Tetrahedron 72 (2016) 1238–1243

Contents lists available at ScienceDirect

Tetrahedron

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

Rhodium-catalyzed tandem C–H activation and aza-Michael addition of 2-arylquinazolin-4-ones with acrylates for the synthesis of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one derivatives

Xin Jiang [a], Qin Yang [a], Jianjun Yuan [a], Zhihong Deng [a], Xuechun Mao [a], Yiyuan Peng [a,*], Chuyi Yu [b]

[a] Key Laboratory of Functional Small Organic Molecules, Ministry of Education, Jiangxi Province's Key Laboratory of Green Chemistry, and Jiangxi Normal University, Nanchang 330022, PR China
[b] CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, 330022, PR China

ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form 12 January 2016
Accepted 13 January 2016
Available online 15 January 2016

Keywords:
Rhodium catalysis
C–H activation
Aza-Michael addition
Quinazolin-4-one
Pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one
Tandem reaction

ABSTRACT

In this paper, a rhodium-catalyzed reaction of 2-arylquinazolin-4-ones with acrylates is described, leading to pyrrolo[2, 1-*b*]quinazolin-9(1*H*)-one derivatives with high efficiency and good tolerance of functional groups. In the reactions, it is believed that tandem C–H activation and aza-Michael addition are involved.

1. Introduction

Quinazoline scaffold was ubiquitous in many natural products and bioactive molecules, which thus attracted ever-growing attention of synthetic chemists.[1] As a result, the construction of quinazoline and derivatization of quinolines has been an intensive research focus in synthetic chemistry. As one of our interests, our group was intensively focused on quinazoline-based chemistry, including synthetic methodology development and late-stage elaboration of quinazolines. In the past decade, MnO_2-mediated single electron transfer oxidation,[2] palladium-catalyzed C–O bonds cleavage,[3] rhodium-catalyzed C–H bond activation[4] *etc.* were employed in our group to deliver diverse functionalized quinazolines, and bioactivity assay of these compounds are ongoing in our group. As we know, *N*-containing polycyclic compounds were prevalent in medicine and material science, probably due to a plausible fact that a polycyclic compound might contain bioactivity and performance of sub-frameworks.[5] For example, asperlicin, a polycyclic compound containing quinazolin-4-one, derived from the fungus *Aspergillus alliaceus*, is a mycotoxin (Fig. 1).

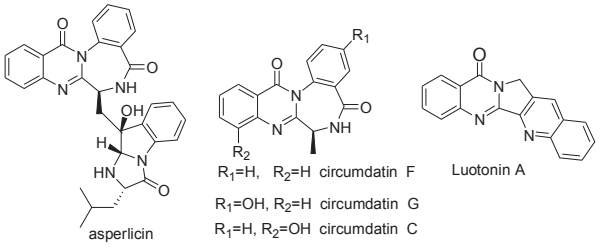


Fig. 1. Polycyclic compound containing quinazolin-4-one.

It acts as a selective antagonist for the cholecystokinin receptor CCK_A,[6] and has been used as a lead compound for the development of a number of novel CCK_A antagonists with potential clinical applications.[7] Circumdatins have been isolated from *Aspergillus ochraceus* and have been suggested as good chemo-taxonomic markers for anti viral therapy of Hepatitis.[8]

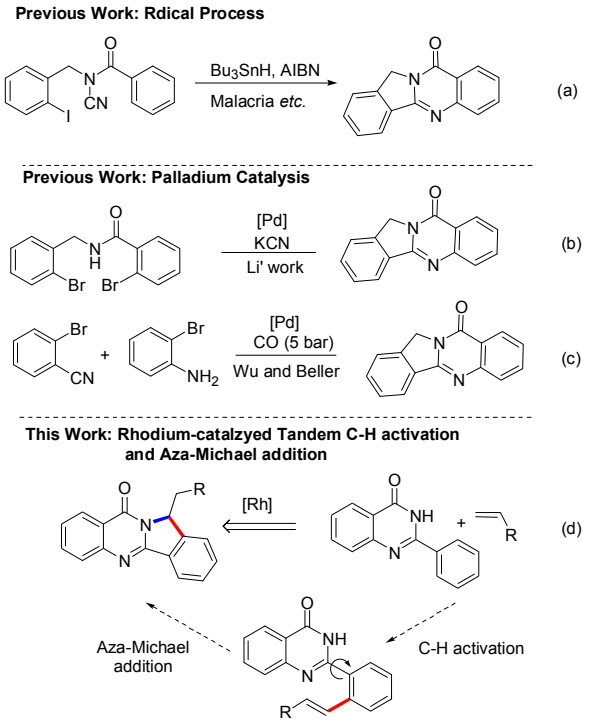
Pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one motif, a polycyclic compound comprised by quinazolin-4-one and pyrrole frameworks, was valuable skeleton with a range of promising biological activities. For example, Luotonin A, a cytotoxic alkaloid, isolated from the plant *Peganum nigellastrum*.[9] This plant has a history of use in

* Corresponding author. Tel./fax: +86 791 88120388; e-mail address: yypeng@jxnu.edu.cn (Y. Peng).

http://dx.doi.org/10.1016/j.tet.2016.01.020
0040-4020/

Chinese medicine for the treatment of rheumatism and inflammation.

Towards this polycyclic core, traditional methods resorted to condensation reactions of special substrates.[10] A radical process was also employed by Malacria and co-workers to offer this polycycles when *N*-acyl cyanamides were starting materials in the presence of Bu_3SnH and AIBN (Scheme 1a).[11] With the development of organometallic chemistry, palladium catalysis enabled the formation of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones in an one-pot procedure with high efficiency. For example, with palladium catalysis, *N*-(2-bromobenzyl)-2-bromobenzamides went through a tandem cyanation/N-arylation process to produce pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones (Scheme 1b).[12a] Besides, starting from commercial available substrates, a palladium-catalyzed carbonylation developed by Beller, Wu and Li group allowed for a straightforward synthesis of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones (Scheme 1c).[12b] In these reactions, sequential carbonylation–cyclization–isomerization–carbonylation steps were involved.



Scheme 1. Reaction design.

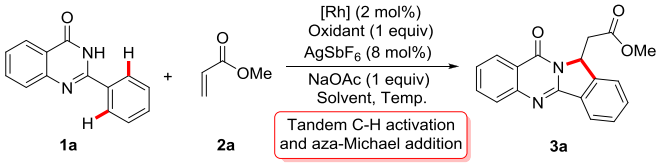
On the other hand, rhodium catalysis has been generally accepted as one of versatile tools towards the formation of carbon–carbon bonds[13] and as a powerful tool for the assembly of *N*-containing heterocycles. Compared with palladium catalysis, rhodium catalysis was popular and efficient in direct C–H functionalization due to its stronger metallicity. In our group, rhodium catalysis was also used into late-stage elaboration of 2- arylquinazolines.[4] With assistance of quinazoline core, direct amination, and arylation were realized via C–H bond activations. Interestingly, according to our findings, chelating property between two nitrogen atoms in quinazolines core was different, and C–H functionalization was thus regioselective. Inspired by what mentioned above and considering the importance of polycyclic compound pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones, we would like to explore synthetic mythology development towards pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones through rhodium catalysis. Given the advantage of tandem reaction in the synthesis of polycyclic compounds,[14,15] we hypothesized that tandem rhodium-catalyzed olefination of C–H bond and aza-Michael addition could provide the desired pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones when 2-arylquinazolin-4-ones and acrylates were used as substrates (Scheme 1d). To verify the possibility of this projected transformation, we then optimized the reaction.

2. Results and discussion

The reaction of 2-phenylquinazolin-4-one **1a** with methyl acrylate **2a** was employed as a model reaction. The preliminary experiment showed that tandem C–H activation and aza-Michael addition seemed reliable under rhodium catalysis. The desired pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones **3a** was afforded in 49% isolated yield when 2 mol % $[Cp^*RhCl_2]_2$ was used as catalyst, 8 mol % $AgSbF_6$ as additive, and 1.0 equiv $Cu(OAc)_2$ as oxidant at 100 °C in methanol (Table 1 entry). Encouraged by this result, the result-affecting factors including solvent, oxidant, rhodium source and temperature were evaluated, and the results are listed in Table 1.

The results of solvent screening implied that the use of solvent such as C_2H_5OH, DMF, MeCN and toluene could make significant improvement on the reaction (Table 1, entries 2–7). By switching to 1,4-dioxane, the efficiency of the reaction was drastically

Table 1
Screening of the reaction condition



Entry	[Rh]	Oxidant	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	MeOH	49
2	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	C_2H_5OH	77
3	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	MeCN	56
4	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	CH_2Cl_2	40
5	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	DMF	60
6	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	THF	Trace
7	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	Toluene	71
8	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2$	Dioxane	98
9	**$[Cp^*RhCl_2]_2$**	**$Cu(OAC)_2{\cdot}H_2O$**	**Dioxane**	**98**
10	$[Cp^*RhCl_2]_2$	$Cu(OCOCF_3)_2$	Dioxane	98
11	$[Cp^*RhCl_2]_2$	$CuCl_2$	Dioxane	Trace
12	$[Cp^*RhCl_2]_2$	$CuBr_2$	Dioxane	31
13[c]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	67
14	$RhCl_2$(*p*-cymene)	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
15	Rh(acac) (1,5-cyclooctadiene)	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
16	$RhCl_2PPh_3$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
17	$Rh(Ac)_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
18[d]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	82
19[e]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	80
20[f]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	64
21	$[Cp^*RhCl_2]_2$	—	Dioxane	NR
22	—	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
23[g]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	NR
24[h]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	90
25[i]	$[Cp^*RhCl_2]_2$	$Cu(OAC)_2{\cdot}H_2O$	Dioxane	60

Optimized conditions are denoted in bold.
[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.4 mmol), [Rh]-catalyst (2 mol %), oxidant (0.2 equiv), $AgSbF_6$ (8 mol %), 100 °C, 5 h.
[b] Yields based on isolation.
[c] The reaction was carried out at 70 °C.
[d] 1 mol % $[Cp^*RhCl_2]_2$ was used.
[e] 4 mol % $AgSbF_6$ was used.
[f] The reaction was performed in absence of $AgSbF_6$.
[g] The reaction was performed in absence of NaOAc.
[h] 1.5 equiv methyl acrylate **2a** was used.
[i] 1.0 equiv methyl acrylate **2a** was used.