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# Self-assisted tandem Michael-aldol reactions of α,β-unsaturated ketones with aldehydes

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***Received (in Cambridge, UK) 11th July 2001, Accepted 24th August 2001***
***First published as an Advance Article on the web 10th September 2001***

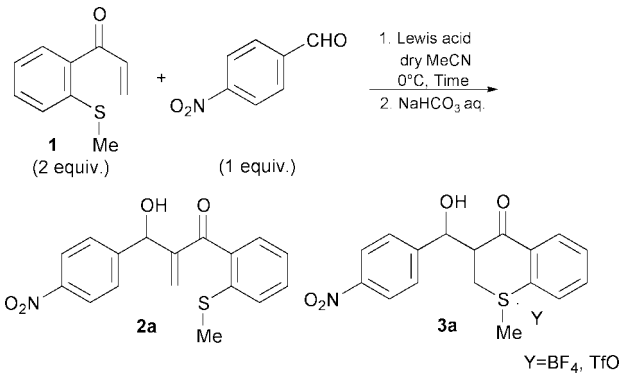


**The tandem Michael-aldol reaction of 1-[2-(methylsulfanyl)-phenyl]prop-2-en-1-one (1) or the seleno congener 4 with *p*-nitrobenzaldehyde in the presence of $BF_3{\cdot}Et_2O$ gave the Baylis–Hillman adduct 2 or 5 and onium salt 3 or 6, respectively, and selenochromanone 7 from 4.**

The Baylis–Hillman reaction is one of the most popular reactions, and a great number of papers have been recently published on it.[1] This reaction is quite slow, and many changes have been made to it to overcome this drawback.[2] We developed the chalcogenide–$TiCl_4$-mediated reactions of electron-deficient alkenes with aldehydes.[3] The reactions had been deemed to be a chalcogenide version of the Baylis–Hillman reaction because the Baylis–Hillman adducts were given after purification of the products by preparative TLC on silica gel. However, a detailed examination of the reactions revealed that the original products were α-chloromethyl aldols and that dehydrochlorination occurred during purification by the preparative TLC on silica gel.[4] Similar reactions using $TiCl_4$ have been reported by other groups.[5] Very recently, we obtained methyl 3-methylsulfanyl-2-(α-hydroxy-*p*-nitrobenzyl)acrylate from the reaction of methyl propiolate with *p*-nitrobenzaldehyde in the presence of $TiBr_4$–$SMe_2$ as a minor product.[6] This finding implied that $SMe_2$ worked as a Lewis base and suggested to us that the intramolecular Michael addition of a sulfanyl group to an enone moiety would proceed more efficiently than the intermolecular one. In other words, the sulfanyl substituent assists the intramolecular Michael addition to form a cyclic sulfonium betaine. Cyclisation of enone sulfides with a Lewis acid has been reported from a different viewpoint.[7] These reports encouraged us to conduct the reactions of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one with aldehydes in the presence of $BF_3{\cdot}Et_2O$. In this paper, we would like to describe a new type of tandem Michael-aldol reaction of an enone sulfide with aldehydes using a Lewis acid.†

A chloride ion reacted with an α,β-unsaturated carbonyl compound as a nucleophile in the reaction of the enone with an aldehyde using chalcogenide–$TiCl_4$.[4] In order to avoid this reaction and allow a chalcogenide to react with the enone instead of a chloride ion, we selected a Lewis acid such as metal fluoride or triflate, which releases non-nucleophilic anion, although $BF_3{\cdot}Et_2O$ and triflates of the lanthanide metals had been ineffective for the intermolecularly chalcogenide-promoted tandem Michael-aldol reactions.[3]

Various Lewis acids were examined for the reactions of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one (**1**)‡ with *p*-nitrobenzaldehyde (Scheme 1). The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. Results of the reactions are summarised in Table 1. Reactions using $BF_3{\cdot}Et_2O$ were monitored by TLC and stopped when *p*-nitrobenzaldehyde disappeared (entries 1–3). The reaction was accelerated with increase of the amount of $BF_3{\cdot}Et_2O$ and the reaction time was shortened. Prolonged reaction time decreased the yield of **3a** and increased **2a** (entries 1 and 4). Reactions using $BF_3{\cdot}Et_2O$–$LiBF_4$ (1:1) or $TiF_4$ afforded **2a** only in low yields (entries 5 and 6). Reaction catalyzed $Yb(TfO)_3$ gave **2a**




**Scheme 1**

(21%) and **3a** (42%)§ (entry 7). When 2 equiv. of $BF_3{\cdot}Et_2O$ were used, the highest yields of **2a** (18%) and **3a** (62%)§ were given from the reaction at 0 °C for 1 h (entry 2). The use of lithium perchlorate and aluminium sulfate gave no product, and **1** was recovered without loss.

Other aromatic aldehydes and 3-phenylpropionaldehyde similarly reacted with **1** to give **2** and **3** in low to moderate yields (Scheme 2 and Table 2). Since the reactions of various aldehydes were slower than that of *p*-nitrobenzaldehyde, the reactions were conducted for 2 h and then worked up with aqueous $NaHCO_3$. Seleno derivative **4**‡ reacted with aromatic aldehydes to give α-methylene aldol **5**, aldol selenonium salt **6**§, and 3-(α-hydroxybenzyl)selenochromanone **7**. Demethylation of **6** occurred more easily during the reactions than that of **3** to give **7** as a mixture of diasteroisomers. The *syn*- and *anti*-diastereoisomers were assigned in comparison of the coupling constants of the methine protons [C-CH(OH)-C], *syn*- (0–2.4 Hz) and *anti*-isomer (7.8–8.3 Hz), with those of the cyclohexanone derivative.[8]

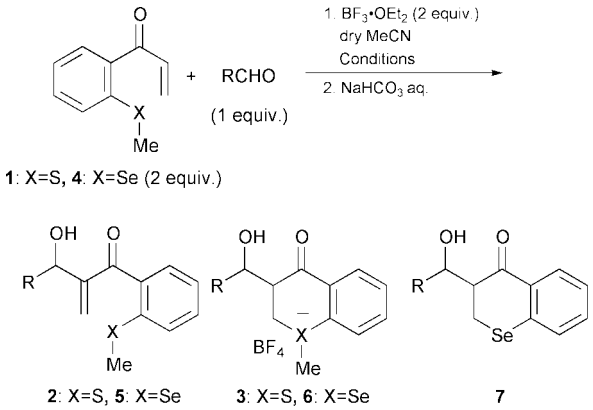
$^1H$ NMR spectra of the residues obtained by concentration of the reaction mixtures were measured in order to examine whether α-methylene aldol **2** or **5** was formed *via* the Baylis–Hillman reaction or the β-elimination of **3** or **6** by a work-up with a saturated aqueous $NaHCO_3$ solution. Vinyl proton

**Table 1** Lewis acids for reactions of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one **1** with *p*-nitrobenzaldehyde.

| Entry | Lewis acid (equiv.) | Time | Products (Yield %) |
|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ (1) | 2 h | **2a** (24), **3a** (50) |
| 2 | $BF_3{\cdot}Et_2O$ (2) | 1 h | **2a** (18), **3a** (62) |
| 3 | $BF_3{\cdot}Et_2O$ (3) | 45 min | **2a** (36), **3a** (34) |
| 4 | $BF_3{\cdot}Et_2O$ (1) | 24 h[a] | **2a** (42), **3a** (29) |
| 5 | $BF_3{\cdot}Et_2O$–$LiBF_4$ (1:1) | 2 h | **2a** (10) |
| 6 | $TiF_4$ (2) | 2 h | **2a** (33) |
| 7 | $Yb(TfO)_3$ (2) | 2 h | **2a** (21), **3a** (42) |

[a] Room temperature.

 DOI: 10.1039/b106022h




**Scheme 2**

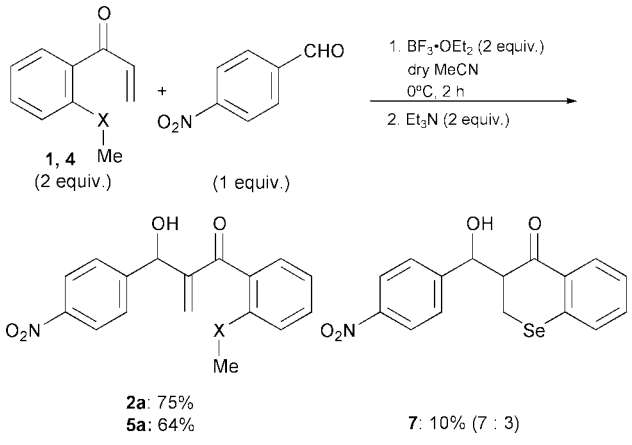
**Table 2** Reactions of 1-[2-(methylchalcogenyl)phenyl]prop-2-en-1-ones **1** and **4** with aldehydes.

| Entry | Aldehyde, R | Conditions | Products (Yield %) |
|---|---|---|---|
| 1 | *p*-$ClC_6H_4$ | 0 °C, 2 h | **2b** (24), **3b** (37) |
| 2 | *p*-$CF_3C_6H_4$ | 0 °C, 2 h | **2c** (49), **3c** (17) |
| 3 | Ph | 0 °C, 2 h then rt, 3 h | **2d** (24), **3d** (37) |
| 4 | $PhC_2H_4$ | 0 °C, 2 h then rt, 3 h | **2e** (54) |
| 5 | *p*-$NO_2C_6H_4$ | 0 °C, 2 h | **5a** (30), **6a** (45), **7a** (15) (3:2)[a] |
| 6 | *p*-$ClC_6H_4$ | 0 °C, 2 h | **5b** (25), **6b** (25), **7b** (28) (3:2)[a] |

[a] Diastereoisomer ratio (*syn*:*anti*-isomer).

signals of **2** and **5** were observed in the region of $\delta$ 5.80, 6.09 and $\delta$ 5.76, 6.06, respectively. This indicates that α-methylene aldol **2** or **5** was formed during the reaction. However, the intensities of the $^+$X-Me signals of **3** and **6** were decreased, and those of the X-Me signals of **2** and **5** were increased after treatment with saturated aqueous $NaHCO_3$ solution. Therefore, some of the onium salts **3** or **6** suffered β-elimination by the work-up with the saturated aqueous $NaHCO_3$ solution to form **2** or **5**, respectively.§

Next, the residue obtained from the reaction of **1** or **4** (2 equiv.) with *p*-nitrobenzaldehyde (1 equiv.) using $BF_3$·$Et_2O$ (2 equiv.) as a Lewis acid was treated with triethylamine (2 equiv.) instead of saturated aqueous $NaHCO_3$ solution in order to obtain α-methylene aldol **2** or **5** (Scheme 3). The reaction of sulfide **1** afforded **2a** in 75% yield, but the reaction of the selenium congener **4** gave **5** (64%) and the demethylated product **7** (10%).




**Scheme 3**

The reaction conditions presented here were not sufficiently optimised, but this methodology will be the starting point for the development of tandem Michael-aldol reactions as well as the Baylis–Hillman reaction.

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research (C), 12672056.

## Notes and references

† A typical example: $BF_3$·$OEt_2$ (126 μl, 1.00 mmol) was added to a stirred solution of *p*-nitrobenzaldehyde (76 mg, 0.50 mmol) and 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one (**1**) (178 mg, 1.00 mmol) in dry MeCN (1.5 ml) at 0 °C. The mixture was stirred at the same temperature for 2 h, and the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (3 ml). The precipitate of the inorganic material was removed by filtration through Celite and washed with MeCN. The filtrate and the washing were combined, and the solvent was evaporated under reduced pressure. The residue was washed with $CH_2Cl_2$, and crystals were filtered and recrystallised from MeCN–$CH_2Cl_2$ to give 3-[(4-nitrophenyl)(hydroxy)methyl]-1-methyl-4-oxo-3,4-dihydro-2*H*-thiochromenium tetrafluoroborate (**3a**), as a white powder of a mixture of diastereoisomers: major isomer: $\delta_H$ 3.10 (3H, s, SMe), 3.60 (1H, dd, $J$ = 5 and 15), 3.61 (1H, ddd, $J$ = 3, 5 and 10), 4.02 (1H, dd, $J$ = 10 and 15), 4.36 (1H , d, $J$ = 4, OH), 5.79 (1H, dd, $J$ = 3 and 4, benzylic H), 7.71 (2H, d, $J$ = 9, ArH), 7.89–7.94 (3H, m, ArH), 8.29 (2H, d, $J$ = 9, ArH), 8.38 (2H, dd, $J$ = 2 and 7, ArH). The $^1$H NMR signals of the minor isomer could not be clearly assigned because of the overlapping absorptions. The washing was concentrated to dryness, and the residue was purified by preparative TLC on silica gel (ethyl acetate–hexane = 1:2, v/v) to give 2-[(4-nitrophenyl)(hydroxy)methyl]-1-[2-(methylsulfanyl)phenyl]-prop-2-en-1-one (**2a**) as yellow oil: $\delta_H$ 2.40 (3H, s, $SCH_3$), 3.50 (1H, br s, OH), 5.80 and 6.09 (each 1H, s, olefinic H), 5.91 (1H, s, benzylic H), 7.17 and 7.43 (each 1H, t, $J$ = 8, ArH), 7.27 and 7.34 (each 1H, d, $J$ = 8, ArH), 7.66 and 8.21 (each 2H d, $J$ = 9, ArH); $\delta_C$ 17.0 (q), 72.4 (d), 123.8 (d), 124.6 (d), 127.3 (d), 127.4 (d), 129.7 (d), 130.1 (t), 131.7 (d), 136.9 (s), 139.3 (s), 147.5 (s), 149.1 (s), 149.2 (s), 198.2 (s); EIMS *m*/*z* 329 ($M^+$); Found: C, 61.9; H, 4.9; N, 4.0. $C_{17}H_{15}NO_4S$ requires C, 62.0; H, 4.6; N, 4.3%.

‡ Compounds **1** and **4** were prepared in a similar way as for 1-[2-(ethylsulfanyl)-4,5-dimethoxyphenyl]prop-2-en-1-one in Ref. 7*b*.

§ The onium salts **3** and **6** were obtained as mixtures of stereoisomers based on two chiral carbons and a chalcogenide atom. However, their stereostructures and isomer ratios could not be determined. The stereostructures of onium salts **3** and **6** and their reactivity against a base will be described in the full paper.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