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One-pot synthesis of allyl thioacetate from benzaldehydes and activated alkenes using the Morita–Baylis–Hillman reaction as a key step

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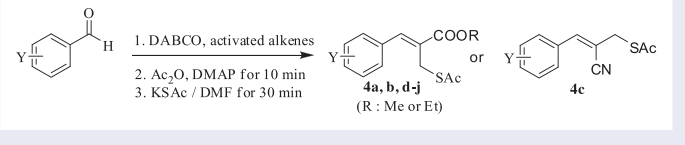
ABSTRACT

An efficient, regioselective and steresoselecitive one-pot protocol for the synthesis of (*Z*)-*S*-2-alkoxycarbonyl-3-acylallyl ethanethioates and (*E*)-*S*-2-cyano-3-acylallyl ethanethioates from benzaldehydes and activated alkenes (methyl acrylate and acrylonitrile) was developed. Our method consisted of Morita–Baylis–Hillman reaction of benzaldehydes and activated alkenes using DABCO followed by acetylation using acetic anhydride and a catalytic amount of DMAP, and S_N2' reaction with potassium thioacetate in DMF. The first two reactions proceeded under solvent-free condition.



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One-pot reaction; benzaldehyde; activated alkene; Morita–Baylis–Hillman reaction; allyl thioacetate

1. Introduction

One-pot reactions and solvent-free reactions have obtained significant attention in organic synthesis. The development of one-pot reactions is therefore very important to minimize the use of reagents, catalysts, and solvent, as well as to reduce the number of isolation steps which generate waste.[1,2] Solvent-free reaction conditions are attractive from the point of view of environmentally benign and clean technologies.[3,4]

The Morita–Baylis–Hillman (MBH) reaction is an important carbon–carbon bond-forming reaction affording alkenes with several functional groups.[5–7] MBH adducts and their acetates are valuable synthetic intermediates for the synthesis of a variety of heterocycles.[8–15] They are also used as intermediates for the preparation of trisubstituted alkenes bearing various functional groups by nucleophilic substitution [16–18] or a cross-coupling reaction with organometallics [19–22] using palladium and rhodium as a catalyst or alkyl halides using zinc [23] and trialkylindium.[24] Organic compounds containing the sulfur moiety are important for the construction of target molecules, such as

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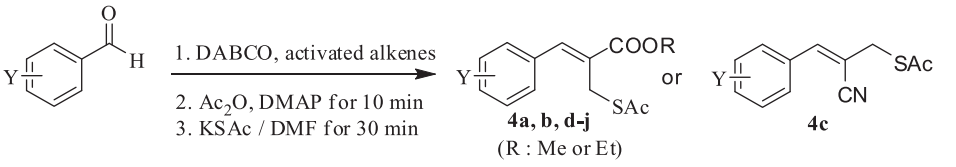


Scheme 1. One-pot synthesis of allyl thioacetate from benzaldehyde.

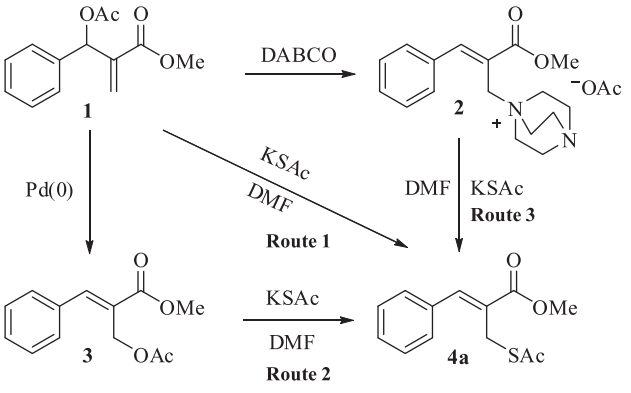
sulfur-containing drugs. The stereoselective and regioselective S_N2' reaction of acetates of MBH adducts have been reported to provide one of the important methods for the preparation of bioactive organic compounds containing sulfur.[25,26]

Herein, we wish to report an efficient regioselective and stereoselective one-pot protocol for the synthesis of (*Z*)-*S*-2-alkoxycarbonyl-3-acylallyl ethanethioates and (*E*)-*S*-2-cyano-3-acylallyl ethanethioates from benzaldehydes and activated alkenes via an MBH reaction using DABCO followed by acetylation using acetic anhydride and a catalytic amount of DMAP, and nucleophilic substitution using potassium thioacetate in DMF at RT. (Scheme 1)

2. Results and discussion

For the success of our one-pot consecutive synthesis of (*Z*)-*S*-2-alkoxycarbonyl-3-acylallyl ethanethioates and (*E*)-*S*-2-cyano-3-acylallyl ethanethioates from benzaldehydes and activated alkenes (methyl acrylate and acrylonitrile), we were faced with either finding the proper reaction condition in the plethora of reported reaction conditions or the development of new valid reaction conditions for each of the three-steps: MBH reaction, acetylation, and nucleophilic substitution. Among the plethora of MBH reactions of aryl aldehyde with activated alkene described in the literature, the neat conditions developed by an Indian group [27] was found to be the best for our one-pot reaction on the basis of a test study with benzaldehyde and acrylonitrile as a model system. However, excess methyl acrylate (3 equiv.) and DABCO (1 equiv.) rather than a catalytic amount of DABCO and 1 equiv. of acrylate used in their report was identified as a requirement to achieve a reasonable reaction time. The choice of acetylation protocols was the reaction of an MBH adduct with acetic anhydride as acetylating agent and DMAP as a catalyst at room temperature in the absence of a solvent.[28]

For the thioacetate substitution of the MBH acetate, thioacetic acid in methylene chloride [29] and potassium thioacetate in methanol [30] have been reported in literature. When thioacetic acid protocol was applied to our one-pot method, the reaction was complicated. In addition, thioacetic acid is nasty, foul-smelling, and toxic. When the reaction of MBH acetate generated under one-pot conditions was conducted with potassium thioacetate in methanol, the reaction was clean, but the yield was relatively low due to the formation of the side product. Therefore, substitution reaction of an MBH acetate generated using potassium thioacetate was tried in a variety of solvent systems such as THF, THF/H_2O, CH_3CN, and DMF (route 1 of scheme 2). Finally, DMF was found as the best choice for the solvent. The formation of isomer **3** [31] and DABCO salt **2** (The isomerization result of Baylis–Hillman acetate using a catalytic amount of DABCO will be reported in a separate publication.) [32] in the middle of the substitution reaction was



Scheme 2. Mechanical study of nucleophilic substitution MBH acetate.

observed (The isomer **3** and DABCO salt **2** were characterized using TLC and ^{1}H NMR spectroscopy.). However, an independent study showed that isomer **3** and DABCO salt **2** prepared from MBH adduct acetate **1** undergoes nucleophilic substitution to give the target molecule thioacetate **4** in excellent yield in S_N2 manner regioselectively (route 2 and 3 of Scheme 2). An interesting finding is that the substitution of acetate isomer **3** with thioacetate proceeded in spite of the poor leaving ability of the acetate, which has not been reported before. All reactions were monitored with TLC and ^{1}H NMR spectroscopy.

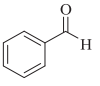
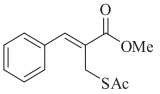
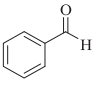
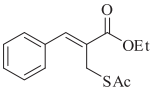
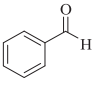
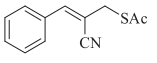
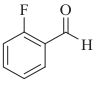
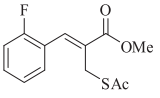
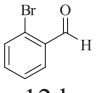
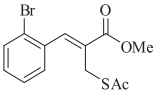
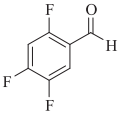
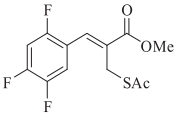
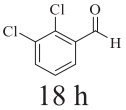
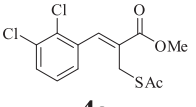
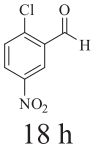
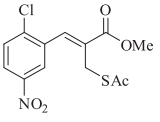
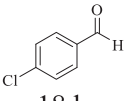
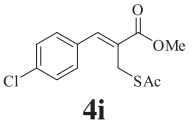
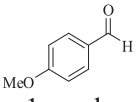
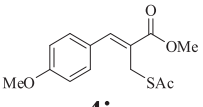
One the basis of the optimized conditions for each of the three-steps, the reaction was conducted as follows (entry 1). After benzaldehyde and methyl acrylate (3 equiv.) in the presence of DABCO (1 equiv.) was stirred for 48 h, acetic anhydride (1.2 equiv.) and DMAP (0.2 equiv.) were added to the reaction mixture. After the resulting solution was stirred for 10 min, DMF and potassium thioacetate (2 equiv.) were added and the solution was stirred for 30 min at RT to give (*Z*)-*S*-2-methoxycarbonyl-3-phenylallyl ethanethioate regioselectively and stereoselectively in 92% yield.

This new one-pot reaction under our optimal conditions was conducted with a variety of benzaldehydes with electron-withdrawing (Entries 2 and 4–9) and electron-donating groups (Entry 10) attached to the aromatic rings and methyl acrylate to afford the corresponding allyl thioacetates **4** in excellent yields with (*Z*)-stereoselectivity as shown in Table 1. The one-pot reaction of benzaldehyde and acrylonitrile gave a allyl thioacetate **4c** with (*E*)-stereoselectivity in 87% isolated yield. The stereochemistry of the products was established by comparing ^{1}H NMR parameters for the protons of the product with literature values.[29] The reaction times of the first step depend on the substrate and are listed in Table 1.

3. Conclusion

In summary, a mild and efficient synthesis of (*Z*)-*S*-2-alkoxycarbonyl-3-acylallyl ethanethioates and (*E*)-*S*-2-cyano-3-acylallyl ethanethioates from benzaldehydes and activated alkenes (acrylate and acrylonitrile) in one-pot reactions were developed. The method consists of an MBH reaction using DABCO followed by acetylation using acetic anhydride and a catalytic amount of DMAP and nucleophilic substitution using KSAc in DMF at RT.

Table 1. Synthesis[a] of allyl thioacetates from benzaldehydes and activated alkenes.

Entry	Aldehyde	Product	Yield[b] (%)
1	 48 h[c]	 **4a**[d]	92
2	 72 h	 **4b**	98
3	 12 h	 **4c**	87
4	 12 h	 **4d**	87
5	 12 h	 **4e**	90
6	 12 h	 **4f**	97
7	 18 h	 **4g**	95
8	 18 h	 **4h**	95
9	 18 h	 **4i**	96
10	 1 week	 **4j**	85

[a]Reaction conditions: 1st step: benzaldehydes (1 equiv.), activated alkenes (3 equiv.), and DABCO (1 equiv.). 2nd step: acetic anhydride (1.2 equiv.) and DMAP (0.2 equiv.). 3rd step: KSAc (2 equiv.) and DMF (2 ml).

[b]Isolated yield.

[c]MBH reaction time.

[d]All products are known and their spectroscopic data are consistent with reported one.[29]

4. Experimental

4.1. General procedure

A mixture composed of benzaldehyde (200 mg, 1.884 mmol), methyl acrylate (512.4 μL, 3 equiv.), and DABCO (211.4 mg, 1 equiv.) was stirred at room temperature for 48 h. After the completion of the reaction (monitored by TLC), to the reaction mixture was added acetic anhydride (213.4 μL, 1.2 equiv.) and DMAP (46.0 mg, 0.2 equiv.) and the resulting solution was stirred for 10 min. Then potassium thioacetate (430.4 mg, 2 equiv.) and DMF (2 ml) were added to the reaction and the resulting solution was stirred for 30 min at room temperature. After the completion of the reaction, it was diluted with ethyl acetate (30 mL) and washed with water (20 mL × 3) and brine (20 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated and chromatographed on silica gel using a solution of ethyl acetate and hexane (1:16) to afford a (*Z*)-*S*-2-methoxycarbonyl-3-phenylallyl ethanethioate in 92% isolated yield. Selected data of products are given below.

4.2. Spectroscopic data of products

4a: oil, IR (KBr) 1715, 1693, 1630, 1435, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.36 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2), 7.37–7.42 (m, 5H, Ar), 7.82 (s, 1H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 195.00, 167.55, 142.69, 142.66, 134.64, 129.62, 129.39, 128.86, 128.71, 126.94, 52.52, 52.47, 30.43, 30.40, 27.03.

4b: oil, IR (KBr) 1709, 1631, 1448, 1369, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 (t, J = 7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 4.29 (q, J = 7.2 Hz, 4H, OCH_2), 7.36–7.43 (m, 5H, Ar), 7.81 (s, 1H, CH); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 194.98, 167.04, 142.36, 142.33, 134.72, 129.58, 129.30, 128.83, 127.32, 61.43, 30.40, 26.98, 26.95, 14.37.

4c: oil, IR (KBr) 2214, 1698, 1620, 1576, 1496, 1448, 1408, 1356, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.40 (s, 3H, CH_3), 3.86 (s, 2H, CH_3), 7.21 (s, 1H, CH), 7.40–7.43 (m, 3H, Ar), 7.73–7.78 (m, 2H, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 194.98, 167.04, 142.36, 142.33, 134.72, 129.58, 129.30, 128.83, 127.32, 61.43, 30.40, 26.98, 26.95, 14.37.

Disclosure statement

No potential conflict of interest was reported by the authors.

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