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Manganese Dioxide-Mediated Oxidative Coupling of 1,3-Dicarbonyl Compounds with α,β-Unsaturated Ketones: Direct Access to 3,4-Dicarbonyl Substituted Furans

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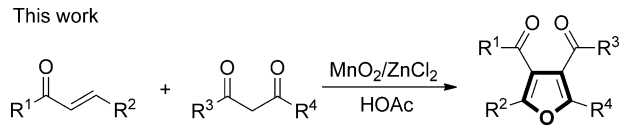
Abstract: An efficient manganese dioxide-mediated and highly selective oxidative C–H/C–H functionalization of 1,3-dicarbonyl compounds with α,β-unsaturated ketones for the construction of tetrasubstituted furans in one step has been demonstrated. This catalytic system converts two C–H bonds and C=O bonds to C=C and C–O bonds. This reaction provides a facile and regio-defined method for the synthesis of 3,4-dicarbonyl substituted furans.

Keywords: 1,3-dicarbonyl compounds; 3,4-dicarbonyl substituted furans; manganese dioxide; oxidative coupling; α,β-unsaturated carbonyl compounds

Direct functionalization of α,β-unsaturated carbonyl compounds through conjugate addition initiated domino reactions has emerged as a powerful synthetic strategy with widespread applications in the synthesis of pharmaceuticals and natural products.[1–3] Therefore it is still a great challenge to develop an efficient and highly selective conjugate addition of α,β-unsaturated carbonyl compounds. Such reported examples were often limited to activation of the β-position of α,β-unsaturated carbonyl compounds.[4–6] However, to the best of our knowledge, there have been only few examples, up to now, in which the radical is able to attach to the α-position of the α,β-unsaturated carbonyl compounds facilitated by manganese complexes.[7] Thus, it is both synthetically and mechanistically important to investigate the effect of electron density on this type of transformation in order to develop an efficient C–H addition reaction to attack the α-position of α,β-unsaturated carbonyl compounds.

Substituted furans and their derivatives are important commodity chemicals, valuable synthetic building blocks for agrochemicals, and active pharmaceutical ingredients.[8] In spite of the various methods available for constructing these furan building blocks, the direct regio-defined synthesis of polysubstituted furans from basic chemical materials has always attracted the attention of chemists. Many efforts have been made by several research groups to develop elegant transition metal-catalyzed processes to form furan derivatives,[9–14] but the synthesis of 3,4-dicarbonyl substituted furans is rarely reported. Considering sustainability and environmental criteria, commercially available and environmentally benign manganese complexes are attractive because manganese is one of the most abundant elements in nature.[15] As we have known, manganese salts have been used for many transformations, however, application of the easily available MnO_2 as a sole oxidant to directly mediate oxidative coupling reactions has rarely been reported. Herein, we have successfully demonstrated an oxidative coupling of 1,3-dicarbonyl compounds with α,β-unsaturated ketones mediated by MnO_2, which led to the efficient construction of polysubstituted furans in one step. This reaction eliminates the need for cumbersome preactivation and functional group manipulation, thereby minimizing the number of synthetic steps and chemical waste (Scheme 1).

It is well-known that dihydrofuran can be generated *via* a single-electron-transfer (SET) process mediated by manganese dioxide. The reactivity of the free radical depends on the energy level of the singly occupied

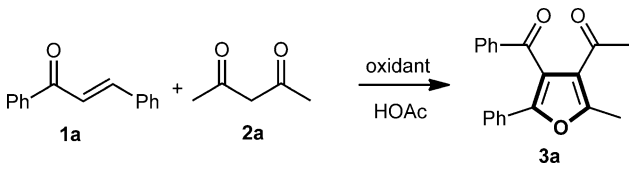


Scheme 1. Approaches to 3,4-dicarbonyl substituted furans.

molecular orbital (SOMO). An electrophilic radical having low potential energy behaves as a stable radical. The 1,3-dicarbonyl radical is electrophilic, and then attacks the α-position of α,β-unsaturated carbonyl compounds. This step would be favored to form compound **A** because the α-position of α,β-unsaturated carbonyl compounds has a higher electron density than the β-position and it induces a 1,3-dicarbonyl carbon-centered radical attacking at the α-position to generate a key intermediate. Then, the active species is transformed into the 3,4-dicarbonylfurans by an oxidative dehydrogenation reaction (Scheme 2).

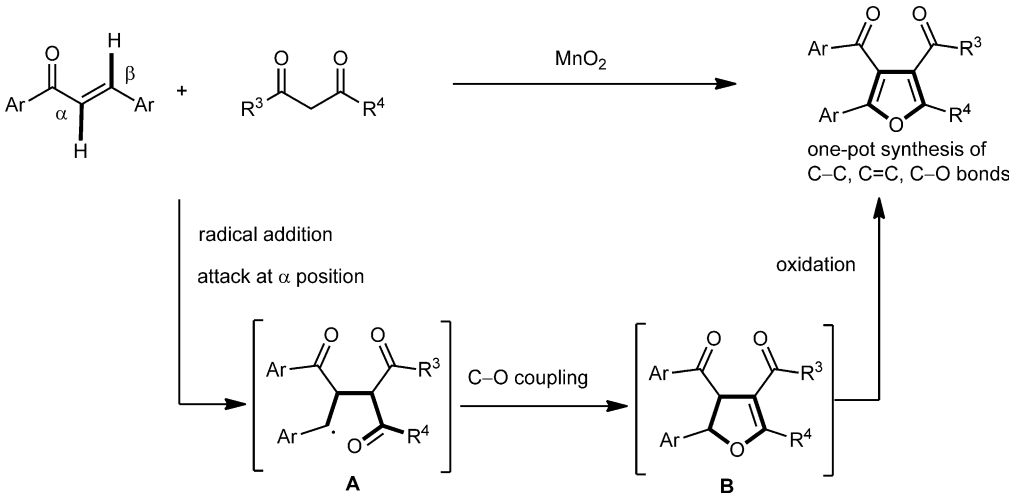
Initially, we wanted to develop a simple and efficient oxidative coupling reaction of 1,3-dicarbonyl compounds and the α,β-unsaturated carbonyl compounds to construct tetrasubstituted furans mediated by oxidative metal salts. Thus we chose chalcone **1a** and acetylacetone **2a** as our model substrates in order to optimize the reaction conditions. When the reaction was performed in DMF at 80 °C under an N_2 atmosphere mediated by Ag_2CO_3 in the presence of KOAc in a sealed reaction vessel according to the conditions reported by Lei et al.,[14a] the anticipated tetrasubstituted furan was not observed (Table 1, entry 1). We proposed that the radical of the 1,3-dicarbonyl compound might not be generated by Ag_2CO_3. We tried to utilize $Cu(OAc)_2$ as the catalyst, the desired product was not detected either (Table 1 entry 2). Furthermore, we began to apply other metal catalysts that prefer a one-electron redox process to the oxidative coupling (Table 1, entries 3–12). Generally, dihydrofuran derivatives were generated from radical cyclizations of carbonyl compounds with various alkenes in the presence of $Mn(OAc)_3$.[15b] In our reaction, a significant amount of dihydrofuran was indeed observed when $Mn(OAc)_3$ was utilized as the oxidant, while only a trace amount of the final furan was observed (Table 1, entry 4), indicating that $Mn(OAc)_3$ might be less effective for converting a dihydrofuran to the final furan. Moreover, it also shows that dihydrofuran might be a reaction intermediate

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant (equiv.)	Solvent	Temp. [°C]	Yield [%][b]
1	Ag_2CO_3, 1.0	DMF	80	0
2	$Cu(OAc)_2$, 1.0	CH_3CN	90	0
3	$Mn(OAc)_2$, 3.0	HOAc	120	trace
4	$Mn(OAc)_3$, 3.0	HOAc	120	trace
5	MnO_2, 4.0	HOAc	130	26
6	MnO_2, 6.0	HOAc	120	30
7	$BaMnO_4$, 4.0	HOAc	120	20
8	MnO_2, 4.0/$FeCl_3 \cdot 6H_2O$, 0.05	HOAc	120	33
9	MnO_2, 4.0/$ZnCl_2$,0.5	HOAc	130	27
10	MnO_2, 5.0/$ZnCl_2$, 1.0	HOAc	130	36
11[c]	MnO_2 (a), 4.0	HOAc	130	38
12[c]	MnO_2 (a), 4.0/$ZnCl_2$, 3.0	HOAc	130	57
13[c]	MnO_2 (a), 6.0/$ZnCl_2$, 6.0	HOAc	130	71
14[c]	MnO_2 (a), 7.0/$ZnCl_2$, 7.0	HOAc	130	71

[a] *Reaction conditions:* **1a** (0.50 mmol), **2a** (2.5 mmol), solvent (3.0 mL), in air.
[b] Yield of the isolated product.
[c] MnO_2 (a) is activated MnO_2



Scheme 2. Direct synthesis of 3,4-dicarbonyl substituted furans.

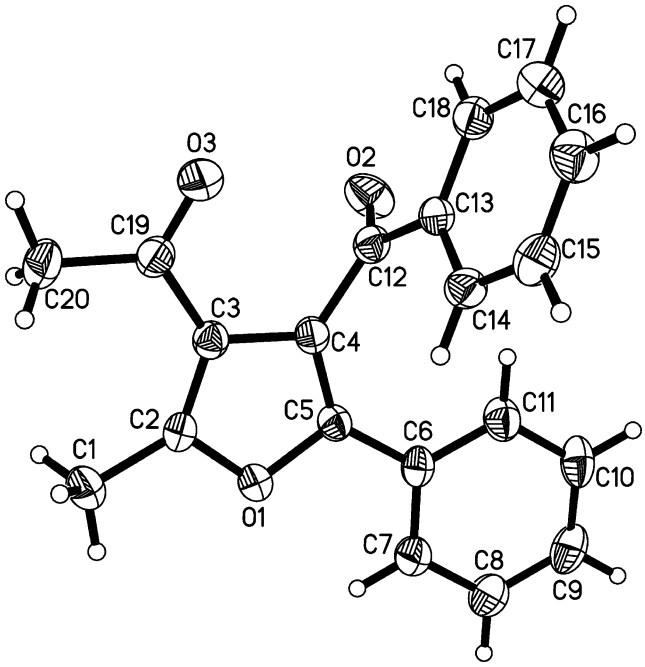
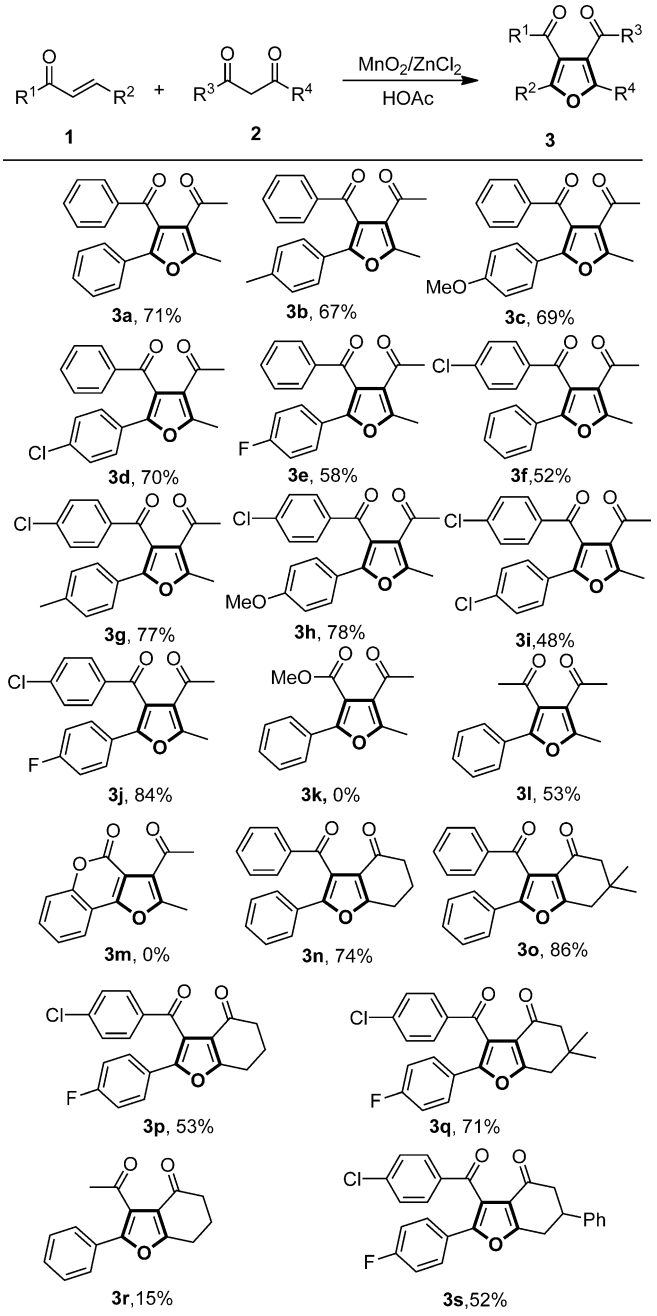


Figure 1. Single crystal X-ray structure of polysubstituted furan **3a**.

for this transformation. Unfortunately, the catalytically activated manganese dioxide was not effective for this reaction (for more details, see the Supporting Information). Extensive screening revealed that activated MnO_2 represented the most effective catalyst (Table 1, entry 11). Encouraged by this initial finding, we then optimized the reaction conditions by changing the activated MnO_2 and Lewis acids. When the amount of $ZnCl_2$ was increased from 4.0 equiv. to 6.0 equiv., the yield of **3a** also increased from 38% to 71% (Table 1, entries 12 and 13). When the amount of $ZnCl_2$ was 7.0 equiv., the yield of the target product did not change markedly (Table 1, entry 14). From the above results, the optimum conditions were affirmed as follows: chalcone **1a** (1.0 equiv.), acetylacetone **2a** (5.0 equiv.), MnO_2 (a) (6.0 equiv.), and $ZnCl_2$ (6.0 equiv.) in HOAc at 130 °C for 24 h. As a Lewis acid, $ZnCl_2$ is more likely to coordinate with the 1,3-dicarbonyl compound to stabilize the C-radical and increase the activity of the C-radical to attack to the chalcone. The structure of **3a** was unambiguously confirmed by asingle-crystal X-ray diffraction analysis (Figure 1).[16]

With the optimized conditions in hand, various α,β-unsaturated carbonyl compounds **1** were reacted with acetylacetone **2a** to prepare the corresponding polysubstituted furans **3** (Table 2). α,β-Unsaturated carbonyl compounds bearing either electron-donating or electron-withdrawing substituents reacted successfully with acetylacetone to give products (**3a**–**3j**) in 48–84% yield. It was noteworthy that electronic effect had little influence on this oxidative coupling. Unfortunately, the direct oxidative coupling of methyl cinnamate and coumarin with acetylacetone did not give the desired product (**3k**, **3m**). To our delight, benzylidene acetone worked well with **2a**, and gave the desired product (**3l**) in moderate yield. Moreover, other 1,3-dicarbonyl compounds were also found to be suitable reaction partners with α,β-unsaturated car-

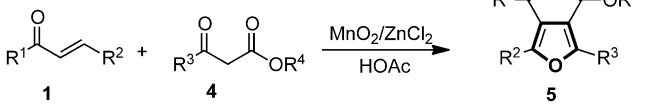
Table 2. Oxidative coupling of the 1,3-dicarbonyl compounds and chalcones.[a,b]

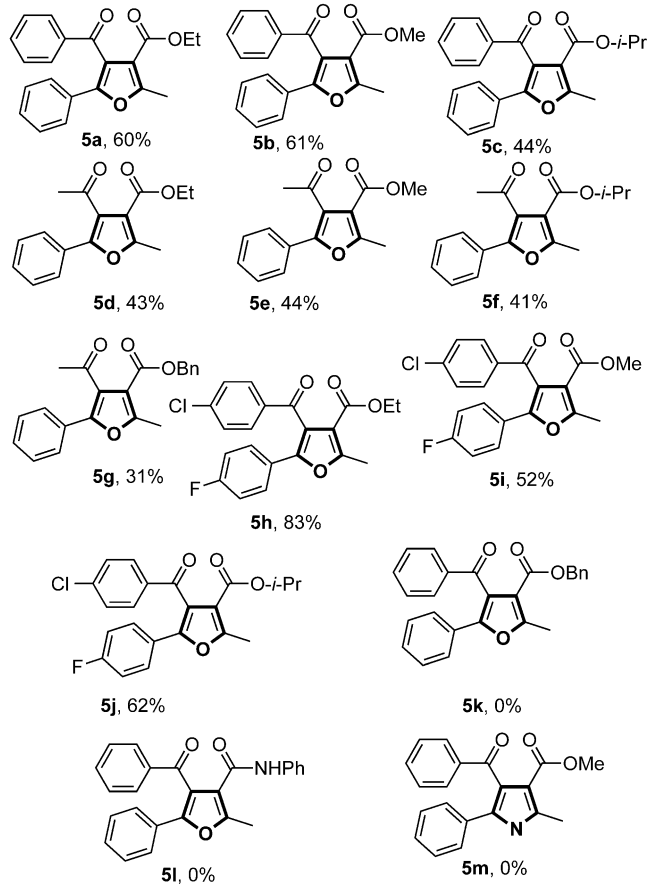


[a] *Reaction conditions:* **1** (0.50 mmol), **2** (2.5 mmol), MnO_2 (a) (6.0 equiv.), $ZnCl_2$ (6.0 equiv.), HOAc (3.0 mL), in air.

[b] Yield of the isolated product.

Table 3. Oxidative coupling of the β-keto esters and α,β-unsaturated ketones.[a,b]



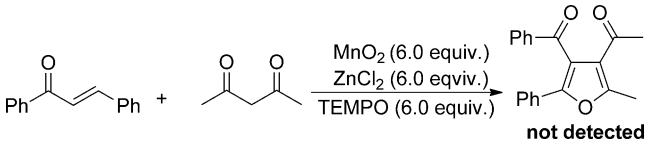


[a] *Reaction conditions:* **1** (0.50 mmol), **2** (2.5 mmol), MnO_2 (a) (6.0 equiv.), $ZnCl_2$ (6.0 equiv.), HOAc (3.0 mL), in air.

[b] Yield of the isolated product.

bonyl compounds. Various 1,3-dicarbonyl compounds, including cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, and 5-phenylcyclohexane-1,3-dione were effective substrates and gave the target products (**3n**–**3s**) in yields of 15–86%. Overall, no adjustments to the reaction conditions are necessary to afford good yields of specially substituent furans from the different 1,3-dicarbonyl compounds and chalcones.

With the successful demonstration of this new strategy for the construction of diverse furan derivatives, we turned our attention to more functionalized β-keto esters and α,β-unsaturated ketones. Delightfully, when we employed ethyl acetoacetate **4a** as a substrate, the oxidative coupling with chalcone afforded the desired product (**5a**) in 60% yield. Furthermore,



Scheme 3. Preliminary mechanistic study.

other β-keto esters with different substituents (Table 3) were well tolerated (**5b**, **5c**). In addition, we discovered that the standard procedure for the synthesis of polysubstituted furans produced the corresponding products in moderate yields in the presence of benzylideneacetone (**5d**–**5g**). Moreover, for α,β-unsaturated carbonyl compounds bearing electron-withdrawing substituents, the oxidative coupling afforded the target products in a slightly higher yield under the same conditions (**5h**–**5j**). Unfortunately, benzyl acetoacetate, acetoacetanilide and methyl (*E*)-3-(phenylimino)butanoate were not suitable for the reaction because they were decomposed by MnO_2 under the current conditions (**5k**–**5m**).

The preliminary studies on the mechanism were carried out subsequently. The desired furan product **3a** was not obtained when 6.0 equiv. of 2,2,6,6-tetramethylpiperidine-*N*-oxyl, a radical inhibitor, were employed in the system, suggesting that a radical initiation pathway may be involved in the reaction (Scheme 3). In order to further investigate the regioselectivity, the structures of **S1** and **S2** from the 1,3-dicarbonyl radical attacking the α- and β-positions of chalcone, respectively, were modeled and optimized at the same level (Figure 2). The calculated results demonstrated that the energy of **S1** was 12.28 kcal mol^{-1} lower than that of **S2**, indicating that the benzyl radical **S1** was more stable than **S2**. As a result, the carbon-centered radical compound **I** was induced to attack the α-position to generate benzyl radical **S1**. On the basis of the results described above,[7b,11g] a tentative reaction mechanism for the direct oxidative coupling mediated by MnO_2 (a) was postulated as shown in Figure 3. In the presence of activated MnO_2 and $ZnCl_2$, 1,3-dicarbonyl compounds would produce the carbon-centered radical compound **I** which is also

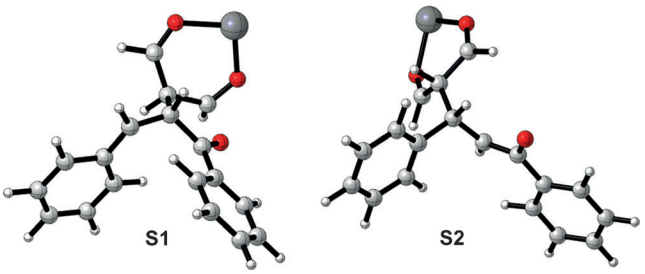


Figure 2. Optimized structures **S1** and **S2** at the B3LYP/6-31+G(d) level in HOAc solvent.

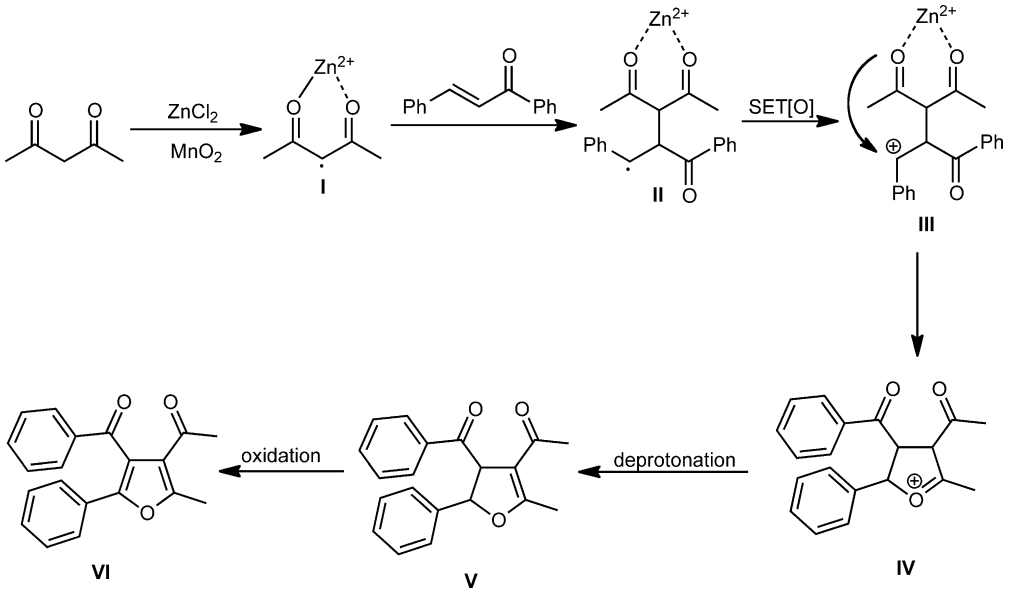


Figure 3. Proposed reaction mechanism.

stabilized by $ZnCl_2$. Since the α-position of α,β-unsaturated ketones has a higher electron density than the β position, it induces the carbon-centered radical compound **I** to attack the α-position to generate benzyl radical **II**. The benzyl radical **II** then converts to the intermediate **III** by a further single oxidation. The intermediate **III** undergoes intramolecular cyclization to form the dihydrofuran product **IV** and affords the desired product **VI** after deprotonation and oxidation.

In summary, we have successfully developed an MnO_2-mediated regioselective oxidative coupling of α,β-unsaturated ketones to prepare the 3,4-dicarbonyl substituted furans. A variety of 1,3-dicarbonyl compounds and α,β-unsaturated carbonyl compounds were used to afford the corresponding polysubstituted furans in moderate to excellent yields. This procedure provides an atom-economic, environmentally benign, and practical approach to complement the oxidative coupling reaction of 1,3-dicarbonyl compounds for the construction of carbon-carbon and carbon-heteroatom bonds with complete regioselectivity. Further investigations on synthetic applications of this reaction are now in progress.

Experimental Section

General Procedure

Substrate **1** (0.50 mmol), substrate **2** (2.50 mmol), activated MnO_2 (3.0 mmol), $ZnCl_2$ (3.0 mmol), and HOAc (3.0 mL) were added to Schlenk in air, and then the mixture was heated at 130 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed by TLC on silica gel using hexane/ethyl acetate as eluent to give the desired 3,4-dicarbonyl substituted furans.

Acknowledgements

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[16] CCDC 980611 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

