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Letter

# Cascade Reactions Assisted by Microwave Irradiation: Ultrafast Construction of 2-Quinolinone-Fused $\gamma$ -Lactones from *N*-(*o*-Ethynylaryl)acrylamides and Formamide

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T he construction of heterocycles is an important field in organic chemistry, especially in the production of new pharmaceutically relevant compounds.<sup>1</sup> In this context, *N*-heterocycles stand out, because of their vast presence in natural and bioactive compounds.<sup>2</sup> Among several classes of *N*-heterocycles, the 3,4-dihydro-2-quinolinone is an important scaffold that is present in a variety of pharmacologically active compounds, such as FDA-approved drugs: cilostazol (vaso-dilator), carteolol (glaucoma treatment) and aripiprazole (schizophrenia and bipolar disorder treatments) (Figure 1).<sup>3</sup>



Figure 1. Examples of 3,4-dihydro-2-quinolinone rings.

A literature survey revealed that 1,7-enynes are used as starting materials to produce 2-quinolinones, through reactions with different radical species.<sup>4</sup> Despite these advances using radical reactions, no study of reactivity toward carbamoyl radicals has been conducted. We recently established a research program focused on exploring the synthetic potential of the simplest carbamoyl radical (•CONH<sub>2</sub>), for the synthesis of highly functionalized compounds.<sup>5</sup> Carbamoyl radical can be generated from formamide in the presence of Fenton's

reagents  $(H_2O_2, FeSO_4, and H_2SO_4)$ .<sup>6</sup> With this in mind, we hypothesized that combining the reactivity of carbamoyl radicals and 1,7-enynes might be result in a powerful approach to the synthesis of novel heterocycles.

In this scenario, we disclose herein the previously unknown, microwave-assisted ultrafast synthesis of 2-quinolinone-fused  $\gamma$ -lactones enabled by a cascade reaction between 1,7-enynes and hydroxyl and carbamoyl radicals, which were generated from Fenton's reagents in formamide. Surprisingly, after only 10 s, a novel class of quinolinones was diastereoselectively obtained (Scheme 1).

Formamide revealed itself as the key compound to achieve the synthesis of highly functionalized 2-quinolinone-fused  $\gamma$ lactones. Our hypothesis was that two new C–C and three C– O bonds were formed after six key reactions, as follows: generation of hydroxyl and carbamoyl radicals and quinolinone formation, hydroxylation, epoxidation, and lactone formation via epoxide ring opening.

To the best of our knowledge, this is the first report using 1,7-enynes as starting materials for complex heterocycles in a 10 s process. Microwave irradiation is an important technology that has gained great attention in organic synthesis.<sup>7a-d</sup> Currently, several chemical reactions can be performed under microwave irradiation, revealing excellent results for the

 Received:
 May 11, 2021

 Published:
 June 21, 2021





Scheme 1. Ultrafast Construction of Novel Heterocycles from 1,7-Enynes<sup>a</sup>



 $^aFenton's$  reagent (H2O2, FeSO4, and H2SO4) in formamide; 10 s under microwave irradiation.

synthesis of organic compounds. It can also be considered a green technology since it improves yield and productivity, reduces reaction time, and consequently reduces energy consumption.<sup>7e,f</sup>

This study was initiated by performing the reactions while heating in an oil bath (Table 1). 1,7-Enyne **1a** was selected as a

Table 1. Reaction of the N-(o-ethynylaryl)acrylamide 1a with Fenton's Reagents in Formamide<sup>4</sup>



<sup>*a*</sup>Reaction conditions: *N*-(*o*-ethynylaryl)acrylamide **1a** (100 mM), formamide (5 mL), 80 °C and magnetic stirrer. The yields were obtained after removal of formamide by distillation and purification of crude material by chromatographic column. <sup>*b*</sup>A solution of H<sub>2</sub>O<sub>2</sub> in formamide (2.5 mL) was added under continuous flow conditions (10.4  $\mu$ L/min) onto a solution of substrate **1a** (0.5 mmol), formamide (2.5 mL), H<sub>2</sub>SO<sub>4</sub>, and FeSO<sub>4</sub>. <sup>*c*</sup>Fenton's reagents were added proportionally every hour. <sup>*d*</sup>The full amount of Fenton's reagents was added up to 4 h.

model substrate to evaluate its reactivity toward formamide and Fenton's reagents ( $H_2O_2$ , FeSO<sub>4</sub>, and  $H_2SO_4$ ). In the Fenton process,<sup>6</sup> iron(II) is the most employed catalyst for hydroxyl radical generation from  $H_2O_2$ . Few other metals (i.e., copper and chromium) can be used to replace iron in systems known as Fenton-like reactions;<sup>8</sup> however, we decided to consider the most efficient and inexpensive catalyst with good solubility in formamide,  $FeSO_4$ . In addition, the Fenton reaction is not efficient in the absence of acid, especially in the presence of formamide as a solvent.

Aiming to improve the solubility of 1a in formamide, we performed the reactions at 80 °C for 4 and 8 h. The first experiment showed only traces of a compound, which was unexpectedly characterized as the 2-quinolinon-fused  $\gamma$ -lactone 2a (Table 1, entry 1). This compound would result from an initial carbamoyl radical conjugate addition, followed by a second radical addition across the triple bond and radical hydroxylation. The resulting double bond would then be epoxidized and a 5-exotet ring opening and hydrolysis would yield the final observed product (for more details, see the reaction mechanism). It is noteworthy that, after the comprehension of the reaction mechanism for production of 2-quinolinon-fused  $\gamma$ -lactone 2a, we focused on the simplest carbamoyl radical (•CONH<sub>2</sub>) generated from formamide. In this case, NH<sub>3</sub> can be released as a coproduct (a gas of low molecular weight).

Motivated by the possibility of producing a novel highly functionalized 2-quinolinone, we pursued further reaction optimization. We tried to generate continuous hydroxyl radicals by adding a solution of hydrogen peroxide with a flow apparatus (Table 1, entry 2). The results provided enough material to isolate and fully characterize **2a** by NMR. The best result was found when higher amounts of reactants (4 equiv of  $H_2O_2$ , 2 equiv of  $H_2SO_4$ , and 1 mol % of FeSO<sub>4</sub>) were added every hour, yielding the product **2a** (39%; Table 1, entry 3). This result indicated that excess of hydrogen peroxide is important to increase the yield of compound **2a**. However, a longer reaction time did not increase the yield (Table 1, entry 5). It is noteworthy that the highest expected yield for the diastereoselective formation of 2-quinolinone-fused  $\gamma$ -lactone **2a** is 50%.

However, while pursuing an optimized protocol, we decided to put all the chemicals in a round-bottom flask and expose them to a domestic microwave oven. Surprisingly, product **2a** was obtained in 17% yield after 10 s (Figure 2).



Figure 2. Exploratory experiment conducted in a domestic microwave oven.

The fact that 1,7-enyne **1a** was not fully consumed using a domestic microwave oven (87% conversion by GC-MS analysis, see the Supporting Information) motivated us to apply a monomodal microwave reactor (see Table 2).

The first reaction condition, which was evaluated in a monomodal microwave reactor, showed only trace amounts of product 2a (80 °C, 10 s; see Table 2, entry 1). However, conducting the reaction under microwave irradiation at 80 °C for 40 s and adding the same amount of Fenton's reagents every 10 s gave the desired product 2a in 35% yield (Table 2, entry 2). This result was similar to that of the best reaction under conventional heating (4 h, Table 1, entry 2). Increasing the reaction time and amount of reagents decreased the

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Table 2. Reaction of N-(o-Ethynylaryl)acrylamide 1a with Fenton's Reagents in Formamide under Microwave Irradiation<sup>a</sup>



<sup>a</sup>Reaction conditions: N-(o-ethynylaryl)acrylamide 1a (100 mM), formamide (4 mL), t-BuOH (1 mL) and Fenton's reagents (H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub> and FeSO<sub>4</sub>) in a microwave tube (10 mL). The yields were obtained after the removal of formamide by distillation and purification of the crude material by column chromatography. <sup>b</sup>Fenton's reagents were added proportionally every 10 s. <sup>c</sup>The reaction mixture was added directly to a chromatographic column without formamide distillation.

1

130

10

43

2

product yield (Table 2, entry 3). Since we were convinced that a longer reaction time (>40 s) and higher amount of Fenton's reagents would not improve the yield of the desired product 2a, we decided to evaluate the effect of the reaction temperature. At 100 °C for 10 s (Table 2, entries 4-6), the results were similar to those of previous experiments at 80 °C (Table 2, entry 4). However, when the reaction was performed at 130 °C for 10 s, a high yield for the product 2a was obtained, even using the smallest amount of Fenton's reagents (Table 2, entry 7). Once again, the increase in Fenton's reagents and reaction time did not give better results (Table 2, entries 8 and 9). In addition, the reaction workup (Table 2, entry 7) was improved by avoiding the formamide distillation step. In this case, the crude reactional mixture was added directly to the chromatographic column for product purification (43% isolated yield, Table 2, entry 10).

NOESY-NMR experiments for compound 2a and several others (see the Supporting Information) have been performed to confirm the syn-stereochemistry assignment (Figure 3). The key NOESY interaction was observed between the hydrogens of the aromatic ring (H-2,6 of the benzoyl group) and the methyl hydrogen (position 3a).

In addition, the syn-stereochemistry of products 2 was essential to propose a reaction mechanism in which the lactone formation would result from a precursor with proper stereochemistry.

Having the optimized conditions, we focused our attention on the reaction scope (see Figure 4).



Figure 3. Key NOESY interaction of compounds 2.



Figure 4. Substrate scope (isolated yield in parentheses).

The overall yield was not over 50%, since a diastereoselective formation of 2-quinolinone-fused  $\gamma$ -lactones was observed. Aromatic rings containing fluorine at the paraposition to nitrogen (2l, 2m, 2n) led to a decrease in the yield. Otherwise, the presence of fluorine on the aromatic ring of the benzoyl group (2d, 2k) did not show any special influence. The large benzoyl group bonded to nitrogen resulted in a smaller yield (20).

Scheme 2 shows the proposed mechanism for the synthesis of 2-quinolinone-fused  $\gamma$ -lactones 2a-20 from 1,7-enynes 1a-





**10.** The first step is the generation of hydroxyl radicals via Fenton's reaction.<sup>6</sup>  $H_2O_2$  and Fe(II) in acidic media promote the formation of hydroxyl radicals, water, and Fe(III). Fe(II) can be regenerated from the reaction between Fe(II) and  $H_2O_2$ .<sup>6b,9</sup> Then, the carbamoyl radical is generated from formamide by the action of hydroxyl radical.<sup>5a</sup> Next, the carbamoyl radical attacks the carbon–carbon double bond of the acrylic amide moiety and subsequently undergoes cyclization with the carbon–carbon triple bond, generating vinyl radical II. The recombination reaction of hydroxyl and vinyl radicals II yields enol III.<sup>10</sup>

Intermediate III (enol) can be converted to racemic epoxide IV through an epoxidation reaction. Other authors have demonstrated that peroxides in the presence of iron can oxidize C–C double bound conjugated to aromatic rings into epoxides.<sup>11</sup> The pathway for the construction of lactone is via a selective epoxide opening reaction through SN<sub>2</sub>-type mechanism.<sup>12</sup> This step explains the maximum yield (50%) for this process. Once intermediate IV is formed with the proper stereochemistry (*anti*), a 5-exo-tet cyclization can occur,<sup>13</sup> in which a nucleophilic attack of the amide group occurs from the backside of the epoxide via an SN<sub>2</sub>-type mechanism,<sup>12</sup> giving intermediate V (geminal diol). After simple hydrolysis and dehydration of V, product 2 is formed with the loss of ammonia.

In conclusion, cascade reactions assisted by microwaves enabled the ultrafast diastereoselective synthesis of novel 2quinolinone-fused  $\gamma$ -lactones from 1,7-enynes in only 10 s. The role of Fenton's reagents (H<sub>2</sub>O<sub>2</sub>, FeSO<sub>4</sub>, and H<sub>2</sub>SO<sub>4</sub>) in the formamide was essential to achieve such a highly functionalized heterocycle. In addition, the use of formamide as a solvent under microwave irradiation allowed the ultrafast generation of hydroxyl and carbamoyl radicals and, consequently, 2-quinolinone formation, hydroxylation, epoxidation, and finally, diastereoselective lactone formation via epoxide ring opening. Despite the high complexity of this process involving several reactions in 10 s, we can expect further synthetic application for Fenton's reagents in formamide under microwave-assisted reactions.

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01606.

A description of experimental procedures, characterization of the new compounds and photographs of the reaction and MW equipment (PDF)

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## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank Prof. Erick Leite Bastos (USP) and Prof. Ana Maria da Costa Ferreira (USP) for their loan of a monomodemicrowave equipment. We also appreciate CNPq (Grant No. 312751/2018-4), FAPESP (Grant Nos. 2019/24784-7, 2019/ 10762-1, and 2017/02854-8), and CAPES (Grant No. 88882.328246/2019-01) for the financial support.

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