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An Efficient Three-component Tandem Reaction Leading to Pentacyclic Isoindole-fused Benzo[*b*,*e*][1,4]diazepines in Water

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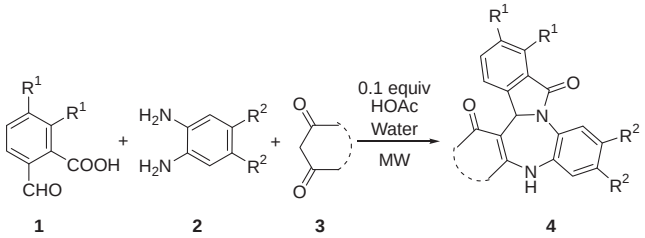
An efficient methodology for the synthesis of highly functionalized pentacyclic isoindole-fused benzo[*b*,*e*][1,4]-diazepine derivatives from readily available common reactants in water has been developed. The tandem reaction resulted in efficient assembly of two new rings and four σ bonds including three C–N bonds in a one-pot operation.

The search for efficient approaches to chemical and potentially biological products, containing C–N bonds and bridgehead nitrogen moieties, from common starting materials has become an important issue in modern organic synthesis.[1] In this regard, multicomponent domino reactions, particularly those performed in aqueous media, have become increasingly useful tools for the synthesis of natural products and their building blocks[1f,2] due to their atom economy and green chemistry characteristics. Those processes can avoid time-consuming protection–deprotection, and tedious workup as well as purifications in multistep reactions. In addition, these reactions often proceed with excellent chemo- and regioselectivies.[3]

On the other hand, heterocycles containing bridgehead nitrogen moieties constitute an important class of natural and unnatural products and many of them exhibit useful biological activities.[4] For example, 1,4-diazepine containing heterocycles has been proven to control cell proliferative disorders, particularly oncological disorders,[5] and to be useful in the prevention or treatment of several other diseases.[6] In addition, benzodiazepine derivatives show remarkable depressant activity in the central nervous system[7] and HCV NS5B polymerase inhibitors.[8] Orlov and co-workers reported the synthesis of benzodiazepines via three-component reaction of 5,5-dimethylcyclohexane-1,3-dione with benzene-1,2-diamine and aromatic aldehydes.[9] These products were also obtained by reacting 4-(2-aminophenylamino)furan-2(5*H*)-one with aldehydes in organic media.[10] However, to the best of our knowledge, the synthesis of pentacyclic isoindole-fused benzo[*b*,*e*][1,4]diazepines containing bridgehead nitrogen moieties using *o*-formylbenzoic acid in water has not been reported so far.

During our continuous efforts on the development of multicomponent domino reactions for the construction of useful heterocyclic compounds,[11] herein, we would like to report a green three-component tandem approach to pentacyclic isoindole-fused benzo[*b*,*e*][1,4]diazepine derivatives (Scheme 1). This reaction was achieved by reacting 2-formylbenzoic acids, 1,2-diamines, and 1,3-dicarbonyl compounds as starting materials in water under microwave irradiation without the use of any strong acids or metal catalysts.

Water is usually among the first choices for MW-assisted reactions due to its efficient absorbance of microwave irradiation.[12] We thus started performing the reaction of 2-formylbenzoic acid (**1a**) with benzene-1,2-diamine (**2a**), and furan-2,4(3*H*,5*H*)-dione (**3a**) in the presence of 0.1 equiv of various acids, such as HOAc, *p*-toluenesulfonic acid (TsOH), and trifluoroacetic acid (TFA) as a Brønsted acid catalyst at 100 °C.



1 2 3 4

Scheme 1.

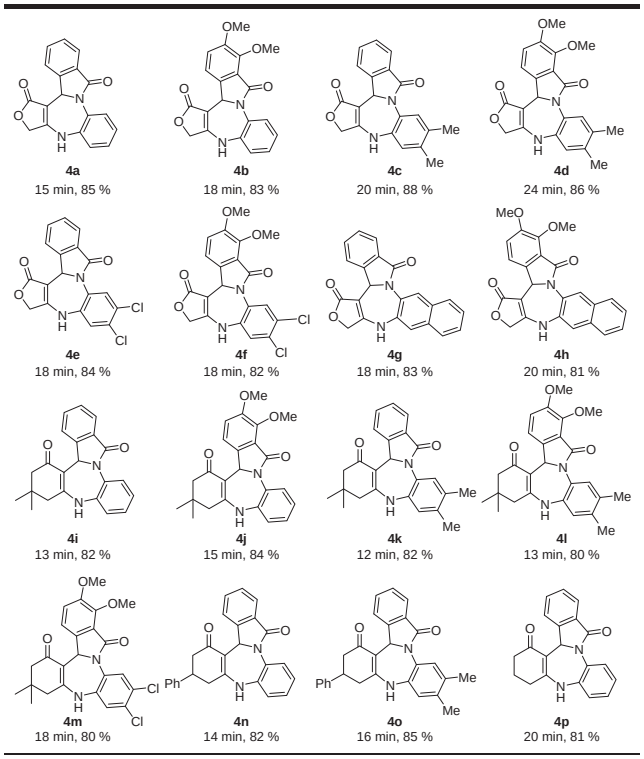
Table 1. Optimization of reaction conditions for **4a**

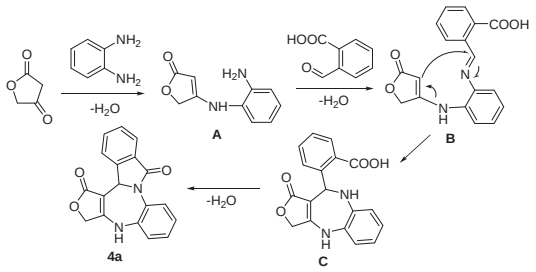
Entry	HOAc/equiv	*T*/°C	Time/min	Yield/%
1	0	100	15	21
2	0.1	100	15	40
3	0.2	100	15	40
4	0.3	100	15	41
5	0.1	120	15	68
6	0.1	150	15	85
7	0.1	160	15	84

Although the isoindole-fused benzo[*b*,*e*][1,4]diazepines **4a** can be generated in the presence of all of these acids, only HOAc resulted in a good yield of 40%. In fact, a poor yield (21%) product **4a** was observed in the absence of HOAc. We next carefully examined the use of different amounts of HOAc and reaction temperatures. As revealed in Table 1, no significant improvement in chemical yields was observed even when more than 0.1 equiv of HOAc was used (Table 1, Entries 3 and 4). Interestingly, performing the reaction in the presence of a catalytic amount of HOAc (10 mol %) under microwave irradiation resulted in a higher yield of 85%. The reaction was furnished within 15 min at 150 °C in a sealed vessel (Entry 6).

With this result in hand, the scope of the methodology was investigated under the above optimized conditions. As shown in Table 2, the reaction of 2-formylbenzoic acids, 1,2-diamines, and furan-2,4(3*H*,5*H*)-dione in water provided a series of new pentacyclic isoindole-fused benzo[*b*,*e*][1,4]diazepine **4a**–**4h** in 81–88% yields within a short period (15–24 min). It is worth noting that there has not been a literature precedent for the synthesis of highly functionalized pentacyclic isoindole-fused benzo[*b*,*e*][1,4]diazepine yet.

Table 2. The synthesis of isoindazole-fused benzodiazepine **4**[13,14]





Scheme 2.

To expand the scope of this domino reaction, a series of 2-formylbenzoic acids and 1,2-diamines were used as substrates, giving the corresponding isoindole-fused benzodiazepines **4i**–**4p** in chemical yields of 80–85%.

On the basis of the resulting products, a reasonable mechanism is proposed as shown in Scheme 2 and represented by the formation of **4a**. The first step involves the condensation of furan-2,4(3*H*,5*H*)-dione (**3a**) with benzene-1,2-diamine (**2a**) to give an enaminone **A**, and then the reaction between enaminone **A** and 2-formylbenzoic acid (**1a**) occurred to provide intermediate **B**, which underwent intramolecular cyclization to give intermediate **C**. The intermediate **C** was next dehydrated to final product **4a**.

Similar to our previous multicomponent domino processes,[11] the present reaction also showed *the following attractive characteristics*: (1) an environmentally friendly process in which water is the major by-product without additional use of organic solvent during reaction; (2) a convenient workup which only needs simple filtration since the products directly precipitate out after the reaction is finished or when its mixtures are diluted with cold water; (3) readily available starting materials of 2-formylbenzoic acids, 1,2-diamines, and cyclic-1,3-dicarbonyl compounds; (4) high atom-economy and bond-forming economy. Moreover, the two C=O bonds were cleaved and up to two new rings and four new σ bonds including three C–N bonds were formed. *The novelty of the present tandem reaction is shown by the fact that multiple chemical bond breaking and forming were simultaneously achieved in an intermolecular manner and in a one-pot operation*.

In summary, a new tandem process has been established for the construction of pentacyclic isoindole-fused benzo-[*b*,*e*][1,4]diazepines that are of potential chemical and biomedical importance. The tandem reaction was conducted in aqueous solution with microwave irradiation using readily available and inexpensive starting materials. The reactions proceed very fast (within 12–24 min) in good to excellent chemical yields without tedious workup and isolations.

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13 Experimental section: In a 10-mL reaction vial, benzene-1,2-diamine **2** (1 mmol), cyclic-1,3-dicarboxy compounds **3** (1 mmol), acetic acid (0.1 mmol), and water (2 mL) were mixed and then stirring for 8 min. Subsequently, 2-formylbenzoic acid **1** (1 mmol) was added to the reaction mixture, and the reaction vial was capped and prestirring for 20 s. The mixture was subjected to microwave irradiation (initial power 100 W, maximum power 200 W) at 150 °C for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, filtered to give the crude product, which was further washed with 50% EtOH to give pure product. **4b*H*-Benzo[2,3]furo[3′,4′:5,6][1,4]-diazepino[7,1-*a*]isoindole-5,14(7*H*,8*H*)-dione (4a)** Mp: 286–289 °C; IR (KBr): 3277, 3220, 3147, 3108, 1734, 1704, 1688, 1595, 1543, 1506, 1397, 1348, 1194, 1045, 1023, 766, 757, 743, 708, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, NH), 8.41 (d, $J = 8.0$ Hz, 1H, ArH), 7.78 (d, $J = 7.6$ Hz, 1H, ArH), 7.70–7.66 (m, 1H, ArH), 7.59–7.55 (m, 1H, ArH), 7.40–7.34 (m, 2H, ArH), 7.21–7.14 (m, 2H, ArH), 5.74 (s, 1H, CH), 4.83 (d, $J =$ 15.2 Hz, 1H, CH_2), 4.78 (d, $J = 15.2$ Hz, 1H, CH_2); HRMS (ESI) m/z: $[M - H^+]$ calcd for $C_{18}H_{11}N_2O_3$: 303.0764; found: 303.0761.

14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

