ORGANIC LETTERS

2003
Vol. 5, No. 1
75−78

A General and Expeditious One-Pot Synthesis of Sulfoxides in High Optical Purity from Norephedrine-Derived Sulfamidites

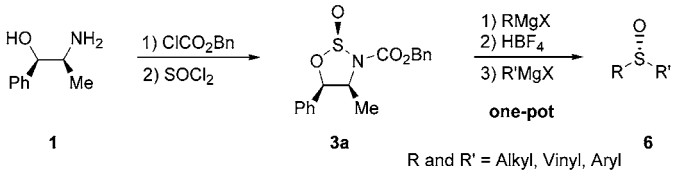
José L. García Ruano,* Carlos Alemparte, M. Teresa Aranda, and María M. Zarzuelo

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

joseluis.garcia.ruano@uam.es

Received November 5, 2002

ABSTRACT



A general and simple procedure for preparing any kind of enantiomerically enriched sulfoxide starting from norephedrine-derived *N*-benzyloxycarbonylsulfamidite 3a is reported. After one-pot reaction of 3a with RMgX, HBF_4, and R′MgX, a variety of sulfoxides 6 are obtained in ee usually higher than 93% and isolated yields ranging between 50 and 78%. The obtained configuration is tunable by simply electing the order of the addition of the reagents.

The great importance of enantiomerically enriched sulfoxides in asymmetric synthesis can be inferred from the large number of papers concerning their use as chiral auxiliaries[1] and, more recently, as chiral ligands in asymmetric catalysis.[2] As a consequence, the search of general and efficient methods to prepare any kind of chiral nonracemic sulfoxides has been a matter of great interest.[3] Excluding resolution, asymmetric oxidation of sulfides and nucleophilic substitution on chiral sulfur derivatives are the two main methodologies for the preparation of chiral sulfoxides.[3] Despite many efforts made in this field, the procedure reported by Andersen forty years ago,[4] and substantially improved by Solladié,[5] is still the most frequently used method for the synthesis of these compounds. The procedure consists of the reaction of diastereomerically pure menthyl sulfinates with Grignard reagents. However, only arenesulfinates are achievable in optically pure form. Other chirality sources have been employed to circumvent these drawbacks such as diacetone D-glucose, DAG methodology described by Khiar, Alcudia et al.,[6] and *trans*-2-phenylcyclohexanol introduced by Whitesell's group.[7] Sulfinylating agents different than

(1) (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717 and references therein. (b) Hua, D. H. *Adv. Heterocycl. Nat. Prod. Synth.* **1996**, *3*, 151. (c) Abu-Jusef, I. A.; Harpp, D. N. *Sulfur Rep.* **1997**, *20*, 1. (d) Kita, I. *Phosphorous, Sulfur, Silicon Relat. Elem.* **1997**, *120*, 145. (e) Allin, S. M. *Organosulfur Chem.* **1998**, *2*, 157. (f) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973. (g) García Ruano, J. L.; Cid, B. In *Topics in Current Chemistry*; Page, P. C. B., Ed.; Springer: Berlin, 1999; Vol. 204, p 1.

(2) For recent references see: (a) Priego, J.; García Mancheño, O.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346. (b) Pezet, F.; Ait-Haddou, H.; Daran, J.-C.; Sasaki, I.; Balavoine, G. G. A. *Chem. Commun.* **2002**, 510. (c) Watanabe, K.; Hirasawa, T.; Hiroi, K. *Chem. Pharm. Bull.* **2002**, *50*, 372.

(3) Khiar, N.; Fernandez, I.; Alcudia, A.; Alcudia, F. *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press, Inc.: Stanford, 2000, Vol. 2, p 57 and references therein.

(4) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93. (b) Andersen, K. K.; Gafield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, J. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637. (c) Andersen, K. K. *Int. J. Sulfur. Chem.* **1971**, *6*, 79.

(5) (a) Mioskowski, C.; Solladie, G.; *Tetrahedron* **1980**, *36*, 227. (b) Solladié, G. *Synthesis* **1981**, 185. (c) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

(6) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789. See also ref 3.

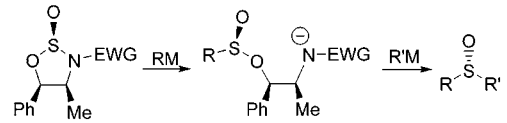
10.1021/ol027232i CCC: $25.00
Published on Web 12/14/2002

sulfinates have also been utilized, especially *N*-*p*-tolylsulfinylsultam introduced by Oppolzer,[8] *N*-acylsulfinamides developed by us,[9] Ellman's *tert*-butyl *t*-butanethiosulfinate,[10] *N*-sulfinyloxazolidinones reported by Evans,[11] of a wider scope, and Naso's recent approach based on the use of carbanionic leaving groups.[12] All these methodologies have a limited scope.

Chiral sulfur compounds containing two leaving groups attached to the SO unit are especially attractive. In this sense, several approaches have been reported. Kagan[13] described the use of optically pure cyclic sulfites as starting compounds, but a lack of regioselectivity in the first attack restricts their usefulness for the synthesis of *tert*-butylsulfoxides and determines the need of purification of the intermediate hydroxysulfinate. This problem was solved with the use of cyclic sulfamidites, initially reported by Wudl and Lee[14] and further improved by Benson and Snyder.[15] After reaction with RMgX (R cannot be Ar), sulfinamides are obtained and, due to the low reactivity of these compounds, activation with Me_3Al prior to addition of the second Grignard reagent is required. The obtainment of epimeric mixtures of sulfinamides in some cases and the use of different solvents in each step preclude the possibility of a one-pot procedure.

On the basis that *N*-acylated sulfinamides are at least 2 orders of magnitude more reactive than sulfinates,[9a,11] we reasoned that *N*-EWG-substituted sulfamidites would exhibit a quite better reactivity pattern in sulfinylation reactions.[16] The more favored cleavage of the S−N bond versus the S−O bond should afford a sulfinate, sufficiently reactive to evolve into a sulfoxide upon reaction with a second organometallic reagent without needing any additive. These two steps can now be performed in a single flask (Scheme 1). In this paper

Scheme 1

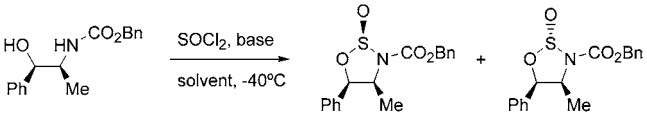


we report the use of *N*-benzyloxycarbonylsulfamidites derived from (1*R*,2*S*)-(−)-norephedrine **1** as starting compounds in the one-pot synthesis of any kind of enantiomerically enriched sulfoxides by consecutive reaction with two different Grignard reagents.[17]

Despite the diversity of conditions studied, all our attempts to obtain the *N*-acetylsulfamidite derived from norephedrine **1** failed. However, treatment of **1** with $ClCO_2Bn$ and reaction of the resulting carbamate **2** with $SOCl_2$ in the presence of a base smoothly afforded *N*-benzyloxycarbonyl derivatives **3a** and **3b**.

The observed diastereomeric ratio greatly depends on the reaction conditions, with the base and solvent being critical (Table 1). Thus, isomer **3a** is favored in CH_2Cl_2, whereas the amount of **3b** increases in less polar solvents (entries 1−3). The use of DMAP provided the highest de (84%, entry 4), **3a** being the major isomer. The opposite diastereoselectivity was observed by using methylpyridines (86 and 84% de, entries 13 and 16), though lower yields were obtained.

Table 1. Synthesis of *N*-Benzyloxycarbonylsulfamidites **3a** and **3b**



2 **3a** **3b**

entry	base	solvent[a]	**3a**/**3b**[b]
1	NEt_3	A, B, C	76/24
2	NEt_3	D, E	57/43
3	NEt_3	F	49/51
4	DMAP	A	92/8[c]
5	DMAP	B	76/24
6	DMAP	D, E	70/30
7	DMAP	F	46/54
8	DMAP	C	
9	DBU	A	76/24
10	pyridine	A	45/55
11	imidazole	A	21/79
12	*i*-Pr_2NEt	A	70/30
13	2,6-lutidine	A	7/93[d]
14	2,6-lutidine	D	complex mixture
15	2,6-lutidine	F	complex mixture
16	2,4,6-colidine	A	8/92

[a] A, CH_2Cl_2; B, acetone; C, CH_3CN; D, THF; E, Et_2O; F, toluene. [b] Determined by ^1H NMR from the reaction crude. [c] Isolated yield of **3a** = 62%. [d] Isolated yield of **3b** = 44%.

(7) Whitesell, J. K.; Chen, H. H.; Lawrence R. M. *J. Org. Chem.* **1985**, *50*, 4663.

(8) Oppolzer, W.; Froelich, O.; Wiaux-Zamar, C.; Bernardelly, G. *Tetrahedron Lett.* **1997**, *38*, 2825.

(9) (a) Alonso, R.; García Ruano, J. L.; Noheda, P.; Zarzuelo, M. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1133. (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Gomez-Arrayás, R.; Zarzuelo, M. M. *J. Org. Chem.* **1997**, *62*, 2139.

(10) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

(11) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.

(12) (a) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289. (b) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933. (c) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843. (d) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Fracciolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999**, *121*, 4708.

(13) (a) Reviere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991. (b) Reviere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659.

(14) Wudl, F., Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.

(15) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.

(16) A similar strategy for preparing enantiomerically pure sulfinamides from the *N*-tosylsulfamidite obtained by reaction of (1*R*,2*S*)-*N*-tosylaminoindanol with $SOCl_2$ has been reported very recently (Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880).

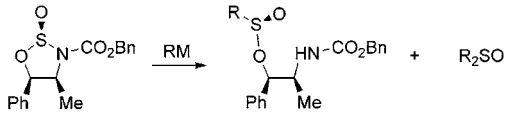
(17) Preliminary results have been presented: Alemparte, C.; Zarzuelo, M. M.; García Ruano, J. L. *Book of Abstracts*, Belgian Organic Synthesis Symposium, 9th ed., Namur, Belgium, July, 2002; TH 016.

The best results were achieved at −40 °C. Worse diastereomeric ratios and significant amounts of byproducts were detected at higher and lower temperatures, respectively. The preparation of **3a** can be performed in a one-pot procedure starting from norephedrine **1** (both enantiomers are commercially available) by reaction with $ClCO_2Bn$ in CH_2Cl_2 and subsequent addition of $SOCl_2$ in the presence of DMAP. Sulfamidite **3a** is isolated in 57% overall yield after chromatographic purification.

The configurational assignment of both diastereoisomers was initially based on the deshielding of the heterocyclic protons when they are in a cis arrangement with regard to the sulfinylic oxygen[14] and further confirmed from the absolute configuration of the obtained sulfoxides.

The results obtained in the reactions of **3a**[18] with different organometallic reagents (1 equiv) are depicted in Table 2.

Table 2. Reactions of **3a** with Organometallic Reagents



3a **4** **5**

entry	RM	solvent	T (°C)	**3a/4/5**[a]	**4**[b]
1	Me_2CuLi	THF/CH_2Cl_2	−20	37/0/43[c]	
2	MeLi	THF	−78	55/15/30	
3	MeMgBr	THF	−78	45/43/12	
4	MeMgBr	toluene	−78	18/60/22	
5	MeMgBr	hexane	0	81/3/16	
6	MeMgBr	$CHCl_3$	−50	45/28/27	
7	MeMgBr	CH_2Cl_2	0	34/26/40	
8	MeMgBr	CH_2Cl_2	−78	12/71/17	65
9	*t*-BuMgCl[d]	CH_2Cl_2	−40	10/90/0	82
10	*i*-PrMgCl	CH_2Cl_2	−78	5/91/4	81
11	EtMgBr	CH_2Cl_2	−78	26/54/20	46
12	PhMgBr	CH_2Cl_2	−78	6/90/4	74
13	*p*-anisylMgBr	CH_2Cl_2	−78	3/89/8	75
14	vinylMgBr	CH_2Cl_2	−78	30/50/20	

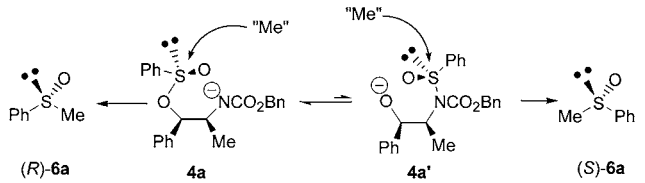
[a] Determined by ^1H NMR of the reaction crude. [b] Isolated yield. [c] Corresponding *sulfonate* (20%) was also detected. [d] Used 1.5 equiv.

The reaction mixtures are usually composed by the envisioned sulfinates **4**, symmetric sulfoxides **5** (obtained by reaction of **4** with a second molecule of RM), and consequently, the equivalent amount of unreacted **3a**. Since *N*-acylsulfinamides have been shown to be quite more reactive than sulfinates,[9a,11] the formation of compound **5** in significant amounts was not expected and suggests that sulfinates **4** could be better sulfinylating agents than the usual sulfinates, thus making easier the second attack of RM.[19]

Optimization of the organometallic nucleophile was investigated by comparing different methylating reagents. MeMgBr (entry 3) provided better results than MeLi (entry 2) or Me_2CuLi (entry 1). No reaction was observed with Me_2Zn and $MeCeCl_2$. The use of CH_2Cl_2 as a solvent at −78 °C proved to be critical (entry 8). These optimal reaction conditions were applied to other Grignard reagents (except to the less reactive *t*-BuMgCl, which required −40 °C and 1.5 equiv of nucleophile, entry 9). As shown in Table 2, only ethyl (entry 11) and vinyl (entry 14) Grignard reagents led to significant amounts of **3a** and **5**, whereas Me, *i*-Pr, *t*-Bu, and different aryl derivatives (entries 8−10, 12, and 13) provided sulfinate **4** in high proportion. These results must be taken into account when deciding the addition order of the reagents for the one-pot synthesis.

The first one-pot reaction attempt carried out was the formation of (*R*)-methylphenylsulfoxide **6a** by consecutive reaction of compound **3a** with PhMgBr and MeMgBr. Sulfoxide **6a** was cleanly obtained in 70% yield after chromatographic purification, though with only 73% ee.[20] It is well-known that reactions of RMgX with both *N*-acylsulfinamides and sulfinates evolve with complete inversion of the configuration at sulfur. We reasoned that racemization could be produced as a consequence of an intramolecular *N*-sulfinylation of the deprotonated benzenesulfinate intermediate **4a** (Scheme 2) yielding benzenesulfinamide **4a′** with the opposite configuration at sulfur. Both species are able to act as sulfinylating agents in the attack of the second Grignard reagent to yield opposite enantiomers of **6a**, thus decreasing its ee. This equilibrium must be mostly shifted toward **4a** (only sulfinates are isolated when the reaction is quenched after the first addition of Grignard reagent), but the higher reactivity of **4a′** could be responsible for the observed racemization.

Scheme 2

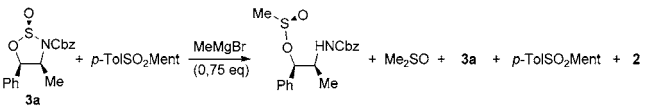


If this assumption was true, the use of 1 equiv of any electrophilic additive able to trap the nitrogen anion would avoid this equilibrium and therefore the racemization. Consequently, we explored the influence of different electrophilic additives on the ee of **6a**.

The best results (93% ee) were achieved by addition of 1.2 equiv of HBF_4 after the first Grignard reagent and prior

(18) The reactivity of both diastereoisomers was found to be similar, but **3a** was the substrate of choice because it could be prepared in higher yield.

(19) This higher reactivity would be interesting in the target one-pot two-step procedure. It was confirmed from the results obtained in the following competence experiment:

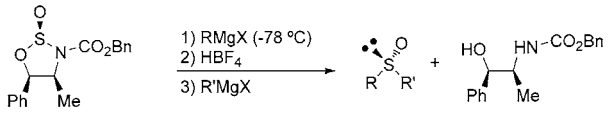


where DMSO is formed by the attack of MeMgBr on sulfinate **4**, whereas menthyl sulfinate remains unaltered (no menthol was detected).

(20) Enantiomeric excess was 99% when a two-step synthesis of **6a** (purifying intermediate sulfinate **4a** before its reaction with MeMgBr) was performed.

to the addition of the second one.[21] This simple procedure[22] was applied to the synthesis of a wide number of structurally diverse sulfoxides (Table 3), evidencing the great scope of this methodology. Alkylaryl (entries 1, 2, 5, 6, 9 11, 12, and 14), diaryl (entries 7 and 10), dialkyl (entries 4, 15, and 16), and arylvinyl (entries 3, 8, and 13) sulfoxides were readily prepared in 50−78% yield and high ees. The configuration of the resulting sulfoxides was unequivocally established by comparison of their specific rotations with those reported in the literature.

Table 3. Synthesis of Sulfoxides from **3a** by the One-Pot Procedure



3a **6** **2**

entry	R	R′[a]	yield	configuration (ee)[b]
1	Ph	Me	54	*R* (93)
2	Ph	*i*-Pr	58	*R* (93)
3	Ph	vinyl	53	*R* (95)
4	*i*-Pr	Et	52	*R* (−)[c]
5	*i*-Pr	Ph	75	*S* (95)
6	*p*-anisyl	Et	56	*R* (93)
7	*p*-anisyl	*p*-Tol	57	*R* (95)
8	*p*-anisyl	vinyl	61	*R* (93)
9	*p*-anisyl	*t*-Bu	52	*R* (76)
10	mesityl	*p*-Tol	71	*R* (97)
11	mesityl	Me	73	*R* (97)
12	mesityl	Me	78	*S*[d] (98)
13	mesityl	vinyl	64	*R* (95)
14	Me	mesityl	53	*S* (86)
15	cyclohexyl	*i*-Pr	60	*R* (90)
16	cyclohexyl	decyl	50	*R* (93)
17	*t*-Bu	Me		
18	*t*-Bu	*p*-anisyl		
19[e]	*t*-Bu	*p*-anisyl	70	*S* (77)

[a] Temperature and number of equivalents employed in the second step were variable (see Supporting Information). [b] By HPLC. [c] Could not be determined. [d] Starting from **3b**. [e] Without adding HBF_4.

The observed decrease in the ee in entries 9 and 14 could be due to the lower reactivities of MesMgBr and especially *t*-BuMgCl, allowing the equilibration shown in Scheme 2 to take place to a greater degree. More intriguing are the results obtained when *t*-BuMgCl was used in the first step. Under the usual conditions, the formation of the corresponding sulfoxide did not occur (entries 17 and 18). However, in the absence of HBF_4, the product was formed in 70% yield (entry 19), although in a predictable low ee.[23]

The best ees (95−98%) and yields (64−78%) are obtained when MesMgBr is used in the first step (entries 10−13), but no large differences with the results obtained in other cases are observed. As expected, the order of the addition of the reagents determines the observed absolute configuration of the sulfoxides (compare entries 2 and 5 or 11 and 14).

In conclusion, the one-pot reaction of compound **3a** with RMgX, HBF_4, and R′MgX must be considered a very general and powerful approach for the synthesis of sulfoxides in good yields and very high enantiomeric excess. Dialkyl, alkylaryl, arylvinyl, and diarylsulfoxides can be efficiently prepared in a single laboratory operation starting from a common precursor. The obtained configuration is tunable by simply electing the order of the addition of the reagents. Studies directed toward clarifying and solving the problems associated with the synthesis of *tert*-butylsulfoxides are in progress.

Acknowledgment. We thank CAICYT (Grant PB2000-196) for financial support. C.A. thanks Ministerio de Educación, Cultura y Deportes for a grant.

Supporting Information Available: Experimental procedures, $[\alpha]_D$, and ^1H and ^{13}C NMR data for compounds **3a**, **3b**, sulfinates **4**, and sulfoxides **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027232I

(21) Rates of the acid−base reaction of R′MgX with the NH proton and the substitution on sulfur are in the same range (the reaction between an isolated sulfinate **4** and 1 equiv of R′MgX gave rise to 30% conversion to the sulfoxide). Thus, only a proportion of molecules of **4** are deprotonated (with the consequent possibility of O → N sulfinyl migration) when reacting with R′MgX.

(22) Experimental one-pot procedure: RMgX (1 equiv) was added to a solution of **3a** in dry CH_2Cl_2 at −78 °C. Then, HBF_4 (1.2 equiv) was added after 10−25 min and R′MgX (2.5−5 equiv) 5 min later followed by quenching with aqueous NH_4Cl. The usual workup and chromatography afforded the sulfoxides in good overall yields.

(23) (*S*)-*t*-BuSO-*p*-anisyl and (*R*)-*t*-BuSOMe can be successfully prepared by addition of the corresponding Grignard reagents to isolated *t*-butanesulfinate **4**.