Organic Letters

Letter

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Direct Oxidative Coupling of Enamides and 1,3-Dicarbonyl Compounds: A Facile and Versatile Approach to Dihydrofurans, Furans, Pyrroles, and Dicarbonyl Enamides

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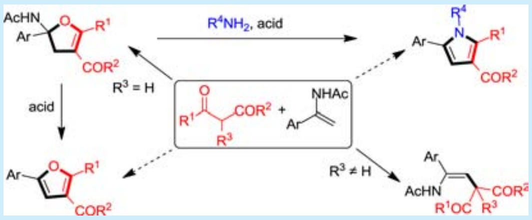
Supporting Information

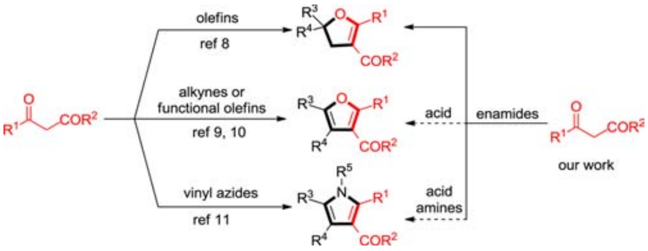
ABSTRACT: An efficient manganese(III)-mediated oxidative coupling reaction between α-aryl enamides and 1,3-dicarbonyl compounds has been developed. A series of dihydrofurans and dicarbonyl enamides were synthesized in moderate to good yields. Moreover, these dihydrofurans could be readily transformed into the corresponding furans and pyrroles via the Paal−Knorr reaction.



C−C Bond formation via direct oxidative coupling of two different C−H bonds is of great significance and a challenge.[1] The radical-driven process has recently provided an important approach by which to realize these oxidative coupling reactions, and the addition of free radicals to olefins has attracted particular attention.[2] Enamides are versatile and powerful building blocks in organic synthesis.[3,4] However, the oxidative coupling of free radicals and enamides has been rarely reported.[5] The electron-rich character of enamides could be expected to promote their reactivity with electron-deficient radicals.

Five-membered heterocycles (dihydrofurans, furans, and pyrroles) are important scaffolds and building blocks in natural products, pharmaceuticals, and functional materials.[6] 1,3-Dicarbonyl compounds are usually utilized to build five-membered heterocycles,[7] prepare dihydrofurans from olefins,[8] and create furans from alkynes or functional olefins.[9,10] They can also be used to synthesize pyrroles from vinyl azides[11] (Scheme 1). Although preparations of dihydrofurans, furans, and pyrroles have been separately developed, a simple and mild strategy for realizing the diverse synthesis of all these heterocycles is highly interesting and desirable. As part of our continuing interest in free radical chemistry and the synthesis of heterocyclic compounds,[12] we herein report a $Mn(OAc)_3$-mediated direct oxidative coupling of 1,3-dicarbonyl compounds to versatile enamides to readily yield three kinds of heterocycle and dicarbonyl enamides.

Scheme 1. Synthesis of Five-Membered Heterocycles from 1,3-Dicarbonyl Compounds



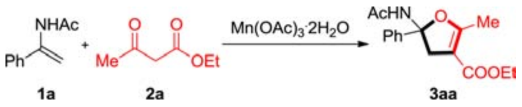
Considering that enamides are electron-rich and versatile, our initial investigations focused on the reaction of *N*-(1-phenylvinyl)acetamide (**1a**) with ethyl 3-oxobutanoate (**2a**). Gratifyingly, the desired dihydrofuran **3aa** was isolated in 69% yield in the presence of 3 equiv of $Mn(OAc)_3$ (Table 1, entry 1), which is usually considered to be a good single-electron oxidant in the field of free radical chemistry.[13] The present reaction also proceeded smoothly in other solvents, such as DMF, MeCN, EtOAc, and MeOH (Table 1, entries 2−5). MeCN was the most suitable solvent, giving the desired product **3aa** in 80% yield (Table 1, entry 3). However, the reaction did not occur in H_2O (Table 1, entry 6). In addition, temperature variation only slightly affected the reaction efficiency (Table 1, entries 7 and 8). By reducing the amount of $Mn(OAc)_3$ to 2.5 equiv, the yield of **3aa** dropped to 68% (Table 1, entry 9). Running the reaction under an argon atmosphere increased the yield of **3aa** to 87% (Table 1, entry 10).

In order to test the practicality of this approach, a gram-scale synthesis of **3aa** (2.37 g, 82% yield) was successfully performed (Table 1, entry 11).

With these optimized conditions in hand (Table 1, entry 10), we turned to examining the scope and limitations of this method (Scheme 2). The unsymmetrical 1,3-dicarbonyl compounds gave the corresponding products (**3ab** and **3ac**)

Received: October 13, 2014
Published: November 4, 2014

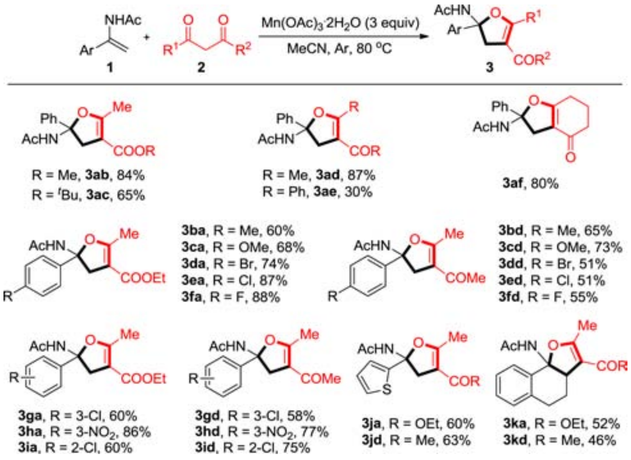
Table 1. Reaction Optimization[a]



entry	solvent	temp (°C)	yield (%)
1	DMSO	80	69
2	DMF	80	62
3	MeCN	80	80
4	EtOAc	80	72
5	MeOH	80	69
6	H_2O	80	0
7	MeCN	100	74
8	MeCN	50	66
9[b]	MeCN	80	68
10[c]	MeCN	80	87
11[c,d]	MeCN	80	82

[a] All reactions were carried out on a 0.2 mmol scale in 2 mL of solvent for 6 h. Isolated yield. [b] 2.5 equiv of $Mn(OAc)_3·2H_2O$. [c] Under argon. [d] The reaction was carried out on a 10 mmol scale in 100 mL of MeCN under argon in 250 mL Schlenk tubes for 24 h.

Scheme 2. Synthesis of Dihydrofurans from Enamides and 1,3-Dicarbonyl Compounds[a]

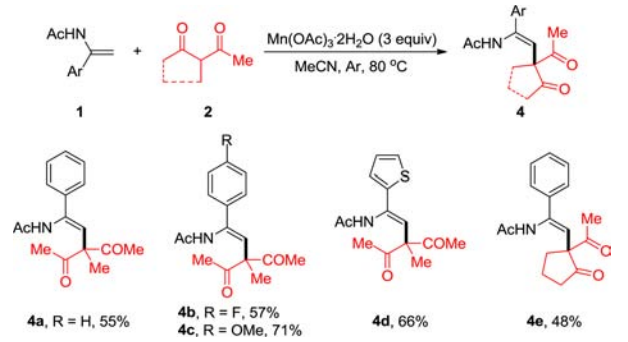


[a] A mixture of enamides (0.2 mmol), 1,3-dicarbonyl compounds (0.3 mmol), and $Mn(OAc)_3·2H_2O$ (0.6 mmol) in 2 mL of MeCN was stirred under argon in 50 mL Schlenk tubes at 80 °C for 6 h. Isolated yields.

in good yield, and the yield of **3ac** was lower than that of **3ab**, owing to the steric hindrance. The symmetrical 1,3-dicarbonyl compounds with an alkyl substituent afforded the desired products (**3ad** and **3af**) in 87% and 80% yields, respectively. Unfortunately, the aryl substituted 1,3-dicarbonyl compounds gave a much lower yield of **3ae** (30% yield), and the larger sized dipivaloylmethane even failed to give the corresponding dihydrofuran.[14] Fortunately, various aromatic enamides with electron-donating (Me and OMe) and electron-withdrawing groups (Br, Cl, F, and NO_2) all worked well with unsymmetrical and symmetrical 1,3-dicarbonyl compounds, affording the desired dihydrofurans in 88% to 46% yields, respectively (**3ba**–**3ka** and **3bd**–**3kd**). With ethyl 3-oxobutanoate **2a**, the *para*-substituted aromatic enamides with electron-withdrawing groups (**3da**–**3fa**) gave rise to better results than electron-donating groups (**3ba** and **3ca**). Contrastingly, the *para*-substituted aromatic enamides with electron-donating groups (**3bd** and **3cd**) showed higher yields than those with withdrawing groups (**3dd**–**3fd**) when reacted with pentane-2,4-dione **2d**. In addition, the aromatic enamides substituted with electron-withdrawing groups (Cl and NO_2) at the *ortho*- or *meta*-positions could also be efficiently converted to the expected dihydrofurans in 86–58% yields (**3ga**–**3ia** and **3gd**–**3id**). To our delight, other representative enamides derived from heteroaromatic ethanone (1-(thiophen-2-yl)ethanone) and cyclic ketone (α-tetralone) were also found to be suitable for this transformation (**3ja** and **3jd**, **3ka** and **3kd**).

Replacing 1,3-dicarbonyl compounds with the 2-substituted 1,3-dicarbonyl compounds in the reaction with enamides can selectively produce the (*Z*)-dicarbonyl enamides **4** through direct oxidative coupling (Scheme 3). The stereochemistry of dicarbonyl enamides **4** was further unambiguously confirmed by the X-ray diffraction (XRD) analysis of a representative product **4a** (CCDC 1026793) (Figure 1). The aromatic enamides with electron-withdrawing groups (F) or electron-donating groups (OMe) gave the corresponding products in moderate-to-good yield (**4b** and **4c**). The oxidative coupling reactions of heteroaromatic enamides or cyclic 1,3-dicarbonyl compounds also proceeded smoothly, yielding, for example, the corresponding **4d** and **4e**.

Scheme 3. Synthesis of Dicarbonyl Enamides[a]



[a] A mixture of enamides (0.2 mmol), 1,3-dicarbonyl compounds (0.3 mmol), and $Mn(OAc)_3·2H_2O$ (0.6 mmol) in 2 mL of MeCN was stirred under argon in 50 mL Schlenk tubes at 80 °C for 6 h. Isolated yields.

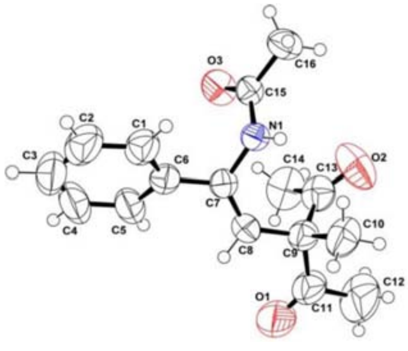
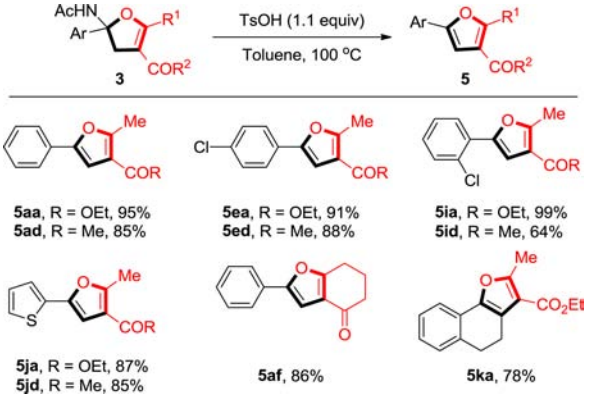


Figure 1. Single crystal structure of **4a**.

Owing to the versatility of amide groups, the above dihydrofurans **3** could be easily transformed into the corresponding furans by using amide as an easy leaving group in the presence of *p*-toluenesulfonic acid (Scheme 4). As expected, the dihydrofurans (**3aa** and **3ad**) converted into the

Scheme 4. Synthesis of Furans from Dihydrofurans[a]

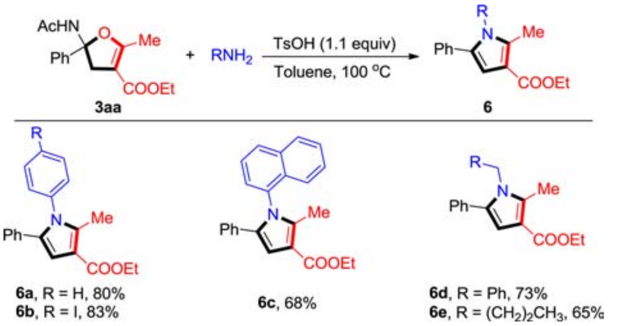


[a]A mixture of dihydrofurans (0.2 mmol) and TsOH (0.22 mmol) in 2 mL of toluene was stirred in 15 mL pressure tubes at 100 °C for 2 h. Isolated yields.

corresponding furans (**5aa** and **5ad**) in 95% and 85% yields, respectively.[15] Dihydrofurans with electron-withdrawing groups (Cl) at the *ortho*- or *para*-position afforded corresponding furans in 99% to 64% yield (**5ea** and **5ed**, **5ia** and **5id**). To our delight, the typical heteroaromatic dihydrofurans also gave the desired products in excellent yields (87% of **5ja** and 85% of **5jd**). In addition, other representative dihydrofurans derived from cyclic 1,3-dicarbonyl compounds or cyclic enamides all worked efficiently in the transformation from dihydrofuran to furan (**5af** and **5ka**).

Encouraged by the above results in the Paal−Knorr reaction, we decided to react these dihydrofurans with amines to obtain the corresponding pyrroles. To our delight, both aromatic and aliphatic amines were suitable for this transformation (Scheme 5). The aromatic amines afforded the desired pyrroles in 83% to 68% yield (**6a**−**6c**), and aliphatic amines also gave the corresponding product in 73% to 65% yield (**6d** and **6e**).

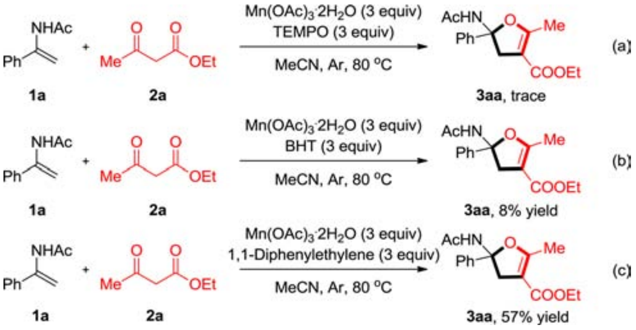
Scheme 5. Synthesis of Pyrroles from Dihydrofurans and Amines[a]



[a]A mixture of dihydrofurans (0.2 mmol), TsOH (0.22 mmol), and aromatic amines (0.3 mmol) or aliphatic amines (0.6 mmol) in 2 mL of toluene was stirred in 15 mL pressure tubes at 100 °C for 2 h. Isolated yields.

To validate the original design of the present radical process involving a Mn-initiated single electron transfer, a series of control experiments were carried out. The oxidative coupling reaction could be very effectively prevented by the addition of the radical inhibitors TEMPO (2,2,6,6-tetramethylpiperidinooxy) or BHT (butylated hydroxytoluene) (Scheme 6a and b).

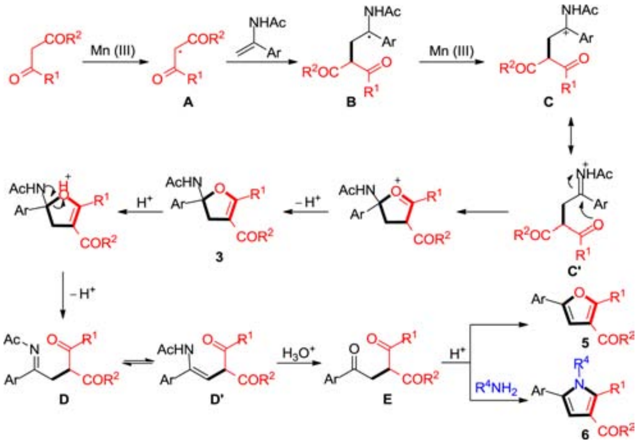
Scheme 6. Radical Trapping Experiments



However, 1,1-diphenylethylene, as another radical scavenger, could not stop this reaction, indicating that enamides show higher activity than 1,1-diphenylethylene in reacting with the radical species of 1,3-dione. We have also demonstrated that enamides are good alternatives to alkenes for reactions with the radical species (Scheme 6c).

Based on the above control experiments, a proposed mechanism is shown in Scheme 7. Initially, the 1,3-dicarbonyl compound generates an electron-deficient radical **A** in the presence of $Mn(OAc)_3$. **A** then adds to the electron-rich enamides to afford radical **B** which can be further oxidized by $Mn(OAc)_3$ into carbocation **C** or iminium ion **C′**, which undergoes cyclization/deprotonation to give the desired dihydrofurans **3**. It can be seen from the reaction pathway that oxidative coupling theoretically needs 2 equiv of $Mn(OAc)_3$. With the help of acid, the dihydrofuran **3** goes through ring cleavage to generate imine **D** or enamide **D′**, which can further hydrolyze to afford another versatile 1,4-dione **E** intermediate that can be isolated.[15] Eventually, **E** would then afford the corresponding furan **5** and pyrrole **6** via the Paal−Knorr reaction.[16]

Scheme 7. A Plausible Mechanism



In summary, we have developed a versatile approach to dihydrofurans and dicarbonyl enamides. Notably, these transformations can be efficiently scaled up. In addition, these unique dihydrofurans with amide substituents can smoothly transform into furans and pyrroles via another versatile 1,4-dione intermediate. Other diverse syntheses through the addition of different radical partners with enamides are under investigation in our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental details, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Chinese Academy of Sciences and the National Natural Science Foundation of China (21133011 and 21373246) for generous financial support.

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(14) The 2,2,6,6-tetramethyl-4-(2-oxo-2-phenylethyl)heptane-3,5-dione (**3ag**) was obtained in 20% yield. The progress could only occur by oxidative coupling of enamide (**1a**) and the 1,3-dicarbonyl compound (**2g**), followed by the hydrolysis itself.

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