COMMUNICATION

The chalcogeno-Baylis–Hillman reaction of ketones and α-dicarbonyl compounds

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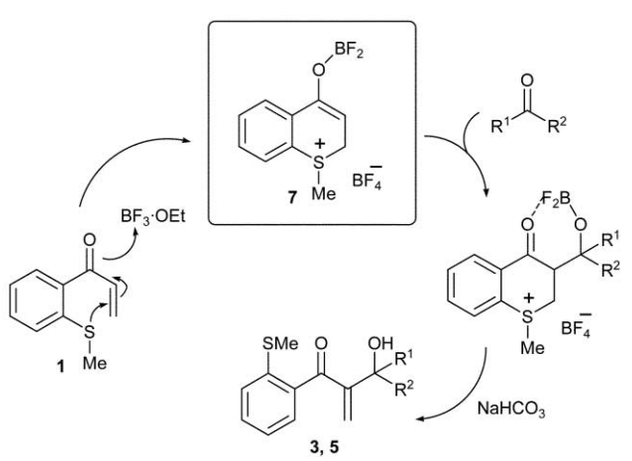
1-[2-(Methylsulfanyl)phenyl]prop-2-en-1-one reacted with ketones, α-diketones, and α-keto esters in the presence of BF_3·Et_2O to give Morita–Baylis–Hillman adducts.

The Morita–Baylis–Hillman reaction, in which a tertiary amine or phosphine catalyzes the coupling of an activated alkene with an aldehyde, is one of the most popular C–C bond-forming reactions.[1] However, this reaction suffers from a low reaction rate and a generally long reaction time, sometimes more than one week. Therefore, we developed the chalcogenide–$TiCl_4$-mediated Morita–Baylis–Hillman reaction (chalcogeno-Baylis–Hillman reaction), which is much faster than the original reaction.[2] This reaction is applicable to reactions of α-keto esters[3,4] and thioesters[5] with active alkenes and to reactions of aldehydes with active alkynes,[6] which cannot proceed under *tert*-amine-catalysed reaction conditions.

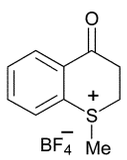
In addition to aldehydes, various carbonyl compounds have been used as electrophiles in the Morita–Baylis–Hillman reaction. Ketones react with activated alkenes only under high pressure, and this reaction requires specialised equipment.[7] Nevertheless, when activated ketones such as highly fluorinated ketones have undergone the Morita–Baylis–Hillman reaction,[8] non-enolizable α-diketones have reacted with electron-deficient alkenes,[9] but no reaction of enolizable α-diketones has been reported. α-Keto esters are very reactive electrophiles in the Morita–Baylis–Hillman reaction, and their reactions with acrylonitrile, acrylate, and but-3-en-2-one (MVK) have been well documented.[3,10,11] However, the matches among alkenes, α-keto esters, and catalytic systems are important to the success of the reaction.[3,11]

We recently developed a self-assisted tandem Michael–aldol reaction *via* a cyclic sulfonium ion intermediate.[12] The intermediate was confirmed to be a γ-sulfonio boron enolate (**7**) in Scheme 1 by the ^{1}H NMR spectral data. † Since vinyloxy borons (boron enolates) react with carbonyl compounds under mild conditions, they are useful intermediates for the synthesis of a variety of β-hydroxy ketone (aldol) derivatives.[13] These encouraged us to conduct the reaction of 1-[2-(methylsulfanyl)-phenyl]prop-2-en-1-one with various carbonyl compounds which are not subject to the traditional Baylis–Hillman reaction.



Scheme 1

We first carried out the reaction of 2 equiv. of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one (**1**) with 1 equiv. of 4′-nitroacetophenone (**2a**) under various conditions in the presence of 2 equiv. of BF_3·Et_2O (Table 1). The reaction mixture was quenched by pouring it into an $NaHCO_3$ solution and was extracted with CH_2Cl_2. The best result was obtained from the reaction at 0 °C for 30 min.



6

A white precipitate appeared from the reaction mixture during stirring and was designated 1-methyl-4-oxothiochromanium tetrafluoroborate **6** from the ^{1}H NMR spectrum. ‡ Once the precipitate separated out, the yields were not improved even though the reaction was continued. The yields were decreased when the reaction was conducted for 1 h or at room temperature (Table 1, entries 2 and 3). Other ketones similarly reacted with **1** to give adduct **3** in low to moderate yields (entries 4–7). This is the first example of inactivated ketones reacting as electrophiles under mild conditions in the Morita–Baylis–Hillman reaction.

Next we examined reactions of α-diketones and α-keto esters as electrophiles with enone **1**. The reactions were similarly conducted and stopped when a white salt, 1-methyl-4-oxothiochromanium tetrafluoroborate (**6**), appeared. The results are summarized in Table 2. Not only benzil but also diacetyl, which is enolizable, reacted with enone **1** to give adducts **5a** and **5b**, respectively (Table 2, entries 1 and 2). Ethyl pyruvate, the reaction of which with MVK was unsuccessful under various Morita–Baylis–Hillman reaction conditions,[3] produced **5c** in a 70% yield (Table 2, entry 3).

A possible mechanism is shown in Scheme 1. First, the carbonyl group of enone **1** chelates with BF_3·Et_2O, followed by the intramolecular Michael addition of a sulfanyl group to the enone moiety to form the γ-sulfonio boron enolate (**7**). This boron enolate **7** was detected by ^{1}H NMR experiments as mentioned above. The boron enolate reacts with a carbonyl compound to give the Morita–Baylis–Hillman adduct.

In conclusion, we have shown the first example of ketones undergoing the chalcogeno-Baylis–Hillman reaction under mild conditions and of enolizable α-dicarbonyl compounds such as diacetyl and ethyl pyruvate giving Morita–Baylis–Hillman adducts. The design and synthesis of the new enone–chalcogenides are in progress in order to extend the scope of

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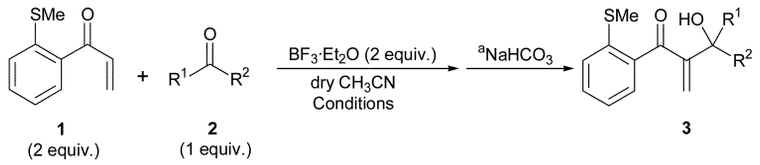
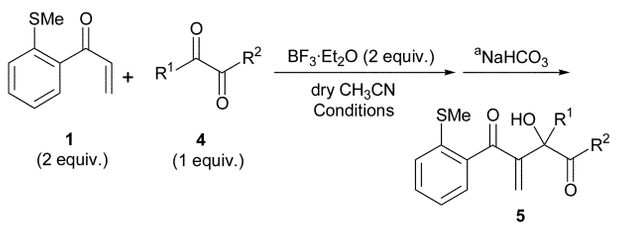
Table 1 The reaction of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one with ketones



Entry	Ketone **2**	Conditions	Product (% yield)
1	**2a** $R^1 = p\text{-}NO_2C_6H_4$, R^2 = Me	0 °C, 30 min	**3a** (47)
2	**2a** $R^1 = p\text{-}NO_2C_6H_4$, R^2 = Me	0 °C, 1 h	**3a** (41)
3	**2a** $R^1 = p\text{-}NO_2C_6H_4$, R^2 = Me	rt, 30 min	**3a** (14)
4	**2b** R^1 = Ph, R^2 = Me	0 °C, 30 min	**3b** (19)
5	**2b** R^1 = Ph, R^2 = Me	0 °C, 1 h	**3b** (11)
6	**2c** R^1 = Ph, $R^2 = (CH_2)_5$	0 °C, 30 min	**3c** (56)
7	**2c** $R^1 = R^2 = (CH_2)_5$	0 °C, 1 h	**3c** (26)

[a] Reaction mixture was poured into an $NaHCO_3$ solution.

Table 2 The reaction of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one with various carbonyl compounds



Entry	**4**	Conditions	Product (% yield)
1 [b]	**4a** $R^1 = R^2$ = Ph	0 °C, 2 h	**5a** (41)
2	**4b** $R^1 = R^2$ = Me	0 °C, 1 h	**5b** (29)
3	**4c** R^1 = Me, R^2 = OEt	rt, 2 h	**5c** (70)
4	**4d** R^1 = Ph, R^2 = OMe	rt, 2 h	**5d** (37)

[a] Reaction mixture was poured into an $NaHCO_3$ solution. [b] $BF_3{\cdot}Et_2O$ (3 equiv.) was used.

the tandem intramolecular Michael–aldol reaction or the chalcogeno-Baylis–Hillman reaction.

Experimental

Reactions of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one 1 of a carbonyl compound 2 or 4

A typical example: To a stirred solution of 4′-nitroacetophenone (82 mg, 0.5 mmol) and 1-[2-(methylsulfanyl)phenyl]-prop-2-en-1-one **1** (178 mg, 1.0 mmol) was added dropwise $BF_3{\cdot}Et_2O$ (127 μl, 1.0 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min and then poured into an $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluted with hexane–AcOEt (5 : 1, v/v) to give 3-hydroxy-2-methylene-1-(2-methylsulfanyl)-3-(4-nitrophenyl)butanone (**3a**).

Yellow needles (AcOEt–hexane). Mp 100–101 °C. IR (KBr; cm^{-1}) 3448 (OH), 1631 (C=O), 1509 and 1347 (NO_2). δ_H (400 MHz; $CDCl_3$) 1.76 (3H, s, CH_3), 2.40 (3H, s, SCH_3), 4.98 (1H, s, OH), 5.90 (1H, s, olefinic H), 6.31 (1H, S, olefinic H), 7.19 (1H, t, J = 7.5, ArH), 7.31 (1H, d, J = 7.5, ArH), 7.33 (1H, d, J = 8, ArH), 7.44 (1H, t, J = 8, ArH), 7.71 (2H, d, J = 8.5, ArH), 8.20 (2H, d, J = 8.5, ArH); δ_C (100 MHz; $CDCl_3$) 16.8 (q), 29.0 (q), 76.1 (d), 123.5 (d × 2), 124.4 (d), 126.0 (d × 2), 127.2 (d), 129.4 (d), 130.1 (t), 131.6 (d), 136.8 (s), 139.6 (s), 147.0 (s), 150.5 (s), 154.1 (s), 200.0 (s); MS (EI) m/z: 343 (M^+, 2%). Anal. calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 63.08; H, 5.10; N, 3.98%.

2-(1-Hydroxy-1-phenylethyl)-1-(2-methylsulfanylphenyl)-propenone (3b)

IR (KBr; cm^{-1}) 3445 (OH), 1626 (C=O). δ_H (400 MHz; $CDCl_3$) 1.77 (3H, s, CH_3), 2.40 (3H, s, SCH_3), 5.00 (1H, s, OH), 5.76 (1H, s, olefinic H), 6.19 (1H, S, olefinic H), 7.15 (1H, t, J = 7.5, ArH), 7.22 (1H, t, J = 8, ArH), 7.31–7.35 (4H, m, ArH), 7.41 (1H, t, J = 7.5, ArH), 7.53 (2H, d, J = 8, ArH); δ_C (100 MHz; $CDCl_3$) 16.7 (q), 29.2 (q), 76.3 (s), 124.1 (d), 124.9 (d × 2), 126.90 (d), 126.95 (d), 128.2 (d × 2), 128.7 (t), 130.0 (d), 131.4 (d), 137.1 (s), 139.8 (s), 146.3 (s), 151.6 (s), 200.3 (s); MS (EI) m/z: 298 (M^+, 2%). HRMS calcd for $C_{18}H_{18}O_2S$: 298.1027. Found: 298.1041.

2-(1-Hydroxycyclohexyl)-1-(2-methylsulfanylphenyl)propenone (3c)

IR (NaCl; cm^{-1}) 3484 (OH), 1651 (C=O); δ_H (400 MHz; $CDCl_3$) 1.23–1.32 (1H, m), 1.55–1.62 (2H, m), 1.65–1.83 (5H, m), 1.84–1.95 (2H, m), 2.44 (3H, s, SCH_3), 3.81 (1H, s, OH), 5.54 (1H, s, olefinic H), 6.05 (1H, S, olefinic H), 7.18 (1H, t, J = 7.3, ArH), 7.34 (1H, d, J = 7.3, ArH), 7.42–7.46 (2H, m, ArH); δ_C (100 MHz; $CDCl_3$) 16.5 (q), 21.6 (t × 2), 25.6 (t), 36.3 (t × 2), 72.9 (s), 124.0 (d), 126.1 (t), 126.6 (d), 130.5 (d), 131.3 (d), 137.4 (s), 139.8 (s), 153.7 (s), 200.8 (s); MS (EI) m/z: 276 (M^+, 20%). Anal. calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.25; H, 7.31%.

2-Hydroxy-3-methylene-4-(2-methylsulfanylphenyl)-1,2-diphenylbutane-1,4-dione (5a)

IR (KBr; cm^{-1}) 3412 (OH), 1669, 1613 (C=O); δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, SCH_3), 5.39 (1H, s, OH), 5.70 (1H, s, olefinic H), 5.90 (1H, s, olefinic H), 7.23–7.31 (3H, m, ArH), 7.36 (2H, t, J = 7.5, ArH), 7.40–7.51 (4H, m, ArH), 7.68 (2H, d, J = 7.0, ArH), 7.93–7.97 (3H, m, ArH); δ_C (100 MHz; $CDCl_3$) 16.2 (q), 86.5 (s), 123.7 (d), 125.9 (d), 126.6 (d × 2), 127.8 (d × 2), 128.3 (d), 128.7 (d × 2), 130.8 (d × 2), 130.9 (t), 132.0 (d), 132.4 (d), 132.4 (d), 132.7 (d), 134.8 (s), 135.5 (s), 137.7 (s), 141.1 (s), 152.2 (s), 201.2 (s), 201.3 (s). MS (EI) m/z: 388 (M^+, 1%). HRMS calcd for $C_{24}H_{20}O_3S$: 388.1133. Found: 388.1126.

3-Hydroxy-3-methyl-2-methylene-1-(2-methylsulfanylphenyl)-pentane-1,4-dione (5b)

IR (KBr; cm^{-1}) 3467 (OH), 1717, 1651 (C=O); δ_H (400 MHz; $CDCl_3$) 1.55 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.44 (3H, s, SCH_3), 4.55 (1H, s, OH), 5.72 (1H, s, olefinic H), 6.17 (1H, S, olefinic H), 7.18 (1H, t, J = 7.8, ArH), 7.33 (1H, d, J = 7.8, ArH), 7.45 (1H, t, J = 7.8, ArH), 7.57 (1H, d, J = 7.8, ArH); δ_C (100 MHz; $CDCl_3$) 16.3 (q), 22.9 (q), 23.5 (q), 79.1 (s), 123.9 (d), 126.2 (d), 126.9 (t), 131.4 (d), 131.8 (d), 135.6 (s), 140.7 (s), 150.3 (s), 198.3 (s), 209.4 (s). MS (FAB) m/z: 265 (M^+ + 1, 12%). Anal.

calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.40; H, 5.92%.

2-Hydroxy-2-methyl-3-(2-methylsulfanylbenzoyl)but-3-enoic acid ethyl ester (5c)

IR (KBr; cm^{-1}) 3464 (OH), 1722, 1254, 1146 (ester), 1658 (C=O); δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, J = 7, CH_3), 1.67 (3H, s, CH_3), 2.43 (3H, s, SCH_3), 4.22–4.28 (2H, m, CH_2), 5.75 (1H, s, olefinic H), 6.23 (1H, S, olefinic H), 7.17 (1H, t, J = 7.5, ArH), 7.34 (1H, d, J = 7.5, ArH), 7.42 (1H, d, J = 7.5, ArH), 7.43 (1H, t, J = 7.5, ArH); δ_C (100 MHz; $CDCl_3$) 14.0 (q), 16.4 (q), 23.8 (q), 62.0 (t), 74.2 (s), 124.0 (d), 126.5 (d), 127.9 (t), 130.3 (d), 131.4 (d), 136.4 (s), 139.8 (s), 149.5 (s), 174.8 (s), 198.0 (s). MS (EI) m/z: 294 (M^+, 2%). Anal. calcd for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.16. Found: C, 61.20; H, 6.20%.

2-Hydroxy-3-(2-methylsulfanylbenzoyl)-2-phenylbut-3-enoic acid methyl ester (5d)

IR (KBr; cm^{-1}) 3448 (OH), 1728, 1253, 1120 (ester), 1656 (C=O); δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, SCH_3), 3.81 (3H, s, OCH_3), 4.75 (1H, s, OH), 5.64 (1H, s, olefinic H), 5.78 (1H, s, olefinic H), 7.20 (1H, t, J = 8, ArH), 7.35–7.44 (5H, m, ArH), 7.58 (1H, d, J = 8, ArH), 7.70 (2H, d, J = 8, ArH); δ_C (100 MHz; $CDCl_3$) 16.4 (q), 53.2 (q), 79.5 (s), 124.0 (d), 126.5 (d), 126.7 (d × 2), 128.2 (d × 2), 128.3 (d), 130.6 (d), 131.6 (t), 132.0 (d), 136.2 (s), 137.8 (s), 140.0 (s), 150.8 (s), 174.0 (s), 198.7 (s). MS (EI) m/z: 342 (M^+, 3%). HRMS calcd for $C_{19}H_{18}O_4S$: 342.0926. Found: 342.0934.

Acknowledgements

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Notes and references

† ^{1}H NMR spectrum of a mixture of enone **1** and an equimolar amount of $BF_3{\cdot}Et_2O$ in CD_3CN exhibited three signals at δ 3.90 (1H, dd, J = 18 and 5, H-2), 4.39 (1H, dd, J = 18 and 2, H-2) and 5.27 (1H, dd, J = 5 and 2, H-3) and had good consistency with that of a mixture of **1** and trimethylsilyl triflate (trifluoromethanesulfonate) in CD_3CN showing signals at δ 3.93 (1H, dd, J = 17 and 2, H-2), 4.37 (1H, dd, J = 17 and 3.5, H-2), and 5.27 (1H, dd, J = 3.5 and 2, H-3).

‡ ^{1}H NMR spectrum of the precipitate in CD_3CN was identical to that of an authentic sample.[14]

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