# Synthesis of Sulfinimines by Direct Condensation of Sulfinamides with Aldehydes Using $Cs_2CO_3$ as an Activating and Dehydrating Reagent

Shuhei Higashibayashi, Hiraku Tohmiya, Tomonori Mori, Kimiko Hashimoto, Masaya Nakata*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Kohoku-ku, Hiyoshi, Yokohama 223-8522, Japan

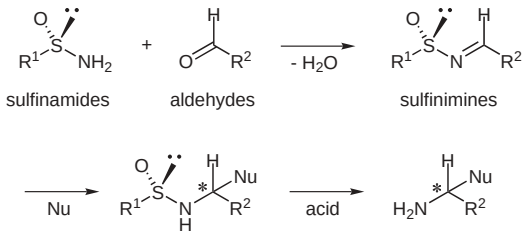
Fax +81(45)5661551; E-mail: msynktxa@applc.keio.ac.jp

*Received 9 December 2003*

**Abstract:** Chiral sulfinimines were prepared from chiral sulfinamides and aldehydes in $CH_2Cl_2$ in the presence of cesium carbonate as an amine-activating and dehydrating reagent.

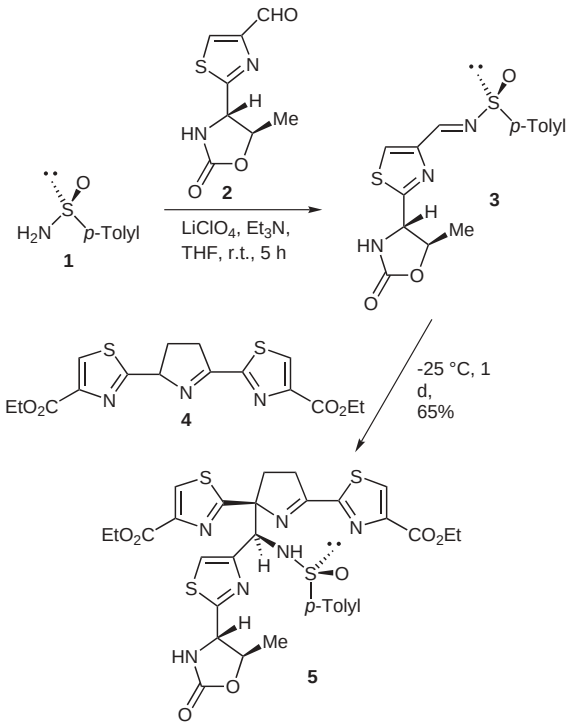
**Key words:** sulfinimines, sulfinamides, cesium carbonate, dehydrations, amine activation

Enantiomerically pure sulfinimines are versatile intermediates for the asymmetric syntheses of amine derivatives. A variety of nucleophiles add to chiral sulfinimines in a highly diastereoselective manner; after addition, the sulfinyl group can be removed by brief treatment with an acid to afford chiral amine derivatives (Scheme 1).[1,2] Two enantiomerically pure sulfinimines have been widely used: *N*-*p*-toluenesulfinimines ($R^1$ = *p*-tolyl, Scheme 1) pioneered by Davis[1], and *N*-*t*-butanesulfinimines ($R^1$ = *t*-butyl, Scheme 1) developed by Ellman.[2,3] Among the several methods to synthesize these sulfinimines,[1,2] the straightforward one is the direct condensation of chiral sulfinamides with aldehydes. However, the lower nucleophilicity of the nitrogen in sulfinamides than that in amines makes the synthesis of sulfinimines more difficult than the synthesis of imines. To overcome this, several precedents have been reported.[1,2,4,5] Ellman realized this condensation using $MgSO_4$,[4] $CuSO_4$,[4b,c] and $Ti(OEt)_4$.[4b,c] Davis also reported this method using CsF,[5a] $Ti(OEt)_4$,[5b,c] and molecular sieves.[5b] In all these cases, however, excess amounts of reagents (typically 2–5 molar amounts, sometimes 10 molar amounts) were needed in order to complete the condensation reactions.




**Scheme 1**

During the course of our synthetic studies on the thiostrepton family of peptide antibiotics,[6] we used the three-component one-pot coupling of the Davis chiral sulfinamide **1**,[5] aldehyde **2**, and dehydropyrrolidine **4** (Scheme 2). In this case, the mixture of $LiClO_4$-triethylamine was very effective for not only the condensation of **1** with **2** but also the stereoselective addition of the azomethine ylide derived from **4** to sulfinimine **3**, giving a good yield of **5**. However, it was found that the mixture of $LiClO_4$-triethylamine was not an effective reagent for the condensation of sulfinimines with more simple aldehydes. In general, Lewis acids are used to realize this condensation as carbonyl activation reagents and water scavengers. Among them, the most effective reagent seems to be $Ti(OEt)_4$.[1,2] However, the drawback of this titanium reagent is its removal from the reaction mixture.[7] It is expected that the condensation would be also accelerated if the amino group of the sulfinamides is activated with basic reagents instead of a carbonyl activation and such bases have the capability as water scavengers. In this letter, we report that $Cs_2CO_3$ is an effective reagent along these lines.

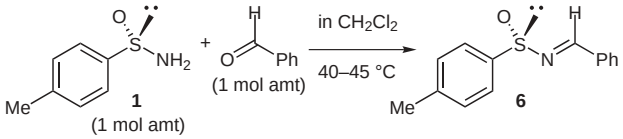



**Scheme 2**

*SYNLETT* 2004, No. 3, pp 0457–0460
Advanced online publication: 12.01.2004
DOI: 10.1055/s-2004-815409; Art ID: U25703ST

Since strong bases are considered to be unsuitable for the condensation, carbonate bases were the first choice of our experiments. The suspension of the Davis sulfinamide **1**[5] (1 molar amount), benzaldehyde (1 molar amount), and a carbonate base (1 molar amount) in $CH_2Cl_2$ (0.2 M for **1**) was vigorously stirred at 40–45 °C for 4 hours. The results are summarized in Table 1. Although the use of $Li_2CO_3$, $Na_2CO_3$, and $K_2CO_3$ resulted in no reaction under these conditions (entries 1–3), an acceptable result was obtained when $Cs_2CO_3$ was used, giving a 3:7 mixture of **1** and **6** (entry 4). After 8 hours at 40–45 °C, the reaction proceeded almost completely (entry 6). Excess amounts of $Cs_2CO_3$ have practically no effect on the result.

**Table 1** Synthesis of Sulfinimine **6** from *p*-Toluenesulfinamide **1** and Benzaldehyde Using Several Carbonate Bases




| Entry | Reagent | Time (h) | Ratio of **1**:**6**[a] |
|---|---|---|---|
| 1 | $Li_2CO_3$ | 4 | NR[b] |
| 2 | $Na_2CO_3$ | 4 | NR |
| 3 | $K_2CO_3$ | 4 | NR |
| 4 | $Cs_2CO_3$ | 4 | 30:70[c] |
| 5 | $Cs_2CO_3$ | 6 | 12:88[c] |
| 6 | $Cs_2CO_3$ | 8 | <1:>99[c] |

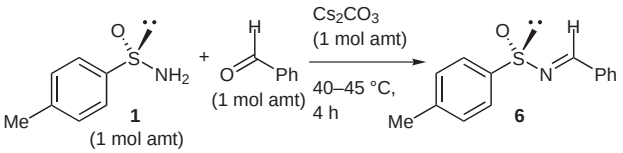
[a] The ratio of **1**:**6** was based on $^1$H NMR analysis of the crude product.
[b] No reaction.
[c] All reactions proceeded cleanly without decomposition (checked by TLC and $^1$H NMR).

Next, solvent optimization was investigated using a 1 molar amount of $Cs_2CO_3$ at 40–45 °C[8] for 4 hours (Table 2), indicating that $CH_2Cl_2$ proved to be the best solvent.

Under these optimized conditions, several aldehydes were subjected to the condensation reactions. These results are compiled in Table 3 and Table 4. Although in the case of *p*-methoxybenzaldehyde (entry 2, Table 3), the yield of the sulfinimine slightly decreased (**1**:**6** = 15:85), the electron-donating (entry 3, Table 3) and electron-withdrawing (entries 4–8, Table 3) substituents on benzaldehyde did not affect the yields of the sulfinimines, thus producing good to excellent yields of the sulfinimines. Moreover, in the case of heteroaromatic compounds (entries 1–5, Table 4) and cinnamaldehyde (entry 6, Table 4), good to excellent yields of the sulfinimines were obtained.

With the satisfactory results using the Davis sulfinamide **1** in hand, our next concern was its application to the Ellman sulfinamide **7**.[4a,9] *t*-Butanesulfinamide (**7**) and several representative aldehydes were subjected to our condensation conditions and the results are shown in Table 5. Sulfinimines **8** were obtained in a slightly lower

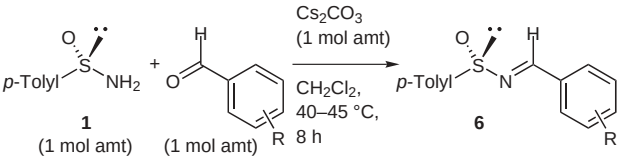
**Table 2** Solvent Optimization for Synthesis of Sulfinimine **6** from *p*-Toluenesulfinamide **1** and Benzaldehyde




| Entry | Solvent | Ratio of **1**:**6**[a] |
|---|---|---|
| 1 | Benzene | 63:37 |
| 2 | Toluene | 56:44 |
| 3 | DME | 60:40 |
| 4 | THF | 58:42 |
| 5 | $CH_2Cl_2$ | 30:70 |
| 6 | $ClCH_2CH_2Cl$ | 36:64 |
| 7 | DMF | 48:52 |
| 8 | $CH_3CN$ | 41:59 |

[a] The ratio of **1**:**6** was based on $^1$H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition (checked by TLC and $^1$H NMR).

**Table 3** Synthesis of Sulfinimine **6** from *p*-Toluenesulfinamide **1** and Several Aldehydes



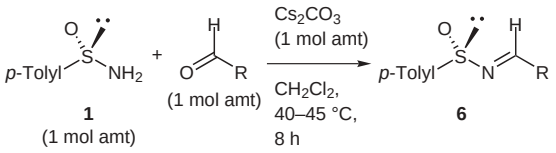

| Entry | R | Ratio of **1**:**6**[a] |
|---|---|---|
| 1 | H | <1:>99 |
| 2 | *p*-OMe | 15:85 |
| 3 | *m*-OMe | 7:93 |
| 4 | *p*-Br | 4:96 |
| 5 | *m*-Br | 6:94 |
| 6 | *m*-Cl | 3:97 |
| 7 | *p*-$NO_2$ | <1:>99 |
| 8 | *m*-$NO_2$ | 1:99 |

[a] The ratio of **1**:**6** was based on $^1$H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition (checked by TLC and $^1$H NMR).

yield than **6** (entries 1 and 2) and in a comparable yield to **6** (entries 3–5).

We next investigated the $Cs_2CO_3$ conditions for the condensation of sulfinamides with aliphatic aldehydes. These data are compiled in Table 6. In the case of the Davis sulfinamide **1**, unfortunately, but not unexpectedly, our

**Table 4** Synthesis of Sulfinimine **6** from *p*-Toluenesulfinamide **1** and Several Aldehydes



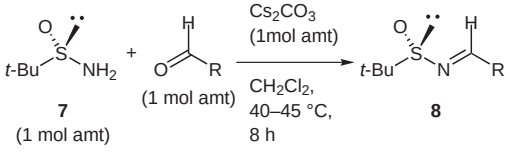

**1** (1 mol amt) — (1 mol amt) — **6**

| Entry | R | Ratio of **1**:**6**[a] |
|---|---|---|
| 1 | 2-Pyridyl | <1:>99 |
| 2 | 3-Pyridyl | 1:99 |
| 3 | 4-Pyridyl | 1:99 |
| 4 | 2-Furyl | 7:93 |
| 5 | 2-Thiazolyl | 1:99 |
| 6 | PhCH=CH– | 7:93 |

[a] The ratio of **1**:**6** was based on $^1$H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition (checked by TLC and $^1$H NMR).

conditions were not suitable for enolizable aliphatic aldehydes, causing aldehyde decompositions and giving sulfinimines in low isolated yields (entries 1 and 2). In contrast, in the case of the Ellman sulfinamide **7**, sulfinimines were obtained in moderate yields together with a small amount of aldehyde decomposition products (entries 4 and 5); the longer the reaction time, the better the isolated yields (entries 4, 5, 7, and 8). The bulky trimethylacetaldehyde gave a moderate yield of sulfinimines (entries 3, 6, and 9).

**Table 5** Synthesis of Sulfinimine **8** from *t*-Butanesulfinamide (**7**) and Several Aldehydes

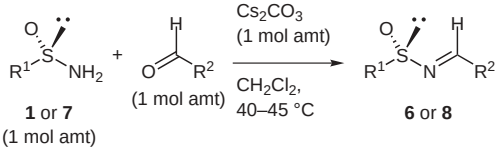



**7** (1 mol amt) — (1 mol amt) — **8**

| Entry | R | Ratio of **7**:**8**[a] |
|---|---|---|
| 1 | Phenyl | 15:85 |
| 2 | *p*-Methoxyphenyl | 45:55[b] |
| 3 | *p*-Nitrophenyl | <1:>99 |
| 4 | 4-Pyridyl | 1:99 |
| 5 | 2-Thiazolyl | 7:93 |

[a] The ratio of **7**:**8** was based on $^1$H NMR analysis of the crude product. All reactions proceeded cleanly without decomposition (checked by TLC and $^1$H NMR).
[b] The ratio of **7**:**8** was based the isolated yield after silica-gel (flash) column chromatography.

**Table 6** Synthesis of Sulfinimines from Sulfinamides and Aliphatic Aldehydes




**1** or **7** (1 mol amt) — (1 mol amt) — **6** or **8**

| Entry | $R^1$ | $R^2$ | Time (h) | Ratio of **1**:**6** or **7**:**8**[a] | Yield of **6** or **8** (%)[b] |
|---|---|---|---|---|---|
| 1 | *p*-Tolyl | *n*-Pentyl | 8 | –[c] | 16 |
| 2 | *p*-Tolyl | 2-Propyl | 8 | –[c] | 15 |
| 3 | *p*-Tolyl | *t*-Bu | 8 | 52:48 | 45 |
| 4 | *t*-Bu | *n*-Pentyl | 8 | 24:76 | 65 |
| 5 | *t*-Bu | 2-Propyl | 8 | 49:51 | 46 |
| 6 | *t*-Bu | *t*-Bu | 8 | 40:60 | 52 |
| 7 | *t*-Bu | *n*-Pentyl | 16 | 10:90 | 73 |
| 8 | *t*-Bu | 2-Propyl | 16 | 17:83 | 76 |
| 9 | *t*-Bu | *t*-Bu | 16 | 35:65 | 59 |

[a] The ratio of **1**:**6** (or **7**:**8**) was based on $^1$H NMR analysis of the crude product.
[b] Since these reactions (except for entries 3, 6, and 9) were contaminated with some decomposition products, the isolated yields after silica-gel (flash) column chromatography were determined.
[c] The ratio could not be determined.

In summary, we have achieved the synthesis of chiral sulfinimines from the Davis and/or Ellman sulfinamides (1 molar amount) and aldehydes (1 molar amount) in $CH_2Cl_2$ in the presence of $Cs_2CO_3$ (1 molar amount). The merits of this method are the easy workup procedure (filtration) and no need to use excess amounts of activating and dehydrating reagents.[10]

## Acknowledgment

This research was supported by a Grant-in Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## References

(1) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.
(2) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(3) See also: Garcia Ruano, J. L.; Fernandez, I.; del Catalina, M. P.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.
(4) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(5) (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555. (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. (c) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.
(6) Higashibayashi, S.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2002**, *43*, 105.
(7) Recently, the modified procedure to remove titanium materials was reported by the Ellman group, see: Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590.
(8) At the reflux temperature of each solvent, considerable decomposition occurred (except $CH_2Cl_2$).
(9) (a) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (b) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.
(10) **Representative Experimental Procedure (Table 3, Entry 1):** To a solution of **1**[5] (80.0 mg, 0.515 mmol) in $CH_2Cl_2$ (2.6 mL) were added $Cs_2CO_3$ (168 mg, 0.515 mmol) and benzaldehyde (0.0523 mL, 0.515 mmol). The resulting suspension was vigorously stirred at 40–45 °C for 8 h. The reaction mixture was filtered with Celite and the filter cake was washed with $CH_2Cl_2$. The filtrates and washings were combined and concentrated. The residue was chromatographed on silica gel (flash) with hexane–EtOAc = 9:1 to afford sulfinimine **6** (119 mg) in 95% yield. The ee of **6** was 97% determined by chiral HPLC analysis (Daicel Chiralcel OD column, 4.6 × 250 mm, 99.5:0.5 hexane–IPA; 1 mL/min, 254 nm, $t_R$ = 36.6 min; enantiomer of **6**, t = 32.7 min), which was identical with that of **1** used (Daicel Chiralcel OD column, 4.6 × 250 mm, 90:10 hexane–IPA; 1 mL/min, 254 nm, $t_R$ = 18.0 min; enantiomer of **1**, $t_R$ = 14.9 min). Compound **6**: mp 78–79 °C (lit.[5a,b] 77–78 °C, lit.[5c] 80–81 °C); $[\alpha]_D^{29}$ +114 (*c* 1.00, $CHCl_3$) {lit.[5a] $[\alpha]_D^{20}$ +117.3 (*c* 1.77, $CHCl_3$), lit.[5b] $[\alpha]_D^{20}$ +117.5 (*c* 1.6, $CHCl_3$), lit.[5c] $[\alpha]_D^{20}$ +122.8 (*c* 1.2, $CHCl_3$)}. $^1$H NMR (300 MHz, $CDCl_3$, TMS = 0 ppm): δ = 2.40 (3 H, s), 7.32 (2 H, d, *J* = 8.0 Hz), 7.41–7.52 (3 H, m), 7.64 (2 H, d, *J* = 8.0 Hz), 7.82–7.87 (2 H, m), 8.75 (1 H, s). Sulfinimine **8** (Table 5, entry 1) was obtained after silica-gel(flash) column chromatography ($CH_2Cl_2$) in 80% isolated yield by the same procedure as described above. The ee of **8** was 99% determined by chiral HPLC analysis (Daicel Chiralcel OD column, 4.6 × 250 mm, 95:5 hexane–IPA; 1 mL/min, 254 nm, $t_R$ = 5.51 min; enantiomer of **6**, $t_R$ = 6.96 min), which was identical with that of **7** used (Daicel Chiralcel OD column, 4.6 × 250 mm, 96:4 hexane–IPA; 1 mL/min, 222 nm, $t_R$ = 41.6 min; enantiomer of **7**, $t_R$ = 35.5 min). Compound **8**: $[\alpha]_D^{28}$ +103 (*c* 1.00, $CHCl_3$) {lit.[3] $[\alpha]_D^{20}$ +104 (*c* 1.00, $CHCl_3$); enantiomer of **8**, lit.[4c] $[\alpha]_D^{23}$ –122 (*c* 1.00, $CHCl_3$)}. $^1$H NMR (300 MHz, $CDCl_3$, TMS = 0 ppm): δ = 1.28 (9 H, s), 7.44–7.55 (3 H, m), 7.83–7.89 (2 H, m), 8.59 (1 H, s).