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## Synthesis of 1-Azulenyl Ketones by Brønsted Acid Mediated Hydration of 1-Azulenylalkynes

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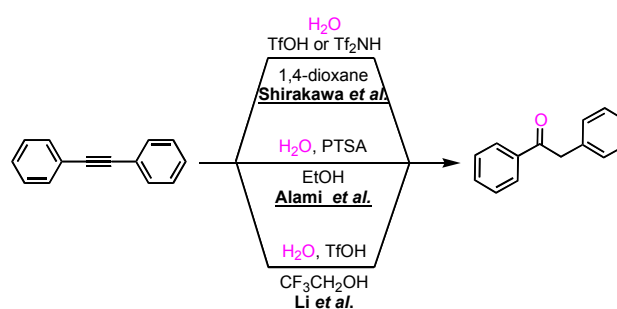
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Preparation of 1-azulenyl ketones was achieved by metal-free hydration of 1-azulenylalkynes using trifluoroacetic acid as a Brønsted acid in good to excellent yields. The reaction was accomplished at relatively low temperature with complete regioselectivity and compatibility of several functional groups.

Hydration of alkynes is one of the general methodologies for the preparation of carbonyl compounds. Previously, hydration of alkynes was performed using mercury catalyst with sulfuric acid to produce the carbonyl compounds in industrial chemistry, which is known as Kutscheroff procedure,<sup>1</sup> but the waste mercury caused a serious pollution.<sup>2</sup> For this reason, transition-metal catalyzed hydration of alkynes was developed for replacing the Kutscheroff procedure.<sup>3</sup> However, there are few reports for the metal-free hydration of alkynes in the literature (Scheme 1).

In 2000, Shirakawa *et al.* reported the hydration of alkynes catalyzed by trifluoromethanesulfonic acid (TfOH) or trifluoromethanesulfonimide (Tf<sub>2</sub>NH) to give the corresponding carbonyl products in good to excellent yields.<sup>4</sup> Alami and co-workers also demonstrated the hydration of alkynes in the presence of *p*-toluenesulfonic acid (PTSA) to afford the carbonyl products in good to excellent yields.<sup>5</sup> More recently, Li *et al.* reported the more efficient hydration protocol of alkynes using TfOH in trifluoroethanol.<sup>6</sup> In the study, they also demonstrated relatively weak acids, such as acetic acid (CH<sub>3</sub>CO<sub>2</sub>H) and trifluoroacetic acid (CF<sub>3</sub>CO<sub>2</sub>H), were not effective toward the hydration, even though the reaction took place in the fluorine-containing solvent. Although these methods should undoubtedly contribute to progress in the metal-free hydration reaction, strong acid catalysts, i.e., sulfonic acid derivatives, were essential to achieve the efficient hydration reaction.



**Scheme 1** Brønsted acid catalyzed hydration of diphenylacetylene.

Azulene has attracted the interest of many research groups owing to its unusual properties as well as its beautiful blue color. Since azulene derivatives are found in numerous natural products with a variety of biological activities,<sup>7</sup> it is important to develop general methods to synthesize or modify such compounds. Their chemistry has been extensively studied, but the functionalization of such compounds has still difficulty owing to their unique reactivities. As similar to the benzenoid aromatic compounds, electrophilic substitutions are frequently employed for the functionalization of the azulene ring at the 1- and 3-positions.<sup>8</sup> Indeed, Friedel-Crafts<sup>9</sup> acylation and Vilsmeier-Haack<sup>10</sup> formylation are often utilized for the preparation of the corresponding carbonyl compounds. However, low products yield and/or formation of 1,3-di(acyl- or formyl)azulenes as by-products are frequently encountered in the preparation of the azulene derivatives by these two methods. As a solution strategy, Lee and co-workers have reported the efficient synthetic method of 1-azulenyl ketones via an oxidative cleavage of the C=C double bond in *N*-sulfonylenamides, recently.<sup>11</sup>

We found unexpectedly hydration of alkyne moiety of azulene derivatives during the decarboxylation of ester function of azulenylalkyne at the 1-position by heating in 100% H<sub>3</sub>PO<sub>4</sub>, which is an efficient condition to remove the functional group.<sup>12</sup> Actually, the reaction of 1-ethynylazulene derivative **1a** exhibited the hydration to give 1-azulenyl ketone **2** along with the removal of the ester function by heating in 100%

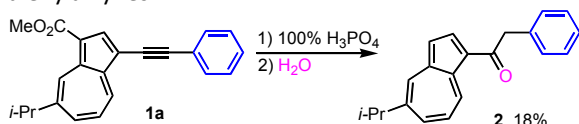
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Electronic Supplementary Information (ESI) available: Experimental details, <sup>1</sup>H, <sup>13</sup>C NMR and HRMS spectra of reported compounds. See DOI: 10.1039/x0xx00000x

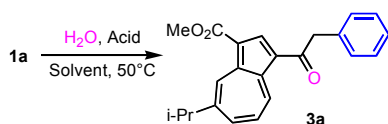
H<sub>3</sub>PO<sub>4</sub>, but in rather low yield (Scheme 2). Since the hydration of 1-ethynylazulene derivatives has never been reported, we have explored the optimization of the reaction conditions for the transformation to the 1-azulenyl ketones. The optimized synthetic procedure should become one of the efficient and convenient methods for the preparation of 1-azulenyl ketones. Herein, we describe the novel synthetic procedure for the 1-azulenyl ketones by the Brønsted acid catalyzed hydration of 1-azulenylalkynes.



**Scheme 2** Decarboxylation of methyl 7-isopropyl-3-(phenylethynyl)azulene-1-carboxylate (**1a**) with 100% H<sub>3</sub>PO<sub>4</sub>.

Initially, the hydration reaction of 1-azulenylphenylacetylene **1a**<sup>13</sup> was selected as a model for the optimization of the reaction conditions by utilizing several Brønsted acids and solvents. At the first, the effect of the Brønsted acid was examined using THF as a solvent for a reaction period of 3 hours under an aerobic condition. As summarized in Table 1, yields of the product were significantly dependent on the acid employed. The reaction of **1a** in THF in the presence of H<sub>2</sub>SO<sub>4</sub> and CF<sub>3</sub>SO<sub>3</sub>H gave the desired product **3a** in 54 and 52% yields, respectively, without decarboxylation of the ester group on the azulene ring (entries 1 and 2). Despite the fact that these acids were successful Brønsted acid in the metal-free hydration of benzenoid compounds, decomposition of compounds was observed during the reaction of the azulene derivative. However, the weaker acid, CH<sub>3</sub>CO<sub>2</sub>H, was not induced the hydration reaction resulted in the recovery of the starting material **1a**, quantitatively (entry 3). Among the Brønsted acids tested, CF<sub>3</sub>CO<sub>2</sub>H was found to be the best with respect to the product yield (98%, entry 4). The hydration of **1a** with CF<sub>3</sub>CO<sub>2</sub>H was also examined in five the other hydrophilic organic solvents (entries 5–9). Thus, we found that THF was the best among the examined solvents. Therefore, the reaction conditions using CF<sub>3</sub>CO<sub>2</sub>H in THF was selected for further investigations.

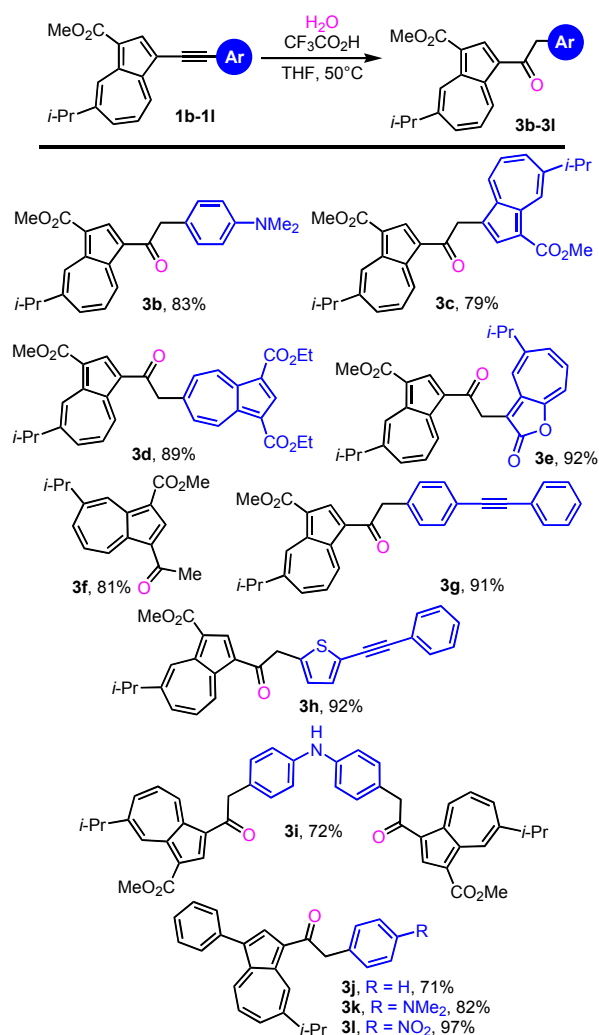
**Table 1** Optimization of the reaction conditions.<sup>a</sup>



entry	Brønsted Acid	Solvent	Yield [%] <sup>a</sup>
1	H <sub>2</sub> SO <sub>4</sub>	THF	54
2	CF <sub>3</sub> SO <sub>3</sub> H	THF	52
3	CH <sub>3</sub> CO <sub>2</sub> H	THF	No reaction
4	CF <sub>3</sub> CO <sub>2</sub> H	THF	98
5	CF <sub>3</sub> CO <sub>2</sub> H	DMSO	33
6	CF <sub>3</sub> CO <sub>2</sub> H	DMF	70
7	CF <sub>3</sub> CO <sub>2</sub> H	1,4-dioxane	50
8	CF <sub>3</sub> CO <sub>2</sub> H	MeCN	61
9	CF <sub>3</sub> CO <sub>2</sub> H	MeOH	75

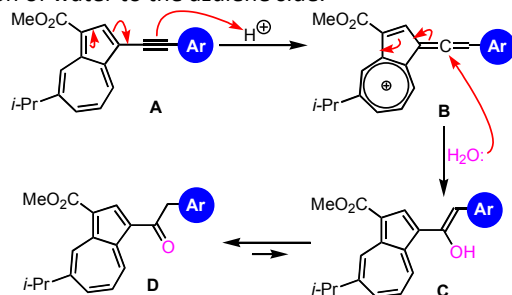
<sup>a</sup>Reaction conditions: alkyne **1a** (0.50 mmol), H<sub>2</sub>O (0.5 mL), Brønsted acid (0.5 mL), solvent (1 mL), 50 °C, 3 h. <sup>b</sup>Isolated yield.

Having the optimized reaction conditions as shown in Table 1, we examined the scope of the hydration of 1-azulenylalkynes possessing several functional groups.<sup>14</sup> The yield and structure of the products are summarized in Fig. 1 (structure of the substrates, 1-azulenylalkynes **1b–1i**, is summarized in the ESI). In general, the products were obtained in good to excellent yields with complete regioselectivity. Alkyne with *N,N*-dimethylaminophenyl group **1b**<sup>15</sup> readily reacted under the conditions to give the desired 1-azulenyl ketone **3b** in 83% yield. Likewise, hydration of bis(azulenyl)acetylenes **1c**<sup>13</sup> and **1d**<sup>16</sup> afforded the corresponding ketones **3c** and **3d** in 79 and 89% yields, respectively. Ketone **3e** was also obtained in 92% yield by the reaction of alkyne **1e** under the similar conditions. As similar to the results described above, terminal alkyne **1f**<sup>13</sup> was reacted to afford the Markovnikov-type addition product, i.e., 1-acetylazulene **3f**, in 81% yield. It is noteworthy that the hydration of **1g**<sup>17</sup> and **1h**<sup>17</sup> with two different alkyne moieties was caused selectively at the alkyne attached to the azulene ring to give the corresponding ketones **3g** (91%) and **3h** (92%) in excellent yields. Hydration of bis-alkyne **1i**<sup>15</sup> and subsequent chromatographic purification on silica gel afforded the desired diketone product **3i** in 72% yield. This means the hydration takes place in 85% yield for each alkyne moiety. 1-Phenyl derivatives of the azulenylalkynes **1j**,<sup>18</sup> **1k**<sup>18</sup> and **1l**<sup>18</sup> were also reacted under the same conditions to give the corresponding azulenyl ketones **3j** (71%), **3k** (82%) and **3l** (97%). From these results, hydration of azulenylalkynes should not be affected by the functional groups to the reaction outcome, since the reaction proceeded in good to excellent yields with complete regioselectivity. Moreover, almost pure products could be obtained simply by filtering the reaction mixture, except for the oily products **3e** and **3i**.



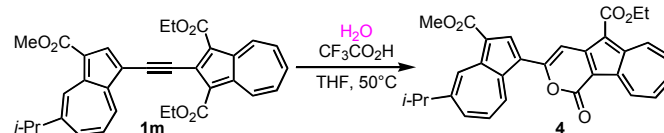
**Fig. 1** Hydration of 1-ethynylazulene derivatives **1b–1l**.

The presumed reaction mechanism is illustrated in Scheme 3. At the first, alkyne **A** is protonated with Brønsted acid to give the azulenum allene intermediate **B** due to the electron-donating nature of the azulene ring at the 1-position. Addition of water to the azulenum allene intermediate **B** should afford the enol **C**, which then tautomerized to form ketone **D**. Although the *N,N*-dimethylamino group of **1b** also behaves as an electron-donating group, protonation of the nitrogen atom under the reaction conditions decreases the electron-donating nature of the Ar moiety that should result in the selective addition of water to the azulene side.



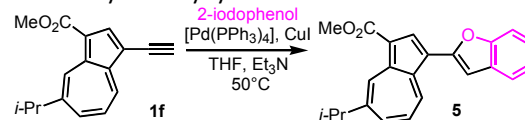
**Scheme 3** Plausible reaction mechanism of hydration.

Instead of the formation of the presumed ketone derivatives, isocoumarin analogue **4** was obtained in 90% yield by the reaction of alkyne **1m**<sup>16</sup> under the similar conditions described above (Scheme 4). Although many heterocycle-fused azulene derivatives have been reported so far,<sup>19</sup> compound **4** is the first example of isocoumarin congener with two azulene moieties in the molecule.



**Scheme 4** Synthesis of isocoumarin congener **4**.

During the preparation of 1-azulenylalkynes by the Sonogashira–Hagihara reaction of 1-ethynylazulene derivative **1f** with 2-iodophenol in the presence of Pd catalyst, we found the formation of 1-(2-benzofuryl)azulene derivative **5** in 55% yield, instead of the corresponding cross-coupled product (Scheme 5). Formation of the heterocycle should occur by the electrophilic addition of hydroxyl group to the alkyne moiety, which might be caused by the similar reaction mechanism for the hydration reaction, that takes place after the usual palladium-catalyzed alkylation.<sup>20</sup>



**Scheme 5** Reaction of 1-ethynylazulene **1f** with 2-iodophenol.

In conclusion, we have discovered an efficient synthetic method of 1-azulenyl ketones by the hydration of 1-azulenylalkynes at the first time. The ketones were available in good to excellent yield by the reaction of the corresponding alkyne derivatives in the presence of CF<sub>3</sub>CO<sub>2</sub>H without metal catalyst. The reaction takes place at relatively low temperature (50 °C) with complete regioselectivity and compatibility of functional groups. Under the reaction conditions, we also found alkyne **1m** was converted into isocoumarin congener **4** in excellent yield. These results should warrant the new synthetic methodology for azulene derivatives.

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