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# Efficient synthesis of benzocyclohexanes via intramolecular Friedel–Crafts reaction of halogen free 6-acetoxy-4-alkenyl arenes

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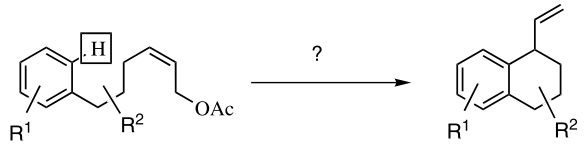
**Abstract**—Benzocyclohexane derivatives were prepared highly stereoselectively by the cyclic Friedel–Crafts reaction of 6-acetoxy-4-alkenyl arenes in moderate to excellent yields in TFA/HOAc (3:1). It was observed that the rate of the cyclization as well as the yields of products depend largely on the substituents of the allylic acetate moiety. 

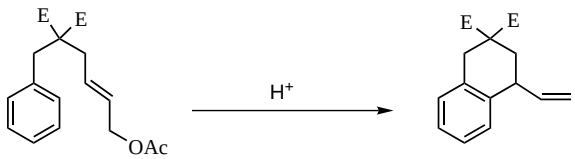
Benzocycles are commonly observed structural units in many natural and unnatural products with biological potential.[1] These compounds are usually prepared by the cyclic radical addition, carbopalladation (including acylpalladation) of the corresponding 2-alkenyl aryl halides or their corresponding alkynic analogues.[2–5] In this paper, we wish to report our recent results of the acid-mediated highly stereoselective cyclization of halogen-free 6-acetoxy-4-alkenyl arenes for the efficient synthesis of benzocyclohexanes (Scheme 1).

Since its discovery in 1877, the Friedel–Crafts reaction has become one of the most commonly used methodologies for alkylation or acylation of arenes, in which a carbon–carbon single bond is formed neatly from non-halogen-containing arenes.[6] Thus, it is an environmentally benign process for the synthesis of substituted arenes. However, the intramolecular Friedel–Crafts reactions of hydroxyalkylbenzenes providing routes to benzocyclic compounds often encounter the problem of low selectivity.[7] During our study of developing new methodologies employing the chemistry of 6-acetoxy-4-hexenyl-2, 2-bis(methoxycarbonyl)benzene **1a** for the efficient construction of benzocycles, we observed an efficient intramolecular Friedel–Crafts reaction of 6-acetoxy-4-alkenyl arenes (Scheme 2).




**Scheme 1.**

Originally, the reaction of **1a** (Scheme 2) was carried out in trifluoroacetic acid under $Pd(OAc)_2$ catalysis; however, a control experiment showed that $Pd(OAc)_2$ was not required in this transformation (entry 1, Table 1). The reaction of **1a** in pure TFA afforded **2a** in 48% yield (entry 2, Table 1). The reaction did not proceed in AcOH (entry 3, Table 1). With the mixture of TFA and another solvent, such as $CHCl_3$, cyclohexane, 1,2-dichloroethane or toluene, the yields were low (entries 4–7, Table 1). Finally, it was observed that the yield of the reaction was improved to 66% by using TFA–AcOH (3:1) as the solvent (entry 13, Table 1). With a higher or lower ratio of TFA/HOAc, the reaction afforded **2a** in low yields or did not occur (entries 8–12, Table 1).




**1a**
E = $CO_2Me$

**2a**

**Scheme 2.**

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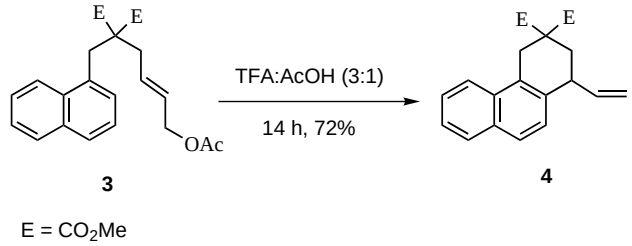
**Table 1.** Intramolecular Friedel–Crafts reaction of **1a**[a]

| Entry | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $CF_3COOH$[b] | 70 | 12 | 46 |
| 2 | $CF_3COOH$ | 70 | 12 | 48 |
| 3 | AcOH | Reflux | 24 | 0 |
| 4 | $CF_3COOH$:$CHCl_3$ (3:1) | 70 | 18 | 30 |
| 5 | $CF_3COOH$:cyclohexane (3:1) | 70 | 16 | 35 |
| 6 | $CF_3COOH$:$ClCH_2CH_2Cl$ (3:1) | 70 | 18 | 34 |
| 7 | $CF_3COOH$:toluene (3:1) | 70 | 24 | 27 |
| 8 | $CF_3COOH$:AcOH (1:1) | 50 | 12 | 0 |
| 9 | $CF_3COOH$:AcOH (1:2) | 70 | 8.5 | Trace |
| 10 | $CF_3COOH$:AcOH (2:1) | 70 | 14 | 46 |
| 11 | $CF_3COOH$:AcOH (1:1) | 70 | 14 | 42 |
| 12 | $CF_3COOH$:AcOH (4:1) | 70 | 14 | 52 |
| 13 | $CF_3COOH$:AcOH (3:1) | 70 | 14 | 66 |

[a] The reaction was carried out using **1a** (0.5 mmol) in solvent (1.0 mL).
[b] 5 mol% of $Pd(OAc)_2$ was used.

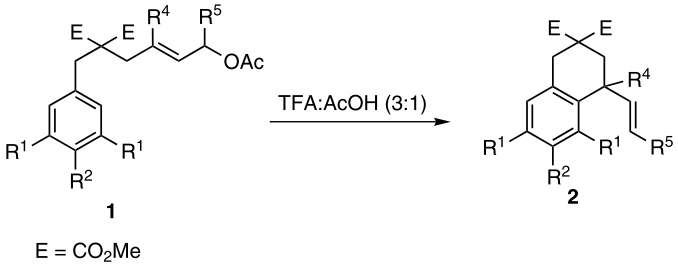
Using TFA/AcOH (3:1) as the standard reaction medium, the reaction of **1** with different substituents on the aryl and the allylic moieties was studied (Table 2). It should be noted that (1) substitution on the aryl part can be introduced (entries 1–4, Table 2); (2) when substitution on the allylic acetate part was introduced ($R^4$ or $R^5$), the yields of **2** were improved dramatically (entries 5–9, Table 2); (3) introduction of $R^4$ and $R^5$ also increased the rate of the cyclization reaction (compare entries 1–4 with 5–9, Table 2). With the introduction of $R^5$, the reaction occurred even at rt (entries 7–9, Table 2); (4) tertiary carbon centers can also be formed in high yields with this cyclic Friedel–Crafts allylation (entries 5 and 6, Table 2).

Tricyclic compound **4** can be prepared in 72% yield under the same reaction conditions starting from 1-(6′-acetoxy-2′,2′-bis(methoxycarbonyl)-4′-hexenyl)naphthalene **3** (Scheme 3).




**Scheme 3.**

**Table 2.** Intramolecular Friedel–Crafts reactions of allylic acetates **1**[a]




| Entry | **1** | | | | Temperature (°C) | Time (h) | Yield of **2** (%) |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^4$ | $R^5$ | | | |
| 1 | H | H | H | H | 70 | 14 | 66 (**2a**) |
| 2 | H | $CH_3$ | H | H | 70 | 14 | 66 (**2b**) |
| 3 | H | $CH_3O$ | H | H | 70 | 14 | 66 (**2c**) |
| 4 | $CH_3$ | H | H | H | 70 | 14 | 68 (**2d**) |
| 5 | H | H | $CH_3$ | H | 70 | 3 | 84 (**2e**) |
| 6 | H | $CH_3$ | $CH_3$ | H | 70 | 4 | 85 (**2f**) |
| 7 | H | H | H | $C_4H_9$ | rt | 1 | 85 (**2g**)[b] |
| 8 | H | $CH_3$ | H | $C_4H_9$ | rt | 1.5 | 99 (**2h**)[b] |
| 9 | H | $CH_3$ | H | Ph | rt | 0.5 | 94 (**2i**)[b] |

[a] The reaction was carried out using **1** (0.5 mmol) in solvent (1.0 mL).
[b] The configuration of the C=C bond was determined to be *E* from the coupling constants of the olefinic protons.

The reaction was applied to the synthesis of *N*-containing bicyclic compound **6** (Scheme 4). Like the results shown in Table 2, due to the presence of the $C_4H_9$ chain in the allylic moiety, the reaction of **5** occurred smoothly at rt to afford **6** in 92% yield. The configuration of the C=C bond in **6** was determined to be exclusively *E* ($J = 15.3$ Hz).

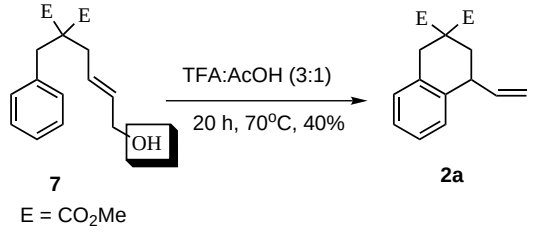
The reaction is believed to proceed via the generation of an allylic cation from the allylic acetate moiety followed by an intramolecular electrophilic substitution reaction. To the best of our knowledge, this is the first example of using an allylic acetate as the intramolecular alkylation reagent in Friedel–Crafts reactions.[8] As a comparison, the corresponding reaction of the alcoholic analogue **7** afforded **2a** in only 40% yield (Scheme 5).

This reaction can also be applied to the highly stereoselective synthesis of tricyclic skeleton as exemplified by the cyclization of *cis*-**8** (Scheme 6). The ring junction was established as *cis*-fused by an X-ray diffraction study of **9**.[9]

In conclusion, we have developed an efficient methodology for the synthesis of benzocyclohexane derivatives, the yields and rates of the cyclization depending largely on the substituents in the substrates. Due to the advantages of simple operation, readily available starting materials, good to high yields and excellent stereoselectivity, this reaction will show its utility in organic synthesis. Further studies on the scope of this reaction and its synthetic application are being carried out in our laboratory.


**5** **6**

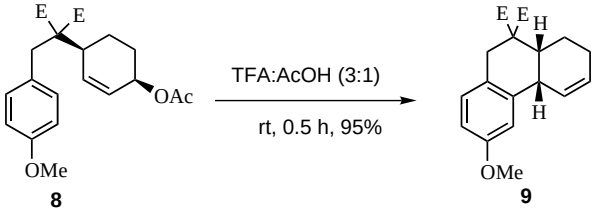
**Scheme 4.**




**7** **2a**

E = $CO_2Me$

**Scheme 5.**




**8** **9**

E = $CO_2Me$

**Scheme 6.**

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