Catalysis Communications 73 (2016) 109–112

Contents lists available at ScienceDirect

Catalysis Communications

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

Short communication

Au(I)-catalyzed domino intramolecular cyclization for the synthesis of 2,4-disubstituted pyrimidines

Haiying Zhan, Longbin Chen, Jingwen Tan, Hua Cao *

School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Zhongshan 528458, P.R. of China

ARTICLE INFO

Article history:
Received 6 August 2015
Received in revised form 10 October 2015
Accepted 12 October 2015
Available online 23 October 2015

Keywords:
Pyrimidines
Gold
Domino reaction
Synthesis
Intramolecular cyclization

ABSTRACT

An efficient Au-catalyzed domino intramolecular cyclization reaction has been developed for the construction of pyrimidine derivatives from ynals and amidines at room temperature for 3 h. This transformation provides a new method for the formation of C–C and C–N bonds via intramolecular cyclization.

1. Introduction

Pyrimidines and its derivatives as important fine chemicals [1–3] have been frequently found in many natural products and drugs and have exhibited a wide range of biological activities, such as anticancer, [4] anti-inflammatory properties, [5] antibacterial [6] and ca-sensing receptor antagonists [7]. It is not surprising, therefore, that great efforts have been directed toward developing synthetic routes [8–18] for the construction of this privileged structure. The availability of convenient synthetic transformations to prepare heterocyclic units for the synthesis of those compounds is of great demand. The classical method for the construction of pyrimidine derivatives mainly involves condensation of amidines with 1,3-dicarbonyl compounds [19] (Scheme 1).

Recently, one of the ways to achieve this aim is the development of domino process that allow the sequential transformation of two or more reactions in the same reaction vessel, thereby minimizing the number of laboratory operations, the generation of waste chemicals, time, and cost. Several synthetic routes have been described for the synthesis of these heterocycles. In 2014 Fandrick [20] described a general and rapid process to prepare pyrimidines utilizing amidines and activated olefins (Scheme 2); in 2013 Frutos and Wei [21] described one-step process for the synthesis of 2,5-disubstituted pyrimidines from Nitriles; Konakahara [22] developed three-component coupling reaction for the synthesis of pyrimidine derivatives involving a variety of functionalized enamines, triethyl orthoformate, and ammonium acetate, and Hu [23] developed facile reaction for the construction of benzofuro [3,2-d]pyrimidines from 3-chlorochromenones and amidines. However, an efficient, environmentally benign and atom-economic reaction synthesis of pyrimidines still remains a challenge.

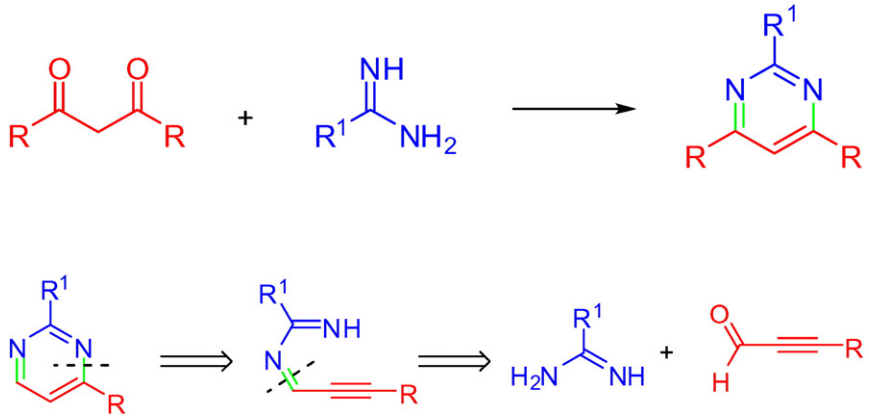
Gold-catalyzed reactions [24–35] are probably the most versatile and extensively used processes for the synthesis of heterocyclic compounds in one single operation. Due to their synthetic efficiency they have attracted attention in organic chemistry. Therefore, the development of new and efficient domino reaction for the synthesis of various heterocyclic compounds through gold-catalyzed reactions continues to attract broad interest. Herein, an efficient Au-catalyzed domino reaction has been described for the synthesis of pyrimidine derivatives.

2. Results and discussion

Initially, 3-phenylpropiolaldehyde (1a) and cyclopropanecarboximidamide (2a) were chosen as the substrates to investigate the synthesis of 2-cyclopropyl-4-phenylpyrimidine (3a). The results of the optimization study for the domino intramolecular cyclization reaction synthesis of 3a are summarized in Table 1. We were pleased to observe that the desired product 3a was obtained in 63% yield in the presence of AuCl and K_2CO_3 in DMF at 50 °C for 3 h (entry 1). Subsequently, the desired product 3a was obtained in 51% and 78% yields in the presence of $AuCl_3$ and PPh_3AuCl, respectively

* Corresponding author.
E-mail address: caohua@gdput.edu.cn (H. Cao).

http://dx.doi.org/10.1016/j.catcom.2015.10.017
1566-7367/



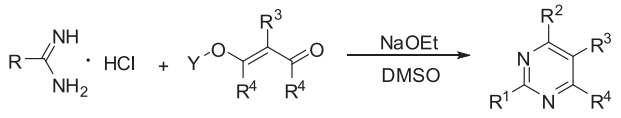
Scheme 1. Formation of pyrimidines

(entries 2–3). Other bases were next tested. But, the product 3a was formed with low yield or not detected in the presence of Cs_2CO_3, NaOH, *t*-BuOK, DBU, NEt_3 (entries 4–8). Among them, K_2CO_3 was a more efficient base than the other tested. The result encouraged us to improve the yield of this domino reaction by employing different solvents. Other solvents (entries 9–15), such as DMSO, EtOH, THF, CH_2Cl_2, CH_3CN, dioxane, and toluene were also afforded in moderate to good yields. Among the solvents, we were pleased to find that the product 3a was readily formed in 88% yield in CH_2Cl_2. Finally, the optimization of reaction temperature showed that room temperature is optimal. The control experiment without gold was carried out and only a trace of desired product was formed.

Under the optimized conditions, the substrate scopes were explored, and the results are described in Table 2. 1a was fixed as the substrate to test various substituted amidines (entries 1–10). All of the reactions proceeded smoothly under the optimized conditions and provided the 2,4-disubstituted pyrimidine derivatives in good yields. It was also worth noting that alkyl and aryl substituted amidines were proved to be suitable for this Au-catalyzed domino process. Notably, the results had showed that F, Cl, Br, CH_3 and OCH_3 substituted on the pyridine ring were also well-tolerated under the optimized conditions and led to a beneficial effect on the reaction outcome. In addition, nicotinimidamide was also afforded in 77% yield. Subsequently, oct-2-ynal (1b) was employed as the substrate (entries 11–16). The corresponding products were also obtained in 80–84% yields.

To gain further insight into the mechanism of this Au-catalyzed transformation, a control reaction was carried out (Scheme 3). The intermediate product 4 was treated with Ph_3PAuCl and the product 3c was formed in 93% yield. On the basis of these experimental results, a tentative mechanistic was proposed in Scheme 4. K_2CO_3-promoted dehydration of 1a with 2a formed intermediate A which then was activated by a gold catalyst to give the intermediate B. The intermediate B underwent the nucleophilic attack of nitrogen toward alkyne to generate intermediate C prior to the formation of product 3.

In summary, we have developed a general and efficient Au-catalyzed domino intramolecular cyclization process synthesis of 2,4-disubstituted pyrimidines in CH_2Cl_2 at rt. This method provides a simple route to prepare pyrimidines which are broadly applicable for the synthesis of biologically active molecules.



Scheme 2. Synthesis of pyrimidines

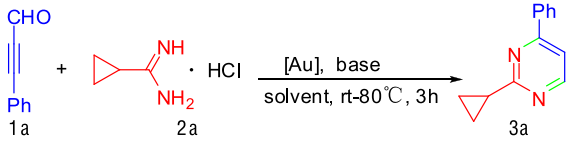
Acknowledgments

This research was financially supported by National Natural Science Foundation of China (21302023) and the Project of Department of Education of Guangdong Province (2013KJCX0111 and 2014KTSCX120).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2015.10.017.

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Base	Solvent	T(°C)	Yield(%)[b]
1	AuCl	K_2CO_3	DMF	50	63
2	$AuCl_3$	K_2CO_3	DMF	50	51
3	Ph_3PAuCl	K_2CO_3	DMF	50	78
4	Ph_3PAuCl	Cs_2CO_3	DMF	50	74
5	Ph_3PAuCl	NaOH	DMF	50	5<
6	Ph_3PAuCl	*t*-BuOK	DMF	50	–
7	Ph_3PAuCl	DBU	DMF	50	30
8	Ph_3PAuCl	NEt_3	DMF	50	27
9	Ph_3PAuCl	K_2CO_3	DMSO	50	66
10	Ph_3PAuCl	K_2CO_3	EtOH	50	42
11	Ph_3PAuCl	K_2CO_3	THF	50	70
12	Ph_3PAuCl	K_2CO_3	CH_2Cl_2	50	88
13	Ph_3PAuCl	K_2CO_3	CH_3CN	50	81
14	Ph_3PAuCl	K_2CO_3	dioxane	50	77
15	Ph_3PAuCl	K_2CO_3	toluene	50	75
16	Ph_3PAuCl	K_2CO_3	CH_2Cl_2	80	56
17	Ph_3PAuCl	K_2CO_3	CH_2Cl_2	rt	91
18[c]	–	K_2CO_3	CH_2Cl_2	rt	5<
19[d]	Ph_3PAuCl	–	CH_2Cl_2	rt	–

[a] Reaction conditions: catalyst (3 mol%), 1a (0.5 mmol), 2a (0.6 mmol), base (1.0 mmol), solvent (3.0 mL).
[b] Yields determined by GC analysis using n-octadecane as internal standard.
[c] In the absence of Ph_3PAuCl.
[d] In the absence ofKCO_3.