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Chalcogeno−Morita−Baylis−Hillman Reaction of Enones with Acetals: Simple α-Alkoxyalkylation of Enones

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Abstract: 1-[2-(Methylsulfanyl)phenyl]prop-2-en-1-one (**1**) and the seleno congener (**2**) reacted with acetals **3** and **21** in the presence of BF_3·Et_2O to give α-alkoxyalkyl enones **4**, **5** and **22**, **23** in good yields. When the reaction mixtures were worked up with a saturated $NaHCO_3$ solution instead of Et_3N, onium salts **6** and **7** were obtained together with **4** and **5**. Reactions with cyclic acetal **14** gave α-(*β*-hydroxyethoxy) enones **15** and **16** accompanied by dimeric products **17** and **18**.

The Morita−Baylis−Hillman reaction, α-hydroxyalkylation of activated olefins, is one of the most important carbon−carbon bond-forming reactions because it allows the synthesis of highly functionalized and useful intermediates in a single step.[1] Although this reaction has the potential to be synthetically useful, it has a poor reaction rate. We have developed a tandem Michael-aldol reaction of an active alkene or alkyne with aldehydes using a chalcogenide and $TiCl_4$ to overcome this drawback to the Morita−Baylis−Hillman reaction.[2] Our method is advantageous because it proceeds much faster than the Morita−Baylis−Hillman reaction and provides the Morita−Baylis−Hillman adducts after treatment of the reaction mixtures with preparative TLC on silica gel or DBU.[3] Recently, we reported a new reaction, the chalcogeno−Morita−Baylis−Hillman reaction, involving the intramolecular Michael addition of a chalcogenide group to an enone or ynone moiety in the presence of BF_3·Et_2O.[4]

On the other hand, acetals act as electrophiles in the presence of a Lewis acid such as TMSOTf, $TiCl_4$, or BF_3·Et_2O.[5] Noyori et al. first used acetals and ortho esters for α-alkoxyalkylation of α,*β*-unsaturated ketones.[6] This procedure involves a trimethylsilyl trifluoromethansulfonate-catalyzed conjugate addition of a phenyl silyl selenide to α,*β*-unsaturated ketones followed by the aldol reaction of enol silyl ethers with acetals or ortho esters, oxidation of selenides, and *β*-elimination of selenoxides. Kim et al. and Zibuck et al. later reported procedures for α-alkoxyalkylation of α,*β*-unsaturated ketones via pyridiniosilylation and sulfoniosilylation.[7] Hosomi and coworkers also reported similar α-alkoxyalkylation via aminosilylation.[8]

If acetals are used instead of aldehydes for the chalcogeno−Morita−Baylis−Hillman reaction, BF_3·Et_2O works for the formation of both chalcogenonio enolates and α-alkoxy carbocations, and α-alkoxyalkylation of enones can be achieved. In this paper, we report the simple procedure for the α-alkoxyalkylation of enones via the tandem Michael-aldol reaction of chalcogenide-enones **1** and **2** with acetals using BF_3·Et_2O.

First, we examined reactions of 1-[2-(methylsulfanyl)-phenyl]prop-2-en-1-one (**1**) with benzaldehyde dimethyl acetal **3** in the presence of BF_3·Et_2O (Table 1). The reaction mixture was quenched with 2 equiv of Et_3N. A reaction of compound **1** and 2 equiv of **3** with 2 equiv of BF_3·Et_2O in CH_2Cl_2 gave the Morita−Baylis−Hillman adduct **4** in 82% yield (entry 1). Compound **4** showed ^{1}H NMR signals due to a methoxy group at δ 3.36 and two vinyl protons at δ 5.44 and 6.10. The use of 1 equiv of **3** also provided the adduct **4** in 79% yield (entry 2). When 1 equiv of BF_3·Et_2O was used, the yield of **4** was decreased to 57% (entry 3). The use of MeCN as a solvent also provided the adduct **4** in 78% yield (entry 4). Treatment of the reaction mixture with saturated aqueous $NaHCO_3$ instead of Et_3N gave **4** (43%) and sulfonium salt **6** (40%) (entry 5). The order in which the reagents were mixed did not affect the yield of **4**. A reaction of 1-[2-(methylselanyl)phenyl]prop-2-en-1-one (**2**) and acetal **3** with 2 equiv of BF_3·Et_2O in CH_2Cl_2 was similarly conducted. α-(α-Methoxybenzyl)enone **5** (79%) and selenochromanone **8** (syn only, 5%) were obtained after treatment of the reaction mixture with Et_3N (entry 6). Product *syn*-**8** was isomerized to the anti isomer *anti*-**8** during separation of the raw product by preparative TLC

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(1) (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052. (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891.

(2) (a) Kataoka, T.; Iwama, T.; Tsujiyama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 197−198. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813−11824. (c) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358−2360. (d) Kinoshita, S.; Kinoshita, H.; Iwamura, T.; Watanabe, S.; Kataoka, T. *Chem. Eur. J.* **2003**, *9*, 1496−1502.

(3) (a) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsujiyama, S.; Tsurukami, Y.; Iwamura, T.; Watanabe, S. *Synlett* **1999**, 197−198. (b) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsurukami, Y.; Tsujiyama, S.; Fujita, M.; Honda, E.; Iwamura, T.; Watanabe, S. *J. Organomet. Chem.* **2000**, *611*, 455−462. (c) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725−4731.

(4) (a) Kataoka, T.; Kinoshita, S.; Kinoshita, H.; Fujita, M.; Iwamura, T.; Watanabe, S. *J. Chem. Soc., Chem. Commun.* **2001**, 1958−1959. (b) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2043−2045. (c) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T. *Tetrahedron Lett.* **2002**, *43*, 7039−7041.

(5) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043−1054.

(6) (a) Suzuki, M.; Kawahigashi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809−1812. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron.* **1981**, *37*, 3899−3910.

(7) (a) Kim, S.; Kim, Y. G.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 2043−2044. (b) Kim, S.; Park, J. H.; Kim, Y. G.; Lee, J. H. *J. Chem. Soc., Chem. Commun.* **1993**, 1188−1189. (c) Wang, F.; Zibuck, R. *Synlett* **1998**, 245−246.

(8) Hojo, M.; Nagayoshi, M.; Fujii, A.; Yanagi, T.; Ishibashi, N.; Miura, K.; Hosomi, A. *Chem. Lett.* **1994**, 719−722.

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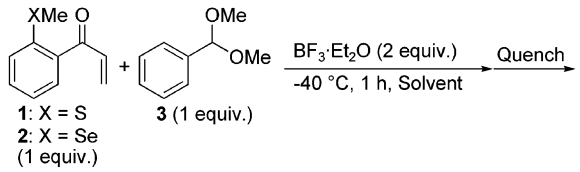
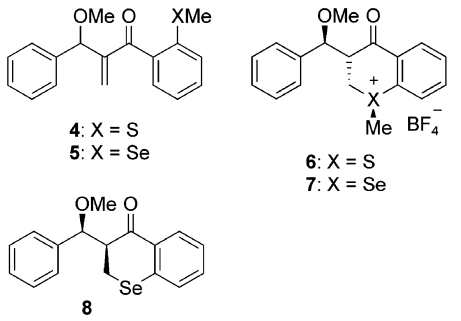
TABLE 1. Reaction of 1-[2-(Methylchalcogenyl)phenyl]-prop-2-en-1-ones 1 and 2 with Benzaldehyde Dimethyl Acetal 3

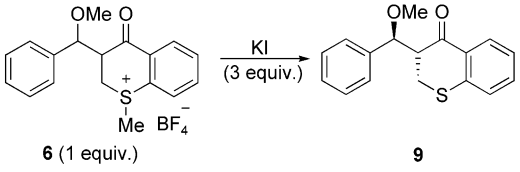




entry	X	$BF_3{\cdot}Et_2O$ (equiv)	solvent	quench	products (% yield)
1[a]	S	2	CH_2Cl_2	Et_3N (2 equiv)	**4** (82)
2	S	2	CH_2Cl_2	Et_3N (2 equiv)	**4** (79)
3	S	1	CH_2Cl_2	Et_3N (2 equiv)	**4** (57)
4	S	2	MeCN	Et_3N (2 equiv)	**4** (78)
5	S	2	MeCN	sat. $NaHCO_3$	**4** (43), **6** (40)
6	Se	2	MeCN	Et_3N (2 equiv)	**5** (79), **8** (5)
7	Se	2	MeCN	sat. $NaHCO_3$	**5** (36), **7** (51)

[a] Acetal (2 equiv) was used.

SCHEME 1

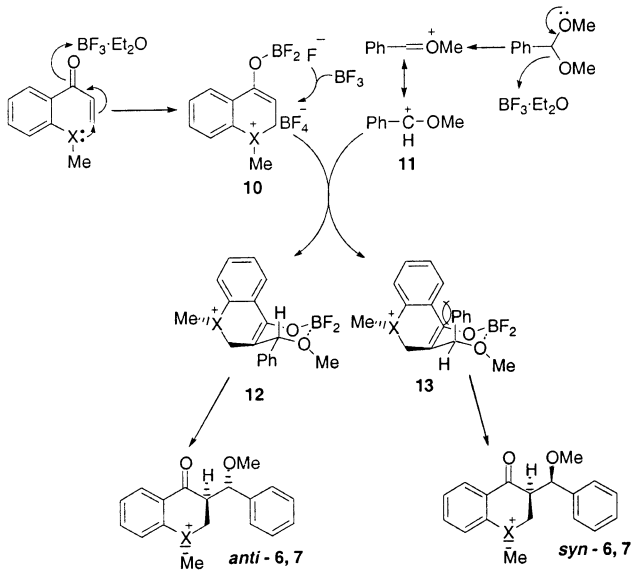


on silica gel. Stereochemical assignment for **8** was determined by a coupling constant between the methine proton at the 3-position and the benzylic proton in comparison with those of 2-(α-hydroxybenzyl)cyclohexanone, showing $J = 2.5$ Hz for the syn isomer and $J = 8.3$ Hz for the anti isomer.[9] One of the isomers of **8** with $J = 4.9$ Hz and the other with $J = 8.3$ Hz were assigned to be the syn and the anti isomers, respectively. A workup of the reaction mixture with saturated aqueous $NaHCO_3$ instead of Et_3N gave **5** (36%) and the selenonium salt **7** (51%) (entry 7). The ORTEP drawing of **7** (see Figure S1 in the Supporting Information) shows that the stereochemical relations between the methoxy group and the CH_2Se moiety and between the α-methoxybenzyl side chain and the *Se*-methyl group were anti and trans configurations, respectively.

Moreover, to investigate the stereostructure assignment of sulfonium salt **6**, demethylation of **6** with 3 equiv of potassium iodide was carried out, and thiochromanone **9** was given (Scheme 1). Since the ^1H NMR spectrum of

(9) Stiles, M.; Winker, R. R.; Chang, Y.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337−3342.

SCHEME 2

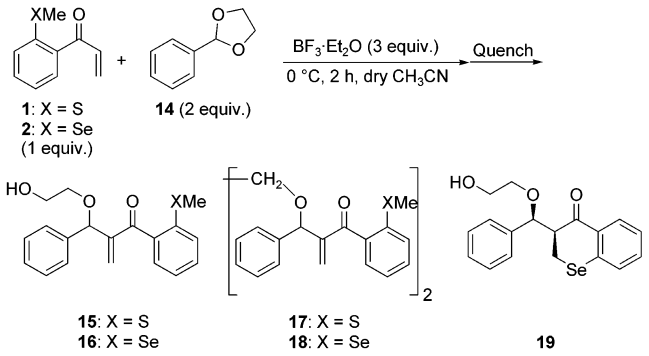


9 showed a big coupling constant (7.7 Hz) between the methine proton at the 3-position (H(3)) and the benzylic proton, the stereochemistries of the C(3)−C(2) bond and the OMe group were determined to be anti configurations. The methoxybenzyl group and the *S*-methyl group are presumed to be trans configurations because the NOE enhancement (2%) between the *S*-methyl group and H(3) was observed. Incidentally, the corresponding selenonium salt **7** did not show the NOE enhancement between the *Se*-methyl group and H(3), although they occupied the same side on the X-ray analysis (see Figure S1 in the Supporting Information). This difference is probably attributable to the fact that the C−S bond is shorter than the C−Se bond.

A possible mechanism is shown in Scheme 2. First, the carbonyl group of an enone coordinates with $BF_3{\cdot}Et_2O$, followed by the intramolecular Michael addition of a chalcogenyl group to the enone moiety to form the γ-sulfonio boron enolate **10**. On the other hand, the reaction of an acetal with $BF_3{\cdot}Et_2O$ affords α-alkoxy carbocation **11**. Diastereoselectivity between the methoxybenzyl group and the C(3)−C(2) bond would be induced in the reaction step of the boron enolate **10** with α-alkoxy carbocation **11**. The transition state **12** with an equatorial phenyl group is favored over **13** with an axial phenyl group, and the anti isomer is favorably formed. When the α-alkoxy carbocation **11** approaches enolate **10**, the methyl group on the chalcogen atom takes the opposite position to **11**, i.e., the trans configuration. A workup of the reaction mixture with Et_3N gives the Morita−Baylis−Hillman adduct (Table 1, entries 1−4 and 6), whereas treatment with a saturated aqueous $NaHCO_3$ solution causes the partial deprotonation to give salt **6** or **7** and enone **4** or **5**.

Next, we examined reactions of 2 equiv of a cyclic acetal (2-phenyl-1,3-dioxolane, **14**) and chalcogenide-enones **1** and **2** with 3 equiv of $BF_3{\cdot}Et_2O$ in MeCN at 0 °C for 2 h (Table 2). Reactions of enones **1** and **2** with acetals were sensitive to the steric hindrance around the nucleophilic center, and reactions of cyclic acetal **14** were slow compared with those of acyclic acetal **3**. The Morita−

TABLE 2. Reaction of 1-[2-(Methylchalcogenyl)phenyl]-prop-2-en-1-ones 1 and 2 with 2-Phenyl-1,3-dioxolane 14



entry	X	quench	products (% yield)
1	S	Et_3N (3 equiv)	**15** (56), **17** (6)
2	Se	Et_3N (3 equiv)	**16** (39), **18** (19), **19** (19)
3	S	sat. $NaHCO_3$	**15** (45)
4	Se	sat. $NaHCO_3$	**16** (45), **18** (10), **19** (7)

Baylis−Hillman adduct **15**[10] was given in 56% yield together with dimeric product **17**[10] (6%) after treatment of the reaction mixture with 2 equiv of Et_3N (entry 1). A reaction of the selenium congener **2** gave adduct **16** (39%), dimer **18** (19%), and selenochromanone **19** (syn only, 19%) (entry 2). When the reaction mixture of sulfide-enone **1** was quenched with a saturated aqueous $NaHCO_3$ solution instead of Et_3N, only adduct **15** (45%) was obtained (entry 3). The similar treatment of the selenium congener **2** gave adduct **16** (45%), dimer **18** (10%), and selenochromanone **19** (syn only, 7%) (entry 4).

The formation of a dimeric product has been reported in the reaction of methyl acrylate with aromatic aldehydes in supercritical CO_2.[11] Since this experiment has been conducted under very specific conditions, we examined the reactions shown in Scheme 2 to elucidate the mechanism for the formation of dimers **17** and **18**. Treatment of **15** with 0.5 equiv of $BF_3{\cdot}Et_2O$ gave dimer **17** in 4% yield. Dimeric product **17** would be produced via the following pathway: Monomeric product **15** reacts with $BF_3{\cdot}Et_2O$ to form alkoxyborane **20**, and alkoxyborane **20** attacks another molecule of **20** and gives **17** (Scheme 3).

Furthermore, we examined reactions of chalcogenide-enones **1** and **2** and 2 equiv of trimethyl orthoformate **21** with 3 equiv of $BF_3{\cdot}Et_2O$ in MeCN at −40 °C for 13 h (Table 3). The reaction of sulfide-enone **1** with ortho ester **21** afforded Morita−Baylis−Hillman adduct **22** in 89% yield after workup with Et_3N (2 equiv) (entry 1). Compound **22** showed ^1H NMR signals due to two methoxy groups at δ 3.43 and two vinyl proton signals at δ 5.76 and 6.24. A reaction of the selenium congener **2** with **21** gave adduct **23** (65%) (entry 2). A workup of the reaction mixture with a saturated aqueous $NaHCO_3$ solution instead of Et_3N gave adduct **22** (55%) from sulfide-enone **1** (entry 3) and adduct **23** (54%) from selenium congener **2** (entry 4).

SCHEME 3

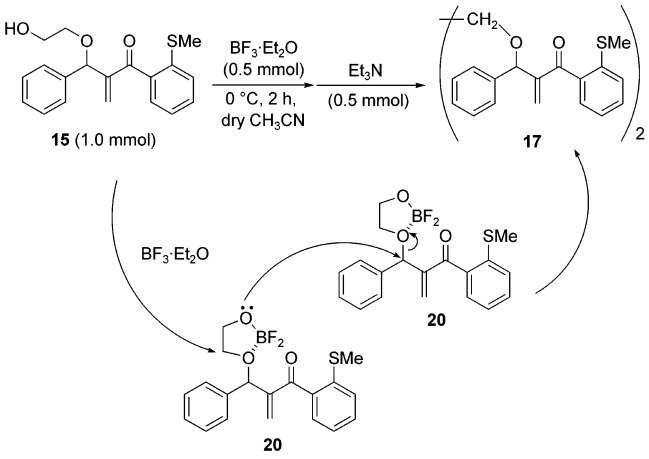
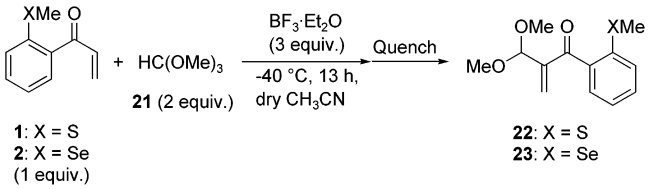


TABLE 3. Reaction of 1-[2-(Methylchalcogenyl)phenyl]-prop2-en-1-ones 1 and 2 with Trimethyl Orthoformate 21



entry	X	quench	product (% yield)
1	S	Et_3N (2 equiv)	**22** (89)
2	Se	Et_3N (2 equiv)	**23** (65)
3	S	sat. $NaHCO_3$	**22** (55)
4	Se	sat. $NaHCO_3$	**23** (54)

In conclusion, we have shown the simple procedure for α-alkoxyalkylation of enone utilizing the chalcogeno−Morita−Baylis−Hillman reaction of acetals. This method has advantages in that α-alkoxyalkyl enones can be prepared without trimethylsilyl triflate and can be directly synthesized from enones and acetals, unlike the two-step synthesis involving the Morita−Baylis−Hillman reaction of enones with aldehydes and etherification of the resulting allyl alcohols.[12]

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Supporting Information Available: X-ray crystal data and ORTEP view of **7**, experimental comments, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Compound **15** exhibited signals at δ 2.34 (1 H, br s, OH), 2.40 (3 H, s, SMe), 3.55−3.65 (2 H, m, $-CH_2OCPh$), 3.75 (2 H, br s, CH_2-OH), 5.62 (1 H, s, benzylic H), 5.70 and 5.92 (each 1 H, s, olefinic H) in the ^1H NMR spectrum. Product **17** showed signals at δ 2.36 (6 H, s, SMe), 3.62−3.67 (4 H, m, OCH_2), 5.58 (2 H, s, benzylic H), 5.65 (2 H, s, olefinic H), and 6.16 (2 H, s, olefinic H), and the intensity ratio of the signals due to the SMe and the OCH_2CH_2O groups was 3:2. High-resolution mass spectrometry gave the molecular formula $C_{36}H_{34}O_2S_2$.

(11) Rose, P. M.; Clifford, A. A.; Rayner, C. M. *J. Chem. Soc., Chem. Commun.* **2002**, 968−969.

(12) Matsumoto, S.; Mikami, K. *Synlett.* **1998**, 469−470.