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Tandem Michael-aldol reaction via 6-*endo*-dig cyclization of ynone-chalcogenides: synthesis of 2-unsubstituted 3-(hydroxyalkyl)chalcogenochromen-4-ones

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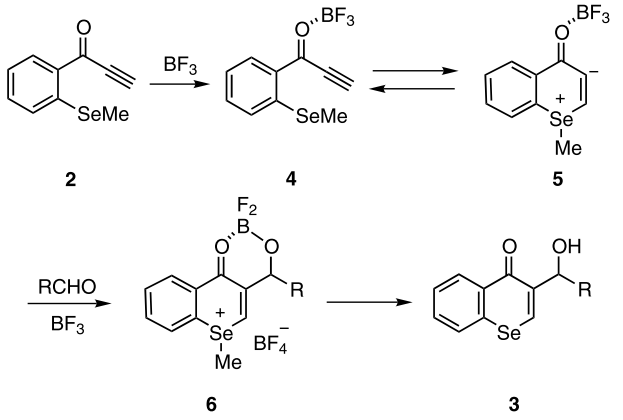
Abstract—The reactions of 1-(2-methylchalcogenophenyl)propynone with aldehydes gave 3-(hydroxyalkyl)chalcogenochromen-4-ones via the 6-*endo*-dig cyclization and aldol reaction. Selenochromen-4-ones were obtained in higher yields than the thiochromen-4-ones. © 2002 Published by Elsevier Science Ltd.

The Morita–Baylis–Hillman reaction involves the α-hydroxylalkylation and α-aminoalkylation of Michael acceptors by electrophilic carbonyl compounds or imines in the presence of a nucleophilic catalyst such as a tertiary amine or phosphine.[1] We have developed a tandem Michael–aldol reaction of an active alkene with aldehydes using a chalcogenide and $TiCl_4$ in order to overcome a drawback to the Morita–Baylis–Hillman reaction.[2] Our method is advantageous because it proceeds much faster than the Morita–Baylis–Hillman reaction, and the Morita–Baylis–Hillman products are produced after treatment of the reaction mixtures with DBU. Li and his co-workers reported similar reactions using only $TiCl_4$.[3] Very recently, we reported a new reaction involving the intramolecular Michael addition of a chalcogenide group to an enone moiety.[4] Although the Morita–Baylis–Hillman reaction goes through an elimination reaction in the last step of the reaction and cannot be applied to reactions of ynones with aldehydes, the reactions developed by Li's group and us proceed without the elimination step and can be used for the reactions of ynones[5,6] and acetylenic esters.[6] If 1-(2-methylchalcogenophenyl)propynone reacts with aldehydes in the presence of $BF_3{\cdot}Et_2O$, we can synthesize 3-(hydroxymethyl)chalcogenochromen-4-ones. Modification at the position 3 of the 2-substituted chromen-4-ones has been carried out by lithiation of the chromen-4-ones with LDA followed by a reaction with an electrophile.[7] When this method was employed for thiochromen-4-ones and selenochromen-4-ones, the 3-substituted chalcogenochromen-4-ones or the ring-opened acetylenic products were produced depending upon the electrophile.[8] The reactions of the 2-unsubstituted chalcogenochromen-4-ones with 2 mol equiv. of LDA formed the ring-opened dianions.[8] Although the synthesis of 3-(hydroxymethyl)- and 3-(α-substituted benzyl)chromen-4-ones has been published,[9] our method could be useful for the synthesis of the 3-substituted chalcogenochromen-4-ones. On the other hand, the first step of this reaction is an intramolecular Michael addition with the 6-*endo*-dig cyclization, and is interesting from the viewpoint of the Baldwin rule. It is anticipated that the cyclization of 1-(2-methylchalcogenophenyl)propynone could follow two pathways, i.e. the 6-*endo*-dig and/or 5-*exo*-dig ring closure. Cyclization of the 1-(2-hydroxyaryl)-3-phenylpropynones using K_2CO_3 in acetone predominantly produced flavones (the Michael products), while the



Scheme 1.

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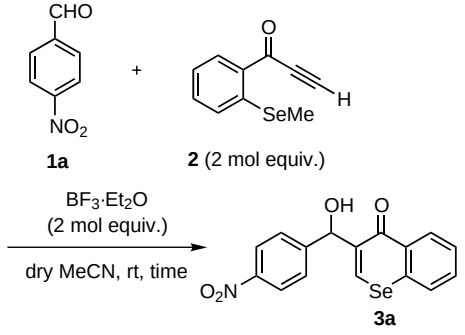
reaction using K_2CO_3 in ethanol produced (*Z*)-aurones (the *anti*-Michael products) as the major products.[10] Saito and his co-workers examined cyclization of 1-(2-hydroxyphenyl)propynones under basic conditions from the theoretical and experimental standpoints and showed that the presence of a small amount of a proton donor effecting the protonation of the chromene anion intermediate was essential for the high 6-*endo*-dig selectivity.[11] The selenium analogues were cyclized in the 6-*endo*-dig mode under basic conditions.[12]

In this paper, we report the new synthesis of 3-(hydroxyalkyl)chalcogenochromen-4-ones via the tandem Michael–aldol reaction of ynone-chalcogenides using $BF_3{\cdot}Et_2O$. The reactions of *p*-nitrobenzaldehyde (**1a**) and 2 mol equiv. of 1-(2-methylselanylphenyl)-propynone (**2**) were conducted using 2 mol equiv. of $BF_3{\cdot}Et_2O$ as a Lewis acid, because one mol equiv. of $BF_3{\cdot}Et_2O$ is consumed for formation of the alkoxyborane and the other becomes a counter anion (BF_4^-) of the onium salt after combination with the fluoride liberated (see Scheme 1).[4] We first examined the reaction conditions and the results are summarized in Table 1. The highest yield (74%) of adduct **3a** was obtained from the reaction in CH_2Cl_2 at −20°C for 24 h (entry 7).[13] The product **3a** did not show the signals due to the acetylenic proton and carbons and the *Se*–Me group, but showed new signals due to an olefinic proton at the position 2 and two olefinic carbons in the ^1H and ^{13}C NMR spectra.[13] This indicated that the 6-*endo*-dig ring closure took place and then the methyl group was eliminated. The selenonium salt **6** should have been obtained as the product shown in Scheme 1, but selenochromen-4-one **3a** was actually produced.

Table 1. Reaction of 1-(2-methylselanylphenyl)propynone with *p*-nitrobenzaldehyde



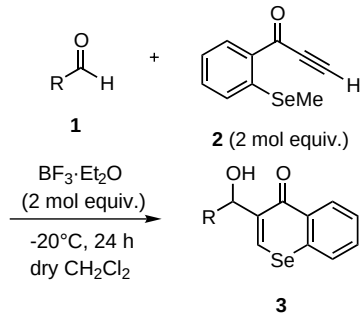
Entry	Time	Yield (%)
1	5 min	**3a** (28)
2	30 min	**3a** (27)
3	3 h	**3a** (40)
4	24 h	**3a** (47)
5	50 h	**3a** (42)
6[a]	24 h	**3a** (72)
7[a,b]	24 h	**3a** (74)

[a] The reaction was conducted at −20°C.
[b] CH_2Cl_2 was used.

Demethylation of **6** would easily have occurred because a boron Lewis acid coordinated with the carbonyl group of the selenochromen-4-one **6** and the selenopyranone ring was more positively charged. It is still not clear how the methyl group was eliminated. To ensure the generality of this reaction, the reactions of several aldehydes with the ynone-selenide **2** were conducted under conditions similar to those of entry 7 in Table 1. Both aromatic and aliphatic aldehydes produced adducts **3b–e** in moderate yields (Table 2).

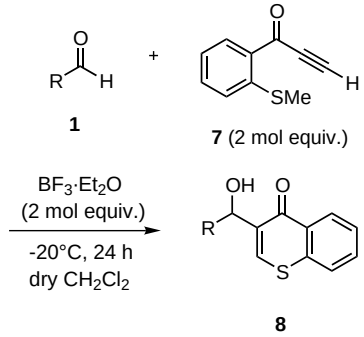
Next, the reactions of the sulfur congener, 1-(2-methylsulfanylphenyl)propynone (**7**) were carried out (Table 3). Both aromatic and aliphatic aldehydes produced adducts **8a–e** in low to moderate yields. The yields of

Table 2. Reaction of 1-(2-methylselanylphenyl)propynone with aldehydes



Entry	R	Yield (%)
1	*p*-CNC_6H_4 (**1b**)	**3b** (65)
2	*p*-ClC_6H_4 (**1c**)	**3c** (62)
3	Ph (**1d**)	**3d** (56)
4	$PhCH_2CH_2$ (**1e**)	**3e** (58)

Table 3. Reaction of 1-(2-methylsulfanylphenyl)propynone with aldehydes



Entry	R	Yield (%)
1	*p*-$NO_2C_6H_4$ (**1a**)	**8a** (56)
2	*p*-CNC_6H_4 (**1b**)	**8b** (36)
3	*p*-ClC_6H_4 (**1c**)	**8c** (28)
4	Ph (**1d**)	**8d** (42)
5	$PhCH_2CH_2$ (**1e**)	**8e** (31)

the sulfur products **8a**–**e** were lower than those of the selenium derivatives **3a**–**e**. This would be attributable to the higher nucleophilicity of the selenide over the sulfide. In summary, this is the useful method for the synthesis of 2-unsubstituted 3-(hydroxyalkyl)-chalcogenochromen-4-ones, the derivatives of which are expected to show biological activity.[14]

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13. A typical example: To a stirred solution of *p*-nitrobenzaldehyde (75 mg, 0.5 mmol) and 1-(2-methylselanylphenyl)propynone (223 mg, 1.0 mmol) was added dropwise $BF_3{\cdot}Et_2O$ (127 μl, 1.0 mmol) at −20°C. The mixture was stirred at the same temperature for 24 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitate was removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluted with hexane–AcOEt (2:1, v/v) to give **3a**. **3-[Hydroxy-(4-nitrophenyl)methyl]selenochromen-4-one (3a)** Yellow needles (acetonitrile/ether). Mp 168–169°C. IR (KBr; cm^{-1}) 3419 (OH), 1584 (C=O), 1517 and 1346 (NO_2). ^1H NMR (400 MHz; $CDCl_3$) δ: 4.10 (1H, brs, OH), 6.03 (1H, s, benzylic H), 7.53 and 7.57 (each 1H, dt, $J=2$ and 7.8, ArH), 7.66 (2H, d, $J=8.8$, ArH), 7.68 (1H, dd, $J=2$ and 7.8, ArH), 8.20 (2H, d, $J=8.8$, ArH), 8.31 (1H, s, olefinic H), 8.58 (1H, dd, $J=2$ and 7.8, ArH). ^{13}C NMR (100 MHz; $CDCl_3$) δ: 74.4 (d), 123.6 (d), 127.4 (d), 128.1 (d), 128.6 (d), 130.5 (d), 131.7 (d), 132.6 (s), 136.0 (s), 137.0 (d), 138.1 (s), 147.3 (s), 149.0 (s), 181.0 (s). MS (EI) m/z: 361 (M^+, base). Anal. calcd for $C_{16}H_{11}NO_4Se$: C, 53.35; H, 3.08; N, 3.89. Found: C, 53.33; H, 3.11; N, 3.86%.
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