An Atom-Economical Approach to the Synthesis of Potentially Bioactive 2*H*-Chromenes via CuI-Catalyzed Reactions of Alkyl/Aryl-(*E*)-(*o*-Propargyloxy)styryl Ketones

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Abstract: A series of potentially bioactive 2*H*-chromenes have been synthesized in good yields (60–82%) via CuI-catalyzed reactions of alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketones in an atom-economical approach.

Keywords: aldol condensation, alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketones, copper(I) iodide, 2*H*-chromenes, atom economy

2*H*-Chromenes (2*H*-benzopyrans) are an important class of oxygenated heterocyclic compounds.[1] Many naturally occurring pharmacologically active compounds possess the 2*H*-chromene moiety, for example, 5,7-dimethoxy-2-methyl-2*H*-benzopyran (**1**) and 5,7-dimethoxy-2,8-dimethyl-2*H*-benzopyran (**2**, Figure 1). Both **1** and **2** were isolated from the leaf essential oil of *Calyptranthes tricona*.[2] Calanolide F (**3**, Figure 1), isolated from *Calophyllum teysmannii* var. *inophylloide*,[3] also contain the 2,2-dimethylchromene moiety and exhibits anti-HIV activity. On the other hand, 3-(6-chloro-2*H*-chromen-3-yl)propen-1-one (**4**, Figure 1), a synthetic compound bearing the 2*H*-chromene unit, exhibits in vitro antileishmanial activity at noncytotoxic concentrations.[4]

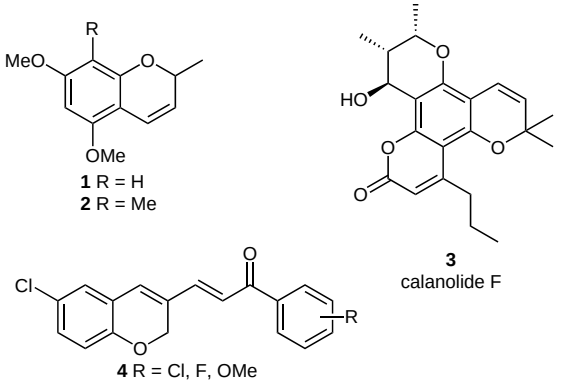

Figure 1

Moreover, it is also found that several compounds with antitumor,[5] antibacterial/antimicrobial,[6] fungicidal,[7] insecticidal,[8] and also antioxidant[9] properties contain the 2*H*-chromene moiety. In addition to biological applications, these are also widely used as photochromic materials.[10]

The bioactivity and application potential of these compounds has attracted a number of research groups to develop several methodologies for the synthesis of this class of compounds. The approaches in use include intramolecular cyclization of Wittig intermediates,[11] microwave-assisted reaction of salicylaldehyde with enamines,[12] catalytic Petasis reaction of salicylaldehydes,[13] ring-closing olefin metathesis,[14] Baylis–Hillman reaction of salicylaldehydes with methyl vinyl ketones,[15] Claisen rearrangement of propargyl phenyl ethers,[16] Pd-catalyzed ring closure of 2-isoprenyl phenols,[17] electrocyclic ring closure of vinylquinone derivatives,[18] ylide annulation reaction,[19] molecular iodine[20] as well as $Ph_3PAuNTf_2$[21]-catalyzed cyclization of aryl propargyl ethers, reaction of salicylaldehyde and potassium vinyltrifluoroborate in the presence of secondary amine,[22] iron-catalyzed intramolecular alkyne–aldehyde metathesis of the alkynyl ether of salicylaldehydes,[23] and the reaction of 5-chloro-2-hydroxybenzaldehyde with acrolein in the presence of potassium carbonate followed by Claisen–Schmidt condensation with various acetophenones in ethanolic NaOH.[4] All these routes were not devoid of any drawback. Some required the use of expensive catalysts[14,17,18,21] or reagents,[13,14b,22] some involved greater number of reaction steps[14b] and also longer reaction time[13a] for the cyclization step. To avoid these problems, there is a demand for even an improved protocol for the synthesis of this class of compounds. Herein, we report a convenient and efficient approach for the synthesis of 2*H*-chromenes from the reaction of readily accessible substrates alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketones in the presence of CuI as a catalyst.

The starting precursors, alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketones **7a**–**j** were prepared in 68–85% yields from the reaction of their corresponding alkyl/aryl-(*E*)-(*o*-hydroxy)styryl ketones **6a**–**j** with propargyl bromide in refluxing acetone for 5–6 hours in the presence of anhydrous K_2CO_3 and a catalytic amount of NaI (Scheme 1). The compounds **6a**–**h**[24,25] (R^5 = Me, Et) were, in turn, prepared by the aldol condensation of 2-hydroxybenzaldehydes **5a**–**f** with K_2CO_3 in acetone or ethyl methyl ketone under reflux for 10–12 hours. The compounds **6i**,**j** (R^5 = aryl) were prepared from 2-hydroxybenzaldehydes by the

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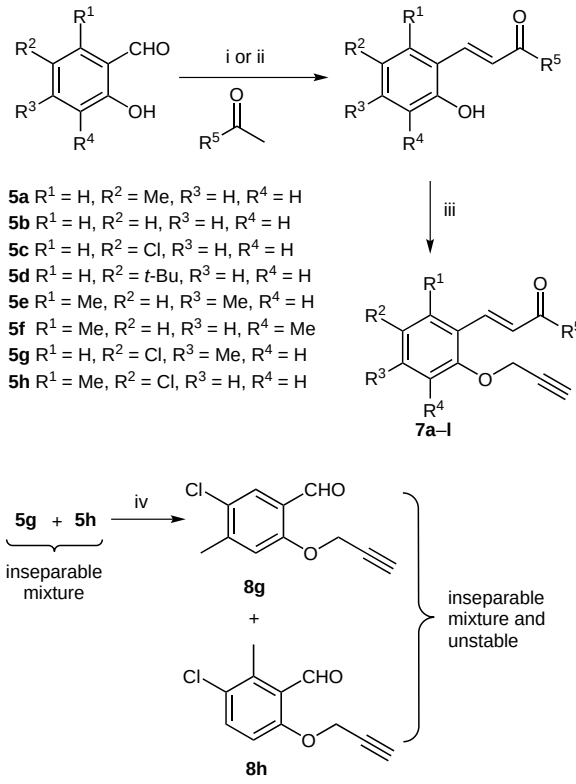
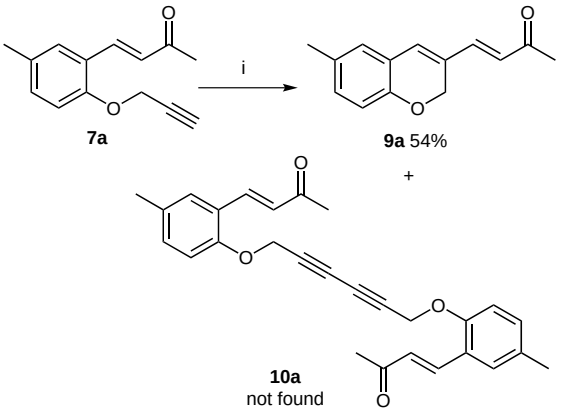
aldol condensation with acetophenones and methanolic KOH at room temperature for 2–3 hours followed by acidification with dilute HCl. Similarly, the starting precursors **7k** and **7l** (inseparable mixture) were also synthesized in 70% overall yield in the ratio of **7k**/**7l** = 1.4:1.0 (determined from the ^{1}H NMR spectrum) following the same reaction sequence from the inseparable mixture of 2-hydroxy benzaldehydes **5g** and **5h**, Reimer–Tiemann products of 4-chloro-3-methyl phenol.



Scheme 1 *Reagents and conditions*: (i) (when R^5 = Me, Et): K_2CO_3, reflux, 10–12 h; (ii) (when R^5 = aryl): KOH, MeOH, r.t., 2–3 h, then 4 N HCl; (iii) propargyl bromide, anhyd K_2CO_3, NaI (cat.), dry acetone, reflux, 5–6 h; (iv) propargyl bromide, anhyd K_2CO_3, NaI (cat.), dry MeCN, reflux, 2 h.

Products of every step were inseparable; therefore, an alternative reaction pathway was explored for their synthesis. When the inseparable mixture of 2-hydroxybenzaldehydes **5g** and **5h** were made to react with a propargyl bromide–K_2CO_3 mixture in refluxing acetonitrile in the presence of a catalytic amount of NaI, again an inseparable mixture of the expected *o*-propargyloxy benzaldehydes **8g** and **8h** were obtained that readily underwent decomposition.

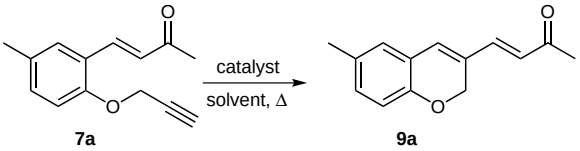
We have used compound **7a** as a model precursor for our study. The substrate **7a** was treated with 5 mol% of CuI in DMF at 100 °C for four hours (Table 1, entry 1) and 2*H*-chromene **9a**[26] was isolated in 54% yield, without the formation of expected product 1,3-diyne[27] derivative **10a** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) CuI (5 mol%), DMF, 100 °C, 4 h.

To optimize the reaction conditions we then performed a series of experiments by changing the variable parameters such as solvent, catalyst, reaction temperature, and reaction time (Table 1). Thus, the substrate (*E*)-4-[5-methyl-2-(prop-2-ynyloxy)phenyl]but-3-en-2-one (**7a**) was made to

Table 1 Optimization of the Reaction Conditions



Entry	Solvent	Catalyst (mol%)	Temp (°C)	Time (h)	Yield (%)
1	DMF	CuI (5)	100	4	54
2[a]	DMF	CuI (10)	100	2	68
3	DMF	CuI (15)	100	2	68
4	DMF	CuI (10)	80	5	43
5	DMF	CuI (10)	130	2	36
6	DMSO	CuI (10)	100	3	63
7	1,4-dioxane	CuI (10)	reflux	5	n.r.
8	DCE	CuI (10)	reflux	5	n.r.
9	MeCN	CuI (10)	reflux	5	n.r.
10	THF	CuI (10)	reflux	5	n.r.
11	toluene	CuI (10)	100	5	n.r.
12	DMF	$FeCl_3$ (10)	100	2	[b]
13	DMF	$CuCl_2 \cdot 2H_2O$ (10)	100	4	n.r.
14	DMF	$InCl_3$ (10)	100	2	[c]
15	DMF	–[d]	100	6	n.r.

[a] Optimized reaction conditions.
[b] Several inseparable spots formed.
[c] Decomposition of the starting material occurred.
[d] Absence of catalyst; n.r. = no reaction occurred.

react with 10 mol% of CuI in DMF at 100 °C for only two hours to complete the reaction giving the 2*H*-chromene **9a** in 68% yield (Table 1, entry 2).

Further increase in the amount of CuI did not improve the yield of the product **9a** (Table 1, entry 3). The yield of the 2*H*-chromene **9a** was found to be appreciably lower when the reaction was carried out at either higher or lower than 100 °C (Table 1, entry 4, 5). Different solvents viz. DMSO, 1,4-dioxane, 1,2-dichloroethane (DCE), MeCN, THF, and toluene were also examined, but only the DMSO gave the 2*H*-chromene **9a** in a higher yield (63%, Table 1 entry 6). The other solvents did not give even a trace of the 2*H*-chromene **9a**, and the starting material **7a** was recovered (Table 1, entries 7–11). Again, $FeCl_3$, $CuCl_2 \cdot 2H_2O$, and $InCl_3$ were also tested for their catalytic activity but these were found to be ineffective for this reaction (Table 1, entries 12–14).

In the absence of CuI as catalyst, the substrate **7a** remained unaffected (Table 1, entry 15). Thus a combination of (*E*)-4-[5-methyl-2-(prop-2-ynyloxy) phenyl]but-3-en-2-one (**7a**), and 10 mol% of CuI in DMF at 100 °C provides the best result (Table 1, entry 2).

To test the generality of the reaction, other substrates **7b–j** were treated under the optimized reaction conditions, and the 2*H*-chromene derivatives **9b–j** were obtained in 60–82% yields (Table 2).

Surprisingly, the reaction of the inseparable mixture of the substrates **7k** and **7l** under the optimized reaction conditions afforded only one isolable product, the 2*H*-chromene **9k** (Table 2, entry 11). Although three spots, one for **9k** (R_f = ca. 0.5), one deep spot on the base line (perhaps from decomposition), and another spot with higher R_f value (ca. 0.9) were observed on the TLC (silica gel, 1:9 EtOAc–PE). However, during chromatographic separation and also on keeping the upper fraction, the products underwent rapid decomposition and thereby we failed to characterized the product from **7l**.

The structures of 2*H*-chromenes **9** were determined from their spectral and analytical data, and the final assignment was made from the NOESY (^{1}H–^{1}H correlation) experiment (Figure 2).

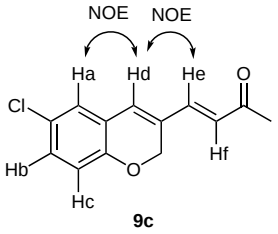
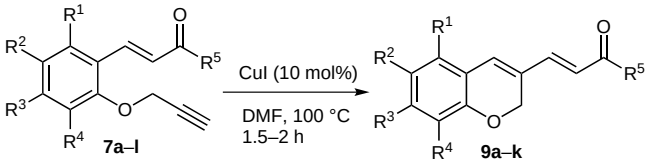


Figure 2 NOESY correlation of the compound **9c**

Table 2 Synthesis of 2*H*-Chromene Derivatives

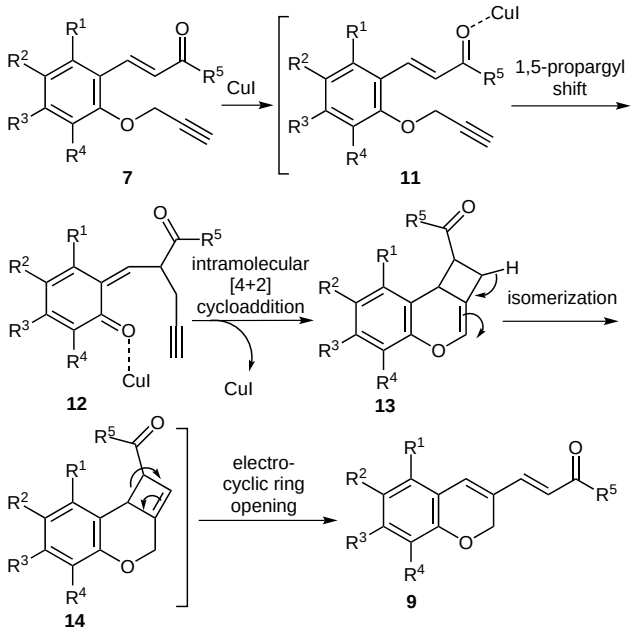


Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Product	Time (h)	Yield (%)[a]
1	**7a**	H	Me	H	H	Me	**9a**	2	68
2	**7b**	H	H	H	H	Me	**9b**	2	73
3	**7c**	H	Cl	H	H	Me	**9c**	2	82
4	**7d**	H	*t*-Bu	H	H	Me	**9d**	2	64
5	**7e**	Me	H	Me	H	Me	**9e**	2	65
6	**7f**	Me	H	H	Me	Me	**9f**	2	62
7	**7g**	H	H	H	H	Et	**9g**	2	71
8	**7h**	H	Me	H	H	Et	**9h**	2	69
9	**7i**	H	H	H	H	Ph	**9i**	1.5	60
10	**7j**	H	Cl	H	H	2-ClC_6H_4	**9j**	1.5	63
11	**7k**[b]	H	Cl	Me	H	Me	**9k**	2	69[c]
12	**7l**[b]	Me	Cl	H	H	Me	–	2	–

[a] Isolated yield of the product.
[b] Inseparable mixture of **7k** and **7l** was used.
[c] Isolated yield of the product of **9k** with respect to the starting material **7k**.

The NOESY spectrum of the compound **9c** shows two important NOE interactions, one between H_a (δ_H = 7.05, d, J = 2.8 Hz) and H_d (δ_H = 6.70, s) and the other between H_d (δ_H = 6.70, s) and H_e (δ_H = 7.19, d, J = 16.0 Hz). Moreover, the spectral data and melting point of the compound **9j** were also consistent with the literature reported values.[4]

A probable reaction mechanism for the formation of 2*H*-chromene **9** is depicted in Scheme 3. Initially the CuI may facilitate a 1,5-propargyl shift of **7** via the intermediate **11** to form the intermediate **12** which may readily undergo an intramolecular [4+2] cycloaddition[28] to generate the fused species **13**. The strained species **13** may then isomerize to produce **14** that on facile electrocyclic ring opening[29] may give the product **9**.



Scheme 3 Probable reaction mechanism for the formation of 2*H*-chromenes

In short, the product of the reaction can be regarded as the enyne metathesis product of alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketone catalyzed by CuI.

In conclusion, a series of potentially bioactive 2*H*-chromenes have been synthesized in good yields via CuI-catalyzed reactions of easily available alkyl/aryl-(*E*)-(*o*-propargyloxy)styryl ketones of which the compound **9j** is known to exhibit in vitro antileishmanial activity at non-cytotoxic concentration.[4] The attractive features of this methodology are the mild reaction conditions, high atom-economy, use of inexpensive starting materials, and eco-friendly catalyst. Moreover, this protocol can introduce α,β-unsaturated carbonyl functionality in the 2*H*-chromene unit. Thus, the reaction described adds a more general and efficient approach to the functionalized 2*H*-chromenes.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(25) Majumdar, K. C.; Ansary, I.; Sinha, B.; Roy, B.; Sridhar, B. *Synthesis* **2011**, 3287.
(26) **Typical Procedure for the Synthesis of (*E*)-4-(6-Methyl-2*H*-chromen-3-yl)but-3-en-2-one (9a):** A mixture of compound **7a** (150 mg, 0.70 mmol), and CuI (14 mg, 10 mol%) was stirred in dry DMF (4 mL) at 100 °C for 2 h. The reaction mixture was cooled to r.t., and then it was poured into H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was washed with H_2O (3 × 15 mL), brine (20 mL), and then dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure to give a crude mass which was chromatographed over silica gel (230–400 mesh) using EtOAc–PE (1:19 v/v) as an eluent to afford the 2*H*-chromene **9a** as a sole product; yield 68%; mp 68 °C. IR (KBr): ν_{max} = 2918, 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.33 (s, 3 H), 4.93 (s, 2 H), 6.03 (d, 1 H, *J* = 16.4 Hz), 6.73–6.75 (m, 2 H), 6.89 (s, 1 H), 6.99 (dd, 1 H, *J* = 8.4, 1.6 Hz), 7.21 (d, 1 H, *J* = 16.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 27.7, 65.0, 115.6, 121.6, 125.5, 128.3, 128.7, 131.1, 131.6, 132.0, 140.4, 152.4, 198.0. ESI-HRMS: *m/z* calcd for $C_{14}H_{14}O_2Na$ [M + Na]: 237.0892; found: 237.0931.
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