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Pd/C-catalyzed alkynylation of β-chloroacroleins

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Abstract—The first Pd/C-mediated Sonogashira coupling of β-chloroacroleins with terminal alkynes is described here. Pd/C–CuI–PPh_3 was found to be an efficient catalyst system for this coupling reaction. Using this economic and general process a variety of 4-alkynyl-2*H*-chromene-3-carbaldehydes and 5-alkynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehydes were prepared in good yields.
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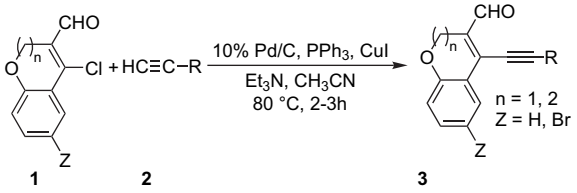
1. Introduction

Transition metal mediated cross-coupling reactions are among the most powerful carbon–carbon bond forming reactions in organic synthesis. Among them, those involving palladium catalysis especially alkynylation of sp^2 species such as aryl and alkenyl halides (the Sonogashira coupling)[1] are particularly useful for the preparation of arylalkynes or conjugated enynes, owing to excellent levels of selectivity and high functional group compatibility. Based on various halides used in Sonogashira reactions the general reactivity order of the sp^2 species can be presented as vinyl iodide≥vinyl triflate>vinyl bromide>vinyl chloride>aryl iodide>aryl triflate-≥aryl bromide≥aryl chloride.[1b] Thus the Sonogashira alkynylation process usually proceeds smoothly when the more reactive but more expensive vinyl and aryl iodides are used. Notably, vinyl chloride although less reactive amongst the vinyl halides is more reactive than aryl iodides and therefore has been utilized in the synthesis of natural products and numerous biologically active compounds.[2] Despite its potential utility, the use of β-chloroacroleins (–CCl═CCHO–) in cross-coupling reaction has not been explored until recently[3] and to the best of our knowledge only four examples involving the use of β-chloroacroleins under Sonogashira condition have been reported.[4] Because of its cheap availability and high catalytic activity,[5] Pd/C has been used in Sonogashira coupling by us and several other groups.[6] Herein we report a very facile and general method for the alkynylation of β-chloroacroleins under Pd/C–copper catalysis.

2. Results and discussion

To determine the feasibility of this approach, 4-chloro-2*H*-chromene-3-carbaldehyde (**1**, *n*=1, Z=H) was treated with terminal alkynes (**2**, R=alkyl, hydroxyalkyl, aryl, etc.) in acetonitrile in the presence of 10% Pd/C (0.026 equiv), PPh_3 (0.12 equiv), CuI (0.05 equiv), and Et_3N (3.0 equiv) under nitrogen. The reaction proceeded well and 4-alkynyl-2*H*-chromene-3-carbaldehydes (**3**, *n*=1, Z=H) were obtained in good to excellent yields (Scheme 1). The results are summarized in Table 1.



Scheme 1. Pd/C-mediated alkynylation of β-chloroacroleins.

While acetonitrile was used as a solvent in the present coupling reaction (entry 1, Table 1), the use of aqueous media such as dimethoxyethane (DME)/H_2O (4:1) was also found to be effective (entry 2, Table 1). The use of pure water as a solvent did not provide any product perhaps due to the poor solubility of the halide **1** in water alone. The use of an inorganic base, e.g., K_2CO_3 in place of triethylamine provided the desired product albeit in lower yield (entry 3, Table 1). As outlined in Table 1, 4-chloro-2*H*-chromene-3-

Keywords: β-Chloroacroleins; Terminal alkynes; Palladium catalyst.
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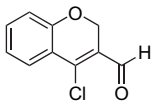
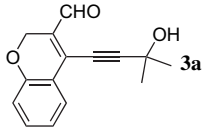
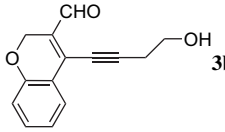
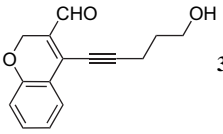
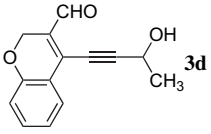
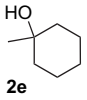
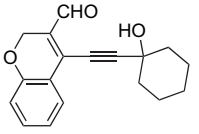
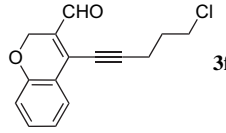
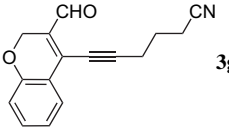
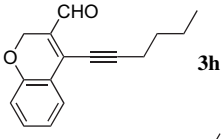
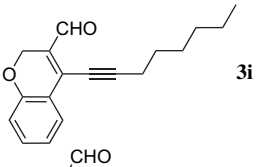
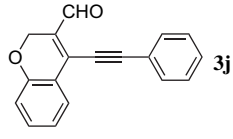
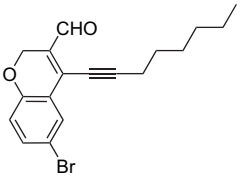
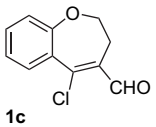
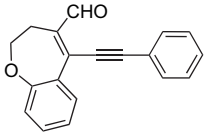
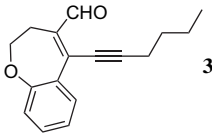
Table 1. Synthesis of 4-alkynyl-2*H*-chromene-3-carbaldehydes (**3a–k**) and 5-alkynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehydes (**3l–m**)[a]

Entry	β-Chloroacroleins (**1**)	Alkynes (**2**), R=	Products[b] (**3**)	Yield[c] (%)
1	 **1a**	–$C(CH_3)_2OH$ **2a**	 **3a**	85
2[d]	**1a**	**2a**	**3a**	80
3[e]	**1a**	**2a**	**3a**	30
4	**1a**	–$(CH_2)_2OH$ **2b**	 **3b**	80[f]
5	**1a**	–$(CH_2)_3OH$ **2c**	 **3c**	81[f]
6	**1a**	–$CH(OH)CH_3$ **2d**	 **3d**	77[f]
7	**1a**	 **2e**	 **3e**	87
8	**1a**	–$(CH_2)_3Cl$ **2f**	 **3f**	82[f]
9	**1a**	–$(CH_2)_3CN$ **2g**	 **3g**	79[f]
10	**1a**	–$(CH_2)_3CH_3$ **2h**	 **3h**	79[f]
11	**1a**	–$(CH_2)_5CH_3$ **2i**	 **3i**	90[f]
12	**1a**	–C_6H_5 **2j**	 **3j**	80
13	**1b**	**2i**	 **3k**	60[f]

(*continued*)

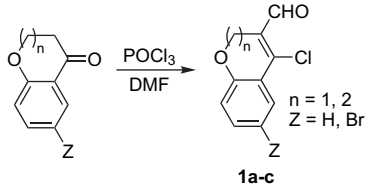
Table 1. (*continued*)

Entry	β-Chloroacroleins (**1**)	Alkynes (**2**), R=	Products[b] (**3**)	Yield[c] (%)
14	 **1c**	$-C_6H_5$ **2k**	 **3l**	70
15	**1c**	$-(CH_2)_3CH_3$ **2l**	 **3m**	79[f]

[a] All the reactions were carried out using **1** (1.0 equiv), **2** (2.0 equiv), 10% Pd/C (0.026 equiv), PPh_3 (0.12 equiv), CuI (0.05 equiv), and Et_3N (3.0 equiv) at 80 °C for 2–3 h.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.
[d] DME/H_2O (4:1) was used as solvent.
[e] K_2CO_3 was used as a base.
[f] This product was stored at 0 °C due to its apparent instability at room temperature.

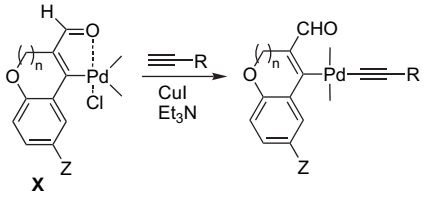
carbaldehyde (**1a**) showed good reactivity toward the present coupling reaction and a variety of terminal alkynes were employed under the conditions studied (entries 4–12, Table 1). Various functional groups including both hydrophobic and hydrophilic substitutents, e.g., aryl, alkyl, hydroxy, ether, etc., present in the terminal alkynes were well tolerated. This allowed the preparation of a variety of 4-alkynyl-2*H*-chromene-3-carbaldehyde (**3a**–**k**) under mild condition. Generally, yields of products were not affected by the nature of alkynes used. The greater reactivity of the vinyl chloride moiety over an aryl bromide that is also present in the molecule allowed us to prepare the corresponding 6-bromo derivative (**3k**) in good yields (entry 13, Table 1). The use of an alternate β-chloroacrolein derivative containing a seven membered ring, e.g., 5-chloro-2,3-dihydro benzo[*b*]oxepine-4-carbaldehyde (**1c**, *n*=2) was also investigated and it afforded good yields of the desired products when coupled with terminal alkynes under the condition employed (entries 14 and 15, Table 1).

β-Chloroacroleins(**1a**–**c**) are readily prepared from the corresponding ketones by a Vilsmeier–Haack–Arnold reaction[7] according to Scheme 2. All the terminal alkynes used are commercially available.



Scheme 2. Preparation of β-chloroacroleins.

Mechanistically, the reaction seems to proceed via generation of Pd(0) species in situ from Pd/C and PPh_3. This then catalyzes the coupling of β-chloroacrolein **1** with copper(I) acetylide (generated in situ from the terminal alkyne) via intermediate **X** leading to the corresponding alkynyl derivatives. This coupling reaction is perhaps favored because of the intramolecular coordination of the neighboring carbonyl oxygen to the palladium during the chloride displacement step (Scheme 3). Nevertheless, the high reactivity showed by β-chloroacroleins toward Pd/C-mediated alkynylation reaction is due to the presence of electron withdrawing aldehyde group, which activated the vinyl chloride moiety and allowed C–C coupling reaction under mild condition.



Scheme 3. Effect of neighboring group on the coupling of **X** with a terminal alkyne.

3. Conclusion

In conclusion, we have demonstrated that Pd/C–CuI–PPh_3 can be used as an efficient catalyst system for Sonogashira coupling of β-chloroacroleins with terminal alkynes. The reactions proceed well to afford a variety of 4-alkynyl-2*H*-chromene-3-carbaldehydes and 5-alkynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehydes in good yields. This is a general and economical process and opens an easy way to access alkynyl substituted acroleins. Since the development of effective methods for the functionalization of oxygen containing heterocycles represents a major synthetic challenge toward the synthesis of biologically important heterocycles the present process would find wide usage.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed in dried glassware under a nitrogen atmosphere. All the solvents used were commercially available and distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing

with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform, and methanol. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solutions on Varian Gemini 200 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). Coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FTIR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–vis recording spectrophotometer. Melting points were determined using a Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data were generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the condition specified in each case: column, mobile phase (range used), flow rate (range used), detection wavelength, retention times. All the terminal alkynes used are commercially available.

4.1.1. Synthesis of 4-alkynyl-2*H*-chromene-3-carbaldehydes. In a typical procedure a mixture of 4-chloro-2*H*-chromene-3-carbaldehyde (0.5 g, 2.57 mmol), 10% Pd/C (85 mg, 0.08 mmol), PPh_3 (81 mg, 0.30 mmol), CuI (26.4 mg, 0.13 mmol), and triethylamine (780 mg, 7.71 mmol) in acetonitrile (20 mL) was stirred at 25–30 °C for 30 min under nitrogen. The acetylenic compound (5.14 mmol) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 2–3 h. After completion of the reaction (as indicated by TLC), the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The organic layers were collected and concentrated. The crude residue was purified by column chromatography on silica gel, using light petroleum (60–80 °C)/ethyl acetate (19:1) to afford the desired product.

4.1.1.1. 4-(3-Hydroxy-3-methyl-but-1-ynyl)-2*H*-chromene-3-carbaldehyde (3a). Pale yellow oil; R_f (25% ethyl acetate/light petroleum) 0.38; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.06 (s, 1H), 7.65 (dd, J=7.5, 1.6 Hz, 1H), 7.44–7.40 (m, 1H), 7.14–7.10 (m, 1H), 6.94 (dd, J=8.1, 0.8 Hz, 1H), 5.75 (br s, D_2O exchangeable, 1H, –OH), 4.94 (s, 2H), 1.54 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.1 (–CHO), 155.1, 133.5, 131.8, 131.6, 127.3, 122.2, 120.3, 116.4, 109.6, 72.0, 62.5, 63.9 (CH_2), 31.0 ($2CH_3$); IR (cm^{-1}, $CHCl_3$) 3427, 2211 (–C≡C–), 1646, 1041; *m/z* (ES Mass) 243.1 (M+1, 100%); HPLC 98.0%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35, flow rate: 1 mL/min; UV 210 nm, retention time: 9.93 min; HRMS (ESI): calcd for $C_{15}H_{14}O_3Na[(M+Na)^+]$ 265.0841, found 265.0851.

4.1.1.2. 4-(4-Hydroxy-but-1-ynyl)-2*H*-chromene-3-carbaldehyde (3b). Pale yellow oil; R_f (40% ethyl acetate/light petroleum) 0.14; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.07 (s, 1H), 7.69 (dd, J=7.8, 1.6 Hz, 1H), 7.43–7.39 (m, 1H), 7.12–7.08 (m, 1H), 6.95 (dd, J=8.1, 0.8 Hz, 1H), 4.93 (s, 2H), 3.67 (t, J=6.5 Hz, 2H), 2.74 (t, J=6.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.3 (–CHO), 156.0, 133.5, 132.4, 131.7, 127.5, 122.2, 120.7, 116.4, 103.9, 72.5, 62.5 (CH_2), 59.2 (CH_2OH), 23.7 (CH_2); IR (cm^{-1}, $CHCl_3$) 3401, 2225 (–C≡C–), 1658; *m/z* (ES Mass) 229.2 (M+1, 100%); HPLC 99.0%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 7.57 min; HRMS (ESI): calcd for $C_{14}H_{11}O_3[(M–H)^+]$ 227.0708, found 227.0702.

4.1.1.3. 4-(5-Hydroxy-pent-1-ynyl)-2*H*-chromene-3-carbaldehyde (3c). Pale yellow oil; R_f (20% ethyl acetate/light petroleum) 0.09; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.15 (s, 1H), 7.64 (dd, J=7.8, 1.6 Hz, 1H), 7.34–7.32 (m, 1H), 7.04–7.0 (m, 1H), 6.88 (dd, J=8.3, 1.07 Hz, 1H), 4.98 (s, 2H), 3.85 (t, J=6.2 Hz, 2H), 2.73 (t, J=7.3 Hz, 2H), 1.96–1.92 (m, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.7 (–CHO), 155.7, 133.2, 131.6, 129.5, 127.6, 121.8, 120.1, 116.5, 104.2, 72.7, 62.9 (CH_2), 61.2 (CH_2), 30.9 (CH_2), 16.3 (CH_2); IR (cm^{-1}, $CHCl_3$) 3409, 2219 (–C≡C–), 1659, 1042; *m/z* (ES Mass) 243.1 (M+1, 100%); HPLC 98.76%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35, flow rate: 1 mL/min; UV 210 nm, retention time: 8.49 min; HRMS (ESI): calcd for $C_{15}H_{13}O_3[(M–H)^+]$ 241.0865, found 241.0859.

4.1.1.4. 4-(3-Hydroxy-but-1-ynyl)-2*H*-chromene-3-carbaldehyde (3d). Brown oil; R_f (40% ethyl acetate/light petroleum) 0.17; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.14 (s, 1H), 7.63 (dd, J=7.7, 1.6 Hz, 1H), 7.36–7.31 (m, 1H), 7.05–7.02 (m, 1H), 6.90 (dd, J=8.1, 1.1 Hz, 1H), 4.99 (s, 2H), 4.89 (m, 1H), 1.64 (s, 3H); IR (cm^{-1}, $CHCl_3$) 3391, 2219 (–C≡C–), 1661, 1217; *m/z* (ES Mass) 229.1 (M+1, 100%); HPLC 98.2%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35, flow rate: 1 mL/min; UV 210 nm, retention time: 8.22 min; HRMS (ESI): calcd for $C_{14}H_{12}O_3Na[(M+Na)^+]$ 251.0684, found 251.0680.

4.1.1.5. 4-(1-Hydroxy-cyclohexylethynyl)-2*H*-chromene-3-carbaldehyde (3e). Off white solid, mp 97.5–98.9 °C; R_f (40% ethyl acetate/light petroleum) 0.31; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.09 (s, 1H, CHO), 7.67 (dd, J=7.8, 1.6 Hz, 1H), 7.45–7.40 (m, 1H), 7.15–7.1 (m, 1H), 6.65 (dd, J=8.1, 0.8 Hz, 1H), 5.76 (br s, 1H, OH), 4.95 (s, 2H, CH_2), 1.98–1.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 189.4 (–CHO), 155.7, 133.4, 133.0, 132.0, 127.6, 122.0, 120.7, 116.6, 106.8, 82.9, 69.3, 62.9 (CH_2), 39.6 (2C, CH_2), 24.9 (CH_2), 23.3 (2C, CH_3); IR (cm^{-1}, KBr) 3485, 2929, 2852, 2213 (–C≡C–), 1662 (C=O), 1073; *m/z* (ES Mass) 283.4 (M+1, 100%); HPLC 99.7%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35, flow rate: 1 mL/min; UV 210 nm, retention time: 14.2 min; HRMS (ESI): calcd for $C_{18}H_{19}O_3$ $(M+H)^+$ 283.1334, found 283.1337.

4.1.1.6. 4-(5-Chloro-pent-1-ynyl)-2*H*-chromene-3-carbaldehyde (3f). Brown oil; R_f (25% ethyl acetate/light petroleum) 0.47; ^{1}H NMR ($CDCl_3$), 400 MHz) δ 10.14 (s, 1H),

7.64 (dd, J=7.8, 1.6 Hz, 1H), 7.35–7.32 (m, 1H), 7.04–7.0 (m, 1H), 6.88 (dd, J=8.1, 0.8 Hz, 1H), 4.98 (s, 2H), 3.73–3.7 (m, 2H), 2.8 (t, J=6.7 Hz, 2H), 2.17–2.10 (m, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.4 (–CHO), 155.7, 133.4, 133.1, 131.9, 127.5, 121.9, 121.0, 116.6, 102.4, 73.3, 62.9 (CH_2), 43.4 (CH_2), 30.9 (CH_2), 17.2 (CH_2); IR (cm^{-1}, $CHCl_3$) 3312, 2221 (–C≡C–), 1661; *m/z* (ES Mass) 261.1 (M+1), 263.1 (M+3); HPLC 99.6%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 17.09 min; HRMS (ESI): calcd for $C_{15}H_{14}ClO_2$ $(M+H)^+$ 261.0682, found 261.0687.

4.1.1.7. 6-(3-Formyl-2*H*-chromen-4-yl)hex-5-ynenitrile (3g). Brown oil; R_f (40% ethyl acetate/light petroleum) 0.40; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.13 (s, 1H), 7.60 (dd, J=7.8, 1.6 Hz, 1H), 7.35–7.33 (m, 1H), 7.05–7.01 (m, 1H), 6.89 (dd, J=8.1, 0.8 Hz, 1H), 4.98 (s, 2H), 2.78 (t, J=7.0 Hz, 2H), 2.57 (t, J=7.0 Hz, 2H), 2.09–2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 189.2 (–CHO), 155.7, 133.3, 132.1, 131.7, 127.4, 121.9, 120.7, 118.5 (CN), 116.7, 101.1, 74.0, 62.9 (CH_2), 24.2 (CH_2), 18.8 (CH_2), 16.4 (CH_2); IR (cm^{-1}, $CHCl_3$) 3312, 2221 (–C≡C–), 1661; *m/z* (ES Mass) 252.1 (M+1, 100%); HPLC 98.9%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 11.97 min; HRMS (ESI): calcd for $C_{16}H_{13}NO_2K[(M+K)^+]$ 290.0583, found 290.0593.

4.1.1.8. 4-Hex-1-ynyl-2*H*-chromene-3-carbaldehyde (3h). Brown oil; R_f (25% ethyl acetate/light petroleum) 0.58; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.15 (s, 1H), 7.65 (dd, J=7.8, 1.6 Hz, 1H), 7.33–7.3 (m, 1H), 7.25–7.01 (m, 1H), 6.87 (dd, J=8.1, 1.1 Hz, 1H), 4.97 (s, 2H), 2.56 (t, J=7.0 Hz, 2H), 1.7–1.63 (m, 2H), 1.55–1.5 (m, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.7 (–CHO), 155.8, 134.0, 133.1, 131.5, 127.7, 121.8, 121.3, 116.5, 105.1, 72.5, 63.0 (CH_2), 30.4 (CH_2), 22.1 (CH_2), 19.5 (CH_2), 13.5 (CH_3); IR (cm^{-1}, $CHCl_3$) 2219 (–C≡C–), 1659, 1216; *m/z* (ES Mass) 241.2 (M+1, 100%); HPLC 98.9%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35, flow rate: 1 mL/min; UV 210 nm, retention time: 20.11 min; HRMS (ESI): calcd for $C_{16}H_{17}O_2$ $(M+H)^+$ 241.1229, found 241.1226.

4.1.1.9. 4-Oct-1-ynyl-2*H*-chromene-3-carbaldehyde (3i). Greenish yellow oil; R_f (25% ethyl acetate/light petroleum) 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.15 (s, 1H), 7.66 (dd, J=7.8, 1.6 Hz, 1H), 7.33–7.3 (m, 1H), 7.03–6.99 (m, 1H), 6.88 (dd, J=8.1, 0.8 Hz, 1H), 4.97 (s, 2H), 2.57 (t, J=7.0 Hz, 2H), 2.43–2.34 (m, 2H), 1.70–1.64 (m, 2H), 1.58–1.26 (m, 4H), 0.93–0.87 (m, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.7 (–CHO), 155.8, 134.0, 133.0, 131.5, 127.7, 121.8, 121.2, 116.5, 105.1, 72.5, 62.9 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 22.5 (CH_2), 19.8 (CH_2), 13.9 (CH_3); IR (cm^{-1}, $CHCl_3$) 2219 (–C≡C–), 1659, 1217; *m/z* (ES Mass) 269.2 (M+1, 100%); HPLC 92.65%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 23.9 min; HRMS (ESI): calcd for $C_{18}H_{21}O_2$ $(M+H)^+$ 269.1542, found 269.1548.

4.1.1.10. 4-Phenylethynyl-2*H*-chromene-3-carbaldehyde (3j). Yellow solid; mp 132.6–134.1 °C; R_f (25% ethyl acetate/light petroleum) 0.53; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.22 (s, 1H), 7.83–7.77 (m, 3H), 7.57–7.43 (m, 4H), 7.17 (m, 1H), 6.98 (dd, J=8.3, 1.1 Hz, 1H), 5.00 (s, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 188.9 (–CHO), 155.1, 133.5, 132.1 (2C), 131.9, 131.2, 130.3, 128.8 (2C), 127.4, 122.3, 120.7, 120.2, 116.5, 102.1, 80.5, 62.6 (CH_2); IR (cm^{-1}, $CHCl_3$) 2203 (–C≡C–), 1664, 1216; *m/z* (ES Mass) 275.2 (M+1, 100%); HPLC 99.8%, column: Luna C18 (2) (150×4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 19.2 min. Elemental analysis: found C, 83.15; H, 4.62; $C_{18}H_{12}O_2$ requires C, 83.06; H, 4.65.

4.1.1.11. 6-Bromo-4-oct-1-ynyl-2*H*-chromene-3-carbaldehyde (3k). Brown oil; R_f (25% ethyl acetate/light petroleum) 0.65; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.04 (s, 1H), 7.69 (d, J=2.4 Hz, 1H), 7.59 (dd, J=8.4, 2.4 Hz, 1H), 7.29–7.26 (m, 2H), 6.95 (d, J=8.4 Hz, 1H), 4.96 (s, 2H), 2.65 (t, J=6.8 Hz, 2H), 1.66–1.59 (m, 2H), 1.5–1.43 (m, 2H), 1.35–1.23 (m, 4H), 0.90–0.81 (m, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.9 (–CHO), 156.0, 134.2, 133.5, 131.7, 127.7, 121.9, 116.5, 115.9, 105.5, 73.1, 63.2 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 23.0 (CH_2), 19.6 (CH_2), 14.0 (CH_3); IR (cm^{-1}, $CHCl_3$) 2216 (–C≡C–), 1663, 1216; *m/z* (ES Mass) 347.0 (M+1, 100%); HRMS (ESI): calcd for $C_{18}H_{20}BrO_2$ $(M+H)^+$ 347.0647, found 347.0649.

4.1.2. Synthesis of 5-alkynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehyde. A mixture of 4-chloro-2*H*-chromene-3-carbaldehyde (0.536 g, 2.57 mmol), 10% Pd/C (85 mg, 0.08 mmol), PPh_3 (81 mg, 0.30 mmol), CuI (26.4 mg, 0.13 mmol), and triethylamine (780 mg, 7.71 mmol) in acetonitrile (20 mL) was stirred at 25–30 °C for 30 min under nitrogen. The acetylenic compound (5.14 mmol) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 2–3 h. After completion of the reaction (as indicated by TLC), the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The organic layers were collected and concentrated. The crude residue was purified by column chromatography on silica gel, using light petroleum (60–80 °C)/ethyl acetate (9.5:0.5) to afford the desired product.

4.1.2.1. 5-Phenylethynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehyde (3l). Brown oil; R_f (25% ethyl acetate/light petroleum) 0.51; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.47 (s, 1H), 7.99 (dd, J=7.8, 1.6 Hz, 1H), 7.7–7.68 (m, 1H), 7.51–7.44 (m, 3H), 7.31–7.26 (m, 2H), 7.14–7.12 (m, 1H), 6.95–6.93 (m, 1H), 4.43 (t, J=5.6 Hz, 2H), 2.68 (t, J=5.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 188.9 (–CHO), 155.1, 133.6, 132.1 (2C), 131.9, 131.2, 130.3, 128.8 (2C), 127.4, 122.3, 120.7, 120.2, 116.5, 102.1, 80.5, 62.6 (CH_2); IR (cm^{-1}, $CHCl_3$) 2203 (–C≡C–), 1664, 1216; *m/z* (ES Mass) 275 (M+1, 100%); HRMS (ESI): calcd for $C_{19}H_{15}O_2$ $(M+H)^+$ 275.1072, found 275.1081.

4.1.2.2. 5-Hex-1-ynyl-2,3-dihydro benzo[*b*]oxepine-4-carbaldehyde (3m). Brown oil; R_f (25% ethyl acetate/light petroleum) 0.59; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.4 (s, 1H, CHO), 7.86 (dd, J=7.8, 1.6 Hz, 1H), 7.37–7.33 (m, 1H), 7.18–7.14 (m, 1H), 7.06 (dd, J=8.1, 1.2 Hz, 1H), 4.44 (t, J=6.0, 2H), 2.67 (t, J=6.0 Hz, 2H), 2.52 (t, J=7.6 Hz, 2H), 1.67–1.60 (m, 2H), 1.55–1.50 (m, 2H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 192.2 (–CHO), 157.0, 142.5, 139.3, 131.4, 130.8, 129.4, 123.1, 122.2, 103.0, 76.5 (2C), 30.3 (CH_2), 25.9 (CH_2), 22.0 (CH_2), 19.4 (CH_2), 13.5 (CH_3); IR (cm^{-1}, $CHCl_3$) 3020, 2962, 2215 (–C≡C–), 1661 (C=O), 1216; *m/z* (ES Mass) 255 (M+1, 100%); HPLC 99.3%, column: Luna C18 (2) (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B): 0/35, 25/90, 30/90, 31/35; flow rate: 1 mL/min; UV 210 nm, retention time: 19.35 min; HRMS (ESI): calcd for $C_{17}H_{19}O_2(M+H)^+$ 255.1385, found 255.1374.

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