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The first one-pot oxidative 1,2-acetoxysulfenylation and 1,2-disulfenylation of Baylis–Hillman alcohols in an ionic liquid

Lal Dhar S. Yadav *, Chhama Awasthi

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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ABSTRACT

The first example of tandem oxidation and 1,2-acetoxysulfenylation/1,2-disulfenylation of Baylis–Hillman (BH) alcohols to afford 1,2-acetoxysulfides/1,2-dithioethers is reported. The reaction involves oxidation of BH alcohols with IBX in [bmim]Br to give β-ketomethylene compounds in situ followed by CuI-imidazole-catalyzed 1,2-acetoxysulfenylation with an organodisulfide and acetic acid under air to afford vicinal acetoxysulfides in excellent yields with complete regioselectivity. In the absence of the Cu(I) catalyst, 1,2-disulfenylation takes place to give vicinal dithioethers in 81–90% yields.

Improving the efficiency of organic synthesis including minimizing the energy, cost, and chemical waste is the major part of current research area in organic chemistry. In this regard one-pot sequential multistep reactions are of increasing academic, economical, and ecological interest for the synthesis of new chemical entities with diverse functionalities.[1] Introduction of sulfur functionality into unsaturated organic molecules is an important process for the drug development and other fine chemical synthesis.[2] Transition metal-catalyzed introduction of a sulfide group to an unsaturated C–C bond is an important procedure in synthetic organic chemistry.[3]

1,2-Hydroxysulfides are versatile building blocks for the synthesis of higher functionalized organic molecules,[4] namely, thioketones,[5] allyl alcohols,[6] cyclic sulfides,[7] benzothiazepines[8], and benzoxathiepines.[9] They exhibit great synthetic utility in the field of pharmaceuticals[10] and natural products,[11] particularly for the synthesis of leukotrienes (LTs) such as LTC_4 and LTD_4. These compounds have been synthesized by ring opening of epoxides,[12] and thiol-oxygen co-oxidation (TOCO) reactions of olefins,[13] but the methods have various disadvantages such as poor regioselectivity, lower yields, and undesirable side products. However, methods for a transition metal-catalyzed preparation of 1,2-hydroxysulfides using olefin and disulfide are very limited,[14] which has been the main driving force for the present investigation.

The addition of disulfides to olefins is a simple and reliable way for the synthesis of various sulfur-containing compounds. Previous reports on this type of reactions revealed the utility of mild acid catalysts, either in a stoichiometric or a catalytic amount, which includes $BF_3{\cdot}OMe_2$,[15] PhIO–TfOH,[16] and $GaCl_3$[17] or a catalytic amount of transition metal complexes such as [CpRuCl(Cod)].[18]

Recent times have witnessed a considerable upsurge of interest in the application of Baylis–Hillman (BH) adducts in organic synthesis.[19] The three chemospecific groups in BH adducts could be appropriately tailored to generate an array of chemically and pharmaceutically important molecules.[20] Similarly, among hypervalent iodine reagents,[21] 2-iodoxybenzoic acid (IBX) has become a reagent of choice due to its easy handling, ready availability, tolerance to moisture,[22] mild reaction conditions, zero toxic waste generation, and selective oxidation of alcohols.[23] Ionic liquids (ILs) have recently gained recognition as possible alternative solvents in various chemical processes because of their many fascinating properties. Although ILs are still significantly greener than volatile organic solvents, there are environmental issues with their biodegradability and toxicity, hence recently considerable attention has been paid in this regard.[24] Moreover, ILs are simple, easy to recycle, inexpensive to prepare, and their properties can be fine tuned by changing the anion or the alkyl group attached to cation.[24]

Prompted by the above reports and pursuing our work on the development of new one-pot synthetic methodologies,[25] especially using BH adducts,[25c–e] we devised a novel one-pot oxidative 1,2-acetoxysulfenylation/disulfenylation of BH adducts to form 1,2-acetoxysulfides/1,2-dithioethers in excellent yields. Our initial

* Corresponding author. Tel.: +91 5322500652; fax: +91 5322460533.
E-mail address: ldsyadav@hotmail.com (L.D.S. Yadav).

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Table 1
Optimization of Cu-catalyst for the synthesis of 1,2-acetoxysulfide **4a** (R^1 = H, R^2 = Ph)

Entry	Cu-catalyst	Catalyst loading (mol %)	Reaction time[a] (h)	Yield[b] (%)
1	CuBr	5	10	48
2	CuI	2	7	80
3	CuI	5	7	90
4	CuI	10	7	90
5	CuCl	5	10	7
6	$CuCl_2$	5	10	10
7	CuOAc	5	10	11
8	$Cu(OAc)_2$	5	10	10

[a] Stirring time at 50 °C (Scheme 1).[26]
[b] Yield of isolated and purified product **4a**.

Table 2
One-pot oxidative synthesis of 1,2-acetoxysulfides **4** (Scheme 1)

Product **4**	R^1	Organic disulfide **3**	Reaction time[a] (h)	Yield[b,c] (%)
a	H	PhS–SPh	7	90
b	OMe	PhS–SPh	7	93
c	Cl	PhS–SPh	8	89
d	NO_2	PhS–SPh	8.5	86
e	H	n-C_3H_7S–SC_3H_7-n	8.5	87
f	OMe	n-C_3H_7S–SC_3H_7-n	8	89
g	Cl	n-C_3H_7S–SC_3H_7-n	8.5	85
h	NO_2	n-C_3H_7S–SC_3H_7-n	9	83

[a] Stirring time at 50 °C.
[b] Yield of pure product **4** after column chromatography.
[c] All compounds gave C, H, and N analyses within ±0.37% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

efforts to probe the desired oxidative acetoxysulfenylation of BH alcohols **1** were focused on the reactivity of combined CuI/imidazole/$(R^2S)_2$ system for transfer of the equivalent of RS^+ to double bond, which is the active species for sulfenylation. The reaction was performed in open air and it did not take place under nitrogen atmosphere, that is, oxygen is necessary for the present reaction conditions.

In order to optimize Cu-catalyst, a brief study of several readily available copper salts was carried out. Different copper-catalysts such as CuCl, $CuCl_2$, CuI, CuOAc, $Cu(OAc)_2$, and CuBr were investigated in the presence of imidazole. Among these CuCl, $CuCl_2$, CuOAc, and $Cu(OAc)_2$ gave no appreciable effect on the reaction as they afforded only poor yields (7–10%) of product **4a** (Table 1, entries 5–8). However, CuBr was found to be active, but the yield of **4a** was moderate (Table 1, entry 1). CuI gave the best results (Table 1, entries 2–4) among all the copper salts. Furthermore, for optimization of catalyst loading we carried out the reaction by using 2, 5, and 10 mol % of CuI and the excellent yield of **4a** was obtained with 5 mol %. No improvement in the yield was noticed on increasing the catalyst loading from 5 mol % to 10 mol % (Table 1, entries 3 and 4). Hence, we utilized 5 mol % of CuI/imidazole catalyst system in our experiments. Interestingly, in the absence of copper-catalyst, 1,2-dithioethers **5** were exclusively obtained instead of 1,2-acetoxysulfides **4**.

The presence of a ligand is prerequisite for the success of the present reaction, thus several amine ligands were investigated, and it was found that the bulky ligand DABCO was less effective than L-proline or imidazole.

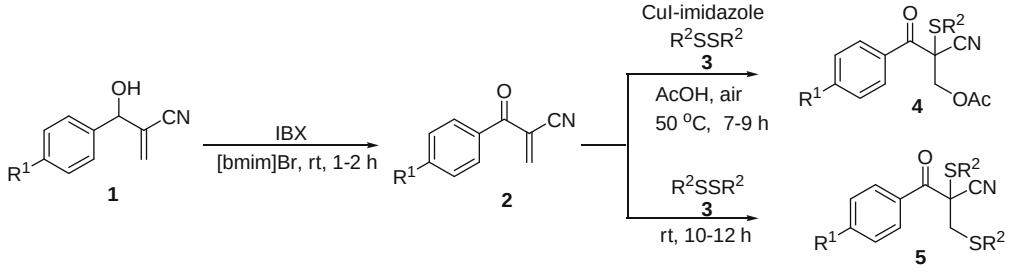
However, imidazole was more effective than L-proline, therefore, we opted imidazole as the ligand in the present experiments.[26]

Next, the effect of ILs was examined. We tested the present reaction in six different ILs, 1-butyl-3-methylimidazolium (bmim) tetrafluoroborate ([bmim]BF_4), [bmim]PF_6, [bmim]Br, butylpyridinium (bpy) tetrafluoroborate (bpyBF_4), bpyPF_6, bpyBr. Among these ILs, [bmim]Br dissolved IBX at rt and gave the best result in the one-pot oxidative 1,2-acetoxysulfenylation and 1,2-disulfenylation leading to **4** and **5** (Scheme 1). The other five ILs tested did not dissolve IBX even when heated to 80 °C in the presence of small amount of water (0.5 mL) and did not give satisfactory yields of **4**. Thus, the present optimized procedure involves stirring of BH alcohols **1** with IBX in [bmim]Br at rt for 1–2 h followed by the addition of 5 mol % CuI-imidazole, AcOH, and organic disulfide **3** in the same reaction vessel and stirring at 50 °C for 7–9 h to afford the corresponding hitherto unknown 1,2-acetoxysulfides **4** in 83–93% yields (Table 2) with complete regioselectivity.[26]

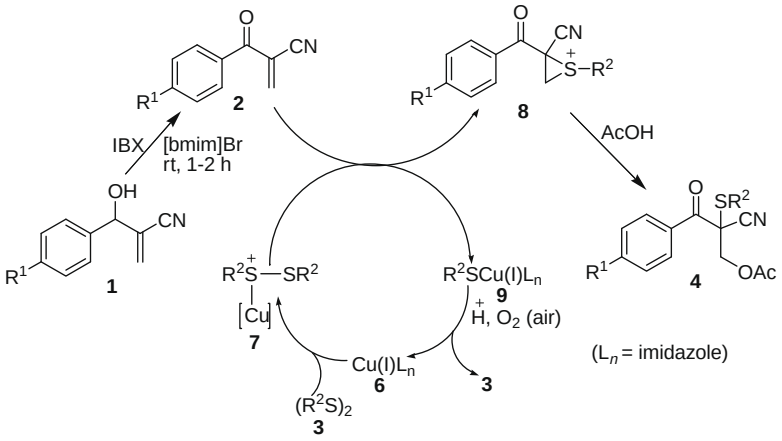
A plausible mechanism for the formation of 1,2-acetoxysulfide **4** is depicted in Scheme 2. The CuI-catalyst **6** reacts with disulfide **3** to furnish the sulfonium species **7** which transfers the electrophile R^2S^+ to BH olefin **2** leading to the final product **4** via three-membered cyclic sulfonium ion **8**. The intermediate $R^2SCu(I)L_n$ **9** formed in the reaction cannot sulfenylate **2** as such, but it is recycled to disulfide **3** under acidic conditions in air to establish the sulfenylation cycle.[14b] Thus, both the organosulfide groups of disulfide are utilized in the 1,2-acetoxysulfenylation (Scheme 2).

After a successful attempt at the synthesis of 1,2-acetoxysulfides **4**, we tried one-pot oxidative disulfenylation of BH alcohols **1** using IBX followed by organic disulfides **3** in [bmim]Br (Scheme 1). The reaction worked well in the absence of the Cu-imidazole catalyst system. Probably, the acidic nature of [bmim]Br promotes the reaction (Scheme 3, structure 10). The procedure involves the oxidation of BH alcohol **1** with IBX in [bmim]Br followed by the addition of organic disulfide **3** in the same reaction vessel and stirring at rt for 10–12 h to afford dithioether **5** in excellent yields (Table 3).[27] When we used acetic acid with organic disulfide **3** in the reaction, only dithioether **5** was obtained instead of 1,2-acetoxysulfide **4**. The reason behind it could be the more nucleophilicity of R^2S^- than AcO^-. It shows the importance of copper-catalyst in 1,2-acetoxysulfenylation of **2**, where R^2S^- is readily converted into R^2SSR^2 **3** in the presence of air and AcO^- is available as the only effective nucleophile to afford **4** (Scheme 2).

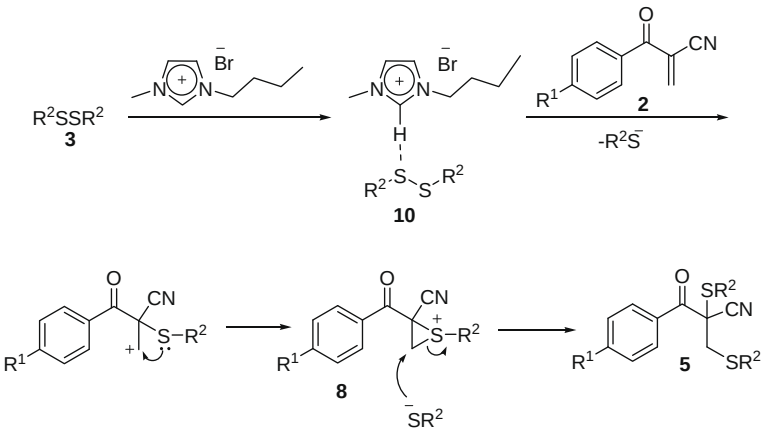
A plausible mechanistic pathway for the formation of dithioethers **5** is depicted in Scheme 3. Due to the acidity of C-2 proton of imidazolium cation,[28] its hydrogen bond interaction with the sulfur of disulfide **3** increases electrophilicity of the disulfide (structure **10**). This facilitates the transfer of R^2S^+ species to the



Scheme 1. One-pot oxidative 1,2-acetoxysulfenylation and 1,2-disulfenylation of BH alcohols **1**.



Scheme 2. Plausible mechanism for the synthesis of 1,2-acetoxysulfides **4** from BH alcohols **1**.



Scheme 3. Plausible mechanism for the formation of **5**.

BH olefin **2** to afford the desired product **5** through cyclic sulfonium ion **8**.

The requisite BH alcohols and ILs were prepared by employing known methods.[29–31] After isolation of products **4** and **5**, the IL [bmim]Br could be recycled for four times with up to 76% recovery and reused without any loss of efficiency.[26,27]

In summary, we have documented, for the first time, a one-pot oxidative 1,2-acetoxysulfenylation and 1,2-disulfenylation reactions as a novel entry to vicinal acetoxysulfides/dithioethers directly from BH alcohols in the IL [bmim]Br. This reaction regioselectively affords the product and enables the use of both organosulfide groups of disulfide. The present methodology opens up a new aspect of the synthetic utility of BH adducts.

Table 3
One-pot oxidative synthesis of 1,2-dithioethers **5** (Scheme 1)

Product **5**	R^1	Organic disulfide **3**	Reaction time (h)[a]	Yield[b,c] (%)
a	H	PhS–SPh	11	88
b	OMe	PhS–SPh	10	90
c	Cl	PhS–SPh	10.5	87
d	NO_2	PhS–SPh	12	85
e	H	*n*-C_3H_7–SC_3H_7-*n*	11.5	86
f	OMe	*n*-C_3H_7–SC_3H_7-*n*	11	87
g	Cl	*n*-C_3H_7–SC_3H_7-*n*	11.5	83
h	NO_2	*n*-C_3H_7–SC_3H_7-*n*	12	81

[a] Stirring time for the conversion of **2** into **5**.
[b] Yield of pure product **5** after column chromatography.
[c] All compounds gave C, H, and N analyses within ±0.38% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.030.

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26. *General procedure for the synthesis of 1,2-acetoxysulfides* **4**: A mixture of [bmim]Br (3 mL), water (0.5 mL), and IBX (1 mmol) was stirred at rt for 5–10 min followed by addition of BH alcohol **1** (1 mmol) and stirring at rt for 1–2 h. After complete oxidation (monitored by TLC), CuI (0.05 mmol), imidazole (0.05 mmol), organodisulfide **3,** (0.5 mmol) and acetic acid (0.7 mL) were added and the reaction mixture was stirred for a further 7–9 h at 50 °C under air (Table 2). Then, it was diluted with saturated $NaHCO_3$ solution (10 mL) and extracted with ether (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography using hexane/ethyl acetate (9.7:0.3) as eluent to afford an analytically pure sample of **4**. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (2×10 mL) to remove any organic impurity and filtered. The filtrate was extracted with CH_2Cl_2 (3×10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford [bmim]Br, which was used in subsequent runs without further purification. Physical data of representative compounds. Compound **5a**: Yellowish solid, yield 90%, mp 156–158 °C. IR (KBr) ν_{max} 3055, 2992, 2858, 2242, 1743, 1698, 1583, 1451, 760, 697 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.08 (s, 3H, $OCOCH_3$), 4.72 (d, 1H, J = 12.2 Hz, β-H_a), 4.98 (d, 1H, J = 12.2 Hz, β-H_b), 7.08–7.64 (m, 8H_{arom}), 7.98 (t, 2H, J = 7.6 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 20.1, 52.4, 61.7, 116.9, 122.3, 124.8, 126.0, 127.5, 128.6, 133.6, 137.7, 139.4, 174.3, 198.9. EIMS (m/z): 325 (M^+). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.50; H, 4.65; N, 4.30. Found: C, 66.80; H, 5.02; N, 3.98. Compound **4e**: yellowish solid, yield 87%, mp 120–122 °C. IR (KBr) ν_{max} 3052, 2990, 2857, 2240, 1743, 1698, 1581, 1452, 759, 695 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 0.89 (t, 3H, J = 7.1 Hz, CH_3), 1.40–1.43 (m, 2H, CH_2), 2.07 (s, 3H, $OCOCH_3$), 2.47 (t, 2H, J = 7.2 Hz, CH_2), 4.73 (d, 1H, J = 12.2 Hz, β-H_a), 4.89 (d, 1H, J = 12.2 Hz, β-H_b), 7.53 (t, 1H, J = 7.7 Hz, H_{arom}), 7.64 (t, 2H, J = 7.4 Hz, H_{arom}), 7.97 (t, 2H, J = 7.6 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 15.0, 20.3, 23.5, 31.0, 50.4, 62.1, 116.9, 127.4, 128.6, 133.2, 138.9, 173.3, 198.7. EIMS (m/z): 291 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.89; H, 5.88; N, 4.81. Found: C, 61.52; H, 6.08; N, 4.52.
27. *General procedure for the synthesis of 1,2-dithioethers* **5**: A mixture of [bmim]Br (3 mL), water (0.5 mL), and IBX (1 mmol) was stirred at rt for 5–10 min followed by addition of BH alcohol **1** (1 mmol) and stirring at rt for 1–2 h. After complete oxidation (monitored by TLC) organodisulfide **3** (0.5 mmol) was added and the reaction mixture was stirred for a further 10–12 h at rt (Table 3). Then, saturated aqueous $NaHCO_3$ solution (10 mL) was added and organic phase was extracted with ether (3×10 mL) then washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the crude product that was purified by silica gel column chromatography using hexane/ethyl acetate (9.8:0.2) as eluent to afford an analytically pure sample of **5**. Ionic liquid was recovered by the same method as given above[26] and used for subsequent runs without further purification. Physical data of representative compounds. Compound **5a**: yellowish solid, yield 88%, mp 178–180 °C. IR (KBr) ν_{max} 3054, 2989, 2857, 2239, 1696, 1451, 1580, 759, 698 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 3.33 (d, 1H, J = 12.2 Hz, β-H_a), 3.79 (d, 1H, J = 12.2 Hz, β-H_b), 7.09–7.66 (m, 13H_{arom}), 7.99 (t, 2H, J = 7.6 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 38.5, 62.1, 116.9, 123.3, 123.7, 124.8, 125.2, 126.0, 126.6, 127.5, 128.6, 129.3, 133.7, 137.8, 138.9, 198.8. $C_{22}H_{17}NOS_2$: C, 70.45; H, 4.56; N, 3.73. Found: C, 70.07; H, 4.28; N, 3.91. Compound **5e**: yellowish solid, yield 86%, mp 133–135 °C. IR (KBr) ν_{max} 3051, 2988, 2856, 2238, 1697, 1580, 1451, 758, 697 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 0.83 (t, 3H, J = 7.1 Hz, CH_3), 0.89 (t, 3H, J = 7.1 Hz, CH_3), 1.38–1.43 (m, 4H, 2 × CH_2), 2.39 (t, 2H, J = 7.2 Hz, CH_2), 2.47 (t, 2H, J = 7.2 Hz, CH_2), 3.18 (d, 1H, J = 12.2 Hz, β-H_a), 3.41 (d, 1H, J = 12.2 Hz, β-H_b), 7.52 (t, 1H, J = 7.7 Hz, H_{arom}), 7.63 (t, 2H, J = 7.4 Hz, H_{arom}), 7.96 (t, 2H, J = 7.6 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 15.1, 15.4, 22.4, 23.1, 32.0, 33.3, 35.8, 51.4, 116.8, 127.9, 128.5, 133.4, 138.8, 198.7. EIMS (m/z): 307 (M^+). Anal. Calcd for $C_{16}H_{21}NOS_2$: C, 62.57; H, 6.89; N, 4.56. Found: C, 62.95; H, 6.54; N, 4.25.
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