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Rhodium(III)-catalyzed intermolecular cascade annulation through C-H activation: Concise synthesis of rosettacin

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ABSTRACT

An intermolecular annulation of 2-acetylenic aldehydes or ketones with *O*-substituted *N*-hydroxybenzamides or *N*-hydroxyacrylamides through rhodium(III)-catalyzed C–H activation for the synthesis of isoquinolones and indolizinones is developed. This reaction features excellent functional-group tolerance and broad substrate scope, including annulation of various heterocyclic substrates. This approach evaluates the chemoselectivity of the reaction when sterically hindered diaryl-substituted alkynes are incorporated. This method also furnishes an efficient approach for the total synthesis of rosettacin and a topoisomerase I inhibitor.

1. Introduction

Tetracyclic heteroring scaffolds are extensively presenting as the core of many natural products and medicines candidates (Fig. 1), such as rosettacin [[1]], oxypalmatine [1f,2], norketoyobyrine [3] and camptothecin [1e,4], which have been widely investigated for their variety of interesting biological activities such as antifungal, antitumor and antimicrobial properties. Although several approaches for the synthesis of tetracyclic heterorings have been reported [1–4], most of them comprise a multistep reaction sequence or harsh conditions. Therefore, developing a concise and novel synthetic methodology is still of great value.

Transition-metal-catalyzed C–H activation has recently emerged as one of the most efficient and attractive strategy to construct new carbon-carbon and carbon-heteroatom bonds [5]. Despite enormous development in the recent decade, the strong coordination of medicinally important heterocycles continues to constitute major challenge for transition-metal catalysts, often resulting in the poisoning of the catalyst or undesired C–H bond activation [[6]]. Although several methods provide significant improvements in the C–H activation of heterocycles, they show many limitations in substrate scope [6c,7].

Recently rhodium(III)-catalyzed C–H activation followed by annulation with alkynes has received significant interest for the construction of N-heterocycles and carbocycles owing to efficient metal-substrate interactions [8]. Although great progress has been achieved for intermolecular annulation reactions, most of them lead to the formation of a single ring and inevitably go through uncontrolled regioselectivity, resulting in the mixtures of positional isomers, which are mostly difficult to be isolated by flash column (Scheme 1) [9]. Especially when unbiased unsymmetrical alkynes are employed, the regioselectivity depends on the distinction between both substituents of alkynes. The utilization of terminal aryl alkynes or alkyl-aryl disubstituted alkynes usually gives the main annulation products with aryl substituent being installed at the 3-position of the heterocycle. When unsymmetrical dialkyl-substituted alkynes are used, the more sterically alkyl group will typically be placed at the 4-position. Using terminal alkyl alkynes, the alkyl group will mainly be placed at the 3-position. However, when alkynes bearing two aryl substituents with slight difference are utilized, what will happen? So far no literature has been devoted to such situation. Thus it is of great value to systemically investigate the annulations with diaryl-substituted alkynes and find a way to isolate the mixtures of positional isomers by flash column. Herein we report the formation of isoquinolones and indolizinones based on a Rh^{III}-catalyzed intermolecular annulation (Scheme 1). This approach evaluates the performance of diaryl-substituted alkynes employed in annulation and provides an efficient method to isolate positional isomers. The utility of this method is demonstrated by accomplishing the synthesis of diverse heterocyclic products including rosettacin and a topoisomerase I inhibitor [10].

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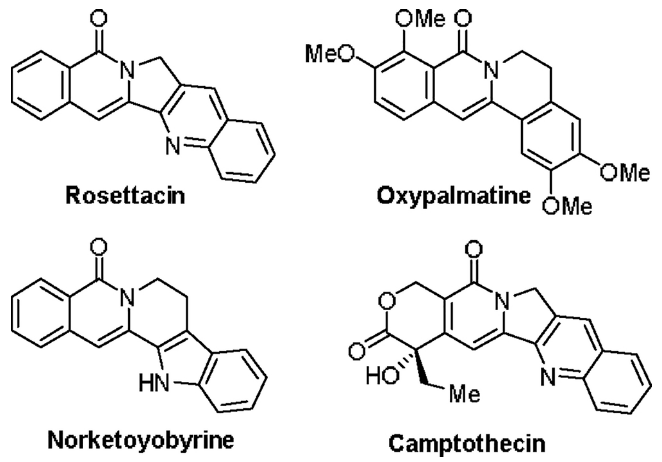

Fig. 1. Representative examples of natural products with a tetracyclic scaffold.

2. Experimental

2.1. Materials and methods

Commercially available reagents were used without additional purification. Column chromatography was performed with silica gel (70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM (300 or 400 or 600 MHz) spectrometer at ambient temperature using $CDCl_3$ or DMSO-d_6 as solvent. HRMS (ESI) spectrometry data were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer [Synapt G2 high definition mass spectrometer (HDMS), Waters, Milford, MA]. Samples were infused at 3 μL min^{-1}, and spectra were obtained in the positive ionization mode with a resolution of 15,000 [full width at half maximum (FWHM)] with leucine encephalin as lock mass. Melting points were recorded on a Reichert Thermovar apparatus and are uncorrected. IR spectra were recorded on Bruker Alpha FT-IR spectrometer.

2.2. Preparation of substrates **1j**, **1r** and **1s**

In a 100 mL round-bottom flask [11], *O*-pivaloylhydroxamine triflic acid (3.6 mmol) and K_2CO_3 (6.0 mmol) were combined in a 2:1 mixture of EtOAc (20 mL) and H_2O (10 mL). The flask was capped and the mixture was cooled in an ice bath. No special precautions were taken to exclude moisture or oxygen. The acid chloride (3.0 mmol) was added dropwise and the mixture was stirred to r.t over 16 h. The reaction mixture was then diluted with EtOAc and washed twice with sat. $NaHCO_3$ and brine. The organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate) to give the products **1j**, **1r** and **1s**.

2.3. Preparation of substrates **2s**

To a solution of corresponding 2-bromoketone (5.0 mmol) and ethynylbenzene (6.0 mmol) in Et_3N (20 mL) were added $Pd(PPh_3)_2Cl_2$ (0.25 mmol) and CuI (0.15 mmol) at room temperature under argon [1e]. Then the reaction mixture was gradually warmed up to 60 °C and stirred at the same temperature for 16 h. After cooling down to room temperature, the crude mixture was filtered and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford **2 s**.

2.4. Preparation of products **3** and **4**

To a Schlenk flask equipped with a stir bar were added **1** (0.3 mmol), **2** (0.45 mmol), $[Cp^*RhCl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol), PivOH (0.6 mmol) and CH_3CN (1.5 mL) without any particular precautions to extrude oxygen or moisture. The reaction was stirred for 8 h at 60 °C, cooled to room temperature. The solvent was removed in *vacuo* and the remaining residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford the product **3** and **4**.

2.5. Preparation of compound **5a**

To the solution of **4 ag** (0.2 mmol) in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [1a]. To the resulting solution, Et_3SiH (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford **5a**.

2.6. Preparation of compound **5b**

A 25 mL round-bottomed flask equipped with a stirring bar is charged with **4ak** (0.3 mmol), *tetra-n*-butylammonium fluoride (TBAF, 1 M in THF, 0.6 mL, 0.6 mmol) and 2 mL of anhydrous THF [12]. Then allowed to stir at room temperature for 12 h. The solvent was removed and the residue was used in next step without further purification. To the solution of above residue in DCM (3 mL) was added $BF_3{\cdot}Et_2O$ (0.3 mmol) at 0 °C and stirred for 5 min [1a]. To the resulting solution, Et_3SiH (0.9 mmol) dissolved in DCM (1.5 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford **5b**.

To the solution of **4 al** (0.2 mmol) in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [1a]. To the resulting solution, Et_3SiH (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate) to afford **5b**.

3. Results and discussion

We selected *O*-substituted *N*-hydroxybenzamide **1a** and ethynylbenzaldehyde **2a** as our model substrates (Table 1). When the reaction was performed in MeOH with $[RhCp^*Cl_2]_2$ (5 mol%) and CsOAc (2 equiv.) at 60 °C for 8 h, the isoquinolone **3aa** was obtained in 48% yield, together with indolizinone **4aa** in 17% yield (Table 1, entry 1). On the base of these promising results, a set of various solvents were screened, such as 1,4-dioxane, DMF, toluene, DCE, THF and CH_3CN, showing that CH_3CN was the best one, which yielded **3aa** in 47% and**4aa** in 33% (Table 1, entries 2–7). Application of $[Ru(p\text{-cymene})Cl_2]_2$ resulted in a lower yield of **3aa** and almost no conversion into **4aa** (Table 1, entry 8). Further investigation showed that a lower or higher temperature could not improve the reaction (Table 1, entries