JOC*Note*

Synthesis of Enantiopure Sulfinimines (Thiooxime *S*-Oxides) Catalyzed by $Yb(OTf)_3$ from *p*-Toluenesulfinamide and Aldehydes in Mild Reaction Conditions

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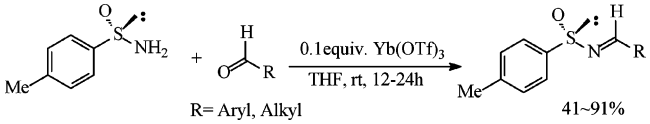

Enantiomerically pure sulfinimines as important building blocks in the asymmetric synthesis of amine derivatives are prepared in good to excellent yields from chiral *p*-toluenesulfinamide with aromatic, heteroaromatic, and aliphatic aldehydes. The unprecedented feature of the reported procedure is that the formation of the sulfinimines was achieved by the catalytic action of $Yb(OTf)_3$ in THF at room temperature. The reaction conditions were also applicable to Ellman's sulfinimines.

Asymmetric synthesis of functionalized amino compounds has been the subject of intensive studies, partly because a majority of drugs and drug candidates are incorporating amine functionality. A particularly venerable synthetic route toward the preparation of homochiral amine derivatives is the elaboration of chiral sulfinimines pioneered by Davis[1] and Ellman.[2] The two important sulfinimines, *N*-*p*-toluenesulfinimines and *N*-*tert*-butanesulfinimines, developed by them, respectively, have been demonstrated as versatile intermediates for the asymmetric syntheses of amine derivatives,[1−3] α- and β-amino acids,[4] α- and β-amino phosphonates,[5] and heterocycles.[6] Their achievements have triggered various groups to develop new asymmetric syntheses by using these sulfinimines as chiral induction groups.[7] Among the several methods to synthesize these sulfinimines,[1,2] the straightforward one is the direct condensation of chiral sulfinamides with aldehydes under fairly drastic conditions. To mitigate the seemingly forced conditions required for making sulfinimines, several improved procedures have emerged.[8−10] Ellman realized the condensation of *N*-*tert*-butanesulfinimines with aldehydes using $MgSO_4$,[8a] $CuSO_4$,[8a,b] and $Ti(OEt)_4$.[8b,c] At the same time, Davis reported the condensation of *N*-*p*-toluenesulfinamide with aldehydes using CsF,[9a] $Ti(OEt)_4$,[9a,b] and molecular sieves.[9b] Recently, Cs_2CO_3 was reported as an activating and dehydrating reagent to facilitate the transformation.[10] Although the reported methods rendered the preparation of sulfinimines much easier, excess Lewis acid or stoichiometric base had to be used.

To further simplify the preparation route of the titled compounds, under the mediation of microwave we found the condensation could be effected in good to excellent yields.[11] On the other hand, an excess amount of $Ti(OEt)_4$ was adopted by many investigators as the reagent of choice to promote the condensation reaction. Its removal after the reaction sometimes is problematic, however, and

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(11) Unpublished results.

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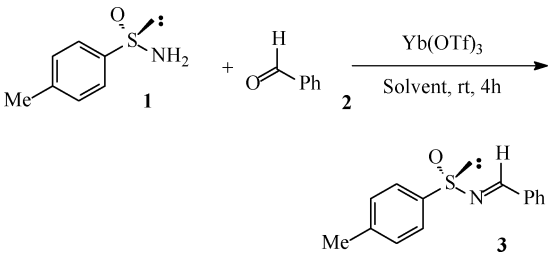
TABLE 1. Condition Optimization for Synthesis of Sulfinimine from *p*-Toluenesulfinamide and Benzaldehyde



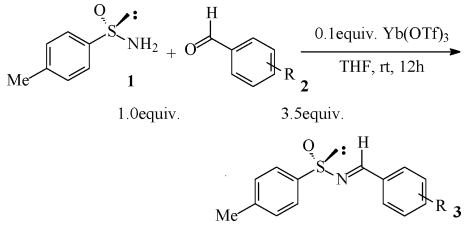
entry	solvent	ratio sulfinamide:aldehyde	equiv of $Yb(OTf)_3$	ratio **1**:**3**[a]
1	dioxane	1:3.5	0.1	7:93
2	toluene	1:3.5	0.1	31:69
3	DMF	1:3.5	0.1	30:70
4	CH_2Cl_2	1:3.5	0.1	23:77
5	CH_3CN	1:3.5	0.1	21:79
6	$CHCl_3$	1:3.5	0.1	49:51
7	THF	1:3.5	0.1	6:94
8	THF	1:3.5	0.5	1:99
9	THF	1:3.5	1.0	2:98
10	THF	1:1	1.0	27:73
11	THF	1:1	2.0	10:90
12	THF	1:1	3.0	<1:>99

[a] The ratio of **1**:**3** was based on ^{1}H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition, as indicated by TLC and ^{1}H NMR.

the high reaction temperature at refluxing THF may cause the decomposition of some unstable adducts.[3f] The popular use of ytterbium(III) triflate as catalysts in recent literature for a number of transformations prompted us to undertake the investigation whereby expeditious formation of chiral sulfinimines could be realized.[6b,12] We describe in this report that the facile condensation of *N*-*p*-toluenesulfinamide and aldehydes could be realized by using catalytic amount of $Yb(OTf)_3$ at very mild conditions. Under systematic studies, the optimized reaction condition for making sulfinimines exemplified by benzaldehyde emerged. First, THF emerged as the solvent of the choice for the transformation (Table 1, entries 1−7). In the presence of 0.1 equiv of $Yb(OTf)_3$ in THF at room temperature, benzaldehyde (3.5 equiv) reacted smoothly with 1 equiv of *N*-*p*-toluenesulfinamde **1**, affording the product with a minimum amount of the starting material left (Table 1, entry 7). The reaction rate of the condensation could be expedited by increasing the amount of $Yb(OTf)_3$ to 0.5 or more (Table 1, entries 8 and 9). If only a 1:1 ratio of aldehyde to sulfinamide was used, 3.0 equiv of $Yb(OTf)_3$ had to be employed to drive the reaction to completion (Table 1, entries 10−12). It was later found that such condition is not suitable for the preparation of sulfinimines from aliphatic aldehydes, as well as aromatic aldehydes possessing electron-donating groups.

To define the scope of the procedure, monosubstituted aromatic aldehydes were subjected to the condensation conditions, and consistent with the mechanism, the electronic nature of the second substituent exerted a dominant impact on the yield of the products. Aromatic aldehydes bearing an electron-withdrawing group condensed more effectively with sulfinamide than those bearing an electron-donating group (Table 2, entries 1−7 versus 9−12).

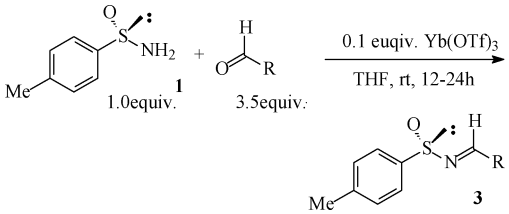
TABLE 2. Synthesis of Sulfinimine 3 from *p*-Toluenesulfinamide 1 and Several Aromatic Aldehydes

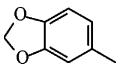
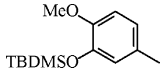
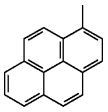
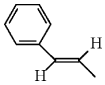


entry	R	ratio **1**:**3**[a]	product	yield (%)[b]
1	*p*-CN	<1:>99	**3a**	91
2	*o*-NO_2	1:99	**3b**	81
3	*p*-CHO	1:99	**3c**	91
4	*m*-CHO	1:99	**3d**	84
5	*p*-F	10:90	**3e**	85
6	*p*-Cl	12:88	**3f**	84
7	*p*-Br	2:98	**3g**	94
8	*p*-H	1:99	**3h**	90
9	*p*-MeO[c]	37:63	**3i**	57
10	*p*-MeO[d]	30:70		*f*
11	*p*-MeO[e]	23:77		*f*
12	*p*-MeS	46:54	**3j**	41

[a] Determined by ^{1}H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition, as indicated by TLC and ^{1}H NMR). [b] Isolated yield based on sulfinamide used. [c] 0.1 equiv of $Yb(OTf)_3$. [d] 0.5 equiv of $Yb(OTf)_3$. [e] 1.0 equiv of $Yb(OTf)_3$. [f] Not determined.

TABLE 3. Synthesis of Sulfinimine 3 from *p*-Toluenesulfinamide 1 with Several Heteroaromatic and Complex Aromatic Aldehydes



entry	R	equiv of Yb(OTf)3	product	ratio **1**:**3**[a]	yield (%)[b]
1		0.1	**3k**	*c*	58
2		0.1	**3l**	*c*	76
3		0.5	**3m**	1:99[d]	52
4		0.5	**3n**	41:59	47
5		0.1	**3o**	8:92	79
6		0.1	**3p**	1:99	72

[a] The ratio of **1**:**3** was based on ^{1}H NMR analysis of the crude product. [b] Isolated yield. [c] The ratio could not be determined. [d] Other byproducts were found.

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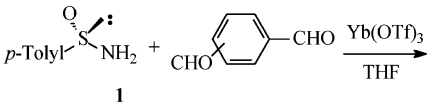
TABLE 4. Synthesis of Monosulfinimine 4 from *p*-Toluenesulfinamide 1 and Several Bisaldehydes



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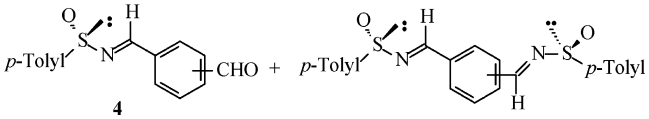

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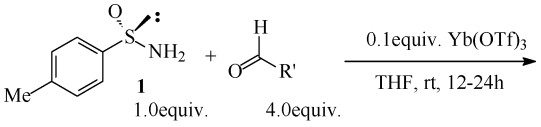
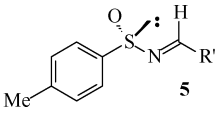
entry	bisaldehydes	ratio **1**:**5**	equiv of $Yb(OTf)_3$	*T* (°C)	reaction time (h)	yield of **4**[b]
1	*o*-CHO	1:3.5	0.1	rt[a]	12	nr
2	*m*-CHO	1:3.5	0.1	rt	12	84
3	*m*-CHO	6:1	0.1	rt	12	77
4	*m*-CHO	8:1	0.5	reflux	24	72[c]
5	*p*-CHO	1:3.5	0.1	rt	12	91
6	*p*-CHO	6:1	0.1	rt	12	57
7	*p*-CHO	8:1	0.5	reflux	24	78

[a] rt = room temperature. [b] Isolated yield. [c] Trace bis-sulfinimines were found from TLC and ^{1}H NMR.

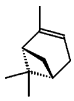
TABLE 5. Synthesis of Sulfinimines 5 from *p*-Toluenesulfinamide and Aliphatic Aldehydes



1 1.0equiv. 4.0equiv.



5

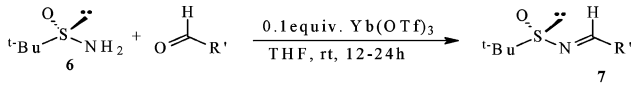
entry	R′	product	ratio **1**:**5**	yield (%)[b]
1	CH_3CH_2-	**5a**	<1:>99	87
2	$CH_3CH_2CH_2$-	**5b**	7:93	77
3	2-butyl	**5c**	1:99	80
4	*c*-C_6H_{11}-	**5d**	1:99	81
5	t-Bu	**5e**	*c*	62
6	(*E*)-CH_3CH=CH-	**5f**	99:1	81
7		**5g**	*c*	86

[a] The ratio of **1**:**5** was based on ^{1}H NMR analysis of the crude product. [b] Isolated yield. [c] The ratio could not be determined.

The protocol has been extended to the preparation of sulfinimines from heteroaromatics (Table 3, entries 1 and 2), polysubstituted aromatics (Table 3, entries 3 and 4), a polyaromatic (Table 3, entry 5), and cinnamaldehyde (Table 3, entry 6). Modest to good yield of the products was invariantly obtained in each of the cases.

In contrast, our attempt to prepare bis-sulfinimines from the three phthalaldehydes was unfruitful. First, the steric hindrance of *o*-phthalaldehyde completely restricted the formation of the condensed product (Table 4, entry 1). Furthermore, the preparation of monosulfinimines from both *m*- and *p*-phthalaldehyde could be accomplished, using the developed reaction protocol (Table 4, entries 2 and 5). Neither by increasing the amount of the sulfinamide/$Yb(OTf)_3$ nor by prolonging the heating time of the reaction was any trace amount of desirable bis-product obtained (Table 4, entries 3, 4, 6 and 7).

TABLE 6. Synthesis of Sulfinimines 7 from *tert*-Butanesulfinamide 6 and Aldehydes



6 **7**

1.0equiv. 3.5equiv. (aromatic aldehydes)
4.0equiv. (aliphatic aldehydes)

entry	R′	product	ratio **1**:**7**[a]	yield (%)[b]
1	Ph	**7a**	1:99	84
2	2-butyl	**7b**	7:93	87
3	(*E*)-CH_3CH=CH-	**7c**	1:99	87

[a] The ratio of **1**:**7** was based on ^{1}H NMR analysis of the crude product. [b] Isolated yield.

On the other hand, it is gratifying to find that the reaction conditions developed can be also used to synthesize sulfinimines from *p*-toluenesulfinimine and a variety of aliphatic aldehydes. In the presence of 0.1 equiv of $Yb(OTf)_3$, excess of aldehyde was used to react with the sulfinamide, affording good to excellent yield of the product. Remarkably, $Yb(OTf)_3$ was shown to be highly effective in promoting the reaction even for sterically hindered aliphatic aldehydes (Table 5, entries 4, 5, and 7). Finally, in the case of the Ellman sulfinimine **6**, sulfinamides were obtained in equally good yields under the same conditions (Table 6, entries 1−3).

In summary, a general, mild, and effective method for the synthesis of chiral sulfinimines from *N*-*p*-toluenesulfinamide and aldehydes was developed. The advantages of this method are the easy workup procedure, very mild reaction conditions, and the need of using only a catalytic amount of Lewis acid.

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Supporting Information Available: Detailed experimental procedures and compound characterization data (^{1}H and ^{13}C spectra of every compound and HRMS spectra of new compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

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