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## Synthesis of 1,2,3,4-tetrasubstituted naphthalenes through cascade reaction triggered by silyl acetal activation

Hikaru Yanai, \*,<sup>a</sup> Nobuyuki Ishii,<sup>a</sup> and Takashi Matsumoto\*,<sup>a</sup>

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1,2,3,4-Tetrasubstituted naphthalenes bearing four different substituents were synthesized in a regioselective manner by fluoride-induced cascade reaction of lactol silyl ethers, which could be easily prepared from 4-alkynylisocoumarins and ketene silyl acetal.

Polysubstituted naphthalenes are found in nature as second metabolites. Their interesting biological activities<sup>1</sup> make such structural motif an attractive target of organic synthesis.<sup>2</sup> However, combination of classical electrophilic aromatic substitution (SEAr) reactions is less effective because steric congestion by the substituent(s) encumbers the bond formation. Precise control of the regiochemistry is still more difficult. As the alternatives, several benzannulation approaches have been reported. For example, (4+2) cycloaddition chemistry,<sup>3</sup> anionic annulation reactions,<sup>4</sup> ring-closing methathesis-aromatization,<sup>5</sup> and transition metal-catalyzed benzannulation reactions<sup>6</sup> provide the effective routes to 1,2,3- or 1,2,4-trisubstituted naphthalenes. The Hauser annulation of  $\alpha$ , $\beta$ unsaturated carbonyls with phthalide derivatives was also used to construct the polycyclic systems including natural products.<sup>7</sup> However, an effective access to 1,2,3,4-tetrasubstituted naphthalenes bearing four different substituents, which are found in some lignans<sup>8</sup> and polyketides,<sup>9</sup> are still challenging.<sup>10</sup>

Recently, we reported that acidic zwitterion  $1^{11}$  nicely promoted the addition reaction of ketene silyl acetals (KSAs) to 1*H*isochromen-1-one derivatives to give the lactol silyl ethers in excellent yields as exemplified by the reaction of lactone **2** with a KSA derived from ethyl acetate (Scheme 1).<sup>12</sup> This finding prompted us to conceive an idea of a novel cascade reaction using alkynylated lactol silyl ether **A** for a regioselective synthesis of the 1,2,3,4tetrasubstituted naphthalenes (Fig 1).



<sup>+</sup> Electronic Supplementary Information (ESI) available: Details of experiments, NMR data for all compounds. For ESI see DOI: 10.1039/x0xx00000x



 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme1} & \mbox{Zwitterion-induced addition reaction of KSA to 1$$$ 1$$$ H-isochromen-1-one (Tf = CF_3SO_2, TBS = $t$-BuMe_2Si) \\ \end{array}$ 

Upon treatment of alkynylated lactol silyl ether **A** with suitable fluoride sources, desilylative ring-opening reaction (formation of **B**) followed by proton transfer would occur to yield enolate intermediates **C** and/or **D**. Here, intramolecular aldol reaction of **C** could take place to give 4-alkynylnaphthalene **E**. On the other hand,



6<sup>c</sup>

8h

3.0

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intermediate **D** could vield 4-acvInaphthalene **F** through intramolecular Michael reaction or  $6\pi$ -electrocyclization. The formation of E might be disfavored because the formation of intermediates C from B would be reversible, despite of irreversible formation of allenyl ketone D. We anticipated selective formation of F via D.13 Herein we report successful implementation of this idea.

The starting lactones were easily available. Typical synthesis is shown in Scheme 2. Under the Larock's conditions,<sup>14</sup> methyl o-(phenylethynyl)benzoate 5, which was obtained by the Sonogashira reaction of methyl o-iodobenzoate 4 with ethynylbenzene, smoothly cyclized by treating with ICl to give 6-membered iodolactone 6 in 92% yield. The following Sonogashira reaction of 6 with hex-1-yne or with ethynylbenzene yielded 4-alkynyl-1Hisochromen-1-ones 7a and 7b in 88% and 95% yields, respectively.<sup>15</sup> According to similar procedure, several lactones were prepared in good to excellent overall yields (see, ESI). The obtained lactone 7a was subjected to the addition reaction of KSA in the presence of a catalytic amount of zwitterion 1, and the desired adduct 8a was isolated in 95% yield. Likewise, 8b was obtained in 90% yield from 7b.



With these lactol silvl ethers in hands, we conducted model reactions with tetrabutylammonium fluoride (TBAF) as a conventional fluoride source.<sup>16,17</sup> The reaction of **8a** with 1.0 equiv of TBAF at room temperature gave desired 4-benzoylnaphthalene 9a in 53% yield along with a small amount of divinyl ether 10a (entry 1). At the same time, 1H-isochromen-1-one 7a was also isolated in 24% yield. The formation of 7a suggested fluorideinduced retro-aldol type reaction and the following protonation of the resulting enolate by some proton sources existing in the reaction mixture. Higher reaction temperature and additional loading of TBAF were not effective to improve the yield of 9a (entries 2 and 3). Finally, we found that the yield was dramatically increased by using molecular sieves (MS) 4A as an additive. The use of 1.0 g of MS4A powder per 1.0 mL of the TBAF solution resulted in quantitative formation of 9a (entry 4). MS4A would work as a dehydrating agent for the reaction system and cause enhancement of both nucleophilicity and basicity of fluoride ion. In TLC analysis of this reaction, we observed a spot of 10a within short reaction time with accompanying formation of 9a. After enough reaction time (3 h), completed consumption of 10a led to clean formation of 9a. As

Table 1 Survey of effective reaction conditions





<sup>a</sup> Isolated yield. <sup>b</sup> 1H-isochromen-1-one 7a was also isolated in 24% yield. <sup>c</sup> 1 g of MS4A powder per 1 mL of the TBAF solution was used.

MS4A

70

3

92 0



Scheme 3 Plausible mechanism

shown in Scheme 3, divinyl ether 10 would be formed by kinetically favored O-cyclization of **D**, while it also was transformed to **D** via  $\beta$ elimination reaction in a reversible manner in the presence of MS4A. In a case of phenylethynyl substrate 8b, MS4A was not necessary; the reaction of 8b with 3.0 equiv of TBAF at 70 °C gave 4benzoylnaphthalene 9b in 91% yield without formation of the corresponding divinyl ether 10b (entry 5). The use of MS4A gave an essentially same result (entry 6). The structures of naphthalenes 9a and **9b** were determined by X-ray crystallographic analyses (Fig 2).

To reveal substrate scope of this two-step naphthalene synthesis, we examined the application of several lactones (Table 2). The zwitterion-induced addition reaction of KSA to 1H-isochromen-



Fig 2 ORTEP drawings of 9a (a) and 9b (b)

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1-one derivatives **7c-7o** was smoothly proceeded to give the corresponding adducts **8c-8o** in excellent yields under optimized

#### conditions (1 mol% of 1, 1.2 equiv of KSA). Notably reacidic zwitterion 1 did not affect acid-sensitive DRUhetlohandies SU2P1 as thienyl, acetyloxy, and MOM groups. The ring rearrangement reaction of these adducts also worked nicely. In the reaction of 8c bearing phenyl group on the alkyne moiety, MS4A was not necessary and the desired naphthalene 9c was obtained in 92% yield by using 1.0 equiv of TBAF. On the other hand, lactol silyl ether 8d bearing a butyl pendant on the alkyne moiety required MS4A to meet excellent yield of naphthalene 9d (96% yield). Likewise, in the presence of MS4A, arylated alkynes 8e-8i yielded the corresponding 3-(arylmethyl)naphthalenes 9e-9i without formation of undesired regioisomers. Naphthylmethyl and thienylmethyl naphthalenes 9i and 9k were also obtained in excellent yields. The reaction of silyl ethers 8m and 8n bearing some protecting groups such as acetyl and MOM groups was also proceeded to give the corresponding naphthalenes 9m and 9n in 70% and 93% yields, respectively. In the reaction of lactol silyl ether 80 (3.0 equiv of TBAF), the trimethylsilyl group on alkynyl moiety did not survive, affording 3methylnaphthalol 90 in 91% yield. The use of 1.0 equiv of TBAF also resulted in selective formation of 90 (62% yield).

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The naphthalene synthesis from lactone **7p** is worth of comment (Scheme 4). In this case, zwitterion-induced reaction using 2.2 equiv of KSA gave bis-silylated product **8p**, which was formed by the TBS protection of the hydroxyl group and the simultaneous Mukaiyama aldol type reaction. The treatment of **8p** with 3.0 equiv of TBAF and MS4A successfully produced primary alcohol **9p** in 97% yield.



Scheme 4 Naphthalene synthesis from primary alcohol **7p** 

In order to demonstrate synthetic utilities of the present methodology, we finally examined synthesis of higher polycyclic systems (Scheme 5). By using TfOH as a superacidic media, we realized the direct intramolecular Friedel-Crafts acylation of 9b having an ethyl ester functionality as the acyl donor part;<sup>18</sup> when a solution of 9b in TfOH was stirred for 2 h at room temperature, additional ring formation proceeded to give tetracenone 11 in 86% yield. Moreover, the reaction of lactol silyl ether 8q, which was obtained from lactone 7g, with TBAF gave tetrahydrotetraphene 12 in 67% yield. This reaction would proceed via fluoride-induced ringreaction, intramolecular Michael reaction, opening 6πelectrocyclization of intermediate G, and the following dehydrative aromatization.



In summary, we successfully developed a synthetic methodology for 1,2,3,4-tetrasubstituted naphthalenes bearing four different substitutens from 4-alkynyl-1*H*-isochromen-1-ones, which were easily synthesized in good to excellent overall yields. The present methodology included the Mukaiyama aldol type reaction induced by acidic zwitterion **1** and the ring rearrangement reaction of thus obtained adducts with TBAF. This ring rearrangement reaction took place in a wide range of lactol silyl ethers and undesired regioisomers were not formed. In addition, further ring formation directed to higher polycyclic systems was achieved.

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#### Notes and references

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