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Synthetic Approach to Benzocyclobutenones Using Visible Light and a Phosphonate Auxiliary

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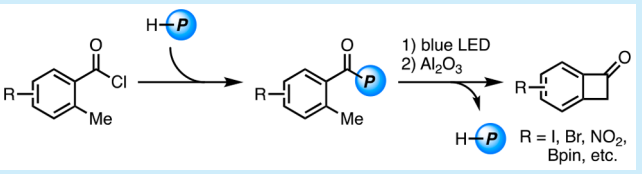
Supporting Information

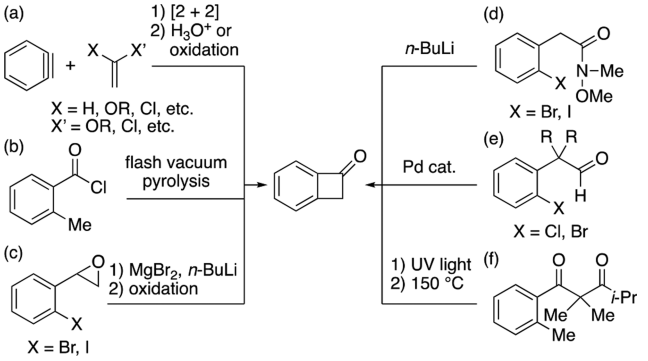
ABSTRACT: Reported herein is a two-step procedure to synthesize benzocyclobutenones from (*o*-alkylbenzoyl)-phosphonates. It consists of a visible-light-driven cyclization reaction forming phosphonate-substituted benzocyclobutenols and subsequent elimination reaction of the H-phosphonate, which assumes a key role as the recyclable auxiliary. A wide variety of functionalized benzocyclobutenones, which include those difficult to synthesize by conventional methods, are efficiently synthesized.



Benzocyclobutenone and its derivatives exhibit unique reactivities to open its four-membered ring in various modes. The ring-opening reactivities have found a wide range of applications in organic synthesis,[1] thermoset polymers,[2] and pharmaceuticals.[3] Recently, exploitation of transition-metal catalysis has unveiled an unconventional mode of ring opening,[4] which offers a new synthetic route to benzo-fused cyclic skeletons.[5] This has spurred a renewed demand to develop a more convenient method to synthesize benzocyclobutenones with a wide functional group tolerance starting from easily accessible materials.

The most frequently utilized synthetic method is a [2 + 2] cycloaddition reaction of arynes with enol derivatives followed by hydrolysis or oxidation (Scheme 1, method a).[6] This

Scheme 1. Conventional Synthesis of Benzocyclobutenones



method is powerful, particularly for the synthesis of benzocyclobutenones having an oxy substituent at the 6-position, which dictates the regioselectivity of the [2 + 2] cycloaddition.[6c−e,g,j] In the cases of other substituted benzocyclobutenones, however, it is often difficult to control the regioselectivity of the [2 + 2] cycloaddition reaction. Flash vacuum pyrolysis of aroyl chlorides (method b)[7] offers an alternative access to benzocyclobutenones. It requires rigorous heating (e.g., at 630 °C), which diminishes its practicality. The four-membered ring can be constructed by intramolecular nucleophilic addition of aryllithium generated from (*o*-halophenyl)epoxides (method c)[8] and (*o*-halophenyl)acetamides (method d)[9] and by a palladium-catalyzed cyclization reaction of (*o*-halophenyl)acetaldehydes (method e).[10] UV light induced cyclization of *o*-alkylphenyl ketones followed by a thermally induced retro-aldol reaction (method f)[11] merits special attention because it dispenses with the use of organolithium reagents. However, the photocyclization suffers from low yields; the yields of 8 examples out of the 10 listed in the table[11b] are less than 50%.

Here, we report a new, two-step procedure to synthesize benzocyclobutenones through visible light induced cyclization of (*o*-alkylbenzoyl)phosphonates that we have recently developed.[12] An H-phosphonate assumes a key role as the recyclable auxiliary; the H-phosphonate is readily introduced onto aroyl chlorides, facilitates visible light induced construction of the four-membered ring skeletons, and is removed for regeneration of a carbonyl group, recovered, and reused. Of note is the broad functional group tolerance; the present method allows a diverse array of functional groups including those incompatible with the conventional methods mentioned above.

o-Alkylphenyl ketones undergo an endergonic cyclization reaction upon irradiation with UV light to give benzocyclobutenols.[13] Although the reaction offers a concise way to construct a four-membered ring, successful and reproducible examples are significantly limited. We recently reported that the photoinduced cyclization of (*o*-alkylbenzoyl)phosphonates **1** forming phosphonate-substituted benzocyclobutenols **4** is far more efficient and reproducible than that of ordinary ketones (Scheme 2).[12] The origin of the efficiency is mainly ascribed to the electron-accepting nature of the phosphonate substituent.

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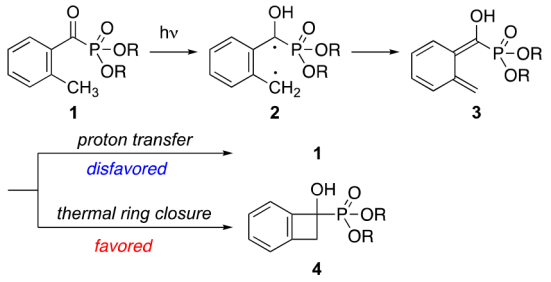
Scheme 2. Photoinduced Cyclization of 1

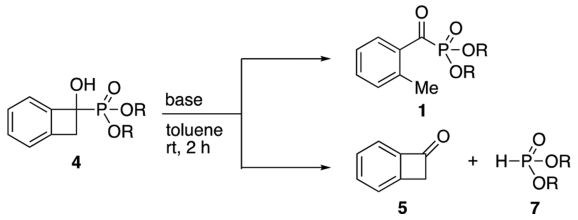


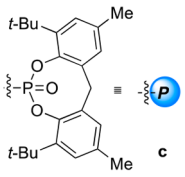
The key intermediate to form a four-membered ring by 4π-electron cyclization is *o*-quinodimethane **3**.[14] The electron-accepting phosphonate substituent lowers the activation energy of the 4π-electron cyclization to accelerate it.[15] The electron-accepting nature also retards the competing nonproductive proton-transfer process by lowering the basicity of the diene moiety. As a result, the photoinduced cyclization of (*o*-alkylbenzoyl)phosphonate **1** becomes a highly efficient process to produce phosphonate-substituted benzocyclobutenols **4** in excellent yield.

Addition of H-phosphonates onto carbonyl compounds forming α-hydroxyalkylphosphonates is a reversible process.[16] We envisioned that the photocyclized product **4** would undergo elimination of an H-phosphonate to regenerate a carbonyl group upon treatment with a base, acting as the precursor of benzocyclobutenone. However, **4** can follow another pathway opening the four-membered ring, which is driven by release of its ring strain.[17] Thus, we examined an elimination reaction of an H-phosphonate from phosphonate-substituted benzocyclobutenols **4**, which were prepared by photoinduced cyclization of (*o*-alkylbenzoyl)phosphonates (Table 1).[12] When dimethyl phosphonate derivative **4a** was treated with triethylamine in toluene at 70 °C for 2 h, a base-induced ring-opening reaction selectively took place to afford **1a** in 13% yield, and 75% of **4a** remained (entry 1). Benzocyclobutenone **5** was not formed at all. Treatment of **4a** with inorganic bases such as NaOH, K_2CO_3, and K_3PO_4 at room temperature afforded a complex mixture (entries 2−4). On the other hand, diphenyl phosphonates **4b** successfully underwent elimination of the diphenyl phosphonate moiety upon treatment with Et_3N or K_3PO_4 to afford **5** in 85% and 89% yield, respectively (entries 5 and 6). Preference for the elimination of diphenyl H-phosphonate over the opening of the four-membered ring can be ascribed to the superior acidity of the diphenyl H-phosphonate (calculated pK_a = 9.0 in DMSO),[18] which is far stronger than dimethyl H-phosphonate (calculated pK_a = 18.4 in DMSO).[18] The higher acidity leads to a better leaving ability. Comparable results were obtained with cyclic diaryl phosphonate **4c** to produce benzocyclobutenone **5** in good yields (84−88%, entries 7−9).

Thus, the diaryl phosphonates **4b** and **4c** turned out to be suitable precursory intermediates, leading to benzocyclobutenone **5**. The sterically bulkier phosphonate **4c** was our choice for further examination because of the following advantages. First, the acylphosphonate **1c** was readily synthesized by a base-induced addition reaction of H-phosphonate **7c**[19] to *o*-toluoyl chloride **6** (Scheme 3). On the other hand, the addition of diphenyl H-phosphonate **7b** to **6** afforded a mixture of the acylphosphonate **1b** and bis-phosphonate **8**, which resulted from further addition of the diphenyl H-phosphonate to **1b** followed by a phospha-Brook-type rearrangement.[20] Second,

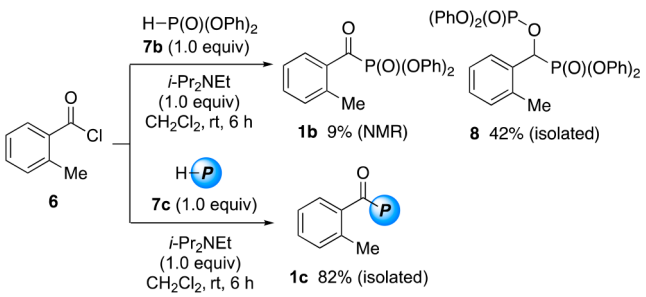
Table 1. Elimination of H-Phosphonate from 4[a]



entry	-P(O)(OR)$_2$	base	results (yield, %)[b]
1[c]	-P(O)(OMe)$_2$ **a**	Et_3N	**1a** (13)
2		NaOH	complex mixture
3		K_2CO_3	complex mixture
4		K_3PO_4	complex mixture
5	-P(O)(OPh)$_2$ **b**	Et_3N	**5** (85)
6		K_3PO_4	**5** (89)
7	 **c**	Et_3N	**5** (88)
8		K_3PO_4	**5** (84)
9[c]		Al_2O_3 (basic)	**5** (87)

[a]Reaction conditions: **4** (0.20 mmol), base (0.20 mmol), toluene, 1 mL, rt. [b]Isolated yields. [c]Basic Al_2O_3 (200 mg).

Scheme 3. Preparation of 1b and 1c



the carbonyl moiety of **1c** was sterically protected against hydrolysis and stable enough to be purified by column chromatography on silica gel. In contrast, **1b** was susceptible to hydrolysis and difficult to isolate by column chromatography on silica gel. Third, it was high-yielding to recover and easy to reuse the H-phosphonate **7c** after its elimination, whereas diphenyl phosphonate **7b** was difficult to recover after the elimination reaction due to its lability.

We next performed a sequential procedure consisting of the photoinduced cyclization and the following elimination of the H-phosphonate in one pot (Scheme 4). Photoirradiation of **1c** in toluene with a blue LED lamp (peak at 425 nm)[21] induced cyclization and, after 8 h, yielded benzocyclobutenol **4c** quantitatively. Then, basic alumina was directly added to the toluene solution containing **4c**, and the reaction mixture was stirred at 30 °C for 3 h to complete elimination of the

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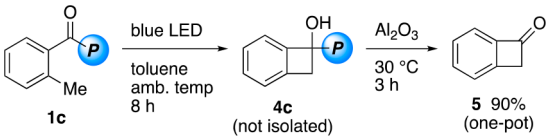
Scheme 4. Synthesis of Benzocyclobutenone 5



phosphonate moiety. Purification by chromatography on silica gel gave benzocyclobutenone **5** in 90% isolated yield. H-Phosphonate **7c** was recovered in 84% isolated yield at the same time. The recovered **7c** could be used for preparation of the acylphosphonate **1c** from *o*-toluoyl chloride **6** without any problem.

A wide variety of substituted benzocyclobutenones were successfully synthesized (Figure 1). The synthesis of methylated benzocyclobutenones showcases its synthetic advantage. 3-Methylbenzocyclobutenone **9** was selectively produced in 88% isolated yield from (2,3-dimethylbenzoyl)phosphonate. The methyl group ortho to the carbonyl group selectively joined the cyclization with the *m*-methyl group remaining intact. On the other hand, it has been reported that the conventional [2 + 2] cycloaddition pathway from 2-bromotoluene and 1,1-dimethoxyethene furnishes a 3:1 mixture of 6-methylbenzocyclobutenone (major) and 3-methyl-substituted one (minor) in 38% combined yield.[6c] 4-Methylbenzocyclobutenone **10** and 5-methylbenzocyclobutenone **11** were also selectively synthesized, both in 94% yields from the corresponding (dimethylbenzoyl)phosphonates, respectively.[22] Another synthetic advantage is shown in the synthesis of halo-substituted benzocyclobutenones **12**–**15**. 4-Bromobenzocyclobutenone **12** was synthesized in 88% isolated yield. In addition, fluoro-, chloro-, and even iodo-substituted benzocyclobutenones **13**–**15** were all successfully synthesized. The halo-substituted benzocyclobutenones thus prepared are valuable synthetic intermediates because a wide variety of derivatizations would be feasible based on the halogen substituents. On the other hand, it has been reported that [2 + 2] cycloaddition of an aryne derived from 1,4-dibromobenzene and sodium amide with a 1,1-dialkoxyalkene affords a 1:4 mixture of 4- and 5-bromobenzocyclobutenones in 21% combined yield.[6f] Functional groups that were sensitive toward strong bases such as ester (**18**, **21**, and **26**), secondary carbamate (**19**), nitro (**20**), and cyano (**22**) groups survived under the present reaction conditions. Boryl (**23**), alkynyl (**25**), and acrylate (**26**) groups, which would serve for further derivatization, also remained intact. Of particular note is the tolerance of the acrylate functional group. Although the *o*-quinodimethane intermediate derived from *o*-alkylphenyl ketones undergoes a [4 + 2] cycloaddition reaction with acrylate to produce a six-membered product,[23] the intermediate generated from acylphosphonate underwent 4π-electrocyclization selectively without touching the acrylate functional group. The visible light induced cyclization of the substrates having a longer alkyl chain at the ortho position ($R^2 \neq H$) was sluggish under the standard reaction conditions.[24] However, the reaction was accelerated by adding thioxanthone.[25] α-Substituted benzocyclobutenones **27**–**30** were synthesized in yields ranging from 59% to 79% by the modified procedure using thioxanthone.[26]

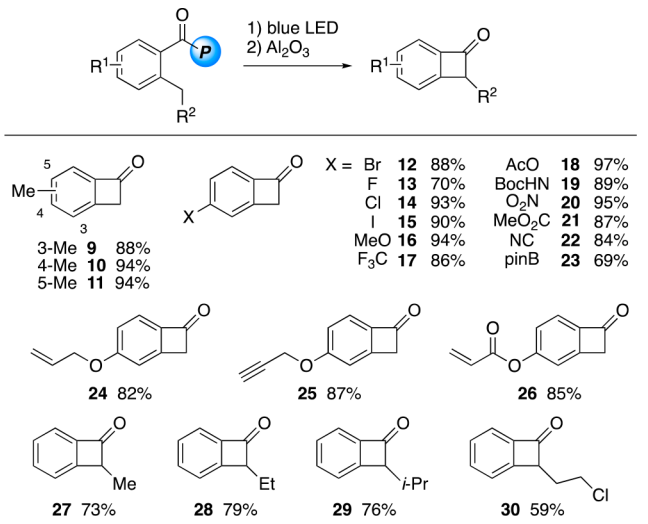
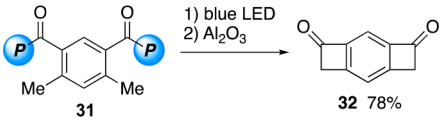


Figure 1. Substituted benzocyclobutenones synthesized. The reaction conditions for **9**–**26** were identical to those shown in Scheme 4. Isolated yields. For **27**–**30**, photoirradiation was performed in the presence of thioxanthone (0.75 mmol, 0.75 equiv) for 16 h.

Although benzenes fused with two cyclobutenone rings are intriguing synthetic targets,[27] synthesis of **32** has never been reported in the literature. We applied the present method to synthesize **32** selectively. The bisphosphonate **31** was prepared from commercially available 4,6-dimethylisophthalic acid and **7c**. Irradiation of **31** with a blue LED lamp successfully induced double photocyclization. Subsequent treatment with basic Al_2O_3 gave **32** in 78% yield (Scheme 5).

Scheme 5. Synthesis of 32



In conclusion, we have developed a new, convenient way to synthesize benzocyclobutenones through a visible light driven cyclization reaction of (*o*-alkylbenzoyl)phosphonates and subsequent elimination of the H-phosphonate. The starting substrates, (*o*-alkylbenzoyl)phosphonates, are readily obtained from aroyl chlorides and H-phosphonates. The H-phosphonate assumes a key role as the auxiliary that facilitates construction of the four-membered ring and, afterward, is removed for regeneration of a carbonyl group, recovered, and reused. The mild reaction conditions allow a diverse array of functional groups that conventional methods hardly tolerate. A benzene fused with two cyclobutenone rings was also synthesized in two steps from a commercially available dicarboxylic acid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00160.

Experimental and computational details and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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(22) Our attempt to synthesize (2,6-dimethylbenzoyl)phosphonate failed due to the steric congestion around the carbonyl carbon.

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