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Rhenium-Catalyzed Synthesis of 1,3-Diiminoisoindolines via Insertion of Carbodiimides into a C−H Bond of Aromatic and Heteroaromatic Imidates

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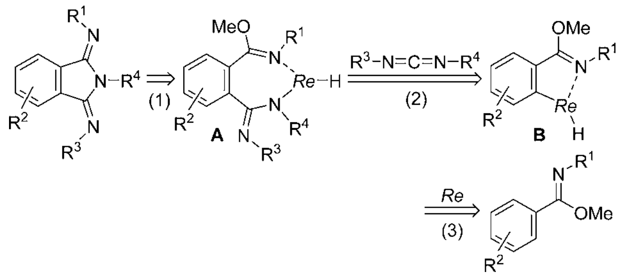
Supporting Information

ABSTRACT: The rhenium-catalyzed synthesis of 1,3-diiminoisoindolines and their related compounds from aromatic or heteroaromatic imidates and carbodiimides are reported via C−H bond activation. This reaction is the first example of a transition-metal-catalyzed insertion of carbodiimides into an aromatic or heteroaromatic C−H bond and a novel method for synthesizing 1,3-diiminoisoindolines and their related compounds. Unsymmetrical 1,3-diiminoisoindolines were easily obtained using this method. The reaction proceeded in good to excellent yield using a variety of substrates.

1,3-Diiminoisoindolines are diimidated phthalimides and partial structures of phthalocyanines and their metal complexes. Phthalocyanines and their metal complexes are useful as organic functional materials, such as pigments, organic electroluminescence, and organic field effect transistors.[1] In addition, 1,3-diiminoisoindolines and their derivatives exhibit several biological activities as a complement component 3a antagonist and antimalarial candidates.[2] Synthetic reactions of 1,3-diiminoisoindolines, however, are still rare.[3] In addition, synthesis of unsymmetrical 1,3-diiminoisoindolines using previously reported synthetic methods remains difficult.

Scheme 1. Retrosynthetic Route of 1,3-Diiminoisoindolines

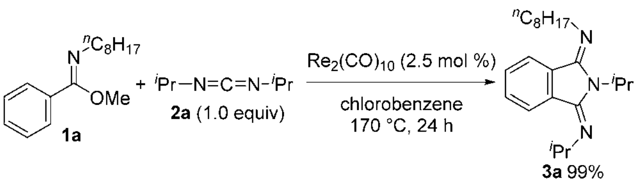


We considered a new synthetic method of 1,3-diiminoisoindolines via C−H bond activation (Scheme 1): (1) a 1,3-diiminoisoindoline is obtained by intramolecular nucleophilic cyclization of intermediate **A** and elimination of methanol; (2) intermediate **A** is formed by the insertion of a carbodiimide into a rhenium−carbon bond of intermediate **B**; and (3) intermediate **B** is generated by oxidative addition of an aromatic imidate to a rhenium catalyst (C−H bond activation).

Transition-metal-catalyzed C−H insertion reactions of unsaturated molecules have recently received considerable attention, and many reactions using several types of transition metal catalysts have been developed.[4] To the best of our knowledge, however, there are no examples of transition-metal-catalyzed insertion of carbodiimides into an aromatic C−H bond. We reported new synthetic reactions of cyclic compounds by the insertion of unsaturated molecules into a C−H bond of various substrates and successive intramolecular nucleophilic cyclization under rhenium catalysis.[5−7] We then considered that synthesis of 1,3-diiminoisoindolines, shown in Scheme 1, could be achieved using a rhenium catalyst. Herein we report the rhenium-catalyzed synthesis of 1,3-diiminoisoindolines from aromatic imidates and carbodiimides.

We began our studies with several transition metal complexes and salts using aromatic imidate **1a** and *N,N′*-diisopropylcarbodiimide (**2a**) as model substrates. A rhenium complex, $Re_2(CO)_{10}$, exhibited high catalytic activity. Treatment of **1a** with **2a** in the presence of the $Re_2(CO)_{10}$ catalyst in chlorobenzene at 170 °C for 24 h gave 1,3-diiminoisoindoline **3a** in 99% yield (Scheme 2). Several other transition metal complexes promoted the annulation reaction, but the yields of **3a** were low.[8] The stereochemistry of the imino groups was

Scheme 2. Rhenium-Catalyzed Synthesis of 1,3-Diiminoisoindoline from Aromatic Imidate and Carbodiimide



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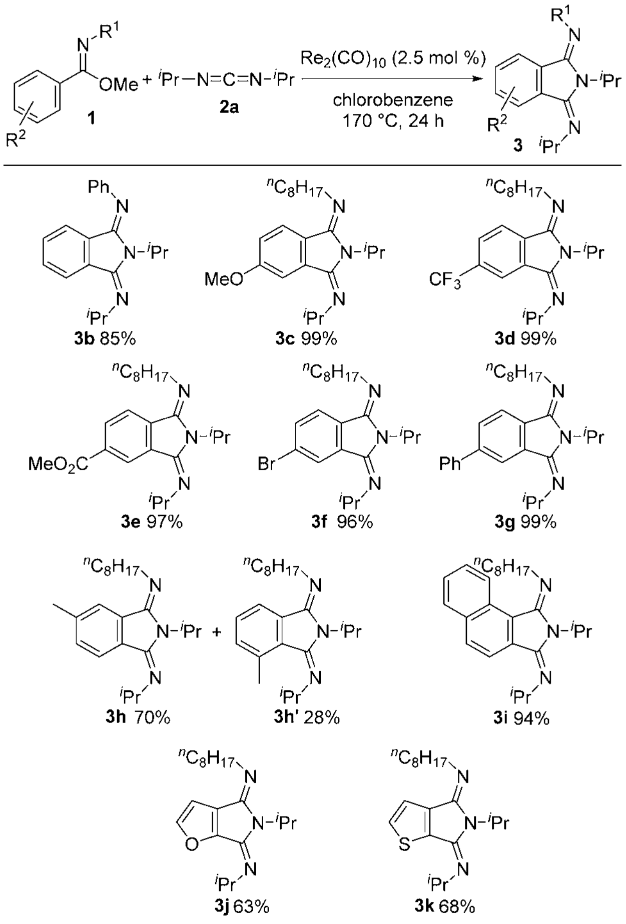
determined by nuclear Overhauser effect experiments using (*E*)-*N*-((*E*)-5-bromo-2-isopropyl-3-(isopropylimino)-1-isoindolinylidene)-1-propanamine **3A** (see Supporting Information for details). Interestingly, the desired reaction proceeded in advance of the consumption of **2a** by the addition of methanol (byproduct) to **2a**.[9] This reaction is the first example of transition-metal-catalyzed insertion of a carbodiimide into a C−H bond of aromatic and heteroaromatic compounds and a novel example of the synthesis of an unsymmetric 1,3-diiminoisoindoline derivative.

We then investigated the substrate scope of aromatic and heteroaromatic imidates (Scheme 3). The desired reaction proceeded, and 1,3-diiminoisoindoline **3b** was obtained in 85% yield when an aromatic imidate with a phenyl group on the nitrogen, **1b**, was used as a substrate. In the case of *N*-octyl aromatic imidates bearing an electron-donating or -withdrawing group, **1c**−**1g**, the corresponding 1,3-diiminoisoindolines **3c**−**3g** were afforded in 96%−99% yield. In these substrates, the functional groups remained unchanged during the reactions. A mixture of two regioisomers, **3h** and **3h′**, was formed when an aromatic imidate with a methyl group at the *meta*-position, **1h**, was used as a substrate. In this reaction, the major product **3h** was produced by the reaction at the sterically less hindered site. The desired reaction also proceeded regioselectively when naphthyl imidate **1i** and heteroaromatic imidates **1j** and **1k** were used as substrates.

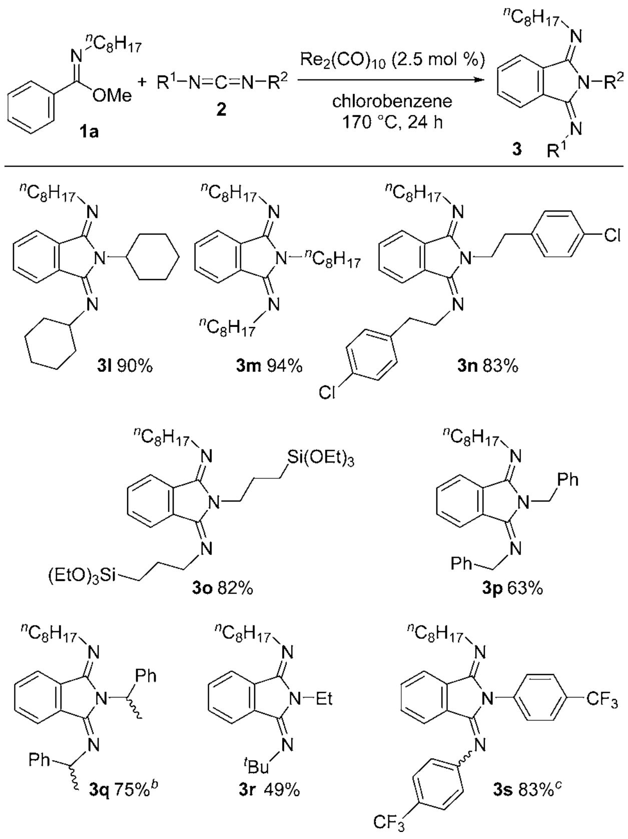
Scheme 3. Reactions between Several Aromatic or Heteroaromatic Imidates 1 and *N*,*N*′-Diisopropylcarbodiimide 2a[a]



[a]**2a** (1.0 equiv).

Next, we examined the substrate scope of carbodiimides (Scheme 4). Dicyclohexylcarbodiimide (**2b**) afforded the corresponding 1,3-diiminoisoindoline **3l** in 90% yield. Carbodiimides bearing primary alkyl groups, **2c**−**2e**, also produced 1,3-diiminoisoindolines **3m**−**3o** in 82%−94% yield without loss of the functional groups. The corresponding 1,3-diiminoisoindolines **3p** and **3q** were obtained in good yield using dibenzylic carbodiimides as substrates. Interestingly, the regioselectivity was completely controlled in the reaction between **1a** and unsymmetric carbodiimide **2h**, and a single product **3r** was produced. A diaryl carbodiimide **2i** also gave the corresponding 1,3-diiminoisoindoline **3s** in 83% yield.

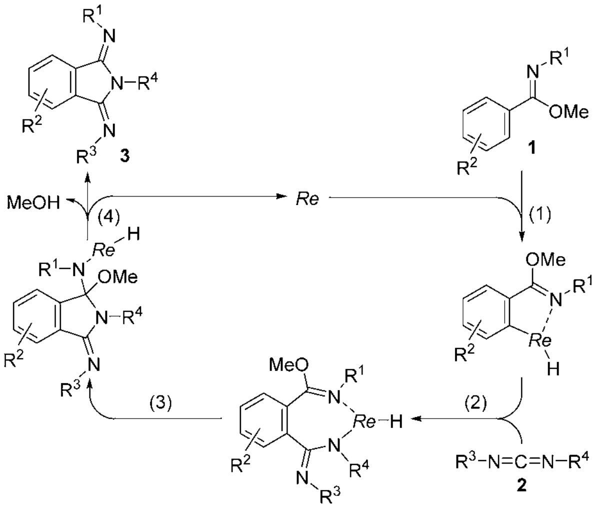
Scheme 4. Reactions between Aromatic Imidate 1a and Several Carbodiimides 2[a]



[a]**2** (1.0 equiv). [b]dr = 2:1. [c]*E*/*Z* = 5:1.

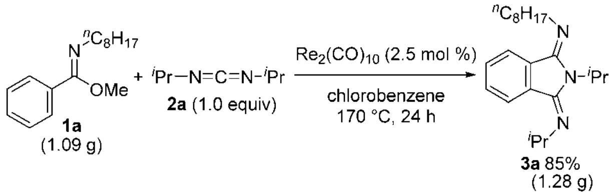
A proposed mechanism for the formation of 1,3-diiminoisoindolines **3** is shown in Scheme 5: (1) oxidative addition of aromatic imidate **1** to a rhenium catalyst (C−H bond activation); (2) insertion of carbodiimide **2** into the formed rhenium−carbon bond; (3) stereoinversion of a C=N double bond to avoid the steric repulsion between substituents R^3 and R^4, and intramolecular nucleophilic cyclization; and (4) reductive elimination and elimination of methanol to give 1,3-diiminoisoindoline **3** and regenerate the rhenium catalyst. As described above, the stereochemistry of product **3** was determined by nuclear Overhauser effect experiments. In addition, the formation of methanol was detected by ^{1}H NMR of the crude mixture.

Scheme 5. Proposed Mechanism for the Formation of 1,3-Diiminoisoindolines 3



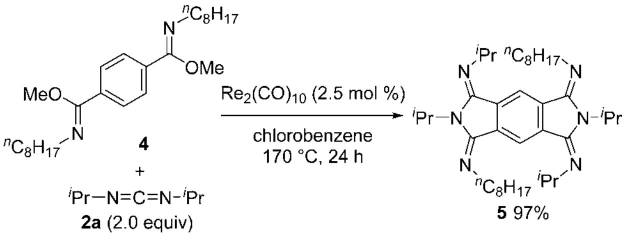
The annulation reaction proceeded in excellent yield, even in gram scale (Scheme 6). An annulation reaction of 1.09 g of aromatic imidate **1a** with carbodiimide **2a** gave 1.28 g of the desired product **3a** in 85% yield.

Scheme 6. Gram-Scale Synthesis of 1,3-Diiminoisoindoline



A double annulation reaction also proceeded in excellent yield (Scheme 7). Treatment of aromatic diimidate **4** with *N*,*N*-diisopropylcarbodiimide (**2a**) in the presence of the $Re_2(CO)_{10}$ catalyst in chlorobenzene at 170 °C for 24 h gave 1,3-diiminoisoindoline **5** in 97% yield as a single product. The reaction proceeded highly regioselectively, and only product **5** was obtained, whereas a regioisomer could be formed.

Scheme 7. Double Annulation Reaction



In summary, we successfully applied rhenium catalysis to synthesize 1,3-diiminoisoindolines and their related compounds from aromatic or heteroaromatic imidates and carbodiimides via C−H bond activation. The desired reaction proceeded in advance of the consumption of carbodiimides by the addition of methanol (byproduct) to carbodiimides. To the best of our knowledge, this is the first example of a transition-metal-catalyzed C−H insertion of carbodiimides, and this reaction is a novel method for synthesizing 1,3-diiminoisoindolines and their related compounds. Introduction of different substituents on the imino groups of 1,3-diiminoisoindolines by previously reported synthetic methods remains difficult. From this point of view, the present method is useful for synthesizing unsymmetrical 1,3-diiminoisoindolines. The reaction proceeded in good to excellent yield using a variety of substrates, even in gram scale. Double annulation also proceeded in excellent yield to give the desired product as a single product. We hope that the present reaction will become a useful method to synthesize 1,3-diiminoisoindolines and their related compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01012.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(8) For the results of reactions between **1b** and **2a** in toluene at 150 °C: $ReBr(CO)_5$, 26%; $[ReBr(CO)_3(thf)]_2$, 30%; $Re_2(CO)_{10}$, 33%; $[Rh(OH)(cod)]_2$/*rac*-BINAP, 8%; $[Cp^*IrCl_2]_2$, 16%. The desired reaction did not proceed using the following transition metal complexes and salts: $Mn_2(CO)_{10}$, $MnBr(CO)_5$, $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_3$, $[RuCl_2(p\text{-cymene})]_2$, $RhCl(PPh_3)_3$, $[Cp^*RhCl_2]_2$, $[Ir(OMe)(cod)]_2$/dtbpy, $Pd(OAc)_2$, and $Cu(OAc)_2$.

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