Ynonylation of Acyl Radicals by Electroinduced Homolysis of 4-Acyl-1,4-dihydropyridines

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ABSTRACT: Herein we report the conversion of 4-acyl-1,4-dihydropyridines (DHPs) into ynones under electrochemical conditions. The reaction proceeds via the homolysis of acyl-DHP under electron activation. The resulting acyl radicals react with hypervalent iodine(III) reagents to form the target ynones or ynamides in acceptable yields. This mild reaction condition allows wider functionality tolerance that includes halides, carboxylates, or alkenes. The synthetic utility of this methodology is further demonstrated by the late-stage modification of complex molecules.
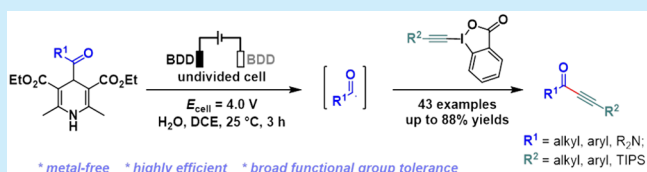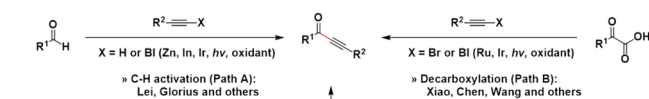
Ynones and their derivatives are versatile synthons in organic synthesis due to their abilities for diverse transformations to C−B, C−C, C−N, and C−O bonds.[1] The combination of the highly reactive alkyne group with an adjacent carbonyl group creates the unique reactivity of ynones. As a case in point, this important function of ynones makes them an attractive target for synthetic chemists. Several strategies have been successfully developed for the preparation of ynones utilizing the oxidation of propargyl alcohols, alkynyl organometallic reagents, and the metal-catalyzed carbonylative Sonogashira coupling, although the selectivity and substrate scope are limited in these methods.[2] In addition to these traditional methods, a series of catalytic metal-mediated methods, such as gold-catalyzed decarbonyl aerobic oxidation,[3] Zn/In-cocatalyzed dehydrogenative cross-coupling,[4] and Rh, Ir-catalyzed chelation-assisted C−H bond activation[5] have been developed (Scheme 1, path A). More recently, photo-
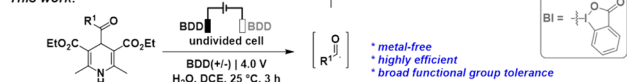
## Scheme 1. Synthetic Approaches for Ynones

redox catalysis has been elegantly employed by the groups of Wang,[6] Chen,[7] and Xiao[8] for the preparation of ynones using alpha-keto acids as carbonyl radical precursors (Scheme 1, path B).[9] Glorius and coworkers reported a visible-light-catalyzed homolysis of formyl C−H alkynylation, which exhibited a broad functional group tolerance and substrate scope.[10]

However, alkynylation in the presence of carboxylic acids[11] and iodide,[12] bromide,[13] and chloride[14] groups under photoredox reaction conditions has proven elusive due to their high potential for reactivity. The development of a synthetic strategy allowing a broader functional group tolerance, a rapid reaction time, and the avoidance of precious metals is still in high demand. To address these issues, we questioned whether electrochemistry could address these challenges via fine-tuning the electrode potential, which is difficult to be solved by the current methods.[15] We envisioned that an electrochemical generation of acyl and carbamoyl radicals might be a new activation mode for the preparation of more complex ynones with much milder conditions and broader functional group tolerance.[16] Electrochemistry, which enables a wide application of radical generation under milder conditions, can generate highly reactive intermediates under an applied potential without experiencing an excited state,[17] such as alkene functionalization,[18] cyclization,[19] bond construction (C−N,[20] C−O,[21] C−C[22]), and other diverse reactions.[23] Despite this progress, the electrochemical construction of $C_{sp^2}(O)−C_{sp}$ bonds remains elusive.

Herein we report a novel coupling of 4-acyl and carbamoyl dihydropyridines (DHPs) with hypervalent iodine(III) reagents (HIRs), affording ynones and ynamides under electrochemical conditions, where the ability to produce acyl and carbamoyl radicals in the absence of metal and photoredox catalysts allowed a broad functional group tolerance. Motivated by the recent studies of 4-substituted 1,4-dihydropyridines
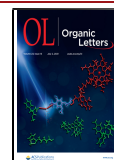
acting as readily accessible radical precursors,[24] we wondered if it was feasible to harness the electrochemistry of DHPs in carbonyl radical additions to the HIR. In this Letter, we show the coupling of 4-acyl and carbamoyl DHPs with HIRs under mild conditions, which permits the late-stage modification of complex pharmaceutical molecules.

At the beginning of our exploration, we started with the preparation of an ynone from the coupling of 4-benzyl dihydropyridine (**1a**, 1.5 equiv) and **2a** (1.0 equiv). The reaction was conducted under 4.0 V conditions with a boron-doped diamond (BDD) anode and cathode using n-Bu$_4$NPF$_6$ (0.25 M) as the electrolyte in 1,2-dichloroethane (DCE) at 25 °C in the presence of H$_2$O (10 equiv). Product **3** was smoothly obtained in 76% yield (Table 1, entry 1) in 3 h. Water played a

**Table 1. Optimization of Reaction Conditions for Electrochemical Ynonylation**[a]

entry	change from standard conditions	yield (%)[b]
1	none	76 (75)
2	without H$_2$O	41[c]
3	5.0 equiv of H$_2$O	52
4	15.0 equiv of H$_2$O	71
5	graphite as anode	12
6	Pt as anode	59
7	Ni as anode	41
8	glassy carbon as cathode	40
9	MeCN as solvent	66
10	TFE as solvent	58
11	DMF as solvent	46
12	6.0 V	56
13	under air	53
14	no current	trace

[a]Standard conditions (0.15 mmol): **1a** (1.5 equiv), **2a** (1.0 equiv), H$_2$O (10.0 equiv), n-Bu$_4$NPF$_6$ (0.25 M), DCE (1.5 mL), BDD electrodes, 4.0 V, undivided cell, 25 °C, N$_2$ atmosphere, 3 h. [b]Yields were determined using ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard. Isolated yield is given in parentheses. [c]Reaction time: 6 h.

crucial role in this reaction, and the absence of water resulted in a decrease in the current from ∼3.0 to ∼0.7 mA and a drop in the reaction efficiency (entry 2). We presume that the addition of water increased the conductivity of the mixture, whereas diminished yields were obtained with 5.0 or 15.0 equiv of water (entries 3 and 4). Electrode materials such as Pt, Ni, and glassy carbon were demonstrated to be less effective (entries 5−8). DCE was shown to be a better solvent than solvents such as acetonitrile, 2,2,2-trifluoroethanol (TFE), and dimethylformamide (DMF) (entries 9−11). The increase in voltage to 6.0 V gave a reduced yield (entry 12). This transformation could be conducted under air, although a diminished yield was obtained (entry 13). The electric current was essential for this reaction (entry 14).
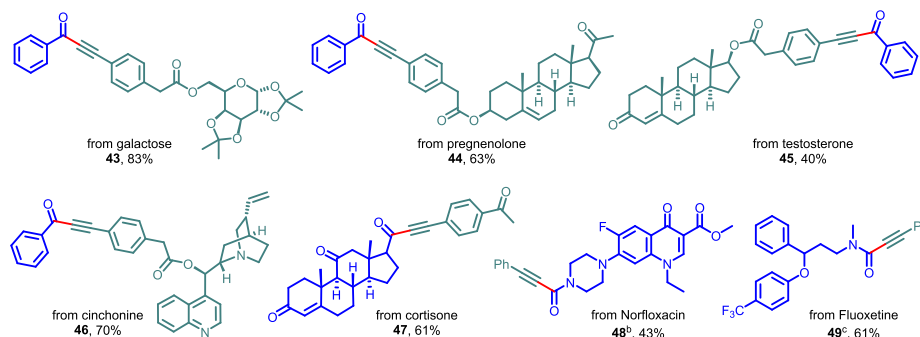
As shown in Scheme 2, we next evaluated the applicability of this transformation using the optimized conditions. First, a diverse series of 4-acyl DHPs were coupled to **2a** to verify the versatility and generality of this protocol (Scheme 2). With

Scheme 2. Substrate Scope of Electroinduced Ynonylation Reactions[a]
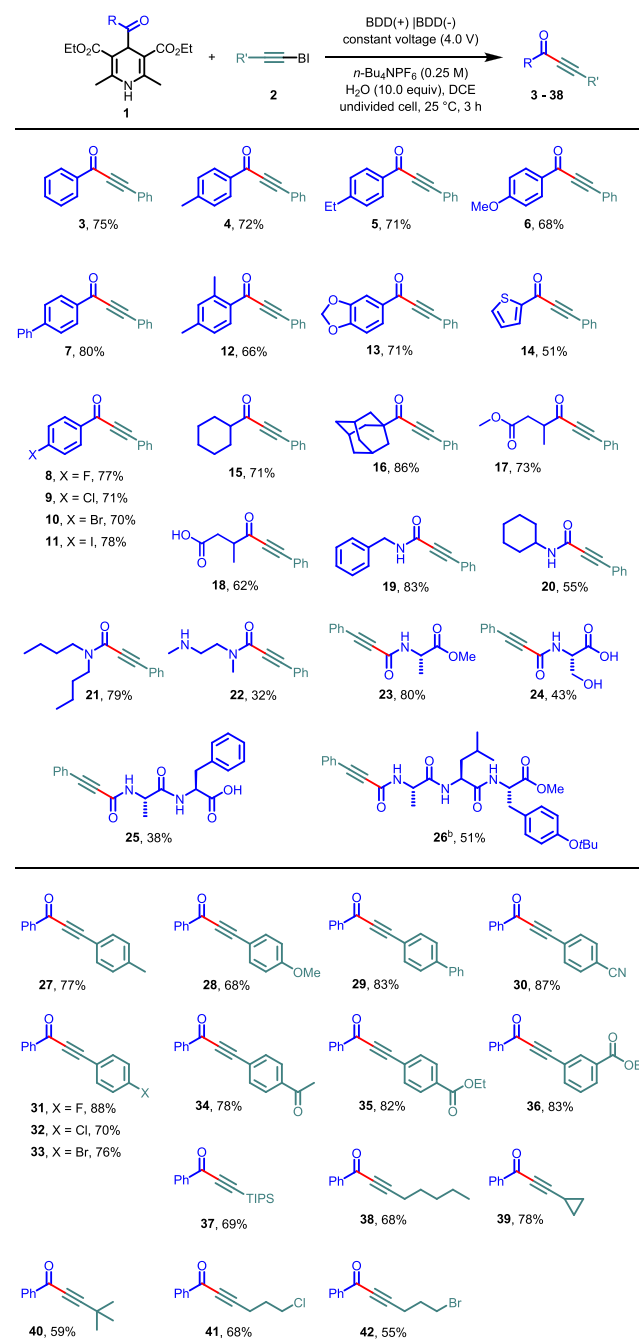
[a]Reaction conditions (0.15 mmol): **1** (1.5 equiv), **2** (1.0 equiv), H$_2$O (10.0 equiv), and n-Bu$_4$NPF$_6$ (0.25 M) in DCE (1.5 mL), BDD electrodes, 25 °C, 4.0 V, undivided cell. [b]Using peptidyl DHP **1x** (1.0 equiv; for the structure, see the Supporting Information) and **2a** (2.0 equiv).

respect to acyl DHPs with different electron-rich or -deficient aryl groups, the alkynylation products (**3−14**) were obtained in good yields. The ability to tolerate an aryl halogen atom (F, Cl, Br, I, **8−11**) showed that this method enables further functionalization and is orthogonal to cross-coupling reactions. Acyl DHPs with alkyl substituents smoothly gave ynones (**15−18**) in 62−86% yields. Ynamides (**19−22**) could be accessed from carbamoyl derivatives, which are useful building blocks in synthesis that have been less explored in synthetic chemistry.

Scheme 3. Late-Stage Functionalization of Pharmaceutical Molecules[a]

from galactose
43, 83%

from pregnenolone
44, 63%

from testosterone
45, 40%

from cinchonine
46, 70%

from cortisone
47, 61%

from Norfloxacin
48[b], 43%

from Fluoxetine
49[c], 61%

[a]Reaction conditions (0.15 mmol): **1** (1.5 equiv), **2** (1.0 equiv), H_2O (10.0 equiv), and n-Bu_4NPF_6 (0.25 M) in DCE (1.5 mL), BDD electrodes, 25 °C, 4.0 V, undivided cell. [b]Using norfloxacin-derived DHP **1z** (1.0 equiv; for the structure, see the Supporting Information) and **2a** (3.0 equiv) in DCE/TFE (14/1, 1.5 mL), at 6.0 V, 50 °C for 10 h. [c]Using fluoxetine-derived DHP **1aa** (1.0 equiv; for the structure, see the Supporting Information) and **2a** (3.0 equiv) at 5.0 V, 50 °C for 10 h.

Peptides are important therapeutics, and the modification of the peptide N-terminus is crucial for the improvement of their bioavailability and stability. This transformation can be employed in peptide chemistry. The DHP scaffold can be readily introduced into the N-terminus of peptides. (See general procedure C in the Supporting Information.) Subsequently, peptidyl acyl-DHPs gave the corresponding peptides **23−26** in decent yields. DHPs bearing carboxylic acids (**18**, **25**), esters (**17**, **23**, **26**), amides (**25**, **26**), amine (**22**), alcohol (**24**), and ^{t}Bu-protected Tyr (**26**) were well tolerated in this transformation. Unfortunately, we failed to demonstrate the reaction efficiency with acyl DHPs bearing linear alkyl chains because of the lack of synthetic methods to obtain the corresponding DHPs. In addition, the reactions employing acyl DHPs featuring an α-^{t}Bu moiety or free phenols were unsuccessful.
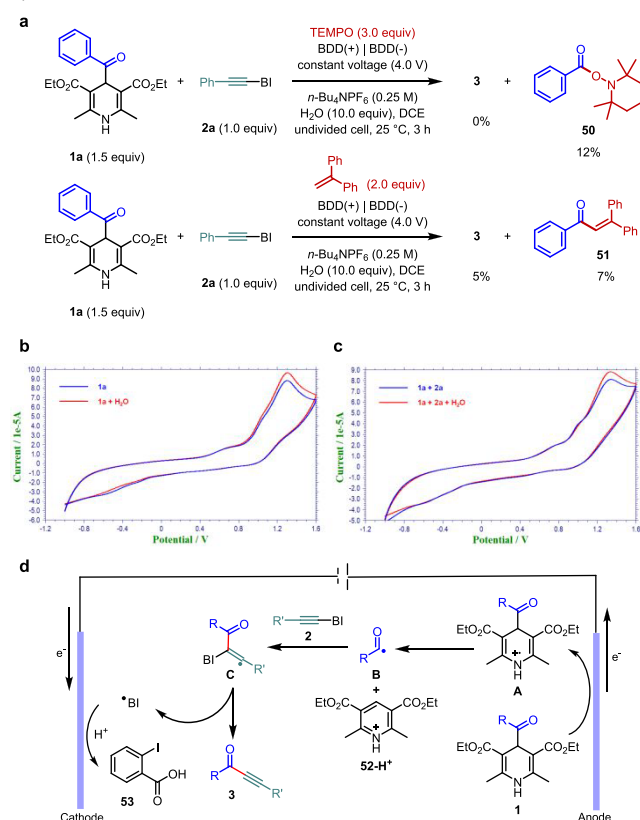
To explore the universality of the reaction further, we investigated a wide range of various alkynyl benziodoxolones (BI-alkynes) under electrochemical conditions. The HIR with various electron-rich or electron-deficient aryl substitutions reacted well to provide ynones **27−36** in good yields. TIPS-ynones are important scaffolds involved in synthesis. The corresponding product **37** was successfully achieved in good yield. Next, the coupling of DHP **1a** with the alkyl-substituted HIR provided ynones **38−42** in good yields. It is noteworthy that the formation of ynones bearing alkyl chloride (**41**) and bromide (**42**) by radical and metal-catalyzed chemistry was challenging due to the high reactivity of halogens. These examples demonstrated that the tunability of electrochemistry established on the proper applied potential enabled the selective activation of substrate functional groups.

This strategy was next demonstrated via its application to the late-stage functionalization of complex pharmaceutical molecules (Scheme 3). Galactose (**43**), pregnenolone (**44**), testosterone (**45**), and cinchonine (**46**) derivatives were obtained in moderate to good yields. 4-Acyl DHPs bearing cortisone, norfloxacin, and fluoxetine were selectively alkynylated to smoothly provide products **47−49**. A broad range of functional groups (esters, olefins, ketones, and ketenes) can be employed in this reaction. To further explore the functional tolerance and robustness of this transformation, we investigated the impact of additives in this transformation. (See page S10 in the Supporting Information.) It was found that the addition of alcohol, alkene, alkyne, alkyl halogens (Cl, Br, I), and carboxylic acids had no negative impact on the efficiency

of this transformation. Amino acids, such as histidine with an imidazole, serine, and tyrosine, moderately suppressed this reaction. (See page S10 in the Supporting Information for details.) Recent seminal works in this field using photoredox catalysis can provide ynones and ynamides under mild conditions. Furthermore, functional groups like halogen, carboxylic acid, and amino acid residues[25] (Trp,[26] Met[27]) were proven to be excellent substrates for photoinduced transformations, whereas electrochemistry enabled the selective activation of the DHP moiety under proper potential, with these photosensitive functional groups remaining intact. As a result, our reaction showed a different range in comparison with the existing strategies with regard to functional group tolerance. As demonstrated by the late-stage functionalization of these complex molecules, a unique advantage of electrochemistry was the selectivity and tunability of the reaction based on the redox potentials of the functional groups present in the molecule.

Next, we proceeded to investigate the mechanism of this electrochemical transformation. No desired product was isolated in the presence of TEMPO (3.0 equiv), and the reaction was inhibited with the addition of 1,1-diphenyl-ethylene (2.0 equiv). Furthermore, the corresponding coupling products **50** and **51** were isolated, and these results indicated that an acyl radical was generated under electrochemical conditions (Scheme 4a). Subsequently, cyclic voltammetry (CV) experiments were conducted. As shown in Scheme 4b, the redox behavior of substrate **1a** (+1.31 V) was recorded. An obvious peak current increase was observed with the addition of 0.2% water, whereas no new peaks were detected by CV analysis. **2a** did not show any obvious redox signal. (See page S12 in the Supporting Information.) Meanwhile, the mixtures of these substrates showed no obvious change (Scheme 4c), suggesting no interaction between both partners (further confirmed using UV−vis spectrophotometer analysis; see page S11 in the Supporting Information).

Compound **2a** was not redox-active within this potential range, and only **1a** exhibited an oxidation peak at +1.31 V. This provided evidence that the reaction was initiated by the anodic oxidation of DHP reagents. Importantly, the addition of 0.2% water increased the conductivity of the reaction system and thus significantly accelerated the reaction. CV analysis demonstrated no obvious change after the addition of water. On the basis of these experimental studies, a possible mechanism for this transformation is proposed in Scheme

Scheme 4. Mechanistic Proposal for the Electrochemical Synthesis of Ynones[a]

[a](a) Control experiment with the addition of TEMPO or 1,1-diphenylethylene. (b) Cyclic voltammograms of 1a at 0.1 V·s⁻¹ with or without H_2O. (c) Cyclic voltammograms of a mixture of 1a and 2a at 0.1 V·s⁻¹ with or without H_2O. (d) Proposed main reaction pathway for electroinduced 4-acyl radical formation and ynonylation.

4d. First, 1 was activated by anodic oxidation; then, C−C bond homolysis of the newly formed radical cation intermediate A released the key acyl radical B together with pyridine byproduct 52. B was captured by the BI-alkynes, which underwent elimination to give the target product 3. Byproduct 53 was detected upon cathodic reduction of the BI radical.

In summary, we have developed an unprecedented and general approach that converts 4-acyl and carbamoyl DHPs into ynones and ynamides via electrochemistry. The DHP moiety was selectively activated without metal catalysts, and a diverse range of functional groups including halide moieties, activated alkenes, alkynes, and alcohols were tolerated in this transformation. The merits of the electromediated alkynylation were further exhibited in the synthesis of structurally more complex compounds. This work provides a new set of tools to the existing ynonylation methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01243.

Experimental procedures, characterization data, CV measurements, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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