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Simple and highly efficient synthesis of oxaziridines by tetrabutylammonium Oxone®

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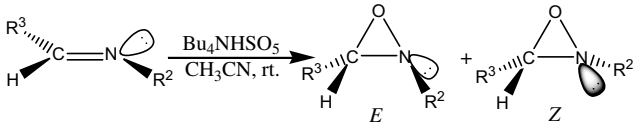
Abstract—Oxygenation of various aldimines with tetrabutylammonium monoperoxysulfate produced the corresponding *E*- or a mixture of *E*- and *Z*-oxaziridines with very high yields (⩾90%) and good to excellent selectivities (75–100%) within 20 min to 10 h in CH_3CN at room temperature (~25 °C). The *E*/*Z* isomer ratio critically depends on the stereo-electronic nature of the substituents in the oxaziridines, solvent, and the presence of Lewis acids and bases.

The development of efficient synthetic methods for the preparation of oxaziridines, which have important applications in organic syntheses, is a significant goal and represents a considerable challenge.[1–5] Oxaziridines have been employed as both nitrogen transfer[6,7] and oxygen transfer[8,9] reagents in synthetic organic chemistry. They are also extensively used in asymmetric syntheses.[4,5,10] Very recently, the potential of oxaziridines as antifungals has been reported.[11] Oxidation of imines with *m*-chloroperbenzoic acid (MCPBA) is the most general method for the preparation of oxaziridines.[12–16] Other oxidizing agents such as H_2O_2 in combination with acetic anhydride,[17] nitriles,[18,19] and urea,[20] have also been used in this regard. *tert*-Amyl hydroperoxide[21] and O_2,[22,23] as oxygen sources in association with transition metal complexes are also reported for this purpose. However, most of these methods suffer from disadvantages such as harsh reaction conditions, formation of side products, and difficult work-up procedures.[20]

Although Oxone® (potassium peroxymonosulfate) has been introduced as a useful oxidizing agent in the oxidation of imines,[24,25] its employment requires a buffered two-phase system, and gives only the *E*-isomer. We now report the use of tetrabutylammonium Oxone® (TBAO)[26] in CH_3CN as a highly efficient oxidant for the synthesis of oxaziridines from aldimines,[27] under very mild reaction conditions and with a very simple work-up procedure (Scheme 1).[28] Different electronic and structural effects of the aldimine substituents on the reaction rate and formation of *E*- and *Z*-isomers are also considered in this study.

The results presented in Table 1 illustrate the high efficiency and 100% selectivity (except for entries 6, 7, 11, 12) of this oxidation system. Oxidation of benzylidenephenylamine (entry 14) gives benzaldehyde as the sole product. Electron donating and acceptor substituents on the carbon site of the azomethines have a pronounced effect on the rate of oxygenation. It was observed that the presence of $-OCH_3$ as a π-donating substituent on the phenyl group of the aldimine (entry 3) decreases the rate of the reaction in comparison with aldimines having no substituent on the ring (120 vs 50 min, entry 1). Whereas, a substrate with an electron withdrawing $-NO_2$ group on the phenyl ring displays a shorter reaction time (35 min, entry 4), under the same conditions. The oxidation of an aldimine bearing a rather good π-acceptor such as a pyridyl substituent (entry 5) shows



Scheme 1.

Keywords: Oxidation; Oxaziridines; Tetrabutylammonium Oxone®; Aldimines.

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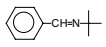
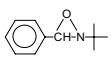
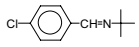
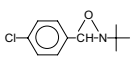
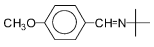
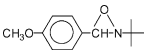
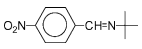
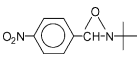
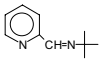
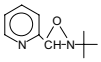
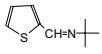
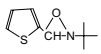
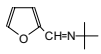
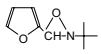
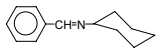
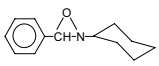
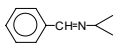
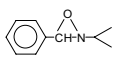
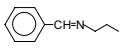
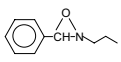
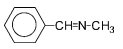
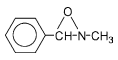
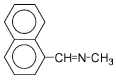
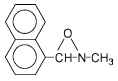
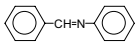
Table 1. Oxygenation of aldimines with TBAO in CH_3CN[a]

Entry	Aldimine	Conversion (%)	Product	Yield (%)[b]	δ_H (ppm)[c]	Time (min)
1		100 [75]		100 (*E*)	4.50	50 [40]
2		100		100 (*E*)	4.49	60
3		90[d]		90 (*E*)	4.44	120
4		94[d]		94 (*E*)	5.13	35
5		100		100 (*E*)	4.74	20
6		100		91 (*E*)[e]	4.80	10 (h)
7		90[d]		68 (*E*)[e]	4.60	10 (h)
8		100		51 (*E*) 49 (*Z*)] 100	4.32 5.09	45
9		100		55 (*E*) 45 (*Z*)] 100	4.30 5.08	45
10		100		56 (*E*) 44 (*Z*)] 100	4.31 5.06	35
11		100		35 (*E*) 57 (*Z*)] 92[e]	4.29 5.05	35
12		100		10 (*E*) 86 (*Z*)] 96[e]	4.96 5.52	20
13		100		75 (*E*) 25 (*Z*)] 100	3.50 3.90	60
14		98		98	—	10 (h)

[a] Reaction conditions are given in the text and the identities of the products were confirmed by ^1H NMR spectral data.[29,30]
[b] ^1H NMR yields are based on the starting aldimines.
[c] The chemical shifts (CCl_4+TMS) of the oxaziridine ring hydrogen.
[d] The reactions were not complete.
[e] The only by-product is the corresponding aldehyde: entry 6 (9%), entry 7 (22%), entry 11 (8%), entry 12 (4%).

a much higher rate (20 min) than entry 1. The reactions of *tert*-butylthiophen-2-ylmethylenamine and *tert*-butylfuran-2-ylmethylenamine (entries 6, 7) are very slow (~10 h) but display excellent selectivities (100%) for the formation of the *E*-isomer. Presumably, the π-resonance effect of the lone pairs of the oxygen and the sulfur are responsible. It should be emphasized that the influences of electron withdrawing and electron donating substituents on the carbon site of azomethine are in complete contrast with those of MCPBA in the oxidation of imines.[31]

It is known that the oxidation of aldimines with a bulky *tert*-butyl substituent on the nitrogen site (entries 1–7) gives solely the *E*-oxaziridine isomers, and that aldimines with smaller substituents produce a mixture of *E*- and *Z*-isomers.[30] Inspection of our results indicate that the smaller the size of the substituent on the nitrogen, the larger is the percentage of the *Z*-isomer, as expected (entries 8–12). Oxygenation of the aldimine with a small methyl substituent (entry 11) gives an even higher yield of the *Z*-isomer (57%) than the *E*-isomer (35%). Replacement of the phenyl by a bulky naphthyl group on the carbon (compare entries 11 and 12) also dramatically increases the amount of the *Z*-isomer (86%). These results are consistent with the oxidation of imines using MCPBA leading to 51% *Z*-2-methyl-3-phenyloxaziridine and 75% *Z*-2-methyl-3-1-naphthyloxaziridine.[30]

Table 2. Solvent effect on the *E*/*Z* ratio and rate of formation of 2-methyl-3-phenyloxaziridine[a]

Solvent	Conversion (%)[b]	*E*/*Z*	Conversion (%)[c]	*E*/*Z*
CH_2Cl_2	85	1	90	0.2
$CHCl_3$	93	0.8	100	0.3
CH_3CN	90	2	100	0.6
$(CH_3)_2CO$	38	4	41	1.2
t-BuOH	67	2	100	1.4
EtOH	100	10	100	4.5

[a] Reaction conditions are given in the text.
[b] Reactions were run for 15 min.
[c] Reactions were run for 30 min.

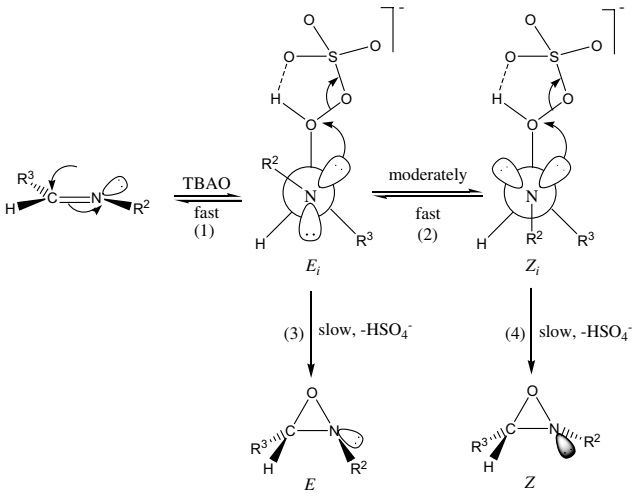
Table 3. Effect of Lewis acids and bases on the *E*/*Z* ratio in the formation of 2-methyl-3-phenyloxaziridine in CH_2Cl_2[a]

Lewis reagent	Conversion (%)[b]	*E* (%)[c]	*Z* (%)[c]	*E*/*Z*
None	90	14	70	0.2
$BF_3{\cdot}Et_2O$	100	21	62	0.3
$PhSnCl_3$	94	31	48	0.6
Quinuclidine	96	23	67	0.3
Bu_3N	95	21	67	0.3

[a] The molar ratio for aldimine–TBAO–Lewis reagent is 20:20:1.
[b] Reactions were run for 30 min.
[c] ^{1}H NMR yields were based on the starting aldimines.

To investigate the factors that might influence isomerization in this system, the effects of different solvents on the *E*/*Z* ratio, in the synthesis of 2-methyl-3-phenyloxaziridine were examined (Table 2). The overall trend in the ratio implies that solvents with a greater ability for H-bonding favor the formation of the *E*-isomer.[30] It was also observed that addition of both Lewis acids and bases can cause an increase in the *E*/*Z* ratio (Table 3). Interestingly, larger Lewis reagents seem to enhance the formation of the *E*-isomer. It is also notable that in the formation of 2-methyl-3-phenyloxaziridine the *E*/*Z* ratio decreases as oxidation of the corresponding aldimine proceeds (Table 2).

We propose a multistep mechanism for the oxidation of aldimines by TBAO in Scheme 2. The first step resembles the first step of the Baeyer–Villiger oxidation of ketones, which is a simple reversible nucleophilic attack upon the empty π^* orbital of the C=N bond, centered at the carbon site of the azomethine.[32,33] This interaction, leading to a C=N bond order reduction, should facilitate free rotation around this bond making *Z*-, *E*-isomerization possible in the second step. Since we start with *E*-aldimines,[30,34] addition of TBAO should initially give the *E*-intermediate (E_i), Scheme 2. Depending upon the nature of the aldimine, this intermediate may either collapse completely to the corresponding oxaziridine (step 3) or undergo a reversible conversion into the *Z*-intermediate (Z_i) (step 2), which in turn can produce the related *Z*-oxaziridine (step 4).



Scheme 2.

To explain the *E*-, *Z*-isomerization, two opposing factors, that is, steric interaction between R^2 and R^3, and n–π repulsion between the nitrogen lone pairs and the aromatic π clouds of either phenyl or naphthyl group in Z_i or E_i, seem to be quite important.[30] In the cases where steric repulsions are totally dominant, we can only have the E_i intermediate which exclusively gives the *E*-isomer (entries 1–7). But when n–π repulsions and steric interactions are of comparable strength, then *Z*-, *E*-isomerization may occur (entries 8–12). It is notable that the rather bulky naphthyl group on the C site (entry 12), gives the highest proportion of the *Z*-isomer reflecting a high n–π repulsion.

Another factor which apparently influences the *E*/*Z* ratio is the relative rate of ring closure (steps 3 and 4) and 'equilibration' between E_i and Z_i (step 2). However, since the nucleophilicity of the nitrogen of azomethine is low,[31,32b] and also the ring closure requires some major structural changes at both C and N sites of E_i and Z_i, with high energy barrier, it is expected to be relatively slow and presumably is the rate determining step.

Consistent with the proposed mechanism is the observed increase in the proportion of the *Z*-isomer in the course of formation of 2-methyl-3-phenyloxaziridine (vide supra).

Interestingly, H-bonding solvents and Lewis agents increase the rate of formation of oxaziridine (Tables 2 and 3). EtOH with highest ability for H-bonding among the solvents used in this study and $BF_3{\cdot}Et_2O$ as the strongest Lewis acid are the most effective ones in this regard. These results may reflect the extent of their specific interactions with the coordinated HSO_5^-, which may contribute to both O–O bond cleavage and stabilization of the leaving anionic group (HSO_4^-).

It is noteworthy that, while TBAO in combination with manganese *meso*-tetraphenylporphyrin acts as an effective and selective catalytic system for epoxidation of alkenes,[35] the same system yielded oxaziridines with low selectivity. For instance, complete oxidation of entry 1 resulted in only 46% oxaziridine and 54% of the corresponding aldehyde within 10 min.

In conclusion, this report presents a single phase, inexpensive, and very simple method for the synthesis of oxaziridines with excellent yields and selectivity under mild reaction conditions.

Acknowledgements

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