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Domino Nicholas and Pauson–Khand process induced by nitroarene reduction

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ABSTRACT

We have developed an exceptional one-pot domino cyclization process, in which a nitroarene reduction step initiates an endocyclic Nicholas reaction followed by an intramolecular Pauson–Khand cyclization. Remarkably, all reactions in this process can be mediated by a cobalt carbonyl complex under mild conditions.

Introduction

Domino cyclization reactions initiated by reduction of a nitro group are of significant use for concise and rapid construction of bioactive heterocyclic compounds.[1] In fact, there are numerous synthetic examples of indole and quinoline derivatives including natural products synthesized through nitroarene reduction/cyclization processes.[2]

During the course of our studies on Pauson–Khand (PK) reactions,[3] we discovered the exceptional domino cyclization process of an alkyne cobalt complex containing a nitro group, in which 4-[but-3-enyl-(2-nitrobenzenesulfonyl)-amino]-but-2-ynyl acetate (**1**) was converted into unprecedented tetracyclic compound **3** in a one-pot reaction. We predicted that product **3** was constructed via four reaction sequences: (a) complexation with dicobalt octacarbonyl to generate alkyne cobalt complex **2**, (b) reduction of the nitro group on **2**, (c) nucleophilic substitution reaction, such as Nicholas-type reaction,[4] to form a nine-membered ring, and (d) PK cyclization reaction to form cyclopentenone **3** (Scheme 1).

To the best of our knowledge, although the combination of Nicholas and PK reactions has been used to gain quick access to target molecules,[5] this is the first report on a domino version of these reaction sequences involving a nitroarene reduction step. Encouraged by the novelty of our discovery, we decided to investigate the domino cyclization process and develop a new methodology for rapid construction of a heterocyclic multi-ring system. Moreover, the structure of **3** inspired our interest of disclosure of its bioactivity to support synthetic utility of hetero medium sized ring products.

Results and discussion

Synthesis of **1** is described in Scheme 2. Our strategy was to apply the Fukuyama amine protocol[6] to the synthesis of enyneamide **7** using nosyl strategies under Mitsunobu conditions.[7] Thus, we synthesized *N*-Boc-2-nitrobenzenesulfonamide (**4**) as a nitrogen source according to a literature procedure.[6b] Treatment of but-2-yne-1,4-diol with **4** in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (PPh_3) in tetrahydrofuran (THF) gave mono-alkyneylamide **5** in 90% yield. Removal of the *tert*-butoxycarbonyl (Boc) protecting group was accomplished by heating at 120 °C. Without any work-up procedure, *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole were added to the reaction mixture to give siloxyether **6** in 82% yield over two steps. *N*-butenylation of **6** was performed using the Mitsunobu protocol, in which we selected di-2-methoxyethyl azodicarboxylate (DMEAD),[8] developed by the Sugimura group, instead of the more common alkyl azodicarboxylates such as DEAD or DIAD. This was because alkenylamide **7** could then be successfully isolated from the reaction mixture by extraction. Replacement of the TBS group for an Ac group was conducted via intermediate alcohol **8** to give **1** in 79% yield over 2 steps.

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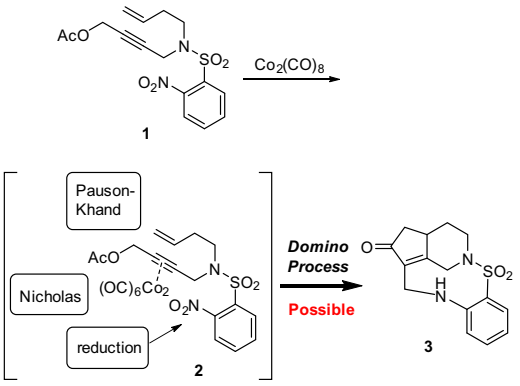
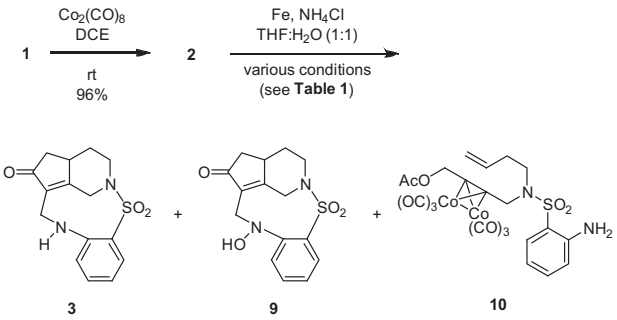


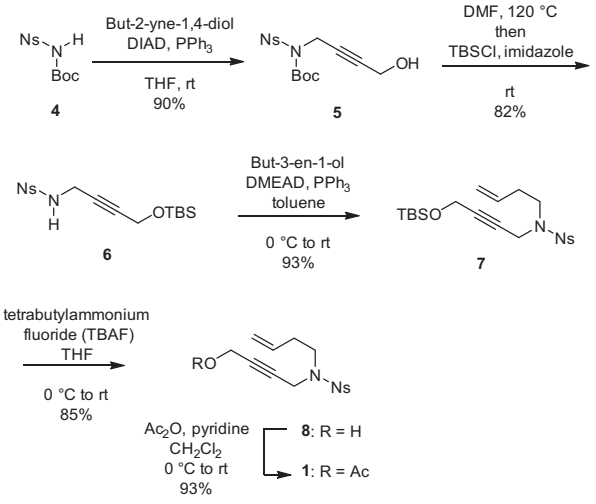
Scheme 1. Proposed synthetic pathway for conversion of **1**–**3**.



Scheme 3. Unprecedented transformation of **1**.

According to our proposed pathway in Scheme 1, we first synthesized alkyne cobalt complex **2** (Scheme 3). Complexation of **1** with stoichiometric amounts of $Co_2(CO)_8$ in dichloroethane (DCE) for 2 h at room temperature efficiently provided **2** in 96% yield. Next, we explored various reducing conditions as there have been no reports providing selective reducing reagents for nitroarene-containing cobalt alkyne complexes. Considering coexistence of the cobalt carbonyl moiety, we selected the Fe/NH_4Cl system, a mild and chemoselective reducing protocol reported by the Ramadas group[9a] and the Xiao group.[9b] Use of this system with **2** afforded three major products, tetracycles **3**, *N*-hydroxyl derivative **9**, and aminoarene complex **10**, in various ratios depending on the reaction conditions. These results are summarized in Table 1 and the structure of **3** recrystallized from EtOH was confirmed by single-crystal X-ray crystallography,[10] as displayed in Figure 1.

An initial attempt using 10 equivalents of both Fe and NH_4Cl in 0.05 M concentration of THF:H_2O (1:1) at room temperature for 48 h afforded products **3**, **9**, and **10** in 35%, 14%, and 14% yields, respectively (entry 1). When the concentration was diluted to 0.005 M an increase in all product yields occurred due to inhibition of the intermolecular reaction (entry 2). Furthermore, increase in the amount of Fe and NH_4Cl promoted synthesis of **3** (entry 3). The best yield obtained for **3** is shown in entry 4. Surprisingly, heating at 60 °C for 1 h gave **9** and **3** in 62% and 16% yields, respectively (entry 5); however, extended heating resulted in decomposition of **9** (entry 6). For reference,[11] treatment of **2** with Fe in 1 M HCl:THF (1:1, 0.005 M) solution gave **3** in only 25% yield, along with trace amounts of **9** and **10** (entry 7). Therefore, we recognized that the domino process slowly proceeded in dilute concentrations in THF:H_2O in the presence of excess amounts of Fe/NH_4Cl at room temperature. Both heating at 60 °C and using with 1 M HCl did not enhance the process.



Scheme 2. Synthesis of **1**.

Interestingly, the Shea group reported that use of a sequential combination of Nicholas and PK reactions enabled rapid construction of unique tricyclic heterocycles.[12] Furthermore, (+)-epoxydictimene was synthesized by the Schreiber group using these two reactions.[13] However, to the best of our knowledge, there have been no reports conducting Nicholas and PK reactions either simultaneously or sequentially under the same conditions, i.e., one-pot reaction. Thus, it was surprising that both reactions were able to occur under the same conditions, particularly as these were mild neutral conditions. In particular, the Nicholas reaction generally requires the use of a Lewis acid such as BF_3 or HBF_4 to generate the activated cationic intermediate.[4] Therefore, in our case, a mechanically different substitution reaction, as opposed to the Nicholas reaction, might have taken place. Furthermore, the generation of *N*-hydroxyl cyclic product **9** proves that the cyclization step has already begun prior to completion of the nitroarene reduction.

To determine the cyclization steps, we attempted to isolate intermediate **12**. We first reduced the nitro group on **1** to corresponding amine **11** in 88% yield by adopting the Fe/NH_4Cl/EtOH/H_2O protocol.[9a] Since the stepwise conditions for Nicholas and PK reactions have been demonstrated by the Shea group, we followed their representative procedures.[12a] Treatment of **11** with $Co_2(CO)_8$ afforded corresponding cobalt alkyne complex **10** in 96% yield. The intramolecular Nicholas cyclization occurred in the presence of $BF_3{\cdot}OEt_2$ in DCE to give nine-membered cyclized intermediate **12** in 72% yield. The following PK step from **12** was performed by heating at 60 °C in DCE for 2.5 h to give **3** in 90% yield. In contrast, cyclization from **10** to **3** successfully proceeded under the NH_4Cl/THF/H_2O conditions, in which **12** was not observed (Scheme 4).

While studying cobalt reagents, we simplified this procedure. $HCo(CO)_4$ generated from H_2O and $Co_2(CO)_8$ has been reported as a mild and chemoselective reductant.[14] Thus, we expected that in situ generated $HCo(CO)_4$ could induce this domino process. Treatment of **1** with two equivalents of $Co_2(CO)_8$ in anhydrous THF at room temperature for 2 h gave the cobalt alkyne complex. Then, this was used in dilute THF:H_2O (1:1, 0.005 M) solution with NH_4Cl (10 equiv) at 60 °C for 3 h to afford **3** in 49% yield, in which we did not detect the formation of **9** and **10** (Scheme 5). Furthermore, the reduction step became slower when the reaction was conducted either at room temperature or without adding NH_4Cl. Although the overall yield of **3** was moderate over four steps, this procedure was the simplest and most elegant,