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Formation of Cyclopenta[*c*]pyridine Derivatives from 2,5-Disubstituted Pyrroles and 1,4-Dibromo-1,3-butadienes via Pyrrole-Ring One-Carbon Expansion

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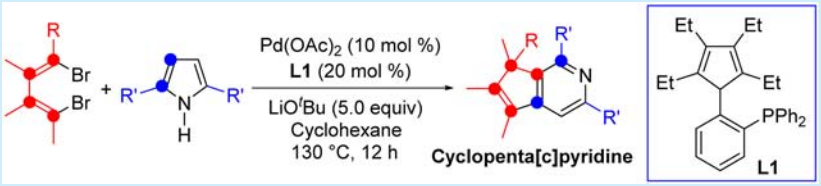
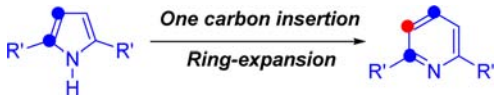
Supporting Information



ABSTRACT: Reactions between 1,4-dibromo-1,3-butadienes and 2,5-disubstituted pyrroles afforded cyclopenta[*c*]pyridine derivatives in high yield, catalyzed by palladium and a cyclopentadiene-phosphine ligand (**L1**). Insertion of one terminal carbon of the butadienyl skeleton into one C═C double bond in the pyrrole ring resulted in ring expansion, along with a 1,2-shift of an alkyl or an aryl substituent on the butadienes.

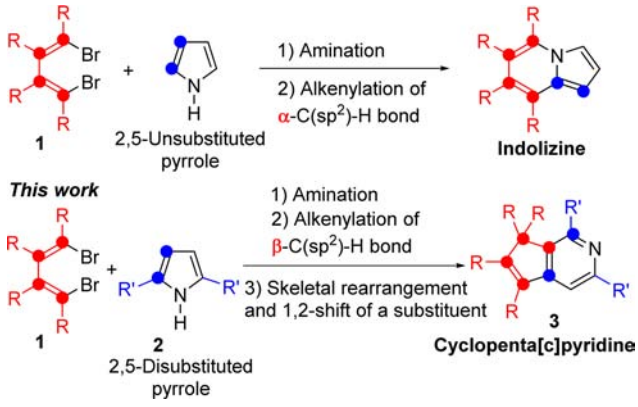
Ring-expansion reactions serve as a useful strategy in organic chemistry for the synthesis of larger cyclic compounds.[1] Both five-membered pyrrole derivatives and six-membered pyridine derivatives are common compounds and useful building blocks. One-carbon expansion of the pyrrole skeleton should lead to the formation of pyridine derivatives (Scheme 1). However, although it has been known for a long time that pyrrole can be transformed to pyridine with a dihalomethane and a strong base (the Reimer−Tiemann reaction conditions),[2−4] such a transformation via one-carbon expansion of the pyrrole skeleton forming pyridine derivatives has not been well developed.

Scheme 1. Formation of Pyridine Derivatives via Pyrrole-Ring One-Carbon Expansion



We have been recently working on the reaction between 1,4-dibromo-1,3-butadienes **1** and amines including pyrroles, aiming at the development of synthetic methods for N-containing compounds, especially azacycles.[5] Indolizine derivatives were obtained in good yields from the reaction between **1** and 2,5-unsubstituted pyrroles, via alkenylation of the α-C(sp^2)−H bond of pyrrole (Scheme 2).[6] However, in this work we found that when 2,5-disubstituted pyrroles **2** were treated with **1** under catalytic conditions using palladium and the cyclopentadiene-phosphine ligand (**L1**), totally different products, cyclopenta[*c*]pyridine derivatives **3**,[7] were obtained selectively in high yields (Scheme 2). In this reaction process, the C(sp^2)−N bond formation (e.g., amination) was followed by alkenylation of the β-C(sp^2)−H bond of pyrrole and skeletal rearrangement along with a 1,2-shift of an alkyl or an aryl substituent on the butadienyl skeleton.

Scheme 2. Different Reactions between 1 and Pyrrole Derivatives with Different Substitution Patterns



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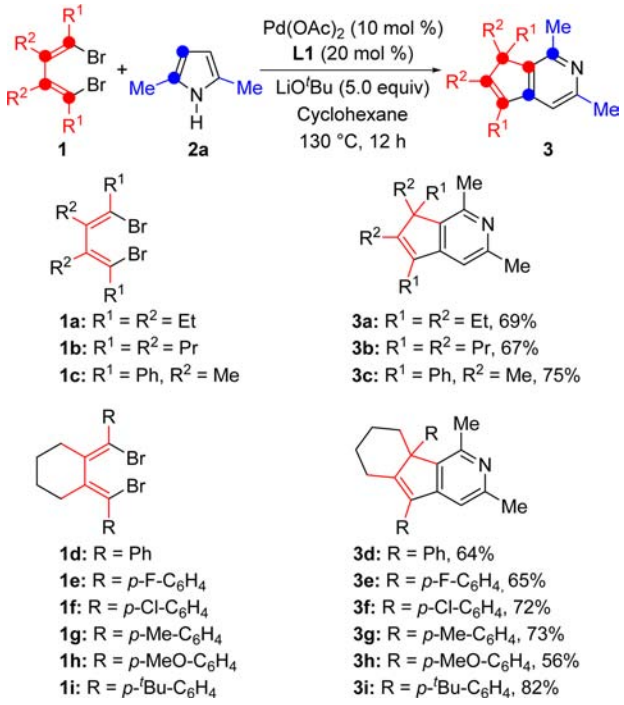
Multisubstituted 1,4-dibromo-1,3-butadienes **1** are now readily available.[5] Reaction of 1,4-dibromo-1,3-butadiene **1a** with 2,5-dimethyl pyrrole **2a** was utilized as a model reaction to screen reaction conditions, including the Pd source, ligands, and bases. Finally, we found that **3a** could be obtained in 69% isolated yield by using $Pd(OAc)_2$ (10%) as the catalyst, LiO^tBu as the base, and cyclopentadiene-phosphine (**L1**)[8] as the ligand in cyclohexane at 130 °C for 12 h (for a detailed screening of reaction conditions, see Supporting Information). The reaction of a variety of **1** with 2,5-dimethyl pyrrole **2a** afforded the cyclopenta[*c*]pyridine derivatives **3** in good isolated yields under the optimized reaction conditions (Scheme 3). The

Scheme 3. Palladium/Cyclopentadiene-Phosphine Ligand (L1)-Catalyzed Reaction of Dibromides 1 with 2,5-Dimethyl Pyrrole 2a



substituent R^1 of 1,4-dibromo-1,3-butadienes **1** can be an alkyl group or an aromatic group substituted with electron-withdrawing or electron-donating groups. Both the alkyl or the aromatic substituents (R^1) could undergo the same 1,2-shift. The structure of product **3g** was determined by single-crystal X-ray structural analysis (Figure 1). It should be noted that, when R^1 of the 1,4-dibromo-1,3-butadienes **1** was a trimethylsilyl group, or an ortho- or meta-substituted phenyl group, yields of their corresponding cyclopenta[*c*]pyridine derivatives **3** were very low, probably due to the steric effect. In these cases, most of **1** remained unreacted.

As shown in Scheme 4, when 2-methylindole derivatives **2b–e** were subjected to a reaction with 1,4-dibromo-1,3-butadiene **1a**, cyclopenta[*c*]quinolone derivatives **3j–m** could be obtained in good isolated yields. Pyridine-fused cyclic compounds are very useful. However, their synthetic methods are very limited.[9]

When 2,4-dimethyl pyrrole and parent indole were used, their reactions with 1,4-dibromo-1,3-butadiene **1a** afforded indolizine derivatives.[6] No formation of their corresponding cyclopenta[*c*]pyridine derivatives **3** was observed. These experimental results shed light on the reaction mechanism.

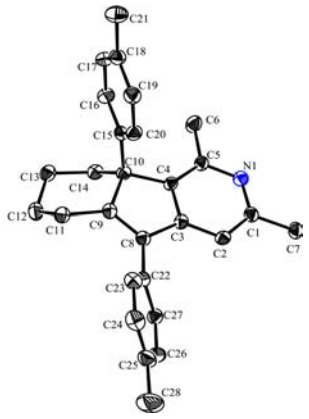
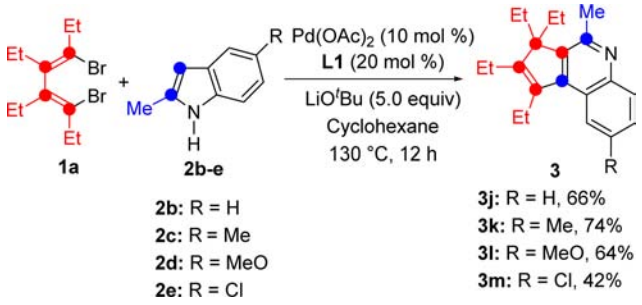


Figure 1. ORTEP drawing of **3g** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

Scheme 4. Reaction of Dibromide 1a with 2-Methyl Indole Derivatives 2b–e



Based on the above experiments and previous work,[6,10] a possible mechanism is proposed in Figure 2. The dibromide **1**

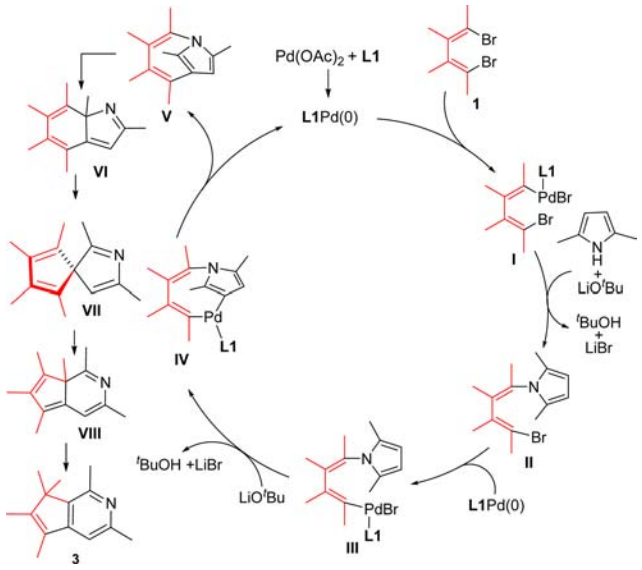


Figure 2. Proposed reaction mechanism.

underwent oxidative addition/amination/oxidative addition to form the intermediate **III**. Then, with the assistance of LiO^tBu, the intermediate **IV** was formed via an electrophilic palladation at the β-C(sp^2)–H bond of disubstituted pyrrole. The intermediate **IV** underwent reductive elimination to give the intermediate **V**. According to the Bredt's rule, the intermediate **V** with a bridgehead double bond is highly strained and thus

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will go through rearrangement quickly. Through a multistep rearrangement,[11,12] the intermediate **V** transformed to the final product **3**.

In order to have a comprehensive understanding of this rearrangement, we investigated the transformation from the intermediate **V** to product **3** with DFT calculations. In order to simplify the computation, all the substituents on the skeletons of intermediates and products were methyl groups. All calculations were carried out with the GAUSSIAN 09 program package.[13] All the minima and transition states were fully calculated at the B3LYP/6-31+G* level[14] in the gas phase. The results are shown in Figure 3.

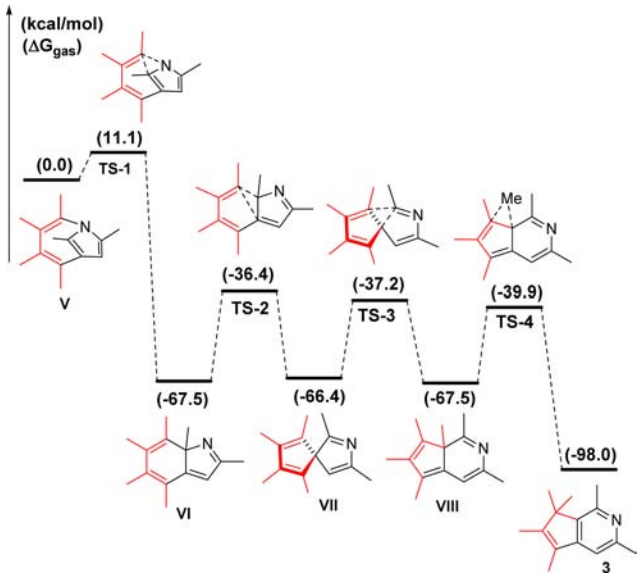

Figure 3. DFT-calculated potential-energy surfaces of the rearrangement.

As shown above in Figure 3, the intermediate **V** went through a three-membered transition state **TS-1** to give intermediate **VI**. The energy barrier of this transformation is 11.1 kcal/mol, and the total energy decreases by 67.5 kcal/mol. This may be due to the release of ring strain in **V**. Then the intermediate **VI** underwent a two-step 1,2-alkyl rearrangement[11] to give the intermediate **VIII**. The energy barriers of these two steps are about 30 kcal/mol, which could be realized under 130 °C reaction conditions. Finally, with the rearomatization as the driving force,[12] the intermediate **VIII** went through transition state **TS-4** to give the final product, the cyclopenta[*c*]pyridine **3**.

In summary, we have developed an efficient method to synthesize the multisubstituted cyclopenta[*c*]pyridine derivatives from disubstituted pyrrole and alkenyl bromides via a Pd/cyclopentadiene-phosphine catalyzed one-carbon ring-expansion reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03431.

Experimental details, X-ray data for **3g**, scanned NMR spectra of all new products (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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