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Domino Coupling Relay Approach to Polycyclic Pyrrole-2-carboxylates

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Pyrroles represent an important class of nitrogen heterocycles, which are found in various biologically active natural compounds.[1] Specifically, pyrrole-2-carboxylate is an interesting cyclic amino acid motif, which is found in natural and artificial functional molecules such as bioactive natural products,[2] selective DNA-binding ligands,[3] and conformationally constrained peptides.[4] The construction of multiply substituted pyrrole rings is, however, still relying largely on the classical condensation methods such as Paal−Knorr synthesis,[1] although catalytic multicomponent coupling approaches have attracted recent attention as environmentally benign alternatives.[5] The convergent synthesis of highly valuable polycyclic analogues along this line has also remained to be developed. In this context, we explored a novel four-component coupling strategy to synthesize polycyclic pyrrole-2-carboxylates. Complexity-generating domino multicomponent coupling processes have become increasingly important in terms of the diversity-oriented synthesis toward the construction of small molecular libraries.[6,7] Our approach comprises the relay process of the following two catalytic domino reactions: (1) the Cu-catalyzed three-component condensation giving rise to glycinate-tethered 1,6-enynes and (2) the subsequent Ir-catalyzed cycloisomerization/Diels−Alder cycloaddition/dehydrogenative aromatization.

Glycinate-tethered α,ω-enynes are fascinating precursors for the synthesis of constrained cyclic α-amino acids (Figure 1).[8] The preparation of 1,6-enynes **A**, however, has not been reported to date, while similar 1,7-enynes **B** were synthesized from a protected glycine through four-step operations.[8b] To realize a single-step assembly of the enyne **A**, we first developed the Cu-catalyzed Mannich condensation route to alkynylglycinate (Scheme 1).[9,10] According to the recent report of Knochel et al.,[11] several copper salts were examined as catalysts toward the reaction of 1 equiv each of ethyl glyoxalate, dibenzylamine, and phenylacetylene in toluene containing molecular sieve 4A at room temperature. The reaction proceeded in the presence of 10 mol % CuBr, and the formation of the desired alkynylglycinate **1a** (R = Ph) was confirmed by the ^{1}H NMR measurement of the crude product. Purification with column chromatography on silica gel or alumina, however, led to the decomposition of **1a** to ketoester **2a** and dibenzylamine. To avoid the decomposition, the crude materials were rapidly purified by the short column chromatography on Florisil. As a result, **1a** was obtained in 89% yield. In a similar manner, $CuBr_2$ and $CuCl_2$ gave **1a** in 85 and 79% yields, respectively. In contrast, $Cu(OAc)_2$ and CuI proved to be ineffective. On the basis of these results, further explorations were carried out with $CuBr_2$, which is cheaper and more robust than CuBr. Under the optimal reaction conditions, 1-hexyne and trimethylsilylacetylene similarly gave rise to **1b** (R = ^{n}Bu) or **1c** (R = TMS). The former was isolated in 81% yield, but the latter was decomposed during the Florisil chromatography.

As the next step, we attempted the Cu-catalyzed three-component coupling synthesis of glycinate-tethered 1,6-enynes **3** and its

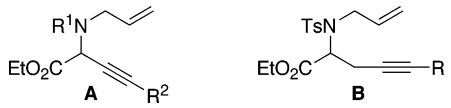
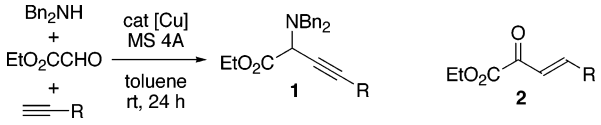
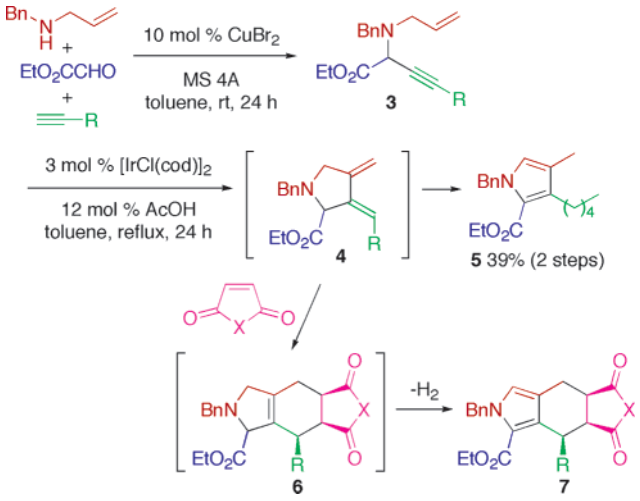


Figure 1. Glycinate-tethered α,ω-ethynes.

Scheme 1



Scheme 2

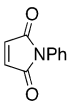
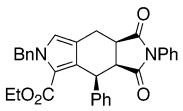
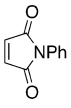
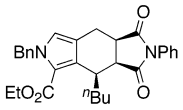
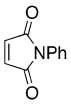
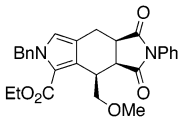
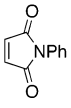
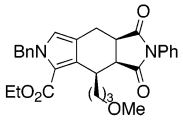
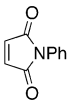
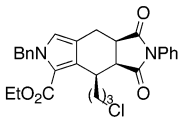
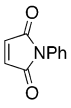
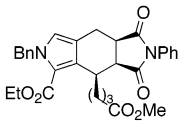
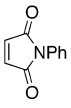
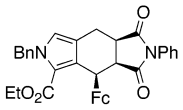
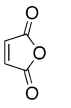
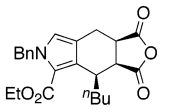
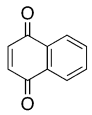
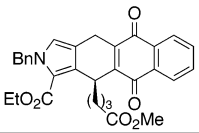


cycloisomerization (Scheme 2). The cycloisomerization of enynes is known as a powerful method to obtain exocyclic 1,3-dienes, which can be utilized as diene components of Diels−Alder reaction.[12] Toward this end, we carried out the reaction of 1 equiv each of *N*-benzylallylamine, ethyl glyoxalate, and 1-hexyne to obtain the desired enyne **3b**. After filtration to remove MS 4A, the crude enyne **3b** was submitted to the reported palladium-catalyzed cycloisomerization conditions (5 mol % $Pd_2(dba)_3$, 10 mol % PPh_3, 10 mol % AcOH, toluene reflux, 24 h)[12c] to result in the formation of an intractable product mixture. Thus, we turned our attention to the recently developed iridium catalyst system of Chatani, Murai, and co-workers.[13] According to their report, crude **3b** was treated with 3 mol % $[IrCl(cod)]_2$ and 12 mol % AcOH in refluxing toluene for 24 h. As a result, the iridium-catalyzed conditions proved to be viable for the cycloisomerization of **3b**, but the obtained product was unexpected pyrrole-2-carboxylate **5**, which was probably formed by the iridium-catalyzed isomerization of exocyclic diene **4**.

To trap putative intermediate **4** with Diels−Alder reaction, we further carried out the cycloisomerization of **3b** in the presence of 1.1 equiv of *N*-phenylmaleimide.[14] Gratifyingly, a 1:1 cycloadduct

10.1021/ja053408a CCC: $30.25

Table 1. Synthesis of Fused Pyrrolecarboxylates **7**

run	alkyne	dienophile	product, yield/% (2 operations)
1			 **7aa**, 54
2			 **7ba**, 62
3			 **7ca**, 41
4			 **7da**, 51
5			 **7ea**, 62
6			 **7fa**, 74
7			 **7ga**, 54
8			 **7bb**, 52
9			 **7fc**, 35

of **3b** and the maleimide was formed, but the following structural analyses revealed that the obtained product is fused pyrrolecarboxylate **7ba**. In its ^{1}H NMR spectrum, a singlet peak of the pyrrole proton α to the nitrogen atom appeared at δ 6.7 ppm. In addition, the molecular ion peak M^+ was observed at *m*/*z* 484 instead of *m*/*z* 486 expected for Diels−Alder adduct **6ba**. Although the detailed mechanism is ambiguous, it is considered that **7ba** was formed by the dehydrogenative aromatization of **6** via C−H activation of the 3,4-dehydroproline with Ir species.[15] It is noteworthy that the yield of the cycloisomerization/Diels−Alder reaction/dehydrogenative aromatization resulting in **7ba** (62%) was much higher than that of the cycloisomerization leading to **5** (39%).

Next, the generality of the four-component coupling approach to polycyclic pyrrolecarboxylates was demonstrated as summarized in Table 1. The use of phenylacetylene led to the formation of **7aa** in 54% yield with two steps (run 1), while trimethylsilylacetylene failed to give the corresponding adduct because of the decomposition of the enyne intermediate under the cycloisomerization conditions. Although methyl propargyl ether furnished **7ca** in rather lower yield of 41% (run 3), 5-methoxy-1-pentyne, 5-chloro-1-pentyne, and methyl 5-hexynoate uneventfully gave rise to pyrrolecarboxylates **7da**, **7ea**, and **7fa** in 51−74% yields (runs 4−6). Ethynylferrocene was employed as a teminal alkyne component to afford **7ga** in 52% yield (run 7), and its structure was unambiguously established by X-ray crystallographic analysis (see Supporting Information). In addition to *N*-phenylmaleimide, maleic anhydride can be used as a dienophile in the second step to afford **7bb** in 52% yield (run 8). On the other hand, the use of 1,4-naphthoquinone led to the formation of **7fc** possessing both pyrrole and naphthoquinone rings albeit in lower yield of 35% (run 9). The formation of **7fc** can be considered as a result of the double dehydrogenation under the influence of the iridium species.

In conclusion, we successfully established the novel domino-coupling relay approach to polycyclic pyrrole-2-carboxylates through the Cu-catalyzed Mannich condensation of *N*-benzylallylamine, ethyl glyoxalate, and terminal alkynes, and the Ir-catalyzed cycloisomerization/Diels−Alder reaction/dehydrogenative aromatization of the resultant glycinate-tethered 1,6-enynes.

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Supporting Information Available: Experimental procedure and analytical data for products (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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