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ARTICLE

Synthesis of benzoimidazoquinazolines by cobalt-catalyzed isocyanide insertion-cyclization

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Abstract:

An efficient and practical protocol for the synthesis of benzoimidazoquinazoline amines in moderate to good yields by the reaction of isocyanides and benzo[d]imidazol-anilines via a cobalt-catalyzed isocyanide insertion cyclization reaction into the two N-H active bonds is reported.

Introduction

Isocyanide core is a well known scaffold for the construction of many building blocks and the importance of isocyanides is well recognized because of their nucleophilicity and electrophilicity potential in multi-component reactions [1]. Although the first century of isocyanide chemistry was focused on multi-component reactions, isocyanide-based reactions using transition metal catalysts have received significant attention during the past several years [2]. Among of the metal-catalyzed isocyanide-based reactions, isocyanide insertion (also called imidoylative reaction) is a powerful strategy in the synthesis chemistry. The isocyanide insertion refers to the metal-catalyzed direct insertion of isocyanide into a heteroatom/carbon–hydrogen or carbon–halogen bond to give an imidoylative intermediate, which can be trapped by various nucleophiles [3]. Recently, isocyanide insertion-cyclization reactions with different nucleophiles have been developed for the synthesis of various *N*-heterocyclic compounds [4] (Fig. 1). Among these reports, transition-metal catalyzed isocyanide insertion-cyclization with C–H or C–halogen bonds are very popular [5] and direct isocyanide insertion reaction into the active N–H bonds are still rare [6]. It is notable that the most of the previous isocyanide insertion reactions were carried out using palladium catalysts which have exhibited high catalytic activity for a wide range of substrates [7].

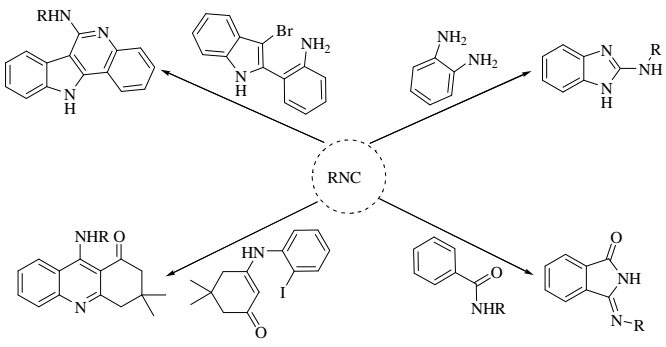

Figure 1. Synthesis of heterocycles via isocyanide insertion reaction.

However, the high cost of palladium has constricted a more general use of such protocol in large scale productions. Therefore, the development of new and more inexpensive catalyst systems and their application on isocyanide insertions are desirable. To the best of our knowledge, there are only a few reports of isocyanide insertion-

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cyclization for the synthesis of heterocycles by using the other transition metals catalysts [8]. In 2014, Shun-Jun Ji *et al* reported $NiCl_2$-catalyzed cascade reaction of isocyanides with functionalized anilines for the synthesis of 2-aminobenzimidazole, 2-aminobenzothiazole and 2-aminobenzoxazole [8a]. Since Kharaschs pioneering works [9] on the homocoupling reactions of Grignard reagents, cobalt catalysts, which are widely available, not expensive, and have low toxicity, have received particular attention [10]. Recently, a cobalt-catalyzed insertion reaction has reported for the reaction of amine-based bisnucleophiles and isocyanides [8b].

As a privileged scaffold, benzimidazole is a ubiquitous subunit in many medically important products with remarkable biological activities [11] and its derivatives have been employed as antiviral [12], antibiotic [13], antitumor [14] and antimicrobial agents [15]. Similarly, quinazolines are one of the most scaffolds which possess a broad spectrum of biological activities [16] and especially they have attracted considerable attention due to their diverse anticancer activities [17]. The combined molecules of benzimidazole and quinazoline frameworks, benzimidazoquinazoline derivatives **I** (Fig. 2), are valuable substrates with various biological activities, and they exhibit a wide range of therapeutic properties [18]. On the other hand, compounds bearing the Guanidine functional groups are found in numerous biologically active natural products and several drugs and drug Candidates [19]. The benzimidazoquinazolines containing Guanidine framework have been presented significant biological activities. For example, benzo[4,5]imidazo[1,2-c]quinazolin-6-amine **II** (Fig. 1) is a new anti tumour compound and can bind to DNA by intercalation and are cytotoxic to tumour cells in tissue culture and bis[N-(benzimidazo[1,2-c]quinazolyl)-3-aminopropyl]methylamine **III** has cytotoxicity effect on the human colon tumour cells [20].

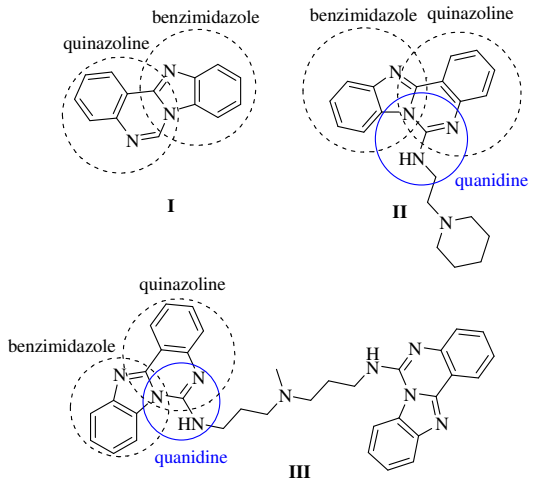


Figure 2. Biologically active benzimidazoquinazoline derivatives.

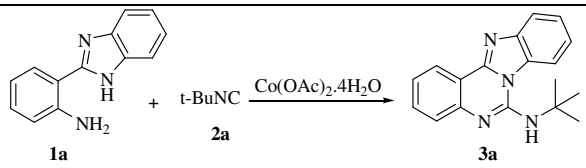
The methods for the synthesis of benzimidazoquinazoline amines are rare [21]. Most of these methods are multi-component and multi-step process. In this context, benzoimidazoquinazoline amines show interesting features that make them attractive for use in the cobalt-catalyzed isocyanide insertion reaction into the active N–H bonds.

According to above reports and as part of our previous works on the development of new method for the isocyanide-based heterocycles synthesis [22], we herein investigate the feasibility of the formation of benzimidazoquinazoline amines via cobalt-catalyzed isocyanide insertion-cyclization reaction into the N–H bonds.

Results and discussion

Our study commenced with the reaction of 2-(1*H*-benzo[d]imidazol-2-yl)aniline (**1a**) and *t*-butyl isocyanide (**2a**) as a model reaction to search for the optimal reaction conditions (Table 1). As shown in Table 1, the best result was obtained with $Co(OAc)_2.4H_2O$ (10 mol%), $K_2S_2O_8$ (1 eq) and NaOAc (2 eq) in DMF at 80 °C and N-(tert-butyl)benzo[4,5]imidazo[1,2-c]quinazolin-6-amine (**3a**) was obtained in 65% yield after 12 h (entry 5). As shown in Table 1, different solvents were screened in the model reaction using $Co(OAc)_2.4H_2O/K_2S_2O_8$ system and it was found that DMF is the optimal solvent (entry 5). It should be mentioned that when the reaction was carried out in the absence of $Co(OAc)_2.4H_2O$ or $K_2S_2O_8$ no reaction could be observed (entry 6 and 7). When this reaction was carried out with other oxidants such as, H_2O_2, ^{t}BuOOH, 4-methylmorpholine 4-oxide and O_2 the yield of the expected product was reduced (entries 8-11). To study the effect of temperature on this synthesis, we performed three experiments at room temperature, 50, 80, and 100 °C in $Co(OAc)_2.4H_2O/K_2S_2O_8$ system in DMF. It was observed that a lower reaction temperature leads to a lower yield (entry 13 and 14), while a higher reaction temperature did not affect either the reaction time or the yield (entry 15).

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Oxidant	Base	Yield [%][b]
1	$PhCH_3$	$K_2S_2O_8$	NaOAc	56
2	Dioxane	$K_2S_2O_8$	NaOAc	60
3	CH_3CN	$K_2S_2O_8$	NaOAc	51
4	H_2O	$K_2S_2O_8$	NaOAc	Trace

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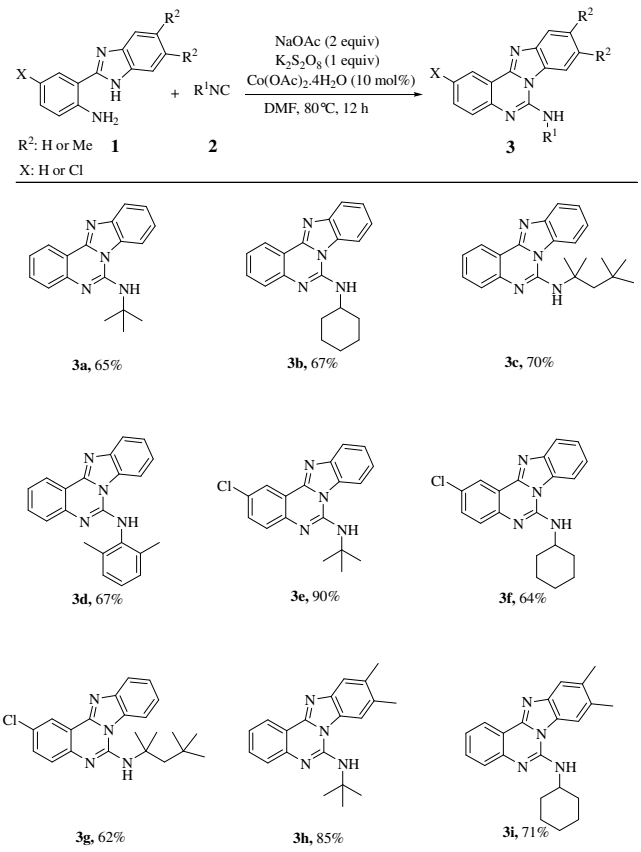
5	DMF	$K_2S_2O_8$	NaOAc	65
6[c]	DMF	$K_2S_2O_8$	NaOAc	Trace
7	DMF	-	NaOAc	Trace
8	DMF	H_2O_2	NaOAc	45
9	DMF	TBHP	NaOAc	43
10	DMF	4-methylmorpholine 4-oxide	NaOAc	49
11	DMF	O_2	NaOAc	47
12	DMF	$K_2S_2O_8$	K_2CO_3	61
13[d]	DMF	$K_2S_2O_8$	NaOAc	22
14[e]	DMF	$K_2S_2O_8$	NaOAc	41
15[f]	DMF	$K_2S_2O_8$	NaOAc	65

[a] Benzoimidazol-aniline 1a (1 eq), *t*-BuNC (1.5 eq), base (2 eq), oxidant (1 eq), $Co(OAc)_2.4H_2O$ (10 mol%), 80 °C, 12 h.
[b] Isolated yields.
[c] Catalyst-free
[d] Room temperature.
[e] Reaction temperature = 50 °C
[f] Reaction temperature = 100 °C.

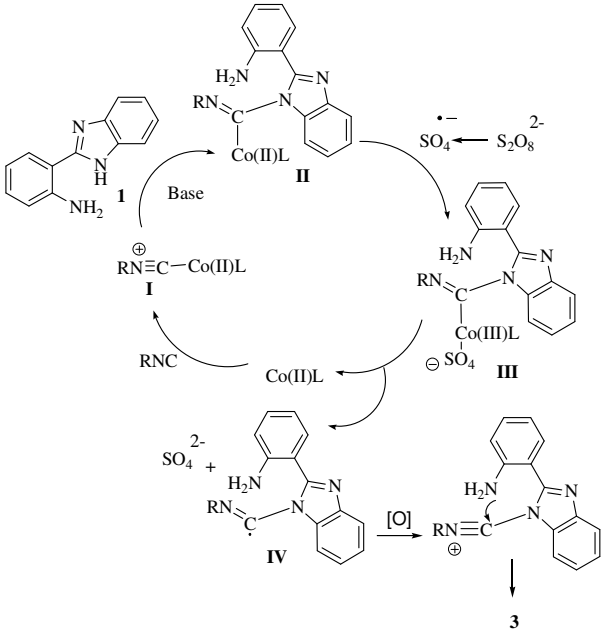
With optimal conditions in hand, we extended the cobalt-catalyzed isocyanide insertion cyclization reaction to various isocyanides **2** and benzo[d]imidazol-anilines **1** to afford desired of benzoimidazoquinazoline amines **3a-i** in moderate to good isolated yields (Table 2).

Table 2 Synthesis of benzoimidazoquinazoline amines **3**



The structures of benzoimidazo[1,2-c]quinazolin-6-amines **3** were fully characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

Based on literature reports [8b, 10, 23] and the chemistry of isocyanides [6], a plausible mechanism is proposed in Scheme 1. Catalyst **I** (formed *in situ* by the reaction of $Co(OAc)_2$ and isocyanide) reacts with the benzoimidazol-aniline **1** under basic conditions to form cobalt (II)-isocyanide carbene complex **II** [10, 23b]. Then, the complex **II** was oxidize by $SO4^{\cdot-}$ originating from the decomposition of $K_2S_2O_8$ [24] to give cobalt (III)-isocyanide carbene complex **III** [10, 23b]. The complex **III** undergoes homolysis to afford the active radical intermediate **IV** and the catalyst Co(II) salt to complete the catalytic cycle. Oxidation of intermediate **IV** followed by intramolecular nucleophilic addition affords the product **3**.



Scheme 1. Proposed mechanism

As expected, when the benzoimidazol-aniline **1** was replaced by 2-(1*H*-tetrazol-5-yl)aniline **4** or 2-amino-benzamides **5**, the desired tetrazolo[1,5-*c*]quinazolin-5-amine **6** or quinazolin-4(3*H*)-ones **7** were obtained in good yields under the same reaction conditions (Scheme 2).

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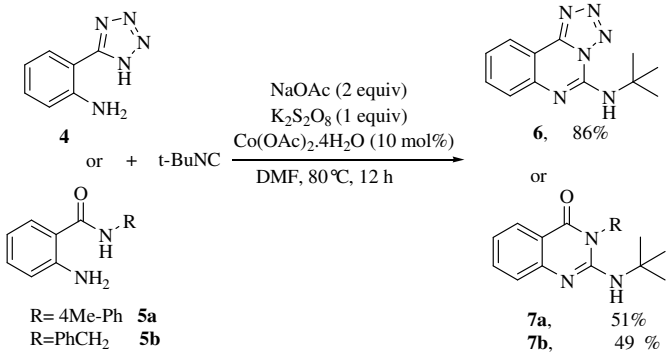

Scheme 2. Synthesis of tetrazoloquinazolin-5-amine and quinazolin-4(3H)-one

Conclusions

We disclosed an easy access to the benzoimidazoquinazoline amines framework by direct reactions of isocyanides with compounds containing active N–H bonds utilizing inexpensive cobalt catalyst. The methodology is highly practical and it provides a straightforward approach to a series of benzoimidazoquinazoline amines. The comparison between the present cobalt-catalyzed system with the analogous reaction under palladium catalysis [6b] shows that both methods have advantages and disadvantages. The pd-catalyzed system is more expensive, needs more reaction times and should carry out in the presence of 4 Å MS. However, it must be mentioned that aerobic oxidation with only water as a by-product in absence of base are advantages of Pd-system. On the other hand, cobalt-catalyzed system is cheaper, but needs $K_2S_2O_8$ (1 eq) as an oxidant, along with NaOAc (2 eq) as a base. Consequently, the Pd-catalyzed system is more benign from a green chemistry perspective and cobalt-catalyzed system is more acceptable from industrial point of view.

Acknowledgements

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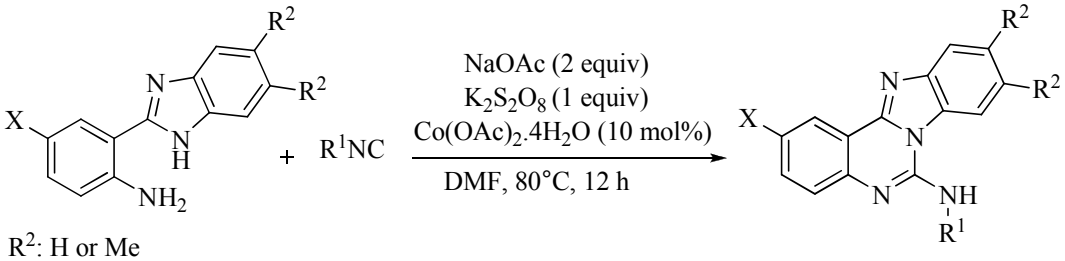

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The synthesis of benzoimidazoquinazoline amines by the reaction of isocyanides and benzo[d]imidazol-anilines via a cobalt-catalyzed isocyanide insertion reaction into the two N-H active bonds is reported.