Synthesis of Novel 3-Bromo-2*H*-chromene Derivatives: Palladium-Mediated Intramolecular Cyclization of Aryl Propargyl Ethers

Gurunathan Savitha, Kulandhai Felix, Paramasivan T. Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India
Fax +91(44)24911589; E-mail: ptperumal@gmail.com

Received 31 March 2009

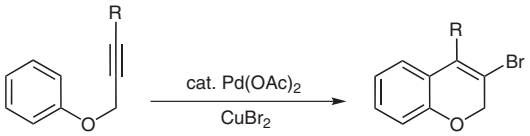
Abstract: Aryl propargyl ethers were cyclized in the presence of catalytic amount of $Pd(OAc)_2$ in conjunction with stoichiometric amount of $CuBr_2$ and LiBr to the corresponding 3-bromo-2*H*-chromene derivatives in good yields. The protocol was further extended to synthesize 3-bromo-benzofused 2*H*-chromene derivatives.

Key words: palladium-mediated cyclization, 3-bromo-2*H*-chromenes, aryl propargyl ethers, LiBr, $CuBr_2$

2*H*-1-Benzopyrans, commonly known as 2*H*-benzopyrans or 2*H*-chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The 2*H*-benzopyran daurichromenic acid is known to exhibit anti-HIV properties,[1] while coutareagenin possesses antidiabetic activity.[2] Derivatives of 3,4-diphenylchromans are known to have estrogenic activity.[3] Numerous derivatives of 2*H*-benzopyrans are useful for the treatment of proliferative skin disorders and microbial infections[4] and show potent antifungal activity.[5] Derivatives of 2*H*-benzopyrans, like 2,4-diphenyl-2*H*-benzopyran and 2,2,4-triphenyl-2*H*-benzopyran, have been studied for their photochromic behavior.[6] Owing to their biological and pharmaceutical importance, there has been a constant research in the development of new methodologies for the synthesis of 2*H*-chromene derivatives.[7]

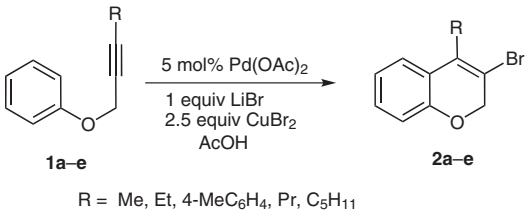
To contribute to this area of research, we are interested in developing a methodology that provides facile access to 2*H*-chromene derivatives. Our methodology towards the synthesis of 2*H*-chromene derivatives involves the cyclization of aryl propargyl ethers using catalytic amount of $Pd(OAc)_2$ in the presence of $CuBr_2$ and LiBr.

Henry and co-workers have reported that $CuBr_2$ and $CuCl_2$ can facilitate the palladium(II)-catalyzed enantioselective intermolecular dibromination and chlorohydration of olefins.[8–10] In these reactions, halogen transfer occurs more rapidly than hydride elimination, a common terminating event in Pd(II)-catalyzed reactions.[11–13] Manzoni et al. have carried out intramolecular amino bromination of olefins by using catalytic amount of Pd(II) in conjunction with stoichiometric amount of $CuBr_2$.[14] Based on these reports we supposed that 3-bromo-2*H*-chromene derivatives could be synthesized from aryl propargyl ethers in the presence of catalytic amount of Pd(II) along with stoichiometric amount of $CuBr_2$. We envisioned that activation of the alkyne will takes place by coordination to Pd(II) followed by a rapid intramolecular nucleophilic attack by the arene. Subsequent halogen-transfer reaction assisted by $CuBr_2$ will furnish the corresponding 3-bromo-2*H*-chromene derivatives (Scheme 1). Herein we wish to report the results of our investigations on the Palladium-mediated cyclization of aryl propargyl ethers to novel 3-bromo-2*H*-chromene derivatives.



Scheme 1

We initially focused our efforts on the cyclization of the aryl propargyl ether **1a** to the corresponding 3-bromo-2*H*-chromene derivative. After a series of trials, the aryl propargyl ether **1a** underwent cyclization in the presence of 5 mol% $Pd(OAc)_2$ in conjunction with 2.5 equivalents of $CuBr_2$ and 1 equivalent of LiBr in acetic acid at room temperature to give the expected 3-bromo-4-ethyl-2*H*-chromene in 68% yield after purification through column chromatography (Scheme 2, Table 1).[15]



Scheme 2

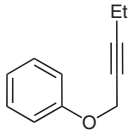
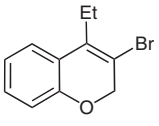
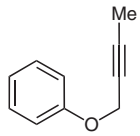
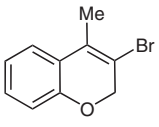
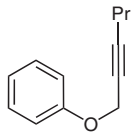
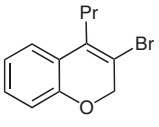
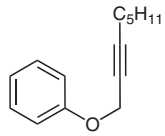
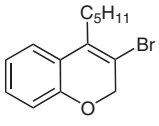
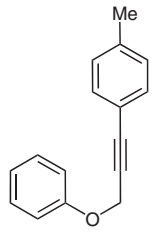
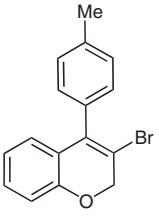
In the ^{1}H NMR spectrum of compound **2a**, the presence of only four protons in the aromatic region confirmed the cyclization of the aryl propargyl ether **1a** to the corresponding 3-bromo-4-ethyl-2*H*-chromene **2a**. Further the absence of the alkynyl carbon signals in the ^{13}C NMR spectrum confirmed the formation of the chromene derivative **2a**. Finally, mass spectral studies supported the formation of **2a**.[16]

SYNLETT 2009, No. 13, pp 2079–2082
Advanced online publication: 15.07.2009
DOI: 10.1055/s-0029-1217563; Art ID: G08909ST

It was found that the reaction did not proceed in the absence of either $Pd(OAc)_2$ or $CuBr_2$, thereby illustrating their significant role in the reaction, and with the use of LiBr the reaction was clean and proceeded to completion in short reaction times.

Having established the optimum conditions for the reaction, a variety of aryl propargyl ethers **1b–e** were cyclized following similar procedure (Scheme 2). In all the cases the reaction proceeded smoothly within 10 minutes furnishing the corresponding 3-bromo-2*H*-chromene derivatives in good yields. The results are summarized in Table 1.

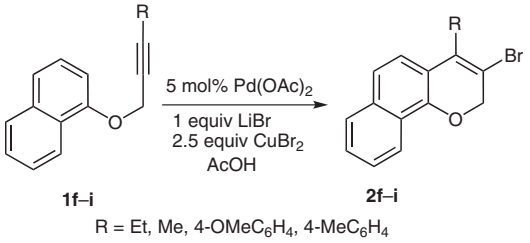
Table 1 Synthesis of 3-Bromo-2*H*-chromene Derivatives

Entry	Aryl propargyl ether **1**	3-Bromo-2*H*-chromene **2**	Time (min)	Yield (%)[a]
1	 **1a**	 **2a**	5	68
2	 **1b**	 **2b**	5	70
3	 **1c**	 **2c**	6	63
4	 **1d**	 **2d**	6	72
5	 **1e**	 **2e**	10	75

[a] Isolated yield.

Encouraged by this, we further extended the protocol to prepare various 3-bromo benzofused 2*H*-chromene derivatives from the corresponding naphthyl propargyl ethers under optimized reaction conditions (Scheme 3 and Scheme 4).

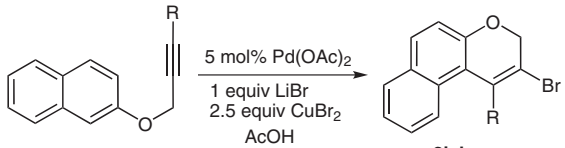
In all the cases the reaction proceeded smoothly affording the corresponding cyclized product in moderate to good yields, and the results are summarized in Table 2.



1f–i **2f–i**

R = Et, Me, 4-$OMeC_6H_4$, 4-MeC_6H_4

Scheme 3



1j–l **2j–l**

R = Et, 4-$OMeC_6H_4$, 4-MeC_6H_4

Scheme 4

Table 2 Synthesis of 3-Bromo Benzofused 2*H*-Chromene Derivatives

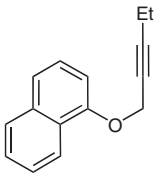
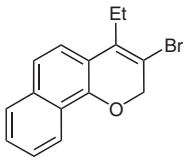
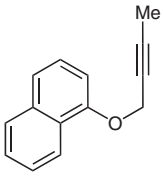
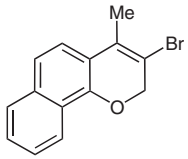
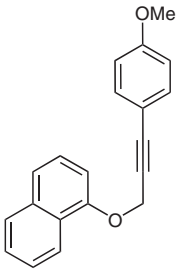
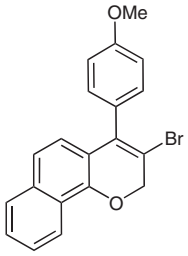
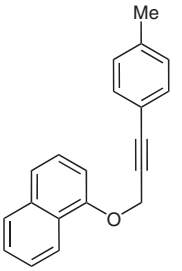
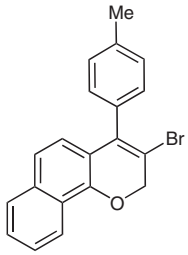
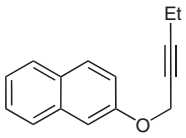
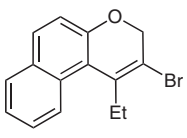
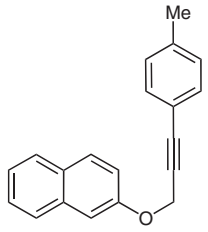
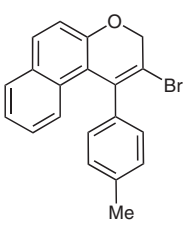
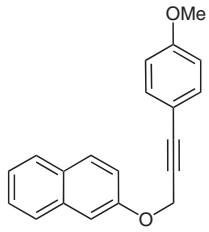
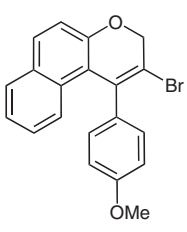
Entry	Aryl propargyl ether **1**	Product **2**	Time (min)	Yield (%)[a]
1	 **1f**	 **2f**	10	72
2	 **1g**	 **2g**	15	69
3	 **1h**	 **2h**	15	68
4	 **1i**	 **2i**	15	65

Table 2 Synthesis of 3-Bromo Benzofused 2*H*-Chromene Derivatives (continued)

Entry	Aryl propargyl ether **1**	Product **2**	Time (min)	Yield (%)[a]
5	 **1j**	 **2j**	10	72
6	 **1k**	 **2k**	15	71
7	 **1l**	 **2l**	15	73

[a] Isolated yield.

The structure of the compounds **2f–l** was confirmed through ^{1}H and ^{13}C NMR spectroscopic analysis and mass-spectrometry.[17]

A plausible mechanism for the formation of 3-bromo-2*H*-chromene derivatives from the corresponding aryl propargyl ethers is given in Scheme 5.

The mechanism involves the cyclization of the aryl propargyl ether via carbopalladation, wherein activation of the alkyne by coordination to Pd(II) is followed by intramolecular nucleophilic attack by the arene furnishing the organometallic intermediate **i**. This intermediate may be converted into the palladium(IV) species **ii**, which may decompose through reductive elimination to give the product **2**. Formation of Pd(IV) species and their subsequent reductive elimination reactions were supported by Canty and co-workers.[18–20]

The product **2** can also be formed from **i** via intermediate **iii** following an alternative mechanism analogous to that proposed by Henry and co-workers in his olefin dibromination and chlorohydration reactions,[8–10] in which copper(II) assists in ligand transfer and also retaining palladium in its +2 oxidation state.

The role of LiBr can be explained from the structures of the intermediate **i** and **ii** in which palladium is coordinated to bromide and acetate ions. The use of LiBr increases the bromide ion concentration thereby increases the ratio of the number of bromide ions to that of acetate ions coordinated to palladium in the intermediate **i** and **ii** and thus facilitating the reaction to proceed smoothly to furnish the product **2** in shorter reaction times.

In conclusion we have developed an efficient methodology which gives rise to 3-bromo-2*H*-chromene derivatives in good yields from the easily accessible starting materials under mild reaction conditions. The methodology was also applied to synthesize 3-bromo benzofused 2*H*-chromene derivatives. We believe that this simple protocol will find further application in the palladium-mediated synthesis of various cyclic frameworks.

Acknowledgment

One of the authors, G.S., expresses her gratitude to the Council of Scientific and Industrial Research, New Delhi, for a research fellowship.

References and Notes

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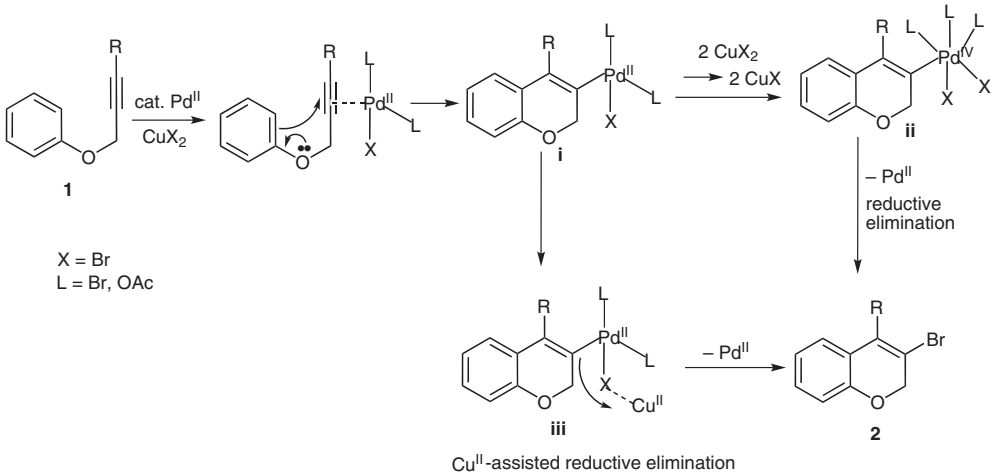

Scheme 5

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(14) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618.
(15) **General Procedure for the Synthesis of 3-Bromo-2*H*-chromene Derivatives 2a–l**
To a stirred mixture of the aryl propargyl ether **1a–l** (1 mmol) in AcOH, $Pd(OAc)_2$ (5 mol%), LiBr (1 mmol), and $CuBr_2$ (2.5 mmol) were added at r.t. The reaction mixture was stirred until completion of the reaction as monitored by TLC. A sat. solution of $NaHCO_3$ was then added to neutralize the reaction mixture, which was then extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhyd Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography on silica gel using hexane as eluent to afford the pure product.
(16) **3-Bromo-4-ethyl-2*H*-chromene (2a, Table 1, Entry 1)**
Colorless oily liquid. IR (KBr): ν_{max} = 3062, 2966, 2851, 2354, 1629, 1467 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, 3 H, *J* = 7.5 Hz), 2.65 (q, 2 H, *J* = 7.5 Hz), 4.86 (s, 2 H), 6.86 (d, 1 H, *J* = 8.0 Hz), 6.95 (t, 1 H, *J* = 7.5 Hz), 7.16 (t, 1 H, *J* = 7.5 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 23.8, 70.8, 112.9, 116.3, 121.9, 122.6, 123.6, 129.1, 134.6, 153.3. ESI-MS: *m/z* = 239 [M^+ + 1], 241 [M^+ + 3]. Anal. Calcd (%) for $C_{11}H_{11}BrO$: C, 55.26; H, 4.65. Found: C, 55.31; H, 4.71.
(17) **3-Bromo-4-ethyl-2*H*-benzo[*h*]chromene (2f, Table 2, Entry 1)**
Colorless oily liquid. IR (KBr): ν_{max} = 3062, 2956, 1738, 1642, 1561, 1466 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.96 (t, 3 H, *J* = 7.7 Hz), 2.75 (q, 2 H, *J* = 7.7 Hz), 5.06 (s, 2 H), 7.38 (d, 1 H, *J* = 8.2 Hz), 7.45–7.49 (m, 3 H), 7.76–7.8 (m, 1 H), 8.17–8.19 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6, 24.1, 71.3, 110.7, 117.3, 121.2, 121.4, 122.2, 124.6, 125.9, 126.8, 127.6, 134.0, 135.3, 149.1. ESI-MS: *m/z* = 289 [M^+ + 1], 291 [M^+ + 3]. Anal. Calcd (%) for $C_{15}H_{13}BrO$: C, 62.30; H, 4.53. Found: C, 62.21; H, 4.65.
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