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Multicomponent Cascade Reactions for the Synthesis of 2,3-Dihydrobenzofuran Derivatives

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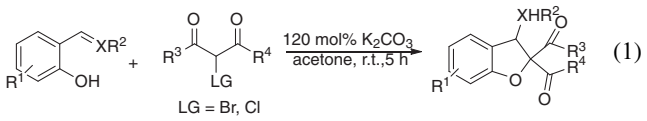
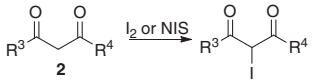
A multicomponent cascade reaction for the synthesis of highly substituted 2,3-dihydrobenzofuran derivatives with moderate to good yields was developed. The synthetic utilities of these 2,3-dihydrobenzofurans were also further explored. Ethyl 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate and ethyl benzofuran-2-carboxylate were easily obtained from 2,3-dihydrobenzofurans.

Multicomponent cascade reactions have garnered significant recent attention from the synthetic community as a means to swiftly assemble complex molecules from simple starting materials with minimal time, waste, high atom- and step-economy as well as manipulation of reaction intermediates.[1] In particular, these strategies are powerful in the total synthesis of natural products and bioactive molecules.[2] 2,3-Dihydrobenzofurans (DHB) are recognized to be very important due to their biological activities[3] and their applications in a wide range of chemical transformations, and other important targets. The remarkable significance of the 2,3-dihydrobenzofuran ring system has motivated chemists to develop various approaches for the construction of them, such as radical[4] and transition-metal-mediated cyclizations[5] and benzyne,[6] electrocyclic,[7] anionic,[8] organocatalytic, and dehydrative techniques.[9] Recently, a novel domino annulation between sulfur ylides and salicyl-*N*-thiophosphinylimines was developed by Huang.[10] However, most of the reported methods have one or more of the following drawbacks: for example, use of rather specific substrates, low yields of products, complicated reaction assembly, tedious processes for purification, etc. As such, simple and robust facile methodologies to provide 2,3-dihydrobenzofuran derivatives wherein we could vary the different substitutions, represent an important and attractive objective at the forefront of synthetic chemistry.



(1)



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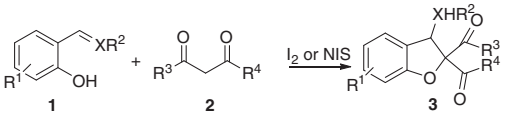
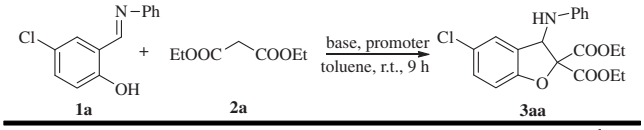


(3)

Recently, an efficient, mild, and convenient domino reaction to synthesize differently substituted 2,3-dihydrobenzofurans in moderate to excellent yields from readily available starting materials has been developed in our group (eq 1).[11] In our further studies, we found that α-monoiodinated 1,3-dicarbonyl compounds were easily obtained by oxidative iodination of 1,3-dicarbonyl compounds (eq 2).[12] Inspired by the above reports, we envisioned that the new multicomponent cascade reactions of **1**, 1,3-dicarbonyl compounds **2**, and iodine or NIS (*N*-iodosuccinimide) would be possible, as outlined in eq 3, giving a facile protocol to 2,3-dihydrobenzofuran derivatives with multiple substitutions.

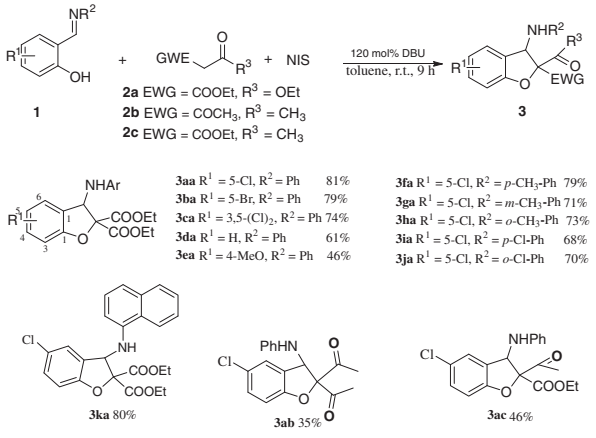
Table 1. Reaction of *N*-phenylsalicylideneamine (**1a**) to diethyl malonate (**2a**) under different conditions[a]



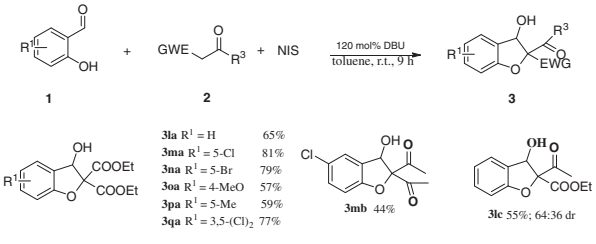
Entry	Base	Promoter	Yield/%[b]
1	DABCO	NIS	trace
2	DBU	NIS	81
3	K_2CO_3	NIS	trace
4	KOH	NIS	36
5	DBU	NBS	68
6	DBU	NCS	42
7	DBU	I_2	70

[a]All the reactions were performed with 0.2 mmol of **1a**, 0.48 mmol of **2a**, 0.4 mmol of promoter, and 120 mol % of base in 1.5 mL toluene at room temperature for 9 h. [b]Isolated yields.

A series of organic solvents and bases were screened for multicomponent cascade reactions and representative results are shown in Table 1. We initiated our investigation by subjecting 5-chloro-*N*-phenylsalicylideneamine (**1a**) to diethyl malonate (**2a**) in the presence of promoter NIS and DABCO in toluene at room temperature. However, no product **3aa** was obtained (Table 1, Entry 1). To our delight, the domino reaction proceeded smoothly to provide desired product **3aa** with good yield when the reaction was carried out in the presence of DBU [1,8-diazabicyclo(5,4,0)undec-7-ene] in toluene at room temperature for 9 h (Entry 2). Optimization of the reaction conditions revealed that bases and solvents strongly influenced the yield. Inorganic base K_2CO_3 was inert in this reaction (Entry 3). Very poor results were observed when KOH was applied (Entry 4). Other halogen sources such as NBS, NCS, and molecular iodine were also screened. However, all of them gave the final product in low to moderate yields (Entries 5–7). Screening of the solvents (such as acetone, DCM, THF, and MeOH) gave toluene as the solvent of choice. The optimal reaction conditions [DBU (1.2 equiv), NIS (2.0 equiv), toluene, and room temperature] is shown in Entry 2. With the best reaction conditions, various



Scheme 1. Synthesis of 2,3-dihydrobenzofurans from *N*-phenylsalicylideneamines.

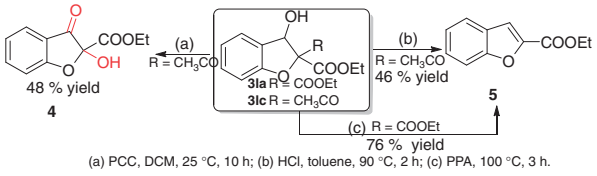


Scheme 2. Synthesis of 2,3-dihydrobenzofurans from salicylaldehydes.

N-phenylsalicylideneamines **1** and 1,3-dicarbonyl compounds **2** were applied to investigate the reaction substrate scope, and the results are summarized in Scheme 1.

A variety of substrates with different electronic properties reacted smoothly and efficiently under the present conditions, affording the corresponding 2,3-dihydrobenzofuran products in moderate to good yields (Scheme 1). Good yields of **3aa**–**3ca** were obtained in multicomponent cascade reactions of diethyl malonate and electron-withdrawing substituent (R^1) on aryl ring of salicyl *N*-phenyl imines. On the contrary, an electron-donating substituent (R^1) on *N*-phenylsalicylideneamines tended to decrease the reactivity, and sluggish reaction was observed. Gratifyingly, the cascade reaction proceeded well at 40 °C, and the product **3ea** was achieved in 46% yield after 9 h. It turned out that the substituents (R^1) on the phenyl group of *N*-phenylsalicylideneamines had little influence on the yields of **3fa**–**3ja** with our organocatalytic protocol. *N*-(1-Naphthyl)salicylideneamine exhibited slightly good reactivity, and product **3ka** was obtained in good yield. To extend the scope of the domino reaction further, other 1,3-dicarbonyl compounds **2b** and **2c** were also explored in cascade reaction under the same conditions, but products **3ab** and **3ac** were obtained in low yields.

To further demonstrate the superiority of our methodology and to extend the utility of this cascade reaction, salicylic aldehydes were also explored (Scheme 2). The salicylaldehydes **1m**–**1q** exhibited high reactivity. The domino reaction of salicylaldehydes to diethyl malonate (**2a**) proceeded with clean products **3la**–**3lc** in moderate to good yields. The salicylaldehydes with an electron-withdrawing group gave higher yields than that bearing an electron-donating group (**3ma**–**3qa**). Other 1,3-dicarbonyl compounds **2b** and **2c** showed lower reactivity than diethyl malonate (**2a**), products **3mb** and **3lc** were obtained in only moderate yields.



Scheme 3. Transformation of 2,3-dihydrobenzofurans.

Having established the multicomponent cascade reactions of **1**, 1,3-dicarbonyl compounds **2**, and NIS, the synthetic utilities of these 2,3-dihydrobenzofurans were further explored (Scheme 3). A hydroxy group was directly introduced at the 2-position of 2,3-dihydrobenzofuran **3lc** as well as 3-hydroxy was oxidized in moderate yields when pyridinium chlorochromate (PCC) was used as oxidant. Ethyl benzofuran-2-carboxylate (**5**) was obtained when **3la** was treated with polyphosphoric acid (PPA), as well as the 2,3-dihydrobenzofuran **3lc** was treated with hydrochloric acid in toluene.

In conclusion, a catalytic multicomponent cascade reaction for the synthesis of 2,3-dihydrobenzofuran derivatives was developed.[13] A large variety of substrates (*N*-phenylsalicylideneamines and salicylaldehydes) and 1,3-dicarbonyl compounds were found suitable for this transformation to give 2,3-dihydrobenzofuran derivatives with moderate to good yields. This strategy not only provides a new approach for the construction of substituted 2,3-dihydrobenzofuran derivatives, but also provides benzofuran derivatives and 2-hydroxy-3-oxo-2,3-dihydrobenzofuran.

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