Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8387-8390, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01899-0

Diastereoselective Radical Alkylations of Alkyl Aryl Sulfoxides

Mohamed Zahouily,[a,b] Giulia Caron,[c] Pierre-Alain Carrupt,[c] Nourdine Knouzi[b] and Philippe Renaud[a]*

[a]Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg (Switzerland)
[b]Université Hassan II-Mohammadia Faculté des Sciences Ben M'sik Casablanca (Maroc)
[c]Université de Lausanne, Ecole de Pharmacie, BEP, CH-1015 Lausanne (Switzerland)

Abstract: 1,2-Asymmetric induction in reactions of arylsulfinylated radicals has been examined and compared to the anionic processes. A rule of thumb allowing to predict the stereoselectivity is presented. Copyright © 1996 Published by Elsevier Science Ltd

Radical reactions and in particular cyclization and multiple cyclizations reactions are becoming more and more popular in organic synthesis.[1] In order to access to enantiomerically pure compounds, the use of chiral auxiliaies is highly attractive.[2] We have decided to investigate the use of sulfoxides as chiral templates to control the absolute stereochemistry of compounds prepared from acyclic alkyl radicals.[3,4] In a previous communication, we have shown that the cyclization reactions using *p*-tolyl sulfinyl group are not stereoselective relative to the sulfur chiral center.[3a,5] Further experiments in intermolecular reactions with *ortho*-substituted aryl sulfoxides have demonstrated that a substantial level of stereoselectivity can be achieved in such systems.[6] In this communication, we describe the scope and limitation of substituted aryl sulfoxides in intermolecular reactions. A comparison with the classical alkylation of sulfinylated carbanion will be presented.

Radical precursors **1a-1f** have been prepared from thiophenol and *o*-chlorothiophenol in racemic form by alkylation (RBr or RI, TBAI/NaOH/H_2O/C_6H_6), oxidation (*m*-CPBA) and selanylation (LiHMDS/PhSeCl). Compound **1g** has been prepared by reaction of methyl phenylsulfinate[7] with *t*-$BuCH_2MgI$ and subsequent selanylation. Reaction of **1a-1g** with [2-(methoxycarbonyl)prop-2-en-1-yl]tributylstannane at 10 °C (AIBN/sun lamp irradiation) gave mixtures of *anti*- and *syn*-**2a-g** (Table).[8]

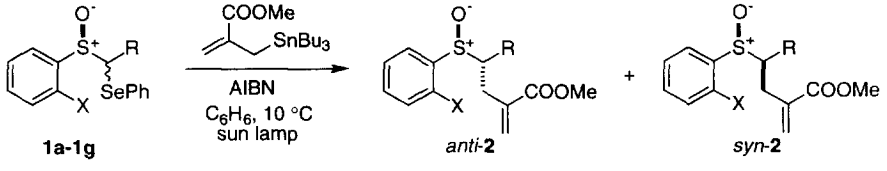
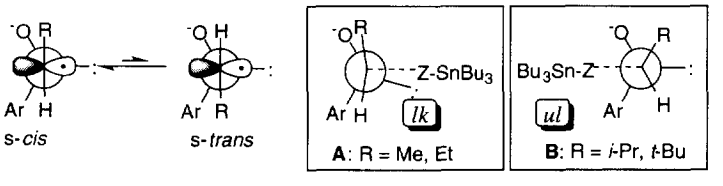


Table. Radical allylation of **1a-1g**

Precursor	R	X	Product	Yield %	*anti/syn*
1a	Me	H	**2a**	67	50:50
1b	Me	Cl	**2b**	66	80:20
1c	Et	H	**2c**	63	39:61
1d	Et	Cl	**2d**	73	72:28
1e	*i*-Pr	H	**2e**	86	22:78
1f	*i*-Pr	Cl	**2f**	82	40:60
1g	*t*-Bu	H	**2g**	61	5:95

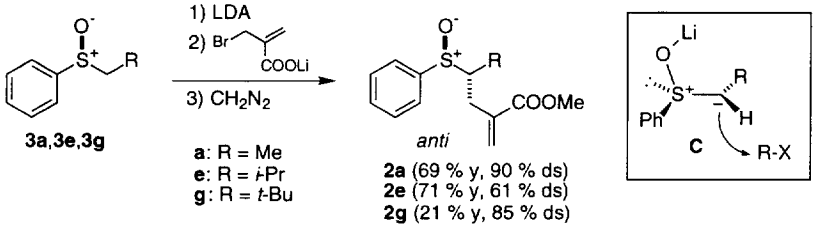
The analysis of the results shows two tendencies: 1) large R groups tend to favor the *syn* configuration; 2) the presence of an *o*-chlorine atom favors the *anti* configuration. Based on this observation, a simple rule predicts that **good *anti* selectivity is observed with small R substitutent (R = methyl, primary alkyl groups) and X = Cl (72-80 % ds). On the other hand, good *syn* selectivity is observed when R is large (R = secondary and tertiary alkyl groups) and X = H (78-95 % ds).**

The stereochemical outcome is difficult to rationalize. However, semi-empirical calculations have shown that the intermediate radicals exist in *s-cis* and the *s-trans* conformations, the *s-cis* being more stable by 1.0-3.5 kcal/mol.[9] The chlorine atom favors the *s-cis* conformation with small R substituent as reported previously.[6] With secondary and tertiary R groups, the *s-cis* configuration is more stable because of strong steric interactions between the R group and the aryl moiety in the *s-trans* conformer. Depending on the size of the R group, the *s-cis* conformer is attacked preferentially with a *like* (*lk*) topicity (R = methyl, primary alkyl groups) or a *unlike* (*ul*) topicity (R = secondary and tertiary alkyl groups). The *lk* topicity is favored by steric factors since the attack occurs *anti* to the bulky aryl group (transition state **A**). The chlorine atom also favors the *lk* topicity because it increases the bulk of the aryl group. Due to pyramidalization in the transition state,[10] the *lk* attack generates eclipsing interactions between the R group and oxygen atom at sulfur. This eclipsing interactions become dominant with large alkyl groups. Attack from the more hindered face (*ul* topicity) leading to the staggered transition state **B** becomes more favorable.



For comparison, the ionic alkylations of **3a**, **3e** and **3g** according to the procedure of Bravo[11] were investigated. After esterification with diazomethane, the reaction afforded the sulfoxide *anti*-**2a**, **2e** and **2g** with moderate to good stereoselectivities. Interestingly, with bulky R groups (R = *i*-Pr, *t*-

Bu) the radical an the ionic alkylation procedures are complementary from a stereochemical point of view. For anionic reactions, the selectivity can be rationalized from the model developed by Boche,[12] preferential attack is occuring *anti* to the sulfoxide oxygen atom (**C**).



In conclusion, we have demonstrated that the *ortho*-chlorophenyl sulfinyl group allows *anti*-stereoselective alkylation of radical substituted by primary alkyl groups. With secondary and tertiary alkyl substituents, good *syn* stereocontrol is obtained when using the classical phenyl sulfoxides. These results are presently exploited in our laboratory to control the stereoselectivity of simple and multiple radical cyclization reactions.

Acknowledgment. This work was supported by the "Office Fédéral pour l'Education et la Science (OFES)" within a European COST-D2 program. We thanks Ciba-Geigy Marly for microanalyses.

REFERENCES AND NOTES

1. Curran, D. P. *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715-777. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bond;* Pergamon ed.; Oxford, 1988. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1992.
2. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions;* VCH; Weinheim, 1996.
3. (a) Renaud, P. *Tetrahedron Lett.* **1990**, *31*, 4601-4604. (b) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803-7805. (c) Renaud, P. *Helv. Chim. Acta.* **1991**, *74*, 1305-1313. (d) Renaud, P.; Moufid, N.; Chen, L. H.; Curran, D. P. *J. Org. Chem* **1994**, *59*, 3547-3552. (e) Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem. Int. Ed.* **1994**, *33*, 1601-1603. (f) Renaud, P.; Carrupt, P. A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* **1994**, *35*, 1703-1706. (g) Renaud, P.; Bourquard, T. *Synlett* **1995**, 1021-1023.
4. Several groups have reported highly stereoselective reactions using 1-sulfinylated radicals bearing an extra stabilizing groups such as esters, amides and ketones: Beckwith, A. L. J.; Hersperger, R.; White, J. M. *J. Chem. Soc. Chem. Commun.* **1991**, 1151-1152. Snider, B. B.; Wan, B. Y-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328-334. De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt,T. *Synlett* **1993**, 871-874.

5. Tsai, Y.-M.; Ke, B.-W.; Lin, C.-H. *Tetrahedron Lett.* **1990**, *31*, 6047-6050.
6. Renaud, P.; Bourquard, T. *Tetrahedron Lett.* **1994**, *35*, 1707-1710.
7. Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051-7054.
8. Typical procedure: a solution of the radical precursor (1 mmol), [2-(methoxycarbonyl)prop-2-en-1-yl]tributylstannane (1.5 mmol) and AIBN (10 mg) in degassed benzene (3 ml) was irradiated with a 300 W sun lamp at 10-15 °C for 8-12 h. Crude products (suitable for ^{1}H-NMR ds determination) were isolated by filtration through silicagel (AcOEt/hexane) and were further purified by flash chromatography. All new compounds have been characterized by ^{1}H-NMR, ^{13}C-NMR, MS, IR and elemental analysis. *syn*-**2e**: ^{1}H-NMR (250 MHz, $CDCl_3$): 7.44-7.55 (*m*, 5H); 6.03 (*d*, *J* = 0.5, 1H); 5.50 (*qdm*, *J* = 6.7, 2.8, 1H); 3.50 (*s*, 3H); 2.75 (*ddd*, *J* = 10.3, 5.1, 3.5, 1H); 2.50-2.65 (*m*, 1H); 2.06-2.25 (*qdm*, *J* = 6.7, 2.8, 1H); 1.23 (*d*, *J* = 6.8, 3H); 1.18 (*d*, *J* = 6.9, 3H).*anti*-**2e**: 7.45-7.60 (*m*, 5H); 6.18 (*d*, *J* = 0.5, 1H); 5.62 (*d*, *J* = 0.5, 1H); 3.68 (*s*, 3H); 2.80 (*ddd*, *J* = 5.5, 2.8, 2.7, 1H); 2.49-2.71 (*m*, 2H); 2.18-2.35 (*qdm*, *J* = 7.0, 2.8, 1H); 1.06 (*d*, *J* = 7.0, 3H); 0.95 (*d*, *J* = 7.0, 3H). The two olefinic signals in ^{1}H-NMR spectra have been used to attribute the *syn/anti* configurations, the signal of the *syn* isomers are shifted to lower field: **2a** (*syn* 6.17/5.53; *anti* 6.28/5.70); **2b** (*syn* 6.19/5.54; *anti* 6.39/5.83); **2c** (*syn* 6.13/5.49; *anti* 6.30/5.73); **2d**(*syn* 6.11/5.44; *anti* 6.39/5.88); **2e** (*syn* 6.03/5.50; *anti* 6.18/5.62); **2f** (*syn* 6.07/5.45; *anti* 6.34/5.88); **2g** (*syn* 5.78/5.37; *anti* 6.04/5.40).
9. The semi-empirical calculations were performed with the AM1 hamiltonian using the Spartan4.0 software (Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA 92715 USA, © 1995, Wavefunction, Inc.). The standard convergence criteria were used and the minima characterized by the analysis of the Hessian matrix. Full details will be published in a forthcoming full paper.
10. Dewar, M. J. S.; Hwang, J. C.; Kuhn, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735-741. Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925-3927.
11. Bravo, P.; Resnati, G.; Viani, F. *Tetrahedron Lett.* **1985**, *26*, 2913-2916.
12. Boche, G. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277-297.

(*Received in France* 29 *July* 1996; *accepted* 20 *September* 1996)