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A one-pot three-step multicomponent synthesis of functionalized allyl dithiocarbamates using Baylis–Hillman reaction

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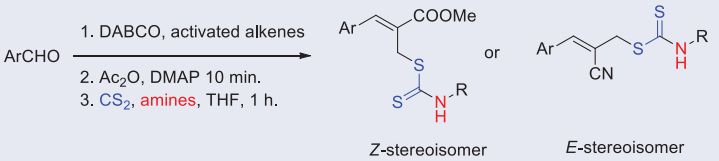
ABSTRACT

A one-pot, pseudo five-component, highly diastereoselective, and mild procedure for the synthesis of functionalized allyl dithiocarbamates is developed. The Baylis–Hillman (BH) reaction of aromatic (heteroaromatic) aldehydes and activated alkenes using DABCO, followed by acetylation of BH adducts with acetic anhydride in the presence of a catalytic amount of DMAP, and nucleophilic substitution reaction by *in situ* prepared dithiocarbamates from amines and CS_2 are three steps of this protocol.

GRAPHICAL ABSTRACT



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KEYWORDS
Allyl dithiocarbamates; Baylis–Hillman reaction; carbon disulfide; multicomponent reactions

Introduction

The Baylis–Hillman (BH) reaction is one of the most popular and important C–C bond forming protocol via the reaction of activated alkenes with aldehydes.[1–2] Baylis–Hillman products and their derivatives are versatile intermediates in organic synthesis and have been used for the preparation of various compounds such as substituted alkenes and heterocycles.[3–7]

An interesting category of BH adducts is BH acetates with numerous applications for the synthesis of trisubstituted alkenes by reacting with various nucleophiles.[8] Nageswar et al. reported the stereoselective synthesis of functionalized aryl allyl sulfides and selenides by the reaction of Baylis–Hillman acetates with arylthiols and arylselenol under neutral conditions in water using β-cyclodextrin as catalyst (Scheme 1A).[9] In addition, a one-pot three-component procedure for highly stereoselective synthesis of [*E*]- and [*Z*]-allyl dithiocarbamates from the acetates of Baylis–Hillman, CS_2 and amines is

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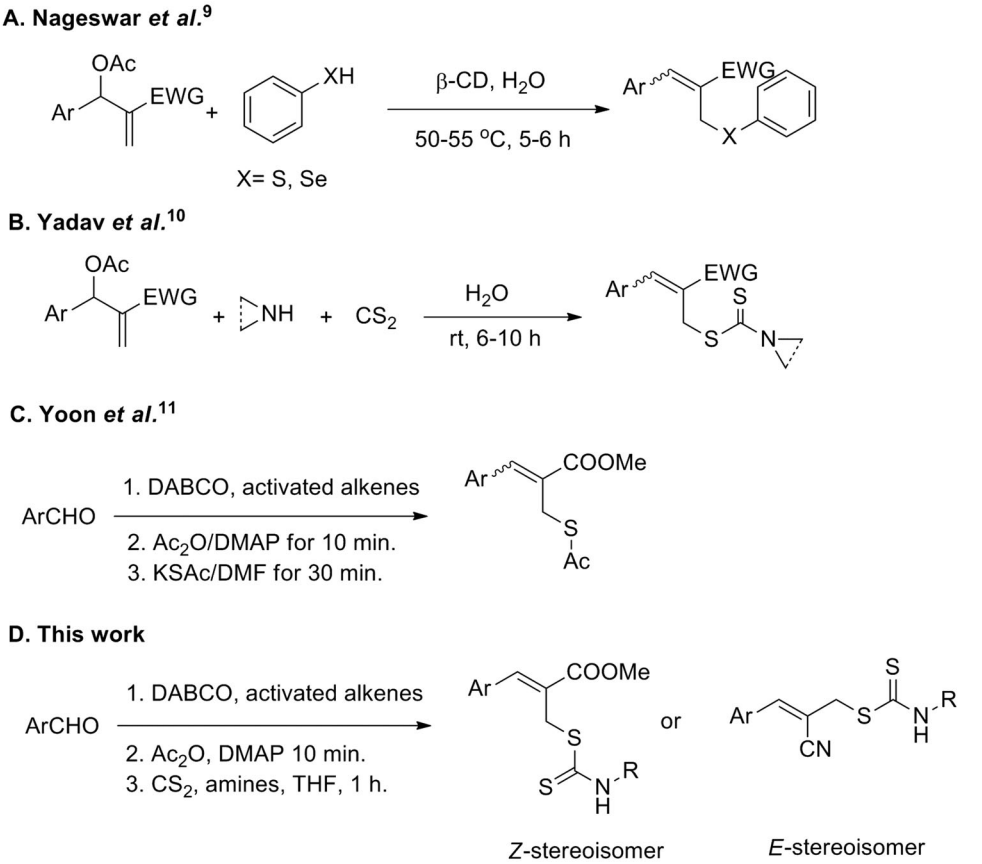
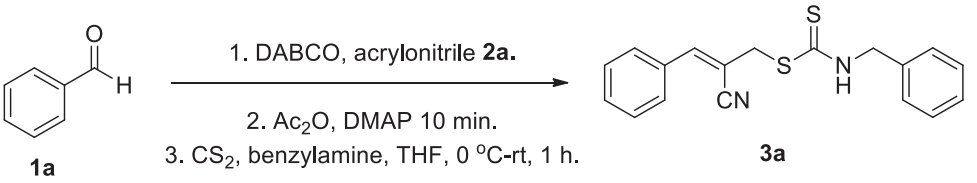


Scheme 1. Published and proposed methods for the synthesis of ally dithiocarbamates and allyl sulfides.

reported by Yadav et al. under catalyst-free conditions in water (Scheme 1B).[10] Recently, Yoon and coworkers described a one-pot synthesis of allyl thioacetates using the BH reaction as a key step. Their method consists of Morita–Baylis–Hillman reaction of aldehydes with activated alkenes, acetylation with acetic anhydride, and nucleophilic displacement (S_N2') with potassium thioacetate (Scheme 1C).[11]

Dithiocarbamates as analogs of carbamates, are valuable and important structural components. These compounds have broad applications in various branches of chemistry including pharmaceutical chemistry, agrochemistry, coordination chemistry, and material science.[12–16] In addition, in synthetic organic chemistry, the dithiocarbamic acids are very efficient nucleophiles in the reaction with various electrophiles via their sulfur and nitrogen atoms.[17–20]

In continuation of our research and interest toward the synthesis of novel dithiocarbamates and their applications in synthetic organic chemistry,[21–25] we herein investigate the multicomponent synthesis of allyl dithiocarbamates via consecutive reactions in a one-pot reaction vessel with focus on Baylis–Hillman reaction as key reaction step (Scheme 1D).



Scheme 2. Reaction of benzaldehyde, acrylonitrile, carbon disulfide and benzyl amine.

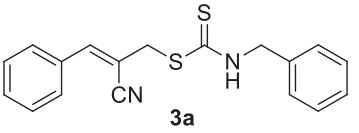
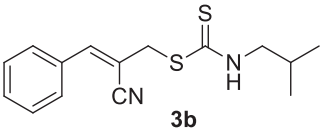
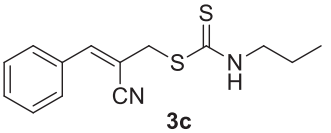
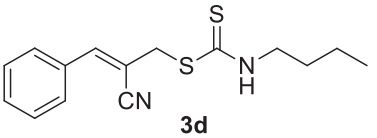
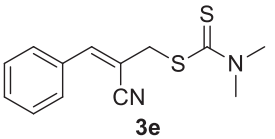
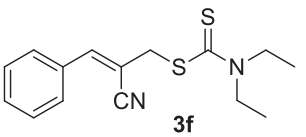
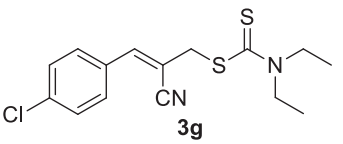
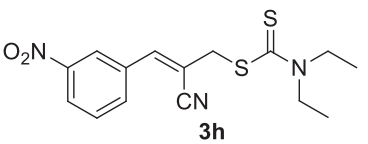
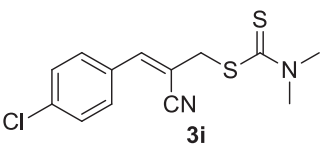
Results and discussion

We started our study using benzaldehyde **1a**, acrylonitrile **2a**, carbon disulfide and benzyl amine as a model reaction (Scheme 2). For optimization of the reaction conditions, the reported protocols[26,27] by Saika and Sakakura were applied for BH and acetylation steps, respectively. We observed that mixing of benzaldehyde (0.5 mmol, 1 equiv.), acrylonitrile (3 equiv.), and DABCO (1 equiv.) under solvent free conditions for 12 h afforded the corresponding BH adduct in quantitative yield. Then acetic anhydride (1.2 equiv.) as the acetylation agent and DMAP (0.2 equiv.) as catalyst were added to the reaction vessel and the resulting mixture was stirred for 10 minutes at the same conditions to afford the acetylated BH product. Finally, nucleophilic displacement of the resulting BH acetate with dithiocarbamic acid was carried out by adding carbon disulfide (1.5 equiv.) and benzyl amine (1 equiv.). Under these conditions, the corresponding (*E*)-2-cyano-3-phenylallyl benzylcarbamodithioate **3a** was obtained in 38% yield. In order to improve the reaction yield, the last step was screened in various solvents such as EtOH, THF, DMF, CH_2Cl_2, and water. The yield was improved to 62% in THF and DMF. Furthermore, reducing the reaction temperature to 0 °C during the addition of amine and CS_2, and further stirring for 1 h at room temperature improved the yield of **3a** to 76%. In summary, performing the BH reaction and acetylation step under solvent-free conditions at room temperature, followed by the addition of CS_2 and an amine in THF at 0 °C and further stirring at rt for 1 h was considered as optimal reaction conditions for further derivatization.

Under optimized reaction conditions, the generality of this reaction was investigated using various aromatic aldehydes, activated alkenes and primary and secondary amines and the results are summarized in Table 1. Various aromatic aldehydes such as benzaldehyde, 4-chlorobenzaldehyde, 3-nitrobenzaldehyde, and thiophene 3-carbaldehyde were applied successfully in this protocol. In addition, various primary and secondary amines such as benzyl amine, *iso*butyl amine, propylamine, butylamine, dimethylamine, diethylamine, and pyrrolidine are suitable substrates in this protocol. While in the reaction of aldehydes with acrylonitrile, the *E*-stereoisomer was obtained with excellent stereoselectivity, the co rresponding *Z*-stereoisomer was achieved with methyl acrylate. The stereochemistry of the products was determined by comparing the ^{1}H NMR value of alkene proton with literature values.[10,11,28] The structure of products was deduced by ^{1}H NMR, ^{13}CNMR, FT-IR and CHN analyses.

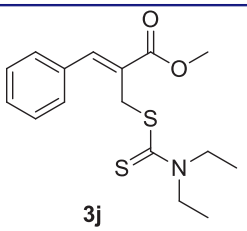
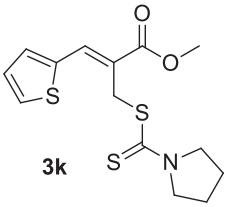
Reaction mechanism is proposed in Scheme 3. Baylis–Hillman reaction of acrylonitrile with benzaldehyde provides the corresponding **BH** intermediate, which can be easily acetylated with acetic anhydride in the presence of DMAP to afford **BH-acetate**. Finally, nucleophilic displacement (S_N2') of the BH-acetate with *in situ* prepared dithiocarbamic acid afforded the product with removal of the acetate group.

Table 1. Diversities in the synthesis of functionalized allyl dithiocarbamates.[a]

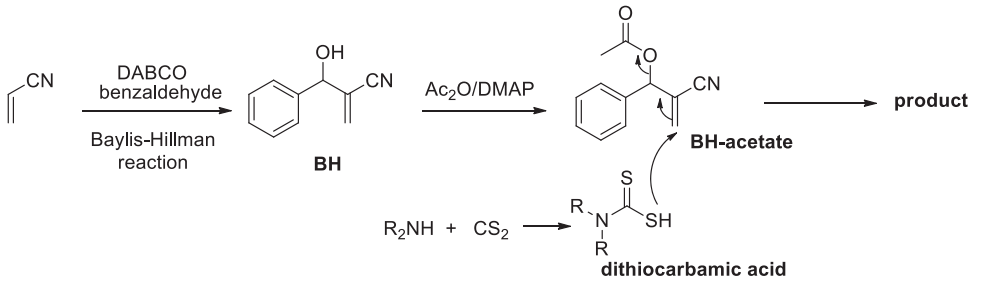
Entry	Aldehyde	Amine	Product	Yield (%)[b]
1	Benzaldehyde	Benzylamine	 **3a**	76
2	Benzaldehyde	*Iso*butylamine	 **3b**	81
3	Benzaldehyde	Propylamine	 **3c**	80
4	Benzaldehyde	Butylamine	 **3d**	79
5	Benzaldehyde	Dimethylamine	 **3e**	84
6	Benzaldehyde	Diethylamine	 **3f**	86
7	4-Cl-benzaldehyde	Diethylamine	 **3g**	91
8	3-NO_2-benzaldehyde	Diethylamine	 **3h**	90
9	4-Cl-benzaldehyde	Dimethylamine	 **3i**	88

(*continued*)

Table 1. Continued.

Entry	Aldehyde	Amine	Product	Yield (%)[b]
10	Benzaldehyde	Diethylamine	 **3j**	85
11	Thiophene-3-carbaldehyde	Pyrrolidine	 **3k**	88

[a]Reaction conditions: aldehyde (1 equiv.), activated alkene (3 equiv.), DABCO (1 equiv.), solvent free, r.t., 12 h for acrylonitrile and 24 h for methyl acrylate; then acetic anhydride (1.2 equiv.) and DMAP (0.2 equiv.), solvent free, r.t., 10 min; then, CS_2 (1.5 equiv.), drop wise adding of amine (1 equiv.) at 0 °C, then 1 h stirring in the THF (3 mL) at room temperature. [b]Isolated yield.



Scheme 3. Proposed mechanism for synthesis of ally dithiocarbamates.

Conclusion

In conclusion, we described a mild, efficient, regioselective, and stereoselective protocol for the synthesis of substituted allyl dithiocarbamates via consecutive reactions in a vessel. The current protocol avoids pre-preparation of Baylis–Hillman adducts and recommended a novel one-pot pseudo-five-component reaction for the synthesis of functionalized allyl dithiocarbamates as potential building blocks for further synthesis.

Experimental

General procedure for the synthesis of functionalized allyl dithiocarbamates

A mixture of an activated alkene (3 mmol), an aldehyde (1 mmol), and DABCO (1 mmol) was stirred at room temperature under solvent-free conditions until completion of the reaction monitored by TLC (12 h for acrylonitrile and 24 h for methyl acrylate). Then DMAP (4-dimethylaminopyridine) (20 mol%) and acetic anhydride

(1.2 mmol) were added in the same vessel and the mixture was stirred at the same temperature for 10 min. Finally, THF (3 mL) and carbon disulfide (1.5 mmol) were added, followed by dropwise addition of an amine (1 mmol) at 0 °C, and further stirring at room temperature for 1 h. In the end, water (5 mL) was added and the product was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The remaining viscous oil was purified by silica-gel column chromatography using petroleum ether-EtOAc (6:1) as eluent.

(E)-2-cyano-3-phenylallyl benzylcarbamodithioate (3a)

Yield: (76%), Pale yellow viscous oil; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.80–7.73 (*m*, 2 H), 7.47–7.40 (*m*, 4 H), 7.38–7.30 (*m*, 6 H), 4.89 (d, $J = 5.1$ Hz, 2 H), 4.36 (*s*, 2 H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.0, 146.3, 135.6, 132.9, 130.5, 128.9, 128.8, 128.7, 128.2, 128.1, 117.9, 106.4, 51.4, 39.9 ppm; IR (KBr) $\nu = 3277$, 3028, 2924, 2213, 1495, 1453, 1383, 931 cm^{-1}; Anal. Calcd. for $C_{18}H_{16}N_2S_2$: C, 66.63; H, 4.97; N, 8.63. Found: C, 67.02; H, 5.09; N, 8.77.

Supporting Information: Full experimental details, characterization data and copies of ^{1}H and ^{13}C NMR spectra for new compounds.

Acknowledgments

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