Tetrahedron Letters 59 (2018) 2748–2751

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Metal-free synthesis of 1,2-amino alcohols by one-pot olefin aziridination and acid ring-opening

Yong-Gang Hua [a], Qian-Qian Yang [a], Yi Yang [a], Mei-Jing Wang [a], Wen-Chao Chu [a], Peng-Yan Bai [a], De-Yun Cui [a], En Zhang [a,b,*], Hong-Min Liu [a,b,*]

[a] School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou 450001, PR China
[b] Collaborative Innovation Center of New Drug Research and Safety Evaluation, Henan Province, Zhengzhou 450001, PR China

ARTICLE INFO

Article history:
Received 1 March 2018
Revised 28 May 2018
Accepted 1 June 2018
Available online 6 June 2018

Keywords:
One-pot reaction
Olefin aziridination
Ring-opening of aziridines
1,2-amino alcohols

ABSTRACT

A one-pot, two-step reaction comprising olefin aziridination and ring-opening of an aziridine intermediate to synthesize 1,2-amino alcohols has been developed. This reaction is suitable for several types of olefin. This methodology allows an efficient and highly stereoselective approach to various 1,2-amino alcohols, readily providing an alternative route to conventional vicinal amino alcohols.

Introduction

1,2-Amino alcohols are important structural features [1] and are ubiquitous in natural products and therapeutic agents possessing a wide variety of biological activities, as well as in chiral ligands and auxiliaries for asymmetric synthesis [2–4]. The hormones epinephrine and norepinephrine [5] are well known amino alcohols (Fig. 1). The α-glucosidase inhibitor miglitol is an approved oral anti-diabetic drug [6]. Metoprolol is a β1 receptor blocker used for the treatment of a number of cardiovascular conditions [7]. Jaspine B, also known as pachastrissamine, is a naturally-occurring novel anhydrosphin-gosine derivative that was isolated from a marine sponge, and is cytotoxic against P388, A549, HT29, and Mell 28 cell lines at an IC_{50} level of 0.01 μg/mL [8,9]. For this reason, much effort has been devoted to the development of new effective methods for the enantioselective synthesis of β-amino alcohols [1]. A variety of powerful procedures has been reported [10–14], including the ring opening of aziridines [15–19].

Aziridines [20] are present in a wide range of biologically active molecules and natural products [21,22], and represent one of the most valuable three-membered ring systems in modern synthetic chemistry. Aziridines are widely recognized as important versatile building blocks for chemical bond elaborations and functional group transformations [23–28]. Numerous olefin aziridination methods involve the use of metal salts or complexes as catalysts [29–34]. From both environmental and economical viewpoints, electrochemical aziridination has been reported, and *N*-aminophthalimide has been used for synthesis of aziridine [35–37]. Moreover, $PhI(OAc)_2$- and aryl iodide-mediated aziridination of

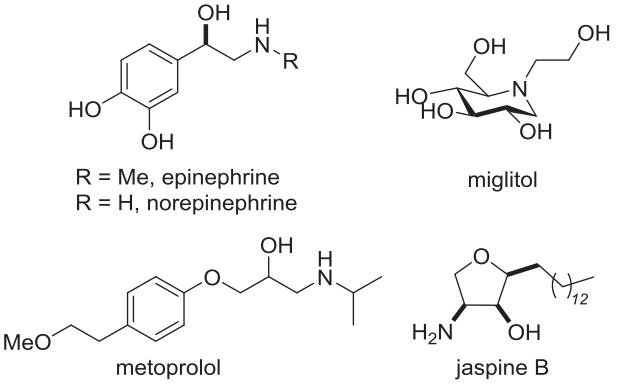
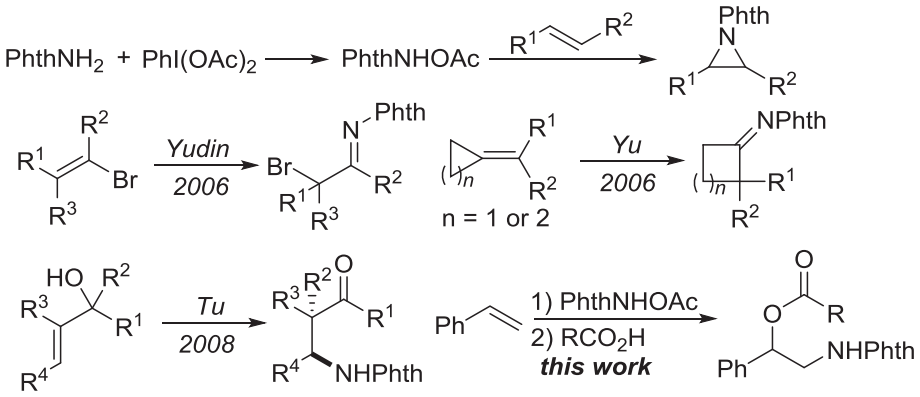


Fig. 1. Molecules with 1,2-amino alcohol substructures.

* Corresponding authors at: School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou 450001, PR China.

E-mail addresses: zhangen@zzu.edu.cn (E. Zhang), liuhm@zzu.edu.cn (H.-M. Liu).

https://doi.org/10.1016/j.tetlet.2018.06.002
0040-4039/



Scheme 1. Nitrene equivalent-mediated reactions of alkenes.

alkenes has been described for metal-free catalyzed C—N bond forming reactions [38–40]. Nitrene equivalent-mediated reactions of alkenyl bromides, alkylidenecy-clopropanes, and allylic alcohols are shown in Scheme 1. [41–43] To the best of our knowledge, there has been no reports on the ring-opening reaction of *N*-phthalimide aziridines with acid as a one-pot reaction (Scheme 1).

Multicomponent reactions (MCRs) are an effective strategy to improve the efficiency of a chemical reaction by avoiding lengthy separation processes and purification of intermediates [44,45]. Many powerful MCRs have been developed and applied to the synthesis of active pharmaceutical ingredients [46].

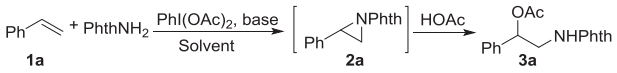
We wish to highlight our results on an MCR involving olefin aziridination and ring-opening of *N*-phthalimide aziridines with various carboxylic acids from our continued efforts to establish novel 1,2-amino alcohol derivatives with good biological activity [47–49] and tandem reaction with olefins [43]. This work is an extension of Che's work (Scheme 1). Different types of olefins and carboxylic acids gave the desired products using this method.

Results and discussion

Our investigations began with a one-pot olefin aziridination, followed by ring-opening with H_2O [16]. In the process, the expected 1,2-amino alcohol **5** and a small amount of unexpected product **3a** were isolated (Scheme 2). Different reaction conditions were screened to improve the yield of **3a**.

Styrene was used as the model substrate, and initial studies revealed that without any base, the reaction yield increased with increasing amounts of *N*-aminophthalimide ($PhthNH_2$) and PhI $(OAc)_2$ (Table 1, entries 1–4). When using a larger dosage of $PhthNH_2$ and $PhI(OAc)_2$, a base was used to improve the reaction yield. K_2CO_3 was selected as the base giving a decrease of both PhthNH2 and $PhI(OAc)_2$ (Table 1, entries 5–7). Treatment of styrene (1 equiv) with 1.4 equiv of $PhthNH_2$, 1.5 equiv of $PhI(OAc)_2$, and 2.8 equiv of K_2CO_3 produced the β-amino ester 3a in 65% yield

Table 1
Optimization of the reaction conditions.

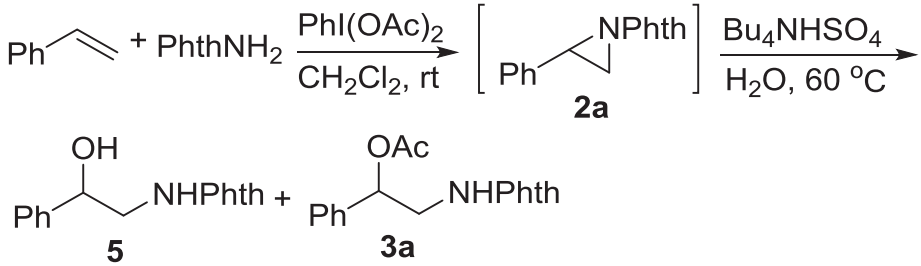


Entry	Solvent	Base	Equiv.[a]	Yield (%)[b]
1	CH_2Cl_2	–	1/1.4/1.5	50
2	CH_2Cl_2	–	1/2/1.5	50
3	CH_2Cl_2	–	1/2/2.2	59
4	CH_2Cl_2	–	1/2.5/2.5	67
5	CH_2Cl_2	K_2CO_3	1/2/1.5/2.8	54
6	CH_2Cl_2	K_2CO_3	1/2/2/4	55
7	CH_2Cl_2	K_2CO_3	1/2.5/2.5/5	65
8	CH_2Cl_2	K_2CO_3	1/1.4/1.5/2.8	65
9[c]	CH_2Cl_2	K_2CO_3	1/1.4/1.5/2.8	57
10	Toluene	K_2CO_3	1/1.4/1.5/2.8	60

[a] All reactions were performed at room temperature for 12 h with styrene (1 mmol)/$PhI(OAc)_2$/*N*-aminophthalimide/base molar ratio.
[b] Isolated yield.
[c] Reaction was performed at −20 °C.

(Table 1, entry 8). When the reaction was conducted at −20 °C, a lower yield was obtained (Table 1, entry 9). Compared with toluene, dichloromethane was a better solvent for this reaction (Table 1, entry 10).

A series of terminal and internal alkenes were then examined to explore the generality of the present procedure (Table 2). Styrenes with electron-donating substituents at different positions of the phenyl ring afforded the desired products in good yields (Table 2, products **3b–3d**). In contrast, styrenes with halogen substituents gave inferior yields (**3e–3i**). This reaction also gave good yields of 1,1-disubstituted styrenes (**3j**). The reaction gave moderate yields with 1-vinylnaphthalene and its conjugate alkene (**3k** and **3 L**).



Scheme 2. One-pot reaction of olefin aziridination followed by ring-opening with H_2O.