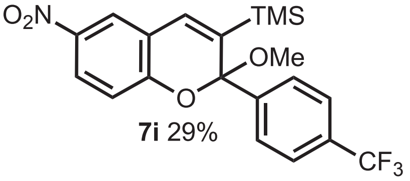
7f 34%



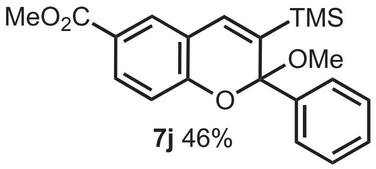
7g 17%



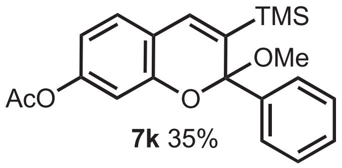
7h N.R.



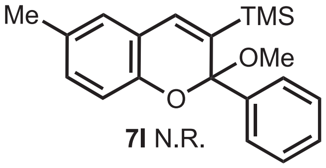
7i 29%



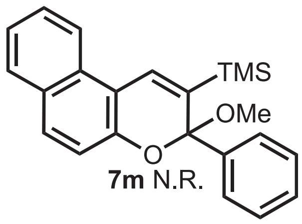
7j 46%



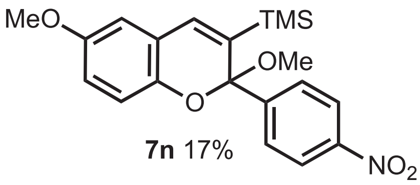
7k 35%



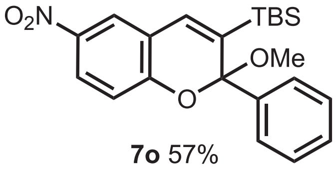
7l N.R.



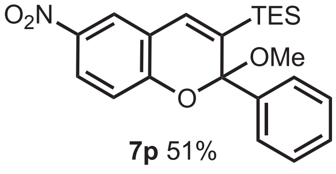
7m N.R.



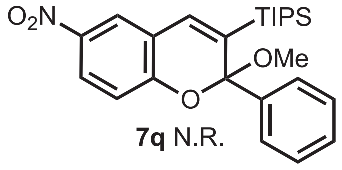
7n 17%



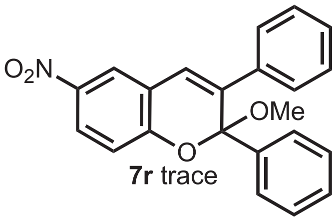
7o 57%



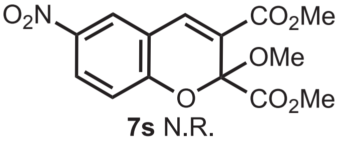
7p 51%



7q N.R.



7r trace

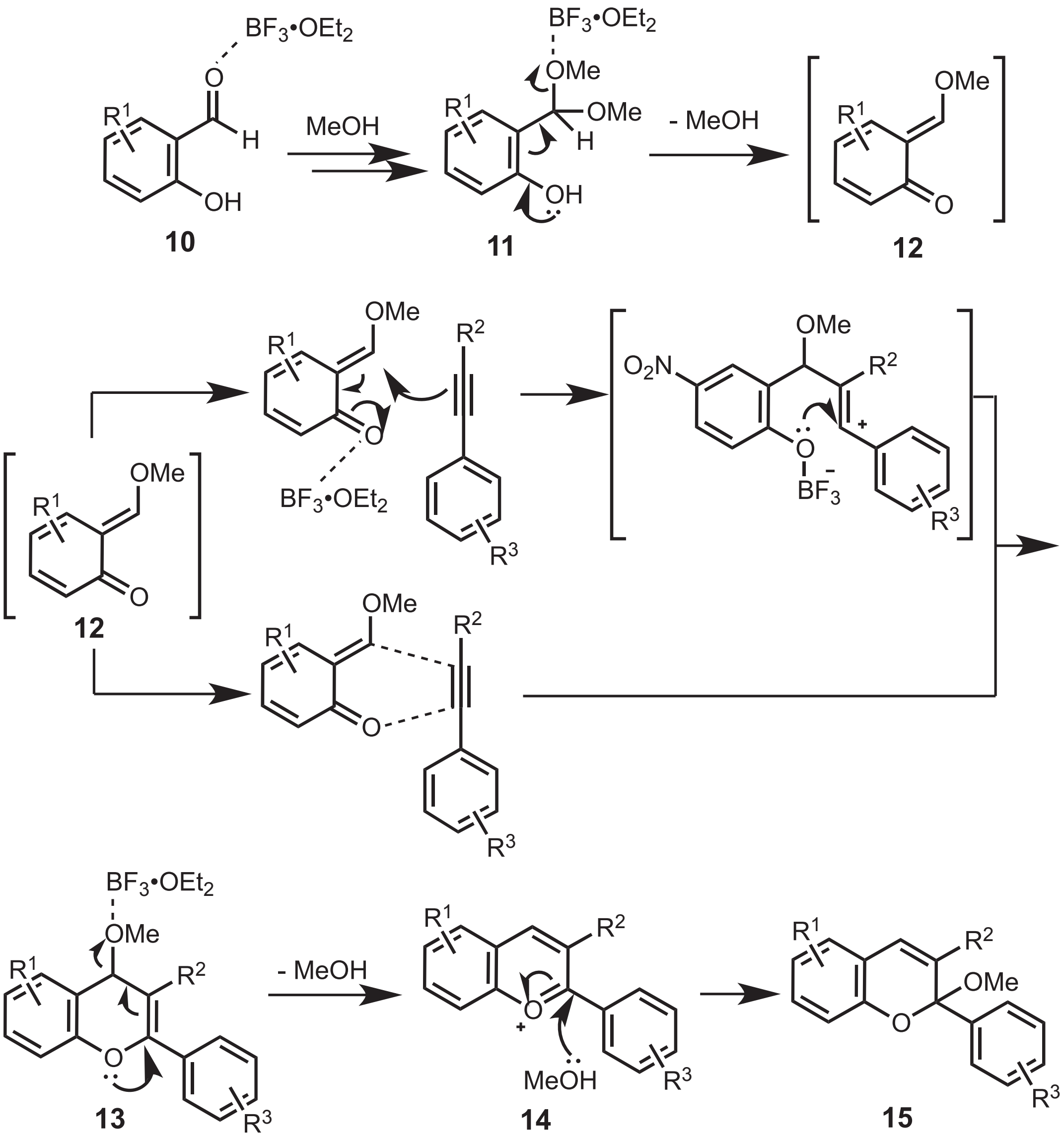


7s N.R.

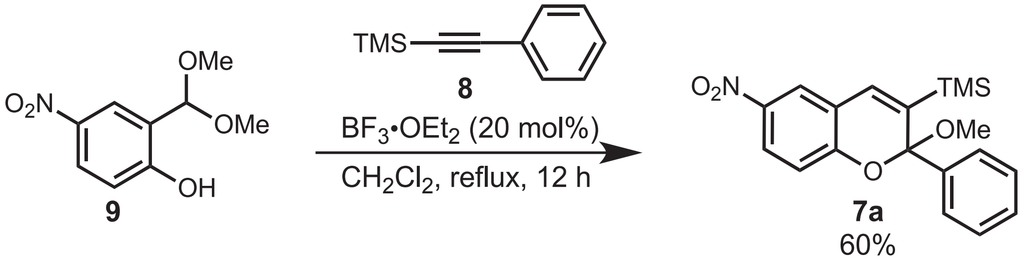
With the optimal reaction conditions in hand, salicylaldehydes and a variety of alkynes were explored to examine the scope and limitation of the reaction (Table 2). Alkynes having an electron-donating group, which are known as good dienophiles for inverse-electron-demand Diels–Alder reaction, gave the corresponding products in medium yields (entries 7a-7g). However, alkyne with NO_2 group on benzene ring did not give the product (entry 7h). But alkyne with CF_3 group gave the corresponding product in 29% yield (entry 7i). Various salicylaldehydes having electron-withdrawing groups smoothly underwent the reaction to give the corresponding products in good yields (entries 7j-7k). In contrast, the reaction of salicylaldehydes having electron-donating groups smoothly did not proceed (entries 7l-7m). TBS and TES groups afforded products in good yields (entries 7o-7p). Interestingly, when sterically demanded silyl group was used, the reaction did not proceed (entry 7q). And diphenylacetylene and dimethyl acetylenedicarboxylate without silyl group did not afford the corresponding products (entries 7r-7s).

A plausible reaction mechanism for the cycloaddition of salicylaldehyde with alkyne is depicted in Scheme 4. First, salicylaldehyde dimethyl acetal (**11**) would be formed by the reaction of salicylaldehyde with $CH(OMe)_3$ in the presence of $BF_3 \cdot OEt_2$. It is well known that 5-nitrosalicylaldehyde **5** could react with $CH(OMe)_3$ under acidic conditions to give acetal **9** as a reaction intermediate.[22] We investigated cycloaddition reaction of acetal **9** with trimethylsilylethynylbenzene **8** without $CH(OMe)_3$ (Scheme 5). This reaction smoothly proceeded to give the corresponding product in 60% yield. It suggests that 5-nitrosalicylaldehyde **5** would be smoothly transformed to acetal **9** in the presence of $CH(OMe)_3$. *o*-Quinonemethide **12** was derived from elimination of methanol from **11**. It is considered that *o*-quinonemethide would react with alkyne by a stepwise or concerted mechanism. It is also of great interest to see whether *o*-quinonemethide **12** has enough reactivity toward electron-rich dienophiles. Then it would react with electron-rich alkyne through inverse-electron-demand Diels–Alder reaction to give cyclic products **13**. However, on the basis of the results shown in Table 2, it is suggested that this reaction would proceed through stepwise cycloaddition reaction. Treatment of **13** with Lewis acid resulted in the formation of flavylium salt **14** from the elimination of the methoxy group, which is reattacked by MeOH at 2-position to afford **15** as the most stable product.

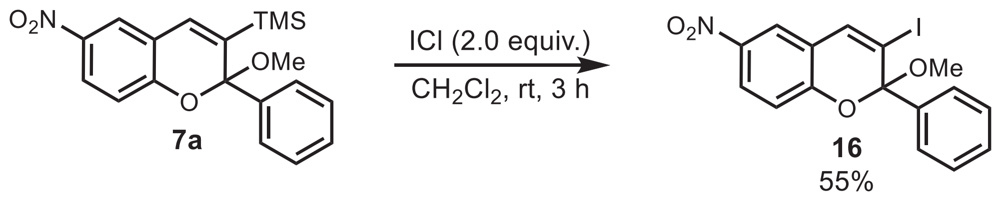
Finally, to further functionalize the reaction products, we intended to convert silylchromene into the corresponding iodo derivative. 3-Silylchromene **7a** was reacted with ICl to afford 3-iodochromene **16** in 55% yield. 3-Iodochromene **16** may be able to act as a coupling partner in transition metal-catalyzed cross-coupling reaction, which provides a new feasible route to biologically and photochemically active chromenes.[2,3a]



Scheme 4. Plausible mechanism for the synthesis of polysubstituted chromenes from various salicylaldehydes and alkynes



Scheme 5. Cycloaddition reaction of acetal **9** with trimethylsilylethynylbenzene **8** without CH(OMe)$_3$



Scheme 6. Conversion of 3-silylchromene **7a** to 3-iodochromene **16**

In summary, we have developed a direct synthesis of 2,2-disubstituted 3-silylchromenes by [4+2] cycloaddition of *in situ* generated *o*-quinonemethides with electron-rich alkynes. The procedure is applicable for easily available starting materials like various substituted alkynylsilanes and salicylaldehydes. The present reaction provides versatile access to functionalized 2*H*-chromenes that would be a useful tool for the synthesis of biologically and photochemically active molecules.

EXPERIMENTAL

General. Infrared (IR) spectra were recorded on a JASCO FT/IR 4100. ^{1}H NMR spectra were recorded on a Bruker DRX-300 (300 MHz) spectrometer or a Bruker DRX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration, and assignment. ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0). Column chromatography was carried out with Cica-reagent silica gel 60 N (spherical, particle size 63-210 μm). Thin-layer chromatography (TLC) was carried out with Merck TLC plates with silica gel 60 F$_{254}$. Unless otherwise noted, reagents were commercially available and were used without purification.

General procedure for the synthesis of 2*H*-chromene 7a: To a mixture of 5-nitrosalicylaldehyde (0.167 g, 1.0 mmol), trimethylsilylethynylbenzene (0.789 mL, 4.0 mmol), and trimethyl orthoformate (0.106 mL, 1.0 mmol) in dry CH_2Cl_2 (5.0 mL) under nitrogen, boron trifluoride diethyl ether complex (0.025 mL, 20 mol%) was added. After being stirred at reflux for 12 h, the reaction mixture was quenched with 5% aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane / EtOAc = 20 : 1) to afford 2*H*-chromene product **7a**.

2-Methoxy-3-trimethylsilyl-6-nitro-2-phenyl-2*H*-1-benzopyran (**7a**)

Yield 68%, brown solid; mp 88.7-89.2 °C; IR (neat): 3084, 2954, 1612, 1515, 1336, 1242, 1068, 835, 748, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.07 (s, 9H), 3.34 (s, 3H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.15 (s, 1H), 7.35-7.39 (m, 3H), 7.50-7.53 (m, 2H), 8.12-8.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.90, 50.7, 105.6, 115.8, 118.3, 122.8, 125.8, 126.3, 128.1, 128.9, 133.4, 138.0, 141.4, 142.1, 158.2. HR-MS (ESI+) *m/z* calcd. for $C_{18}H_{18}NO_3Si$ ($[M\text{-}OMe]^+$): 324.10505, found: 324.10484.

2-Methoxy-3-trimethylsilyl-6-nitro-2-(2-methylphenyl)-2*H*-1-benzopyran (**7b**)

Yield 40%, brown solid; mp 119.6-119.7 °C; IR (neat): 2943, 1605, 1518, 1338, 1265, 1245, 992, 838, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.11 (s, 9H), 2.07 (s, 3H), 3.30 (s, 3H) 7.01-7.03 (m, 1H), 7.18-7.20 (m, 2H), 7.29-7.32 (m, 2H), 7.87-7.89 (m, 2H), 8.17-8.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -1.32, 20.1, 49.7, 104.1, 115.6, 118.6, 123.1, 125.5, 126.0, 129.2, 132.1, 134.2, 135.7, 138.0, 139.3, 141.6, 158.7. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{20}NO_3Si$ ($[M\text{-}OMe]^+$): 338.12070, found: 338.12161.

2-Methoxy-3-trimethylsilyl-6-nitro-2-(3-methylphenyl)-2*H*-1-benzopyran (**7c**)

Yield 60%, brown solid; mp 95.5-95.7 °C; IR (neat): 2955, 1609, 1518, 1338, 1092, 995, 832 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.06 (s, 9H), 2.39 (s, 3H), 3.34 (s, 3H), 6.97-6.99 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 7.24 (m, 1H), 7.29-7.31 (m, 4H), 8.12-8.16 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.86, 21.5, 50.7, 105.6, 115.8, 118.4, 122.9, 123.5, 125.8, 127.1, 128.1, 129.0, 129.6, 132.5, 133.4, 137.8, 138.0, 141.4, 142.0, 158.2. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{20}NO_3Si$ ($[M\text{-}OMe]^+$): 338.12070, found: 338.12257.

2-Methoxy-3-trimethylsilyl-6-nitro-2-(4-methylphenyl)-2*H*-1-benzopyran (**7d**)

Yield 32%, brown amorphous solid. IR (neat): 2958, 1611, 1515, 1337, 1259, 1244, 834, 812 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.06 (s, 9H), 2.39 (s, 3H), 3.34 (s, 3H), 6.95 (m, 1H), 7.13 (s, 1H), 7.20-7.21 (m, 3H), 7.38-7.39 (m, 2H), 8.12-8.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.83, 21.2, 50.7, 105.8, 115.8, 118.4, 122.8, 125.8, 126.3, 128.8, 129.0, 131.9, 133.4, 138.2, 138.8, 139.3, 141.4, 158.3. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{20}NO_3Si$ ($[M\text{-}OMe]^+$): 338.12070, found: 338.12075.

2-Methoxy-6-nitro-2-(4-isopropylphenyl)-3-trimethylsilyl-2*H*-1-benzopyran (**7e**)

Yield 47%, brown solid; mp 116.9-117.6 °C; IR (neat): 2960, 1610, 1514, 1336, 1262, 1068, 998, 837, 823 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.07 (s, 9H), 1.27 (m 6H), 2.97-3.01 (m, 1H), 3.34 (s, 3H), 6.97 (d, *J* = 8.5 Hz, 1H), 7.12 (s, 1H), 7.25 (m, 2H), 7.42 (m, 2H), 8.11-8.18 (m, 2H). ^{13}C NMR (125

MHz, $CDCl_3$): δ -0.93, 24.0, 33.9, 50.7, 105.7, 115.8, 118.5, 122.8, 125.8, 126.1, 126.4, 132.0, 133.2, 138.3, 139.6, 141.4, 149.8, 158.3. HRMS (ESI+) *m/z* calcd. for $C_{21}H_{24}NO_3Si$ ($[M-OMe]^+$): 366.15200, found: 366.15368.

2-Methoxy-6-nitro-2-naphthyl-3-trimethylsilyl-2*H*-1-benzopyran (**7f**)

Yield 34%, yellow solid; mp 146.7-147.1 °C; IR (neat): 1611, 1516, 1269, 1065, 1007, 830, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.06 (s, 9H), 3.44 (s, 3H), 6.98 (m, 1H), 7.23 (s, 1H), 7.51-7.71 (m, 3H), 7.82-8.01 (m, 3H), 8.03-8.18 (m, 2H), 8.20 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.73, 50.9, 105.9, 115.9, 118.4, 123.0, 124.4, 125.2, 126.0, 126.4, 126.8, 127.7, 128.1, 128.8, 132.7, 133.4, 133.9, 137.8, 139.3, 141.5, 158.3. HRMS (ESI+) *m/z* calcd. for $C_{22}H_{20}NO_3Si$ ($[M-OMe]^+$): 374.12070, found: 374.12332.

2-Methoxy-2-(4-methoxyphenyl)-6-nitro-3-trimethylsilyl-2*H*-1-benzopyran (**7g**)

Yield 17%, brown solid; mp 119.6-120.5 °C; IR (neat): 2960, 1610, 1511, 1335, 1244, 1070, 995, 823, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.05 (s, 9H), 3.33 (s, 3H), 3.84 (s, 3H), 6.90-6.96 (m, 3H), 7.13 (s, 1H), 7.41-7.42 (d, *J* = 9.0 Hz, 2H), 8.11-8.14 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.81, 50.8, 55.3, 105.7, 113.4, 118.3, 115.8, 122.8, 125.8, 127.7, 133.4, 134.7, 138.2, 141.4, 158.3, 160.0. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{20}NO_4Si$ ($[M-OMe]^+$): 354.11561, found: 354.11572.

2-Methoxy-6-nitro-2-(4-trifluoromethylphenyl)-3-trimethylsilyl-2*H*-1-benzopyran (**7i**)

Yield 29%, yellow solid; mp 98.5-99.0 °C; IR (neat): 2962, 1611, 1519, 1324, 1260, 1067, 999, 824 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.06 (s, 9H), 3.36 (s, 3H), 6.96-6.97 (d, *J* = 8.7 Hz, 1H), 7.20 (s, 1H), 7.64-7.68 (m, 4H), 8.14-8.17 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.84, 50.8, 105.0, 115.8, 118.1, 123.0, 125.1, 126.1, 126.9, 134.3, 137.1, 141.7, 145.8, 157.8. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{17}NO_3F_3Si$ ($[M-OMe]^+$): 392.09243, found: 392.09230.

Methyl 2-methoxy-6-nitro-2-phenyl-3-trimethylsilyl-2*H*-1-benzopyran-6-carboxylate (**7j**)

Yield 46%, colorless solid; mp 73.8-74.2 °C; IR (neat): 2952, 1715, 1616, 1247, 999, 758, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ -0.09 (s, 9H), 3.33 (s, 3H), 3.92 (s, 3H), 6.93-6.95 (d, *J* = 9.1 Hz, 1H), 7.14 (s, 1H), 7.36-7.37 (m, 3H), 7.52 (m, 2H), 7.93-7.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.84, 50.5, 51.9, 104.8, 115.3, 118.2, 122.7, 126.5, 128.0, 128.6, 129.0, 131.9, 134.6, 135.8, 142.7, 157.0, 166.7. HRMS (ESI+) *m/z* calcd. for $C_{20}H_{21}O_3Si$ ($[M-OMe]^+$): 337.12545, found: 337.12520.

2-Methoxy-7-acetyloxy-2-phenyl-3-trimethylsilyl-2*H*-1-benzopyran (**7k**)

Yield 35%, yellow solid; mp 103.8-104.7 °C; IR (neat): 1756, 1617, 1492, 1202, 1007, 836, 750, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.09 (s, 9H), 2.30 (s, 3H), 3.36 (s, 3H), 6.83-6.71 (m, 2H), 7.08 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.28-7.48 (m, 3H), 7.49-7.70 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.75, 21.1, 50.7, 104.2, 108.8, 114.2, 116.7, 126.7, 127.6, 128.0, 128.5, 134.3, 134.4, 142.9, 151.9, 153.9, 169.1. HRMS (ESI+) *m/z* calcd. for $C_{20}H_{21}O_3Si$ ($[M-OMe]^+$): 337.12545, found: 337.12573.

2,6-Dimethoxy-2-(4-nitrophenyl)-3-trimethylsilyl-2*H*-1-benzopyran (**7n**)

Yield 17%, yellow solid; mp 117.6-118.5 °C; IR (neat): 2955, 1521, 1348, 1236, 1038, 1003, 836 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 9H), 3.49 (s, 3H), 3.98 (s, 3H), 6.91 (s, 1H), 6.99 (s, 1H), 7.00 (s, 1H), 7.44 (s, 1H), 7.88-7.91 (d, *J* = 9.0 Hz, 2H), 8.37-8.40 (d, *J* = 9.0, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.61, 50.63, 55.86, 103.1, 111.3, 115.9, 116.8, 118.6, 123.2, 128.0, 134.1, 136.3, 146.8, 147.7, 149.8, 154.0. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{20}NO_4Si$ ($[M-OMe]^+$): 354.11561, found: 354.11670.

3-*tert*-Butyldimethylsilyl-2-methoxy-6-nitro-2-phenyl-2*H*-1-benzopyran (**7o**)

Yield 57%, yellow solid; mp 101.1-101.7 °C; IR (neat): 2962, 2931, 2857, 1610, 1516, 1337, 1259, 1064, 993, 819, 808, 747, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.04 (s, 3H), -0.02 (s, 3H), 0.79 (s, 9H), 3.39 (s, 3H), 6.94-6.96 (d, *J* = 9.0 Hz, 1H), 7.20 (s, 1H), 7.36-7.38 (m, 3H), 7.50-7.51 (m, 2H), 8.06-8.18 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.46. -3.90, 17.8, 27.0, 50.90, 106.0, 115.7, 118.2, 122.9, 126.0, 126.4, 128.1, 129.0, 135.2, 136.4, 141.4, 142.5, 158.0. HRMS (ESI+) *m/z* calcd. for $C_{21}H_{24}O_3Si$ ($[M-OMe]^+$): 366.15200, found: 366.15197.

2-Methoxy-6-nitro-2-phenyl-3-triethylsilyl-2*H*-1-benzopyran (**7p**)

Yield 51%, yellow amorphous solid; IR (neat): 2955, 2874, 1608, 1518, 1338, 1261, 1091, 995, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26-0.55 (m, 6H), 0.85 (t, 9H), 3.35 (s, 3H), 6.91-6.98 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 7.38-7.40 (m, 3H), 7.50-7.52 (m, 2H), 8.15-8.18 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 3.09, 7.18, 50.78, 105.5, 115.8, 118.4, 122.9, 125.8, 126.3, 128.0, 129.0, 134.3, 135.1, 141.5, 142.0, 158.1. HRMS (ESI+) *m/z* calcd. for $C_{21}H_{24}NO_3Si$ ($[M-OMe]^+$): 366.15200, found: 366.15348.

General procedure for the synthesis of 2*H*-chromene 7 by cycloaddition of trimethylsilylethynylbenzene with acetal 9: To a mixture of acetal **9** (0.213 g, 1.0 mmol), trimethylsilylethynylbenzene (0.789 mL, 4.0 mmol) in dry CH_2Cl_2 (5.0 mL) under nitrogen, boron trifluoride diethyl ether complex (0.025 mL, 20 mol%) was added. After being stirred at reflux for 12 h, the reaction mixture was quenched with 5% aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane / EtOAc = 20 : 1) to afford 2*H*-chromene product **7** in 60%.

Synthesis of 3-iodo-6-nitro-2-methoxy-2-phenyl-2*H*-chromene (16): A solution of ICl (0.082 g 0.5 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise to a solution of **7** (0.089 g 0.25 mmol) in dry CH_2Cl_2 (5.0 mL) at rt. After stirring for 3 h, the reaction was quenched with sat. $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane / EtOAc = 50 : 1) to afford 3-iodo-6-nitro-2-methoxy-2-phenyl-2*H*-chromene (**16**).

3-Iodo-6-nitro-2-methoxy-2-phenyl-2*H*-chromene (**16**)
Yield 55%, white solid; mp 140.5-141.3 °C; IR (neat): 1514, 1337, 1261, 1078, 965, 834, 755, 747, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 9.0, 2.7 Hz, 1H), 8.07 (m, 1H), 7.44-7.60 (m, 3H), 7.42 (m, 3H), 7.02 (m, 1H), 3.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 141.9, 140.7, 137.0, 129.4, 128.2, 126.4, 126.1, 125.8, 125.0, 121.8, 119.5, 116.2, 105.0, 97.3, 51.0. HRMS (ESI+) *m/z* calcd for $C_{15}H_9NO_3I$ ($[M-OMe]^+$): 377.96217, found: 377.96483.

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