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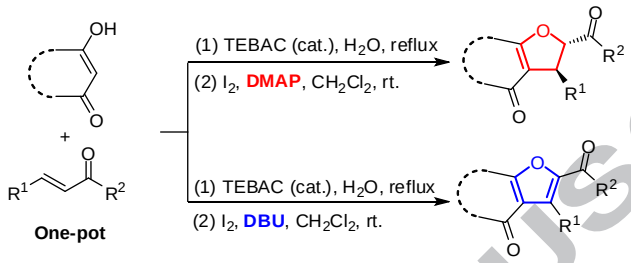

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# Base-Controlled Selective Construction of Polysubstituted Dihydrofuran and Furan Derivatives through an $I_2$-Mediated Cyclization

Chun-Bao Miao,* Rui Liu, Yan-Fang Sun, Xiao-Qiang Sun, Hai-Tao Yang

*Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, China.*

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ABSTRACT

A base-controlled formal [3+2] cycloaddition of 1,3-dicarbonyl compounds to enones *via* an $I_2$-mediated cyclization was reported. Highly functionalized dihydrofurans and furans were selectively obtained under $I_2$/DMAP and $I_2$/DBU conditions in the cyclization step, respectively.



## Introduction

Dihydrofuran and furan skeletons constitute a class of biologically active compounds that are found in many natural products as well as therapeutic agents such as neotanshinlactone,[1] evodone,[2] coumestans,[3] clerodin,[4] azadirachtin,[5] and austocystin A[6] (Figure 1). Their broad bioactivities have inspired chemists to develop versatile efficient synthetic methods. The radical cyclic addition reaction of active methylene compounds with alkenes promoted by transition metal salts such as manganese(III) acetate[7], cerium(IV) ammonium nitrate,[8] Ag (I), and Cu (II)[9] represents one of the mostly used method. However, excess transition metal salts have to be used as oxidants. Furthermore, when electron-poor alkenes were employed as the substrates, the product **I** was obtained selectively (Scheme 1) with the carbon of 1,3-dicarbonyl compounds added at the $\alpha$-position of electron-poor alkenes. A reversed regioselective radical cyclic addition leading to product **II** was rather rare (Scheme 1).[7a] The reaction of diazo compounds with alkenes/alkynes via organometallic catalysis have also attracted much attention.[10] But the chemoselectivity was usually poor. The formal [4+1] annulation of enones with ylides has been widely employed for the construction of heterocycles.[11] Nevertheless the control of the competitive formation of cyclopropane products is a thorny problem. Beside these methods, hypervalent iodine mediated annulation of 1,3-dicarbonyl compounds with alkenes for the construction of dihydrofurans have been explored.[12]

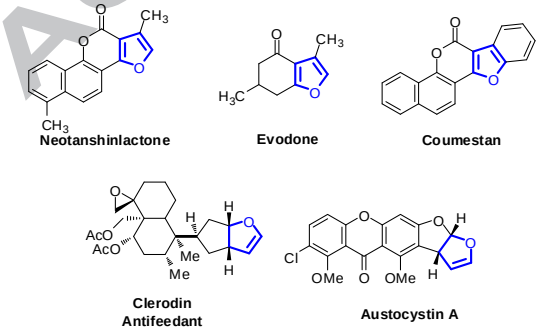
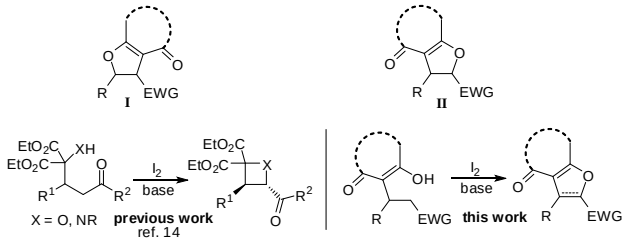



**Fig. 1** Selective Biologically Active Natural Products Bearing Dihydrofuran/Furan Subunits

$I_2$ as an inexpensive, non-toxic, readily available reagent has been found significant application in organic transformations.[13] Most recently, we reported the preparation of four-membered ring heterocycles such as oxetane and azetidine derivatives through an $I_2$-mediated cyclization of the Michael adducts of malonates/amidomalonate with enones.[14] Herein, we would extend this method to the synthesis of five-membered ring heterocycles and demonstrated the preparation of polysubstituted




**Scheme 1**

* Corresponding author.
*E-mail address*: estally@yahoo.com
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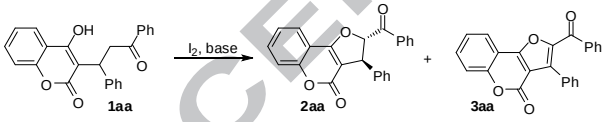
dihydrofurans/furans *via* the $I_2$-mediated annulation.

## Results and discussion

To verify our hypothesis, Michael adduct **1aa** was chosen as the model substrate to react with $I_2$ under various conditions (Table 1). The reaction in DMF with $K_2CO_3$ as the base afforded the desired product **2aa** in 59% yield (Table 1, entry 1). Using $Et_3N$ as the base, the reaction in dichloromethane gave the best yield among the four evaluated solvents (Table 1, entries 2-5). Further screening different bases for this transformation in $CH_2Cl_2$ revealed that pyridine and DABCO were not effective (Table 1, entries 7 and 8) and DMAP was the best base to afford **2aa** in 70% yield within 20 min (Table 1, entry and 6). Although NMI and $Et_3N$ gave comparable yield with that of DMAP, much longer reaction time was needed (Table 1, entries 3 and 9). When the strong organic base DBU was introduced to the reaction, to our surprise, beside the formation of **2aa** a new product with slightly lower polarity was isolated in 21% yield, which was assigned as the furan product **3aa** through NMR analysis (Table 1, entry 10). The **3aa** might be generated from the **2aa** through further iodination and subsequent dehydroiodination, which implied at least 2 equiv of $I_2$ was needed in the transformation. When the amounts of $I_2$ and DBU were increased to 2.7 and 5.4 equiv, respectively, the yield of **3aa** was improved notably to 64% (Table 1, entry 11). It was noteworthy if DMAP was used as the base, even increasing the amounts of $I_2$ and DMAP to 2 and 4 equiv, respectively, no furan **3aa** was generated, which demonstrated that the choice of base was crucial to formation of **3aa** from **2aa**. The reaction of **1aa** with $I_2$/DBU in THF also gave a comparable yield of **3aa** (Table 1, entry 12). However, using $CH_3CN$ or EtOH as the solvent the conversion was incomplete along with surplus of considerable amount of **2aa** even prolonging the reaction time to 10 h (Table 1, entries 13 and 14). Oxidation with stoichiometric amounts of DDQ, $MnO_2$ [15] or oxidative dehydrogenation catalyzed-by Pd at high temperauture for a long time [16] was the commonly used method for the transformation of dihydrofuran to furan. Herein we provided a new approach for this conversion under mild conditions.

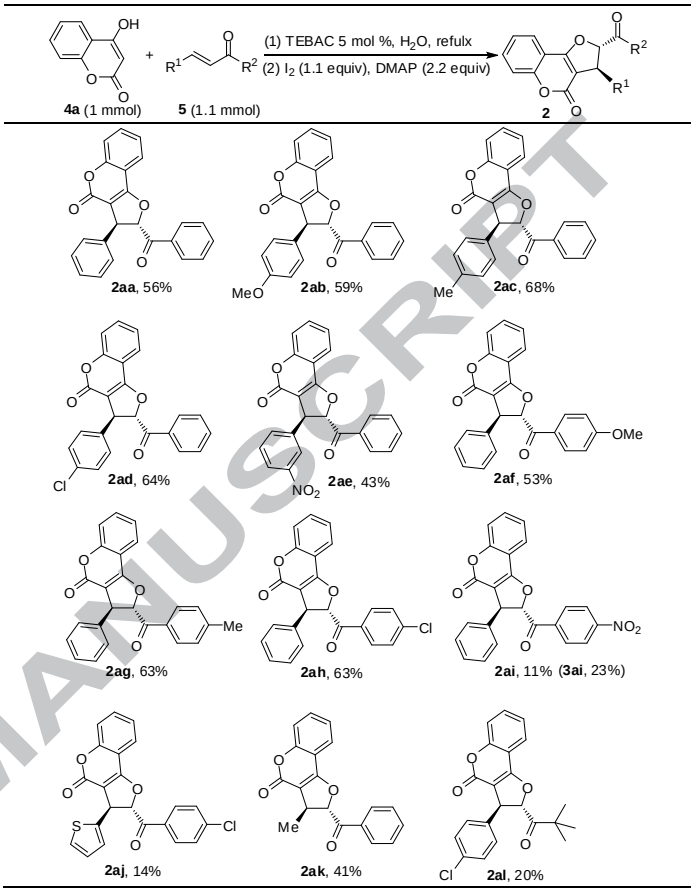
**Table 1**
Screening of the reaction conditions[a]




| entry | base | solvent | **1aa**:$I_2$:base | time (h) | yield[b](%) **2aa** | **3aa** |
|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | DMF | 1:1.1:2.2 | 5 | 59 | 0 |
| 2 | $Et_3N$ | THF | 1:1.1:2.2 | 3 | 62 | 0 |
| 3 | $Et_3N$ | $CH_2Cl_2$ | 1:1.1:2.2 | 3 | 67 | 0 |
| 4 | $Et_3N$ | EtOH | 1:1.1:2.2 | 3 | trace | 0 |
| 5 | $Et_3N$ | $CH_3CN$ | 1:1.1:2.2 | 3 | 51 | 0 |
| 6 | **DMAP** | **$CH_2Cl_2$** | **1:1.1:2.2** | **0.5** | **70** | **0** |
| **7** | pyridine | $CH_2Cl_2$ | 1:1.1:2.2 | 12 | 14 | 0 |
| 8 | DABCO | $CH_2Cl_2$ | 1:1.1:2.2 | 12 | 17 | 0 |
| 9 | NMI | $CH_2Cl_2$ | 1:1.1:2.2 | 2 | 64 | 0 |
| 10 | DBU | $CH_2Cl_2$ | 1:1.1:2.2 | 1 | 30 | 21 |
| 11 | **DBU** | **$CH_2Cl_2$** | **1:2.7:5.4** | **0.5** | **trace** | **64** |
| 12 | DBU | THF | 1:2.7:5.4 | 3 | trace | 58 |
| 13 | DBU | $CH_3CN$ | 1:2.7:5.4 | 10 | 19 | 23 |
| 14 | DBU | EtOH | 1:2.7:5.4 | 10 | 28 | 17 |

[a] A mixture of **1aa** (1 mmol), $I_2$, and base was stirred in 2 mL of solvent at room temperature.
[b] Isolated yield.

**Table 2**
Substrate Scope of Enones for the Preparation of Dihrdrofurans under $I_2$/DMAP conditions

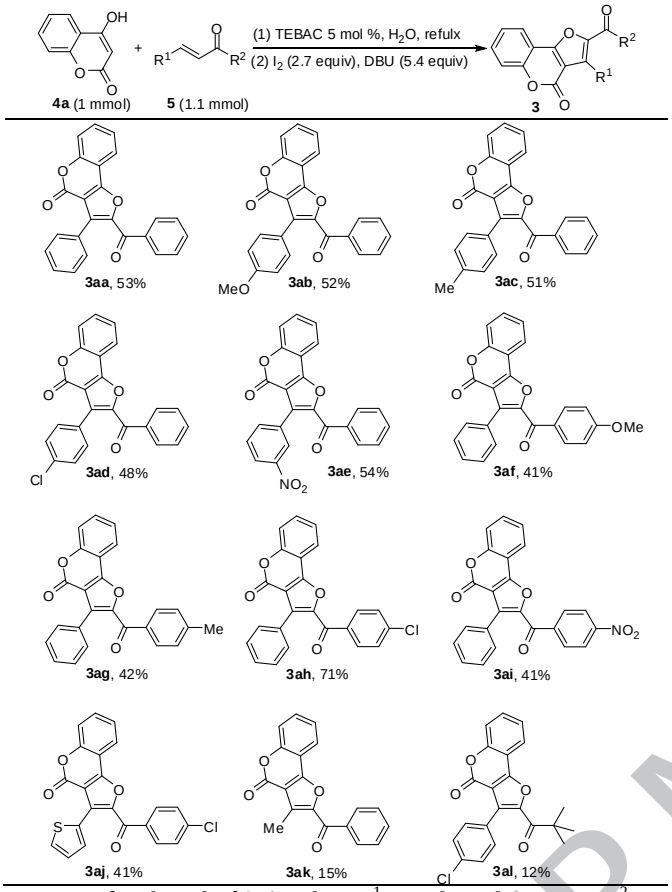



It is interesting that the chemoselective conversion of **1aa** to **2aa** or **3aa** in the presence of $I_2$ is controlled by the base. As we know, tunable highly selective synthesis derived from the same reactants is a formidable challenge in organic synthesis. [17] In order to make this approach easier to operate, the possibility of constructing dihydrofurans/furans *via* a one-pot formal [3 + 2]-cycloaddition process involving a Michael addition and $I_2$-mediated cyclization was tried.

A mixture of 4-hydroxycoumarin, 1.1 equiv of chalcone, and catalytic amount of TEBAC (benzyl triethyl ammonium chloride) was refluxed in water overnight until the disappearance of 4-hydroxycoumarin, then $I_2$, 5 mL of $CH_2Cl_2$, and DMAP (or DBU) were added sequentially and the mixture was stirred at room temperature until the completion of reaction, furnishing **2aa** and **3aa** in 56% and 53% yield, respectively. No workup procedure or the purification of Michael addition mixture and no oxygen-free operation were required, which made the protocol very easy to operate. The generality of this formal [3+2]-cycloaddition for the synthesis of polysubstituted dihydrofurans/furans was evaluated with 4-hydroxycoumarin **4a** and various enones as the substrates (Table 2 and 3).

For most cases, 4-hydroxycoumarin **4a** reacted with enones **5** under $I_2$/DMAP conditions leading to the corresponding dihydrofuran products **2** in moderate yields (Table 2). The reaction tolerated a range of various groups with different electronic demands on the aromatic $R^1$ or $R^2$ ring. If a nitro group connected on the phenyl ring of $R^2$, **2ai** was only obtained in 11%. In addition, **3ai** was also formed in 23% yield. It might be explained by the strong electron withdrawing effect of nitro group, which was benefit to the further iodination at the *α*-

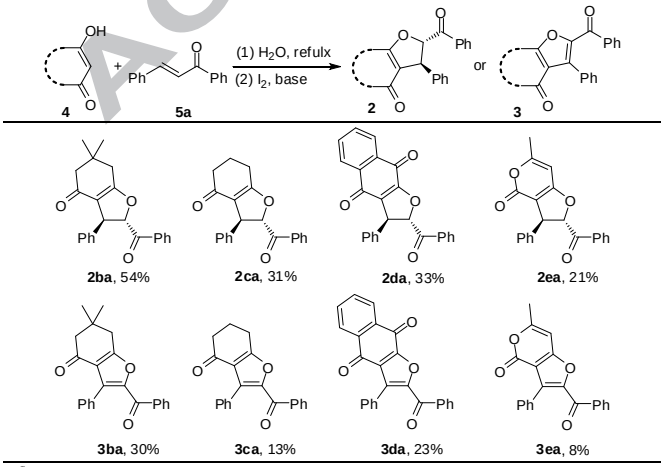
**Table 3**
Substrate Scope of Enones for the Preparation of Furans under $I_2$/DMAP Conditions




position of carbonyl of **2ai**. When $R^1$ was thienyl group or $R^2$ was an alkyl group the yield was very low (Table 2, **2aj** and **2al**).

Under $I_2$/DBU conditions, various furan products **2** were also obtained in moderate yield when $R^1$ and $R^2$ were both aryl rings (Table 3). Thienyl group substituted furan **3aj** was also efficiently constructed in 41% yield. Nevertheless, either $R^1$ or $R^2$ was an alkyl group, a very low yield of the furan product **3ak** or **3al** was provided.

**Table 4**
Other 1,3-Dicarbonyl Compounds in the Formal [3+2] Cycloaddition Reaction Through the $I_2$-Mediated Cyclization[a]

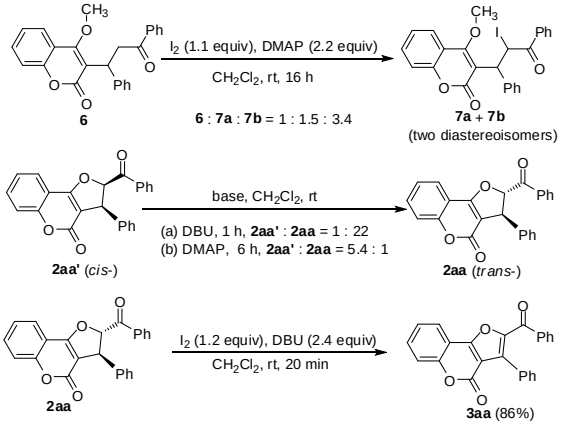



[a] Dihydrofurans **2** or furans **3** were formed under DMAP or DBU conditions, respectively.

Next, the applicability of other 1,3-dicarbonly compounds (**4b**-**e**) in this conversion was also evaluated by performing the reaction of them with chalcone **5a** (Table 4). As can be seen from the results, the dimedone (**4b**), cyclohexane-1,3-dione (**4c**), 2-hydroxynaphthalene-1,4-dione (**4d**), and 4-hydroxy-6-methyl-2H-pyran-2-one (**4e**) were much less effective than 4-hydroxycoumarin **4a** in the formal [3+2] cycloaddition. The low yield of **2ea** and **3ea** was attributed to the first-step of incomplete Michael addition, and large amounts of chalcone remain unreacted. The reason for the low yield of **2ca**, **3ca**, **2da**, and **3da** was not clear although the TLC showed the transformation proceeded well.

All the fused dihydrofurans were obtained with a high diastereoselectivity (*trans*/*cis* > 90:10), and the *trans*-configuration were determined based on the observed coupling constants of 4.4-5.4 Hz between the two methine protons. While the *cis* diastereoisomers were reported to have a larger coupling constants between the two methine protons (10-11 Hz).[11e,15b] The disappearance of two mehtine protons in the $^1$H NMR spectrum and appearance of two new signals in sp$^2$-C region in the $^{13}$C NMR spectrum proved the furan structure of **3**. The known products **2aa-2ah**, **2ba**, **2ca**, **2ea**, **3ba-3da** were confirmed through comparison of their spectral data to those reported in the literature.[12a,18] All of the new compounds were unambiguously characterized by their HRMS, $^1$H NMR, $^{13}$C NMR spectra.

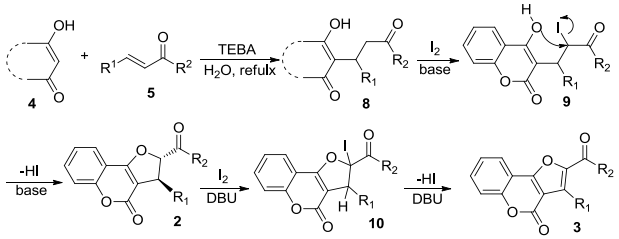
The ketone iodination always requires either tedious conditions or higher temperature.[19] However, in this work the annulation completed within 20 min at room temperature. To prove that the iodination process could proceed smoothly at room temperature, the *O*-methylated product **6** was prepared and then treated with $I_2$ and DMAP. The iodination occurred smoothly to afford the iodinated product **7a** and **7b** as two diastereoisomers (Scheme 2). However, the iodination proceeded very slowly. After 16 h, the ratio of **6a**:**7a**:**7b** was 1:1.5:3.4 as determined by $^1$H NMR analysis. It demonstrated that the existence of intramolecular hydroxyl group accelerated the iodination process notably. The high diastereoselectivity could be explained by the relatively more thermo dynamical stability of *trans*-ismoer. In the presence of catalytic amount of DBU, *cis*-isomer **2aa'** was transformed to *trans*-isomer **2aa** quickly and it reach the equilibrium with a ratio of **2aa'**/**2aa** as 1/22 within 1 h (Scheme 2). However, using DMAP as the base, only 16% conversion of **2aa'** to **2aa** was achieved after 6 h and no change was observed even prolonging the reaction time. Treatment of **2aa** with $I_2$/DBU afforded the furan product **3aa** in 86% yield within 20 min (Scheme 2).




**Scheme2** Controlled experiment

Based on the controlled experiment and our previous work on the $I_2$-mediated transformation,[14a,b] a possible mechanism for the formation of dihydrofuran **2** and furan **3** is depicted in Scheme 3.

Initially, Michael addition of 1,3-dicarbonyl compound to enone affords the Michael adduct **8**. Iodination of **8** furnishes **9**, which undergoes intramolecular substitution to generate dihydrofuran **2**. If a strong organic base (DBU) was used, the further iodination reaction occurs followed by extrusion of HI to give the furan product **3**. It should be noted that the formation of furan product was determined on whether the second iodination could occur. If proper substituents which benefit the enolizaiton and iodination located at the benzoyl ring, even under DMAP conditions, furan products could also be obtained.




**Scheme 3** Proposed mechanism

## Conclusion

In summary, we have developed a one-pot two-step formal [3+2]-cycloaddition of 1,3-dicarbonyl compounds with enones for the efficient synthesis of dihydrofurans and furans *via* a Michael addition and the subsequent $I_2$-mediated cyclization. In the second step of cyclization, chemoselective formation of dihydrofurans and furans could be controlled by using DMAP and DBU as the base, respectively. A new route for the conversion of dihydrofurans to furans was developed. The present method shows the following advantages such as easy operability, metal-free and mild conditions.

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## Supplementary Material

General synthetic procedures, characteristic data, and NMR spectra of the products can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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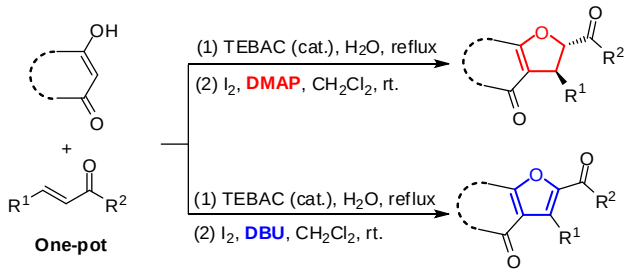
# Base-Controlled Selective Construction of Polysubstituted Dihydrofuran and Furan Derivatives through an $I_2$-Mediated Cyclization

Chun-Bao Miao,* Rui Liu, Yan-Fang Sun, Xiao-Qiang Sun, Hai-Tao Yang




A base-controlled formal [3+2] cycloaddition of 1,3-dicarbonyl compounds to enones *via* an $I_2$-mediated cyclization was reported. Highly functionalized dihydrofurans and furans were selectively obtained under $I_2$/DMAP and $I_2$/DBU conditions in the cyclization step, respectively.



* Corresponding author.

*E-mail address*: estally@yahoo.com

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**Highlight**

1. One-pot two-step formal [3+2] cycloaddition through an $I_2$-mediated cyclization was developed.
2. The chemoselective formation of dihydrofuran or furans was controlled by the base.
3. A new route for the conversion of dihydrofurans to furans was developed