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Nickel-promoted oxidative domino C_{sp3}–H/N–H bond double-isocyanide insertion reaction to construct pyrrolin-2-ones†

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The first nickel-catalyzed oxidative domino C_{sp3}–H/N–H double isocyanide insertion reaction of acetamides with isocyanides has been developed for the synthesis of pyrrolin-2-one derivatives. A wide range of acetamides bearing various functional groups are compatible with this reaction system by utilizing $Ni(acac)_2$ as a catalyst. In this transformation, isocyanide could serve as a C1 connector and insert into the inactive C_{sp3}–H bond, representing an effective way to construct heterocycles.

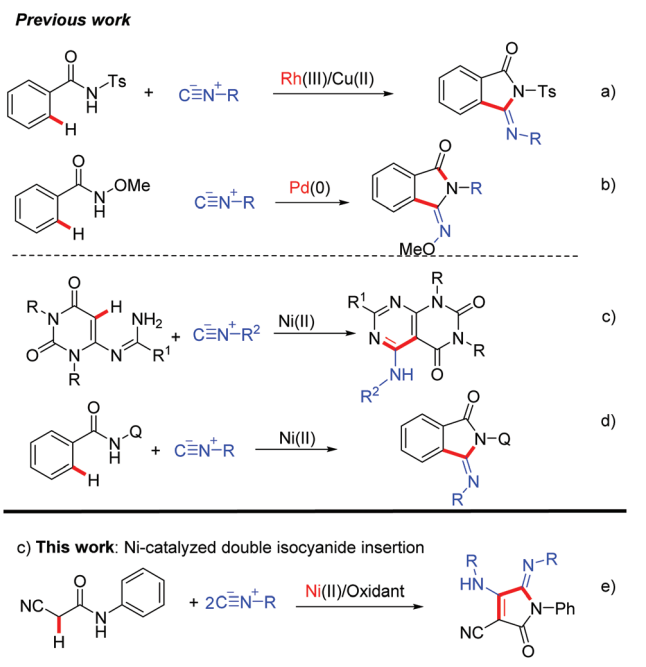
Introduction

The pyrrolin-2-one skeleton is an important scaffold widely distributed in natural products and pharmaceuticals with diverse biologically important properties,[1] including antimycobacterial or antifungal,[2] antimicrobial or antineoplastic,[3] amnesia-reversal,[4] antiepileptic,[5] anti-HIV-1,[6] renin inhibitor,[7] and anticyclooxygenase-2.[8] However, the methods for obtaining pyrrolin-2-ones are still very limited, which may be due to their lack of generality and requirement of inaccessible substrates.[9] Consequently, the synthesis of pyrrolin-2-ones has drawn considerable attention from organic chemists.

During the past decades, isocyanides have been widely applied as valuable C1 sources in organic synthesis, due to their unique nucleo- and electrophilic properties. They have also been applied in the synthesis of biological and pharmacological compounds and great improvements have been made in radical cascade reactions (RCRs), multicomponent reactions (MCRs), and cycloaddition reactions.[10]

The isocyanide insertion reaction catalyzed by transition metals has become an important basic chemical transformation.[11] However, most oxidative isocyanide insertion reactions mainly focused on oxidative single isocyanide insertions.[12] In 2011, Zhu's group described the Rh-catalyzed annulation of *N*-benzoylsulfonamides through a C–H/N–H isocyanide insertion reaction (Scheme 1a).[13] Subsequently, Yu and his coworkers reported an aerobic C_{sp2}–H functionalization for the synthesis of medicinally important lactams using *N*-methoxy amide as the directing group (Scheme 1b).[14] It is worth mentioning that the substrates in the above reactions need directing groups. Moreover, only a few examples of Pd-catalyzed oxidative double isocyanide insertion reactions have been reported in the past few years.[15]

Nickel possesses various oxidation states and mild oxidative addition ability that make it possible to develop a new type of isocyanide insertion reaction.[16] Recently, the group of Maes



Scheme 1 Metal-catalyzed isocyanide insertion transformations.

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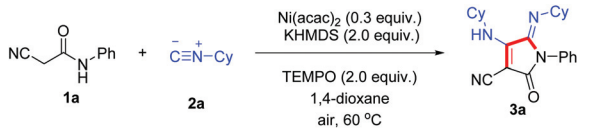
reported a nickel(II)-catalyzed single isocyanide insertion for the construction of pyrimidouracils (Scheme 1c).[16b] Lei's group revealed an oxidative single isocyanide insertion of amides using a bidentate directing group, albeit with a low yield in the case of an unactivated C_{sp3}–H bond (Scheme 1d).[17] The reason why isocyanide insertion reactions under nickel catalysis are less studied may be that isocyanide is very easy to polymerize in the presence of a nickel catalyst, and hence, a directing group is required to promote the transformations.[18] We wonder whether the oxidative double isocyanide insertion reaction of the N–H/C_{sp3}–H bond under nickel catalysis could be achieved without the aid of an auxiliary directing group. As part of our ongoing research interest in the utility of isocyanides as synthons,[19] we previously reported an effective protocol for the synthesis of thiazolidines from thioureas which acted as ligands to activate nickel catalysts in isocyanide insertions.[19e] Following this line, we wonder whether the more challenging double isocyanide insertion across the C_{sp3}–H bond could be fulfilled. Herein we report a novel synthesis of pyrrolin-2-one derivatives and the advantages of the transformations based on the following factors: (1) the requirement of expensive metal catalysts and directing groups was avoided; (2) the achievement of the C_{sp3}–H bond double isocyanide insertion reaction; and (3) avoiding the polymerization of isocyanide in the presence of nickel salts (Scheme 1c).

Results and discussion

Initially, we started our investigation by examining 2-cyano-*N*-phenylacetamide (**1a**) and isocyanocyclohexane (**2a**) under air. To our delight, the desired product pyrrolin-2-one **3a** was successfully furnished with the use of cheap nickel salts. After optimization of the reaction conditions (see the ESI† for details), we were pleased to find that the annulated product **3a** could be obtained in a satisfactory yield of 84% using Ni(acac)$_2$ as a catalyst, KHMDS (potassium bis(trimethylsilyl) amide) as a base, and TEMPO (2,2,6,6-tetramethylpiperidinooxy) and air as co-oxidants at 60 °C for 2 h (Table 1, entry 1). The results showed the combined use of air and TEMPO as the oxidants had a critical influence on the reaction as the reaction was not effectively promoted under air in the absence of TEMPO or TEMPO as a sole oxidant under an argon atmosphere (Table 1, entries 2 and 3). Moreover, TEMPO as the oxidant played a unique role in the annulation presumably due to the prohibition of isocyanide polymerizations and the replacement of TEMPO with metal oxidants such as copper salts led almost to the shutdown of the reaction (Table 1, entry 4). Other solvents such as toluene, CH_3CN or THF were also screened but they decelerated the reaction rate (Table 1, entries 5–7). Strong bases including *t*-BuOLi and NaH could also afford the target product (Table 1, entries 8 and 9), albeit inferior reaction yields were obtained compared to KHMDS. Surprisingly, the increase of the reaction temperature to 80 °C did not give a superior yield (Table 1, entry 10), possibly due to the accelerated decomposition of amide substrate **1a** at a higher reaction temperature. Moreover, a decrease in the reaction temperature with a prolonged reaction time also failed to afford an ideal yield (Table 1, entry 11). Furthermore, other metal catalysts were also tested but they afforded inferior results, especially, precious palladium salts did not give a satisfactory yield (Table 1, entry 12), while Rh(III) salt was not a viable catalyst either (Table 1, entry 13). The result presented a sharp contrast to Zhu's work on the benzoylsulfonamide isocyanide insertion reaction.[13] The control experiment indicated that nickel salts and oxidants were essential, as no reaction took place without Ni(acac)$_2$ and oxidants (Table 1, entries 14 and 15).

Table 1 Optimization of the reaction conditions[a]



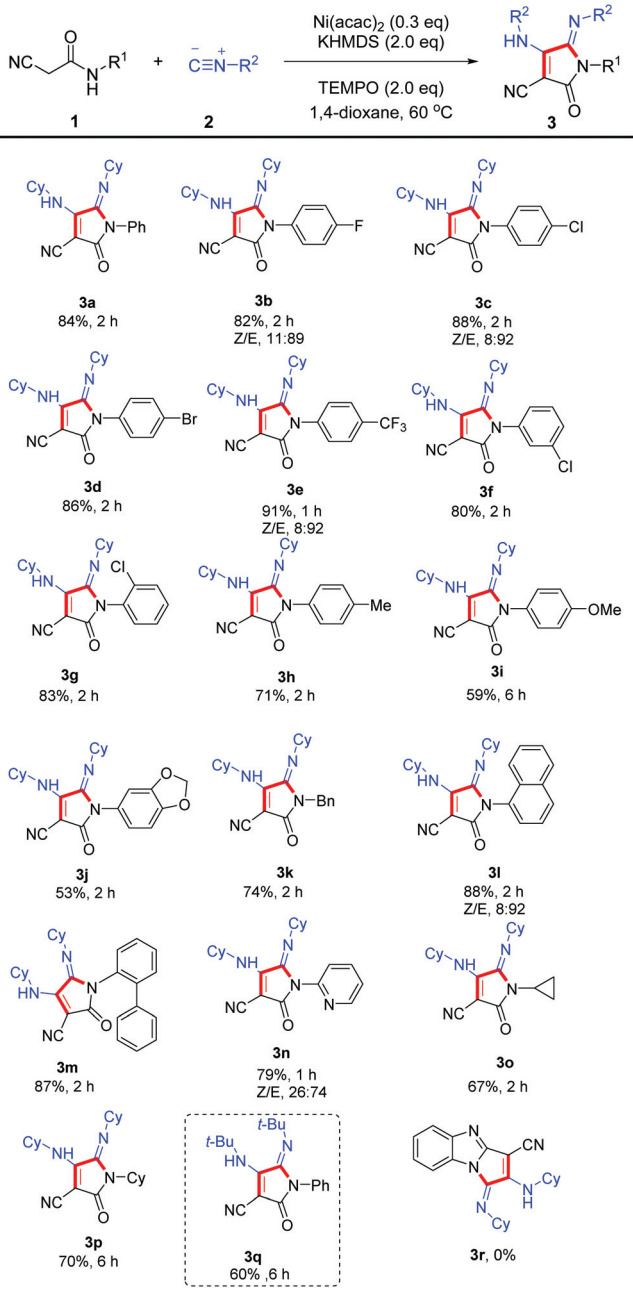
Entry	Deviation from standard conditions	Yield[b] (%)
1	None	84
2	Under argon instead of air	56
3	Under air in the absence of TEMPO	46
4	$CuCl_2$ instead of TEMPO	Trace
5	Toluene instead of 1,4-dioxane	39
6	CH_3CN instead of 1,4-dioxane	52
7	THF instead of 1,4-dioxane	68
8	*t*-BuOLi instead of KHMDS	49[c]
9	NaH instead of KHMDS	65[c]
10	At 80 °C	60
11	At 40 °C	70[d]
12	$Pd(OAc)_2$ instead of Ni(acac)$_2$	19
13	$(Cp^*RhCl_2)_2$ instead of Ni(acac)$_2$	NP[d]
14	No Ni(acac)$_2$	NR
15	In the absence of TEMPO and air	NR

[a] Standard conditions: **1a** (0.6 mmol), **2a** (1.5 mmol), KHMDS (1.2 mL, 1 M in THF) and 1,4-dioxane (1.2 mL), 60 °C, air for 2 h. [b] Isolated yields. [c] Solvent (2.4 mL). [d] Reaction time: 8 h. NP = no product, NR = no reaction, KHMDS = potassium bis(trimethylsilyl)amide, TEMPO = 2,2,6,6-tetramethylpiperidinooxy.

With the optimized reaction conditions in hand, we explored the scope of the isocyanide insertion reaction with 2-cyanoacetamides **1**, as shown in Table 2. The reaction system worked well with a series of substrates bearing various functionalities, furnishing the corresponding annulation products (**3a–3q**) in 53%–91% yields. 2-Cyanoacetamide substrates **1** with electron-withdrawing groups such as halide groups (**1b–1d**) and trifluoromethyl (**1e**) at the *para*-position on the arenes afforded higher yields compared to those with electron-donating groups (**1h–1j**). Moreover, **3d** was further identified by X-ray analysis (see the ESI† for details).

Interestingly, the reactivity of substrates with a chloro group on the *meta*- or *ortho*-position of the arene ring (**1f** and **1g**) showed a similar trend. The naphthalene and biphenyl substituents (**1l** and **1m**) were also compatible with this reaction, providing the desired products **3l** and **3m** in good yields. Heteroarene substrate **1n** was also tolerated under the reaction conditions, producing **3n** in 79% yield. Moreover, the reaction

Table 2 Substrate scope of 2-cyanoacetamides 1 [a]



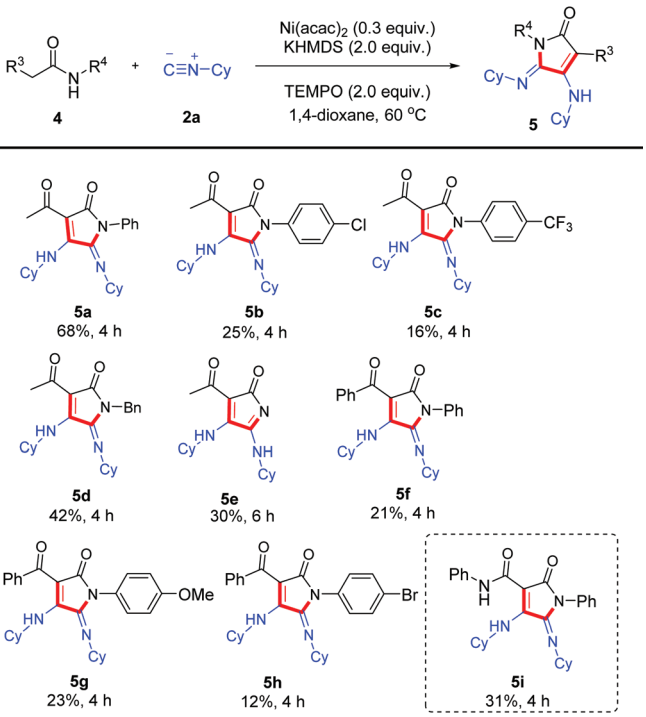
[a] Standard conditions: **1a** (0.6 mmol), **2a** (1.5 mmol), TEMPO (2.0 equiv.), KHMDS (1.2 mL, 1 M in THF) and 1,4-dioxane (1.2 mL), air, 60 °C. Isolated yields.

underwent smoothly to afford the desired compounds **3k**, **3o** and **3p** in 67–74% yields, when the R^1 group of 2-cyano-*N*-acetamides **1** was aliphatic. It is worth noting that *tert*-butyl isocyanide could also act as a reaction partner, affording the corresponding product **3q** in a yield of 60%. Unfortunately, the reaction became sluggish when benzoimidazolyl acetonitrile was employed as the substrate and the corresponding product **3r** was not detected. We also tested several other isocyanides, including aryl isocyanides and TosMIC. Unfortunately, they all did not provide the corresponding annulation products and the reaction system remained messy (see the ESI† for details).

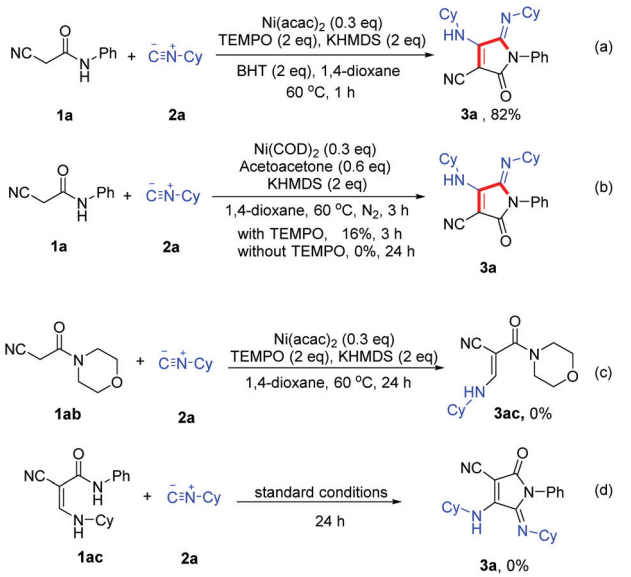
Gratifyingly, changing the substituent "CN" of acetamides **1** to an acetyl or benzoyl group, the corresponding products were also furnished in moderate yields (Table 3). We speculated that the pK_a value of methylene on the acetamide substrates **4** might have a crucial influence on the reaction efficiency. In general, the electron-donating substituents on R^4 of acetamides **4** might promote the reaction compared to the electron-withdrawing functional groups (**5a** *vs.* **5b** and **5c**; **5g** *vs.* **5h**). To our delight, 3-oxobutanamide **4e** could be successfully transformed into pyrrol-2-one derivative **5e**, albeit in a low yield. Moreover, as to substrate **4i**, the reaction underwent smoothly, with the conversion to compound **5i** in 31% yield.

To explore the plausible reaction pathway, several control experiments were carried out (Scheme 2). Firstly, the radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) was introduced into the reaction system and the desired product **3a** could still be obtained without an obvious loss in yield (Scheme 2a), thus excluding radical intermediates. The addition of $Ni(COD)_2$ combined with acetylacetone ligand did not give a satisfactory yield regardless of whether TEMPO was added in the reaction or not (Scheme 2b), indicating that Ni(II) salts might be the real catalyst. Furthermore, the possibility of methylene insertion of isocyanides was excluded due to the following facts: (1) no reaction could take place without the

Table 3 Substrate scope of acetamides 4 [a]



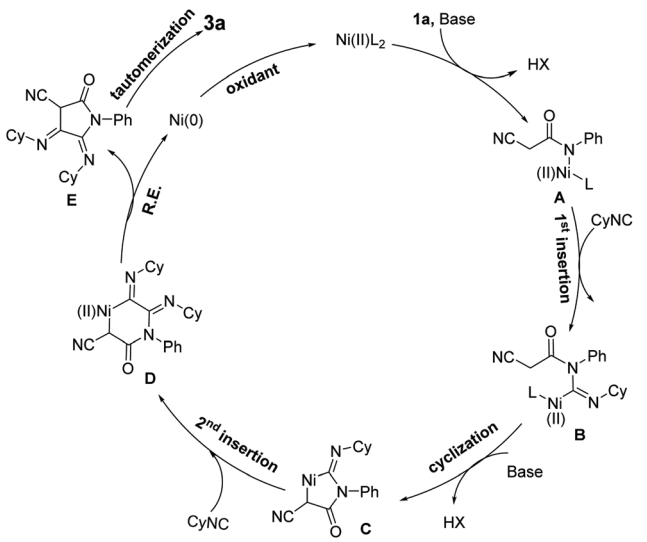
[a] Standard conditions: **4** (0.6 mmol), **2a** (1.5 mmol), TEMPO (2.0 equiv.), KHMDS (1.2 mL, 1 M in THF) and 1,4-dioxane (1.2 mL), air, 60 °C. Isolated yields.



Scheme 2 Control experiments.

acidic N–H bond (Scheme 2c); (2) following Bi's work,[20] **1ac** was synthesized and reacted with **2a**, but target product **3a** was not obtained under the standard reaction conditions (Scheme 2d).

Based on the above control experiments and the literature,[15d,17] a mechanism involving the nickel-catalyzed isocyanide insertion reaction is shown in Scheme 3. We speculated that the deprotonation of the N–H bond of **1a** in the presence of a base firstly takes place to generate the Ni-species **A** with $Ni(acac)_2$. Next, the insertion of isocyanide **2a** into the N–Ni bond affords intermediate **B**, followed by a base-assisted intramolecular C–H metalation event to give the five-membered cyclic Ni(II) species **C**. Subsequently, intermediate **C** could undergo the second isocyanide insertion to form the six-membered intermediate **D**. Reductive elimination of intermediate **D** results in Ni(0) species and annulated product **E**, which undergoes tautomerization to furnish the final product **3a**. The Ni(0) species is oxidized to regenerate Ni(II) species using TEMPO and air for the next catalytic cycle (another route based on the anionic species is given in the ESI†). However, the exact mechanism involved in the process is still unclear to date.



Scheme 3 Proposed reaction mechanism.

Conclusions

In conclusion, we have developed a new strategy for the nickel-catalyzed oxidative domino C_{sp3}–H/N–H bond insertion of double isocyanides for the synthesis of pyrrolin-2-one derivatives. The method is attractive owing to the inexpensive catalyst and its easy handling. Notably, the protocol could suppress the polymerization of isocyanides and a variety of pyrrolin-2-one derivatives could be synthesized in one step. More transformations involving nickel-catalyzed isocyanide insertion are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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