A Mild and Efficient Stereoselective Synthesis of (*Z*)- and (*E*)-Allyl Sulfides and Potent Antifungal Agent, (*Z*)-3-(4-Methoxybenzylidene)thiochroman-4-one from Morita–Baylis–Hillman Acetates[1)]

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A facile stereoselective synthesis of (*Z*)- and (*E*)-allyl sulfides has been accomplished from Morita–Baylis–Hillman acetates in one-pot by treatment with benzene thiol in the presence of catalytic amounts of 15% aqueous NaOH and TBAI in DMSO at room temperature. The method has been applied for the synthesis of (*Z*)-3-(4-methoxybenzylidene)thiochroman-4-one, a potent antifungal compound.

Key words Morita–Baylis–Hillman acetate; benzene thiol; (*Z*)-allyl sulfide; (*E*)-allyl sulfide; (*Z*)-3-(4-methoxybenzylidene)-thiochroman-4-one; antifungal compound

Allyl sulfides have gained significant importance as a class of useful scaffold in organic synthesis.[2—4)] They are used as valuable synthons for the various organic transformations[5—7)] including imidation and subsequent sigmatropic rearrangements[8)] and thio-Claisen rearrangement.[9)] They also served as important synthetic intermediates in agricultural and pharmaceutical chemistry.[10,11)] Hence, the development of efficient methodology for their synthesis is highly essential. Here the Morita–Baylis–Hillman chemistry[12—14)] has been applied for the synthesis of these compounds.

The Morita–Baylis–Hillman reaction is a versatile C–C bond forming reaction which provides functionalized adducts.[12—14)] These adducts and their derivatives have widely been explored for the stereoselective synthesis of trisubstituted alkenes and biologically active natural products.[15—20)] Nucleophilic displacement of the Morita–Baylis–Hillman acetates is an important protocol for the synthesis of trisubstituted alkenes in organic chemistry. Although there exist several methods for the nucleophilic displacement of Morita–Baylis–Hillman acetates with various reagents such as metal halides,[21)] metal hydrides,[22,23)] amide,[24,25)] cyanide,[26,27)] amine[28,29)] and azide[26,27,30)] those afford a variety of trisubstituted alkenes, displacement with sulfur nucleophiles is limited.[31,32)]

In connection with our ongoing research to develop the new synthetic routes for the preparation of trisubstituted alkenes[33—43)] using Morita–Baylis–Hillman adducts, herein we wish to report a one-pot stereoselective synthesis of trisubstituted (*Z*)- and (*E*)-allyl sulfides from Baylis–Hillman acetates by treatment with benzene thiol in the presence of catalytic amounts of 15% aqueous NaOH and TBAI (tetrabutylammonium iodide) in DMSO at room temperature (Chart 1, Table 1). Thus, 3-acetoxy-2-methylene alkanoates **1** (Morita–Baylis–Hillman acetates derived from acrylate esters) on similar treatment afforded the corresponding (*Z*)-allyl phenyl sulfides **3** while 3-acetoxy-2-methylene alkanenitriles **2** (Morita–Baylis–Hillman acetates derived from ac-

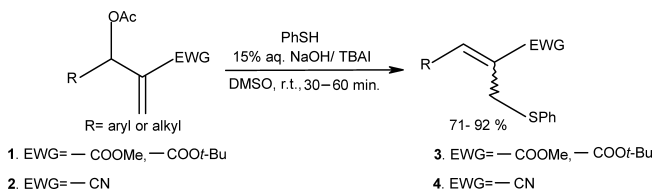
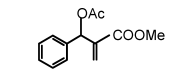
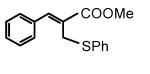
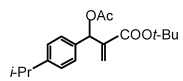
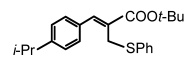
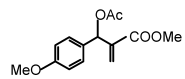
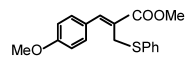
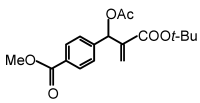
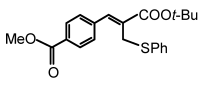
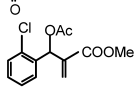
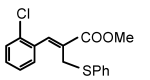
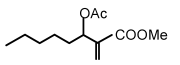
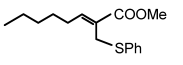
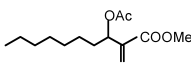
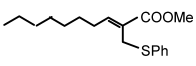
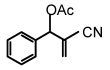
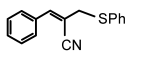
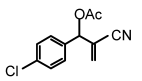
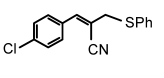
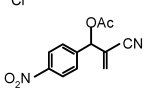
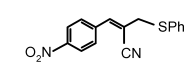
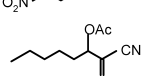
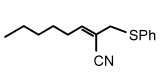


Chart 1

Table 1. Stereoselective Synthesis of (*Z*)-Allylphenyl Sulfides **3**[a)] and (*E*)-Allylphenyl Sulfides **4**[a)] from Baylis–Hillman Acetates

Entry	Baylis–Hillman acetates	Products[b)]	Isolated yields (%)
3a			92
3b			86
3c			89
3d			79
3e			82
3f			75
3g			73
4a			80
4b			77
4c			74
4d			71

a) All the products were characterized from their IR, ^{1}H- and ^{13}C-NMR, and MS spectral data. *b*) *E*/*Z* ratio was determined by the ^{1}H-NMR spectra of the crude products. The other regiomers of the products **4a**—**d** were obtained in *ca.* 5% yields.

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rylonitrile) afforded (*E*)-allyl phenyl sulfides **4**.

Initially the conversion of **1a** (R=Ph, EWG=COOMe) with PhSH was carried out with only aqueous NaOH solution of different concentrations. The yield of the desired product was low. The reaction was next attempted with the addition of a Phase transfer catalyst (such as TBAF, TBAB or TBAI) and using a solvent (such as DMF, DMSO or THF). Considering the yield and the reaction time the best result was obtained by using catalytic amount of the combination of 15% aqueous NaOH and TBAI in DMSO. By the addition of the phase transfer catalyst (TBAI) the yield of the product was increased due to an increased solubility of nucleophile into organic phase. Subsequently utilizing these reagents and DMSO, a series of (*Z*)- and (*E*)-allyl phenyl sulfides (**3**, **4**) were prepared from various Morita–Baylis–Hillman acetates (**1**, **2**). Alkyl, halogen, ether and ester remained intact. The Morita–Baylis–Hillman acetates **1** and **2** underwent the conversion with equal ease. However, the conversions of those derived from aliphatic aldehydes (entry **3f**, **3g**, **4d**) were somewhat low. Moreover, the preparation of allyl sulfides from **1** and **2** generated from aromatic aldehydes required only 0.5 h while generated from aliphatic aldehydes required 1 h.

The present conversion is highly stereoselective. Adduct **1** afforded allyl phenyl sulfides solely with (*Z*)-stereoselectivity while **2** afforded allyl phenyl sulfides with (*E*)-stereoselectivity. The structures and stereochemistry of the products were confirmed from their spectral IR, ^{1}H- and ^{13}C-NMR and MS data. The (*Z*)- and (*E*)-stereochemistry of the allyl sulfides could easily be settled from the assignment of the chemical shift values of the vinyl protons in their ^{1}H-NMR spectra. It is reported that β-vinylic proton *cis* and *trans* to the ester group resonates at *ca.* δ 7.5 and 6.5 respectively when R is aryl.[18,44] The same proton *cis* and *trans* to the ester group appears at *ca.* δ 6.8 and 5.7 respectively when R is alkyl.[45,46] Similarly the β-vinylic proton *cis* and *trans* to the nitrile group appears at *ca.* δ 7.6 and 6.8 respectively when R is aryl[47,48] while the same proton *cis* and *trans* to the nitrile group resonates at *ca.* δ 6.3 and 6.1 when R is alkyl.[49,50] These values are useful in determining the stereochemistry of the prepared allyl sulfides (**3**, **4**). The stereochemistry of **3** and **4** can possibly be explained[16,42,43] by considering the transition state models **A**, **B** and **C** (Fig. 1). Transition state **A** is more favored than **B** when EWG is an ester and (*Z*)-products are formed exclusively. On the other hand, model **C** is more favored than **A** when the EWG is a nitrile as –CN is linear and hence the (*E*)-products are formed predominantly.

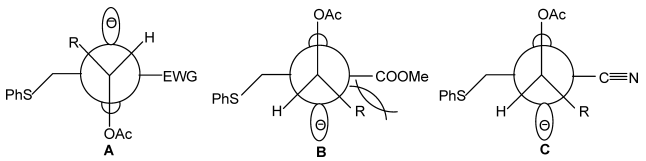

Fig. 1.

The present method has been applied for the synthesis of the antifungal compound, (*Z*)-3-(4-methoxybenzylidene)-thiochroman-4-one (**5**). The compound was found to be significantly active *in vitro* against the pathogenic fungi, *Candida albicans* (MIC=6 μg/ml) and *Torulopsis glabrata* (MIC=6 μg/ml).[51] The allyl sulfide **3c** was utilized for the synthesis of **5**. The ester group of **3c** was hydrolyzed with aqueous KOH to produce the corresponding acid **3c^1**. This acid **3c^1** was next cyclized with TFAA in anhydrous CH_2Cl_2 under reflux to form **5** in high yield (Chart 2). The spectral (IR, ^{1}H- and ^{13}C-NMR and MS) data of the compound clearly established its structure.

In conclusion, we have developed a new, mild and simple protocol for stereoselective one-pot synthesis of (*Z*)- and (*E*)-allyl phenyl sulfides from Morita–Baylis–Hillman acetates by treatment with benzene thiol in the presence of catalytic amount of the combination of 15% aqueous NaOH and TBAI in DMSO as a solvent. The prepared compounds can be utilized for synthesis of useful heterocycles by thio-Claisen rearrangement and other methods. The present protocol has been applied for the synthesis of the potent antifungal compound, (*Z*)-3-(4-methoxybenzylidene)thiochroman-4-one.

Experimental

General Procedure for the Synthesis of Allyl Phenyl Sulfides 3 and 4 To a solution of benzenethiol (110 mg, 1 mmol) dissolved in DMSO (5 ml) were added TBAI (15 mg) and 15% aqueous NaOH solution (0.5 ml). The mixture was stirred at room temperature for 30 min. The Baylis–Hillman acetate **1** or **2** (1 mmol) was added and the solution stirred for another 30 or 60 min. After completion of the reaction (monitored by TLC), the mixture was quenched with water (5 ml) and extracted with Et_2O (3×10 ml). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel, 2% EtOAc in hexane) to afford the pure (*Z*)- or (*E*)-allyl phenyl sulfide **3** or **4**.

The spectral (IR, ^{1}H- and ^{13}C-NMR and MS) and analytical data of some representative products are given below.

Product **3a**: Colorless oil; IR (KBr): ν_{max} 1725, 1622, 1591, 1463 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.71 (1H, s), 7.39—7.28 (6H, m), 7.23—7.14 (4H, m), 3.99 (2H, s), 3.78 (3H, s); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.2, 141.0, 136.1, 135.4, 134.2, 132.0, 130.4, 128.8, 128.5, 128.2, 128.0, 127.7, 126.1, 51.6, 31.7; FAB-MS: *m/z* 307 $[M+Na]^+$.

Product **3c**: Colorless oil; IR (KBr): ν_{max} 1722, 1633, 1585, 1478 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.70 (1H, s), 7.50—7.33 (4H, m), 7.32—7.17 (3H, m), 6.92—6.81 (2H, m), 4.05 (2H, s), 3.85 (3H, s), 3.77 (3H, s);

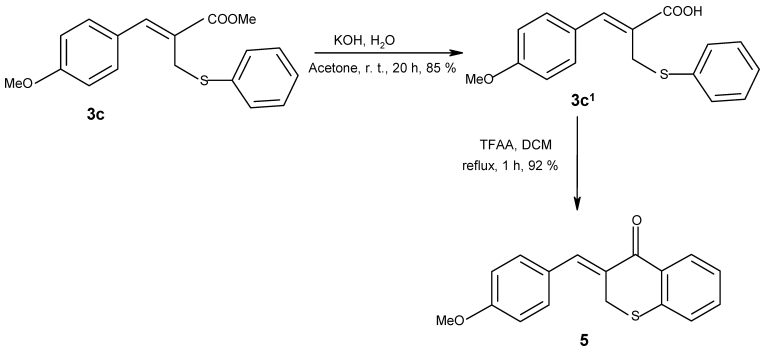

Chart 2

^{13}C-NMR ($CDCl_3$, 75 MHz): δ 168.1, 160.4, 141.8, 136.5, 131.5, 130.4, 128.6, 127.5, 126.8, 125.9, 114.4, 55.2, 52.1, 32.6; FAB-MS: *m/z* 337 $[M+Na]^+$.

Product **3f**: Colorless oil; IR (KBr): ν_{max} 1718, 1642, 1437, 1288 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.40 (2H, dd, *J*=8.0, 2.0 Hz), 7.28—7.19 (3H, m), 6.79 (1H, t, *J*=7.0 Hz), 3.75 (5H, s), 1.99—1.87 (2H, m), 1.38—1.12 (6H, m), 0.90 (3H, t, *J*=7.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 167.2, 145.8, 135.9, 132.2, 128.5, 128.0, 127.2, 52.6, 31.2, 28.5, 28.2, 22.0, 13.7; FAB-MS: *m/z* 301 $[M+Na]^+$.

Product **4a**: Colorless oil; IR (KBr): ν_{max} 2218, 1588, 1486, 1405 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.61—7.20 (10H, m), 6.60 (1H, s), 3.72 (2H, s); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 144.7, 133.4, 132.5, 131.7, 130.3, 128.8, 128.6, 128.5, 127.9, 112.3, 107.4, 41.0; FAB-MS: *m/z* 274 $[M+Na]^+$.

Product **4d**: Colorless oil; IR (KBr): ν_{max} 2219, 1633, 1582, 1439 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.38 (2H, dd, *J*=8.0, 2.0 Hz), 7.32—7.20 (3H, m), 5.92 (1H, t, *J*=7.0 Hz), 3.53 (2H, s), 2.31—2.20 (2H, m), 1.31—1.09 (6H, m), 0.85 (3H, t, *J*=7.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 149.7, 132.1, 128.8, 127.2, 116.2, 111.0, 38.4, 30.9, 30.3, 27.1, 21.6, 13.1; FAB-MS: *m/z* 268 $[M+Na]^+$.

Synthesis of (*Z*)-3-(4-Methoxybenzylidene)thiochroman-4-one Conversion of **3c** into **3c**[1]: To a stirred solution of the allyl sulfide **3c** (2 mM, 0.628 g) in acetone (1 ml) was added aqueous KOH (2 g in 5 ml water) at room temperature. After 20 h, the reaction mixture was neutralized with cold conc. HCl and extracted with ether (3×10 ml). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by crystallization (in MeOH) to afford pure **3c**[1] in 85% yield (0.492 g), as a white solid, mp 210—212 °C; IR (KBr): ν_{max} 3449, 1671, 1600, 1511, 1267 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.86 (1H, s), 7.51 (2H, d, *J*=8.0 Hz), 7.42 (2H, d, *J*=8.0 Hz), 7.31—7.24 (3H, m), 6.90 (2H, d, *J*=8.0 Hz), 4.09 (2H, s), 3.82 (3H, s); FAB-MS: *m/z* 323 $[M+Na]^+$.

Cyclization of **3c**[1]: To a stirred solution of **3c**[1] (1 mM, 0.3 g) in anhydrous dichloromethane was added trifluoroacetic anhydride (TFAA, 1 mM, 0.210 g) and heated under reflux for 1 h. The reaction mixture was diluted with water (4 ml) and extracted with ether (3×10 ml). The combined organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude solid obtained was crystallized (3% EtOAc in hexane) to provide **5** as a yellow crystalline solid in 92% yield (0.259 g), mp 133—136 °C; IR (KBr): ν_{max} 3448, 1663, 1609, 1588, 1438, 1294 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.19 (1H, d, *J*=8.0 Hz), 7.78 (1H, s), 7.39 (2H, d, *J*=8.0 Hz), 7.34—7.22 (3H, m), 6.98 (2H, d, *J*=8.0 Hz), 4.18 (2H, s) 3.85 (3H, s); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 185.2, 160.0, 141.1, 137.6, 132.5, 132.2, 131.0, 130.7, 130.1, 127.3, 127.1, 125.4, 113.8, 55.1, 29.2; FAB-MS: *m/z* 305 $[M+Na]^+$.

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