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Highly Efficient Synthesis of 3a,6a-Dihydrofuro[2,3-*b*]furans via a Novel Bicyclization

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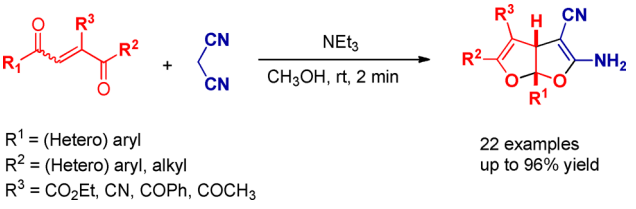
ABSTRACT



R^1 = (Hetero) aryl
R^2 = (Hetero) aryl, alkyl
R^3 = CO_2Et, CN, COPh, $COCH_3$

22 examples
up to 96% yield

A highly efficient method for the construction of 3a,6a-dihydrofuro[2,3-*b*]furan derivatives has been developed via a novel bicyclization, which is very valuable for the synthesis of fused furofuran compounds since it is time-saving and catalyst-free. Based on the bicyclization, a coupled domino strategy has been developed to directly construct 3a,6a-dihydrofuro[2,3-*b*]furan derivatives from methyl ketones.

The furo[2,3-*b*]furan ring system can be found in a wide range of natural products.[1] In particular, the 3a, 6a-dihydrofuro[2,3-*b*]furan (DHFF) unit is an important skeletal structure in various biologically and pharmaceutically active organic molecules (e.g., sterigmatocystin, aflatoxin B_1, versicolorin A) (Figure 1).[2] In addition, the related furofuran fungal metabolites are of great interest due to their role in the etiology of human liver cancer.[2d,g]

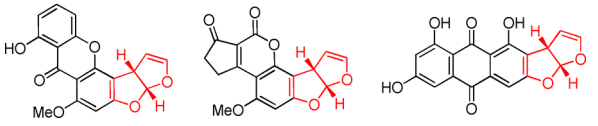


Figure 1. The 3a,6a-dihydrofuro[2,3-*b*]furan skeleton in selected natural products.

As a result, many synthetic methods for the DHFF's skeleton have been exploited (Scheme 1),[3−7] such as, bromination/nucleophilic substitution/intramolecular cyclization of α-cyanoarylacetone with bromomalononitrile (Scheme 1,

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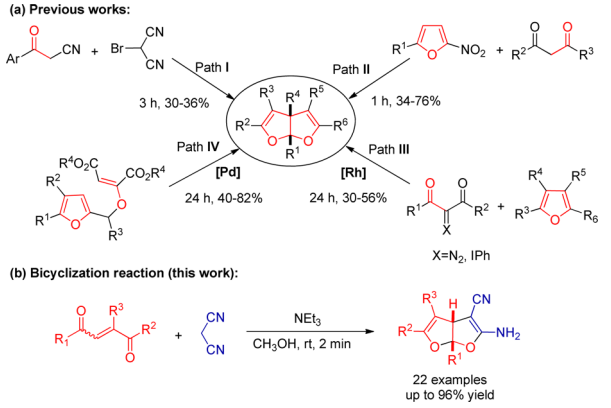
path **I**),[4] cine-substitution/intramolecular Michael type addition of 2-nitrofurans with β-dicarbonyl compounds (Scheme 1, path **II**),[5] rhodium-catalyzed 1,3-dipolar cycloaddition of diazo-carbonyls/iodonium ylides to furans (Scheme 1, path **III**),[6] and palladium-catalyzed dearomatization of furans via electrocyclic ring-closure (Scheme 1, path **IV**).[7]

Scheme 1. Methods for the Synthesis of 3a,6a-Dihydrofuro-[2,3-*b*]furans



In our previous work, we found that 1,3-dicarbonyl compounds could react with methyl ketones easily to afford unsymmetrical 1,4-enediones.[8] On the basis of the facile access to unsymmetrical 1,4-enediones, we considered using these materials as useful precursors to synthesize diverse heterocyclic compounds.[9] Fortunately, the fused ring 3a,6a-dihydrofuro[2,3-*b*]furans were obtained by the reaction of unsymmetrical 1,4-enediones with malononitrile (Scheme 1b). To the best of our knowledge, the transformation of 3a,6a-dihydrofuro[2,3-*b*]furans via the novel bicyclizition reaction has not been reported to date yet.

To optimize the reaction conditions, we attempted to treat ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate (**3a**) with malononitrile (**4**) under different reaction conditions. Various bases and solvents were examined at room temperature, as shown in Table S1 (see Supporting Information (SI)). To our delight, the reaction of **3a** (1.0 mmol) with **4** (1.0 mmol) and MgO (1.0 mmol) performed well to give **5a** in 80% yield in CH_3OH in 2 h (Table S1, entry 1).

Afterward, we examined other inorganic bases, such as CuO and Al_2O_3, both of which led to **5a** in a low yield (Table S1, entries 3–4). However, with K_2CO_3 as the base, **5a** was obtained in 84% yield (Table S1, entry 5). The transformation did not occur in the absence of base (Table S1, entry 6). Then, we examined the influence of diverse organic bases on the reaction, such as pyridine, DABCO, piperidine, DBU, DIPEA, DMAP, and NEt_3 (Table S1, entries 7–13). It was observed that most of the organic bases could promote the reaction. Among these, NEt_3 proved to be the best, where **5a** was isolated in 87% yield (Table S1, entry 13). However, only a low yield was obtained in other solvents (EtOH, CH_2Cl_2, CH_3CN, DMF, and DMSO) (Table S1, entries 14–18). Unfortunately, the targeted product was not detected in AcOH (Table S1, entry 19).

With the optimized conditions in hand, the scope of the unsymmetrical 1,4-enediones was investigated. The results are shown in Scheme 2. It is noteworthy that both electron-rich and -deficient substrates could provide the desired products smoothly in good to excellent yields (64–96%). The 1,4-enediones, bearing substituted groups such as 4-Me, 4-OMe, and 4-NO_2 on the phenyl rings, reacted with **4** smoothly to afford the corresponding products (72–85%, **5b**, **5c**, and **5g**). Good to excellent yields were also obtained for halo-substituted substrates (75–96%, **5d**–**f**, **5i**, and **5j**). Among them, a 2,4-dichloro substituted substrate showed the best result, with a yield of 96% (**3i**). Sterically hindered α-naphthyl and β-naphthyl also afforded the corresponding desired products **5n** and **5o** in 75% and 79% yields, respectively. To our delight, the substrates with a heteroaryl group for R^1, such as 2-furyl, 3-thienyl, and 2-benzofuryl, delivered the products successfully in moderate to excellent yields (64–86%, **5k**–**m**). When R^2 = CH_3, 4-$NO_2C_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, and 2-furyl, the reaction could also be tolerated in 65–76% yields (**5p**–**s**). When R^3 = CN, COPh, and $COCH_3$, good to excellent yields have been achieved (86–91%, **5t**–**v**). Moreover, when R^2 = CH_3 = R^3 $COCH_3$ (**5w**), the reaction performed providing the desired product cleanly in 76% yield. Moreover, the hydroxyl group substituted substrate could not afford the desired product (**5h**). The structure of **5f** and **5g** were further determined by X-ray crystallographic analysis (see SI).

After discovering a novel bicyclization reaction (Scheme 3b), we began to explore a more efficient approach to synthesize the 3a,6a-dihydrofuro[2,3-*b*]furan derivatives from readily available starting materials. We discovered that methyl ketone **1** could be transformed into compound **3** via a domino reaction, which involved iodination,[10] Kornblum oxidation,[11] and Knoevenagel condensation[12] (Scheme 3a). Based on this, we aimed to create a reaction chain consisting of the domino reaction I and domino

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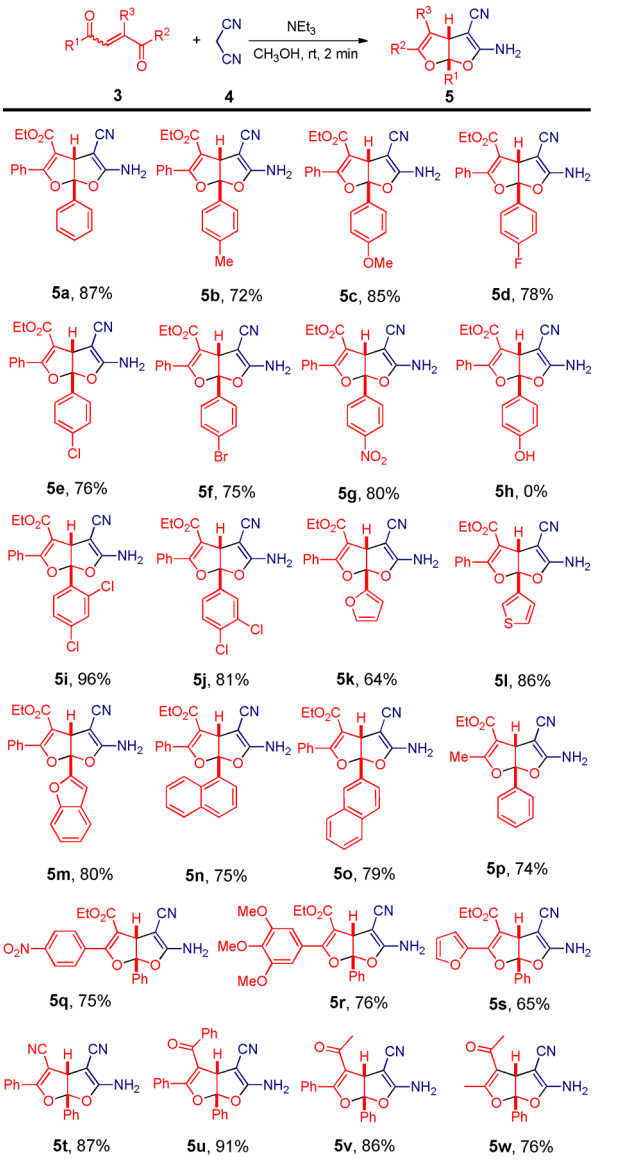
Scheme 2. Synthesis of **5** from 1,4-Enediones[a]



[a] Reactions were carried out with **3** (1.0 mmol), **4** (1.0 mmol), and NEt_3(1.0 equiv) in CH_3OH (3.0 mL) at room temperature for 2 min. Yields of the isolated products were shown.

Scheme 3. Integration of Domino Reactions

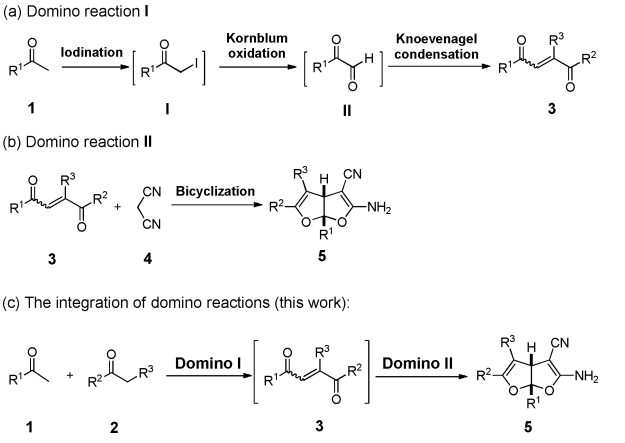
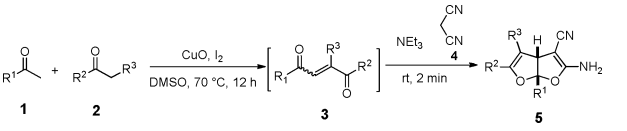


Table 1. Coupled Domino Strategy for the Synthesis of **5** in One Pot[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	Ph	Ph	CO_2Et	**5a**	75
2	4-MeC_6H_4	Ph	CO_2Et	**5b**	74
3	4-BrC_6H_4	Ph	CO_2Et	**5f**	67
4	4-$NO_2C_6H_4$	Ph	CO_2Et	**5g**	68
5	3,4-$Cl_2C_6H_3$	Ph	CO_2Et	**5j**	69
6	3-thienyl	Ph	CO_2Et	**5l**	65
7	2-benzofuryl	Ph	CO_2Et	**5m**	70
8	Ph	4-$NO_2C_6H_4$	CO_2Et	**5q**	58
9	Ph	Ph	COPh	**5u**	71

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuO (1.1 mmol), I_2 (1.1 mmol), in DMSO (3.0 mL) at 70 °C for 12 h, then added **4** (1.0 mmol) and NEt_3 (2.0 mmol) at room temperature for 2 min. [b] Yields of the isolated products.

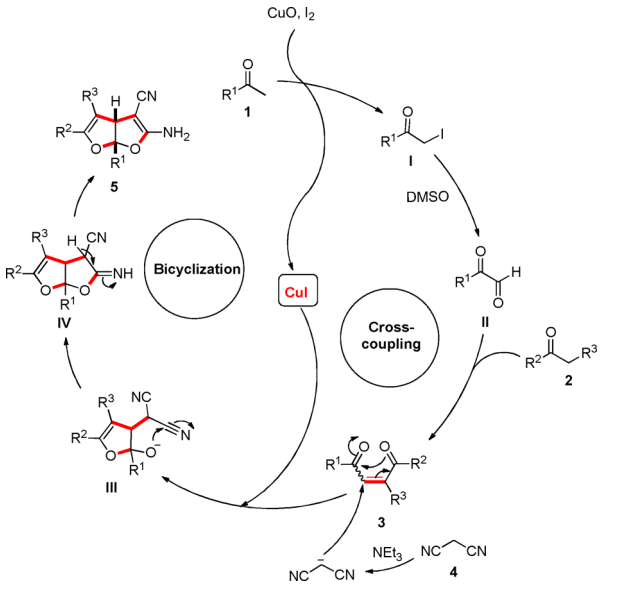
reaction II linked in one pot for the convenient construction of DHFF derivatives via a coupled domino strategy from methyl ketones (Scheme 3c).

The coupled domino strategy consisted of four mechanically different chemical transformations (iodination, Kornblum oxidation, Knoevenagel condensation, and bicyclization). Thus it was crucial to obtain compatible conditions (e.g., solvent, temperature, catalyst, concentration) for all of the associated reactions in the complex domino process. After screening these conditions carefully, we gained the optimal reaction conditions, with methyl ketone **1** (1.0 mmol), 1,3-dicarbonyl compound **2** (1.0 mmol), CuO (1.1 mmol), and I_2 (1.1 mmol) at 70 °C in DMSO (3 mL) for 12 h, followed by the addition of malononitrile **4** (1.0 mmol) and NEt_3 (2.0 mmol), and stirring at room temperature for another 2 min. To our satisfaction, the byproduct CuI could promote the bicyclization progress effectively in the coupled domino strategy (see SI).

Under the optimized conditions, we next investigated the scope of the substrates (Table 1). Methyl ketones bearing electron-donating substituents (Table 1, entry 2) and electron-withdrawing groups (Table 1, entry 4) on the benzene rings were shown to proceed well with good yields. Notably, even halo-substituted methyl ketones performed smoothly to give the corresponding products in 67–69% yields (Table 1, entries 3 and 5). Furthermore, heteroaryl groups, such as 3-thienyl (Table 1, entry 6) and benzofuryl (Table 1, entry 7) were also tolerant, leading to the desired products in 65% and 70% yields, repectively. In the case of

electron-neutral (Table 1, entry 9) and electron-deficient (Table 1, entry 8) 1,3-dicarbonyl compounds, satisfactory yields were also obtained.

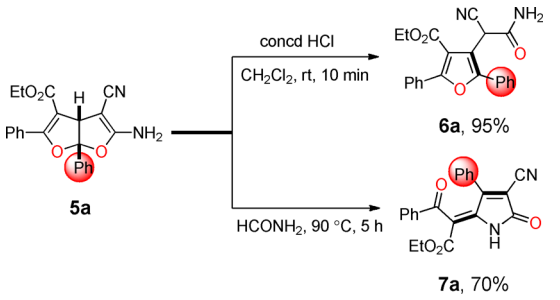
Scheme 4. A Plausible Mechanism



On the basis of the results above, a plausible mechanism is shown in Scheme 4. It is supposed that methyl ketone **1** initially reacted with I_2 and CuO to afford the intermediate α-iodo ketone **I** and byproduct CuI. Subsequently, the intermediate **I** was oxidated in DMSO leading to the intermediate arylglyoxal **II** via Kornblum oxidation, which could react with ketone **2** easily to deliver **3** via Knoevenagel condensation. At the same time, malononitrile **4** was converted into the corresponding anion in the presence of NEt_3, which reacted with **3** by the Michael addition reaction, thus furnishing the 2,3-dihydrofuran intermediate **III**. This process could then be promoted by the previously generated byproduct CuI. The intermediate **III** instigated intramolecular cyclization with ease, affording the furofuran intermediate **IV**. Finally, **IV** underwent intramolecular isomerization and transformed into the desired product **5**.

We further explored the applications of the 3a,6a-dihydrofuro[2,3-*b*]furans in organic synthesis (**5a** as example), shown in Scheme 5. Compound **5a** could be well converted into multisubstituted furan **6a** in 95% yield in the presence of HCl (aq) in CH_2Cl_2 at room temperature in 10 min. Much to our satisfaction, the 3-pyrrolin-2-one **7a** (for crystallographic data, see SI) was smoothly obtained from **5a** in 70% yield in $HCONH_2$ at 90 °C in 5 h. The 3-pyrrolin-2-one derivatives are of great importance owing to their wide range of biological activities and as synthons in the preparation of bile pigments and their derivatives.[13]

Scheme 5. Synthetic Applications of 3a,6a-Dihydrofuro-[2,3-*b*]furans (**5a** as an example)[a]



[a] Yields of the isolated products were shown.

In conclusion, we have developed a novel bicyclization reaction for the efficient synthesis of 3a,6a-dihydrofuro-[2,3-*b*]furans. Furthermore, we have also explored a coupled domino strategy to directly construct the 3a,6a-dihydrofuro[2,3-*b*]furan derivatives from methyl ketones. This strategy provided a valuable example of the logical design for the self-sequential synthesis of complex molecules via a long-distance domino strategy from readily available starting materials. Moreover, the 3a,6a-dihydrofuro[2,3-*b*]furans are very useful for further organic transformations to potential bioactive molecules. Work on a detailed mechanism and applications of this strategy is underway in our laboratory.

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Supporting Information Available. Description of experimental procedures and full characterization data for all 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.