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Water-compatible Cascade Reaction: An Efficient Route to Substituted 2,3-Dihydrofurans

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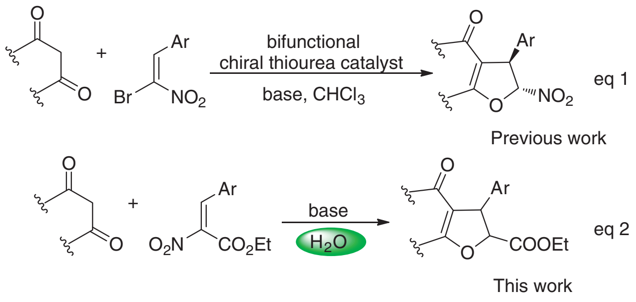
A highly efficient domino Michael addition–alkylation reaction of 1,3-dicarbonyl derivatives with 2-nitroacrylates was developed in water. The procedure tolerates a series of functional groups such as methoxy, bromo, chloro, and heteroaromatic groups, providing three types of 2,3-dihydrofuran derivatives in moderate to good yields.

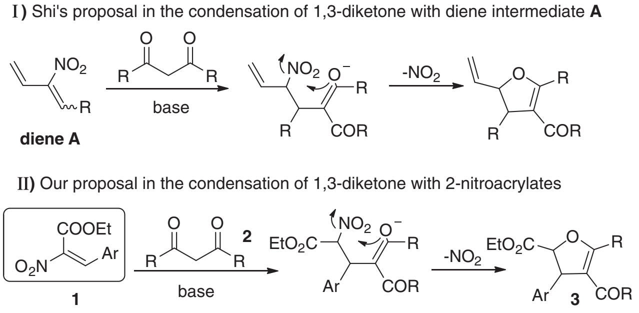
Dihydrofurans, a family of five-membered *O*-heterocycles in plants, are important building blocks in a large number of biologically active compounds.[1] Functionalized dihydrofurans such as 2,3-dihydrofurans are central structural cores of a broad range of natural product and pharmaceutical chemistry.[1b,2] Approaches have been developed for the synthesis of these organic skeletons,[3] among which the methods between 1,3-dicarbonyl compounds and ketones or olefins are particularly important. A well-known method is the "interrupted Feist–Benary (IFB) reaction," which made the condensation of β-dicarbonyl compounds with α-haloketones stop at the hydroxydihydrofuran step.[4] In addition, the entail ionic[5] or radical reactions[2f,6] of 1,3-dicarbonyl compounds with appropriate olefins have also attracted much attention. Recently, we developed an efficient method for the preparation of the 2,3-dihydrobenzofuran derivatives by domino reactions via the Michael alkylation, the Mannich alkylation, and aldol alkylation.[7]

In recent years, there has been growing attention on water that is an attractive medium for many organic reactions,[8] since it has several advantages such as low cost, improved safety and low pollution, and operational simplicity. The use of water as a solvent in the Michael addition has also attracted much attention.[9] Almost at the same time, Rueping and we developed the Michael addition–nucleophilic substitution reaction for the efficient synthesis of dihydrofurans from diketones and (*E*)-β,β-bromonitrostyrenes using harmful chloroform as solvent[10] (Scheme 1, eq 1). Considering the need to develop environmentally acceptable chemical processes, we envisioned this type reaction could use water as solvent to gain the targeted dihydrofuran. Herein, we report a domino Michael addition–alkylation reaction in water for the formation of dihydrofurans using 1,3-dicarbonyl derivatives and 2-nitroacrylates (Scheme 1, eq 2).



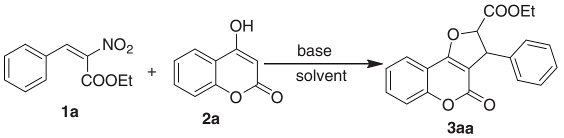
Scheme 1. Synthetic approach to dihydrofurans via domino Michael addition–alkylation reaction.

Shi pointed out 1,3-dicarbonyl compounds could be feasible dinucleophiles to react with nitro-diene **A** and give the desired carbon-substituted dihydrofuran (Scheme 2, **I**).[11] Guided by the successful results, we postulated that 2,3-dihydrobenzofuran derivatives **3** could be synthesized from the reaction of 1,3-dicarbonyl compounds with 2-nitroacrylates **1** via base-promoted two-component condensation (Scheme 2, **II**). Initially, we chose ethyl α-nitrocinnamate (**1a**) and 4-hydroxycoumarin (**2a**) as the model substrates for surveying the reaction parameters (Table 1). After careful screening, we found the choice of base had an important effect on the reaction. Et_3N and DIPEA showed good activity while versatile inorganic bases



Scheme 2. Synthesis of dihydrofuran from 1,3-diketone addition to nitro-ene.

Table 1. Screening for the optimum conditions[a]



Entry	Base	Solvent	Yield/%[b]
1	K_2CO_3	CH_3Cl	trace
2	NaOH	CH_3Cl	0
3	CH_3COONa	CH_3Cl	trace
4	Et_3N	CH_3Cl	90
5	DIPEA	CH_3Cl	80
6	Et_3N	EtOH	trace
7	Et_3N	H_2O	0
8	Et_3N	H_2O	44[c]
9	Et_3N	H_2O	95[d]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), base (200 mol %), rt, 12 h. [b]Isolated yield. [c]Tetrabutylammonium bromide (TBAB) (20 mol %), 40 °C, 6 h. [d]TBAB (20 mol %), 70 °C, 6 h.

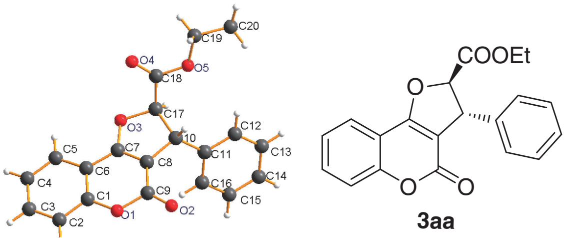
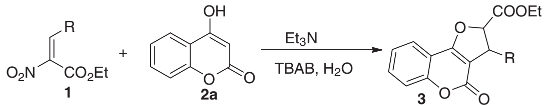
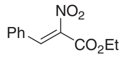
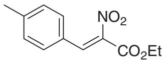
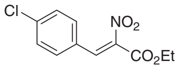
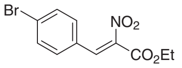
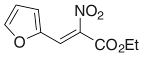


Figure 1. X-ray crystal structure of ethyl 4-oxo-3-phenyl-3,4-dihydro-2*H*-furo[3,2-*c*]chromene-2-carboxylate (**3aa**).

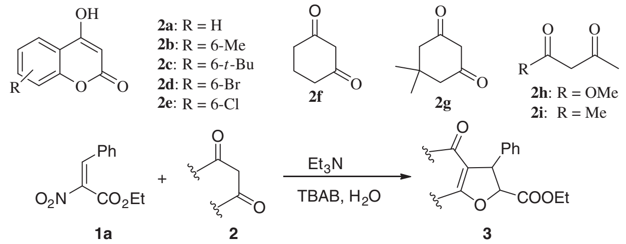
Table 2. Reaction between 4-hydroxycoumarin and various 2-nitroacrylates^a

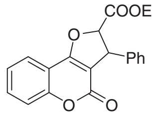
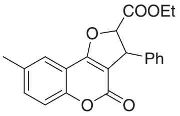
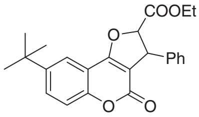
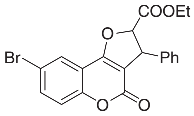
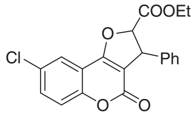
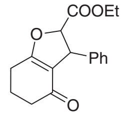
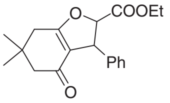
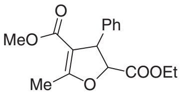
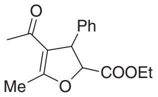


Entry	Substrate **1**		Product **3**	Yield/%^{b}
1		(**1a**)	**3aa**	95
2		(**1b**)	**3ab**	75
3		(**1c**)	**3ac**	60
4		(**1d**)	**3ad**	50
5		(**1e**)	**3ae**	86

^{a}All reactions were run with **1** (0.1 mmol), **2a** (0.2 mmol), Et_3N (200 mol %), TBAB (20 mol %) in 1 mL of H_2O under air at 70 °C for 6 h. ^{b}Isolated yield.

Table 3. Reaction between 1,3-dicarbonyl derivatives and (*E*)-ethyl 2-nitro-3-phenylacrylate^a



Entry	Substrate **2**	Product **3**		Yield/%^{b}
1	**2a**		**3aa**	95
2	**2b**		**3ba**	93
3	**2c**		**3ca**	94
4	**2d**		**3da**	91
5	**2e**		**3ea**	91
6	**2f**		**3fa**	85
7	**2g**		**3ga**	83
8	**2h**		**3ha**	86
9	**2i**		**3ia**	88

^{a}All reactions were run with **1a** (0.1 mmol), **2** (0.2 mmol), Et_3N (200 mol %), TBAB (20 mol %) in 1 mL of H_2O under air at 70 °C for 6 h. ^{b}Isolated yield.

such as K_2CO_3, NaOH, and CH_3COONa had no obvious effect on the reaction in $CHCl_3$ (Table 1, Entries 1–5). The structures of ethyl 4-oxo-3-phenyl-3,4-dihydro-2*H*-furo[3,2-*c*]chromene-2-carboxylate (**3aa**) was established by spectroscopic methods, and was further confirmed by the determination of single-crystal X-ray structures (Figure 1). It confirms the trans configuration as illustrated by the ORTEP diagram depicted in Figure 1. Considering this transformation would use harmful chloroform, we tried to use eco-friendly solvents. To our disappointment, no reaction took place when replacing $CHCl_3$ with other solvents such as EtOH or H_2O (Table 1, Entries 6 and 7). However, the reaction in water afforded the product **3aa** in 95% yield with the addition of TBAB at 70 °C (Table 1, Entry 9). TBAB is crucial for this reaction in water and may serve as a phase-transfer reagent. Thus, the best results were obtained in the presence of Et_3N (200 mol %) in water in combination with TBAB (20 mol %) at 70 °C for 6 h.

With the optimized conditions in hand, we investigated the scope of 2-nitroacrylates. The reaction is presented in Table 2. As expected, all the reactions proceeded smoothly with yields ranging from good to excellent and tolerated various functional groups such as methyl, bromo, and chloro (Table 2, Entries 2–4). Particularly, halogen-substituted ethyl α-nitrocinnamate worked well with 4-hydroxycoumarin (Table 2, Entries 3 and 4) and the surviving halogen atom could be valuable for further manipulation. Heteroaromatic substrates such as (*Z*)-ethyl 2-nitro-3-(tetrahydrofuran-2-yl)acrylate were also observed to be suitable acceptors in this Michael addition–alkylation reaction (Table 2, Entry 5). Unfortunately, the reaction became complicated when 4-hydroxycoumarin was treated with simple nitro alkenes without an ester group under the same conditions as above.

After a broad scope of 2-nitroacrylates was established, we were particularly interested in extending the 1,3-dicarbonyl derivatives (Table 3). We first further pursued synthesis of various 2,3-dihydrofurocoumarins. We found that the 4-hydroxycoumarin bearing functional groups on the phenyl ring reacted smoothly to afford the products in 91–95% yield (Table 3, Entries 1–5). To explore the generality and scope of this procedure, the reactivity of simple cyclohexanedione in this tandem reaction was explored. Cyclohexane-1,3-dione derivatives worked well under the conditions described above (Table 3, Entries 6 and 7). Fortunately, when the branched chain 1,3-dicarbonyl derivatives were treated with ethyl α-nitrocinnamate, good yields were obtained (Table 3, Entries 8 and 9).

In summary, we have succeeded in performing the reaction between 1,3-dicarbonyl derivatives and 2-nitroacrylates in water, avoiding using harmful solvent. This domino Michael addition–alkylation reaction afforded the 2,3-dihydrofuran products in moderate to good yields. Three types of 2,3-dihydrofuran derivatives were prepared: 2,3-dihydrofurocoumarins, 2,3,4,5,6,7-hexahydrobenzofuran, and 2,3,4,5-tetrasubstituted 2,3-dihydrofurans. The reaction showed remarkably broad substrate scope and good functional group tolerance.[12]

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