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Three-step synthesis of substituted isochromenes

Chieh-Kai Chan, Yi-Ling Chan, Meng-Yang Chang*

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan, ROC

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ABSTRACT

A synthetic route toward isochromenes **6**, starting with aldehydes **3**, in good to excellent yield is described herein. This novel approach was carried out by the Henry reaction of **3** with NH_4OAc and nitroalkanes (MeNO_2 or EtNO_2), aerobic Wacker-type oxidation of the resulting nitroalkenes **4**, followed by K_2CO_3 -promoted intramolecular Michael cyclization in modest to good yields.

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1. Introduction

Isochromenes are significant classes of heterocyclic compounds, owing to some natural products and bioactive compound structures containing meaningful moiety.¹ For example, pyranonaphthoquinone exhibits pharmaceutical activity: the carboxamides analog, BCH-2051 (**1**), acts an anticancer agent in its ability to fight cancer cell line SKOV3 and methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate (**2**) displays a moderate antitumor function.² It is noteworthy that, the ubiquitous core skeleton, oxygen-/nitrogen-containing hetero-cycles, has appeared in pharmaceutically important compounds and has also drawn a lot of attention (see Fig. 1).³

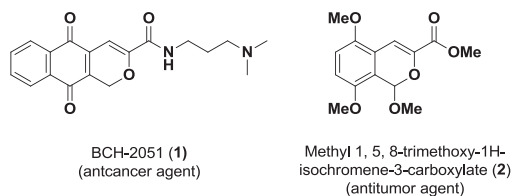


Fig. 1. Bioactive isochromene derivatives.

Many excellent organic chemists are committed to the development of efficient and facile ways to synthesize isochromene and its derivatives.⁴ For example, many procedures for the synthetic isochromene cyclization reaction have been applied using the metal-catalyzed method.^{4a–d} Transition metal-catalyzed cyclization has also been a ubiquitous method, such as the representative Pd(II) Heck reaction,⁵ cycloisomerization of Au(I)^{3b,4e,4k} or Pd(II)^{4f} catalyzed, Os-catalyzed,⁶ Ru(II)-catalyzed,⁷ complex with a tetradentate N–P mixed ligand,⁸ Ir pincer complexes-catalyzed,⁹ or Rh(III)-catalyzed oxidative coupling.¹⁰

Nitromethyl isochromenes have also drawn attention recently. In 2011, copper(II)-catalyzed Henry reaction and gold(I)-mediated cycloisomerization were utilized by Gong's group to produce nitromethyl isochromenes.^{4e} Kundu and co-workers developed a domino reaction to obtain the desired isochromenes.⁴ⁱ

2. Results and discussions

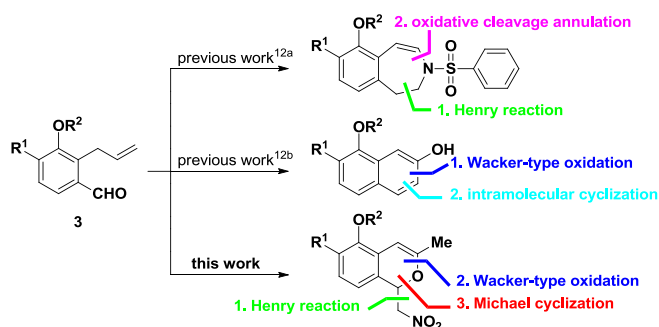
Recently, we have become interested in the development of new synthetic routes for the construction of a benzofused bicyclic system derived from the versatile 2-allylbenzaldehyde **3** including benzazepines and 2-naphthols, as shown in Scheme 1.¹¹ The starting skeleton **3** was easily provided by commercially available isovanillin in moderate overall three-step yields with a reaction sequence of O-allylation and a Claisen rearrangement followed by O-alkylation. In 2012, we studied the treatment of **3** via Henry reaction, reduction and oxidative cleavage annulation providing tetrahydro-3-benzazepine analogs.^{12a} Furthermore, we examined the treatment of **3** by Wacker-type oxidation and intramolecular aldol cyclization which afforded 2-naphthols derivatives in 2013.^{12b}

* Corresponding author. Tel.: +866 7 312 1101x2220; e-mail address: mychang@cc.kmu.edu.tw (M.-Y. Chang).

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Following the experience of our previous work,¹² we aim to develop a facile synthetic route for isochromene based on skeleton **3** by the above synthetic routes (Henry reaction, Wacker-type oxidation and Michael cyclization).



Scheme 1. Synthetic applications of **3**.

Initially, **3a** ($R^1=OMe$, $R^2=Me$) was selected as the model substrate to conduct the Henry reaction to afford **4a** and then, to explore the oxidation conditions. Wacker-type oxidation was also employed to promote the allyl group into methylketone **5a**. In this case, there may be a nitrovinyl group besides the allyl group that enhances the difficulty of the oxidation on the allyl group. Hence, we wanted to examine the catalytic oxidation condition. Some Pd(II) catalysts were tried, such as, PdCl₂, Pd(OAc)₂, PdBr₂, PdCl₂(MeCN)₂, PdCl₂(PPh₃)₂ and Pd₂(dba)₃, as shown in Table 1. As a result, Wacker-type oxidation in this case was not easy under our previous conditions.^{12b} So, **4a** was chosen as the model substrate to try other conditions, such as catalysts, equivalents of CuCl₂ and oxidants. When the catalyst (PdCl₂) and some oxidants (DDQ or CAN) were selected, only 20% and 18% (entries 1–2) and some unknown products were obtained. When the reaction was conducted under air or O₂, the desired **5a** was isolated in 62–87%, and trace amounts of unknown products were isolated under different equivalents of PdCl₂ and CuCl₂ (entries 3–6). When the equivalents of CuCl₂ and PdCl₂ were reduced, **5a** was isolated in 72% and **4a** was also recovered in 5% (entry 7). Besides PdCl₂ being tested, some other Pd(II) catalysts, including Pd(OAc)₂, PdBr₂, PdCl₂(MeCN)₂, PdCl₂(PPh₃)₂, Pd₂(dba)₃ were tested under an O₂ environment, and

the yields were between 70 and 84% (entries 8–12). We have learned that this oxidation step, PdCl₂ (6.5%), CuCl₂ (1.5 equiv) in an oxygen environment is the best condition for this process.

As far as we know, the Michael addition displayed a very common reaction for cyclization.¹³ Considering the characteristics of skeleton **5**, a cyclization reaction may be the required task. Furthermore, cyclization of **5** was our goal. In 2012, Fu and co-workers published a report on K₂CO₃-catalyzed cyclization to synthesize chromones and 4-quinolones.¹⁴ Moreover, the base-promoted Michael cyclization was adopted first in this step. **5a** was employed as the model substrate to test the conditions with different bases such as K₂CO₃, Cs₂CO₃, Na₂CO₃, NaHCO₃ and Et₃N, following this protocol. K₂CO₃ was first tested with the equivalent of 3.5 in acetone at room temperature, showing only a 65% isolated yield and 15% of the starting material was recovered (entry 1). Increasing the reaction temperature to 56 °C, the yield of product **6a** was upgraded to 68% (entry 2). In entry 3, the solvent was changed to THF and the yield reached 72% at room temperature. This phenomenon can be attributed to the fact that solvent was an important factor, therefore, THF was more suitable than acetone. When the equivalent of K₂CO₃ was increased to 4.7, the yield was better than 6.2 in 66 °C reaching 87% (entries 4 and 5). On the basis of these conditions, M₂CO₃ (M=Cs, Na) was examined, perhaps the metal radius of Cs was greater than K, causing the yields of the desired product was not excellent and an unknown product was isolated (entries 6 and 7). Intriguingly, changing the smaller radius of metal like Na₂CO₃, the reaction took a longer time with no good yields (entry 8). NaHCO₃ and Et₃N were also not suitable for this strategy, they not only required a long time but also unknown products appeared (entries 9 and 10). Overviewing the scope of the various bases in THF by different equivalents, we learned that the K₂CO₃ was the best one in this base-mediated strategy (see Table 2).

We next explored the scope and generality of the Henry reaction, Wacker-type oxidation and K₂CO₃-mediated cyclization with the optimized reaction conditions in hand. As shown in Table 3, various substituents (methyl, butyl, cyclopentyl, benzyl or isopropyl) on the R¹ position of **4a–j** were obtained in moderate yields (78–85%) via the Henry reaction. The R¹ position of **5a–e** was a methoxy group, **5f–j** was a hydrogen atom, and all of their isolated yields were between 79 and 87%. Base-mediated cyclization was conducted smoothly, and the desired products were all in good to excellent performance. Entries 1–5, R¹ was an OMe group, R² bearing methyl, butyl, cyclopentyl, benzyl and isopropyl groups,

Table 1
Reaction conditions of **4a**^a

Entry	catalyst (mol %), CuCl ₂ (equiv), oxidants (equiv)	Yield (%) ^b
1	PdCl ₂ (5.1), CuCl ₂ (1.5), DDQ (1.0)	20 ^c
2	PdCl ₂ (5.1), CuCl ₂ (1.5), CAN (1.0)	18 ^c
3	PdCl ₂ (5.1), CuCl ₂ (1.5), air	62 ^d
4	PdCl ₂ (5.1), CuCl ₂ (1.5), O ₂	78 ^d
5	PdCl ₂ (6.5), CuCl ₂ (1.5), O ₂	87 ^d
6	PdCl ₂ (8.2), CuCl ₂ (1.5), O ₂	80 ^d
7	PdCl ₂ (4.3), CuCl ₂ (1.5), O ₂	72 ^e
8	Pd(OAc) ₂ (6.5), CuCl ₂ (1.5), O ₂	76 ^d
9	PdBr ₂ (6.5), CuCl ₂ (1.5), O ₂	70 ^d
10	PdCl ₂ (MeCN) ₂ (6.5), CuCl ₂ (1.5), O ₂	71 ^d
11	PdCl ₂ (PPh ₃) ₂ (6.5), CuCl ₂ (1.5), O ₂	83 ^d
12	Pd ₂ (dba) ₃ (6.5), CuCl ₂ (1.5), O ₂	84 ^d

^a The reactions were conducted on a 1.0 mmol scale with **4a**.

^b **5a** was >95% pure as determined by ¹H NMR analysis.

^c Unknown products were obtained (entry 1, 5%, entry 2, 6%).

^d Trace amounts (<5%) of unknown products were obtained.

^e **4a** was recovered by 15%.

Table 2
Base-mediated cyclization of **5a**^a

Entry	Base (equiv), solvents, time (h), temp (°C)	Yield (%) ^b
1	K ₂ CO ₃ (3.5), acetone, 2, 25	65 ^{c,d}
2	K ₂ CO ₃ (3.5), acetone, 2, 56	68 ^c
3	K ₂ CO ₃ (3.5), THF, 2, 25	72 ^{c,d}
4	K ₂ CO ₃ (4.7), THF, 2, 66	87 ^c
5	K ₂ CO ₃ (6.2), THF, 2, 66	80 ^c
6	Cs ₂ CO ₃ (3.5), THF, 3, 66	25 ^e
7	Cs ₂ CO ₃ (4.7), THF, 2, 66	20 ^e
8	Na ₂ CO ₃ (4.7), THF, 30, 66	53 ^d
9	NaHCO ₃ (4.7), THF, 70, 66	25
10	Et ₃ N (4.7), THF, 4, 66	25

^a The reactions were conducted on a 1.0 mmol scale with **5a**.

^b **6a** was >95% pure as determined by ¹H NMR analysis.

^c Trace amounts (<5%) of unknown products were obtained.

^d **5a** was recovered (entry 1, 15%; entry 3, 10%).

^e Unknown products were obtained (entry 6, 5%; entry 7, 4%).

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