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One-pot synthesis of quinazolin-4(3*H*)-ones and fused quinazolinones by a palladium-catalyzed domino process

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ABSTRACT

An efficient one-pot synthesis of quinazolin-4(3*H*)-ones, benzoimidazo[2,1-*b*]quinazolin-12(6*H*)-ones and imidazo[2,1-*b*]quinazolin-5(1*H*)-ones via a palladium-catalyzed domino process has been developed. The Pd-catalyzed reactions of 2-azidobenzamides **1** with isocyanides **2** produced quinazolin-4(3*H*)-ones **4** at room temperature by a domino Pd-catalyzed cross-coupling/carbodiimide-mediated cyclization. However, as 2-azido-*N*-(2-bromophenyl)benzamides **1** were used under heating condition in the presence of Cs_2CO_3, the benzoimidazo[2,1-*b*]quinazolin-12(6*H*)-ones **5** were directly obtained by twice Pd-catalyzed domino cyclization. A domino reogioselective 5-*exo*-*dig* intramolecular cyclization reaction of alkynyl-containing azides **6** with isocyanides **2** generated imidazo[2,1-*b*]quinazolin-5(1*H*)-ones **9** in 74–93% yields in the presence of catalyst $Pd(PPh_3)_4$ and K_2CO_3.

1. Introduction

Quinazolines and ring-fused derivatives have emerged as well-known class of heterocyclic motifs showing a variety of potential biological and pharmaceutical activities such as antimicrobial,[1] antifungal,[2] antibacterial,[3] nitric oxide synthase (NOS) inhibitive,[4] transient receptor potential A1 (TRPA1) antagonistical[5] and anti-tumor activities.[6] The quinazolinone skeleton have also been found in some natural products and drugs (Fig. 1).[7] Great attention has been paid to them by the organic chemists owing to their widespread biological activities and remarkable chemical structures. Over the past decades, a number of efficient methods for the preparation of quinazolinone skeleton from a range of starting materials have been developed. Classical synthetic routes to the quinazolinone include the utilization of anthranilic acids[8] or its derivatives, such as anthranilamides,[9] isatoic anhydrides[10] and 2-aminobenzonitriles,[11] the microwave-assisted dehydrative cyclization of diamides,[12] the transition-metal catalyzed reactions,[13] and the aza-Wittig reactions.[14] However, despite of their many advantages, these procedures suffer from some drawbacks including high temperature, acid- or base-sensitive substrates, multi-step process and low atom efficiency. Therefore, the development of new and step-economic process is still highly desirable.

Carbodiimides are important chemical reagents in organic chemistry and they have been utilized as intermediates or precursors for some heterocycles.[15] Recently an elegant work for the formation of unsymmetric carbodiimides utilizing palladium-catalyzed cross-coupling reaction of azides with isocyanides was reported by Zhang and co-workers.[16] Inspired by their work, we speculated that if 2-azidobenzamides were used to react with isocyanides in palladium catalyst, quinazolinones would be generated through further cyclization of the carbodiimide intermediate. As a continuation of our interest in developing new synthetic protocols for various heterocycles via isocyanide chemistry,[17] herein, we wish to report a new strategy for one-pot preparation of quinazolin-4(3*H*)-ones, benzoimidazo[2,1-*b*]quinazolin-12(6*H*)-ones and imidazo[2,1-*b*]quinazolin-5(1*H*)-ones via a Pd-catalyzed domino process.

2. Results and discussion

The 2-azido-5-chloro-*N*-*p*-tolylbenzamide **1a** (R^1 = 5-Cl, R^2 = 4-MeC_6H_4, 1 equiv) was initially selected to react with *n*-butylisocyanide **2a** (R^3 = *n*-Bu, 1 equiv) in DMF in the presence of catalyst $Pd(PPh_3)_4$ (0.05 equiv). The palladium-catalyzed cross-coupling reaction was carried out smoothly at room temperature to produce directly the quinazolin-4(3*H*)-one product **4a** in good yield (81%). The above one-pot operation was then applied for various 2-

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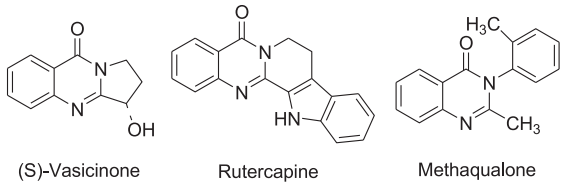

Fig. 1. Some quinazolinone natural products and drugs.

azidobenzamides **1** and isocyanides **2** (Table 1). All of the reactions were carried out smoothly to give the corresponding quinazolin-4(3*H*)-ones **4**, and good yields (72–86%) were obtained with different substituents on the reactants. As indicated in Table 1, good yields were reached no matter the R^2 substituent of the azide **1** was an alkyl group (compounds **4q** and **4r**) or an aryl group with substituents (4-Cl, 4-Br, 2-Br, 2-I, 2-CH_3, 4-CH_3 and 4-OCH_3) on the benzene ring (compounds **4a**-**4p**). Satisfactory yields were also obtained as various alkyl (R^3 = *t*-Bu, cyclohexyl, *n*-Bu) or aryl (R^3 = 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4) isocyanides **2** were utilized. It's noteworthy that good yields (74–80%) of the quinazolin-4(3*H*)-ones (compounds **4d**, **4h**, **4q** and **4r**) were directly obtained at room temperature even when R^3 is the steric *t*-Bu group. The formation of quinazolin-4(3*H*)-ones **4** can be viewed as an initial palladium-catalyzed cross-coupling reaction between 2-azidobenzamide **1** and isocyanide **2** to create the carbodiimide **3** as highly reactive intermediate. Further intramolecular nucleophilic attack of the amide group on the carbodiimide **3** produces quinazolin-4(3*H*)-

Table 1
Preparation of quinazolin-4(3*H*)-ones **4**.