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An easy access to functionalized allyl dithiocarbamates from Baylis–Hillman adducts in water

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ABSTRACT

A facile and direct highly stereoselective synthesis of [*E*]- and [*Z*]-allyl dithiocarbamates has been accomplished from acetates of Baylis–Hillman (BH) adducts in catalyst-free one-pot three-component coupling reactions of carbon disulfide and amine in water under a mild and green procedure with high yields. The reaction pathway involves the nucleophilic displacement (SN2′) of BH acetates by dithiocarbamate anions. The utility of these allyl dithiocarbamates has also been demonstrated in heterocyclic chemistry.

Carbon–sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds, and this has received much attention due to its occurrence in many molecules that are of biological, pharmaceutical, and material interest.[1,2] Organic dithiocarbamates, ubiquitously found in a variety of biologically active molecules,[3] are of high importance in academia as well as in industry.[4] Besides their numerous biological and medicinal properties including applications in the treatment of cancer,[5] they play pivotal roles in agriculture[6] and act as linkers in solid-phase organic synthesis.[7] They are used in the rubber industry as vulcanization accelerators,[8] in controlled radical polymerization techniques,[9], and recently, in the synthesis of ionic liquids.[10] Owing to their strong metal-binding capacity, dithiocarbamates act as inhibitors of enzymes and have a profound effect on biological systems. For these reasons, the synthesis of functionalized dithiocarbamates with different substitution patterns at the thiol chain has become a field of increasing interest in synthetic organic chemistry during the past few years. Conventional methods involve reactions of amines with thiophosgene and its derivatives, which are not desirable for environmental concerns.[11] This has led to a recent surge of several one-pot procedures for the synthesis of *S*-alkyl, aryl, and vinyl dithiocarbamates by the reaction of amine with carbon disulfide and halides, epoxides, or α,β-unsaturated compounds.[12] However, the one-pot synthesis of *S*-allyl dithiocarbamates, synthetic equivalent of β-formyl/halomethyl vinyl anions, is rather limited.[12d] They are used as synthons for the preparation of various enals,[13] which are important features of many natural products including macrocyclic antibiotics, such as pyrenophorin, brefeldin, and cytochalasins.[14] In addition, *S*-allyl dithiocarbamates also serve as versatile intermediates for other synthetic targets, such as the prostaglandins,[15] coriolic and dismorphecolic acids.[16] Herein, Baylis–Hillman (BH) chemistry has been applied for the synthesis of allyl dithiocarbamates (Scheme 1).

The BH reaction[17] has become a popular carbon–carbon bond-forming reaction, which proceeds with a high atom-economic and yields densely functionalized molecules. They, in turn, provide opportunities for developing art in organic synthesis via functional group manipulation, thereby enabling vast applications as versatile building blocks to generate either bioactive compounds or useful synthetic intermediates.[18] Acetates of BH adducts have been well established for the synthesis of trisubstituted alkenes and different multifunctional molecules en route to heterocycles via a nucleophilic displacement protocol either in S_N2 or in S_N2' fashion with various C-, N-, and O-centred nucleophiles.[18a,c,19,20] However, their utilization for generating sulfur-containing products with *S*-centred nucleophiles has been limited and includes only arenesulfinate,[21] thiolates[22], and thiocyanate anions.[23] Until now, the literature records no report on the synthesis of dithiocarbamates using BH chemistry.

Reactions in aqueous media have attracted much attention in recent times due to environmental acceptability, natural abundance, and low cost of water. In addition, water often exhibits unique reactivity and selectivity that cannot be attained in conventional

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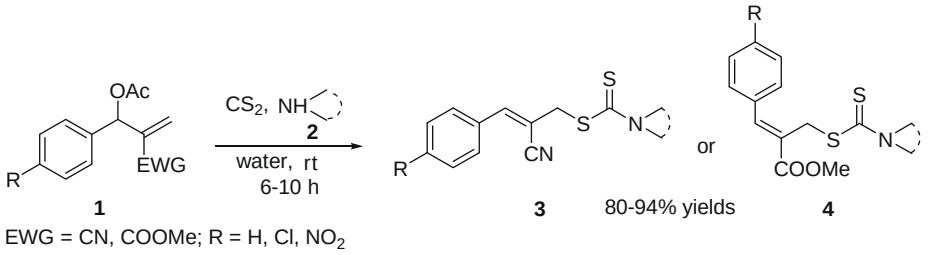


Scheme 1. One-pot synthesis of allyl dithiocarbamates **3** and **4** from BH acetates **1**.

Table 1
One-pot synthesis of allyl dithiocarbamates **3** and **4** from BH acetates **1** Scheme 1

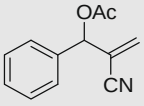
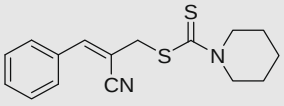
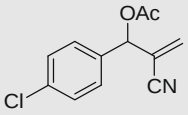
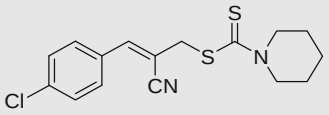
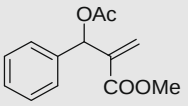
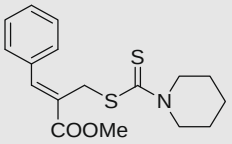
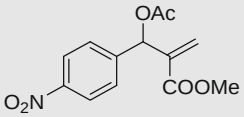
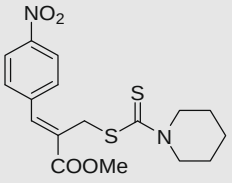
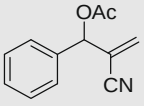
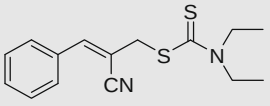
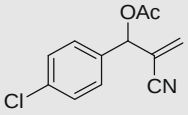
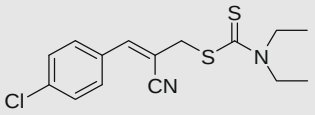
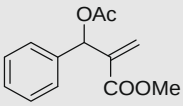
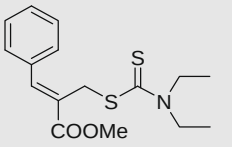
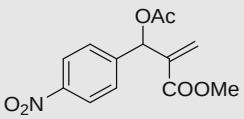
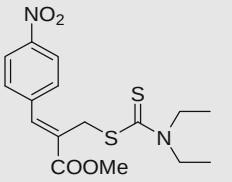
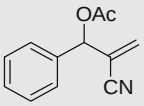
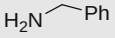
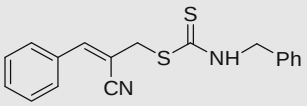
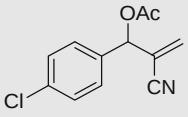
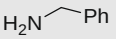
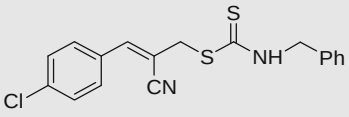
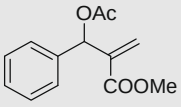
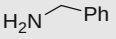
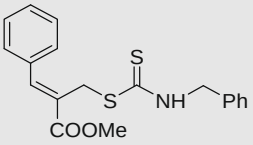
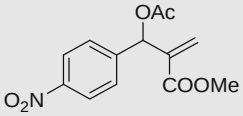
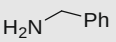
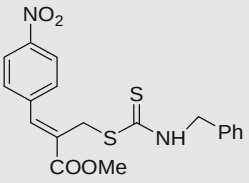
Entry	BH acetate	Amine **2**	Product **3** or **4**	Reaction time[a] (h)	Yield[b,c] (%)
3a				7	84
3b				7.5	80
4a				9	87
4b				6	91
3c				8.5	85
3d				8	87
4c				9.5	88
4d				8.5	92
3e				9	83

Table 1 (*continued*)

Entry	BH acetate	Amine **2**	Product **3** or **4**	Reaction time[a] (h)	Yield[b,c] (%)
3f				9	87
4e				10	90
4f				7.5	94

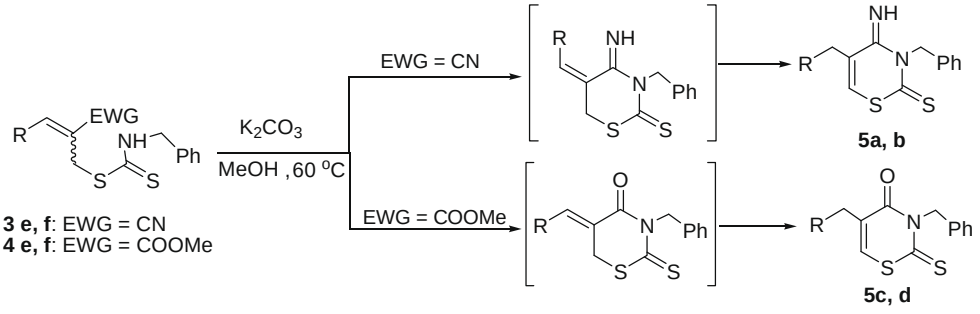
[a] Time for completion of the reaction at rt as indicated by TLC.
[b] Yields of isolated and purified products.
[c] All compounds gave C, H, and N analyses within ±0.37% and satisfactory ^{1}H NMR, ^{13}C NMR, and EIMS data.

organic solvents. Thus, the development of an efficient procedure for an organic reaction using water as the reaction medium has received high priority in the design of a chemical process, and is a challenging goal of aqueous chemistry.[24]

Considering the above valid facts and our continued quest for the development of environmentally friendly alternatives along with the recent interest in synthetic applications of BH adducts,[25] we report herein a one-pot three-component highly stereoselective synthesis of hitherto unknown trisubstituted [*E*]- and [*Z*]-allyl dithiocarbamates **3** and **4** in water at rt without using a catalyst (Scheme 1). The present one-pot procedure was performed simply by stirring a mixture of an amine, CS_2, and an acetate of acrylonitrile/acrylate ester-derived BH adduct in water at rt for 6–10 h to afford the corresponding allyl dithiocarbamates **3** and **4** in 80–94% yields and sole diastereoselectivity (Table 1).[26] The reaction pathway involves nucleophilic displacements (S_N2') of BH adducts by dithiocarbamate anions. Significantly, the reaction is highly stereoselective for both acrylonitrile/acrylate ester-derived BH acetates, but with reversed stereochemical directive effect, that is, acrylonitrile-derived BH acetates (**1**, EWG = CN) afford *E*-allyl dithiocarbamates **3** as the sole product while acrylate ester-derived BH acetates (**1**, EWG = COOMe) exclusively afford [*Z*]-allyl dithiocarbamates **4** under the same reaction conditions. The configuration of allyl dithiocarbamates **3** and **4** was assigned on the basis of the literature precedent,[22b,27] ^{1}H NMR chemical shift of vinyl protons, and was confirmed by NOE experiments. The products **3** and **4** were studied by NOE experiments. Product **4** showed NOE between methylene protons and aromatic protons and showed no NOE between methylene and vinyl protons confirming the *Z* configuration, and product **3** showed NOE between methylene protons and vinyl protons confirming the *E* configuration. Although no mechanistic studies have been carried out, related stereochemical reversals are attributed to differences in relative stabilities of transition states as explained earlier by considering transition state models.[22b,28]

Interestingly, the allyl dithiocarbamates **3e, 3f, 4e,** and **4f** (Table 1) derived from benzyl amine underwent an intramolecular cyclization reaction in the presence of K_2CO_3 in methanol upon warming

Table 2
Cyclization of *N*-benzyldithiocarbamates **3** and **4** into 1,3-thiazines **5**



Product	R	Reaction time[a] (h)	Yield[b] (%)
5a	Ph	4	78
5b	4-ClC_6H_4	4	81
5c	Ph	3	76
5d	4-$O_2NC_6H_4$	3.5	84

[a] Time for completion of the reaction as indicated by TLC.
[b] Yield of isolated and purified products.

the reaction mixture at 60 °C to yield chemically and pharmaceutically interesting entities 3,5-dibenzyl-1,3-thiazines **5a–d** (Table 2).[29] This illustrates the potential of these allyl dithiocarbamates in heterocyclic synthesis.

In summary, we have described a one-pot, efficient, and highly stereoselective green synthetic protocol for hitherto unknown [*E*]- and [*Z*]-allyl dithiocarbamates via the nucleophilic displacement (S_N2') of BH acetates by dithiocarbamate anions in water. This one-pot protocol avoids the use of bases and toxic organic solvents by utilizing water, which plays a dual role, as a solvent and promoter. Furthermore, the utility of these allyl dithiocarbamates in heterocyclic chemistry is demonstrated by their base-catalyzed intramolecular cyclization into chemically and pharmaceutically relevant functionalized 1,3-thiazines.

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26. *General procedure for the synthesis of [E]- and [Z]-allyl dithiocarbamates* (**3**) and (**4**): A mixture of BH acetate **1** (1 mmol), carbon disulfide (1.2 mmol), and amine **2** (1 mmol) was vigorously stirred in 1.5 mL of water at rt for 6–10 h (Table 1). After completion of the reaction (monitored by TLC), the product was extracted with ether/ethyl acetate (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/ethyl acetate 9:1) to afford the desired products (**3**) and (**4**). Physical data for representative compounds. Compound **3a**: Colorless viscous liquid, yield 84%. IR (neat) ν_{max} 2941, 2925, 2854, 2218, 1608, 1480, 1429, 1232, 1210, 1120, 1015, 820, 760, 710 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 1.71 (br, 6H, piperidine ring), 3.76 (s, 2H, CH_2S), 3.90 (br, 2H, NCH_2), 4.27 (br, 2H, NCH_2), 6.91 (s, 1H, PhCH), 7.49–7.68 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 24.7, 25.9, 42.6, 51.8, 52.8, 108.7, 117.1, 128.1, 128.8, 129.5, 135.2, 144.8, 194.7. EIMS (*m/z*): 302 (M^+). Anal. Calcd for $C_{16}H_{18}N_2S_2$: C, 63.54; H, 6.00; N, 9.26. Found: C, 63.81; H, 6.22; N, 9.13. Compound **4c**: colorless viscous liquid, yield 88%. IR (neat) ν_{max} 2983, 2920, 2846, 1709, 1610, 1488, 1269, 1205, 1051, 832, 756, 714 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 1.18–1.30 (m, 6H, 2 × CH_3), 3.57 (q, 2H, J = 7.1 Hz, CH_2), 3.71 (s, 3H, OMe), 3.89 (q, 2H, J = 7.1 Hz, CH_2), 4.03 (s, 2H, CH_2S), 7.35–7.48 (m, $5H_{arom}$), 7.90 (s, 1H, PhCH). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 11.8, 13.3, 31.6, 47.3, 50.2, 52.9, 127.0, 128.7, 129.5, 130.2, 135.4, 141.6, 167.2, 191.9. EIMS (*m/z*): 323 (M^+). Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.78; H, 6.38; N, 4.61. Compound **4e**: colorless viscous liquid, yield 90%. IR (neat) ν_{max} 3282, 3008, 1711, 1610, 1508, 1482, 1254, 1203. 1091, 1058, 814, 762, 698 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 3.71 (s, 3H, OMe), 4.06 (s, 2H, CH_2S), 4.88 (s, 2H, $PhCH_2$), 7.19–7.31 (m, $4H_{arom}$), 7.42–7.53 (m, $6H_{arom}$), 7.91 (s, 1H, PhCH), 8.1 (br, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 31.4, 51.6, 53.0, 126,8, 127.6, 128.2, 128.8, 129.3, 129.9, 130.7, 135.4, 136.5, 141.4, 167.4, 196.0. EIMS (*m/z*): 357 (M^+). Anal. Calcd for $C_{19}H_{19}NO_2S_2$: C, 63.83; H, 5.36; N, 3.92. Found: C, 63.60; H, 5.25; N, 3.55.
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29. *General procedure for the synthesis of 3,5-dibenzyl-1,3-thiazines* (**5**): A solution of allyl dithiocarbamates **3e,f** or **4e,f** (1 mmol) and anhydrous K_2CO_3 (1.2 mmol) in 4 mL methanol was heated at 60 °C for 3–4 h with stirring (Table 2). The reaction progress was monitored by TLC. Upon completion, the reaction mixture was cooled to rt, and methanol was removed under reduced pressure. The residue thus obtained was treated with water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using hexane/ethyl acetate (8.5:1.5) as an eluent to give the pure product **5**. Physical data for a representative compound. Compound **5a**: yellowish viscous liquid, yield 78%. IR (neat) ν_{max} 3309, 3010, 2971, 2810, 1610, 1580, 1450, 1090, 764, 710 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 3.73 (s, 2H, $PhCH_2$), 4.68 (s, 2H, $PhCH_2$ N), 5.81 (br, 1H, NH, exchangeable with D_2O), 6.80 (s, 1H, CHS), 7.21–7.69 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 31.5, 51.8, 112.7, 126.0, 127.1, 127.9, 128.7, 129.8, 135.5, 136.6, 138.1, 157.2, 192.1. EIMS (*m/z*): 324 (M^+). Anal. Calcd for $C_{18}H_{16}N_2S_2$: C, 66.63; H, 4.97; N, 8.63. Found: C, 66.97; H, 4.74; N, 8.46.