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Synthesis of N-Heterocycles via Dehydrogenative Annulation of N-Allyl Amides with 1,3-Dicarbonyl Compounds

Zheng-Jian Wu, Shi-Rui Li and Hai-Chao Xu*

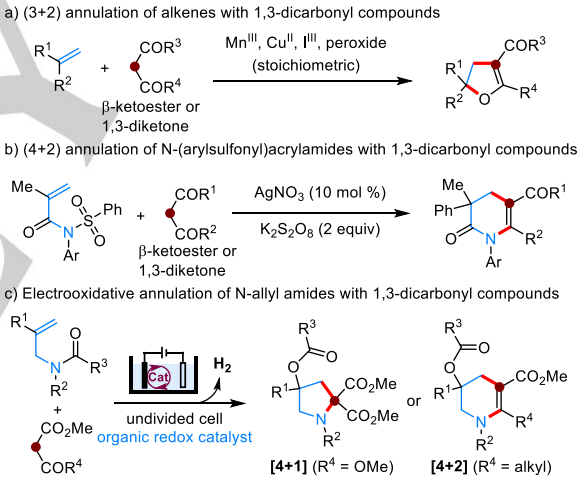
Dedicated to Professor Kevin D. Moeller on the occasion of his 60th birthday.

Abstract: Dehydrogenative annulation under oxidizing reagent-free conditions is an ideal strategy to construct cyclic structures. Herein we report an unprecedented synthesis of pyrrolidine and tetrahydropyridine derivatives through electrochemical dehydrogenative annulation of N-allyl amides with 1,3-dicarbonyl compounds. The electrolytic method employs an organic redox catalyst, which obviates the need for oxidizing reagents and transition-metal catalysts. In these reactions, the N-allyl amides serve as a four-atom donor to react with dimethyl malonate to give pyrrolidines via (4+1) annulation or with β-ketoesters to afford tetrahydropyridine derivatives via (4+2) annulation.

Annulation reactions occupy a prominent position in organic synthesis as they are among the most straightforward and efficient methods for constructing cyclic structures,[1] which are subunits of most bioactive compounds and natural products.[2] Particularly, dehydrogenative annulation under oxidizing reagent-free conditions represents an ideal strategy because it uses less functionalized substrates and in the meantime, minimize steps and waste production. Despite recent significant progress in dehydrogenative bond-forming reactions, these oxidative transformations generally employ undesirable chemical oxidants,[3] which reduce functional group tolerance and bring safety issues for large-scale applications.[4] In addition, the synthesis of sp^3 center-rich structures, especially saturated N-heterocycles, via dehydrogenative annulation reactions remains rare.[5]

1,3-Dicarbonyl compounds are versatile building blocks for organic synthesis. The 1,3-dicarbonyl moiety can be oxidized to produce electrophilic C-radicals that can participate in various C–C bond-forming reactions.[6] Based on this type of reactivity, β-ketoesters and 1,3-diketones have been shown to undergo annualtion reactions with alkenes or N-(arylsulfonyl)acrylamides to produce dihydrofurans[7] (Scheme 1a) or dihydropyridinones[8] (Scheme 1b) in the presence of chemical oxidants.[9] Organic electrochemistry, which employs traceless electrons to achieve redox reactions,[10] has been increasingly studied for promoting dehydrogenative cross-coupling reactions.[11,12] In this context, we have recently developed a Cp_2Fe-catalyzed electrochemical method for the generation of C-radicals from 1,3-dicarbonyl compounds.[13] This method has enabled the synthesis of oxindoles via dehydrogenative cyclization reactions.[13] However, the catalytic system based on Cp_2Fe requires a mixture of MeOH/THF as the solvent,[13,14] which is a good H-atom donor and limits the application to the facile intramolecular reactions.

Given the importance of pyrrolidine and piperidine rings in pharmaceuticals and other bioactive compounds[15] and the lack of dehydrogenative annulation strategies for their synthesis,[16,17] we report herein the synthesis of pyrrolidine and tetrahydropyridine derivatives through unprecedented, electrochemical dehydrogenative annulation reactions of N-allyl amides with 1,3-dicarbonyl compounds (Scheme 1c). The success is attributable to the discovery of a phenothiazine based redox catalyst[10b] that is operative in aqueous solution. To our best knowledge, phenothiazines have not been used as redox catalysts in organic electrosynthesis.



Scheme 1. Synthesis of heterocycles via annulation reactions of 1,3-dicarbonyl compounds.

We began our study by optimizing the electrolysis conditions for the annulation reaction of N-allyl amide **1** with dimethyl malonate **2** (Tables 1 and S1). The optimal reaction system was found to consist of phenothiazine **3** (20 mol %) as the redox catalyst and HCO_2Na (0.3 equiv) as the base additive, in a mixed solvent of *t*BuOMe/MeCN/H_2O (20:3:1) under reflux (entry 1). Under these conditions, the pyrrolidine derivative **4** was isolated in 70% yield. Control experiments revealed that electricity (entry 2), the catalyst (entry 3) and heating (entry 4) were critical for the formation of **4**. Leaving out HCO_2Na led to a reduction in yield (entry 5). Other redox catalysts, such as phenothiazine derivatives **5** and **6** (entry 6) and triarylamines **7**–**9** (entry 7), were less efficient. The composition of the solvent was also found to be important, as the absence of H_2O (entry 8) or *t*BuOMe (entry 9) and the substitution of THF (entry 10) or Et_2O (entry 11) for *t*BuOMe were detrimental to the formation of

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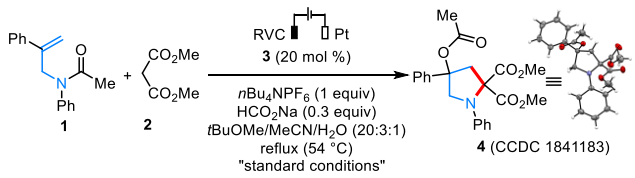
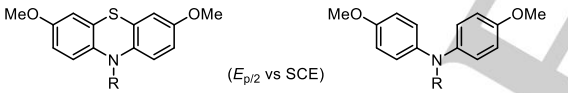
4. Moreover, the reaction showed no apparent sensitivity to oxygen (entry 12) and could be conducted on a decagram scale (entry 13).

Table 1. Optimization of reaction conditions.[a]



Entry	Deviation from standard conditions	Yield [%][b]
1	none	70[c]
2	No electricity, under air	0 (99)
3	No Cat.	0 (95)
4	Reaction at rt	0 (42)
5	No HCO_2Na	50 (5)
6	**5** or **6** as catalyst	64–68
7	**7**, **8**, or **9** as catalyst	5–30
8	*t*BuOMe/MeCN (20:3) as solvent	13 (30)
9	MeCN/H_2O (3:1) as solvent	29 (39)
10	THF/MeCN/H_2O (20:3:1) as solvent	32 (30)
11	Et_2O/MeCN/H_2O (20:3:1) as solvent	37 (34)
12	under air	72 (< 5)
13	10.1 g (40.0 mmol) of **1**, under air	66 **[10.5 g]**

[a] Reaction conditions: RVC anode (100 PPI, 1 cm x 1 cm x 1.2 cm), Pt cathode, **1** (0.3 mmol), **2** (0.6 mmol), solvent (6 mL), argon, 7.5 mA ($j_{anode} \cong 0.1$ mA cm^{-2}), 4.4 h (4.1 F per mol of **1**). [b] Yield determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Unreacted **1** in parenthesis. [c] Isolated yield.

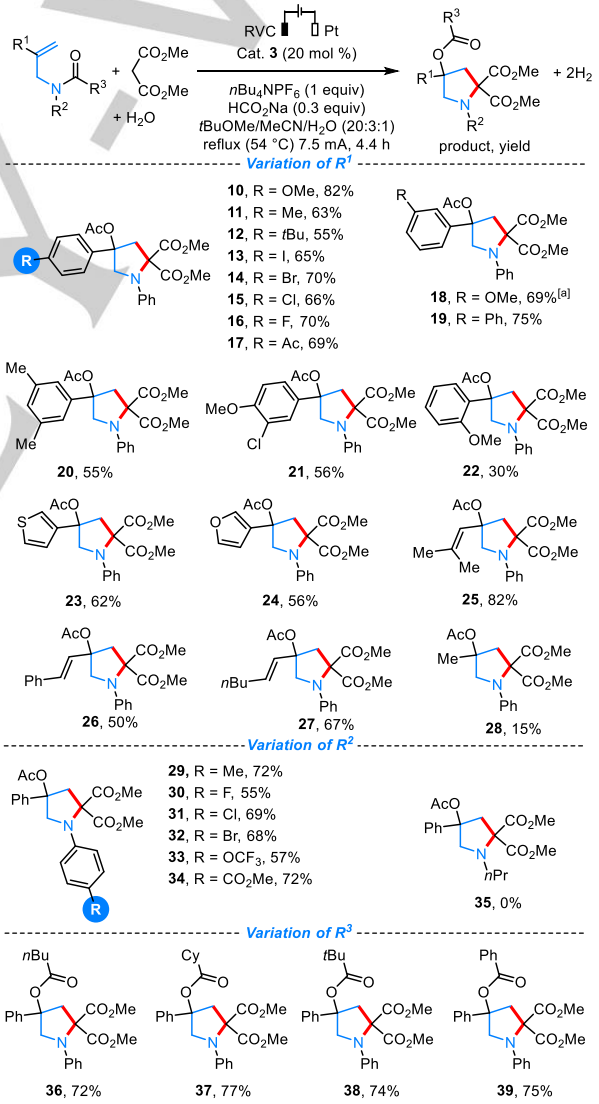


($E_{p/2}$ vs SCE)

3, R = 4-*t*BuC_6H_4 ($E_{p/2}$ = 0.52 V)
5, R = 4-OMeC_6H_4 ($E_{p/2}$ = 0.50 V)
6, R = 4-ClC_6H_4 ($E_{p/2}$ = 0.58 V)
7, R = 4-*t*BuC_6H_4 ($E_{p/2}$ = 0.69 V)
8, R = 4-OMeC_6H_4 ($E_{p/2}$ = 0.62 V)
9, R = 4-ClC_6H_4 ($E_{p/2}$ = 0.78 V)

We then investigated the substrate scope of the reaction by varying the substituents of the N-allyl amide. The phenyl ring on the alkenyl carbon (R^1) could be substituted with a wide range of functional groups with diverse electronic properties at its para- and meta-positions (**10**–**21**). However, attaching an OMe substituent at the ortho-position of the phenyl group (**22**) led to a dramatic reduction in yield. The alkenyl position could also be substituted with a heteroaryl ring, such as 3-thienyl (**23**) and 3-furanyl (**24**), or an alkenyl moiety (**25**–**27**). N-allyl amide with a methyl group at the R^1 position exhibited significantly decreased reactivity and afforded the corresponding product **28** in a low yield of 15%. On the other hand, the R^2 phenyl ring on the amide nitrogen atom showed a broad tolerance of functional groups including Me (**29**), halogens (F, Cl, Br; **30**–**32**), OCF_3 (**33**), as well as electron-accepting CO_2Me (**34**). However, replacing the R^2 phenyl group with an alkyl substituent abolished product formation (**35**). The acyl R^3 could be replaced with a variety of alkyl or aryl groups with different steric properties, such as *n*Bu (**36**), cyclohexyl (Cy, **37**), *t*Bu (**38**) and phenyl (**39**).

When a β-ketoester was employed as the coupling partner (Scheme 3), the resultant (4+2) annulation furnished a tetrahydropyridine product and no pyrrolidine derivative was detected. As the sole exception, the annulation of methyl acetoacetate with an enyne afforded a small amount of pyrrolidine **54** (13%) in addition to the main tetrahydropyridine product **53** (53%). Note that these (4+2) annulation reactions did not need HCO_2Na and benefited from reduced current density. Dihydrofurans, which are common products for the oxidative annulation of alkenes with 1,3-dicarbonyl compounds,[7] were not detected in any of the above reactions. Like what we observed in the (4+1) annulation reactions, the phenyl rings on the alkene and the amide nitrogen atom of the N-allyl amide tolerated a wide range of substituents with diverse electronic properties (**40**–**51**). The N-allyl amide substrate bearing an N-*n*Pr group,



Scheme 2. Scope of pyrrolidine synthesis. Reaction conditions: Table 1, entry 1, 4.1 F per mol of N-allyl amide. [a] 1 equiv of HCO_2Na was employed.

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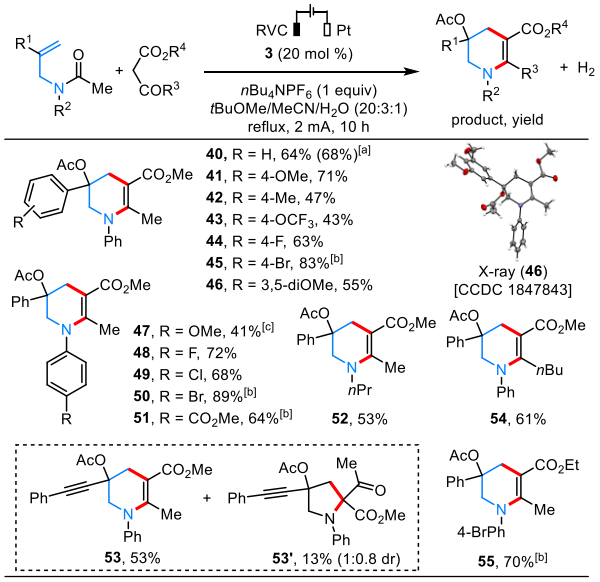
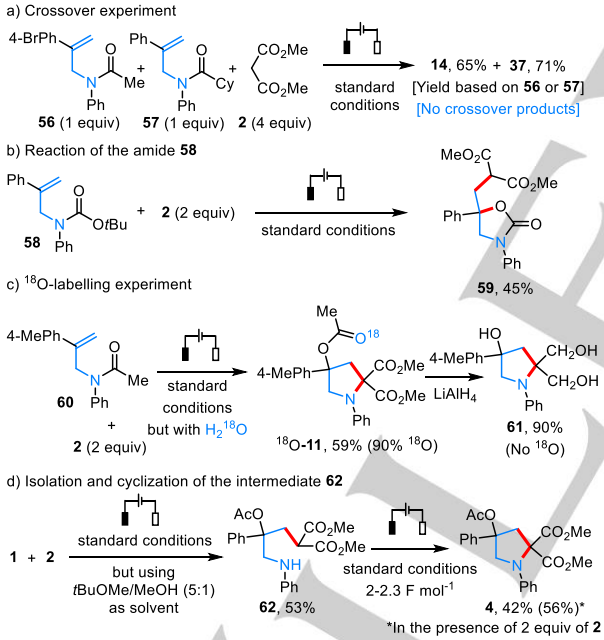


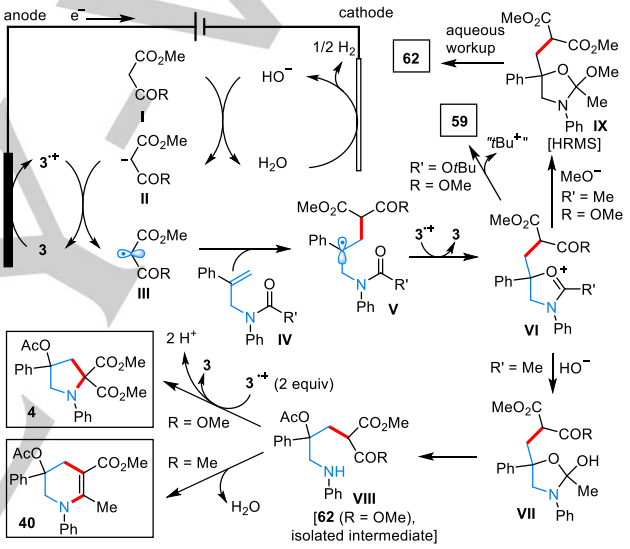
Scheme 3. Scope of tetrahydropyridine synthesis. Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), solvent (6 mL), argon, 2.5 F per mol of N-allyl amide. [a] Reaction for 16 h. [b] 5 equiv of β-ketoester. [c] Reaction for 13.9 h.



Scheme 4. Mechanistic studies.

which exhibited no reactivity toward malonic ester, underwent annulation with methyl acetoacetate to generate the corresponding tetrahydropyridine product **52** in 53% yield. The β-ketoester also tolerated variation to include methyl 3-oxoheptanoate (**54**) and ethyl acetoacetate (**55**) as the coupling partners.

A series of mechanistic studies were carried out to shine light on the reaction mechanism. The electrolysis of a mixture of amides **56** and **57** afforded **14** and **37** without the observation of any cross-over products (Scheme 4a), suggesting that the migration of the acyl group occurred intramolecularly. Replacing the acyl group with a *tert*-butoxycarbonyl (Boc) group (**58**) resulted in the formation of a cyclic carbamate **62** as the only identifiable product (Scheme 4b). The annulation of **60** with dimethyl malonate **2** in the presence of $H_2{}^{18}O$ afforded ^{18}O-**11**, which was reduced by $LiAlH_4$ to generate ^{18}O-free **61** (Scheme 4c). Combined, these experiments provided evidence that the acyl carbonyl oxygen of the pyrrolidine product originated from H_2O. The reaction of **1** with **2** in H_2O-free *t*BuOMe/MeOH led to the generation of an uncyclized amine **62** (53% yield), which cyclized into **4** in 42% yield under the standard electrolysis conditions. These results strongly suggested that **62** was an intermediate for the formation of the pyrrolidine product. The formation of **62** was not observed under the standard conditions, suggesting that it is preferentially oxidized over the dimethyl malonate **2** during the preparative electrolysis.



Scheme 5. Mechanistic proposal.

A possible mechanism has been proposed based on the findings of this work (Scheme 5).[18] The reaction begins with the anodic oxidation of **3** ($E_{p/2}$ = 0.52 V vs SCE) into the corresponding radical cation **3**$^{\bullet+}$. Meanwhile, H_2O is reduced at the cathode to produce H_2 and HO^-, the latter of which then deprotonates the 1,3-dicarbonyl compound **I** [$E_{p/2}$ (**2**) > 2.0 V vs SCE] to generate the more oxidizable anion **II** ($E_{p/2}$ = 0.31 V vs SCE, R = OMe). The oxidation of **II** by **3**$^{\bullet+}$ via single-electron transfer (SET) furnishes a C-radical **III**,[13,19,20] which subsequently adds to the alkenyl moiety of the N-allyl amide **IV** ($E_{p/2}$ = 1.74 V vs SCE) to generate a tertiary C-radical **V**. The intermediate **V** is oxidized and trapped intramolecularly by the carbonyl group of its amide moiety instead of that of the 1,3-dicarbonyl moiety to afford **VI**. In the case of amide **58** (R′ = O*t*Bu), the corresponding cationic intermediate **VI** would lose a *t*Bu group to afford a cyclic carbamate **59**. For other amides, **VI** would react with HO^- or H_2O and proceed with a selective C–N bond cleavage[21] to produce a secondary amine **VIII**, which

undergoes C(sp^3)–H/N–H cross coupling reaction[22] [**62** (R = OMe)] to generate the pyrrolidine product **4** ($E_{p/2}$ = 1.07 V vs SCE) or intramolecular dehydration (R = Me) to afford the tetrahydropyridine **40** ($E_{p/2}$ = 1.15 V vs SCE).[23] When the electrochemical reaction of **1** with **2** was conducted in *t*BuOMe/MeOH (cf. Scheme 4d), an intermediate with *m*/*z* 436.1728 was observed, which was ascribed to **IX** [Scheme 5, theoretical *m*/*z* for (**IX** + Na)$^+$ 436.1731]. These results provide support for the formation of intermediate **VIII** during the electrolysis in aqueous solution. Note that the intermediate amine **62** decomposed quickly in the presence of stoichiometric *n*Bu_4NOH or DBU. Fortunately, under the electrochemical conditions, HO^- is generated in situ and continuously at the cathode to aid the oxidation steps, allowing the annulation reactions to proceed under mildly basic conditions (Scheme 2) or without an external base (Scheme 3).

In summary, we have developed an unprecedented approach for the synthesis of pyrrolidines and tetrahydropyridines via dehydrogenative annulation reactions of easily available materials. The use of a phenothiazine-based redox catalyst enables efficient and selective intermolecular radical reactions of 1,3-dicarbonyl compounds. The application of this organocatalyzed electrochemical system in promoting other oxidative radical reactions of 1,3-dicarbonyl compounds are under investigation in our laboratory.

Acknowledgements

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Keywords: electrochemistry • heterocycles • redox chemistry • radicals • annulation

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[18] See the Supporting Information for more discussion.

[19] Despite the low oxidation potential of **II**, its direct oxidation on the electrode did not occur because this species is generated at low concentration in situ and there is no sufficient amount in the reaction mixture to sustain the current.

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[21] The origin of this unusual selectivity remains unclear.

[22] This dehydrogenative C–N bond forming strategy is also applicable to six-membered ring formation (Scheme S1).

[23] The oxidation potentials of the heterocyclic products and the amine intermediate **VIII** are expected to vary with different N-aryl groups.

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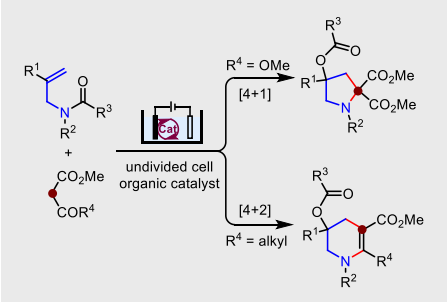
Unprecedented dehydrogenative annulation reactions of N-allyl amides with 1,3-dicarbonyl compounds have been developed for the efficient and modular synthesis of pyrrolidine and tetrahydropyridine derivatives. These electricity-powered reactions employ a phenothiazine based organic redox catalyst, allowing the reactions to proceed under transition metal- and oxidizing reagent-free conditions.



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