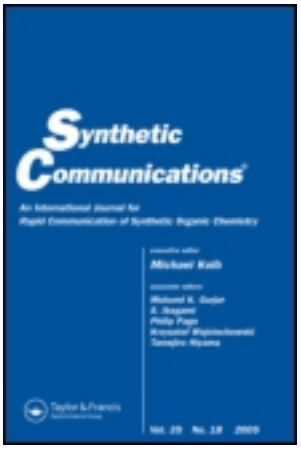

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Intramolecular Heck Reaction on Bromobenzyloxy-Substituted Chromenes: Formation of Chelated Ketones

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INTRAMOLECULAR HECK REACTION ON BROMOBENZYLOXY-SUBSTITUTED CHROMENES: FORMATION OF CHELATED KETONES

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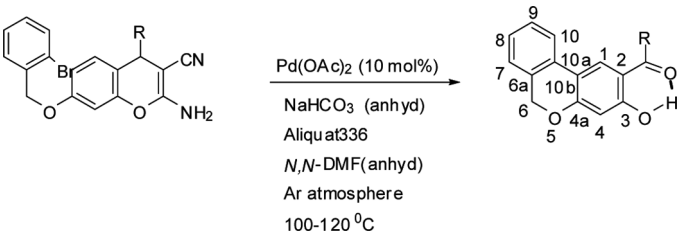
GRAPHICAL ABSTRACT



Abstract *Heck reaction on 2-bromobenzyloxy-substituted 4*H*-chromene derivatives using Pd(OAc)$_2$ in Aliquat 336 and* N,N*-dimethylformamide mixture leads to intramolecular heteroannulation along with hydrolysis, affording chelated 6*H*-benzo[c]chromen-2-yl ketones. The method offers Pd(0)-catalysis and regioselectivity in product formation.*

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Keywords Aliquat 336; chelated ketones; intramolecular Heck cyclization; Pd(0) catalysis

INTRODUCTION

In recent days, ligandless Heck reaction in ionic liquid (IL) catalyzed by simple catalysts such as $PdCl_2$ or $Pd(OAc)_2$ has been widely studied and found to be preparatively significant for the formation of C-C bonds in a variety of organic compounds.[1–10] Its intramolecular version undoubtedly becomes an efficacious methodology for the synthesis of annulated heterocycles. In this context, it is worth noting that though somewhat extensive work has been performed on ligand-demanding intramolecular processes,[11–21] reported data on ligandless intramolecular processes is scanty and still there is much more left to do.[22–25] The intramolecular version of the Heck reaction promoted in ionic liquid is our prime interest for the construction of annulated heterocycles.

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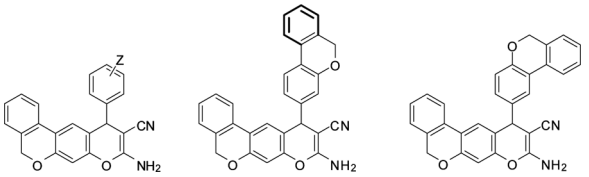


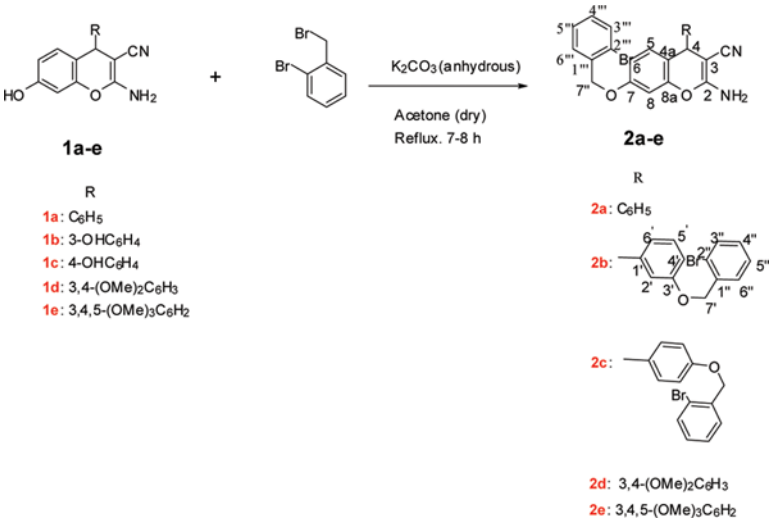
Figure 1. 6*H*-Benzo[*c*]chromene derivatives.

4*H*-Chromene derivatives have been found to exhibit important biological and pharmacological activities.[26–30] With the thought that further heteroannulation may diversify their potential biological and pharmacological behavior, we opted for the synthesis of 6*H*-benzo[*c*]chromene derivatives (Fig. 1). Herein we report the results of our study of Pd(0)-catalyzed ligand-free Heck cyclization on 7-hydroxy-4*H*-chromene derivatives in IL Aliquat 336.[31–36]

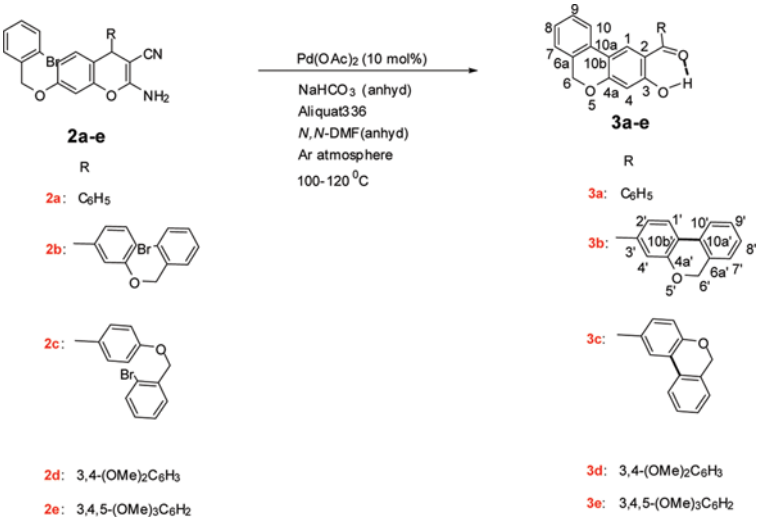
RESULTS AND DISCUSSION

We used newly synthesized 7-(2-bromobenzyloxy)-4*H*-chromene derivatives **2a–e** as starting materials, which were produced via the classical technique by refluxing with 2-bromobenzyl bromide dissolved in anhydrous acetone in the presence of anhydrous K_2CO_3 (Scheme 1).[25]

7-Hydroxy-4*H*-chromene derivatives **1a–e** were synthesized by dimethylaminopyridine (DMAP)–catalyzed condensation of resorcinol, malononitrile, and aromatic aldehydes in water under microwave irradiation. Compounds **2a–e** were susceptible to Pd(0)-catalyzed Heck cyclization when heated with $Pd(OAc)_2$ (10 mol%) along



Scheme 1. Synthesis of 7-(2-bromobenzyloxy)-4*H*-chromene derivatives. (Figure is provided in color online.)

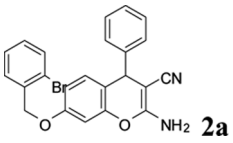
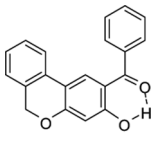
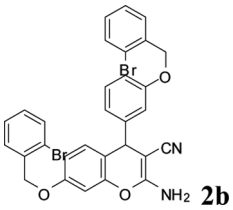
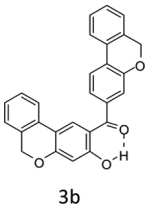
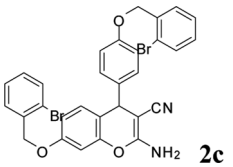
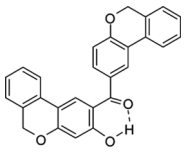
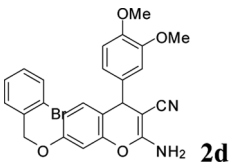
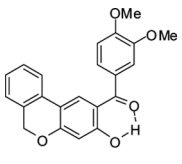
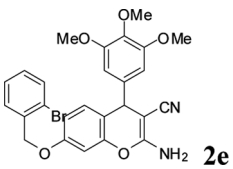
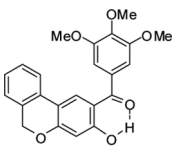


Scheme 2. Intramoleculer Heck cyclization of 7-(2-bromobenzyloxy)-4*H*-chromene derivatives. (Figure is provided in color online.)

with $NaHCO_3$ (anhydrous) and Aliquat 336 (0.12 mmol) in anhydrous *N,N*-dimethyl formamide (30 mL) under stirring in an argon atmosphere for a period of 10–12 h (Scheme 2). The reaction mixture was diluted with water and extracted with dichloromethane. After evaporating the organic layer, actual products were isolated via preparative thin-layer chromatography (TLC) method. It is interesting to find that the final products were not the expected heteroannulated 4*H*-chromene derivatives but instead chelated 6*H*-benzo[*c*]chromen-2-yl ketones **3a–e** in reasonable yield (Table 1). Initial screening of the reaction conditions using substrate **2a** revealed that between $Pd(OAc)_2$ and $PdCl_2$, $Pd(OAc)_2$ was the most suitable catalyst for this reaction. Only 10 (mol%) of this catalyst was sufficient to induce the intramolecular coupling reaction. With $PdCl_2$ as catalyst, no coupling product was produced at all. We have also examined other reaction variables. Various bases, for example, KOAc, NaOAc, and $NaHCO_3$, can be used in this reaction while keeping the reaction media same.

However, the reaction is much cleaner and yield of the product was modest to good (58–75%) in the presence of $NaHCO_3$. With KOAc or NaOAc, the same reaction occurred, affording heteroannulated chelated ketones in 50–55% yield. The reaction rate was temperature dependent. While it took 12 h to yield 70% of **3a** at 80 °C, the reaction time can be shortened (10 h) by raising the reaction temperature to 100 °C without any compromise in product yield. With further increase of temperature, no significant yield improvement of the product was observed. While increasing the reaction temperature seemed to improve the reaction, the temperature range was limited by the boiling point of dimethylformamide (DMF). Thus we chose the optimal reaction temperature to be between 100 and 120 °C. Raising the temperature above 120 °C gave no significant yield improvement of the product. We have studied the effect of increasing Aliquat 336, taking **2a** as substrate. Use of 0.12 mmol of IL is sufficient to bring about a reasonable yield of product.

Table 1. Synthesis of pyrano-fused chelated hydroxy ketones

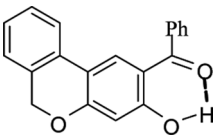
Entry	Substrate **2**	Product **3**	Temp. (°C)	Time (h)	Yield[a] (%)	Mps (obs.) (°C)
1	 **2a**	 **3a**	100	10	70	98
2	 **2b**	 **3b**	110	12	75	176
3	 **2c**	 **3c**	110	12	72	170
4	 **2d**	 **3d**	120	14	58	110
5	 **2e**	 **3e**	120	12	70	158

[a]Yields of pure isolated product.

We also carried out the model study using **2a** with $Pd(OAc)_2$ (10 mol%) and $NaHCO_3$ in different normal solvents [dichloromethane (DCM), MeCN, and *N,N*-DMF] without using IL. In DCM and MeCN, no reaction occurred. In *N,N*-DMF, reaction occurred but the yield of the product **3a** remained very poor (Table 2). We have thus used *N,N*-DMF and Aliquat 336 together as reaction media.

The structures of the newly synthesized compounds received support from extensive NMR studies along with high-resolution mass spectroscopy (HRMS) whereever necessary. The appearance of a singlet signal in the ^1H spectrum of all the compounds in the region above δ 12.0 clearly indicated the presence of chelated

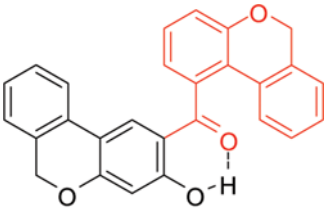
Table 2. Result of different solvents with $NaHCO_3$ as base

Product (**3a**)	DCM	MeCN	*N,N*-DMF[a]	N,N-DMF + IL[a]	Time (h)
	No reaction	No reaction	10%	70%	10

[a]Yields of pure isolated product.

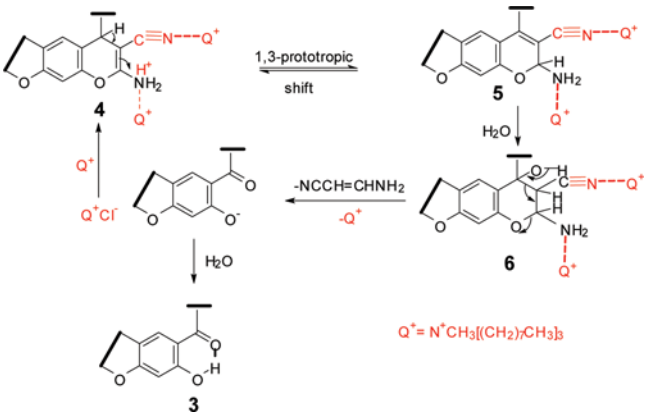
hydroxyl proton. In addition, the presence of a signal in the region ~δ 200.0 for quaternary carbon in the ^{13}C spectrum also supported that it was a chelated hydroxy ketone. Moreover, the presence of two singlets in the ^{1}H spectrum of all the compounds in the regions δ 7.97–8.17 and 6.62–6.94 clearly indicated that the products obtained were linearly fused heterocycles, not its angular analog. Hence, the reaction was regioselective too. The relatively downfield signal was attributed to an aromatic proton *ortho* to the carbonyl, whereas the upfield signal was correlated to the aromatic proton in between two *O*-atoms. In the products **3b** and **3c,** appearance of a *meta* coupled doublet at δ 7.36 ($J = 1.5$ Hz) and 8.17 ($J = 2.1$ Hz), respectively, which are multiple bond correlated with carbonyl carbon signal respectively at δ 199.2 and 199.0, established that intramolecular cyclization in the second aromatic ring is also regioselective. Thus the formation of the other regioisomer for **3b** (Fig. 2) was discarded.

It is noteworthy that this kind of chelation stabilizes the heavily substituted ketones and forces these to be coplanar. The proposed mechanism for this annulation process includes oxidative addition of 7-(2-bromobenzyloxy)-4*H*-chromene derivatives to Pd(0), which were in turn produced in situ by the reduction of the Pd(II) catalyst precursor, forming an aryl-palladium intermediate, which on addition to the double bond produces a σ-allylpalladium intermediate and subsequent β-hydrogen elimination completes the catalytic cycle.[25] The hydrolysis of annulated 4*H*-chromene derivatives to chelated 6*H*-benzo[*c*]chromen-2-yl ketones possibly occurs during workup with DCM-H_2O. This is in contrast to the result of acidic and alkaline hydrolysis of 2-amino-4-aryl-3-cyano-4*H*-benzochromenes to 4-aryl-3-cyano-3,4-dihydrobenzopyran-2-ones.[37] The plausible mechanism (Scheme 3)



(not formed)

Figure 2. Regioisomer of **3b**. (Figure is provided in color online.)



Scheme 3. Plausible mechanism of formation of chelated 6*H*-benzo[*c*]chromen-2-yl ketones from annulated 4*H*-chromene derivatives. (Figure is provided in color online.)

includes a 1,3-prototropic shift of H atom at C-4 of **4**, producing **5**, which on subsequent attack by H_2O molecules generates **6**. The 4-H is acidic because of its dibenzylic-allylic nature and in the presence of aliquat $[Cl^-N^+CH_3[(CH_2)_7CH_3]_3]$ the direction of the 1,3-prototroic shift in **4** can be accounted for if one considers the electrostatic association of Q^+ (quaternaryammonium ion) with the NH_2 group, making the latter less electron donating.[38,39] The driving force for a subsequent step is the good leaving aptitude of $NH_2CH{=}CHCN$ due to the presence of complementary functionalities (NH_2 and CN) and association with quaternaryammonium ions (Q^+), whereby **6** produces chelated hydroxy ketones **3**.

In summary, our effort to heteroannulate 7-(2-bromobenzyloxy)-4*H*-chromene derivatives successfully extended the Pd(0)-catalyzed intramolecular Heck cyclization to the synthesis of a new series of heteroannulated chelated hydroxy ketones. Being ligand-free, this process is much less resource demanding. Yields are modest to good. Moreover, operational simplicity, mildness of reaction condition, and high degree of regioselectivity makes an improved procedure for the preparation of pyrano-fused chelated hydroxy ketones of complex framework.

EXPERIMENTAL

Melting points were recorded on a Toshniwal apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier transform (FT) IR-RXI spectrophotometer using KBr pellets. ^1H (300 MHz), ^{13}C (75 MHz), and 2-D [correlation spectroscopy (COSY), heteronuclear single quantum correlation (HSQC), heteronuclear multiple quantum correlation (HMQC), and heteronuclear multiple bond correlation (HMBC)] NMR spectra were recorded on a Bruker AV 300 Supercon NMR spectrometer in a 5-mm broadband observe (BBO) probe using $CDCl_3$ or dimethylsulfoxide (d_6-DMSO) as solvent. High-resolution mass spectra were taken on a Qtof Micro YA 263 spectrometer.

Compound **3a**: Mp 98 °C; IR (KBr): ν_{max} 3437, 1599, 1492, 1447, 1162, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (2H, s, 6-H_2), 6.64 (1H, s, 4-H),

7.13 (1H, br. d, $J = 7.1$ Hz, 7-H), 7.24 (1H, ddd, $J = 7.4$ Hz, 7.3 Hz, 1.4 Hz, 8-H), 7.30 (1H, ddd, $J = 7.4$ Hz, 7.3 Hz, 1.5 Hz, 9-H), 7.40 (1H, br. d, $J = 7.5$ Hz, 10-H), 7.55 (2H, br. t, $J = 8.5$ Hz, 3′-H, 5′-H), 7.63 (1H, br.t, $J = 8.4$ Hz, 4′-H), 7.72 (2H, br. d, $J = 8.1$ Hz, 2′-H, 6′-H), 7.97 (1H, s, 1-H), 12.47 (1H, s, chelated OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.8 (CH_2, C-6), 105.6 (CH, C-4), 114.7 (C, C-10b), 114.8 (C, C-2), 121.2 (CH, C-10), 124.7 (CH, C-7), 127.4 (CH, C-8), 128.5 (2CH, C-3′, C-5′), 128.8 (CH, C-9), 128.9 (C, C-10a), 129.0 (CH, C-1), 129.1 (2CH, C-2′, C-6′), 129.7 (C, C-6a), 131.8 (CH, C-4′), 138.3 (C, C-1′), 161.7 (C, C-4a), 165.6 (C, C-3), 200.3 (C, C=O). HRMS: m/z, M^+H (%), Found: 303.1011 (90). Calcd. for $C_{20}H_{15}O_3$: 303.1021.

SUPPLEMENTARY DATA

Experimental details; spectral data; copies of ^{1}H, ^{13}C, and 2-D (COSY, HSQC, and HMBC) NMR spectra; and copies of HRMS are incorporated in the Supplementary Data file available online.

ACKNOWLEDGMENTS

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