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Supporting Information

ABSTRACT: A novel radical [2 + 2 + 1] cyclization of ortho-cyanoarylacrylamides with dual α-C−H bonds in alkyl nitriles has been developed. The reaction provides new facile and straightforward access to cyano-substituted pyrrolo[3,2-c]-quinolines, which are important nitrogen-containing polyheterocycles. A possible mechanism for the transformation is proposed.

Pyrrolo[3,2-c]quinolines are an important class of nitrogen-containing polyheterocycles which widely exist in many natural products and biologically active compounds (Figure 1)1; for example, natural product martinelline was found to possess antibacterial activity as well as affinity for muscarinic, adrenergic, and bradykinin receptors.1a Pyrrolo[3,2-c]quinoline II is a 5-HT6R antagonist.1f Compound III is a potassium-competitive inhibitor of gastric (H+/K+)-ATPase.1g Because of their structural importance, great synthetic efforts have been exerted to develop efficient methods for the synthesis of such nitrogen-containing polyheterocycles.1,2 However, multiple synthetic steps or complex substrates are always involved in these approaches. Therefore, new and efficient methods to construct pyrrolo[3,2-c]quinolines are needed.

The [2 + 2 + 1] cyclization of both unsaturated moieties and a one-carbon unit is one of the powerful methods for the construction of five-membered rings due to its high efficiency and atom economy.3 However, in this context, the majority focus on the use of CO as a one-carbon unit (the Pauson−Khand-type reaction).3 Another focus is on the use of CO as a one-carbon unit (the Pauson−Khand-type reaction).3 Recently, the radical-mediated [2 + 2 + 1] cyclization of unsaturated moieties with other carbon units has received increased attention.3,4 The Jiang et al. and Li et al. reported the radical-mediated [2 + 2 + 1] cyclization of benzenelinked 1, n- enynes with the dual C−H bonds on the identical carbon atom.5 The annihilation of 1, n-enynes with α-carbonyl alkyl bromides, aliphatic aldehydes, alkyl carboxylic acids, and dichloromethane as a one-carbon unit has also been developed (Scheme 1a).7 Heinrich and co-workers described a radical [2 + 2 + 1] spirocyclization leading to ortho-spirocyclohexadienones via a highly diastereoselective cascade reaction with alkynes featuring three consecutive carbon−carbon bond formations (Scheme 1b).8 Despite these advances, only alkenes and alkynes were used as unsaturated moieties in these examples, and the radical [2 + 2 + 1] cyclization in which the nitrile group served as

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Figure 1. Selected bioactive pyrrolo[3,2-c]quinoline derivatives.
an unsaturated moiety has not been well-developed until now.\textsuperscript{9,10} On the basis of our continuing interest in developing new radical cascade reactions,\textsuperscript{11} herein, we report a novel radical [2 + 2 + 1] cyclization of ortho-cyanoacrylamides with dual $\alpha$-C–H bonds in alkyl nitriles (Scheme 1c). The reaction generated one C–N bond, two C–C bonds, and two new rings through an $\alpha,\alpha$-C(sp$^3$)–H difunctionalization and annihilation sequence to afford cyano-substituted pyrrolo[3,2-c]quinolines.

At the outset of our investigation, N-(2-cyanophenyl)-N-methylmethacrylamide (1a) was chosen as the model substrate for the cyclization. When ortho-cyanoacrylamide 1a was treated with MeCN (both as reactant and as solvent) and tert-butyl peroxybenzoate (TBPB) at 100 °C for 12 h under an argon atmosphere, the reaction proceeded smoothly and afforded the desired product 3a in 28% yield with 2.0:1 dr (Table 1, entry 1).

Table 1. Reaction Conditions’ Screening\textsuperscript{\textdagger}

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant (equiv)</th>
<th>additive (equiv)</th>
<th>CH$_3$CN (mL)</th>
<th>yield (%)$^k$</th>
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<tr>
<td>1</td>
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<tr>
<td>3</td>
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<td>3</td>
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</tr>
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</tr>
<tr>
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<td>DCP (3.0)</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$S$_2$O$_8$ (3.0)</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
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<td>AcOK (0.2)</td>
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<tr>
<td>17$^d$</td>
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<td>AcONa (0.2)</td>
<td>4.5</td>
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</table>

\textsuperscript{\textdagger}Reaction conditions: 1a (0.30 mmol), oxidant, and additive in CH$_3$CN at 100 °C for 12 h under Ar. \textsuperscript{k}Isolated yield of 3a. The dr value is about 1.5–2.3:1 as determined by $^1$H NMR analysis of the crude products. \textsuperscript{$^a$}At 90 °C. \textsuperscript{$^b$}At 110 °C. \textsuperscript{$^c$}Under an air atmosphere.

When the amount of TBPB was increased to 3.0 equiv, the yield of 3a was increased to 58%. Further increases in the amount of the oxidant resulted in a lower yield (Table 1, entries 2 and 3). Notably, the reaction was sensitive to the oxidant, and TBPB was proven to be the best choice. No reaction occurred when other oxidants such as di-tert-butyl peroxide (DTBP), dicumyl peroxide (DCP), and K$_2$S$_2$O$_8$ were used (Table 1, entries 4–6). Subsequently, the cage effect of solvent was investigated, and the results indicate that 4.5 mL of acetonitrile was preferred (Table 1, entries 7 and 8). A satisfactory yield of 75% was achieved when AcONa was employed as additive, and the appropriate amount of it was 20 mol % (Table 1, entries 9–15) (see the Supporting Information). Different reaction temperatures were also investigated, and the best result was obtained at 100 °C (Table 1, entries 16 and 17). When the reaction was carried out in an atmosphere of air, 3a could be obtained in 61% yield (Table 1, entry 18). The structure of the major isomer of 3a was identified by X-ray crystallographic analysis (Figure 2).

With the optimized reaction conditions, a variety of ortho-cyanoacrylamides were subjected to the optimized conditions to evaluate the scope of the [2 + 2 + 1] cyclization, and the results are summarized in Scheme 2. The N-methyl- and N-benzyl-substituted acrylamides reacted well with MeCN, and the expected products, 3a and 3b, were obtained in 75 and 65% yields, respectively, but the N-acetyl-substituted substrate failed to give the desired product. It was found that N-unprotected phenylmethacrylamide was compatible with this system. For aromatic units, the electronic properties of the substrates had no apparent effect on the efficiency of the reaction. The substrates with both electron-withdrawing and electron-donating groups at the phenyl ring underwent the reaction smoothly, affording products 3e–3q in moderate to good yields. Halogen groups such as Cl and Br also could be well-tolerated in the transformation, which provided opportunities for further functionalization. Steric hindrance in the ortho-substituted acrylamides did not have a considerable influence on the reaction, and satisfactory yields were provided in all cases. The effect of the substituents on olefins was next evaluated, and it was found that substrates with different functional groups such as phenyl, benzyl, ester, and phthalimide at the $\alpha$-position of the olefins were suitable for the reaction (3r–3u). Heterocyclic substrate pyrroleacrylamide was also compatible with this reaction, giving the corresponding pyrrolo[3,2-c]quinoline 3v in 75% yield. With respect to the nitriles employed, 4-chlorobutynitrile, 2-methoxycetonitrile, malononitrile, and 2-(pyridin-2-yl)acetonitrile also reacted well with acrylamide, leading to products 3w–3z in moderate to good yields.

A gram-scale reaction was carried out to show the potential applications of this protocol. As shown in Scheme 3, the reaction of 9.0 mmol of acrylamide 1a with MeCN under the standard reaction conditions gave 1.53 g of the desired product 3a in 71% yield. The result indicate that the [2 + 2 + 1] cyclization could be readily scaled up with similar efficiency.

To probe the reaction mechanism, several control experiments were carried out (Scheme 4). Initially, when radical inhibitors such as 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) were added to the standard reaction conditions, the cyclization process was remarkably suppressed, and TEMPO–CH$_3$CN and BHT–CH$_3$CN could be detected by HRMS. These results indicate that the reaction should proceed through a radical pathway. In addition, a large KIE ($k_{\text{H}}/k_{\text{D}} = 11.5$) was obtained when the reaction was carried out in a 1:1 mixture of CH$_3$CN/CD$_3$CN as the solvent, thus implying that the cleavage of the...
The C(sp³)−H bond of acetonitrile contributed to the rate-determining step.

Based on the above results and literature,6,11a−d,12 a plausible mechanism for the [2 + 2 + 1] cyclization was proposed in Scheme 5. Initially, the thermal hemolytic cleavage of TBPB generates the tert-butoxy radical and benzoate radical. Cyanomethyl radical is formed by hydrogen abstraction reaction of MeCN with benzoate or a tert-butoxy radical. Subsequently, the cyanomethyl radical attacks the carbon−carbon double bond of 1a, giving the alkyl radical intermediate A, which can sequentially react with the nitrile to generate the imine radical B. Intermediate B readily undergoes a 1,5-H shift with the α-C−H bond of nitrile to produce the new alkyl radical intermediate C, followed by a radical cyclization with imine to afford intermediate D. Intermediate D then reacts with TBPB, thus leading to the cation intermediate E. Finally, deprotonation of E by base delivers the product 3a. Product 3a can also be directly generated from intermediate D through hydrogen abstraction on amine by the tert-butoxy radical if the tert-butoxy radical or radical D is long-lived and accumulates in solution.13 The mechanism involving radical anion species cannot also be ruled out.14

In conclusion, we have developed a novel radical-mediated [2 + 2 + 1] cyclization of ortho-cyanoarylacrylamides with dual α-C−H bonds in alkyl nitriles. This transformation is characterized by high atom economy, utilization of readily available reagents, and good functional group tolerance, thus providing an efficient and straightforward way for the construction of cyano-substituted pyrrolo[3,2-c]quinolines. Further studies for the applications of this reaction are underway.

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03638.

Experimental procedures, characterization data of all new compounds, 1H and 13C NMR spectra (PDF)
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REFERENCES


