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# Photodesulfinylation of optically active *N*-sulfinyl amines

Franklin A. Davis *, Tokala Ramachandar, Yanfeng Zhang, Jing Chai, Hui Qiu, Jianghe Deng, Venkata Velvadapu *

*Department of Chemistry, Temple University, Philadelphia, PA 19122, United States*

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ABSTRACT

Photolysis of enantiopure *N*-sulfinyl amines (sulfinamides) in $Et_2O$–MeOH gives amines in good yield without racemization.

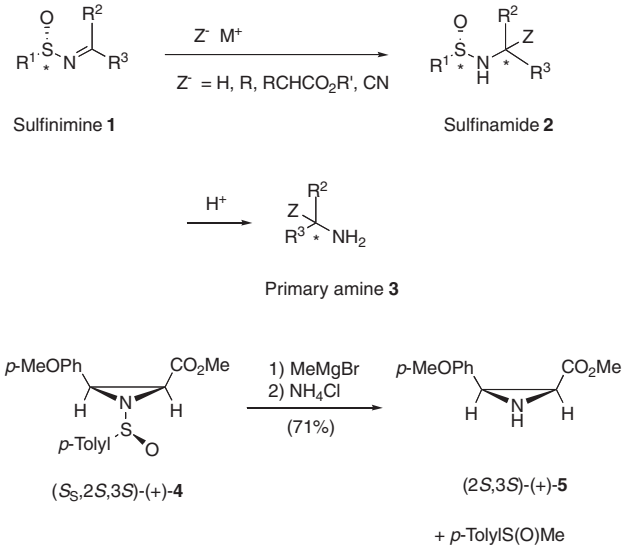


Currently the best and the most reliable method for the asymmetric construction of amine derivatives having a nitrogen attached to stereogenic center is the addition of an organometallic reagent to the C=N bond of an enantiopure sulfinimine **1** (Scheme 1).[1,2] Not only does the reaction give high yields and diastereoselectivities of the product sulfinamide **2** but also the configuration of the new stereogenic center is predictable. In **2**, the *N*-sulfinyl group is an important amine-protecting group because it stabilizes anions at nitrogen preventing undesirable anion reactions such as epimerization. Invariably the *N*-sulfinyl group needs to be removed for further elaboration of the chiral amine **3**.[3] Most often this is accomplished by treatment with acids such as TFA–MeOH or aqueous HCl.[2] If the sulfinyl group is fully substituted as in the acid-sensitive *N*-sulfinyl aziridine ($S_S$,2*S*,3*S*)-(+)-**4**, treatment with methylmagnesium bromide efficiently removes the sulfinyl group affording the NH aziridine (+)-**5** and the sulfoxide in good yield (Scheme 1).[3]

Recently, we reported the first asymmetric synthesis of 2*H*-azirine 3-carboxylates **7** and their Diels–Alder reactions (Scheme 2). In attempts to remove the *N*-sulfinyl group in aziridine (+)-**6** neither acid nor base conditions worked.[4] With acid, decomposition occurred and with MeMgBr 2-substituted aziridine (+)-**8** was obtained formed via addition to the intermediate 2*H*-azirine 3-carboxylate **7**. Photodesulfinylation, which requires neither acid nor base or the use of protic solvents, solved the problem. Here we reported additional details of this methodology demonstrating that photodesulfinylation is an attractive protocol for removal of the *N*-sulfinyl group in enantiopure sulfinamides without epimerization.

The sulfinamide (0.15 mmol) was dissolved in 10 mL of 1:1 $Et_2O$–MeOH in a 15 mL quartz tube and was degassed by bubbling argon through the solution for 5 min. At this time the solution was irradiated at 2537 Å for 16 h in a Raynet apparatus. The amine was isolated by extraction into an aqueous phase using 15% HCl, neutralization to pH 7.5 with solid $Na_2CO_3$, and purified by chromatography to give the known amines. Because even dilute HCl can sometimes hydrolyze sulfinamides it was important to determine whether they were absent prior to work-up. Monitoring the reaction by $^1H$ NMR and TLC confirmed that none of the sulfinamides was present after 16 h of irradiation. These results are summarized in Table 1.

The results in Table 1 reveal that the yields for the photodesulfinylation of sulfinamides are very good and epimerization of the amine product (Table 1).[8] However, there were a few examples where this protocol resulted in decomposition. When the *N*-*p*-tolylsulfinyl group was replaced with a *tert*-butylsulfinyl group, (+)-**11**, decomposition resulted (Table 1, entry 2). Decomposition also resulted in irradiation of *N*-sulfinyl α,β-diamino ester (+)-**22** (Table




**Scheme 1.** Removal of the *N*-sulfinyl group in sulfinamides.

* Corresponding authors. Tel.: +1 215 204 0477; fax: +1 215 204 0478 (F.A.D.).
*E-mail address:* fdavis@temple.edu (F.A. Davis).

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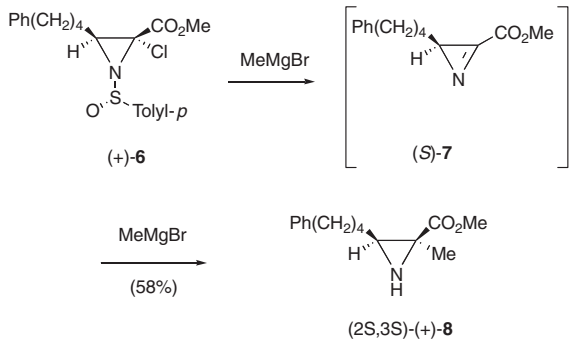
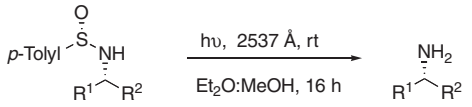



**Scheme 2.** Photodesulfinylation of aziridine (+)-**6**.

1, entry 8). As expected irradiation of the *N*-sulfinyl δ-amino β-keto ester (+)-**20** afforded 6-phenylpiperidine-2,4-dione (+)-**21** in 71% yield (Table 1, entry 7). Cyclization of δ-amino β-keto esters to piperidine-2,4-diones has been reported.[9]

**Table 1**
Photodesulfinylation of sulfinamides at rt for 16 h in 1:1 $Et_2O$–MeOH[5]



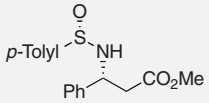
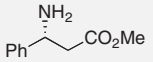
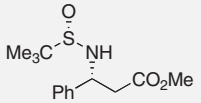
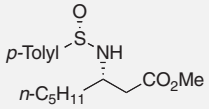
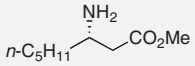
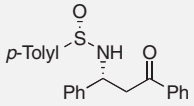
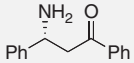
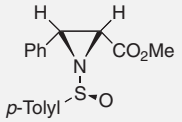
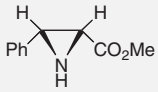
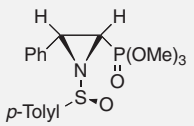
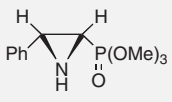
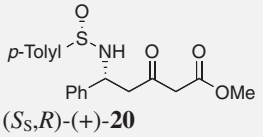
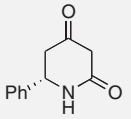
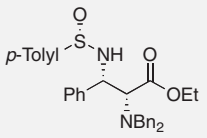

| Entry | Sulfinamide[a] | Amine[b–d] (% yield) |
|---|---|---|
| 1 |  ($S_S$,*R*)-(+)-**9** |  (*R*)-(+)-**10** (82) $[\alpha]^{20}_D$ +21.0 (*c*, 0.95 $CHCl_3$) |
| 2 |  ($S_S$,*R*)-(+)-**11** | Decomposition |
| 3 |  ($S_S$,*R*)-(+)-**12** |  (*R*)-(+)-**13** (85) $[\alpha]^{20}_D$ +11.0 (*c*, 0.41 $CHCl_3$) |
| 4 |  ($S_S$,*R*)-(+)-**14** |  (*R*)-(+)-**15** (83) $[\alpha]^{20}_D$ -5.6 (*c*, 0.50 $CHCl_3$) |
| 5 |  ($S_S$,2*S*,3*S*)-(-)-**16** |  (2*S*,3*S*)-(+)-**17** (87) $[\alpha]^{20}_D$ +24.0 (*c*, 0.65 EtOH) |
| 6 |  ($S_S$,2*S*,3*R*)-(-)-**18** |  (2*S*,3*R*)-(-)-**19** (84) $[\alpha]^{20}_D$ -36.3 (*c*, 0.71 $CHCl_3$) |

**Table 1** (*continued*)

| Entry | Sulfinamide[a] | Amine[b–d] (% yield) |
|---|---|---|
| 7 |  ($S_S$,*R*)-(+)-**20** |  (*R*)-(+)-**21** (71) $[\alpha]^{20}_D$ +123.3.0 (*c*, 0.50 $CHCl_3$) |
| 8 |  ($S_S$,2*R*,3*S*)-(+)-**22** | Decomposition |

[a] Sulfinamides were prepared according to the literature procedures (Ref. 6).
[b] Isolated yields of enantiomerically pure products.
[c] For the properties of the amines see Ref. 7.
[d] Specific rotation of isolated amine.

The photochemical detosylation of sulfonamides ($ArSO_2NHR$) in the presence of reducing agents and sensitizers is well established to involve homolytic cleavage of the S–N bond to produce sulfonyl ($ArSO_2^{\cdot}$) and amino radicals.[10] Photolysis of sulfinamides in aprotoic solvents is reported to give complex mixtures consistent with the formation of sulfinyl ($ArSO^{\cdot}$) and amino radicals.[11] In our studies the photolysis of *p*-toluenesufinamides in $Et_2O$–MeOH gave good yields of amines (Table 1), but complex mixtures of sulfur products including low yields of disulfide (*p*-tolylSStolyl-*p*) and thiosulfonate (*p*-tolylSSO$_2$tolyl-*p*). These products result from initial homolytic cleavage of the S–N bond in the sulfinamide producing sulfinyl (*p*-tolylSO**.**) and amino radicals. Under the protic conditions amines and the sulfenic acid (*p*-tolySOH) are formed with the latter leading to the sulfur products.[12]

In summary, new methodology for removal of the *N*-sulfinyl group in enantiopure sulfinimine-derived sulfinamides not requiring acid or base conditions was introduced. This protocol, photodesulfinylation, involves the photolysis of sulfinamides in $Et_2O$–MeOH. Yields of amines were very good and epimerization of the amine product was not observed. This new protocol for the removal of the *N*-sulfinyl group in chiral sulfinamides is expected to find utility in those sulfinamides having acid-sensitive functional groups.

## Acknowledgments

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4. Davis, F. A.; Deng, J. *Org. Lett.* **2007**, *9*, 1707.
5. *Experimental procedure*: A solution of the sulfinamide (0.15 mmol) was dissolved in 10 mL of 1:1 $Et_2O$–MeOH and placed in a 15 mL quartz tube. Argon was bubbled through the solution for 5 min, the tube was capped and placed in a Raynet UV chamber. The solution was irradiated at 2537 Å for 16 h. At this time the solution was concentrated, EtOAc (10 mL) was added, and the solution was washed with satd $Na_2CO_3$ (2 × 10 mL) and checked by TLC for the

absence of the sulfinamide. The solution was concentrated, the residue was dissolved in $Et_2O$ (15 mL) and washed with 15% HCl (2 × 10 mL), the combined aqueous phases were neutralized to pH 7.5 with solid $Na_2CO_3$ and extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic phases were washed with $H_2O$ (10 mL) and dried ($Na_2SO_4$). Chromatography (EtOAc) afforded the pure amines with spectral properties consistent with literature values.[7]

6. Sulfinamides. (+)-9: (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037; (+)-11: (b) Davis, F. A.; Gaspari, P. M.; Nolt, M. B.; Xu, P. *J. Org. Chem.* **2008**, *73*, 9619; (c) (+)-**12**: clear oil, $[\alpha]_D^{20} + 87.6$ (*c* 1.05, $CHCl_3$).; (+)-14: (d) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184; (e) (−)-**16**: Ref. 3.; (−)-18: (f) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410; (+)-20: (g) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169; (h) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789.
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8. The enantiomeric purity of the isolated amines (Table 1) was determined by comparison with literature values (Ref. 7) indicating that racemization had not occurred.
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11. Tsuda, H.; Minato, H.; Kobayashi, M. *Chem. Lett.* **1976**, 149.
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