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A New General Method for the Preparation of *N*-Sulfonyloxaziridines

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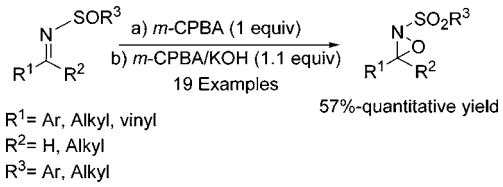
ABSTRACT



A simple procedure to obtain *N*-alkylsulfonyl- and *N*-arylsulfonyloxaziridines from the corresponding *N*-sulfinylimines involving a one-pot, two-step oxidation process with *m*-CPBA (1 equiv) and *m*-CPBA/KOH (1.1 equiv) is reported. The method is applicable to *N*-sulfinylimines derived from aldehydes (aliphatic and aromatic) and ketones (dialkyl and aryl alkyl) and preserves C═C-conjugated double bonds. Almost quantitative yields, very mild conditions (usually less than 5 min at room temperature), and easy purification by filtration are the main features of this new procedure, which can be performed at a gram scale.

Oxaziridines[1] have proven to be interesting reagents[2] with multiple and diverse applications as oxidizing and electrophilic amination reagents. In particular, *N*-sulfonyloxaziridines[3] have been the most widely used probably due to their stability and easy handling.[4] The first general method for synthesizing these compounds, reported by Davis in 1980,[5] involved the oxidation of *N*-sulfonylimines—prepared by condensation of the aldehyde's diethyl acetal with the *N*-sulfonamide at 130−180 °C—followed by a *m*-CPBA two-phase oxidation system ($HCCl_3$/$NaHCO_3$−H_2O). After these initial results, the use of other oxidizing reagents that improve the yields, shorten the reaction times, and facilitated the purification processes have been reported. The most popular reagent for oxidizing the C═N bond at *N*-sulfonylimines is Oxone buffered with $KHCO_3$ or K_2CO_3,[6] which was also

(1) (a) Emmons, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 6208. (b) Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5739. (c) Horner, L.; Jrgens, E. *Chem. Ber.* **1957**, *90*, 2184. (d) Krimm, H. *Chem. Ber.* **1958**, *91*, 1057.

(2) (a) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2911. (b) Wolfe, M. S.; Dutta, D.; Aubé, J. *J. Org. Chem.* **1997**, *62*, 654. (c) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845. (d) Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 6528. (e) Bonnet, D.; Rommes, C.; Gras-Masse, H.; Melnyk O. *Tetrahedron* **1999**, *40*, 7315. (f) Page, P. C. B.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews. D. M. *J. Org. Chem.* **1997**, *62*, 6093. (g) Messina, F.; Botta, M.; Corelli, F.; Paladino, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4895. (h) Messina, F.; Botta, M.; Corelli, F.; Paladino, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4895. (i) Armstrong, A.; Edmods, I. D.; Swarbric, M. E. *Tetrahedron Lett.* **2003**, *44*, 5335. (j) Washington, I.; Houk, K. N. *J. Org. Chem.* **2003**, *68*, 6597. (k) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367. (l) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey R. D. *Org. Lett.* **2005**, *7*, 713.

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(4) For a compiled use of *N*-sulfonyloxazidines, see: Mishra, J. K. *Synlett* **2005**, *3*, 543.

(5) Davis, F. A.; Lamendola, J. Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.

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reported by Davis, but other oxidants[7] (peroximidic acid) have also been used.

The main limitations of all of these methods are related to the difficulties associated with the synthesis of the starting *N*-sulfonylimines by condensation of *N*-sulfonamides with the proper carbonyl compounds.[5,8] It does not give good results for compounds derived from aliphatic aldehydes and ketones containing tautomerizable protons or for *N*-alkylsulfonylamides derivatives, giving low yields in the condensation step. As a consequence, the structural diversity of the *N*-sulfonyloxaziridines reported so far is rather limited, being restricted to those derived from aromatic aldehydes and some bicyclic ketones and in most cases only concerning the *N*-arylsulfonyl derivatives.

We have recently published a new method to prepare *N*-sulfonylimines[9] consisting of the condensation of the carbonyl compounds with *N*-sulfinamides and further oxidation of the resulting *N*-sulfinylimines with *m*-CPBA. As this condensation step lacks the limitations indicated for *N*-sulfonamides, the scope of our method in the synthesis of *N*-sulfonylimines is much wider, which suggests that the structural diversity of the oxaziridines would be now also larger. Moreover, we have just reported the usefulness of *m*-CPBA/KOH as a nucleophilic epoxidizing reagent of highly deficient double bonds able to act as very good Michael acceptors (*gem*-disubstituted by two electron-withdrawing groups).[10] The two main advantages of this reagent, with respect to the peroxides—the most commonly used to obtain epoxides—are its higher reactivity toward the C=C bonds and the higher stability of the resulting epoxide to the anion formed as byproduct (*m*-$ClC_6H_4CO_2^-$ instead of RO^-). Therefore, we reasoned that both these features could be very useful in the synthesis of the oxaziridines if the *m*-CPBA/KOH system is reactive enough to oxidize the C=N of *N*-sulfonylimines. In this paper, we report a new procedure for preparing *N*-sulfonyloxaziridines consisting in the one-pot, two-step oxidation of *N*-sulfinylimines with *m*-CPBA (1 equiv) and *m*-CPBA/KOH (1.1 equiv). It allows the synthesis of *N*-alkyl- and *N*-arylsulfonyloxaziridines with a large structural variety including those derived from aldehydes and ketones containing enolizable protons. This method provides higher yields, requires much shorter reaction times (usually less than 5 min), and involves a simpler purification process (filtration) than the methods reported so far. Moreover it can be used at a gram scale.

We first studied the reaction of *m*-CPBA/KOH with *N*-*p*-tolylsulfonylbenzylideneimine **1**. The addition at room temperature of this imine to a 1:1 mixture of KOH and *m*-CPBA affords instantaneously oxaziridine **2a**, which can be isolated in an almost quantitative yield (entry 4, Table 1) by simple filtration. Significant advantages of using this procedure can be inferred by comparing these results with those obtained with the best methods previously reported for preparing **2a** (see Table 1). This comparison demonstrates that, in terms of reaction times, experimental procedures simplicity, and yields, *m*-$ClC_6H_4COOO^-$ is the most efficient oxaziridinating reagent so far reported for *N*-sulfonylimines. The much shorter reaction times required for our reagent must be due to its use as a suspension in a dry solvent. *The absence of water substantially increases the reactivity of m-*$ClC_6H_4COOO^-$ *with respect to the previously used reagents, all of them requiring the use of water as cosolvent, which solvates the oxygen, substantially reducing their nucleophilic reactivity*.

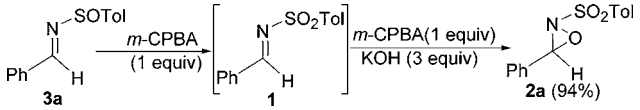
Table 1. Results Obtained in the Conversion of **1a** into **2a** Using Relevant Methods

1 2a

entry	conditions	reaction time	yield (%)	isolation
1	*m*-CPBA two-phase oxidation system ($HCCl_3/NaHCO_3-H_2O$) and PTC[11]	4−5 h	92	extraction + crystallization
2	Oxone, $KHCO_3-H_2O$[6]	2 h	95	extraction + crystallization
3	peroximidic acid (H_2O_2, TBAB, CCl_3CN, CH_2Cl_2, H_2O, $NaHCO_3$)[7]	0.5 h	85	extraction + silica gel chromatography
4	this paper (*m*-CPBA, KOH)	<1 min	100	filtration

As the *N*-sulfinylimines[12] are much more stable than their corresponding *N*-sulfonylimines[13] and the latter compounds can be instantaneously obtained from the former ones by reaction with *m*-CPBA,[9] we reasoned that the use of the *N*-sulfinylimines as the starting products for synthesizing *N*-sulfonyloxaziridines could be made following a two step one pot oxidation, by successive reactions with *m*-CPBA and *m*-CPBA/KOH, without isolating the *N*-sulfonylimine **1** intermediate (Scheme 1).

Scheme 1



This prompted us to study the direct transformation of **3a** into **2a**. After several trials in different conditions, we found

(6) Davis, F. A.; Chattopadhyay, S.; Towso, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.

(7) (a) Kraïem, J.; Othman, R. B.; Hassine, B. B. *C. R. Chimie* **2004**, *7*, 1119. (b) Davandi, J. A. Karami, B.; Zolfigol, M. A. *Synlett* **2002**, 933.

(8) See, for example: (a) Trost, B. M.; Christopher, M. *J. Org. Chem.* **1991**, *56*, 6468. (b) Lee, K. Y.; Lee, C. C.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231 and references therein. (c) Wolfe, J.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607. (d) Jin, T.; Feng, G.; Yang, M.; Li, T. *Synth. Commun.* **2004**, *34*, 1277.

(9) García Ruano, J. L.; Alemán, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179.

(10) García Ruano, J. L.; Fajardo, C.; Fraile, A.; Martin, R. *J. Org. Chem.* **2005**, *70*, 4300.

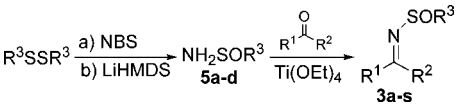
(11) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *7*, 1774. This is a improved synthesis of their previous first synthesis (ref 5).

(12) (a) For *p*-tolylsulfinylimines, see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003 and references therein. (b) For *tert*-butyl-*N*-sulfinylmines, see: Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984 and references therein.

that reaction of **3a** with *m*-CPBA (1 equiv) followed by treatment with a mixture of *m*-CPBA (1.1 equiv) and KOH (3 equiv) at room temperature yielded the desired oxaziridine **2a** in 94% isolated yield. Worthy of notice are the simplicity of the experimental procedure[14] and the easy purification[15] (filtration) of the resulting oxaziridine.

We then prepared *N*-sulfinylimines **3a**−**s** by condensation of the *N*-sulfinamides **5a**−**d** with the corresponding carbonyl compounds (Scheme 2) according to the Davis' protocol[16]

Scheme 2

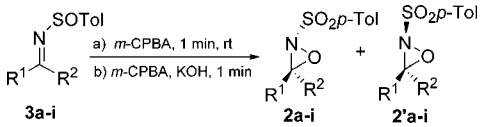


slightly modified in the work up, which allowed the improvement of the yields.[17] *N*-Sulfinamides **5a**−**d** were obtained by reaction of disulfides with NBS/MeOH[18] and further treating with LiHMDS[19] (for more details, see the Supporting Information).

The results obtained in the reactions of the *N*-*p*-tolylsulfinylimines **3a**−**i**, derived from aromatic or aliphatic aldehydes and ketones, with *m*-CPBA and *m*-CPBA/KOH according to the procedure indicated above, are summarized in Table 2.

As we can see, reactions are very efficient in all cases. Aromatic *N*-sulfinylaldimines **3a**−**d**, containing electron-donating or electron-withdrawing groups, afford oxaziridines **2a**−**d** in very high yields. Less than 5 min are required for the whole process. The simplicity of the experimental procedure prompted us to check the multigram scale. It was performed by reaction of 2.4 g of *N*-*p*-tolylsulfinylimine **3a** (0.01 mol) with the reagents, obtaining pure oxazidirine **2a** in a yield (97%) even better than that obtained at a lower scale, which suggests that this transformation is almost quantitative.

Table 2. Preparation of *N*-*p*-Tolylsulfonyloxaziridines **2a**−**i** from *N*-*p*-Tolylsulfinylimines **3a**−**i**



entry	starting material	R^1	R^2	products	yield (%)
1	**3a**	Ph	H	**2a**	94
2	**3b**	3-$MeOC_6H_4$	H	**2b**	89
3	**3c**	4-$NO_2C_6H_4$	H	**2c**	97
4	**3d**	4-CNC_6H_4	H	**2d**	96
5	**3e**	$PhCH{=}CH_2$	H	**2e**	99
6	**3f**	Me	H	**2f**	97
7	**3g**	*i*-Pr	Me	**2g**	99
8[a]	**3h**	Ph	Me	**2h** (74)/**2′h** (26)[c]	89
9	**3i**[b]	Ph	Me	**2i** (86)/**2′i** (14)[c]	80

[a] Similar results were obtained at −40 °C. [b] *N*-*tert*-Butylsulfonyl derivative was used. [c] Diastereoisomeric ratio.

The conjugated double bonds are not affected by the reagents, as suggested by the easy transformation of *N*-sulfinylimine **3e** into **2e** (entry 5, Table 2). Similarly, an excellent result was obtained with the enolizable aldimine **3f**, which indicates that under the basic conditions used in these reactions the possible enolization does not decrease the reactivity of the process (entry 6, Table 2).

Also remarkable are the results obtained from enolizable *N*-*p*-toluenesulfinylketimines **3g**−**i** (entries 7−9, Table 2). Starting from **3g**, the evolution of the reaction is identical to that of the sulfinylaldimines and **2g**, with the sulfonyl group in an *anti* arrangement with respect to the isopropyl group, allowing us to obtain diastereomerically pure *N*-*p*-tolylsulfonyloxaziridine **2g** (entry 7, Table 2). On the contrary, starting from ketimine **3h** (entry 8, Table 2), a 3:1 mixture of *anti*- and *syn*-oxaziridines (**2h** and **2h′**) was obtained, whereas this ratio is even higher (*anti*/*syn* = 86:14) starting from the *N*-*tert*-butylsulfinylketimine **3i**. Considering the low energy required for the *syn*−*anti* isomerization of *N*-arylsulfonyloxaziridines,[20] the composition of the reaction mixtures must be dependent only on the relative stability of the oxaziridines (thermodynamic control) presumably associated with the relative value of the almost eclipsed interactions of the SO_2Tol group with the substituent adopting a *cis* arrangement.

Finally we have also prepared oxaziridines **2j**−**s** bearing different residues at the sulfur atom (Table 3). The interest in the *N*-*o*-methoxyphenylsulfonylimines **2l** and **2m** is related to their possible usefulness in asymmetric processes involving the formation of stable metal chelates with the nitrogen

(13) *N*-Sulfinylimines derived from aliphatic aldehydes or ketones are stable for months at −20 °C, whereas their corresponding sulfonylimines only can usually be stored for less than 1 day.

(14) **General Procedure for the Synthesis of *N*-Sulfonyloxaziridines from *N*-Sulfinylimines.** Dry *m*-CPBA (0.40 mmol) is added in one portion to a solution of the corresponding *N*-sulfinylimine (0.40 mmol) in CH_2Cl_2 (2 mL) at room temperature. Once the reaction is completed (usually it is instantaneous; see the text), the reaction crude is added over a white suspension of *m*-CPBA (0.44 mmol) and powdered KOH (1.4 mmol) in 1 mL of CH_2Cl_2 (previously prepared and maintained for 5 min at room temperature). When this second reaction—which is also instantaneous and can be easily followed by TLC—is finished, the reaction crude is filtered and the solvent evaporated to yield pure *N*-sulfonyloxaziridine.

(15) The use of an excess of KOH is required for transforming the *m*-chlorobenzoic acid generated in the first step in its corresponding insoluble carboxylate, removable by filtration. The use of an alternative procedure involving the reaction of the *N*-sulfinylimine with a 2:1 mixture of *m*-CPBA/KOH in only one step, is also efficient to form the *N*-sulfonyloxazididines, but their isolation is not so simple because *m*-CPBA remains solved in the organic layer.

(16) Davis, F. A.; Zhang, Y.; Andemichae, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

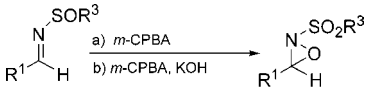
(17) The reaction mixture was treated with MeOH, and some drops of $NaHCO_3$ were added until precipitation of the titanium salts. Then, it was filtered trough a short pad of anhydrous Na_2SO_4, the solvent evaporated, and the residue purified by flash chromatography.

(18) Brownbridge, P.; Jowett, I. C. *Synthesis* **1987**, 252.

(19) This procedure has been used by Davis for synthesizing (*S*)-*p*-tolylsulfinamide from (*S*)-menthyl sulfinate. See ref 16.

(20) A thermodynamic control was detected (*anti*/*syn* 1/3). See: (a) Jennings, W. B.; Watson, S. P.; Tolley, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 8099. (b) Jennings, W. B.; Watson, S.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1988**, 931.

Table 3. Synthesis of Different *N*-Alkyl- and *N*-Arylsulfonyloxaziridines



3j-s **2j-s**

entry	starting material	R^1	R^3	product	yield (%)
1	**3j**	Ph	*o*-$MeOC_6H_4$	**2j**	99
2	**3k**	*i*-Pr	*o*-$MeOC_6H_4$	**2k**	93
3	**3l**	Ph	*t*-Bu	**2l**	99
4	**3m**	*i*-Pr	*t*-Bu	**2m**	99
5	**3n**	Ph	*i*-Pr	**2n**	91
6	**3o**	*i*-Pr	*i*-Pr	**2o**	83
7	**3p**	Ph	*n*-Pr	**2p**	99
8	**3q**	*i*-Pr	*n*-Pr	**2q**	93
9[a]	**3r**	Ph	*p*-$NO_2C_6H_4$	**2r**[b]	57
10[a]	**3s**	*i*-Pr	*p*-$NO_2C_6H_4$	**2s**	(32)[c]

[a] Reactions were performed in only one step with a 6:4 mixture of *m*-CPBA/KOH for longer reaction times (4−12 h). [b] Oxaziridine **2r** was purified by chromatography. [c] Conversion measured by ^1H NMR.

and oxygen atoms. The behavior of **3j** and **3k** in their successive reactions with *m*-CPBA and *m*-CPBA/KOH was identical to that of the tolylsulfonyl derivatives (entries 1 and 2, Table 3).[21] *N*-Alkylsulfonyl-oxaziridines were easily obtained under the conditions of our protocol, from the corresponding *N*-alkylsulfinylimines (entries 3−8, Table 3) with especially good results being obtained for the interesting *tert*-butyl derivatives **2l** and **2m** (entries 3 and 4, Table 3). The only substrates producing less satisfactory results were **3r** and **3s** (entries 9 and 10, Table 3), bearing a *p*-nitrophenylsulfonyl group at nitrogen. The problems observed derive from the already expected difficulty of oxidizing the highly deficient *p*-nitrosulfinyl group into the *p*-nitrosulfonyl one during the first step with *m*-CPBA. This requires much longer reactions times (several hours) for this step, resulting in the decomposition of the starting *N*-sulfinylimines which is especially significant for the less stable alkylimine **3s** (entry 10, Table 3). These reactions were not performed following the general protocol[14] but rather by treating the *N*-sulfinylimines **3r** and **3s** with a 6:4 mixture of *m*-CPBA/KOH for 4 and 12 h, respectively.

In conclusion, we have developed a simple and efficient two-step process for obtaining *N*-sulfonyloxaziridines starting from *N*-sulfinylaldimines consisting of their successive reaction with *m*-CPBA and *m*-CPBA/KOH. It is applicable to aromatic and aliphatic aldimines and ketimines, regardless of the presence of enolizable protons, allows the synthesis of *N*-sulfonyloxaziridines containing different residues at the sulfur atom, and can be performed on a multigram scale. Additionally, it can be applied on substrates containing cyano groups and conjugated C═C bonds.

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Supporting Information Available: Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) We have also tried the synthesis of the *p*-methoxyphenyl derivative (*p*-$MeOC_6H_4C$═NSO-*o*-$MeOC_6H_4$.) The reaction works, but the low stability of the resulting oxaziridine in the basic medium used precludes its isolation. This behavior had already been observed by Davis with the *p*-$MeOC_6H_4$ derivatives (ref 5). As it must be presumably due to the high stability of the benzylcarbacation resulting from the ring opening, which immediately would react with the basic medium, we performed the reaction without using excess of KOH in the second step (the isolation of compound was now different). Nevertheless, under these conditions, we obtained similarly bad results.