$KHSO_4$-Mediated Condensation Reactions of *tert*-Butanesulfinamide with Aldehydes. Preparation of *tert*-Butanesulfinyl Aldimines

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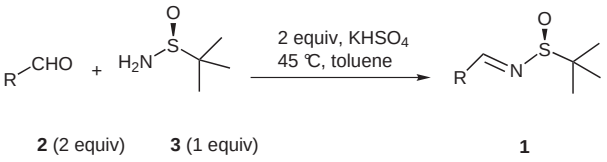
Abstract: Optically pure *tert*-butanesulfinyl aldimines **1** were prepared by direct condensation of chiral *tert*-butanesulfinamide **3** with aldehydes **2** in high yields in the presence of $KHSO_4$. The main advantage of $KHSO_4$ is that it is applicable to the condensation reactions of a variety of aldehydes, including electron deficient and electron rich (hetereo)aromatic aldehydes, as well as aliphatic aldehydes.

Key words: *tert*-butanesulfinamide, aldehyde, *tert*-butanesulfinyl aldimines, potassium hydrogen sulfate, condensation

Optically pure *tert*-butanesulfinyl aldimine **1** has been shown to be an important intermediate for the asymmetric syntheses of chiral amine derivatives through the addition reactions of nucleophilic reagents in recent years.[1] The practical preparation of **1** is the key issue in relation to its application in asymmetric synthesis.

Optically pure aldimines **1** were usually prepared by direct condensations of chiral *tert*-butanesulfinamide **3**[2] with aldehydes in the presence of an activator such as $MgSO_4$(PPTS),[3,4] $Ti(OEt)_4$,[4] $CuSO_4$,[4] and Cs_2CO_3.[5] All of the above reagents are useful in their own right, but each suffers from one or more limitations. For example, $MgSO_4$(PPTS) was not effective for most aldehydes, while $CuSO_4$ was not effective with electron-deficient aromatic aldehydes nor with sterically hindered aliphatic aldehydes, and Cs_2CO_3 was expensive and less effective with electron-rich aromatic aldehydes. Although $Ti(OEt)_4$ can promote the condensation reactions of **3** with electron-deficient and electron-rich aromatic aldehydes, and aliphatic aldehydes in high yields, it is a moisture-sensitive reagent and lacks an easy workup procedure. More recently, a catalytic procedure has been developed using $Yb(OTf)_3$ as a catalyst for the condensation reaction,[6] it still seems highly desirable to find a simple, efficient, economical, and general method for the preparation of **1**. In this communication, we report that inexpensive $KHSO_4$ can serve as a highly efficient and mild catalyst for the condensation reactions of **3** with all types of aldehydes in high to excellent yields (Scheme 1).



2 (2 equiv) **3** (1 equiv) **1**

Scheme 1 The condensation reactions of *tert*-butanesulfinamide with aldehydes catalyzed by $KHSO_4$.

In the previous study,[7] we found that $KHSO_4$ activated the addition reactions of indole to aldimines **1** efficiently to afford bisindolylalkanes in excellent yields. This observation encouraged us to investigate the usefulness of $KHSO_4$ in the condensation reaction of **3** with aldehydes to afford aldimines **1**. Initial work showed that when 1 equivalent of (*S*)-*tert*-butanesulfinamide **3** was stirred with 1.1 equivalents of benzaldehyde at room temperature in CH_2Cl_2 in the presence of two equivalents of $KHSO_4$ for 24 hours, the desired aldimine **1a** (R = Ph) was obtained in 61% yield. Our study was then directed to explore the effects of different solvents on the condensation reaction. The results are depicted in Table 1. For the majority of solvents, the condensation reactions proceeded smoothly to give desired **1a** in good yields (Table 1, entries 1–6). Toluene and $(i\text{-Pr})_2O$ gave the highest yields (over 80%; Table 1 entries 7 and 8). The yield was slightly improved (from 81% to 86%) when the reaction temperature was increased by 20 °C from 25 °C to 45 °C under the same conditions in toluene (Table 1, entries 9 and 10). When 2 equivalents of benzaldehyde were used in order to drive the reaction to completion, the yield was further improved from 86% to 91% (Table 1, entries 9 and 10; 45 °C). Increasing the reaction temperature from 45 °C to 80 °C resulted in a lower yield (Table 1, entry 11, 65%) owing to the competitive decomposition of **1a**.

Next we examined the scope of the $KHSO_4$-mediated condensation reaction of **3** with a variety of aldehydes, using the optimum conditions [toluene, 45 °C, $KHSO_4$ (2 equiv)].[8] The results are shown in Table 2. In general for aromatic aldehydes, condensation reactions usually afforded the corresponding aldimines **1** in over 80% yields (Table 2, entries 1–7). $KHSO_4$ was as effective when compared with $CuSO_4$ for both electron rich and electron deficient aromatic aldehydes, and was superior to Cs_2CO_3 for electron rich aromatic aldehydes[5] (Table 2, entries 3, 5, and 6 compared with entry 4). When conjugated aldehydes were subjected to this reaction, $KHSO_4$ was found

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Table 1 Solvent Optimization for the Preparation of Aldimine **1a** Mediated by $KHSO_4$[a]

Entry	Solvent	Yield[b]	Time (h)
1	CH_2Cl_2	61	24
2	$CHCl_3$	56	24
3	THF	75	24
4	EtOH	70	24
5	MeCN	70	24
6	Benzene	78	24
7	$(i\text{-Pr})_2O$	82	24
8	Toluene	81	24
9	Toluene[c]	86	24
10	Toluene[d]	91	24
11	Toluene[e]	65	24

[a] Conditions: 25 °C, benzaldehyde (1.1 equiv), $KHSO_4$ (2 equiv).
[b] Isolated yields.
[c] Conditions: 45 °C.
[d] Conditions: 45 °C, benzaldehyde (2 equiv).
[e] Conditions: 80 °C, benzaldehyde (2 equiv).

to act as an effective catalyst resulting in excellent yields (Table 2, entries 8 and 9); this is almost as effective as $Yb(OTf)_3$.[6] While $CuSO_4$ mediated the condensation of 2-furylaldehyde in low yield (Table 2, entry 11), and was ineffective for the condensation of 3-pyridylaldehyde, the poor yields resulted from complex formation between $CuSO_4$ and 3-pyridylaldehyde (entry 15).[4] However, we were pleased to discover that $KHSO_4$-mediated the condensation reactions of 2-furylaldehyde, 2-pyridylaldehyde, 3-pyridylaldehyde, and 4-pyridylaldehyde in high yields (Table 2, entries 10, 12–14, and 17).

Also it was gratifying to see that $KHSO_4$ catalyzed the condensation reaction of phenylacetaldehyde to give the desired aldimine **1m** in 60% yield without formation of the enamine product (Table 2, entry 18).[9] For aliphatic aldehydes, condensation reactions gave the corresponding aldimines **1n**–**r** in good to high yields (Table 2, entries 19–23). Even the extremely hindered pivaldehyde underwent $KHSO_4$-catalyzed condensation reaction to afford **1r** in 81% yield (Table 2, entry 23), which was almost as effective as $Ti(OEt)_4$, and in fact was superior to $CuSO_4$, Cs_2CO_3, and $Yb(OTf)_3$ (Table 2, entries 23–27). For volatile aliphatic aldehydes such as butylaldehyde and isobutylaldehyde, 5 equivalents of aldehydes were essential to the success of the reaction. The condensation of 2-phthalimidoacetaldehyde with **3** gave aldimine **1s** in 86% yield (Table 2, entry 28). Unfortunately, when we tested one ketone, acetophenone, it failed to react with **3** even under our optimized conditions (Table 2, entry 29).

Table 2 Preparation of Aldimine **1** Mediated by $KHSO_4$ in Toluene[a]

Entry	**1**	R	Catalyst	Yield[b]
1	**1a**	Ph	$KHSO_4$	91
2	**1b**	4-ClPh	$KHSO_4$	87
3	**1c**	4-MeOPh	$KHSO_4$	80
4	**1c**	4-MeOPh	Cs_2CO_3	<55[5]
5	**1d**	$4\text{-Me}_2\text{NPh}$	$KHSO_4$	87
6	**1e**	$3,4\text{-(MeO)}_2\text{Ph}$	$KHSO_4$	82
7	**1f**	$4\text{-NO}_2\text{Ph}$	$KHSO_4$	92
8	**1g**	(*E*)-PhCH=CH-	$KHSO_4$	91
9	**1h**	$(Me)_2CH=CH\text{-}$[e]	$KHSO_4$	93
10	**1i**	2-Furyl	$KHSO_4$	84
11	**1i**	2-Furyl	$CuSO_4$	40[4]
12	**1i**	2-Furyl	$Ti(OEt)_4$	82[4]
13	**1j**	2-Pyridyl	$KHSO_4$	95
14	**1k**	3-Pyridyl	$KHSO_4$	88
15	**1k**	3-Pyridyl	$CuSO_4$	trace[4]
16	**1k**	3-Pyridyl	$Ti(OEt)_4$	quant.[4]
17	**1l**	4-Pyridyl	$KHSO_4$	93
18	**1m**	$PhCH_2\text{-}$	$KHSO_4$	60
19	**1n**	Pr[e]	$KHSO_4$	80
20	**1o**	Octyl	$KHSO_4$	82
21	**1p**	$Ph(CH_2)_2\text{-}$	$KHSO_4$	86
22	**1q**	2-Pr[c]	$KHSO_4$	80
23	**1r**	*t*-Bu	$KHSO_4$	81
24	**1r**	*t*-Bu	$Ti(OEt)_4$	82[4]
25	**1r**	*t*-Bu	Cs_2CO_3	59[5]
26	**1r**	*t*-Bu	$Yb(OTf)_3$	52[6]
27	**1r**	*t*-Bu	$CuSO_4$	trace[4]
28	**1s**	2-Phthalimidomethyl	$KHSO_4$	86
29	**1t**	Acetophenone	$KHSO_4$	0

[a] Conditions: 45 °C, aldehyde (2 equiv), $KHSO_4$ (2 equiv), toluene.
[b] Isolated yields.
[c] Conditions: aldehyde (5 equiv), sealed tube.

In light of the effectiveness of $KHSO_4$ in the condensation reaction, it is reasonable to believe that $KHSO_4$ acts as both a protic acid and a dehydrating agent. The acidity of $KHSO_4$ in toluene is not strong enough to cause the resulting *tert*-butanesulfinyl aldimines **1** to undergo racemization and to scissor out the *tert*-butanesulfinyl group from the condensation product.[8]

In summary, we have described a highly efficient method for the preparation of optically pure *tert*-butanesulfinyl aldimines **1** by using $KHSO_4$ as a catalyst. $KHSO_4$ is applicable to the condensation reactions of a variety of aldehydes, including electron deficient and electron rich (hetero)aromatic aldehydes, and aliphatic aldehydes. The current method offers several advantages including mild reaction condition, cheap reagent, high yield of product, as well as simple experimental procedure, which makes it a useful and practical method for the syntheses of optically pure *tert*-butanesulfinyl aldimines.

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(8) General procedure: (*S*)-*tert*-Butanesulfinamide (1 mmol) was stirred with benzaldehyde (2 mmol) in toluene (10 mL) in the presence of $KHSO_4$ (2 equiv) for 24 h at 45 °C. $KHSO_4$ was then removed by filtration. The filtrate was concentrated to dryness. The residue was purified by flash chromatography to afford (*S*)-*tert*-butanesulfinyl aldimine (**1a**) as a colorless liquid. $[\alpha]_D^{20}$ +105 (*c* 2.19, $CHCl_3$, Lit.[5,10] $[\alpha]_D^{20}$ +104, $CHCl_3$). ^1H NMR and ^{13}C NMR spectra were identical to that reported in the literature.[5,10] The ee of synthesized aldimine **1**, determined by HPLC analysis (Daicel Chiralcel OD column), was over 99%.[4,5]

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