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In Situ Generated TEMPO Oxoammonium Salt Mediated Tandem Cyclization of β-Oxoamides with Amine Hydrochlorides for the Synthesis of Pyrrolin-4-ones

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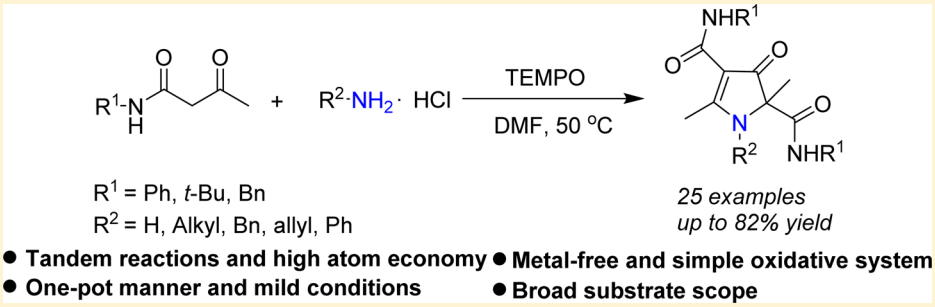
Supporting Information



ABSTRACT: A novel in situ generated TEMPO oxoammonium salt mediated one-pot tandem reaction has been developed for the straightforward construction of pyrrolin-4-ones from readily available β-oxoamides with amine hydrochlorides. The reaction tolerates various functional groups and represents a reliable method for the synthesis of highly substituted pyrrolin-4-ones in good yields under mild conditions. Detailed mechanistic studies disclosed that TEMPO oxoammonium salt generated in situ was crucial for the transformation involving the formation of enaminone precursors in situ by condensation of the β-oxoamides with amines, followed by sequential oxidative coupling with β-oxoamides, intramolecular cyclization, and 1,2-alkyl migration steps.

INTRODUCTION

Pyrrolin-4-ones are prevalent in many pharmaceuticals, biologically active natural products, and materials.[1−3] Compounds belonging to this class have consequently received remarkable attention as privileged *N*-heterocycle building blocks,[4] with particular emphasis on the development of potential drugs with interesting biological activities, such as anticancer, antithrombotic, and antimalarial agents.[5] Various synthetic methods have been developed for the construction of pyrrolin-4-one scaffolds, including the transition-metal-catalyzed/mediated cycloisomerization of 1-amino ynones and the dimerization of enaminones or α-diazo-β-oxoamides.[6,7] Dong, Guan and other groups recently reported three novel approaches to a series of substituted pyrrolin-4-ones using α-diazo-β-oxoamides and enaminones as starting materials.[7] The substrates required for these reactions usually need prefunctionalization from β-oxoamides. In addition, for the methods using enaminones as reaction substrates,[7a−c] half of enaminones were hydrolyzed to the initial β-oxoamides to couple with the rest enaminone precursors in these reaction processes, and these methods suffered from the limitation of some unstable enaminone substrates. In this paper, we report a straightforward method for the direct construction of pyrrolin-4-ones from readily available β-oxoamides and amine hydrochlorides by a simple and eco-friendly one-step reaction. The enaminone precursors were generated in situ in the transformation, avoiding the prepreparation and hydrolysis of the enaminone steps and overcoming the limitations described above.

β-Oxoamides and their derivatives have been widely used as readily available starting materials and reagents to synthesize a wide variety of biologically active heterocyclic compounds.[8] We recently reported the synthesis of 4-pyridones via the self-condensation of β-oxoamides, as well as the construction of a series of 4-olefinated dihydropyridines from β-oxoamides with pyridinium ylides.[8b,9] Given that the approaches of Dong and Guan involved the hydrolysis of half of the enaminone reactants to the corresponding β-oxoamides,[7a,b] we supposed that the direct reaction of β-oxoamides with amines would allow for the one-pot construction of pyrrolin-4-ones. This strategy would therefore provide a straightforward method for the synthesis of pyrrolin-4-ones from readily available β-oxoamides and amines.

The development of metal-free oxidative coupling reactions has attracted considerable interest from synthetic chemists, and reactions of this type have become attractive alternatives to conventional techniques for the direct construction of nitrogen-containing heterocycles. During the past two decades, stable nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl

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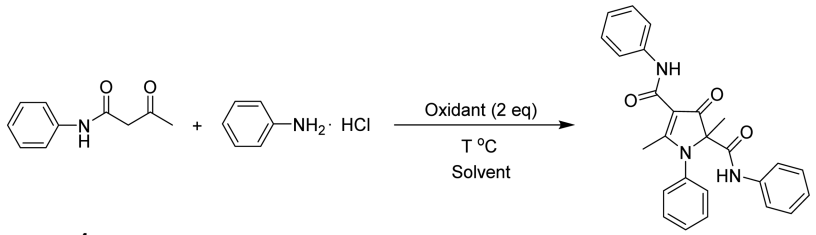
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant	solvent (mL)	T (°C)	yield (%)[b]
1	TEMPO	DMF (10)	120	54
2	TEMPO	DMF (10)	80	73
3	TEMPO	DMF (10)	50	76
4	TEMPO	DMF (10)	30	N.R.
5	TEMPO	CH_3CN (10)	50	55
6	TEMPO	Toluene (10)	50	32
7	TEMPO	THF (10)	50	trace
8	TEMPO	EtOH (10)	50	38
9	TEMPO	DMSO (10)	50	trace
10	TEMPO	CH_2Cl_2 (10)	50	32
11	TEMPO	DMF (5)	50	82
12[c]	TEMPO	DMF (5)	50	80
13[d]	TEMPO	DMF (5)	50	53
14[e]	TEMPO	DMF (5)	50	77
15[f]	TEMPO	DMF (5)	50	83
16	—	DMF (5)	50	N.R.
17	O_2	DMF (5)	50	N.R.
18	$PhI(OAc)_2$	DMF (5)	50	trace
19	TBHP	DMF (5)	50	trace
20	Oxone	DMF (5)	50	trace
21[g]	TEMPO	DMF (5)	50	N.R.
22[h]	TEMPO	DMF (5)	50	80

[a]Reaction conditions: **1a** (0.5 mmol), oxidant (1 mmol), aniline hydrochloride (0.5 mmol), 5 h. [b]Isolated yield. [c]TEMPO (1.5 mmol). [d]TEMPO (0.5 mmol). [e]Aniline hydrochloride (0.4 mmol). [f]Aniline hydrochloride (0.6 mmol). [g]Aniline was used instead of aniline hydrochloride. [h]1 equiv of aniline and aqueous hydrochloric acid were added into the reaction solution instead of aniline hydrochloride.

(TEMPO) have emerged as clean, mild oxidants that can be used to construct C−N bonds via the oxidation of in situ generated imines without the need for a transition-metal catalyst.[10] With this in mind, we investigated the use of TEMPO as an oxidant to evaluate our aforementioned supposition.

RESULTS AND DISCUSSION

We initially selected acetoacetanilide **1a** and aniline hydrochloride **2a** as model substrates to screen the reaction conditions (Table 1). Pleasingly, the reaction of **1a** with **2a** in DMF in the presence of 2 equiv of TEMPO at 120 °C afforded pyrrolin-4-one **3aa** in 54% yield (Table 1, entry 1). Lowering the temperature to 50 °C led to obvious improvements in the yield, although further reducing the temperature to 30 °C resulted in no reaction (Table 1, entries 2−4). A variety of different solvents were also evaluated, including CH_3CN, toluene, THF, EtOH, DMSO, CH_2Cl_2, and DMF, and the results revealed that DMF gave the highest yield of **3aa** when the reaction was conducted at 50 °C with 2 equiv of TEMPO in DMF (Table 1, entries 5−10). By diminishing the solvent volume from 10 to 5 mL, the yield of **3aa** was improved to 82% (entry 11). Increasing the TEMPO loading from 2 to 3 equiv did not lead to any obvious change in the yield (Table 1, entry 12). In contrast, decreasing the TEMPO loading from 2 to 1 equiv led to a considerable decrease in the yield from 82% to 53%, accompanied by 40% recovery of the starting material (Table 1, entry 13). We also found that the aniline hydrochloride loading and the TEMPO loading have a certain effect on the reaction (Table 1, entries 14 and 15). Furthermore, the reaction failed when it was conducted in the absence of TEMPO (Table 1, entry 16). Several other oxidants, including O_2, $PhI(OAc)_2$, *tert*-butyl hydroperoxide (TBHP), and oxone were also evaluated but were found to be ineffective with none of the desired product being formed (Table 1, entries 17−20). For comparison, we also tested aniline instead of aniline hydrochloride, but this reaction also failed to afford any of the desired products, even after 5 h (Table 1, entry 21). Notably, the addition of aqueous hydrochloric acid to a reaction system containing aniline instead of aniline hydrochloride gave the desired product **3aa** in 80% yield (Table 1, entry 22).

With the optimized conditions in hand (Table 1, entry 11), we proceeded to explore the substrate scope of this TEMPO-mediated tandem reaction. Initially, we examined the effect of the R^1 substituent attached to the β-oxoamide substrate. Various aromatic groups with electron-withdrawing and -donating substituents at various positions were well tolerated, giving the corresponding pyrrolin-4-ones in 71% to 82% yields (Table 2, **3aa**−**3ka**). It is noteworthy that *N*-benzyl and *N*-*tert*-

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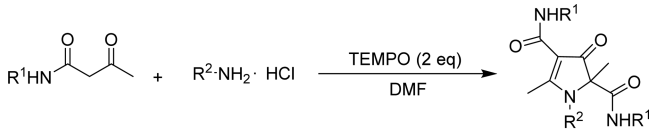
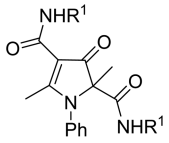
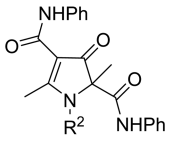
Table 2. TEMPO-Promoted Cyclization of β-Oxoamides with Amine Hydrochlorides[a,b]





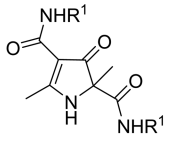
3aa-3ma

R^1 = Ph, **3aa**: 82%; R^1 = 4-MeOPh, **3ba**: 80%; R^1 = 3-MeOPh, **3ca**: 76%; R^1 = 2-MeOPh, **3da**: 73%; R^1 = 4-MePh, **3ea**: 77%; R^1 = 2-MePh, **3fa**: 72%; R^1 = 2,4-Me_2Ph, **3ga**: 71%; R^1 = 4-ClPh, **3ha**: 75%; R^1 = 3-ClPh, **3ia**: 74%; R^1 = 2-ClPh, **3ja**: 71%; R^1 = 4-EtO_2CPh, **3ka**: 77%; R^1 = 4-Bn, **3la**: 54%; R^1 = 4-*t*-Bu, **3ma**: 61%



3ab-3aj

R^2 = 4-MeOPh, **3ab**: 77%; R^2 = 4-MePh, **3ac**: 80%; R^2 = 3-MePh, **3ad**: 69%; R^2 = 2-MePh, **3ae**: 50%; R^2 = 4-ClPh, **3af**: 65%; R^2 = 3-ClPh, **3ag**: 48%; R^2 = ≡CCH_2 , **3ah**: 63%; R^2 = Bn, **3ai**: 70%[c]; R^2 = n-Pr, **3aj**: 72%[c]



3ak-3hk

R^1 = Ph, **3ak:** 64%[c]; R^1 = 4-MeOPh, **3bk:** 68%[c]; R^1 = 4-ClPh, **3hk:** 61%[c]

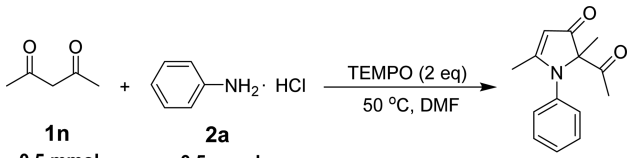
[a]Reaction conditions: β-ketoamides (0.5 mmol), amine hydrochlorides (0.5 mmol), TEMPO (1 mmol) in DMF (5 mL) at 50 °C for 5−7 h. [b]Isolated yield. [c]The reactions carried out at 120 °C for 3 h.

butyl substituted acetoacetamides also reacted smoothly with **2a** to give the corresponding products **3la** and **3ma** in 54% and 61% yield, respectively.

Next, we evaluated a series of amines **2** bearing different substituents at R^2 (Table 2, **3ab**−**3hk**). Aromatic amines bearing electron-withdrawing and -donating substituents at various positions of the phenyl ring reacted with **1a** to afford the corresponding pyrrolin-4-ones **3ab**−**3ag** in satisfactory yields. Notably, amines bearing an electron-donating substituent gave higher yields than those bearing an electron-withdrawing group (e.g., **3ab**, **3ac** vs **3af**; **3ad** vs **3ag**). The scope of this reaction also extended to propynylamine hydrochloride (**2h**), which reacted well with **1a** under the optimized conditions to produce **3ah** in 63% yield. Similarly, the aliphatic and benzyl amines propylamine (**2j**) and benzylamine (**2i**) also underwent this cyclization reaction to afford the corresponding *N*-functionalized pyrrolin-4-ones **3aj** and **3ai** in 72% and 70% yields, respectively. It is noteworthy that these reactions were carried out at an elevated temperature of 120 °C for 3 h. Ammonium chloride (NH_4Cl) was also investigated as an amine source to construct *N*-unsubstituted pyrrolin-4-ones. This amine worked in a similar manner to aliphatic amines, in that it required a higher temperature of 120 °C to produce pyrrolin-4-ones **3ak**, **3bk**, and **3hk** in good yields of 64%, 68%, and 61%, respectively (Table 2). The structure of **3ak** was further confirmed by X-ray single-crystal analysis.[11]

We also surveyed the reaction of acetylacetone **1n** and ethyl acetoacetate **1o** under the standard conditions. In the case of the acetylacetone substrate (Scheme 1), we obtained the deacylation product **4na** in 63% yield, which was formed by the deacylation of the desired 2,5-diacetyl pyrrolin-4-one product.[7a]

Scheme 1. Reactions of Acetylacetone with Aniline Hydrochloride



In contrast, the reaction of ethyl acetoacetate **1o** resulted in the formation of a complex mixture.

To develop a deeper understanding of the reaction mechanism, we conducted a series of control experiments, and the results are shown in Scheme 2. First, no reaction occurred when enaminone **A**, which was generated by the reaction of acetoacetanilide **1a** with aniline **1b**,[12] was treated with 2.0 equiv of TEMPO in DMF at 50 °C (eq 1). In contrast, enaminone **A** reacted smoothly to give **3aa** in 63% yield in the presence of 2 equiv of aqueous hydrochloric acid (eq 2). We also examined the reaction of **A** with **1a** under the same conditions, which resulted in the formation of the desired product **3aa** in 67% yield (eq 3). The results of these screening and control experiments confirmed that hydrochloric acid played a critical role in the formation of the pyrrolin-4-one products. Further experiments proved the current reaction could not occur only in the presence of acid, which was different with the previous reported acid promoted dimerization of alkyl substituted β-oxoamides.[7c] The environmentally friendly oxidant TEMPO therefore promoted the in situ formation of the key enaminone intermediate[10a,13] and the subsequent oxidative coupling reaction. However, the reaction

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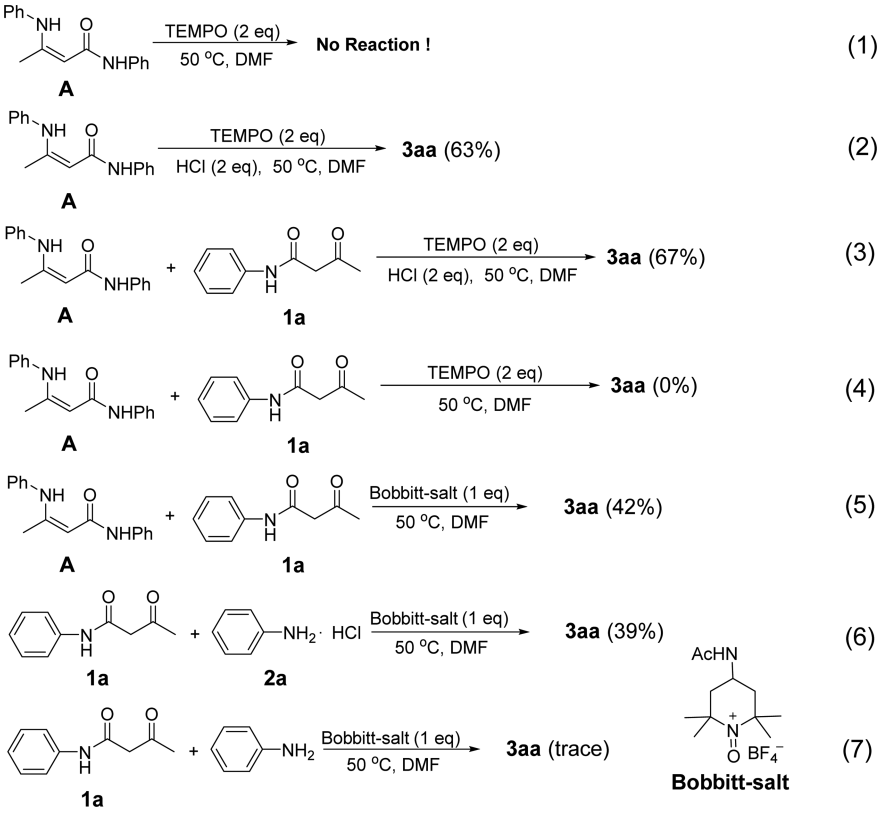
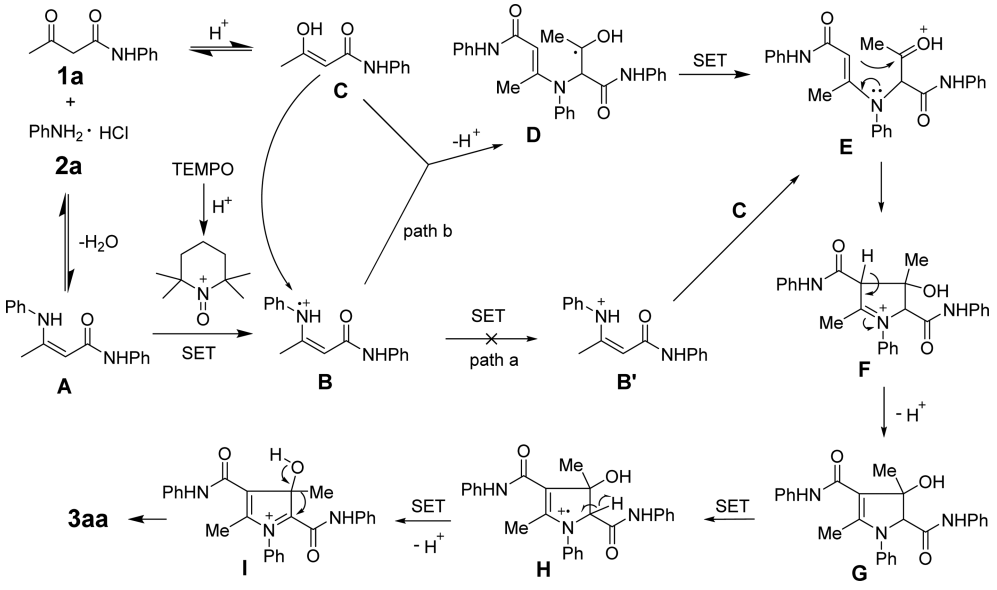
Scheme 2. Control Experiments



Scheme 3. Plausible Mechanism



of **A** with **1a** in the absence of hydrochloric acid did not work (eq 4), indicating that the acid played other roles in addition to helping the formation of intermediate **A**. TEMPO as an oxidant is too weak to oxidize intermediate **A** and then to couple with **1a**. In most reported nitroxide-mediated organic transformations, the active oxidant is not a nitroxide but its oxidized form, the corresponding oxoammonium salt.[14] The reactive TEMPO oxoammonium salt can be readily generated in the presence of acid.[15] Possibly TEMPO oxoammonium salt is required instead of TEMPO to mediate the reaction of **A** with **1a**. Next, we employed the Bobbitt salt as an oxidant to verify this hypothesis. As expected, the product **3aa** could be obtained in 42% yield by the treatment of the reaction of **A** with **1a** using 1 equiv of Bobbitt salt (eq 5). Similarly, the reaction of **1a** with **2a** provided **3aa** in 39% yield (eq 6). In contrast, the reaction of **1a** with aniline instead of aniline hydrochloride **2a** in the presence of 1 equiv of Bobbitt salt afforded a trace amount of **3aa** (eq 7), indicating that enaminone **A** is a key intermediate and the acid is also responsible for the effective generation of enaminone **A**. Thus, the dual roles of the acid are clearly

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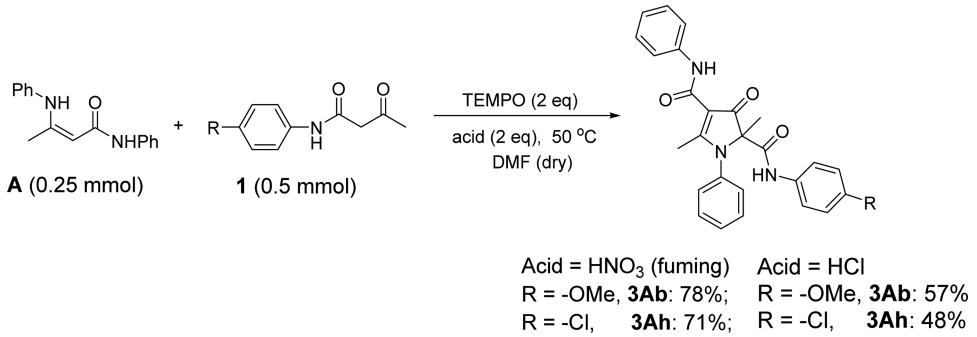
Scheme 4. Cross-Cyclization Reactions of Enaminone with β-Oxoamides



revealed in this unique transformation including the help for effective generation of enaminone **A** and the real oxidant TEMPO oxoammonium salt. In addition, compared to the current reaction system, the Bobbitt salt gave a poor yield, which might be attributed to the consumption of raw materials resulting from its strong oxidation capacity.

In order to further corroborate the reaction mechanism, the redox potentials of the corresponding reactions were determined by cyclic voltammetry in DMF with use of a glassy carbon working electrode (see Supporting Information, Figure S2).[16] The enaminone intermidiate **A** oxidation occurs at potentials of about +0.56 V vs Ag/AgCl in DMF, while TEMPO oxoammonium salt and TEMPO show their oxidation potentials at near +0.61 V and −1.88 V vs Ag/AgCl in DMF, respectively. Meanwhile, we also carried out a theoretical study, and the calculation results are consistent with the experimental data (see Supporting Information, Table S3). All the above-mentioned results further indicate that TEMPO-oxoammonium salt rather than TEMPO plays a critical role in this transformation. Finally, we also examined the redox potentials of the current reaction, which were almost consistent with the above results.

On the basis of the former investigations, and several other reports from the literature,[7a,b,17] we have proposed a plausible mechanism for the synthesis of multisubstituted pyrrolin-4-ones, which was shown in Scheme 3. Consideration of the structural characteristics of this transformation suggested that this reaction involved an oxidative coupling reaction to give a pyrrole core, which was accompanied by a semipinacol rearrangement.[18] This process therefore represents an area of chemical research that has been investigated in detail over the past two decades. According to this rearrangement process, the pyrrolin-4-one products would be produced by sequential 1, 2-methyl migration and vicinal carbonyl group generation steps. Initially, according to the literature,[7a,b] we speculated that a single-electron-transfer (SET) oxidation of the anilinium radical cation **B** generated nitrenium ion **B′** and then the nucleophilic attack of the enol **C** to **B′** produced the intermediate **E** (path a). However, the calculated oxidation potential of the SET step from **B** to **B′** is 2.035 V vs Ag/AgCl in DMF (see Supporting Information, Table S3), indicating that this step could not occur under the current conditions. Therefore, the reaction probably proceeds through pathway b. First, the condensation of β-oxoamide **1a** with amine **2a** would produce the enaminone intermediate **A**. Subsequent single-electron-transfer (SET) reactions with TEMPO-oxoammonium salt generated in situ gave the anilinium radical cation **B**. the aminyl radical **B** would react with the enol **C** to produce the adduct radical **D**. And then, the SET oxidation of radical **D** formed the intermediate **E**. Next, intramolecular cyclization of **E** led to intermediate **F**. Tautomerization followed by two steps of SET oxidations (from **F** to **I**) then generated 3*H*-pyrrol-1-ium intermediate **I**. Finally, the semipinacol rearrangement of **I** would give the desired product **3aa**. With regard to the acetylacetone substrate, the deacylation reaction of **3** would readily occur to afford the corresponding pyrrolin-4-one of type **4** (Scheme 1).

It would be very valuable to realize the cross-coupling reaction of different β-oxoamides to form the pyrrolin-4-ones bearing different amide groups, which will largely enrich the library of polysubstituted pyrrolin-4-ones. For this purpose, as preliminary investigations, the reactions of two β-oxoamides (**1b** and **1h**) with enaminone **A** preprepared from β-oxoamide **1a** were conducted in the presence of 2 equiv of fuming HNO_3 acid to produce the cross-cyclization products **3Ab** and **3Ah** in satisfactory yields (Scheme 4). When aqueous hydrochloric acid was used, the reactions gave relatively lower yields of the products **3Ab** and **3Ah**, and some byproducts (**3aa** and **3ba**, or **3ha**). The water mainly coming from aqueous hydrochloric acid resulted in the hydrolysis of **A**, thereby generating the byproducts.

CONCLUSION

In conclusion, a practical and reliable method has been developed for the straightforward synthesis of highly substituted pyrrolin-4-ones from readily available β-oxoamides and amine hydrochlorides in good yields under mild conditions. This tandem reaction is very simple and features good atom and step economy, as well as a broad substrate scope. In situ generated TEMPO oxoammonium salt is crucial for the success of this transformation, and a plausible reaction mechanism has been proposed for the tandem formation of substituted pyrrolin-4-ones. More importantly, the cross-cyclization products can also be prepared by the reactions of the enaminone intermediate with other different β-oxoamides mediated by TEMPO with the assistance of acid. Further work toward evaluating the reactions of other 1, 3-dione systems, such as acetoacetate and acetylacetone, is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All chemicals, reagents, and solvents were purchased from commercial sources and used without further treatment. ^{1}H NMR and ^{13}C {^{1}H}NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz). Chemical shifts are reported in δ units, parts per million (ppm) relative to the residual chloroform (^{1}H 7.26 ppm

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and ^{13}C 77.16 ppm) in the deuterated solvent. All of the new compounds were analyzed for HRMS on an ESI-QTOF mass spectrometer using electrospray ionization in positive ion mode. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF254 silica gel precoated plates. Flash chromatography was carried out on SiO_2 (silica gel 200−300 mesh).

Typical Procedure for Synthesis of Pyrrolin-4-ones 3aa−3ah. To a round-bottom flask (50 mL) were added a stir bar, β-oxoamides (0.5 mmol), amine hydrochlorides (0.5 mmol), TEMPO (1 mmol), and DMF (5 mL). The flask was heated up to 50 °C, and the resulting reaction mixture was stirred for 5−7 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and then diluted with AcOEt, washed with water and a saturated NaCl (aq) solution, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether and CH_2Cl_2 (v/v = 1:6) as the eluent to **3aa−3ah**.

Typical Procedure for Synthesis of Pyrrolin-4-ones 3ai−3hk. To a round-bottom flask (50 mL) were added a stir bar, β-oxoamides (0.5 mmol), amine hydrochlorides (0.5 mmol), TEMPO (1 mmol), and DMF (5 mL). The flask was heated up to 120 °C, and the resulting reaction mixture was stirred for 3 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and then diluted with AcOEt, washed with water and a saturated NaCl(aq) solution, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether and CH_2Cl_2 (v/v = 1:6) as the eluent to give **3ai−3hk**.

Typical Procedure for Synthesis of Pyrrolin-4-ones 3Ab and 3Ah. To a round-bottom flask (50 mL) loaded with a stir bar, β-oxoamides (0.5 mmol), TEMPO (0.5 mmol), and HCl or fuming HNO_3 (0.5 mmol) in DMF (dry, 5 mL) an enaminone solution (0.25 mmol was dissolved in the 3 mL dry DMF) was slowly added dropwise with a syringe for 4 h at 50 °C. Then, the resulting reaction mixture was stirred for 1 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and then diluted with AcOEt, washed with water and a saturated NaCl (aq) solution, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether and CH_2Cl_2 (v/v = 1:6) as the eluent to give **3Ab** and **3Ah**.

General Procedure for Electrochemical Measurement. The electrochemical experiments were conducted in a three-electrode glass cell, controlled by a CH Instruments 600D potentiostat using a glassy carbon working electrode. A Pt mesh counter electrode and solid Ag/AgCl electrode were used as a counter and reference electrode, respectively. Redox potentials were measured at 50 °C in DMF solution of tetrabutylammonium tetrafluoroborate (TBAF). The scan rate was 0.1 V/s.

3aa:[7] 87.1 mg, 82%; yellow solid; mp 198−200 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.89 (s, 1H), 7.66−7.61 (m, 2H), 7.56−7.51 (m, 2H), 7.51−7.46 (m, 3H), 7.43−7.38 (m, 2H), 7.36−7.28 (m, 4H), 7.16−7.05 (m, 2H), 2.58 (s, 3H), 1.76 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{26}H_{24}N_3O_3$ $[M + H]^+$ 426.1812, found 426.1817.

3ba:[7d] 97 mg, 80%; white solid; mp 156−158 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.72 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.49−7.45 (m, 3H), 7.44−7.36 (m, 4H), 6.85 (d, *J* = 7.8 Hz, 4H), 3.79 (s, 3H), 3.78 (s, 3H), 2.57 (s, 3H), 1.73 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_5$ $[M + H]^+$ 486.2023, found 486.2031.

3ca: 92.5 mg, 76%; yellow solid; mp 162−164 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.80 (s, 1H), 7.51−7.46 (m, 3H), 7.44−7.39 (m, 2H), 7.38 (s, 1H), 7.24−7.17 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.69 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.64 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.58 (s, 3H), 1.75 (s, 3H). ^{13}C {^1H}NMR (150 MHz, $CDCl_3$) δ 195.4, 182.7, 163.3, 161.6, 160.2, 160.2, 139.8, 138.2, 135.8, 129.8, 129.8, 129.7, 129.6, 112.5, 112.4, 110.8, 109.9, 106.0, 105.4, 103.7, 76.8, 55.4, 55.3, 22.3, 16.6. HRMS (ESI) *m/z* calcd for $C_{28}H_{27}N_3O_5Na$ $[M + Na]^+$ 508.1843, found 508.1836.

3da:[7d] 88.3 mg, 73%; white solid; mp 175−177 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 9.00 (s, 1H), 8.52 (d, *J* = 7.8 Hz, 1H), 8.22 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.50−7.39 (m, 3H), 7.40 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.07 (td, *J* = 7.8, 1.2 Hz, 1H), 7.02 (td, *J* = 7.8, 1.2 Hz, 1H), 6.98−6.87 (m, 4H), 3.97 (s, 3H), 3.91 (s, 3H), 2.65 (s, 3H), 1.75 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_5$ $[M + H]^+$ 486.2023, found 486.2016.

3ea:[7d] 87.6 mg, 77%; white solid; mp 178−180 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.81 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.48−7.44 (m, 3H), 7.43−7.35 (m, 4H), 7.11 (t, *J* = 8.0 Hz, 4H), 2.57 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 1.73 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{28}H_{27}N_3O_3Na$ $[M + Na]^+$ 476.1945, found 476.1938.

3fa:[7a,d] 81.9 mg, 72%; white solid; mp 166−168 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.89 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.55−7.45 (m, 5H), 7.24−7.15 (m, 4H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 2.60 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H), 1.83 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_3$ $[M + H]^+$ 454.2125, found 454.2132.

3ga:[7d] 85.2 mg, 71%; yellow solid; mp 183−185 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.75 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.52−7.43 (m, 5H), 7.05−6.96 (m, 4H), 2.59 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H), 2.27(s, 3H), 2.25 (s, 3H), 1.80 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_3O_3$ $[M + H]^+$ 482.2438, found 482.2444.

3ha:[7d] 92.5 mg, 75%; yellow solid; mp 151−153 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.96 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.54−7.47 (m, 5H), 7.42−7.37 (m, 2H), 7.32−7.24 (m, 4H), 2.57 (s, 3H), 1.76 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{26}H_{21}Cl_2N_3O_3Na$ $[M + Na]^+$ 516.0852, found 516.0861.

3ia: 91.0 mg, 74%; yellow solid; mp 169−171 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.93 (s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.56−7.50 (m, 3H), 7.48−7.40 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.26−7.20 (m, 3H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8, 1H), 2.58 (s, 3H), 1.78 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{26}H_{21}Cl_2N_3O_3Na$ $[M + Na]^+$ 516.0852, found 516.0850.

3ja:[7d] 87.6 mg, 71%; yellow solid; mp 158−160 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.57 (s, 1H), 9.22 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.54−7.49 (m, 3H), 7.46−7.42 (m, 2H), 7.39 (t, *J* = 7.8 Hz, 3H), 7.26−7.21 (m, 2H), 7.07 (t, *J* = 7.8, 1H), 7.00 (t, *J* = 7.8, 1H), 2.62 (s, 3H), 1.82 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{26}H_{22}Cl_2N_3O_3$ $[M + H]^+$ 494.1033, found 494.1038.

3ka: 109.8 mg, 77%; yellow solid; mp 151−153 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 9.09 (s, 1H), 8.03−7.96 (m, 4H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.50 (t, *J* = 2.4 Hz, 3H), 7.43 (d, *J* = 3.0 Hz, 2H), 4.38−4.32 (m, 4H), 2.57 (s, 3H), 1.79 (s, 3H), 1.38 (q, *J* = 6.6 Hz, 6H). ^{13}C {^1H}NMR (151 MHz, $CDCl_3$) δ 195.2, 183.2, 166.4, 166.0, 163.5, 161.6, 142.8, 141.1, 135.6, 130.8, 130.8, 129.9, 129.9, 129.7, 126.7, 125.2, 119.4, 119.1, 103.5, 76.8, 61.0, 60.8, 22.7, 16.6, 14.5, 14.4. HRMS (ESI) *m/z* calcd for $C_{32}H_{31}N_3O_7Na$ $[M + Na]^+$ 592.2054, found 592.2054.

3la: 61.5 mg, 54%; yellow solid; mp 202−204 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (t, *J* = 5.6 Hz, 1H), 7.46−7.38 (m, 3H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.30−7.23 (m, 6H), 7.23−7.17 (m, 3H), 4.55 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.47 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.42−4.33 (m, 2H), 2.49 (s, 3H), 1.59 (s, 3H). ^{13}C {^1H}NMR (100 MHz, $CDCl_3$) δ 195.6, 181.8, 165.6, 163.8, 139.1, 137.7, 135.9, 129.6, 129.6, 129.4, 128.8, 128.6, 127.7, 127.7, 127.6, 127.2, 103.3, 76.6, 43.8, 42.5, 21.4, 16.3. HRMS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_3$ $[M + H]^+$ 454.2125, found 454.2125.

3ma: 58.9 mg, 61%; yellow solid; mp 175−177 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.48−7.41 (m, 3H), 7.30 (d, *J* = 7.2 Hz, 2H), 6.43 (s, 1H), 2.49 (s, 3H), 1.53 (s, 3H), 1.43 (s, 9H), 1.32 (s, 9H). ^{13}C {^1H}NMR (150 MHz, $CDCl_3$) δ 196.1, 181.4, 164.7, 163.4, 136.4, 129.9, 129.5, 129.3, 104.3, 76.7, 51.8, 50.6, 29.3, 28.6, 22.1, 16.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{31}N_3O_3Na$ $[M + Na]^+$ 408.2258, found 408.2257.

3ab:[7d] 87.5 mg, 77%; yellow solid; mp 179−181 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.86 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.38−7.29 (m, 6H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.57 (s,

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3H), 1.75 (s, 3H). HRMS (ESI) m/z calcd for $C_{27}H_{25}N_3O_4Na$ $[M + Na]^+$ 478.1737, found 478.1745.

3ac:[7d] 87.6 mg, 80%; yellow solid; mp 170−172 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.82 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.34−7.27 (m, 8H), 7.13 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 2.58 (s, 3H), 2.42 (s, 3H), 1.77 (s, 3H). HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3O_3$ $[M + H]^+$ 440.1969, found 440.1973.

3ad:[7d] 76.1 mg, 69%; yellow solid; mp 178−180 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.78 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.39−7.28 (m, 6H), 7.25−7.18 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 2.59 (s, 3H), 2.42 (s, 3H), 1.77 (s, 3H). HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3O_3$ $[M + H]^+$ 440.1969, found 440.1977.

3ae:[7d] 54.7 mg, 50%; yellow solid; mp 183−185 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.41 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.40−7.29 (m, 7H), 7.15 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 2.56 (s, 3H), 2.16 (s, 3H), 1.65 (s, 3H). HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3O_3$ $[M + H]^+$ 440.1969, found 440.1965.

3af:[7d] 74.5 mg, 65%; yellow solid; mp 189−192 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.89 (s, 1H), 7.65 (d, J = 7.8 Hz 2H), 7.53−7.46 (m, 4H), 7.41 (d, J = 7.8 Hz, 2H), 7.36−7.30 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 2.59 (s, 3H), 1.77 (s, 3H). HRMS (ESI) m/z calcd for $C_{26}H_{22}ClN_3O_3Na$ $[M + Na]^+$ 482.1242, found 482.1248.

3ag: 55.2 mg, 48%; yellow solid; mp 166−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.87 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.54−7.48 (m, 4H), 7.44 (t, J = 7.8 Hz, 1H), 7.38−7.30 (m, 5H), 7.14 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 2.61 (s, 3H), 1.78 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 195.4, 182.6, 163.3, 161.3, 138.5, 137.1, 136.9, 135.1, 130.4, 130.3, 130.0, 129.1, 128.9, 128.6, 125.1, 123.7, 120.3, 120.2, 104.0, 76.6, 22.8, 16.6. HRMS (ESI) m/z calcd for $C_{26}H_{22}ClN_3O_3Na$ $[M + Na]^+$ 482.1242, found 482.1256.

3ah:[7d] 61.3 mg, 63%; yellow solid; mp: 156−158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.27 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.37−7.28 (m, 4H), 7.15 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 5.04 (d, J = 18.6 Hz, 1H), 4.60 (d, J = 18.6 Hz, 1H), 2.97 (s, 3H), 2.41 (s, 1H), 1.89 (s, 3H). HRMS (ESI) m/z calcd for $C_{23}H_{22}N_3O_3$ $[M + H]^+$ 388.1656, found 388.1662.

3ai:[7a,b] 76.8 mg, 70%; white solid; mp 167−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H), 9.20 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.40−7.29 (m, 7H), 7.21−7.12 (m, 3H), 7.07 (t, J = 7.2 Hz, 1H), 5.39−5.24 (m, 2H), 2.75 (s, 3H), 1.72 (s, 3H). HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3O_3$ $[M + H]^+$ 440.1969, found 440.1976.

3aj: 70.3 mg, 72%; white solid; mp 191−193 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.10 (s, 1H), 9.22 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.56−7.50 (m, 2H), 7.36−7.28 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 3.98−3.89 (m, 1H), 3.83−3.75 (m, 1H), 2.84 (s, 3H), 1.90−1.83 (m, 1H), 1.79 (s, 3H), 1.73−1.64 (m, 1H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 194.4, 181.2, 163.9, 161.9, 138.8, 137.1, 129.2, 129.0, 125.0, 123.5, 120.2, 120.2, 102.6, 74.7, 47.4, 23.9, 23.1, 15.2, 11.6. HRMS (ESI) m/z calcd for $C_{23}H_{26}N_3O_3$ $[M + H]^+$ 392.1969, found 392.1972.

3ak:[7d] 56.1 mg, 64%; yellow solid; mp: 203−205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 9.43 (s, 1H), 8.80 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.40−7.29 (m, 4H), 7.18 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 2.76 (s, 3H), 1.77 (s, 3H). HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$ 350.1499, found 350.1507.

3bk: 69.5 mg, 68%; yellow solid; mp: 194−196 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (s, 1H), 9.27 (s, 1H), 8.59 (s, 1H), 7.57−7.51 (m, 2H), 7.50−7.43 (m, 2H), 6.92−6.82 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 2.74 (s, 3H), 1.75 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 196.4, 181.6, 164.6, 161.5, 157.2, 156.0, 131.8, 129.8, 122.0, 121.8, 114.4, 114.2, 103.1, 70.3, 55.6, 55.6, 25.2, 17.7. HRMS (ESI) m/z calcd for $C_{22}H_{24}N_3O_5$ $[M + H]^+$ 410.1710, found 410.1725.

3hk: 63.5 mg, 61%; yellow solid; mp: 201−203 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.85 (s, 1H), 9.28 (s, 1H), 7.78 (s, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 2.77 (s, 3H), 1.76 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 196.1, 181.8, 164.4, 161.3, 137.0, 135.1, 130.5, 129.2, 128.9, 128.5, 121.4, 121.1, 103.0, 70.3, 25.1, 17.7. HRMS (ESI) m/z calcd for $C_{20}H_{17}Cl_2N_3O_3Na$ $[M + Na]^+$ 440.0539, found 440.0545.

3Ab: 64.8 mg, 57%; yellow solid; mp: 176−179 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.70 (s, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.49−7.46 (m, 3H), 7.45−7.37 (m, 4H), 7.31 (t, J = 7.8 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 2.58 (s, 3H), 1.75 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 195.6, 182.6, 163.3, 161.7, 156.9, 138.7 135.9, 130.2, 129.9, 129.7, 129.6, 129.0, 123.7, 122.2, 120.2, 114.3, 103.7, 76.8, 55.6, 22.5, 16.6. HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3O_4$ $[M + H]^+$ 456.1918, found 456.1932.

3Ah: 55.3 mg, 48%; yellow solid; mp: 185−188 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.98 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.54−7.45 (m, 5H), 7.43−7.36 (m, 2H), 7.33−7.27 (m, 4H), 7.08 (t, J = 7.2 Hz, 1H), 2.58 (s, 3H), 1.76 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 195.3, 182.9, 163.5, 161.6, 138.5, 135.7, 135.7, 129.9, 129.8, 129.7, 129.6, 129.1, 128.9, 123.7, 121.6, 120.2, 103.7, 76.6, 22.6, 16.6. HRMS (ESI) m/z calcd for $C_{26}H_{23}ClN_3O_3$ $[M + H]^+$ 460.1422, found 460.1413.

4na: 36.2 mg, 63%; white solid; mp: 166−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 5.4 Hz, 3H), 7.27 (d, J = 9.6 Hz, 3H), 3.95 (s, 1H), 2.47 (s, 6H), 1.37 (s, 3H). ^{13}C {^{1}H}NMR (150 MHz, $CDCl_3$) δ 196.7, 194.4, 180.7, 134.2, 129.9, 129.7, 129.1, 107.9, 90.0, 30.1, 22.2, 16.9. HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1176, found 230.1183.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00686.

X-ray structure of **3ak**, cyclic voltammetry of the corresponding reaction, calculated potentials and Cartesian coordinates, and spectra for all compounds (PDF)

Crystallographic data for **3ak** (CIF)

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Notes

The authors declare no competing financial interest.

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