Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Enantioselective synthesis of functionalized 2-amino-4*H*-chromenes via the *o*-quinone methides generated from 2-(1-tosylalkyl)phenols

Bo Wu [a], Xiang Gao [a], Zhong Yan [a], Wen-Xue Huang [a], Yong-Gui Zhou [a,b,*]

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 20 April 2015
Revised 19 May 2015
Accepted 21 May 2015
Available online xxxx

Keywords:
2-Amino-4*H*-chromenes
o-Quinone methides
2-(1-Tosylalkyl)phenols

ABSTRACT

An efficient bifunctional squaramide-catalyzed Michael addition/cyclization reaction of *o*-quinone methides generated in situ from 2-(1-tosylalkyl)phenols with active methylene compounds bearing a cyano group has been realized to synthesize chiral 2-amino-4*H*-chromenes with excellent enantioselectivities and broad substrate scope.

Chromenes occupy a prominent position in modern hetero-cyclic chemistry attributing to their extraordinary significance in biologically active molecules, natural products, and synthetic drugs.[1] Among the diverse types of chromenes, 2-amino-4*H*-chromenes are recognized to be particularly important as they belong to 'privileged medicinal scaffolds'.[2] For instance, the tumor antagonist HA14-1 and related substituted alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of cancer implicated Bcl-2 protein and induce apoptosis or programmed cell death in tumor cells.[2f] Crolibulin (EPC2407) is a microtubulin inhibitor currently in phase I/II clinical trials as anticancer agent and apoptosis inducer for the treatment of anaplastic thyroid cancer.[2j] IRSP inhibitor acts as an insulin-regulated aminopeptidase inhibitor which is useful in therapeutic application including enhancing memory and learning functions[2k] (Fig. 1). Due to the remarkable importance of 2-amino-4*H*-chromene frameworks, their syntheses are of contemporary interest. Despite various methods for the construction of racemic 2-amino-4*H*-chromenes been reported,[3] asymmetric syntheses of these structures are still limited. In 2008, Zhao group disclosed the first asymmetric synthesis of 2-amino-4*H*-chromenes by bifunctional thiourea catalyzed tandem addition/cyclization reactions of 2-naphthols and α,α-dicyanoolefins with moderate enantioselectivities.[4a] Subsequently, several organocatalytic syntheses of chiral 2-amino-4*H*-chromenes have been developed, including tandem Michael addition/cyclization,[4] Mannich cyclization/tautomerization cascade sequences,[5] three-component cascade reaction,[6] and conjugate addition of nitroalkanes to 2-iminochro-menes.[7] In these organocatalytic strategies, cinchona derivatives, bifunctional thiourea and squaramide were found to be efficient catalysts. In contrast, only two examples of metal complex catalyzed asymmetric synthesis have emerged in recent years. In 2011, Feng group reported enantioselective construction of 2-amino-4*H*-chromenes using salen–cobalt(II) complex or *N*,*N*′-dioxide-Zn(II) complex.[8] In spite of these considerable advances, there are still some drawbacks involving low catalytic efficacy, poor stereoselectivity, and unsatisfactory substrate scope. Hence, developing a facile method for the synthesis of chiral 2-amino-4*H*-chromenes with high enantioselectivities and broad substrate scope is still highly desirable.

o-Quinone methides (*o*-QMs) are a crucial class of intermediates in various biological processes[9] and have been regarded as highly reactive chemical motifs.[10] Despite the wide application of *o*-QMs, only few organocatalytic enantioselective settings of *o*-QMs have been reported owing to their high reactivity and instability.[11] Organocatalytic formal [4+2] cycloaddition of *o*-QMs with active methylene compounds bearing the cyano group is also a streamlined method for the synthesis of optically active 2-amino-4*H*-chromenes. Recently, Han group reported quinine-catalyzed annulation of the electron-rich and stable *o*-QMs with malononitrile to provide 4-arylvinyl, 4-aryl, and 4-vinyl 2-amino-3-cyano-4*H*-chromenes with excellent yields and enantioselectivities. However, the substrate scope was limited.[11u] As our continuing efforts to the employment of *o*-QMs,[11r,12] we focused on bifunctional organocatalytic reactions of *in situ* generated *o*-QMs. In our

* Corresponding author. Tel./fax: +86 411 84379220.
E-mail address: ygzhou@dicp.ac.cn (Y.-G. Zhou).

http://dx.doi.org/10.1016/j.tetlet.2015.05.076
0040-4039/

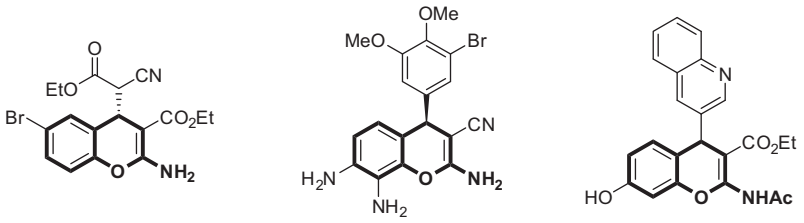
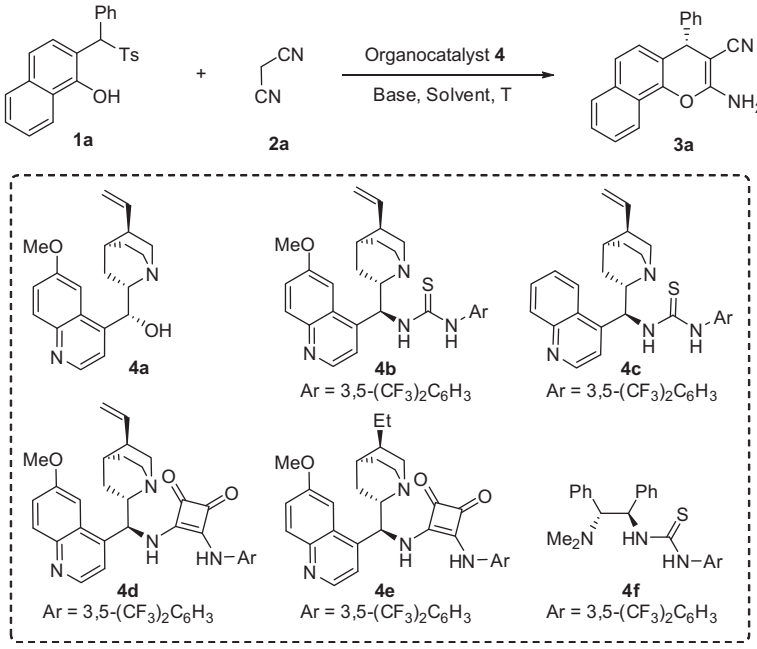


Figure 1. Bioactive 2-amino-4*H*-chromene derivatives.

Table 1
Condition Optimization[a]



Entry	Cat.	Base	Solvent	*t* (h)	Yield[b] (%)	Ee[c] (%)
1	—	K_2CO_3	PhMe	2	80	—
2	—	Na_2CO_3	PhMe	2	Trace	—
3	**4a**	Na_2CO_3	PhMe	24	83	56
4	**4b**	Na_2CO_3	PhMe	24	80	94
5	**4c**	Na_2CO_3	PhMe	24	87	95
6	**4d**	Na_2CO_3	PhMe	72	80	97
7	**4e**	Na_2CO_3	PhMe	24	83	97
8	**4f**	Na_2CO_3	PhMe	24	83	−95
9	**4e**	K_2CO_3	PhMe	4	83	67
10	**4e**	$NaHCO_3$	PhMe	24	Trace	—
11	**4e**	Na_2CO_3	DCM	24	93	93
12	**4e**	Na_2CO_3	THF	24	90	24
13	**4e**	Na_2CO_3	*p*-Xylene	24	97	96
14[d]	**4e**	Na_2CO_3	*p*-Xylene	6	97	97
15[e]	**4e**	Na_2CO_3	*p*-Xylene	4	97	96
16[f]	**4e**	Na_2CO_3	*p*-Xylene	1	43	96

[a] **1a** (0.10 mmol), **2a** (0.12 mmol), cat. (0.01 mmol), base (0.12 mmol), solvent (1.5 mL), 25 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] 40 °C.
[e] 60 °C.
[f] 80 °C.

previous work, we reported the thiourea catalyzed enantioselective amination of *o*-QMs with aqueous ammonia in 33% ee.[12d] Low enantioselectivity possibly attributes to the fact that the *o*-QMs generated in situ from 2-(1-tosylalkyl)phenols under basic conditions may furnish racemic products as a result of an obvious background reaction. Considering active methylene compounds bearing the cyano group had been broadly employed as nucleophilic reagents in asymmetric organocatalytic additions,[13]