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Benzofurans or Isochromenes via the Ring-Opening Cyclization of Cyclopropene Derivatives with Organolithiums

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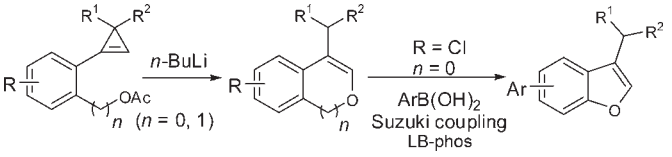
ABSTRACT



A new and efficient approach to benzocycles from cyclopropene derivatives is described. Deprotection by organolithiums and subsequent ring-opening cyclization of the related 2-cyclopropenyl phenyl or benzyl acetates generated benzofurans and isochromenes in one pot.

Heterocyclic structures are prevalent in many natural products, and many of them show interesting biological activities. Particularly, benzofuran and isochromene are two classes of important bicyclic heterocycles. For example, benzofuran derivatives display potent biological properties such as antifungal[1,2] and antibacterial[3] activities, etc. Isochromene derivatives were reported to be a series of D1 agonists,[4] alternethannoxins,[5] etc. Cyclopropene derivatives have attracted much attention in organic chemistry due to their ready availability and the unique reactivities arising from the highly strained structures.[6,7] A ring-opening reaction of cyclopropene derivatives offers an efficient pathway to carbo-[8] and heterocycles.[9] Previously, we have developed a novel I^-- or Br^--triggered ring-opening coupling reaction of cyclopropenes with organic halides leading to polyfunctionalized 1-alkenyl halides with high

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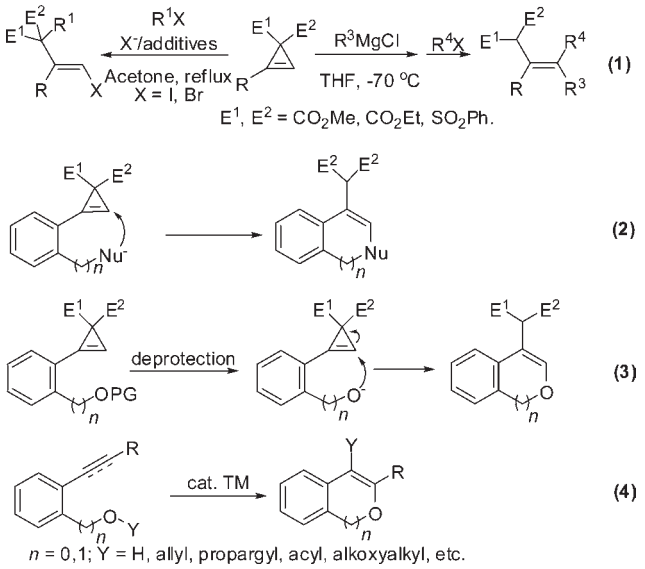
stereoselectivity (Scheme 1, eq 1, left).[10] Further investigation showed that Grignard reagents could also lead to ring-opening reactions of doubly activated cyclopropenes generating a series of 2-(1-alkenyl)malonate-type derivatives as single stereoisomers (Scheme 1, eq 1, right).[11] We reasoned that the intramolecular process of such ring-opening reactions by a heteroatom anion may lead to some useful functionalized heterocycles (Scheme 1, eq 2). Here we wish to present such an intramolecular oxygen-attacked ring-opening cyclization reaction leading to a series of benzofurans and isochromenes (Scheme 1, eq 3), which is different from the well-known general method for those heterocycles via the transition-metal-catalyzed annulation of *ortho*-alkynyl (or alkenyl) aryl or benzyl alcohols or their derivatives (Scheme 1, eq 4).[12] It should be noted that the existing methods leading to benzofurans with 3-alkoxycarbonylmethyl groups mainly use benzopyranones[13] or benzofuranones[14] as precursors; Inter- or intramolecular Heck-type reactions have also been reported.[15]

Scheme 1. Ring-Opening Reactions of Cyclopropene Derivatives and the Syntheses of Benzofurans



At first, we synthesized tetrahydro-2*H*-pyran- and acetoxy-protected phenol-substituted cyclopropenes, which we thought, after deprotection, would be transformed to benzofurans. However, we failed after trying several deprotection reagents such as K_2CO_3, $NaHCO_3$, LiOH, PPTS, etc.[16] Interestingly, when we tried to treat the protected compound dimethyl 2-(2-acetoxyphenyl)cycloprop-2-ene-1,1-dicarboxylate **1a** with 1.2 equiv of *n*-BuLi at −20 °C, benzofuran **2a** was formed directly together with a byproduct which could not be separated by flash chromatography (Table 1, entry 1). When the loading of *n*-BuLi was increased to 2.5 equiv, both the yield and purity were improved (Table 1, entry 2). Lowering the temperature gave higher purity but with lower yields (Table 1, entries 2−5). So we tried to further increase the equivalent of *n*-BuLi (Table 1, entries 6, 7, 10, 13, and 14); the result went better until the loading was up to 6.0 equiv, giving **2a** as a single product in good yield (Table 1, entry 13). Examination of solvent effect or other organolithium reagents failed to show better results (Table 1, entries 8−12). Thus, it requires 6.0 equiv of *n*-BuLi in THF at −60 °C to afford **2a** in good yield as the only product, indicating that a large excess of *n*-BuLi would guarantee good yield and selectivity. So we tried to add **1a** to *n*-BuLi slowly to ensure that the organolithium reagent was in excess during the whole addition process. This did work, as 4.0 equiv of *n*-BuLi were enough to give a competitive result, generating **2a** as the only product in 72% yield (Table 1, entry 15). The structure of the product **2a** was further confirmed by X-ray diffraction studies (Figure 1, left).[17]

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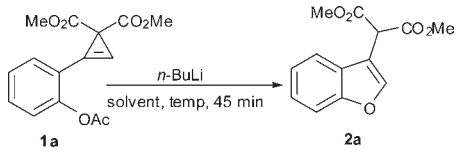
(17) Crystal data for **2a**: $C_{13}H_{12}O_5$, MW = 248.23, Monoclinic, space group *P*2(1), Final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0299, w*R*2 = 0.0825, *R* indices (all data) *R*1 = 0.0304, w*R*2 = 0.0834, a = 6.8563(2) Å, b = 8.0054(2) Å, c = 11.0535(3) Å, α = 90°, β = 102.3850°, γ = 90°, V = 592.58(3) Å^3, T = 123(2) K, Z = 2, reflections collected/unique: 14594/2217 (R_{int} = 0.0288), number of observations [$> 2\sigma(I)$] 1107, parameters: 163. CCDC 832369. For crystallographic data in CIF or other electronic format see Supporting Information.

Table 1. Optimization of Conditions[a]



entry	organolithium (equiv)	conditions solv/temp	isolated yield of **2a** (%)	purity of **2a**[b] (%)
1	*n*-BuLi (1.2)	THF/−20 °C	21	81
2	*n*-BuLi (2.5)	THF/−20 °C	38	87
3	*n*-BuLi (2.5)	THF/0 °C	28	84
4	*n*-BuLi (2.5)	THF/−60 °C	22	94
5	*n*-BuLi (2.5)	THF/−80 °C	20	100
6	*n*-BuLi (3.5)	THF/−60 °C	52	100
7	*n*-BuLi (5.0)	THF/−60 °C	60	100
8	*n*-BuLi (5.0)	CH_2Cl_2/−60 °C	19	66
9	*n*-BuLi (5.0)	Et_2O/−60 °C	11[c]	84
10	*n*-BuLi (5.5)	THF/−60 °C	67	100
11	MeLi (5.5)	THF/−60 °C	61	100
12	*t*-BuLi (5.5)	THF/−60 °C	39	100
13	*n*-BuLi (6.0)	THF/−60 °C	73	100
14	*n*-BuLi (9.0)	THF/−60 °C	73	100
15[d]	*n*-BuLi (4.0)	THF/−60 °C	72	100

[a] Procedures unless noted: the organolithium was added to a solution of **1a** in THF at the indicated temperature and quenched with saturated NH_4Cl after 45 min. [b] An unkown product was formed. The purity was determined based on ^1H NMR analysis on the integration of the methoxy groups. [c] NMR yield. [d] A solution of **1a** in THF was added dropwise to a solution of *n*-BuLi in 10 min and was quenched with saturated NH_4Cl after another 55 min.

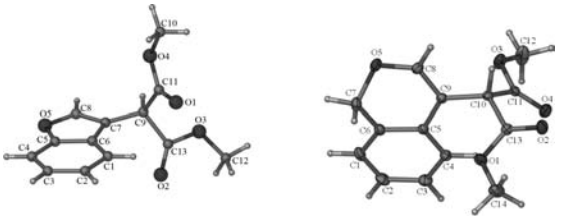
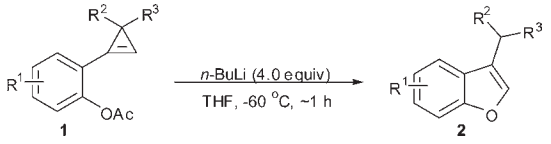


Figure 1. X-ray diffraction studies of **2a** (left) and **4k** (right).

With the optimized conditions, the generality of the reaction was examined (Table 2): Substituents such as methyl (entries 4 and 5), a chlorine atom (entries 6−9), or fluorine atom (entry 10) may be introduced to the phenyl group. For the cyclopropene moiety, in addition to the alkoxycarbonyl group (R^3), R^2 may be CO_2Me (entries 1, 4−6, 8, 10), Ph (entries 2 and 9), and SO_2Ph (entries 3 and 7). It should be noted that, in all the cases presented in Table 2, the reaction afforded **2** exclusively.

Table 2. Scope of *n*-BuLi Participated Ring-Opening Cyclization Reaction of 2-Acetoxyphenyl Cyclopropenes[a]

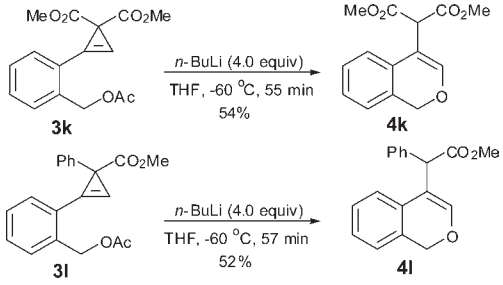


entry	R^1	R^2	R^3	isolated yield of **2** (%)
1	H	CO_2Me (**1a**)	CO_2Me	72 (**2a**)
2	H	Ph (**1b**)	CO_2Me	48 (**2b**)
3	H	SO_2Ph (**1c**)	CO_2Et	44 (**2c**)
4	5-Me	CO_2Me (**1d**)	CO_2Me	53 (**2d**)
5	4-Me	CO_2Me (**1e**)	CO_2Me	67 (**2e**)
6	5-Cl	CO_2Me (**1f**)	CO_2Me	67 (**2f**)
7	5-Cl	SO_2Ph (**1g**)	CO_2Et	59 (**2g**)
8	4-Cl	CO_2Me (**1h**)	CO_2Me	60 (**2h**)
9[b]	4-Cl	Ph (**1i**)	CO_2Me	64 (**2i**)
10	4-F	CO_2Me (**1j**)	CO_2Me	69 (**2j**)

[a] A solution of **1** (0.25 mol) in 3 mL of THF was added dropwise to a solution of *n*-BuLi (1.0 mol, 2.5 M in hexane, 0.4 mL) in 1 mL of THF at −60 °C around 10 min and quenched with saturated NH_4Cl after another 45 min. [b] An unidentified byproduct was isolated.

Furthermore, the reaction with 2-acetoxymethylphenyl cyclopropenes **3k** and **3l** also worked very well under the optimized conditions to give isochromenes **4k** and **4l** in moderate yield (Scheme 2). The structure of **4k** was also confirmed by X-ray diffraction studies (Figure 1, right).[18]

Scheme 2. Syntheses of Isochromenes

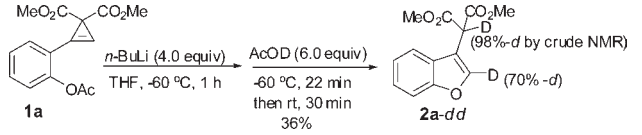


A deuterium experiment was conducted to probe the mechanism (Scheme 3): quenching the reaction of **1a** and 4.0 equiv of *n*-BuLi at −60 °C with AcOD afforded the double-deuterated product **2a**-*dd*. The sp^3 carbon was 98% deuterated as judged by ^1H NMR analysis of the crude product. This deuteration disappeared during chromatographic purification, which was caused by the smooth exchange of this acidic D-atom with the H-atom from the environment. The

(18) Crystal data for **4k**: $C_{14}H_{14}O_5$, MW = 262.25, Orthorhombic, space group *P*2(1)2(1)2(1), Final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0310, w*R*2 = 0.0751, R indices (all data) *R*1 = 0.0342, w*R*2 = 0.0775, *a* = 8.0662(3) Å, *b* = 8.5553(3) Å, *c* = 18.2403(6) Å, α = 90°, *β* = 90°, *γ* = 90°, *V* = 1258.74(8) Å^3, *T* = 173(2) K, *Z* = 4, reflections collected/unique: 6870/1126 (R_{int} = 0.0155), number of observations [$> 2\sigma(I)$] 2072, parameters: 172. CCDC 832370. For crystallographic data in CIF or other electronic format see Supporting Information.

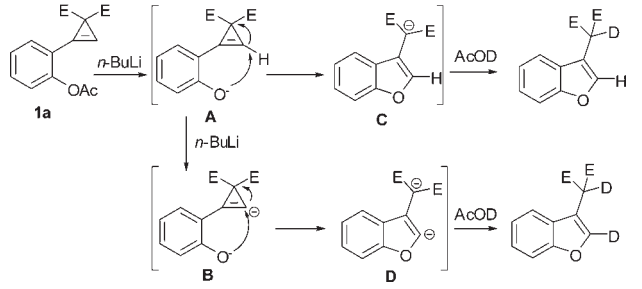
deutaration at the 2-position of the furan moiety was 70%. This result indicated that a dianion intermediate **D** was formed together with the intermediate **C** (Scheme 4).

Scheme 3. Deuterium Experiment



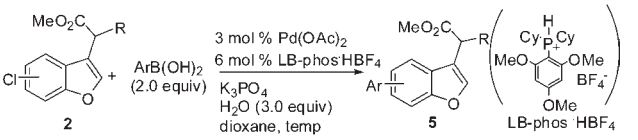
Accordingly, we propose the following mechanism (Scheme 4): the reaction of **1a** with *n*-BuLi forms the intermediate **A**. The oxygen anion in **A** may attack the cyclopropene moiety generating the benzofuranyl anion **C**. Alternatively, an excess of *n*-BuLi may further deprotonate the olefinic proton[11] to generate dianion **B**, which may also undergo ring-opening cyclization forming the benzofuranyl dianion **D**. The reaction of intermediates **C** and **D** with AcOD would form **2a**-*dd*.

Scheme 4. A Plausible Mechanism



Further studies showed that the benzofurans **2** containing C−Cl bonds in the aryl group could be applied to our previously reported Suzuki coupling reaction[19] with LB-phos as the ligand (Table 3). A phenyl (entries 1 and 4), naphthyl (entries 2 and 6), and *p*-methoxyphenyl group (entries 2 and 5) could all be introduced into the products, generating aryl substituted benzofurans **5** in good to excellent yields.

Table 3. Suzuki Coupling Reactions of the Benzofurans Containing C−Cl Bonds



entry	**2**	K_3PO_4 (equiv)/temp (°C)/ time (h)	Ar	isolated yield of **5** (%)
1	**2f**	2.0/80/6	Ph	84 (**5fa**)
2	**2f**	2.0/80/10	*p*-$MeOC_6H_4$	91 (**5fb**)
3	**2f**	2.0/80/6	2-naphthyl	75 (**5 fc**)
4	**2i**	3.5/110/8	Ph	86 (**5ia**)
5	**2i**	3.5/110/5	*p*-$MeOC_6H_4$	87 (**5ib**)
6	**2i**	3.5/110/5	2-naphthyl	84 (**5ic**)

In conclusion, we have developed an efficient method for the synthesis of benzofuran and isochromene derivatives with moderate to good yields and an excellent selectivity from the treatment of 2-acetyl or 2-acetoxymethyl cyclopropenes with *n*-BuLi. The benzofurans containing C−Cl bonds could be further transformed to aryl substituted compounds by Suzuki coupling reactions. The reaction will be useful in organic synthesis and medicinal chemistry. Further study in this area such as preparing other types of useful heterocycles is being pursued in this laboratory.

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Supporting Information Available. Analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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