Tetrahedron 74 (2018) 1486–1491

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal cycloaddition of ethyl 2-aroyl-1-chlorocyclopropanecarboxylates:facile synthesis of diversified tetrahydrocyclopropa[*b*]chromenes

Guoxi Xiong [a, b], Yong Liao [b], Xue-Hui Liu [b], Xiangying Tang [b, *], Yuefa Gong [b, **]

[a] Technology Center of China Tabacco, Hubei Industrial Co. Ltd, Wuhan, 430040, People's Republic of China
[b] School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan 430074, People's Republic of China

ARTICLE INFO

Article history:
Received 1 December 2017
Received in revised form
31 January 2018
Accepted 2 February 2018
Available online 9 February 2018

Keywords:
Cycloaddition
Chromenes
Cyclopropenes
Cyclopropanation
Heterocycles

ABSTRACT

Tandem reaction of ortho-hydroxy chalcone with ethyl 2-aroyl-1-chlorocyclopropanecarboxylates has been disclosed, affording facile synthesis of diversified tetrahydrocyclopropa[*b*]chromenes via electron-deficient cyclopropene intermediate.

© 2018 Elsevier Ltd. All rights reserved.

1. Introduction

Cyclopropenes are highly strained but useful building blocks in organic synthesis.[1] During the last decades, the investigation of cyclopropenes has attracted much attention due to their wide range of reactivities beyond those of olefins, allenes and alkynes.[2] In general, electron-rich cyclopropenes are used as excellent ð–donators which can coordinate with many transition metal catalysts as well as Brønsted acids or Lewis acids. For example, In 2010, Wang and coworkers reported a novel gold catalyzed rearrangement of 1,5-cyclopropene-ynes to afford benzene derivatives.[2f] Shi and coworkers also found that nitrogen or carbon-tethered indolylcyclopropenes could undergo novel intramolecular cycloisomerizations of to furnish biologically and pharmaceutically valuable heterocycles catalyzed by gold- and silver-catalysts or HOTf.[3] However, to our great surprise, the chemistry of electron-deficient cyclopropenes remain largely unexplored, mainly because such molecules are difficult to be activated by metal or acid catalysts and very limited types of such cyclopropenes were reported probably due to their instability.

Polyfunctionalized chromenes are found in many natural scaffolds and drug candidates displaying a broad range of biological and pharmacological activities. In particular, cyclopropane fused chromenes are of great importance, because they are not only served as potential drug candidates in drug discovery, but also are important intermediates in the synthesis of diversified heterocycles. For example, N-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1a-carboxamide (PHCCC), which acts as a glutamate receptor ligand, has been suggested as novel treatments for Parkinson's disease.[4,5] Another related drug molecule, namely CPCCPEt, is used mainly in basic research as a non-competitive antagonist at the metabotropic glutamate receptor subtype mGluR1 (Fig. 1).[6]

Meanwhile, it is reported that transformation of such cyclopropane containing substance into other useful heterocyclic have also been achieved.[7] Traditionally, cyclopropane fused chromenes can be constructed by Michael-initiated ring-closure of methyl ketones with 3-bromochromones (Scheme 1a),[8] or treatment of electron-deficient chromenes with sulfur ylides under basic conditions (Scheme 1b),[9] and also by cyclopropanation of chromenes with carbenoids (Scheme 1c).[10] However, in a sharp contrast, beyond cyclopropanation of chromenes, other methods to access

* Corresponding author.
** Corresponding author.
E-mail addresses: xytang@hust.edu.cn (X. Tang), gongyf@hust.edu.cn (Y. Gong).

https://doi.org/10.1016/j.tet.2018.02.010
0040-4020/© 2018 Elsevier Ltd. All rights reserved.

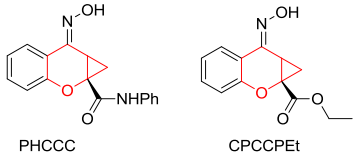
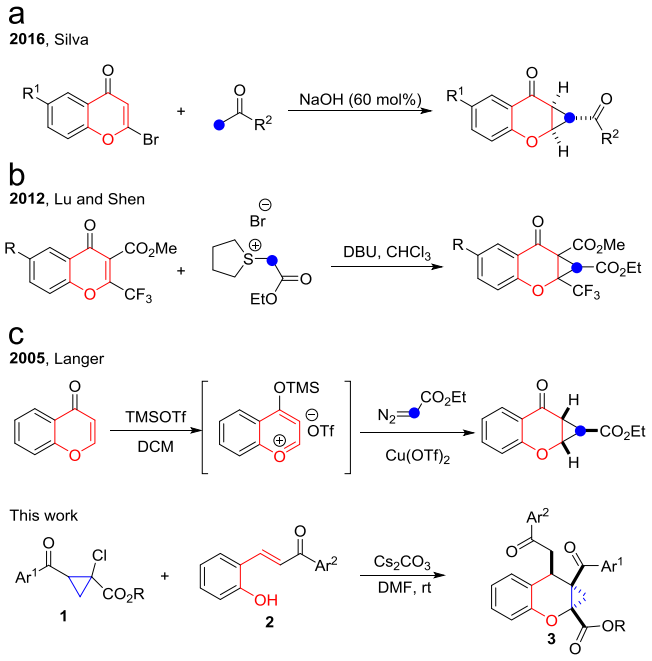


Fig. 1. Bioactive cyclopropane fused chromenes.



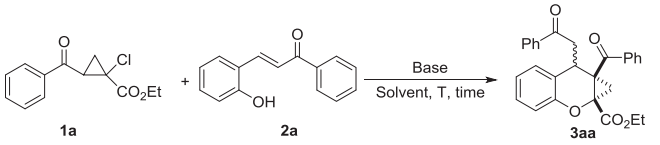
Scheme 1. Reported method to construct cyclopropane-fused chromenes and our method.

cyclopropane fused chromenes are extremely limited. In view of the current circumstances, and also to continue our research interest in electron-deficient cyclopropenes,[11] we envisage that a formal [4 + 2] cycloaddition reaction can take place between ethyl 2-aroyl-1-chlorocyclopropanecarboxylates **1** and (*E*)-3-(2-hydroxyaryl)-1-arylprop-2-en-1-ones **2**, affording the desired cyclopropylchromenes **3**.

2. Result and discussion

Our initial investigation started with the optimization of the reaction conditions using **1a** and **2a** as the model substrates. To our delight, treatment of **1a** and **2a** with Cs_2CO_3 in DMSO (dimethyl sulfoxide) at 25 °C (room temperature) for 6 h, the reaction went on smoothly to give the desired product **3aa** in 56% yield, along with good diastereoselectivity (3.4:1) as determined by crude ^{1}H NMR (Table 1, entry 1). After careful separation of the diastereoisomers by silica gel chromatography and subjected to the 2D NOESY, the major product was determined as *cis* configuration (for details, see Supporting Information). When another highly polar solvent, DMF (N,N-dimethylformamide) was used in replace of DMSO, the yield of **3aa** increased to 88% with a 3.5:1 dr value (Table 1, entry 2). Further solvent effect study revealed that DMF was the best solvent for this transformation (Table 1, entries 3–8). It is worth nothing that the polarity of the solvents plays an important role to control the diastereoselectivity: high polar solvents favor *cis* products, while non-polar solvents have opposite selectivity. Next, using DMF

Table 1
Optimization of the reaction conditions.



entry[a]	base	solvent	T (°C)	t (h)	Yield (%)[b] (*cis*: *trans*)[c]
1	Cs_2CO_3	DMSO	25	6	56 (3.4:1)
2	Cs_2CO_3	DMF	25	6	88 (3.5:1)
3	Cs_2CO_3	CH_3CN	60	12	83 (4:1)
4	Cs_2CO_3	1,4-dioxane	60	12	68 (1:2.3)
5	Cs_2CO_3	THF	25	12	77 (2.5:1)
6	Cs_2CO_3	CH_2Cl_2	25	12	73 (1.1:1)
7	Cs_2CO_3	Toluene	60	12	61 (1:2.5)
8	Cs_2CO_3	1,2-DCE	25	12	57 (1:1)
9	K_2CO_3	DMF	25	24	49 (3.7:1)
10	K_3PO_4	DMF	25	24	78 (3.7:1)
11	KOH	DMF	25	12	30 (2.9:1)
12	LiOH	DMF	25	12	51 (2.8:1)
13	$Mg(OEt)_2$	DMF	80	24	48 (2:1)
14	Et_3N	DMF	25	24	ND
15	DBU	DMF	25	24	<5
16	Cs_2CO_3[d]	DMF	25	24	81 (3:1)
17	Cs_2CO_3[e]	DMF	25	6	85 (3:1)
18	Cs_2CO_3[f]	DMF	25	6	56 (2.9:1)

DMSO = Dimethyl sulfoxide, DMF = Dimethylformamide, THF = tetrahydrofuran, 1,2-DCE = 1,2-dichlorethane.
[a] Reaction conditions: 0.2 mmol (1.0 eq.) of **1a**, 0.2 mmol (1.0 eq.) of **2a**, and 0.4 mmol (2.0 eq.) of base in 2.0 mL of solvent at the specified temperature for the given time.
[b] Isolated total yields of the diastereomers.
[c] Determined by ^{1}H NMR of crude **3aa**.
[d] 0.2 mmol of base (1.0 eq.).
[e] 0.3 mmol of base (1.5 eq.).
[f] 0.5 mmol of base (2.5 eq.).

as the solvent, the effect of different bases was evaluated. When K_2CO_3 and K_3PO_4 were used, the reactions were less effective than Cs_2CO_3, giving the corresponding products in 49% and 78% yields, respectively (Table 1, entries 9–10). For strong base KOH, the yield of **3aa** dropped to 30%, probably due to that the cyclopropene intermediate is formed too fast and undergoes self-polymerization during the reaction process (Table 1, entry 11). Similar results were obtained in the cases of LiOH and $Mg(OEt)_2$ (Table 1, entries 12–13). In addition, because of the nuclephilicity of the nitrogen atom, organic bases such as Et_3N and DBU were found not suitable for this reaction (Table 1, entries 14–15). Based on the above results, we then understood that the base shouldn't be too strong or weak, because the formation of cyclopropene intermediate and deprotonation of the phenol should be kinetically compatible, or cyclopropene intermediate will proceed with polymerization reactions. Therefore, Cs_2CO_3 was chosen as the best base. Further study about the loadings of Cs_2CO_3 revealed that the 2 eq. gave the highest yield as well as diastereoselectivity (Table 1, entries 2 and 16–18).

With the best reaction conditions in hand, we next turned our interest to study the generality of this reaction. As can be seen from Table 2, the reactions of **2a** with various **1b**-**1g** all went smoothly to give the corresponding products in moderate to good yields and moderate diastereoselectivities with no significant electronic effect (Table 2, entries 1–6). In case of 2-thiophenyl group substituted substrate **1f**, lower yield of **3fa** was obtained probably because of the steric hindrance (Table 2, entry 5). Next, taking **1a** as a model substrate, different *ortho*-hydroxy chalcones **2** were investigated. As for substrates **2b** and **2c**, the reactions delivered the desired

Download English Version:

https://daneshyari.com/en/article/7827474

Download Persian Version:

https://daneshyari.com/article/7827474

Daneshyari.com