One-Pot Oxidative Conjugate Hydrothiocyanation–Hydrosulfenylation of Baylis–Hillman Alcohols Promoted by a Protic Ionic Liquid

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Abstract: The first example of one-pot oxidative conjugate hydrothiocyanation–hydrosulfenylation of acrylic ester derived Baylis–Hillman alcohols, that is, methyl 3-aryl-3-hydroxy-2-methylenepropanoate, is reported. The reaction involves protic ionic liquid [Hmim]HSO_4-mediated oxidation of Baylis–Hillman alcohols with $NaNO_3$ to give methyl (*E*)-α-formylcinnamates followed by conjugate addition of sulfur-centered nucleophiles (NH_4SCN/PhSH) to afford the corresponding methyl β-thiocyanato (or β-phenylsulfenyl)-α-formylhydrocinnamates diastereoselectively in 74–87% yields in a one-pot procedure. After isolation of the product, the ionic liquid [Hmim]HSO_4 could be easily recycled for further use without any loss of efficiency.

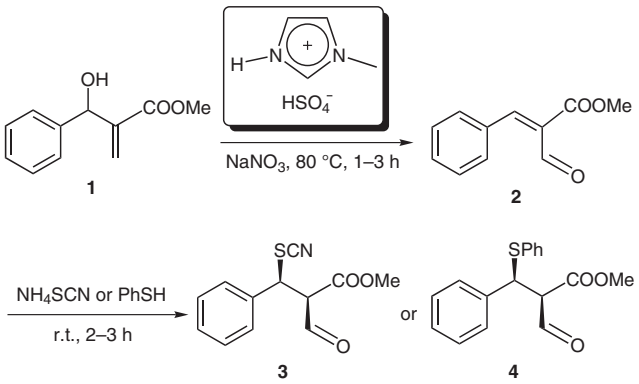
Key words: Baylis–Hillman alcohols, conjugate addition, oxidation, protic ionic liquids, methyl cinnamates, stereoselective synthesis

The Baylis–Hillman reaction is a synthetically useful method for carbon–carbon bond-forming reactions yielding functionalized allylic alcohols,[1] thereby providing handles for further manipulation in a multitude of synthetic organic transformations.[2] The Baylis–Hillman (BH) alcohols, particularly in the form of their modified version (e.g., acetyl derivatives), have been utilized as carbon electrophiles, and their derivatizations with various nucleophilic reagents, including thiocyanates, alkyl or aryl thiolates, providing a wide range of potential synthetic intermediates and precursors for the synthesis of a variety of biologically active natural and unnatural products, have been well documented in the literature.[3–5] The BH alcohols have been employed as Michael acceptors to produce functionalized aldol products with oxygen, sulfur, nitrogen, and carbon-centered nucleophiles.[6] Quite recently, Yadav and co-workers have reported oxidative conjugate addition of carbon-centered nucleophiles to acrylic ester derived BH alcohols.[7] However, there has been no report on oxidative conjugate addition of sulfur-centered nucleophiles to acrylic ester derived BH alcohols.

The conjugate addition of sulfur-centered nucleophiles to α,β-unsaturated carbonyl compounds, constituting a key reaction in biosynthetic processes as well as in organic synthesis,[8] is one of the most important methods for the synthesis of β-sulfur functionalized carbonyl compounds. Sulfur functionalities, such as thiocyanate and thioether, are well known in various areas of organosulfur chemistry and are of considerable importance from both chemical and biological viewpoints.

The thioether structural fragment is an important molecular tool as bioisosteric replacements in rational drug design.[9] Organic thiocyanates, representing a masked marcapto group, are useful scaffolds for synthesis of various heterocycles; some of which exhibit herbicidal and other important biological activity.[10] The thiocyanato group is a prominent functional motif found in certain anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[11] Furthermore, β-sulfenylated carbonyl compounds are an important class of synthons for a wide variety of compounds and thus enhance the versatility of molecules containing sulfur functionalities.[12] Hence, the development of a simple, convenient, and efficient methodology for their synthesis is highly desirable. Herein, Baylis–Hillman chemistry has been applied for this purpose (Scheme 1).

To design a catalyst with high activity and selectivity, and which is benign to environment and easily recovered, is an interesting and rapidly developing area of chemistry. Ionic liquids (IL) have attracted considerable interest as environmentally benign reaction media, catalysts, and reagents and are easy to recycle.[13] Recently, protic ionic liquids (PIL) have been deemed as promising alternatives for acid-catalyzed reactions and play a dual solvent–catalyst role in a variety of reactions including esterification of carboxylic acids, protection of alcohols and carbonyl groups, oxidation of alcohols, alcohol dehydrodimerization, pinacol–benzopinacol rearrangement, in Mannich reactions, and cleavage of ethers.[14]



Scheme 1 Protic ionic liquid promoted oxidative conjugate addition to BH alcohols

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The continued interest of synthetic chemists in the BH reaction and our ongoing efforts to devise one-pot protocols involving conjugate addition[15] has encouraged us to develop the present protic ionic liquid promoted oxidative sulfur functionalization of BH alcohols, which opens a new aspect of their synthetic utility (Table 1).

Table 1 One-Pot Oxidative Conjugate Hydrothiocyanation–Hydrosulfenylation of BH Alcohols

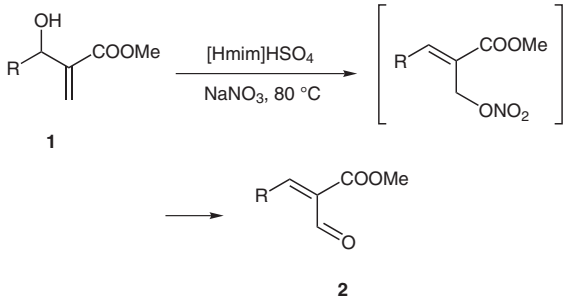
Entry	R^1	Nucleophile	R^2	Time (h)	Yield (%)[a,b]
3a	H	NH_4SCN	CN	3.5	78
4a	H	PhSH	Ph	4	81
3b	4-Me	NH_4SCN	CN	3	80
4b	4-Me	PhSH	Ph	4	84
3c	2-MeO	NH_4SCN	CN	3.5	86
4c	2-MeO	PhSH	Ph	4	87
3d	3-Br	NH_4SCN	CN	5.5	83
4d	3-Br	PhSH	Ph	4	85
3e	4-Cl	NH_4SCN	CN	5	82
4e	4-Cl	PhSH	Ph	4	80
3f	4-O_2N	NH_4SCN	CN	6	74
4f	4-O_2N	PhSH	Ph	5.5	76

[a] Yield refers to pure products after column chromatography.
[b] All compounds gave C, H, and N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

The present one-pot procedure for oxidative hydrothiocyanation–hydrosulfenylation involves stirring an equimolar mixture of $NaNO_3$ and BH alcohol **1** in 1-methylimidazolium hydrogen sulfate [Hmim]HSO_4 at 80 °C for 1–3 hours followed by addition of 1.1 equivalents of NH_4SCN or PhSH and stirring at room temperature for a further 2–3 hours to afford the corresponding β-thiocyanated product **3** in 74–86% yields or β-sulfenylated compounds **4** in 76–87% yields (Table 1).[16] The process proceeds through the formation of isolable methyl (*E*)-α-formylcinnamate **2**. The formation of **3** and **4** was highly diastereoselective in favor of the *syn* isomers. The diastereomeric ratios in the crude isolates were determined by ^{1}H NMR spectroscopy to note any inadvertent alteration of these ratios during subsequent purification. As determined by ^{1}H NMR spectroscopy, the crude isolates of **3** and **4** were found to be diastereomeric mixtures containing 89–93% and 91–94% of the *syn* isomer, respectively. On the basis of ^{1}H NMR spectra and literature precedent,[17] the *syn* configuration was conclusively assigned to **3** and **4**, as the coupling constant ($J_{2,3}$ = 3.9 Hz) for them was lower than that for the minor *anti* isomer (J = 7.8 Hz). Moreover, the *syn* configuration of **4** was also established by its oxidation and subsequent thermal *syn*-elimination of the resulting sulfoxide.[18] The oxidation of **4** with 1-(4-diacetoxyiodobenzyl)-3-methylimidazolium tetrafluoroborate afforded the corresponding sulfoxide,[19] which underwent *syn*-elimination in boiling toluene to furnish methyl (*Z*)-α-formylcinnamate. This observation unequivocally proves the *syn* configuration of **4**.

The methyl (*E*)-α-substituted cinnamates possess interesting as well as important biological profiles.[20] Previously, methyl (*E*)-α-methyl/cyanomethylcinnamates have been synthesized utilizing BH alcohols as well as their acetyl derivatives.[4a,21] However, synthesis of methyl (*E*)-α-formylcinnamates **2** is hitherto unknown in rich literature of Baylis–Hillman chemistry. The present method provides an easy access to compound **2** from unmodified BH alcohols with sole *E*-stereoselectivity in a one-pot reaction using the $NaNO_3$–[Hmim]HSO_4 reagent–solvent system (Table 2).[22]

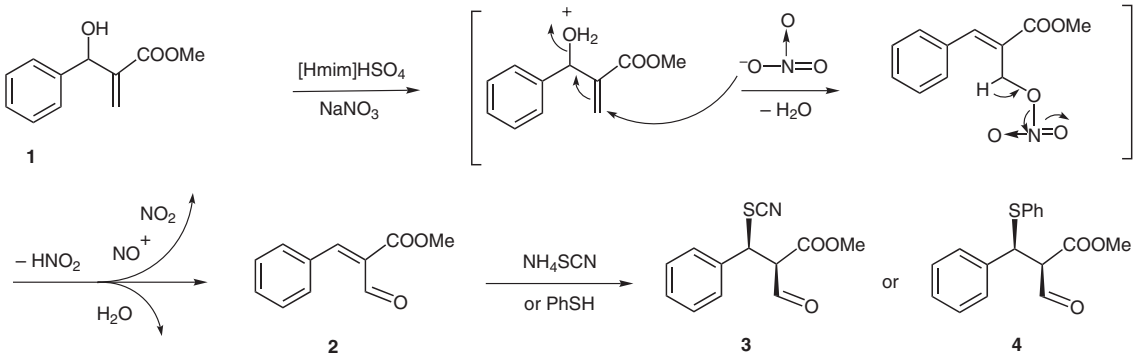
Table 2 Synthesis of Methyl (*E*)-α-Formylcinnamate **2** from BH Alcohols



Product	R	Time (h)	Yield (%)[a]
2a	Ph	1.5	80
2b	4-MeC_6H_4	1.3	83
2c	2-$MeOC_6H_4$	1.5	81
2d	3-BrC_6H_4	2.5	78
2e	4-ClC_6H_4	2	76
2f	4-$O_2NC_6H_4$	3	73

[a] Yields of isolated and purified products.

The *E*-stereochemistry of molecules **2** was assigned on the basis of ^{1}H NMR spectra and literature precedent.[21a,23] Furthermore, strong NOE were observed between the aldehydic proton and the *ortho* protons of the aromatic ring of compounds **2**, which unequivocally proves their *E*-stereochemistry. For example, when aldehydic proton of **2f** was irradiated, 21.3% NOE was observed at *ortho* protons of its aromatic ring. This clearly shows the *E*-stereochemistry of **2f**.



Scheme 2 Plausible mechanism for the formation of **3** and **4**

We also attempted the oxidative conjugate hydrothiocyanation–hydrosulfenylation using $NaNO_3$–$[Hmim]NO_3$ as well as $NaNO_3$–$[Hmim]H_2PO_4$ separately under the same reaction conditions (Table 1). The reaction was unsuccessful in the former case indicating the need for an acidic hydrogen which is absent in $[Hmim]NO_3$ to catalyze the oxidation of the BH alcohols into methyl (*E*)-α-formylcinnamate **2** (Scheme 2). However, the reaction proceeded with the $NaNO_3$–$[Hmim]H_2PO_4$ system but relatively low yields of **3** and **4** (26–37%) were obtained. This is probably due to the lower Brønsted acidity associated with $[H_2PO_4]$. Thus $[Hmim]HSO_4$ plays a dual role, that is, as an acid catalyst and solvent for both oxidation as well as hydrothiocyanation–hydrosulfenylation.

After isolation of the product, the ionic liquid $[Hmim]HSO_4$ could be recycled for four times up to a minimum of 73% recovery and reused without loss of efficiency. The requisite BH alcohols and protic ionic liquids were prepared employing known methods.[24,25]

In summary, we have documented the first example of the one-pot oxidative conjugate addition of sulfur-centered nucleophiles to methyl acrylate derived BH alcohols using the $NaNO_3$–$[Hmim]HSO_4$ system to afford methyl β-thiocyanato (or β-phenylsulfenyl)-α-formylhydrocinnamates, diastereoselectively. Furthermore, application of the same reagent–solvent system for the one-pot isomerization–oxidation of BH alcohols to afford methyl (*E*)-α-formylcinnamates has also been demonstrated.

Acknowledgment

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(16) **General Procedure for the Synthesis of Methyl β-Thiocyanato-α-formylhydrocinnamates 3 and Methyl β-Phenylsulfenyl-α-formylhydrocinnamates 4**
A mixture of BH alcohol **1** (1 mmol) and $NaNO_3$ (1 mmol) was stirred in 1 mL of [Hmim]HSO_4 at 80 °C for 1–3 h (Table 2). The reaction mixture was cooled to r.t. and NH_4SCN or PhSH (1.1 mmol) was added. The mixture was further stirred at r.t. for 2–3 h. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc (3 × 10 mL). The combined extract was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane–EtOAc, 8.5:1.5) to afford the desired product **3** or **4**. After isolation of the product, the remaining ionic liquid was washed with Et_2O (2 × 10 mL) to remove any organic impurity, then H_2SO_4 (2.1 mmol in the case of compound **3** and 1 mmol in the case of **4**) was added, the mixture was stirred at 80 °C for 1 h, and cooled to about –5 °C in an ice–salt bath. The precipitated solid [Na_2SO_4, $(NH_4)_2SO_4$] was filtered out, and the filtrate was dried under vacuum to afford the IL [Hmim]HSO_4, which was used in subsequent runs.
Data of Representative Compounds
Compound **3a**: white solid, yield 78%, mp 104–105 °C. IR (KBr): 3026, 2115, 1745, 1718, 1603, 1578, 1460, 1284, 1194, 764, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.68 (dd, 1 H, *J* = 3.9, 2.1 Hz, 2-H), 3.82 (s, 3 H, MeOCO), 4.86 (d, 1 H, *J* = 3.9 Hz, 3-H), 7.14–7.32 (m, 5 H_{arom}), 9.56 (d, 1 H, *J* = 2.1 Hz, CHO). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 36.6, 63.9, 52.8, 112.4, 126.9, 128.6, 129.2, 140.9, 169.1, 198.3. MS (EI): *m/z* = 249 [M^+]. Anal. Calcd (%) for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.56; H, 4.57; N, 5.43.
Compound **4f**: yellowish solid, yield 76%, mp 132–133 °C. IR (KBr): 3055, 2932, 1746, 1721, 1586, 1520, 1345, 1280, 1186, 760, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.72 (dd, 1 H, *J* = 3.9, 2.1 Hz, 2-H), 3.81 (s, 3 H, MeOCO), 4.68 (d, 1 H, *J* = 3.9 Hz, 3-H), 7.24–8.27 (m, 9H_{arom}), 9.54 (d, 1 H, *J* = 2.1 Hz, CHO). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 30.6, 52.7, 64.2, 121.6, 124.9, 127.4, 129.2, 129.8, 135.8, 148.2, 149.4, 169.0, 198.3. MS (EI): *m/z* = 345 [M^+]. Anal. Calcd (%) for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06. Found: C, 59.33; H, 4.74; N, 3.89.
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(22) **General Procedure for the Synthesis of Methyl (*E*)-α-Formylcinnamates 2**
A stirred solution of BH alcohols **1** (1 mmol) and $NaNO_3$ (1 mmol) in 1 mL of [Hmim]HSO_4 was heated at 80 °C for 1–3 h (Table 2). The reaction progress was monitored by TLC. Upon completion, the reaction mixture was cooled to r.t. and extracted with EtOAc (3 × 10 mL).The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a gradient mixture of hexane–EtOAc (8:2) as eluent to give the pure cinnamates **2**. The remaining ionic liquid was recycled for subsequent runs as described above using H_2SO_4 (1 mmol).[16]
Data of Representative Compound
Compound **2a**: white solid, yield 80%, mp 91–92 °C. IR (KBr): 3076, 2809, 2740, 1724, 1684, 1578, 1462, 1286, 1190, 760, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.87 (s, 3 H, MeOCO), 7.48–7.70 (m, 3 H_{arom}), 7.86 (s, 1 H, CHPh), 8.04–8.12 (m, 2 H_{arom}), 9.66 (s, 1 H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 52.6, 127.7, 129.4, 130.2, 131.3, 134.7, 154.6, 167.9, 187.6. MS (EI): *m/z* = 190 [M^+]. Anal. Calcd (%) for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.81; H, 5.14.
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