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Cyclization Reaction of 2-Azido-1-(2-hydroxyphenyl)ethanones with Terminal Alkynoates Catalyzed by 4-Dimethylaminopyridine (DMAP): Synthesis of 2-Aminobenzofuran-3(2*H*)-one Derivatives

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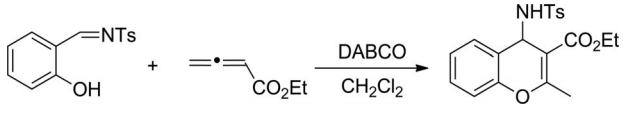
Keywords: Oxygen heterocycles / Alkynes / Fused-ring systems / Cyclization

An unexpected cyclization reaction of 2-azido-1-(2-hydroxyphenyl)ethanones with terminal alkynoates catalyzed by 4-dimethylaminopyridine (DMAP) was developed, and 2-aminobenzofuran-3(2*H*)-one derivatives were obtained in moderate to good yields under mild reaction conditions within 2 h. The scope and limitations of the cyclization reactions were also investigated.

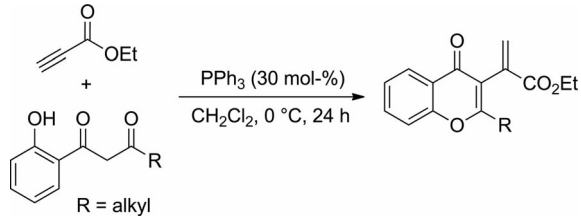
Introduction

Oxygen-containing heterocycles are of great importance in the pharmaceutical industry, as they exhibit favorable biological activity and pharmaceutical significance. The benzofuran-3(2*H*)-one moiety constitutes the key structure of a wide range of compounds that have been used as antifungal agents, tyrosinase inhibitors, antioxidants, an so on.[1] Moreover, they have been also used as valuable synthetic intermediates to build many functionalized molecules.[2] In recent years, a reaction based on nucleophilic catalysis through conjugate addition of N and P nucleophiles has proven to be useful in the development of cycloaddition reactions, providing various carbocycles[3] and heterocycles.[4,5] For example, Shi and Alemán et al. described the reaction of activated allenes or alkynes with salicylaldimines catalyzed by an organic base to produce oxygen-containing heterocycles (Scheme 1).[6]



Scheme 1. Cyclization reaction of an allenic ester with salicyl *N*-tosylimines.[6]

Organic-base-catalyzed cycloaddition reactions with the use of electron-deficient alkynes has received much attention.[7] Recently, Xue reported the PPh_3-catalyzed cycloaddition of 1-(*o*-hydroxyaryl)-3-alkyl-1,3-diketones with ethyl propiolate to provide various chromone derivatives (Scheme 2).[8] In continuation of our interest in developing new annulation reactions, the possibility of 2-azido-1-(2-hydroxyphenyl)ethanones to undergo cyclization with terminal alkynoates catalyzed by organic bases was investigated. To our delight, an unexpected transformation resulting in 2-aminobenzofuran-3(2*H*)-one derivatives occurred in the presence of 4-dimethylaminopyridine (DMAP). To date, there is a general lack of simple procedures to synthesize 2-aminobenzofuran-3(2*H*)-one derivatives from simple and readily available starting materials. Herein, we wish to report this facile synthetic method for the preparation of 2-aminobenzofuran-3(2*H*)-one derivatives starting from 2-azido-1-(2-hydroxyphenyl)ethanones and terminal alkynoates in the presence of DMAP under mild reaction conditions.



Scheme 2. Cycloaddition reaction of 1-(*o*-hydroxyaryl)-3-alkyl-1,3-diketones with ethyl propiolates.[8]

Results and Discussion

Our studies were initiated by the addition of 4-dimethylaminopyridine (DMAP, 20 mol-%) to a solution of 2-azido-1-(2-hydroxyphenyl)ethanone (**1a**) and ethyl propiolate (**2a**) under various reaction conditions, and the results are shown in Table 1. The reaction of **1a** with **2a** in the presence

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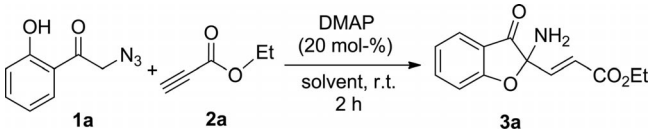
of DMAP (20 mol-%) in CH_2Cl_2 at room temperature for 2 h afforded **3a** as a pale yellow oil in 55% yield, and this compound was characterized by ^1H and ^{13}C NMR spectroscopy and HRMS analysis. The ratio of **1a** to **2a** had an effect on the yield of the reaction. Desired product **3a** was obtained in 63% yield when 1.5 equiv. of **2a** was used, but the yield did not improved with a further increase in the amount of **2a** (Table 1, Entries 3 and 4). The yield of **3a** could not be improved by heating CH_2Cl_2 at reflux, but it decreased sharply when the reaction was carried out at 0 °C (Table 1, Entries 5 and 6). DMAP as a catalyst was crucial for the reaction. Other organic bases in place of DMAP were examined and had a significant influence on the reaction. The use of 1,4-diazabicylco[2,2,2]octane (DABCO) afforded **3a** in 28% yield. Only a trace amount of the desired product was detected by TLC when triethylamine (Et_3N) or pyridine was used as catalyst. With the utilization of PPh_3 or tri(*n*-butyl)phosphane, desired product **3a** was not found. Solvent screening revealed a significant solvent effect. When shifting the solvent to THF, toluene, or acetone, **3a** was obtained in 60, 53 or 31% yield, respectively (Table 1, Entries 7–9). With use of DMF or DMSO as a solvent, product **3a** was isolated in a relatively low yield (Table 1, Entries 10 and 11).

Table 1. Effect of substrate ratio and solvent on the reaction.[a]

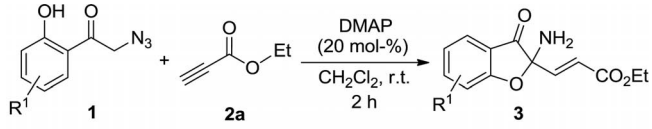


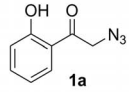
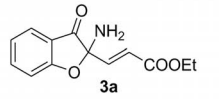
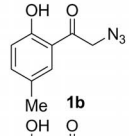
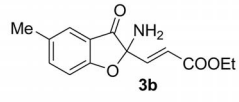
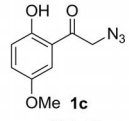
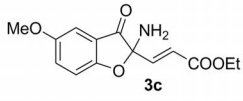
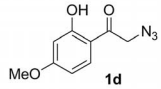
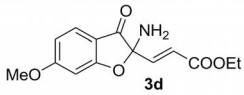
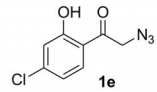
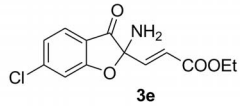
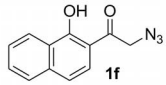
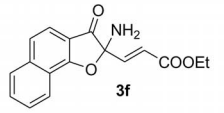
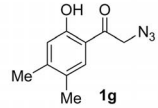
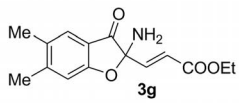
Entry	**1a** [equiv.]	**2a** [equiv.]	Solvent	Yield [%][b]
1	1.0	1.0	CH_2Cl_2	55
2	1.0	2/3	CH_2Cl_2	46
3	1.0	1.5	CH_2Cl_2	63
4	1.0	2.0	CH_2Cl_2	64
5	1.0	1.5	CH_2Cl_2	16[c]
6	1.0	1.5	CH_2Cl_2	62[d]
7	1.0	1.5	THF	60
8	1.0	1.5	toluene	53
9	1.0	1.5	acetone	31
10	1.0	1.5	DMF	<10
11	1.0	1.5	DMSO	<10
12	1.0	1.5	CH_2Cl_2	28[e]
13	1.0	1.5	CH_2Cl_2	trace[f]
14	1.0	1.5	CH_2Cl_2	trace[g]
15	1.0	1.5	CH_2Cl_2	–[h]
16	1.0	1.5	CH_2Cl_2	–[i]

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (amount indicated in Table 1), DMAP (0.06 mmol), solvent (2.0 mL), r.t., in air, 2 h. [b] Isolated yield. [c] At 0 °C. [d] CH_2Cl_2 heated at reflux. [e] DABCO was used as catalyst. [f] Et_3N was used as catalyst. [g] Pyridine was used as catalyst. [h] PPh_3 was used as catalyst. [i] Tri(*n*-butyl)phosphane was used as catalyst.

With the reaction conditions optimized for the formation of **3a** in our hand, the scope and limitations of this reaction were subsequently investigated. A variety of 2-azido-1-(2-hydroxyphenyl)ethanones **1** were subjected to the reaction under the optimized conditions, and the representative results are listed in Table 2. It was found that reaction of **1** with ethyl propiolate (**2a**) afforded corresponding products **3** in moderate yields regardless of the different substitutions on the aromatic ring of **1**. Clearly, substrates with an electron-donating group on the benzene ring gave better yields than those with an electron-withdrawing group on the benzene ring. For example, for substrates with a methyl or methoxy group attached on the benzene ring, the yields of the corresponding products were obtained in the range of 64–67% (Table 2, Entries 2–4). Substrates with a chloride group on the benzene ring gave the desired products in low yields even when the reaction was prolonged for 12 h (Table 2, Entry 5) and most of the starting materials could not be converted into the desired product. Treatment of **1f** with ethyl propiolate gave desired product **3f** in 61% yield. Notably, multisubstituted **1g** could be treated with **2a** to generate desired product **3g** in good yield (Table 2, Entry 8). In many cases, the moderate yields obtained in the reactions can be accounted for by the formation of other byproducts, which could not be isolated by column chromatography.

Table 2. DMAP-catalyzed cyclization reactions of 2-azido-1-(2-hydroxyphenyl)ethanones with ethyl propiolate.[a]

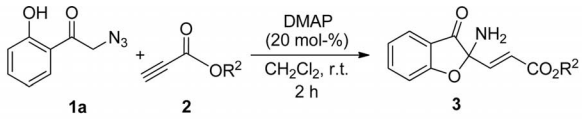


Entry	Substrate **1**	Product **3**	Yield [%][b]
1	 **1a**	 **3a**	63
2	 **1b**	 **3b**	64
3	 **1c**	 **3c**	65
4	 **1d**	 **3d**	67
5	 **1e**	 **3e**	21[c]
6	 **1f**	 **3f**	61
7	 **1g**	 **3g**	62

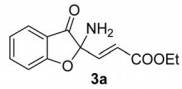
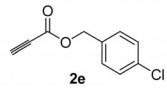
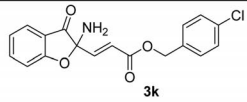
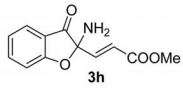
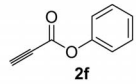
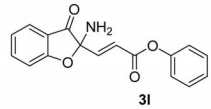
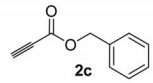
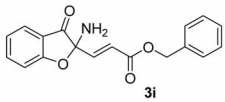
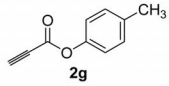
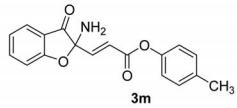
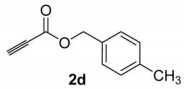
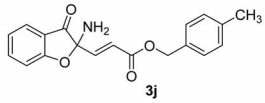
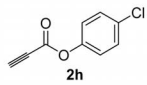
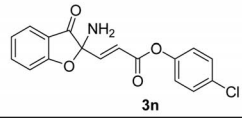
[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.45 mmol), DMAP (0.06 mmol), CH_2Cl_2 (2.0 mL), r.t., in air, 2 h. [b] Isolated yield. [c] The reaction was stirred for 12 h.

To further evaluate the scope of this reaction, a variety of electron-deficient alkynes were examined under the standard reaction conditions, and the results are summarized in Table 3. Desired product **3h** was obtained in 60% yield when methyl propiolate was used as one of the substrates (Table 3, Entry 2). As expected, benzyl or phenyl propiolate, in place of ethyl propiolate, also reacted smoothly with **1a** to give the desired 2-aminobenzofuran-3(2*H*)-one derivatives in moderate to good yields (Table 3, Entries 3–8). Only a trace amount of the desired product was detected by TLC when but-3-yn-2-one was used as the substrate, but the pure product could not be isolated by column chromatography

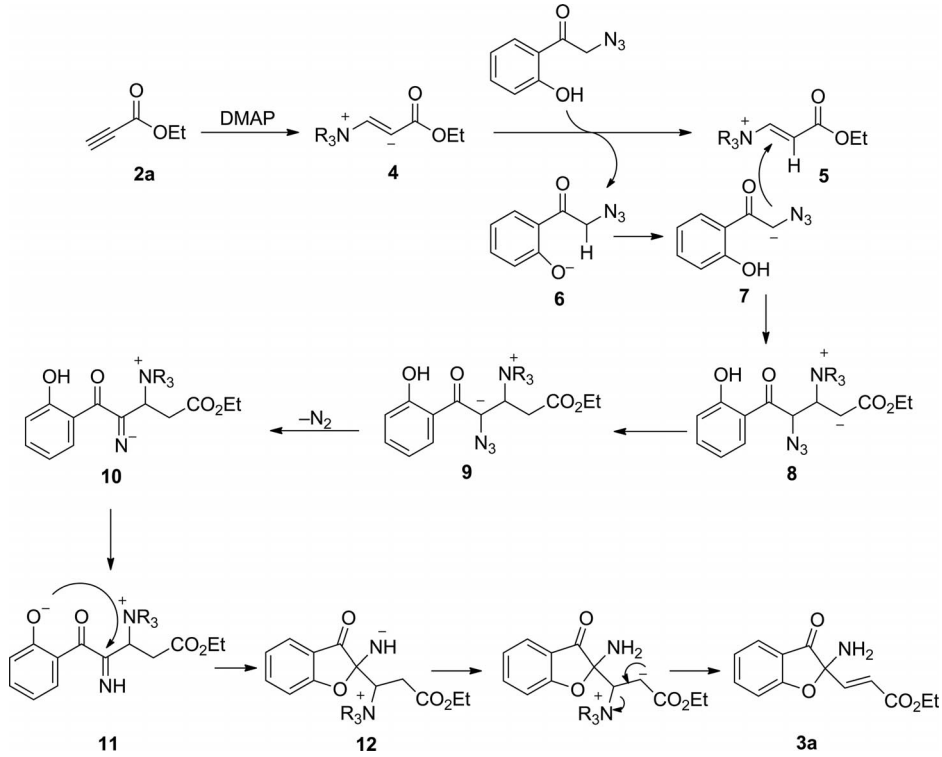
Table 3. DMAP-catalyzed cyclization reactions of electron-deficient alkynes with 2-azido-1-(2-hydroxyphenyl)ethanone.[a]



1a 2 3

Entry	Substrate **2**	Product **3**	Yield [%][b]	Entry	Substrate **2**	Product **3**	Yield [%][b]
1	 **2a**	 **3a**	63	5	 **2e**	 **3k**	69
2	 **2b**	 **3h**	60	6	 **2f**	 **3l**	48
3	 **2c**	 **3i**	67	7	 **2g**	 **3m**	54
4	 **2d**	 **3j**	70	8	 **2h**	 **3n**	41

[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.45 mmol), DMAP (0.06 mmol), CH_2Cl_2 (2.0 mL), r.t., in air, 2 h. [b] Isolated yield.



2a 4 5 6 7 8 9 10 11 12 3a

Scheme 3. Plausible mechanism.

on silica gel. However, dimethyl acetylenedicarboxylate failed to gave the corresponding product under the same reaction conditions.

On the basis of these experiments and previous investigations,[8,9] a mechanistic pathway for this unexpected DMAP-catalyzed cyclization reaction of 2-azido-1-(2-hydroxyphenyl)ethanones with terminal alkynoates was proposed (Scheme 3). The reaction could be triggered by the nucleophilic addition of DMAP to the electron-deficient carbon–carbon triple bond of **2a** to produce zwitterion **4**, which can then deprotonate 2-azido-1-(2-hydroxyphenyl)ethanone to generate intermediate **5** and **6**. Intermediate **6** could give enolate **7** through a proton-transfer step. Enolate **7** then undergoes Michael addition to **5** to give **8** with subsequent generation of **9** through another proton-transfer step. Intermediate **9** loses N_2 to be transformed into **10**,[10] which then affords **11** through yet another proton-transfer step. Intermediate **11** might then undergo intramolecular nucleophilic addition to form intermediate **12**, followed by proton transfer and elimination of DMAP to produce desired product **3a**.

Conclusions

In summary, we have developed an unexpected cyclization reaction of 2-azido-1-(2-hydroxyphenyl)ethanones with terminal alkynoates in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP, 20 mol-%). With the application of this synthetic method, a series of 2-aminobenzofuran-3(2*H*)-one derivatives were prepared in moderate yields under mild reaction conditions. A detailed investigation of the mechanism and the application of this reaction are currently in progress in our laboratory.

Experimental Section

General Procedure for the DMAP-Catalyzed Cyclization of 2-Azido-1-(2-hydroxyphenyl)ethanones with Terminal Alkynoates: To a solution of 2-azido-1-(2-hydroxyphenyl)ethanone (0.30 mmol) and the terminal alkynoate (0.45 mmol, 1.5 equiv.) in dry CH_2Cl_2 (2.0 mL) was added DMAP (0.06 mmol). The mixture was then stirred at room temperature for 2 h. Then, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 5:1) to give desired 2-aminobenzofuran-3(2*H*)-one product **3**.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, characterization data, and NMR spectra of all compounds.

Acknowledgments

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