Construction of Polycyclic γ-Lactams and Related Heterocycles via Electron Catalysis

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ABSTRACT: Cascade radical cyclization of 1,6-enynes for the construction of biologically important polycyclic γ-lactams and related heterocycles is reported. In these radical cascade processes, three new C–C bonds are formed and transition metals are not required to run these sequences. The mild reaction conditions, broad substrate scope, and the importance of the heterocyclic products render the approach valuable.

Nitrogen-containing fused heterocycles are widely found in natural products, biologically active structures, medicinally relevant compounds, and other fine chemicals.1 Among them, the polycyclic γ-lactams have received considerable attention due to their important biological activities (Figure 1). For instance, salinosporamide A was isolated from a marine actinomycete by Fenical and co-workers, which has been proven to be a potent proteasome inhibitor.2 Fusarisetin A, isolated from the soil fungus Fusarium sp. FN080326, was shown to inhibit acinar morphogenesis (77 μM), cell migration (7.7 μM), and cell invasion (26 μM) in these cell lines without any significant cytotoxicity.3 More importantly, polycyclic γ-lactam derivative 1 exhibited efficient inhibitory effects on proliferation of cancer cells.4 This biological activity has made the synthesis of polycyclic γ-lactams quite attractive, and several straightforward and robust methods for the construction of polycyclic γ-lactams have been elegantly established.5

Cascade radical cyclization of 1,6-enynes as aryl radical acceptors for the construction of valuable compounds (Scheme 1).6,7 However, to the best of our knowledge, radical cascade cyclization of 1,6-enynes toward the construction of polycyclic γ-lactams is a largely unexplored research area. More significantly, most of the reported methods for the construction of polycyclic γ-lactams from 1,6-enynes are based on transition-metal catalysis.8 Consequently, developing novel and efficient transformations of 1,6-enynes to synthesize some important heterocyclic compounds under transition-metal-free reaction conditions is still highly desirable.

Within the frame of our program devoted to the development of radical cascade reactions using electron catalysis,9 we recently disclosed that aryl radicals, generated from commercially available anilines,10 can regioselectively undergo radical cascade cyclization with arene-conjugated 1,6-enynes, providing polycyclic π-conjugated materials that show interesting photophysical properties (Scheme 1).11 Motivated by these findings, we became interested in further exploring the reactivity of aryl radicals with other types of 1,6-enynes and assumed that the method might be extended to access biologically relevant heterocyclic ring frameworks, such as polycyclic γ-lactams. Herein we describe the preliminary results of this study.

Our investigations commenced using the nitrogen-tethered 1,6-enyne 2a and aniline 3a as model substrates (Table 1). To our delight, 36% yield of the polycyclic γ-lactam 4aa was obtained by using isoamyl nitrite for in situ diazonium salt...

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generation\textsuperscript{10} in combination with \(n\)-Bu\(_4\)NI as a radical initiator in benzotri fluoride (BTF) at 70 °C for 24 h (Table 1, entry 1). Other reaction parameters including solvent, initiator, and reaction time were then systematically varied. As summarized in Table 1, the reaction media had a significant effect on the reaction efficiency. BTF could be replaced by CH\(_3\)CN albeit with a slightly decrease in yield (31%) (Table 1, entry 2). Other solvents such as EtOAc, CH\(_2\)Cl\(_2\), and toluene turned out to be less suitable for this cascade (Table 1, entries 3−5), and only a trace amount of 4aa was observed in 1,4-dioxane (Table 1, entry 6). To further improve the reaction efficiency, the influence of radical initiator was examined (Table 1, entries 7−9). With NaI yield decreased to 32%, while with KI and LiI yield was improved to 45% and 51%, respectively. Notably, worse results were achieved upon using transition-metal salts as radical initiators (Table 1, entries 10−12). In the absence of any initiator, 4aa was isolated in 39% yield (Table 1, entry 13). Likely, isomyl nitrite acted as the initiator in this case. A further enhancement in the product yield was obtained upon increasing the reaction temperature from 70 to 80 °C (52%) (Table 1, entry 14), and the highest yield was achieved by increasing the amount of 3a and isomyl nitrite (64%) (Table 1, entry 15).

With optimal reaction conditions in hand (Table 1, entry 15), we next investigated the scope and limitations of this radical cascade process by using various substituted anilines in combination with the nitrogen-tethered 1,6-enyne 2a as the reaction partner. As shown in Scheme 2, both electron-donating (Me, OMe, OPh) and electron-withdrawing groups (F, Cl) can be successfully introduced at the \(\text{para}\)-position of the aniline component, revealing that \(\text{para}\)-electronic modification of the aniline does not substantially alter reaction efficiency. The corresponding polycyclic \(\gamma\)-lactams 4ab−af were isolated in moderate to good yields. The structure of 4af was unambiguously confirmed by X-ray diffraction analysis (see Table 1 and Figure S1 in the Supporting Information).\textsuperscript{12}

Table 1. Reaction Optimization between 2a and 3a

| entry | initiator | solvent | yield (%) |
|-------|-----------|---------|-----------|
| 1     | \(n\)-Bu\(_4\)NI | BTF | 36 |
| 2     | \(n\)-Bu\(_4\)NI | CH\(_3\)CN | 31 |
| 3     | \(n\)-Bu\(_4\)NI | EtOAc | 25 |
| 4     | \(n\)-Bu\(_4\)NI | CH\(_2\)Cl\(_2\) | 21 |
| 5     | \(n\)-Bu\(_4\)NI | toluene | 19 |
| 6     | \(n\)-Bu\(_4\)NI | 1,4-dioxane | trace |
| 7     | NaI | BTF | 32 |
| 8     | KI | BTF | 45 |
| 9     | LiI | BTF | 51 |
| 10    | CuI | BTF | trace |
| 11    | FeI\(_2\) | BTF | 17 |
| 12    | NiCl\(_2\) | BTF | 45 |
| 13    | | BTF | 39 |
| 14    | LiI | BTF | 52 |
| 15    | LiI | BTF | 64 |

\textsuperscript{a}Reaction conditions: 2a (0.2 mmol), 3a (0.4 mmol), initiator (0.04 mmol), and isomyl nitrite (0.5 mmol) in solvent (2 mL) were stirred at 70 °C for 24 h under argon atmosphere. \textsuperscript{b}Isolated yield. \textsuperscript{c}Stirred at 80 °C. \textsuperscript{d}After the mixture was stirred for 10 h, additional 0.4 mmol of 3a and 0.5 mmol of isomyl nitrite were added.

However, lower yields were obtained for anilines bearing substituents at the \textit{meta} and \textit{ortho} positions (4ag and 4ah), likely for steric reasons.

Next, the scope of the reaction was examined with respect to the 1,6-enyne component 2. Electron-donating and electron-withdrawing substituents are tolerated at the \(\text{para}\)-position of the R\(_2\)-aryl group, and the corresponding products 4ba−da were obtained in 53−62% yield. Note that a thienyl group can be installed as the alkyne substituent to afford the polycyclic \(\gamma\)-lactam 4ea in 60% yield. The R\(_2\)-aryl substituent can be replaced by an alkyl substituent as documented for the propyl and cyclohexyl congener. The corresponding heterocycles 4fa and 4ga were isolated in 45% and 50% yield, respectively.
Good yields were also obtained when the activating methyl ester moiety was replaced by a bulkier ethyl and tert-butyl ester functionality (4ha and 4ia). We also tested whether the N-tosyl group in the 1,6-enyne can be substituted by other N-protecting groups. While all of our attempts to carry out the reaction with an N-phenyl-protected substrate failed, the N-benzyl-protected 1,6-enyne afforded the targeted product 4ia in 44% yield. Importantly, the reaction of nitrogen-tethered 1,6-enyne 2l with aniline 3a under the optimized reaction conditions afforded polycyclic pyrrole product 4ia in 57% yield, showing that the carbonyl group next to the N atom is not required for this cascade.

To further illustrate the synthetic utility of this methodology, we also applied this radical cascade to the construction of other biologically important polycyclic ring systems. To our delight, we found that our approach can be extended to the synthesis of biologically important polycyclic ring systems. To our delight, we also applied this radical cascade to the construction of other biologically important polycyclic ring systems. To our delight, we found that our approach can be extended to the synthesis of polycyclic γ-butyrolactones. The starting esters 5a–c containing a 1,6-enyne moiety are readily prepared (see the SI), and the cascade was studied using aniline as the aryl radical precursor. Pleasingly, we found that under the conditions optimized for the lactam synthesis the cascade worked well and the targeted γ-butyrolactones 6a–c were obtained in 57–62% yield (Scheme 3). It is worth noting that 6b contains the core structure of collinsin, a natural lignan lactone which exhibits antiviral activity.14

The synthetic value of this method was further demonstrated by investigating follow-up chemistry using 4aa as a substrate (Scheme 4). Treatment of 4aa under acidic conditions for 1 h at room temperature gave the corresponding deotosylated polycyclic γ-lactam 7 in 85% yield.15c Hydrolysis of the ester group was achieved by treating 4aa with LiOH·H2O in a mixture of MeOH, THF, and water at room temperature for 0.5 h to give the corresponding acid in 87% yield.15b Silver-catalyzed oxidative decarboxylation of this acid provided aromatization product 8 in 71% isolated yield.15c

A plausible reaction mechanism is proposed in Scheme 5 to explain the formation of polycyclic γ-lactam 4af. First, 4-

chloroaniline 3b reacts with isoamyl nitrite to the corresponding diazonium salt A. Then, reaction of A with LiI generates aryl radical B in the initiation step. Chemosesective radical addition of B to the activated alkene of 1,6-enyne 2a provides tertiary alkyl radical C,16 which subsequently undergoes a 5-endo cyclization to deliver vinyl radical D. Next, radical D cyclizes onto the arene to give cyclohexadienyl radical E, which in turn gets deprotonated17 by the alcoholate derived from isoamyl nitrite to provide arene radical anion F. Radical anion F is eventually oxidized to generate the final polycyclic γ-lactam product 4af, formally liberating an electron to complete the catalytic cycle.

In conclusion, cascade radical cyclizations of 1,6-enynes with aryl radicals for the construction of polycyclic γ-lactams were developed. Commercially available arylamines were used as radical precursors and LiI as a radical chain initiator. The cascade comprises three C–C bond-forming steps and showed broad substrate scope providing polycyclic γ-lactams in moderate to good yields. More significantly, the method could be efficiently extended to the synthesis of polycyclic pyrrole and γ-butyrolactone derivatives. These cascades proceed by electron catalysis, and transition metals are not required to run these processes.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03267.

Experimental procedures, characterization data, and 1H and 13C NMR spectra (PDF)

X-ray data for compound 4af (CIF)
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