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Cross-Dehydrogenative Coupling between Enamino Esters and Ketones: Synthesis of Tetrasubstituted Pyrroles

Miao Zhao, Fen Wang, and Xingwei Li*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China

xwli@dicp.ac.cn

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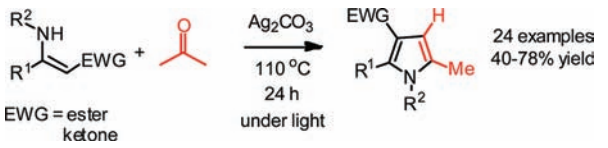
ABSTRACT



Tetrasubstituted pyrroles have been synthesized via the cross-dehydrogenative coupling between enamino esters and acetone. Silver carbonate proved to be an effective oxidant, and no transition metal catalyst is necessary.

Construction of C−E (E = C, N, and O) bonds via the oxidative functionalization of C−H bonds with an E−H group has attracted increasing attention over the past decades.[1] This process is especially important in achieving molecular complexity considering the ubiquity of C−H bonds in organic compounds, and these C−E bonds are key linkages in organics. Two categories of intrinsic pathways can be followed in this process, namely, the (transition-metal-catalyzed) C−H activation pathway[2] and the cross-dehydrogenative coupling (CDC) pathway.[3] While oxidative cross-coupling via the C−H activation pathway has been well-studied in terms of scope, mechanisms, and applications, the construction of C−E bonds via a CDC process has become an increasingly important strategy. Given the abundance of C−H bonds, this strategy represents a step-economic access to C−C bonds in that there is no necessity of prefunctionalization of the C−H bond in either of the precursors. Previous reports indicated that metal or organic single-electron oxidants or combination of metal catalysts and organic oxidants have been widely used for CDC reactions, among which Fe,[4] Cu,[5] and V[6] catalysts have been well-studied.

The pyrrole ring is widely present in numerous natural products, synthetic pharmaceuticals, and molecular metarials. Therefore, considerable attention has been paid to develop efficient methods for the synthesis of these privileged molecules. In recent years, a large number of redox-neutral or oxidative pyrrole syntheses have indeed been reported.[7] While pyrroles and indoles are indeed different, we reason that inspirations on pyrrole synthesis can be

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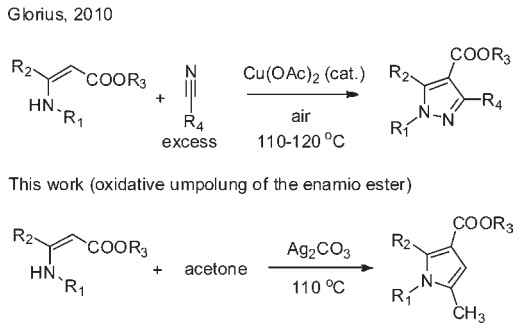
drawn from the synthesis of related indoles that utilize CDC reactions. Recent work has shown that palladium(II),[8] Fe(III),[9] and copper(II)[10] can efficiently catalyze the oxidative cyclization of readily accessible β-enamino esters, affording indole products via oxidative C−C coupling. This oxidative coupling reaction can be alternatively achieved using $PhI(OAc)_2$ as the sole oxidant.[11] Despite these progresses, (intermolecular) CDC reactions that involve β-enamino esters are rare, likely due to the competitive intramolecular oxidative cyclization. In fact, intermolecular C−C coupling via CDC reactions are highly desirable in delivering molecular complexity. Very recently, Glorius reported a highly efficient synthesis of pyrazoles via Cu(II)-catalyzed CDC between a β-enamino ester and a nitrile, a process that involves C−C and N−N bond formation (Scheme 1).[12] We reason that the related coupling of the two CH bonds in β-enamino ester with an unactivated methyl ketone that affords a pyrrole is in principle feasible. However, CDC reactions involving ketones are rather limited. We now report the efficient synthesis of tetrasubstituted pyrroles via cross-dehydrogenative coupling between β-enamino esters and acetone.

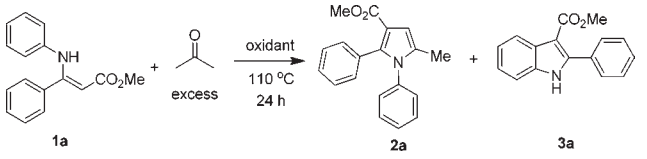
Scheme 1. β-Enamino Esters in CDC Reactions



We feel that nitriles and ketones are significantly different in terms of electrophilicity and nucleophilicity, and coupling with ketones should expand the chemistry of CDC for heterocycle synthesis. We embarked on our studies with the coupling between β-enamino ester **1a** and acetone under oxidative conditions. When $Cu(OAc)_2$ was applied as a stoichiometric oxidant in acetone (sealed tube, 110 °C), the desired pyrrole **2a** was obtained, albeit in rather low yield together with traces of the cyclization product indole **3a** (Table 1, entry 7). Product **2a** was identified as a tetrasubstituted pyrrole on the basis of NMR spectroscopy. In contrast, switching to other copper(II) oxidants such as $CuCl_2$ and $Cu(OTf)_2$ failed to give any improved yield.

In addition, other single-electron oxidants such as $FeCl_3$, DDQ, CAN, and $PhI(OAc)_2$ only afforded pyrrole **2a** in lower yield. Interestingly, reactions using Ag(I) oxidants tend to afford the desired product in improved yield. Thus, when Ag_2CO_3 (2 equiv) was applied in acetone, the desired product **2a** was generated in 64% GC yield, together with a small amount of the cyclization product **3a** (entry 14). We found that the equivalence of acetone and Ag_2CO_3 has rather large effects on the efficiency and selectivity of this reaction. When a smaller amount of acetone was used, the CDC reaction is somewhat lower in both efficiency and selectivity (entries 8−13). Gratifyingly, when 3 equiv of Ag_2CO_3 were provided in a large excess of acetone, the isolated yield of pyrrole **2a** was improved to 70%, although side product **3a** was also obtained (entry 1). Further improvement of the selectivity to favor **2a** met with failure when $Pd(OAc)_2$ (10 mol %) was introduced, under which conditions only indole **3a** was isolated (entry 2). It is noteworthy that this reaction needs to be carried out under laboratory light, while reactions carried out in the dark resulted in lower yield and lower selectivity. Hence, the slow decomposition of Ag_2CO_3 induced by visible light might facilitate this reaction so that the reaction is both more efficient and reproducible under laboratory light. In contrast, other silver(I) oxidants proved less effective, and **2a** was generated only in lower yield using AgOAc, AgF, $AgNO_3$, and Ag_2O with or without the extrusion of light.[13]

Table 1. Screening of Reaction Conditions[a]



				yield (%)[b]	
entry	oxidant (equiv)	acetone (mL)	solvent (mL)	**2a**	**3a**
1	Ag_2CO_3 (3)	3		72 (70[c])	11
2[d]	Ag_2CO_3 (3)	3		trace	61
3	AgOAc (3)	3		66	9
4	$AgNO_3$ (3)	3		23	4
5	AgF (3)	3		<5	trace
6	Ag_2O (3)	3		14	trace
7	$Cu(OAc)_2$ (3)	3		17	trace
8	Ag_2CO_3 (3)	0.5	DMF (1.5)	17	38
9	Ag_2CO_3 (3)	0.5	PhMe (1.5)	18	13
10	Ag_2CO_3 (3)	0.5	THF (1.5)	5	14
11	Ag_2CO_3 (3)	0.5	MeOH (1.5)	14	45
12	Ag_2CO_3 (3)	1		36	30
13	Ag_2CO_3 (3)	2		43	23
14	Ag_2CO_3 (2)	3		64	9
15[e]	Ag_2CO_3 (3)	3		trace	trace
16	DDQ (3)	3			
17	CAN (3)	3			

[a] Conditions: **1a** (0.3 mmol), oxidant, acetone, solvent, 110 °C, sealed tube under nitrogen, 24 h. [b] GC yield with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. [d] $Pd(OAc)_2$ (10 mol %) was added. [e] 1.2 equiv of 2,6-di-*tert*-butyl-4-methyl phenol was added.

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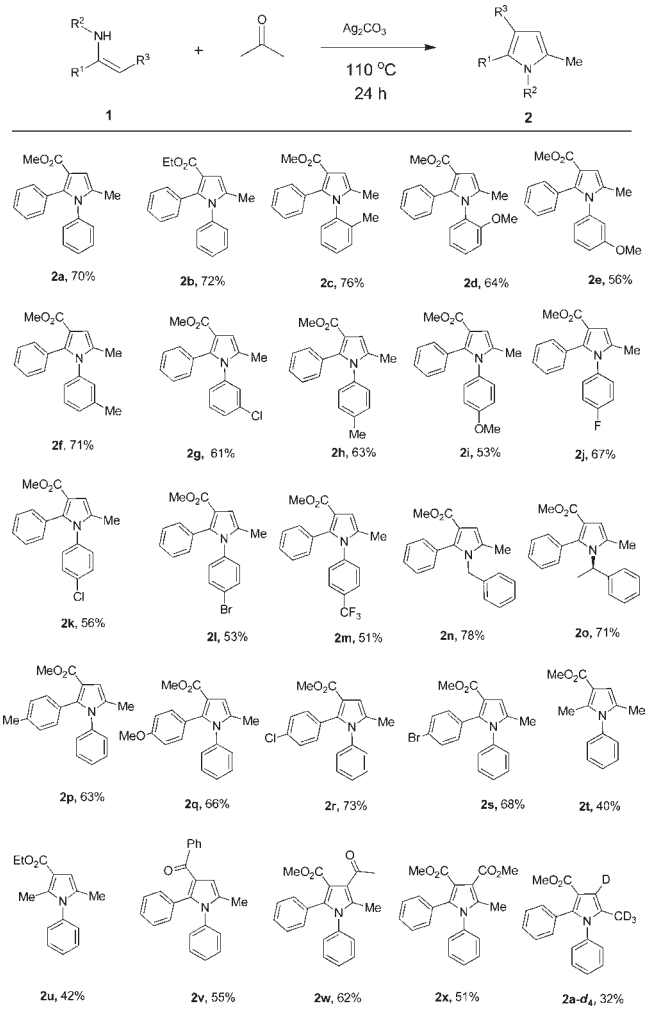
With the optimized conditions in hand, we next explored the scope of the enamino ester substrate (Scheme 2). Substrates with variable *N*-substituents were examined first. Electron-donating (**2c**, **2d**, **2h**, and **2i**), -withdrawing (**2m**), and halogen (**2g**, **2k**, and **2l**) substitutents at the *ortho*, *meta*, and *para* positions of the *N*-aryl group in the substrate are well-tolerated, and the coupled products were isolated in yields ranging from 51 to 76%. Moreover, the *N*-substitutent is not limited to an aryl group; *N*-benzyl-substituted enamino esters, including a sterically hindered 2° benzyl-substituted enamino ester, readily coupled with acetone in high yields (**2n** and **2o**). The high-yielding synthesis of these two products is likely ascribed to the inhibition of the competitive cyclization of the starting enamino ester. The cyclization, if any, would unfavorably afford a nonaromatic six-membered heterocycle. The scope of the substrate in terms of the R_1 group in the enamino ester was further demonstrated. Enamines bearing electron-rich and -poor aryl as well as alkyl (**2p**−**2u**) R_1 groups all underwent smooth coupling with acetone to afford the desired pyrroles in moderate to high yields, although somewhat lower yields were obtained for substrates with an alkyl R_1 group (**2t** and **2u**).

The EWG in the enamino substrate is not limited to an ester group; a β-enamino ketone also readily coupled with acetone to give the expected acyl-functionalized pyrrole (**2v**). Since acetone is relatively less reactive, we reasoned that ketones with activated methylene groups should also undergo this coupling reaction if they are compatible with the oxidation conditions. Indeed, acetylacetone and a β-keto ester readily coupled with the enamino ester to afford fully substituted pyrroles (**2w** and **2x**). We noted that this coupling between β-dicarbonyl compounds and enamino esters has been reported using CAN as an oxidant.[14] However, CDC reactions and catalytic C−H activation of acetone are rare.[5b,15,16] Extension of this reaction to other less reactive ketones such as butanone, however, met with failure, and the indole cyclization product was isolated as the major one.

Several experiments were conducted to probe the reaction mechanism. When **1a** was coupled with acetone-d_6 under the standard conditions, product **2a**-d_4 was isolated in 32% yield, where no deuterium scrambling was detected on the basis of ^{1}H NMR spectroscopy. In addition, two parallel reactions were conducted side by side in acetone and acetone-d_6 (Scheme 3). GC analysis revealed that the distribution of the products depends on the solvent. In acetone, pyrrole **2b** was detected as the major product with a ratio of **2b**:**3b** = 82:18. However, the pyrrole **2b**-d_4 was observed only as the minor products with a ratio of

Scheme 2. Cross-Dehydrogenative Coupling of Enamino Esters with Acetone[a,b]



[a] Conditions: enamino ester (0.3 mmol), Ag_2CO_3 (0.3 mmol), acetone (3 mL), 110 °C, sealed tube under nitrogen, 24 h.
[b] Isolated yield.

2b-d_4:**3b** = 36:64 when acetone-d_6 was used. These results revealed that the CDC and the simple cyclization reactions always occurred in direct competition. The preference for simple cyclization in acetone-d_6 indicated that the rate of the CDC reaction is lowered as a result of kinetic isotope effect. Thus, cleavage of the C−H bond in acetone should be involved in the rate-determining step. When the coupling of **1a** and acetone was carried out in the presence of 1.2 equiv of a radical inhibitor 2,6-di-*tert*-butyl-4-methyl phenol, neither the pyrrole (**2a**) nor the indole (**3a**) was detected in an appreciable amount, indicating the intermediacy of radical species in this reaction. Competition of two enamino esters **1i** and **1l** that differ electronically in the *N*-aryl group revealed that products **2i** and **2l** were generated in nearly equal ratio on the basis of GC analysis. This result suggests that the reaction is insensitive to the electronic nature of the *N*-substituent.

A plausible reaction mechanism is suggested on the basis of these preliminary data and literature precedents

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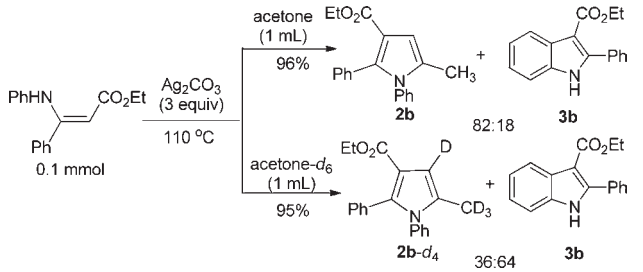
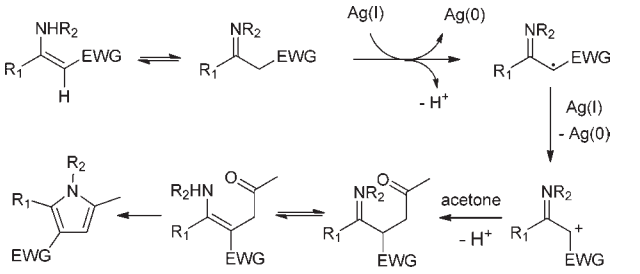
Scheme 3. Isotope Effects in Acetone



Scheme 4. Plausible Mechanism for Pyrrole Synthesis



(Scheme 4). Single-electron oxidation of the anion of the β-imino ester tautomer of the substrate generates a radical intermediate, which is further oxidized by silver(I) to a carbocation.[17] Acetone is proposed to undergo nucleophilic addition to this carbocation, leading to C−C bond formation. Subsequent intramolecular condensation of this enamino ketone intermediate affords the final pyrrole product. It is noteworthy that this mechanism is in sharp contrast to that proposed in the synthesis of pyrrazoles starting from β-imino esters and nitriles, where the β-imino ester acts as a nucleophile that attacks the nitrile.[12] In the case of actone, however, the β-imino ester is an electrophile, where the umpolung is induced by single-electron oxidation.

In summary, we have achieved an efficient and direct synthesis of substituted pyrroles via the cross-dehydrogenative coupling of enamino esters with acetone. In this process, no transition metal catalyst is necessary, C−C and C−N bonds are effectively constructed, and prefunctionalization of neither coupling partner is necessary. A broad scope of enamino ester substrate has been established. This reaction makes direct use of a simple and abundant three-carbon feedstock without the requirement of a stoichiometric amount additive or preformed enolate. Studies are directed toward further applications of this method to the synthesis of other heterocyclic compounds.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.