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# Temperature-Dependent Double Isocyanide Insertion Reaction To Construct a Polycyclic Skeleton

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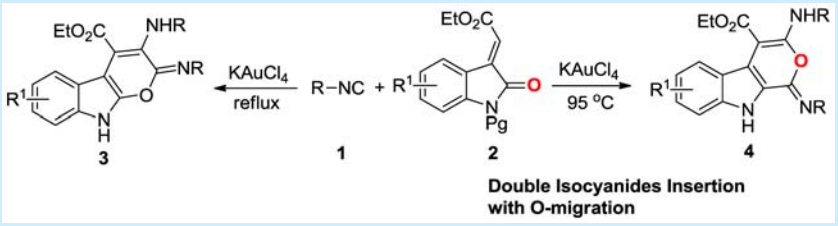
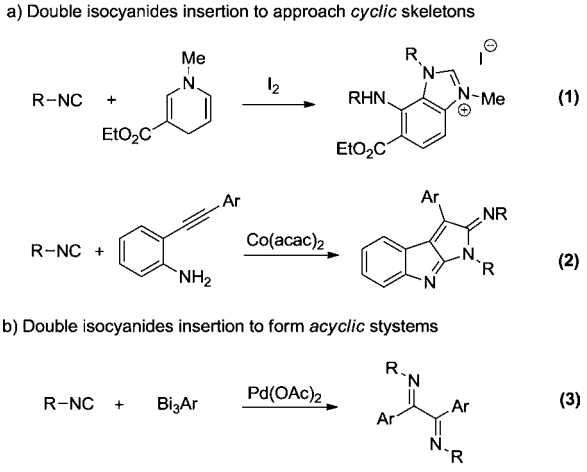
Supporting Information




**ABSTRACT:** A novel strategy to furnish selective double insertion of isocyanides with the aid of potassium tetrachloroaurate(III) has been disclosed. This strategy provides quick access to approach a complex polycyclic skeleton in an efficient manner. Unexpected oxygen migration was also observed when the reaction was conducted at a lower temperature.

As highly versatile building blocks, isocyanides have found wide application in organic synthesis.[1,2] In particular, they are found to be particularly compatible with the construction of a variety of heterocycles.[3] From a mechanistic standpoint, the synthetic versatility of isocyanides mainly arises from their unique carbene-like reactivity,[4] which makes them particularly important starting materials in isocyanide-based multicomponent reactions.[5] Recently, Zhu and co-workers greatly expanded the reactivity profiles of isocyanides by using the isocyano group as a polarized triple bond rather than a carbene.[6] In the past decades, the isocyanide insertion reaction has emerged as a powerful synthetic tool in organic synthesis.[7] Consequently, considerable achievements have been realized in this field.[8−10] Compared with the popularity of single isocyanide insertion, the development of double insertion of isocyanides is far more difficult.[11] To date, only a few successful examples have been reported.[12] Among these reactions, many efforts have been devoted to the construction of cyclic skeletons, thus providing new access to various five- or six-membered rings. For instance, Winkler and co-workers[12a] designed a concise synthesis of a polycyclic ring based on the pioneering [4 + 1] cycloaddition by Saegusa[8e] and Chatani.[8a,b] In 2007, Lavilla and co-workers reported that, in the presence of iodine, reactions of isocyanides and dihydropyridines yielded benzimidazolium salt directly (Scheme 1, eq 1).[12b] This protocol also represents the unprecedented double insertion of an isocyanide unit into a heterocyclic ring. More recently, Jiang and Tu disclosed a cascade bicyclization of isocyanide and 2-ethynylaniline to construct densely functionalized pyrrolo[2,3-*b*]indole (Scheme 1, eq 2).[12c] Regarding the double isocyanide insertion to form an acyclic system, Ogawa and co-workers developed an efficient reaction between isocyanide and triarylbismuthine (Scheme 1, eq 3).[12d] This method allowed for the synthesis of symmetrical $\alpha$-diimine

**Scheme 1. Representative Double Isocyanide Insertion Reactions**




with a broad isocyanide scope. Although challenging, the development of a novel double isocyanide insertion strategy remains desirable since such an achievement could efficiently furnish the construction of structurally unusual systems.

Continuing our efforts on isocyanide chemistry,[13] we became interested in the construction of structurally unusual heterocycles through isocyande insertion reactions. Very recently, we developed an indium-catalyzed multiple isocyanide insertion reaction to synthesize spiro-oxindole.[14] We thus envisioned that there might be a possibility to develop double isocyanide

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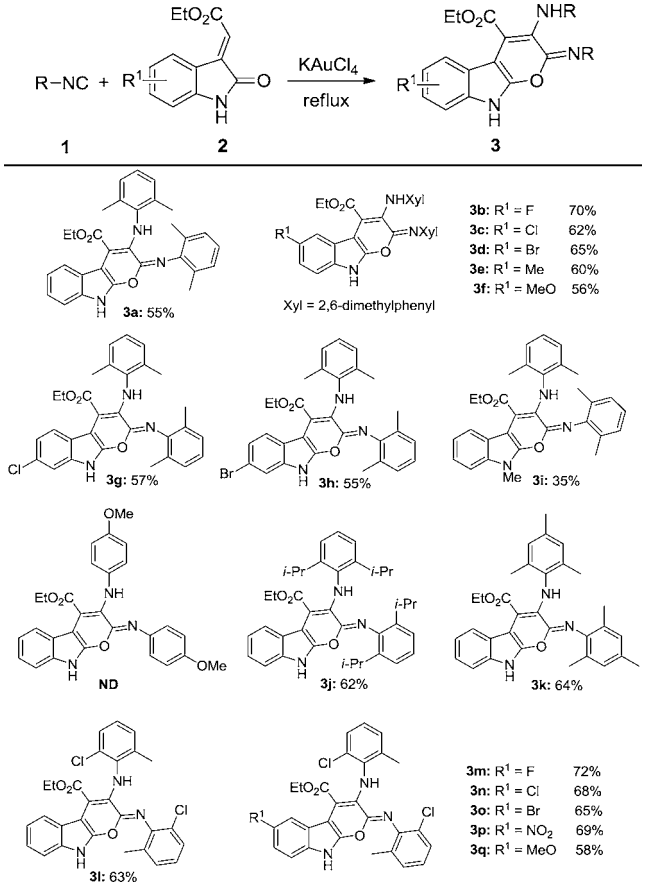
insertion with $\alpha,\beta$-unsaturated carbonyl compounds if we could find appropriate reaction conditions. In this paper, we report that, in the presence of $KAuCl_4$, the reactions of isocyanide and methyleneindolinone afforded polycyclic skeletons using double isocyanide insertion as the key step.

We began our study using 2,6-dimethylphenyl isocyanide **1a** and oxindolylideneacetate **2a** as a model substrate. In the presence of $KAuCl_4$ (15 mol %), heating the mixture of **1a** and **2a** in toluene under reflux gave rise to 55% yield of adduct **3a** (Scheme 2). Encouraged by this result, we subsequently used

**Scheme 2. $KAuCl_4$-Catalyzed Double Isocyanide Insertion with Isocyanide 1 and Oxindolylideneacetate 2[a,b]**

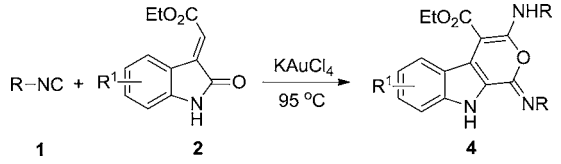


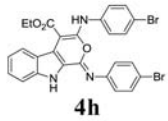
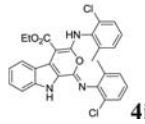

[a]Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), $KAuCl_4{\cdot}2H_2O$ (15 mol %), toluene (5 mL), reflux. [b]Yield of product after silica gel chromatography.

several substituted oxindolylideneacetates **2** to react with isocyanide **1a**, and the representative results are summarized in Scheme 2. Substrates **2** bearing electron-deficient and electron-rich substituents at position 5 (**3b**–**3f**) and position 6 (**3g** and **3h**) on the aromatic ring were well-tolerated to experience a double isocyanide insertion reaction. All new compounds were characterized by $^1$H NMR, $^{13}$C NMR, and HRMS (see the Supporting Information for details). Substrate **2i** bearing a methyl protecting group at the nitrogen atom was also tested to generate product **3i** in lower yield. The structure of compound **3i** was unambiguously confirmed by single-crystal X-ray analysis.[15] The experimental outcome showed that the nature of the substituent R in isocyanide **1** played an important role in the present transformation. No reaction occurred when 4-methoxylphenyl isocyanide **1b** was used. In sharp contrast, sterically hindered aromatic isocyanides, including 2,6-diisopropylphenyl isocyanide **1c**, 2,4,6-trimethylphenyl isocyanide **1d**, and 6-chloro-2-methylphenyl isocyanide **1e**, were found to be particularly effective substrates to react with **2** under the standard conditions, thus affording the desired products **3j**–**3q** with good performance.

New experimental results were observed when the present reaction was conducted at a lower temperature. As shown in Table 1, treatment of **1a** and **2a** in toluene at 95 °C essentially

**Table 1. $KAuCl_4$-Catalyzed Unusual Double Isocyanide Insertion with Isocyanide 1 and Oxindolylideneacetate 2 Involving Oxygen Migration[a]**




| entry | $R^1$ | product | yield (%)[b] |
|---|---|---|---|
| 1 | H | **4a** | 35 |
| 2 | 5-fluoro | **4b** | 58 |
| 3 | 5-chloro | **4c** | 49 |
| 4 | 5-bromo | **4d** | 50 |
| 5 | 6-bromo | **4e** | 40 |
| 6 | 5-methyl | **4f** | 45 |
| 7 | 5,7-dimethyl | **4g** | 48 |
| 8 | H |  **4h** | 44 |
| 9 | H |  **4i** | 45 |

[a]Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), $KAuCl_4{\cdot}2H_2O$ (15 mol %), toluene (5 mL), 95 °C. [b]Yield of product after silica gel chromatography.

generated an unknown compound **4a**. At first glance, it is very easy to wrongly recognize **4a** as **3a** because their polarity is quite similar from TLC detection. The $^1$H NMR spectrum of **4a** clearly shows that two molecular isocyanides participate in the conversion, whereas the chemical shift differs dramatically from compound **3a**. The structure of compound **4a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).[16] The X-ray structure of **4a** clearly showed the occurrence of unusual oxygen migration, which is unknown in reported literature. With this new structure in hand, we turned our attention to the oxindolylideneacetate scope. Changing the substituents of substrate **2** on the aromatic ring was first carried out, and representative results are summarized in Table 1 (entries 2–7). The feasibility of substituted isocyanides **1** was next examined. The present reaction was not limited to sterically hindered aromatic isocyanides. For instance, the less reactive 4-bromophenyl isocyanide **1f** also showed high performance under the standard conditions to afford **4h** in satisfactory yield



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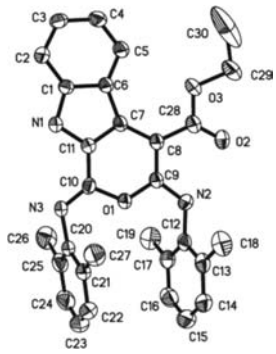
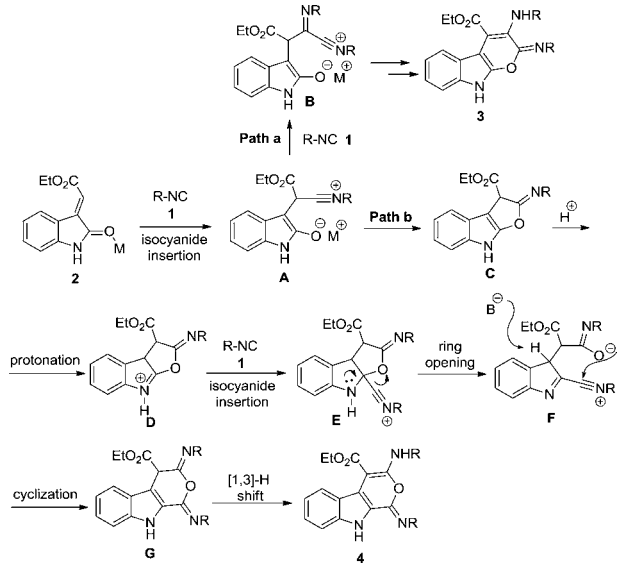


**Figure 1.** Single-crystal X-ray structure for **4a**.

(Table 1, entry 8). The spectra of products **4** were characterized by the peak appearing downfield, with an approximate 10 ppm chemical shift (see the Supporting Information for details). According to our analysis, this proton should be the NH adjacent to the COOEt group since there is a strong H-bond between the NH and CO groups from the X-ray structure of **4a**, whereas an analogous H-bond is absent from the X-ray structure of **3i**. Unfortunately, the employment of other aliphatic isocyanides, such as cyclohexyl and benzyl isocyanides, failed to produce the desired product.

Based on the aforementioned experimental results, a mechanistic proposal is outlined in Scheme 3 to interpret the

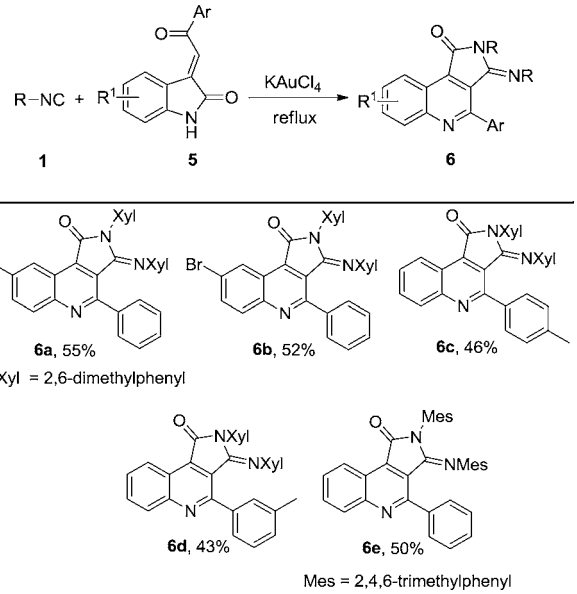
**Scheme 3. Proposed Mechanism**




formation of products **3** and **4**. The beginning of the present cycloaddition may involve the insertion between isocyanide **1** and substrate **2**, thus providing intermediate **A**. According to our assumption, two subsequent pathways are possible. In path a, the electron-deficient nitrene cation in intermediate **A** is directly captured by another molecular isocyanide **1**, which allows for the quick access to product **3** via **B**. Another possibility may involve the intramolecular cyclization to generate intermediate **C** via **A**. Then protonation and the second isocyanide insertion essentially led to intermediate **E**, which is believed to be the key step in the whole transformation. Additionally, ring opening takes place to yield intermediate **F**. The last step comprises the second intramolecular cyclization followed by a [1,3]-H shift, thus furnishing double isocyanide insertion with unusual oxygen migration.

To further demonstrate the versatility of this process, reactions between arenacylideneoxindoles **5** and isocyanides **1** were also carried out (Scheme 4). In such a case, however, only densely

**Scheme 4. Reactions with Arenacylideneoxindoles 5**[a,b]




[a]Reaction conditions: **1** (1 mmol), **5** (0.5 mmol), $KAuCl_4 \cdot 2H_2O$ (15 mol %), toluene (5 mL), reflux. [b]Yield of product after silica gel chromatography.

substituted quinolone derivatives **6** were isolated.[17] The structure of compound **6b** was also confirmed by single-crystal X-ray analysis.[18] The X-ray analysis indicated that this transformation also involved double insertion of isocyanides. Yet, we are not sure about the exact mechanism temporarily. Arenacylideneoxindoles **5**, having different substituents, proceeded readily to yield the corresponding adducts **6a**–**6d**. Experiments with **1d** rather than **1a** were also found to be compatible.

In conclusion, we have disclosed the selective double insertion of isocyanides with oxindolylideneacetate in the presence of catalyst. This protocol offers a new opportunity to approach structurally complex polycyclic skeletons in an efficient manner. Furthermore, we also observed unusual oxygen migration when the reaction was conducted under lower temperature. The reaction mechanism may involve double isocyanide insertion, cyclization, or ring opening followed by isomerization. This strategy is also distinguished by its excellent atom economy, high efficiency, and mild conditions. As a result, the present reaction has the potential to be further applied in organic synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00131.

X-ray crystal structure data for **3i** (CIF)
X-ray crystal structure data for **4a** (CIF)
X-ray crystal structure data for **6b** (CIF)



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Experimental procedures and full characterization of all compounds, spectral data, and $^{1}H$ and $^{13}C$ NMR spectra for all products (PDF)

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### Notes

The authors declare no competing financial interest.

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(15) CCDC 1442739 for compound **3i** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(16) CCDC 1442741 for compound **4a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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(18) CCDC 1442742 for compound **6b** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.




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