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Concise synthesis of functionalized benzocyclobutenones

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ABSTRACT

A concise approach to access functionalized benzocyclobutenones from 3-halophenol derivatives is described. This modified synthesis employs a [2+2] cycloaddition between benzynes generated from dehydrohalogenation of aryl halides using LiTMP and acetaldehyde enolate generated from *n*-BuLi and THF, followed by oxidation of the benzocyclobutenol intermediates to provide benzocyclobutenones. The [2+2] reaction can be run on a 10-g scale with an increased yield. A number of functional groups including alkenes and alkynes are tolerated. Coupling of benzynes with ketene silyl acetals to give 8-substituted benzocyclobutenones is also demonstrated.

1. Introduction

Benzocyclobutenones are a unique class of compounds with rich reactivity, thus often serve as value building blocks for organic synthesis.[1] Ring-opening of benzocyclobutenones is known to be triggered by heat[2] or nucleophiles,[3] and also known to be facilitated by transition metals.[4] Combining further reactions of metal-carbon bonds, transition metal-mediated C–C bond cleavage of benzocyclobutenones can lead to new transformations for preparing novel structures.[5] For example, recently we have developed intramolecular couplings between benzocyclobutenones and olefins to give fused rings and spirocycles, respectively (Fig. 1).[6] A divergent approach has also been developed to access fused β-naphthols and indenes via direct and decarbonylative insertions of alkynes into benzocyclobutenones.[7] Structural motifs generated from these methodologies have been found in a number of natural products.

While these methods are potentially useful and attractive for synthesizing bioactive molecules, one key challenge is that the benzocyclobutenone substrates containing alkene or alkyne functional groups usually required more than six steps to prepare (Fig. 2). For example, we previously employed a slightly modified procedure first developed by Suzuki to access the key intermediate, 3-hydroxybenzocyclobutenone (**3**).[8] Although reliable and scalable, this synthetic route takes about six steps from resorcinol. In addition, while reagent **5** is commercially available, it is expensive and generally prepared in one step from the corresponding ester.[9] The substrates (**1** and **2**) employed in our methodologies are generally prepared with an additional step from **3** via direct alkylation or Mitsunobu reaction, thus requiring 7–8 steps total, which significantly diminished the practicality of these methodologies. Hence, to address the abovementioned challenge, a more efficient and practical synthesis of functionalized benzocyclobutenones is needed. In this article, we describe our development of a concise approach to access the substituted benzocyclobutenones, including those with alkene and alkyne moieties.

The synthesis of benzocyclobutenones is non-trial and has been an ongoing research. While a number of innovative approaches are available,[10] [2+2] cycloaddition between an aryne and a ketene equivalent still represents the most popular way to prepare benzocyclobutenones.[11] In 1982, Bisacchi and Stevens developed the first [2+2] cycloaddition to prepare benzocyclobutenones, in which the benzyne was generated from dehydrobromination of aryl bromides with sodium amide, and 1,1-dimethoxyethylene was used as the ketene equivalent.[12] While this method is widely useful, heating (75–80 °C) is generally required and preparation of 1,1-dimethoxyethylene is not convenient.[13] Consequently, Santelli, Ibrahim-Ouali and co-workers later found 1,1-dimethoxyethylene can be substituted with commercially available 2-methylene-1,3-dioxepane as the [2+2] partner albeit giving lower yields.[14] Due to the harsh conditions to generate benzynes from sodium amide, Suzuki and co-workers developed a mild procedure to synthesize benzocyclobutenones through generating the corresponding arynes via halogen-metal exchange followed by elimination of an *ortho*-triflate (vide supra, Fig. 2).[8] Another advantage of Suzuki's method is using ketene silyl acetals as the coupling partner because

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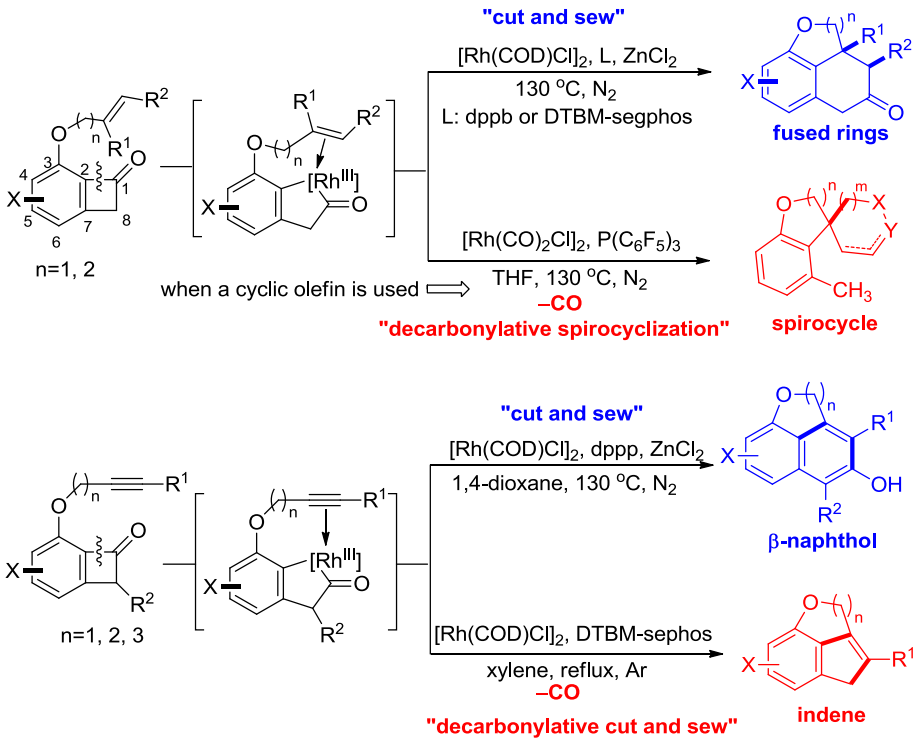

Fig. 1. Rh-catalyzed coupling reactions between benzocyclobutenones and alkenes/alkynes.

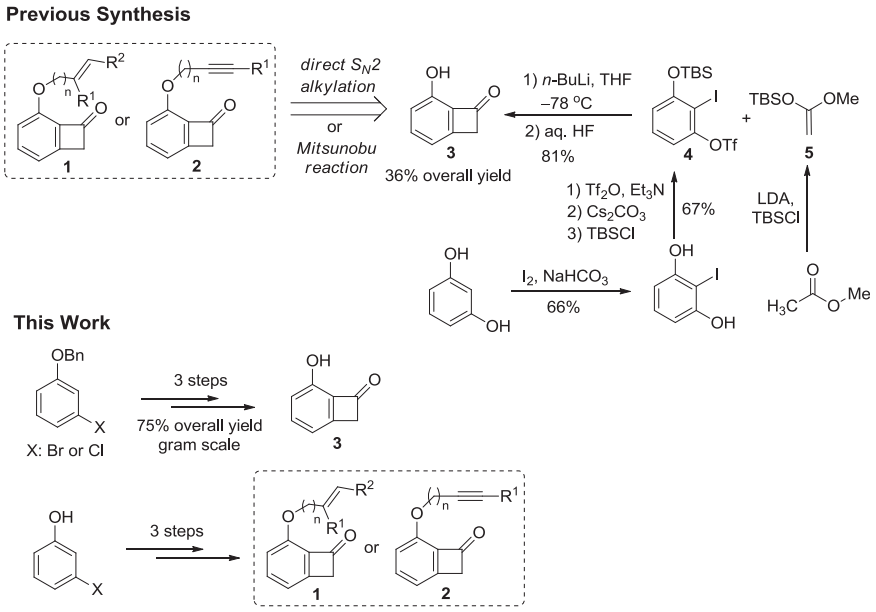

Fig. 2. Synthesis of benzocyclobutenone substrates with alkene and alkyne moieties.

they are more readily available and easier to handle than 1,1-dialkoxyethylene. Nevertheless, both *ortho*-iodo triflates and ketene silyl acetals require additional steps to prepare. Therefore, more efficient synthesis of benzocyclobutenones is still highly sought after.

Our research was inspired by an anthracene synthesis first developed by Fleming in 1975, which involved a benzocyclobutenoxide intermediate from a [2+2] addition between benzynes [prepared from dehydrobromination of aryl bromides with LiTMP (*N*-lithio-2,2,6,6-tetramethylpiperidine)], and acetaldehyde enolates (in situ generated from THF with *n*-BuLi).[15] Olofson and co-workers later found the benzocyclobutenoxide intermediates could be trapped by various electrophiles providing synthetically useful structural motifs.[16] In contrast, utilizing this [2+2] reaction to prepare benzocyclobutenols has been much less developed likely due to the sensitivity of the benzocyclobutenoxide intermediates that can undergo reversible ring opening to give the corresponding highly reactive *o*-quinodimethanes. The work by Durst[17] and more recently by Kraus[18] demonstrated the feasibility to capture the benzocyclobutenol products using Fleming's approach, although few functional groups except methoxy groups have been examined for compatibility. We were stimulated by the simplicity of this