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Efficient and mild synthesis of functionalized 2,3-dihydrofuran derivatives via domino reaction in water

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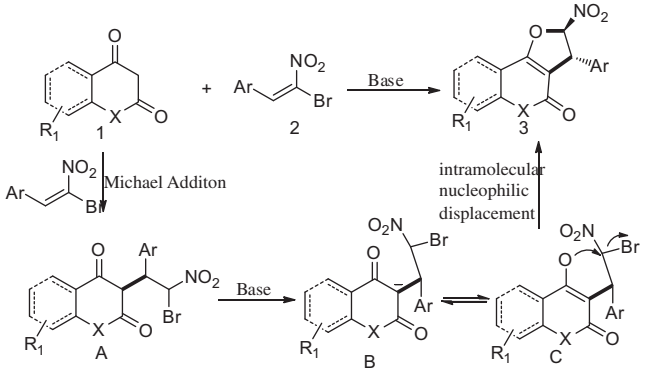
ABSTRACT

An efficient and mild method for the synthesis of functionalized tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and other tetrasubstituted 2,3-dihydrofurans by domino reaction of 1,3-dicarbonyl compounds and α-bromonitroalkenes with a large substrate scope and excellent diastereoselectivity (only trans isomers) in moderate to excellent yield (up to 96%) has been reported.

The dihydrofuran derivatives are an important class of heterocycles, widely present in numerous natural products and biologically active derivatives.[1] Owing to their importance, different approaches toward the synthesis of dihydrofuran derivatives have been reported on the basis of [4+1] annulation of sulfur ylide with α-ylidene-β-diketones[2], and by the reaction of α-ketosulfides with benzothiazole or α-keto polyfluoroalkane sulfones with aldehydes.[3,4] Moreover, dihydrofurans have also been obtained by cyclization[5,6] and ring enlargement reaction.[7,8] Among the methods, the most frequently used synthetic methods for the construction of dihydrofurans are the reactions of 1,3-dicarbonyl compounds with appropriate olefins.[9,10] Very recently, one-pot synthesis of substituted dihydrofurans from Lewis base-catalyzed three-component condensation was reported by Shi's group.[11] However, these approaches have some drawbacks from the viewpoint of atom economy or environmental concern. In the course of our investigations on the use of α-bromonitroalkenes in organic synthesis, the α-bromonitroalkenes are characterized by high and versatile reactivity.[12] Especially, the bromo or nitro group could behave as a better leaving group in the reaction. Therefore, many heterocyclic compounds have been constructed from the α-bromonitroalkenes.[12,13] Recently, our group[14] and Rueping's group[15] have reported a novel domino reaction of 1,3-dicarbonyl compounds and α-bromonitroalkenes to afford chiral tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and tetrasubstituted 2,3-dihydrofurans in high yields and enantioselectivities. Encouraged by the good results, we envisaged that domino reaction would be possible between the α-bromonitroalkenes with 1,3-dicarbonyl compounds **1,** as outlined in Scheme 1. First, the reaction of α-bromonitroalkenes **1** with 1,3-dicarbonyl compounds **2** gives the Michael addition product **A**. Then, the enolate anion **C** was formed under the basic conditions**.** Finally, the subsequent intramolecular nucleophilic displacement of **C** affords the multisubstituted dihydrofuran derivatives **3**.

In an initial study, we investigated the domino reaction between 4-hydroxylcoumarin **1a** and α-bromonitroalkene **2a** in a series of organic solvents and bases. A few representative results are shown in Table 1. To our delight, the domino reaction proceeded smoothly to provide the desired product **3aa** when the reaction was carried out in the presence of bases (120 mol %) in THF at room temperature for 48 h (Table 1, entries 1–4). Good yield was obtained when the domino reactions were catalyzed by NaOAc (86% yield, entry 3). Various bases such as triethylamine, DABCO, were also screened and similar results were achieved (entries 1–2). Lower yield was isolated when the reaction was catalyzed with a more strong base NaOH (31% yield, entry 4). Subsequently we investigated the effects of solvents with NaOAc. Good yields were obtained in DCM and ethanol (entries 6 and 7). Organic solvents can cause significant air pollution, land contamination and water pollution in many synthetic organic processes, and the development of efficient synthetic methodologies for organic



Scheme 1. The novel method for the synthesis of benzopyran derivatives.

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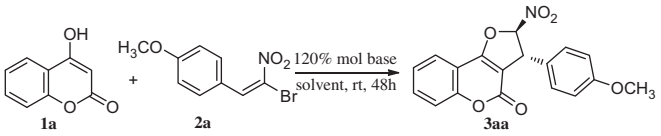
Table 1
Screening studies of the domino reaction of 4-hydroxyl- coumarin **1a** and α-bromonitroalkene **2a**[a]



Entry	Solvent	Base	Yield[b] (%)
1	THF	Et_3N	84
2	THF	DABCO	83
3[c]	THF	NaOAc	86
4[c]	THF	NaOH	31
5[c]	DCM	NaOAc	72
6[c]	Ethanol	NaOAc	87
7[c]	H_2O	NaOAc	80
8[c,d]	H_2O	NaOAc	93

[a] Unless noted otherwise, reactions were performed with 0.20 mmol of **1a**, 0.22 mmol of **2a**, 120 mol % of catalyst in 2.0 mL solvent for 48 h.
[b] Isolated yield.
[c] 20 mol % TBAB was added.
[d] 72 h.

reactions, in the absence of organic solvents, is an important challenge toward reducing the amount of waste.[16,17] An ideal organic reaction would proceed in an environmentally benign solvent, such as water.[18,19] We were pleased to find that the domino reaction proceeded smoothly to provide the desired product **3aa** with good yield using water as solvent (entry 7). we got excellent yield (93% yield) in water catalyzed by NaOAc, while the reaction time should be extended (entry 8).

Consequently, an array of 4-hydroxylcoumarin derivatives (Fig. 1) were explored in the reactions with a variety of α-bromonitroalkenes to establish the general utility of this new methodology. The reactions were generally conducted in water with 120 mol % of NaOAc in water at room temperature. As summarized in Table 2, the electronic characteristics of 4-hydroxylcoumarin derivatives seemed to have limited effects on the yield. Good to excellent yields were obtained for a diversity of 4-hydroxylcoumarin derivatives **1a–1d** bearing electron-withdrawing or donating groups (entries 1–5).[20] In addition, 4-hydorxythiocoumarin **2e** exhibited good reactivity. High yields were also obtained in the reactions of 4-hydroxylcoumarin and electron-withdrawing substituent or electron-denoting substituent on aryl ring of α-bromonitroalkenes substrates **2b–2e** (entries 6–9). It turned out that the substituents on the phenyl group of α-bromonitroalkenes had little influence on the domino reactions. Gratifyingly, raising the temperature to 70 °C, good to excellent yields were obtained, while the reaction time reduced to 3 h (Table 2, entries 1–9, yield in bracket). It is worthy of note that white precipitate was formed when the reactions were carried out at room temperature for 72 h (Fig. 2, e.g., the reaction of α-bromonitroalkenes **1a** with **2d**) and tricyclic 2,3-dihydrofurans were easily isolated by filtration, then washed with ethanol or recrystallized from ethanol to give the pure tricyclic 2,3-dihydrofurans.

Having succeeded in synthesizing tricyclic 2,3-dihydrofurans, we turned our attention to the possible synthesis of bicyclic 2,3-

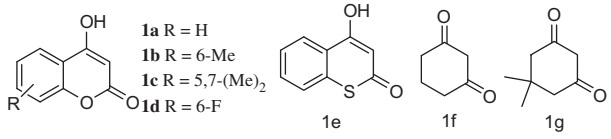
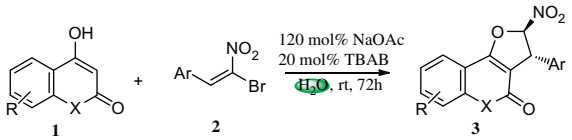


Figure 1. The structures of cyclic 1,3-dicarbonyl compounds.

Table 2
Synthesis of tricyclic 2,3-dihydrofurans 3[a]



Entry	1	Ar	(2)	3	Yield[b] (%)
1	**1a**	*p*-MeO-C_6H_4	(**2a**)	**3aa**	93 (91)
2	**1b**	*p*-MeO-C_6H_4	(**2a**)	**3ba**	95 (82)
3	**1c**	*p*-MeO-C_6H_4	(**2a**)	**3ca**	93 (88)
4	**1d**	*p*-MeO-C_6H_4	(**2a**)	**3da**	88 (86)
5	**1e**	*p*-MeO-C_6H_4	(**2a**)	**3ea**	90(81)
6	**1a**	*p*-Me-C_6H_4	(**2b**)	**3ab**	87(90)
7	**1a**	Ph	(**2c**)	**3ac**	90 (78)
8	**1a**	*p*-Cl-C_6H_4	(**2d**)	**3ad**	96 (89)
9	**1a**	*p*-Br-C_6H_4	(**2e**)	**3ae**	83 (77)
10	**1b**	*p*-Cl-C_6H_4	(**2d**)	**3bd**	96 (90)
11	**1b**	2-Furanyl	(**2f**)	**3bf**	88 (80)

[a] Unless noted otherwise, reactions were performed with 0.20 mmol of **1**, 0.30 mmol of **2a**, 120 mol % of NaOAc, 20 mol %TBAB in 2.0 mL H_2O for 72 h.
[b] Isolated yield.

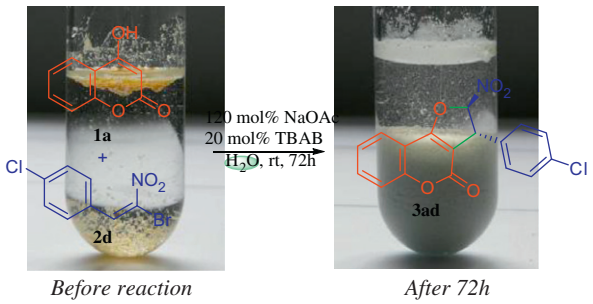
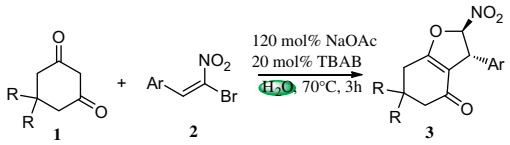


Figure 2. Photo of the reactions of **1a** with **2d** (Table 2, entry 8).

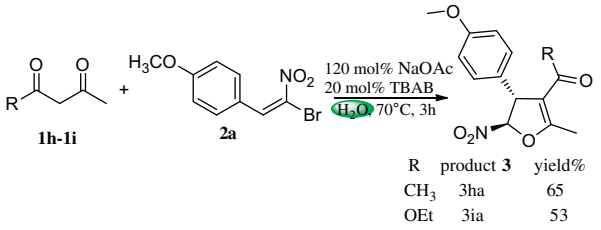
Table 3
Synthesis of bicyclic 2,3-dihydrofurans 3[a]



Entry	1	Ar	(2)	3	Yield[b] (%)
1	**1f**	*p*-MeO-C_6H_4	(**2a**)	**3fa**	76[c]
2	**1f**	*p*-Me-C_6H_4	(**2b**)	**3fb**	70
3	**1f**	Ph	(**2c**)	**3fc**	80
4	**1f**	*p*-Cl-C_6H_4	(**2d**)	**3fd**	83
5	**1f**	*p*-Br-C_6H_4	(**2e**)	**3fe**	79
6	**1g**	*p*-MeO-C_6H_4	(**2a**)	**3ga**	74

[a] Unless noted otherwise, reactions were performed with 0.20 mmol of **1**, 0.30 mmol of **2a**, 120 mol % of NaOAc, 20 mol %TBAB in 2.0 mL H_2O at 70 °C for 3 h.
[b] Isolated yield.

dihydrofurans using 1,3-cyclohexanedione**s** (Fig. 1) as nucleophiles. Unfortunately, very poor results were observed when the domino reaction of **1f–2a** was carried out at room temperature. To our delight, the yields were dramatically increased when the reactions were carried out at 70 °C after 3 h (Table 3). Table 3 shows that α-bromonitroalkenes with electron-withdrawing or donating substituents provided the bicyclic 2,3-dihydrofurans **3fa–3fe** in good yields (70–83%, entries 1–5). For the reaction of



Scheme 2. The reactions of acyclic 1,3-dicarbonyl compounds **1h**–**1i** with **2a**.

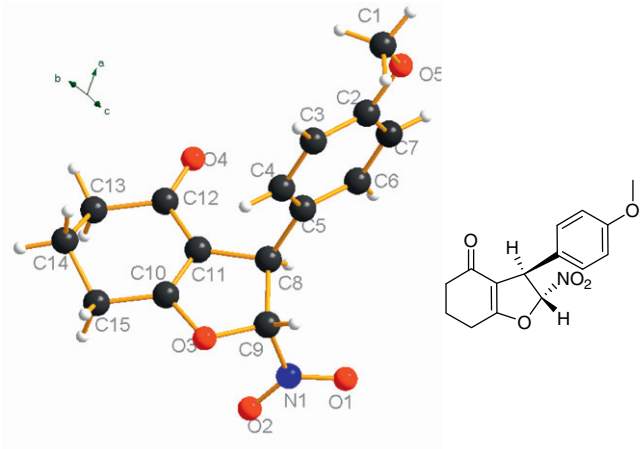


Figure 3. Molecular structure of **3fa**.

α-bromonitroalkene **1a**, good yield was also achieved with 5,5-dimethyl-1,3-cyclohexanedione (entry 6). The reactions of acyclic 1,3-dicarbonyl compounds **1h**–**1i** with **2a** also found to be successful, and tetrasubstituted 2,3-dihydrofurans **3ha–3ia** were obtained with moderate yield (Scheme 2).

The stereochemistries of the products **3** are assigned on the basis of specific coupling constants (*J*) and HPLC in comparison with the literature data,[21] then the stereochemistries of **3** were established unambiguously by X-ray analysis of **3fa** (Fig. 3). It confirms the trans configuration as illustrated by the ORTEP diagram depicted in Figure 3.[22]

In conclusion, an efficient method for the synthesis of functionalized 2,3-dihydrofurans by domino reaction of 1,3-dicarbonyl compounds with α-bromonitroalkenes has been investigated. The domino reaction can proceed smoothly in an environmentally benign solvent–water and provides pure functionalized tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and tetrasubstituted 2,3-dihydrofurans with excellent diastereoselectivity (only trans isomers) in moderate to excellent yield. The reaction's scope proved to be quite broad. Notably, pure tricyclic 2,3-dihydrofurans were easily obtained in a simple procedures. This novel methodology should be of great interest for natural product synthesis and pharmaceutical synthesis for the mild reaction conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.093.

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20. Typical experimental procedure for the domino reaction of 1,3-dicarbonyl compounds with α-bromonitroalkenes 2. *Method A*: 4-hydroxylcoumarin **1a** (0.2 mmol, 1 equiv), α-bromonitroalkene **2a** (0.30 mmol, 1.5 equiv), NaOAc (20 mg, 0.24 mmol) and TBAB (12 mg, 0.024 mol) were stirred at room temperature in H_2O (2 mL) for 72 h, then extracted with ethyl acetate and dried with Na_2SO_4, the solvent was removed and flash chromatography on silica gel (10% ethyl acetate/petroleum ether) or recrystallized from ethanol gave **3aa** as a white solid. *Method B*: 4-hydroxylcoumarin **1a** (0.2 mmol,

1 equiv), α-bromonitroalkene **2a** (0.30 mmol, 1.5 equiv), NaOAc (20 mg, 0.24 mmol) and TBAB (12 mg, 0.024 mol) were stirred at 70 °C in H_2O (2 mL) for 3 h, then extracted with ethyl acetate and dried with Na_2SO_4, the solvent was removed and flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave **3aa** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88–7.86 (d, J = 7.79 Hz, 1H), 7.70 (m, 1H), 7.47–7.43 (dd, J = 10.72, 8.49 Hz, 2H), 7.20–7.18 (d, J = 8.60 Hz, 2H), 6.92–6.90 (d, J = 8.68 Hz, 2H), 6.21 (d, J = 2.16 Hz, 1H), 4.90 (d, J = 1.77 Hz, 1H), 3.79 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.4, 160.5, 157.9, 155.5, 133.8, 128.3, 128.3, 127.5, 124.8, 123.1, 117.3, 114.9, 114.9, 111.6, 111.2, 105.1, 55.4, 53.1. IR (KBr) cm^{-1} 3075, 2998, 2892, 1753, 1446, 688; ESI-HRMS: calcd for $C_{18}H_{13}NO_6$ + Na 362.06382, found 362.06375.

21. For example, compound **3ca** [6.16 (d, J = 1.82 Hz, 1H), 4.85 (d, J = 1.22 Hz, 1H)] exhibited coupling constants (J) data identical to that reported in the literature [Compound **4ca** 6.17 (d, J = 1.8 Hz, 1H), 4.86 (d, J = 1.2 Hz, 1H); (*J. Org. Chem*. **2010**, *75*, 8716]. Diastereoselectivity (**3ca**) was also determined by HPLC analysis on chiral Chiralpak columns and the HPLC data was identical to that reported in the literature (**4ca**, *J. Org. Chem*. **2010**, *75*, 8716).
22. Crystal data for **3fa** $C_5H_{15}NO_5$ (289.28), Monoclinic, space group $C2/c$, a = 22.0833(10), b = 7.0950(3), c = 20.9180(10) Å, U = 2856.5(2) Å^3, Z = 8, specimen 0.653 × 0.263 × 0.248 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.102 mm^{-1}, reflections collected 21781, independent reflections 3315 [R(int) = 0.0258], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 3315/0/190, goodness-of-fit on F^2 = 1.039, final R indices [I >2σ(I)] $R1$ = 0.0431, $wR2$ = 0.1166, R indices (all data) $R1$ = 0.0561, $wR2$ = 0.1283, largest diff. peak and hole 0.219 and −0.249 e Å^{-3}.