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Synthesis of Enantiopure *tert*-Butanesulfinamide from *tert*-Butanesulfinyloxazolidinone

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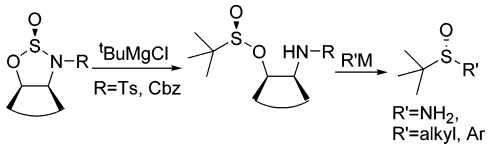
Received August 15, 2004

Abstract: A three-step procedure for the preparation of enantiopure *tert*-butanesulfinamide **6** in 51% overall yield is described starting from (1*R*,2*S*)-*N*-Cbz-1,2-diphenylaminoethanol. The key step is the reaction of *tert*-butylmagnesium chloride with *N*-Cbz-4,5-diphenyl-1,2,3-oxathiazolidine-2-oxide **2** to afford the optical pure *tert*-butylsulfinyl-4,5-diphenyl-1,3-oxazolidinone **5** via an 1,5-alkoxy anion rearrangement, which is then subject to ammonia hydrolysis with $LiNH_2$ in liquid ammonia to give (*R*)-*tert*-butanesulfinamide **6**.

Since its introduction by Ellman in 1997 as a versatile ammonia equivalent, chiral *tert*-butanesulfinylamide[1] (TBSA, **6)** has been demonstrated as a very useful auxiliary as a result of the characteristics of high stereoselectivity in asymmetric induction and ease of removal of the sulfinyl group compared with other amine auxiliaries.[2−5] Recently, chiral TBSA has also been used as a ligand in asymmetric catalysis.[6] Considering the importance of TBSA in asymmetric synthesis, the search for an efficient method for the preparation of enantiopure TBSA is a most interesting topic in synthetic chemistry. After surveying the literature, there were only two methods found for the preparation of enantiopure TBSA. One was the elegant synthesis reported by Ellman for the asymmetrically catalytic oxidation of di-*tert*-butylsulfide as the key step.[7,8] A second synthesis was reported by Senanayake, who used chiral sulfinate as a key intermediate.[9]

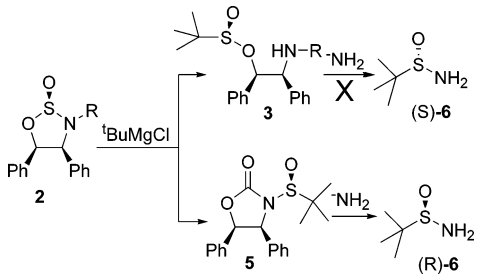
It is well-established that N-acylated sulfinamides are at least 2 orders of magnitude more reactive than sulfinates.[10] Using the differential reactivity between the sulfonamide bond and the sulfinate bond to selectively cleave the N−S bond rather than the O−S bond in the N-acylated 1,2,3-oxathiazolidine-2-oxide system by a Grignard reagent leads to the formation of the chiral sulfinate, an intermediate suitable for further syntheses of optical pure TBSA and sulfoxides, as has been described in Senanayake's synthesis of TBSA[9] and in the Ruano's syntheses of sulfoxides (Scheme 1).[11]

SCHEME 1



Encouraged by the above reports, our synthesis of enantiopure TBSA (**6**) was originally envisaged to use the similar strategy, namely, by the Grignard addition to structurally similar N-acylated (4*S*,5*R*)-4,5-diphenyl-1,2,3-oxathiazolidine-2-oxide **2** to form sulfinate **3**, followed by ammonia hydrolysis of resulting sulfinate **3** to give **6**. However, this plan encountered an unexpected problem in the ammonia hydrolysis step. In this paper, we report an unusual 1,5-alkoxy anion rearrangement of **2** to afford the *tert*-butylsulfinyl-4,5-diphenyl-1,2,3-oxazolidinone **5**, which serves as a key intermediate for the synthesis of enantiopure TBSA (Scheme 2).

SCHEME 2



According to the original plan, our attention was first directed to the preparation of optical pure N-acylated

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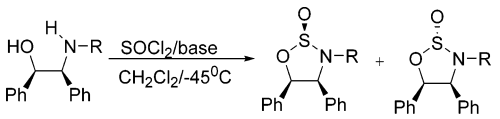
10.1021/jo048576k CCC: $27.50
Published on Web 11/02/2004

TABLE 1. Synthesis of 4,5-Diphenyl-1,2,3-oxathiazolidine-2-oxide 2



1a R=Ts, **1b** R=Boc
1c R=Cbz,**1d** R=COOMe

endo-2 **exo-2**

entry	1	base[a]	**2** (*endo/exo*)[b]	yield[c]
1	**1a**			
2	**1b**	TEA	71/29	70
3	**1b**	2,4,6-colidine	14/86	83
4	**1b**	DMAP	91/9	68
5	**1c**	TEA	75/25	86
6	**1c**	2,4,6-colidine	33/67	46
7[d]	**1c**	DMAP	74/26	61
8[e]	**1c**	DMAP	99/1	45
9	**1c**	DMAP	99/1	69
10[f]	**1c**	DMAP	83/17	92
11	**1d**	TEA	71/29	82
12	**1d**	2,4,6-colidine	16/84	16
13	**1d**	DMAP	89/11	87

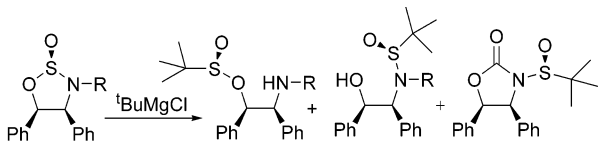
[a] Conducted by mixing compound **1** with base in CH_2Cl_2 at −45 °C, followed by addition of $SOCl_2$. [b] Determined by ^1H NMR, the assignment of the stereochemistry of endo/exo-**2** is based on the deshielding of the heterocyclic protons which are cis to the sulfinylic oxygen, see ref 11 and 13. [c] Isolated yield. [d] At 25 °C. [e] At −78 °C. [f] Inverted addition order of DMAP with $SOCl_2$.

1,2,3-oxathiazolidine-2-oxides **2**. Because a variety of protective groups at the nitrogen of 1,2-diphenylaminoethanol **1**[12] with different sizes may induce different diastereoselectivities of 4,5-diphenyl-1,2,3-oxathiazolidine-2-oxides **2**, investigation of the steric effect of that substituent on the diastereoselectivity of ring formation was conducted by choosing Ts, Boc, Cbz, and methoxycarbonyl groups as nitrogen protecting groups. The results are shown in Table 1.

Initial efforts of synthesizing *N*-tosylate **2a** have failed (Table 1, entry 1) as a result of the very poor solubility of **1a** in most aprotic solvents. Compounds **1b,c** also showed poor solubility in most solvents, and CH_2Cl_2 was found to be the best choice of solvent in light of solubility. In Ruano's systematic study of the preparation of 1,2,3-oxathiazolidine-2-oxides bearing an *N*-Cbz norephedrine skeleton, it was found that a temperature around −45 °C usually gave the best diastereoselectivity and yield. We roughly tested the reaction at three temperatures (25, −45, and −78 °C) in the preparation of **2c** using DMAP as base. At room temperature, significant amounts of byproducts were produced with the loss of yield and diastereoselectivity (entry 7). At −78 °C, the reaction proceeded slowly to give **2c** in 99/1 endo/exo selectivity and low yield (45% yield, entry 8) compared with the reaction conducted at −45 °C (69% yield, entry 9).

After screening the effect of bases TEA, 2,4,6-colidine, and DMAP on the diastereoselectivity, we observed that DMAP provided the best endo/exo selectivity with a ratio of 91/9 for **2b** (entry 4), a ratio of 99/1 for **2c** (entry 9), and a ratio of 89/11 for **2d** (entry 13) in good yields. The endo product was the major isomer, whereas 2,4,6-collidine inverted the endo/exo selectivity, with the exo product being the major isomer (entries 3, 6, and 12). Most interestingly, for the preparation of **2c**, the yield (92%) was greatly increased by simply switching the addition order of DMAP and $SOCl_2$ with sacrifice of the endo/exo selectivity from 99/1 to 83/17 (entry 10). Although the endo/exo isomers of **2b** and **2c** were inseparable by chromatography, the major isomers endo-**2b** and endo-**2c** could be easily recrystallized from a mixture of EtOAc/petroleum ether to give pure endo product. Endo-**2d** could be readily separated from the minor diastereomer exo-**2d** by chromatography.

TABLE 2. Syntheses of Sulfinate 3 and *tert*-Butylsulfinyl-4,5-diphenyl-1,3-oxazolidinone 5



2b R=Boc, **2c** R=Cbz
2d R=COOMe

3 **4** **5**

entry	**2**	solvent	(temp) °C	**3** (%)	**4** (%)	**5** (%)
1	**2b**	DMC	−45	25	51	
2	**2b**	DMC	−78	63	31	
3	**2b**	toluene	−45	tr	tr	
4	**2b**	THF	−45	13	28	
5	**2c**	DMC	−45	61	23	
6	**2c**	THF	−45	7	tr	83
7	**2d**	DMC	−45	19	24	46
8	**2d**	THF	−45	21	tr	76

For the preparation of **2c**, we did improve the diastereoselectivity from 86% de to 99% de with a slight enhancement of the yield from 57% to 69% under similar condition when compared to Ruano's synthesis of norephedrine-derived *N*-Cbz-1,2,3-oxathiazolidine-2-oxide.[11] The improved diastereoselectivity is ascribed to the size change of substituent at position 4 of **2** from a methyl group (norephedrine) to a phenyl group (1,2-diphenylaminoethanol).

According to our original plan for selective cleavage of the N−S bond of N-acylated 4,5-diphenyl-1,2,3-oxathiazolidine-2-oxides **2** by *tert*-butylmagnesium chloride to afford the sulfinates **3** for the further synthesis of TBSA, **6**, we explored the addition of *tert*-butylmagnesium chloride (1.5 equiv) to the endo-**2** at low temperature in different solvents as depicted in Table 2.

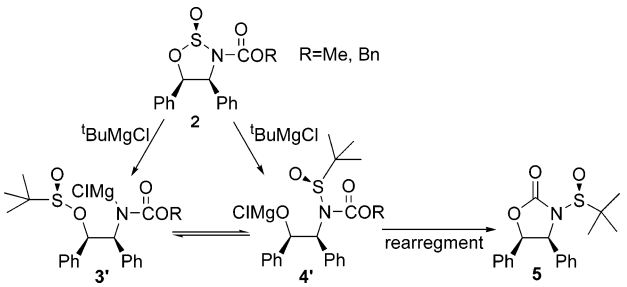
Unfortunately we were not able to prepare the sulfinates **3** in yields greater than 63% by the addition reaction of *tert*-butylmagnesium chloride to **2** under a variety of reaction conditions. The lower temperature provided a slight selectivity preference for the formation of sulfinate **3** when **2b** (R = Boc) reacted with *tert*-butylmagnesium chloride in DMC but required a longer reaction time (entries 1 and 2). Toluene was not the suitable solvent for the addition reaction (entry 3). THF provided sulfinate **3b** and sulfinamide **4b** in low yields (entry 4). The poor reactivity and selectivity of **2b** were probably due to the steric effects of the Boc group on the nitrogen and phenyl group at the 4 position, which shielded the attack of the bulky *tert*-butylmagnesium chloride at the more reactive N−S bond. Evidence for this

(12) (1*R*,2*S*)-*N*-Alkoxycarbonyl-1,2-diphenylamino-ethanols **1** were prepared by treatment of (1*R*,2*S*)-1,2-diphenylaminoethanol with TsCl, Boc_2O, CbzCl, and MeOCOCl in aqueous THF in the presence of Na_2CO_3 in yields of 93% (**1a**), 97% (**1b**), 94% (**1c**), and 99% (**1d**), respectively.

steric effect was obtained by exchanging the Boc group (**2b**) for the less hindered Cbz group (**2c**). The reaction with *tert*-butylmagnesium chloride in DMC provided more selectivity to afford **3c** as the major product (entries 1 and 5). Surprisingly, when **2c** and **2d** reacted with *tert*-butylmagnesium chloride in THF at −45 °C, the reaction gave the *tert*-butylsulfinyl-4,5-diphenyl-1,3-oxazolidinone **5** as the major product (83% for **2c**, entry 6 and 76% for **2d**, entry 8), as well as sulfinates **3** (7% for **2c**, entry 6 and 21% for **2d**, entry 8). When the reaction of **2d** with *tert*-butylmagnesium chloride was conducted in DMC, **5** was also isolated in 46% yield, as well as **3** (19% yield) and **4** (24% yield, entry 7).

In view of the mechanism for the formation of **5**, it was reasonable to believe that **5** was derived from **4′** by a consecutive intramolecular nuclephilic attack of alkoxy anion formed during the reaction under basic conditions (Scheme 3). Compound **4′** could be produced either by the

SCHEME 3. A Plausible Mechanism for the Formation of 5

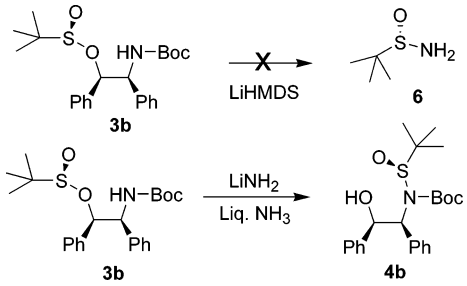


direct attack of *tert*-butylmagnesium chloride at the less active and less hindered S−O bond of **2** or by the attack of *tert*-butylmagnesium chloride at the more active but more hindered S−N bond of **2** to afford **3′**, followed by the migration of sulfur atom in **3′** from oxygen atom to nitrogen atom. Because a similar ratio of **3b** to **4b** (2.3:1) is obtained by treatment of **3b** with $LiNH_2$ at −78 °C (see next paragraph), the observed different ratios of **3b** to **4b** at −78 °C (2.0:1, Table 2, entry 2) and at −45 °C (1:2.0, Table 2, entry 1) could be rationalized by the equilibration of the reaction mixture at the higher temperature rather than a kinetic selectivity of addition. Because the Boc protecting group is more stable under basic conditions and is more hindered than Cbz and methoxycarbonyl groups, which are sensitive to the attack by alkoxy anion, it is not surprising that the addition reaction of *tert*-butylmagnesium chloride with **2b** does not form **5**.

Because the *tert*-butylsulfinate **3b** could be prepared in 63% yield from **2b** and a similar sulfinates had been converted to TBSA with LiHMDS or $LiNH_2$ at −78 °C,[9] we attempted to hydrolyze the sulfinate **3b** with LiHMDS at −78 °C in THF. However, our efforts were not successful (Scheme 4),[14] affording complete recovery of **3b**. Instead of yielding **5** or **6**, partial intramolecular migration of sulfur atom occurred to produce **4b** (29%

(13) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.
(14) The cleavage of noncyclic *N*-acyl-*tert*-butylsulfinamide sometimes was not successful; see ref 4.

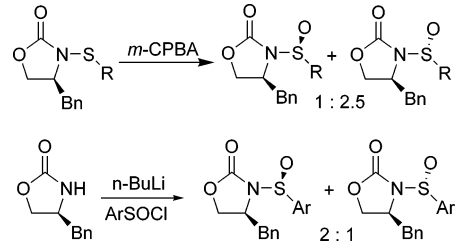
SCHEME 4. Ammonia Hydrolysis of Sulfinate 3b



conversion) when *tert*-butylsulfinate **3b** was reacted with $LiNH_2$ in liquid ammonia at −78 °C for 0.5 h.

Having failed at our attempts to convert *tert*-butylsulfinate **3b** to TBSA (**6**) with LiHMDS or $LiNH_2$, we turned our attention to the conversion of *tert*-butylsulfinyl-4,5-diphenyl-1,3-oxazolidinone **5** to **6**. Sulfinyloxazolidinones are potentially versatile intermediates for the syntheses of chiral sulfoxides, sulfinates, and sulfinamides. Evans has described the syntheses of 2-benzylaminoethanol-derived sulfinyloxazolidinones by oxidization of *N*-(arylthio)-oxazolidinone and *N*-(alkylthio)-oxazolidinone with *m*-CPBA in less than 2.5:1 diastereoselectivity or by sulfinylation of oxazolidinone with arylsulfinyl chloride in less than 2:1 diastereoselectivity (Scheme 5).[10b]

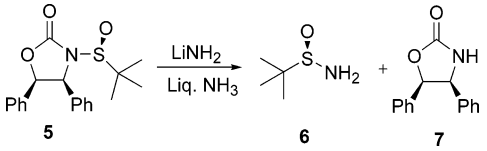
SCHEME 5. Evans Synthesis of Sulfinyloxazolidinone



Apparently, the latter method was limited to the availability of alkylsulfinyl chloride.

Because *tert*-butylsulfinyl-4,5-diphenyl-1,3-oxazolidinone **5** should be more reactive than sulfinate **3** and was synthesized in 83% yield from the easily prepared **2c**, ammonia hydrolysis of **5** would be an alternative to synthesize TBSA (**6**). Indeed, when **5** was treated with in situ prepared $LiNH_2$ in liquid ammonia at −78 °C, 4,5-diphenyl-1,3-oxazolidinone **7** and (*R*)-**6** were isolated in 91% yield and 89% yield (98.6% ee), respectively (Scheme 6). A single recrystallization from hexane provided the

SCHEME 6. Synthesis of TBSA (6)



enantiopure (*R*)-**6**.

In summary, we have developed a new synthetic route to synthesize *tert*-butylsulfinyl-4,5-diphenyl-1,3-oxazoli-

dinone **5** from the easy prepared **2c** and **2d**. Importantly, **5** has been well demonstrated as a key intermediate for the synthesis of enantiopure TBSA **6** in high yield in our study.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (no. 20372048), Ministry of Education (under the Excellent Young Teachers Program), and the Excellent Youth Foundation of Sichuan Province, P. R. China.

Supporting Information Available: Detailed experimental procedures and mp, $[\alpha]^{25}_{D}$, IR, ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analyses data for compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048576K