SHORT PAPER

J. Chem. Research (S), 2000, 190–192

The stereoselective synthesis and the nitrogen interconversion studies of 2-(*tert*-butoxymethyl)-1-[N′-(4-methylbenzenesulfonyl) (4-methylphenoxy) imidoyl] aziridine†

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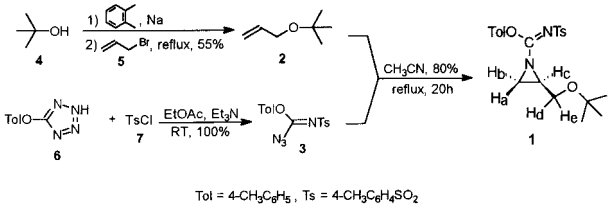
One-pot synthesis of the title compound **(1)** is achieved from *tert*-butyl allyl ether (**2)** and the N′(4-methylbenzenesulfonyl) (4-methylphenoxy) imidoyl azide **(3)** in high yield. The energy barrier of nitrogen interconversion of the title compound **(1)** was investigated by dynamic NMR. The free energies of activation ($\Delta G^{\ddagger}$) are 11.11 kcal/mol (T_c = 238 K) and 11.30 kcal/mol (T_c = 242 K) in acetone-d_6 and chloroform-d, respectively, and are attributed to nitrogen inversion of aziridine ring nitrogen.

Aziridines are very important precursors to a wide range of biologically active molecules such as amino acids, antibiotics, alkaloids, and many others.[1] The two most important aspects of this class of compounds have been the stereo-regio-selectivity of their synthesis and energy barrier of nitrogen inversion.[1–3] Both aspects have very important effects on their physical and/or chemical behaviours. Lwowski and co-workers reported a highly stereoselective synthesis of aziridines via a reaction of imidoyl nitrene with olefines.[4] Dabbagh and coworkers reported that certain imidoyl nitrenes are known to have moderate reactivity with higher selectivity.[5,6] Recently, Atkinson and co-workers have described the preparation of range of aziridines via reagent-controlled diastereoselective aziridination of alkenes using 3-acetoxyaminoquinazolinones.[7] They further reported the acid-catalysed aziridine ring-opening with retention of configuration. Furthermore, the interconversion of the isomers on nitrogen of nitrogen-containing organic compounds has been the cornerstone of research interests for the last half century.[2,8] Generally, the rapid nitrogen inversion of ordinary amines focused the attention on aziridine with its much lower inversion rate, because of strain in the three member ring.[2,9] The aziridines' nitrogen inversion has been investigated in detail.[2,3,9]

The strategy in this report is the use of imidoyl group (Tol–O–C=N–Ts)- in order to control the stability of the azide and to increase the selectivity of nitrene. In addition, we hope that the bulky imidoyl group can affect the direction of the aziridine ring opening by nucleophiles.[10] In this paper, the synthesis of aziridine **1** is reported and its structure is assigned on the basis of IR, ^{13}C-NMR, ^{1}H-NMR (500 MHz), elemental analysis and mass spectra data. The effect of the *tert*-butoxymethyl group, or bulky groups on imidoyl and/or the extended conjugation of aziridine nitrogen lone pair with the tosyl group on the rate of interconversion of imidoyl (imine) and/or the aziridine nitrogen is sought.

The *tert*-butyl ether **2** was prepared from *tert*-butyl alcohol **4** and allyl bromide **5** using the procedure described by Kwart[11], Scheme 1. The *tert*-butyl group was selected because (a) most aromatic rings react with the nitrenes;[5,6] (b) the complexity of the ^{1}H-NMR is reduced; (c) the steric hindrance of the bulky groups may be used to control the regio- and/or stereoselectivity[1]; and (d) deprotection of the *tert*-butyl group would take place under mild conditions.[12]



Scheme 1

The N-(*p*-toluenesulfonyl) (4-methylphenoxy) imidoyl azide **3** was prepared from 5-(4-methylphenoxy) tetrazole **6** and *p*-toluenesulfonyl chloride **7** by the previously described general method[4–6] (in anhydrous THF and 1.0 equivalent Et_3N) which was modified to give quantitative yields[13] in EtOAc and 1.3 equivalent Et_3N, Scheme 1. The decomposition of azide **3** was tested in the presence of ether **2** under different conditions. The highest yield and the minimum by-products were achieved in a 10:1 molar ratio of ether **2** and azide **3** in acetonitrile (0.20 molar azide **3** in acetonitrile). The polymerization of **2** and/or **3** resulted when other reaction conditions prevailed.

The ^{1}H-NMR (500 MHz) spectrum of **1** showed fairly broad peaks at δ (ppm) 2.636, 2.753, 3.06, 3.384, 3.675 at 300 K, but these peaks were clearly split at 340 K (in $CDC1_3$), Fig. 1. Since in aziridines J_{cis} is always larger than J_{trans} and $J_{gem} \leq$ 1:[14] (J_{ab} = 0 Hz, J_{bc} = 6.0 Hz, J_{ac} = 4.07 Hz, $J_{de} = J_{ed}$ = 10.62 Hz) thus chemical shifts are easy to identify, Fig. 1.

The mass spectrum of **1** did not display a molecular ion. Initial fragmentations involve the loss of the side chains, Scheme 2. The most intense peak corresponds to Tol-group. A typical major fragmentation pattern by Chapman rearrangement[15] is shown in Scheme 2.

The results of temperature dependence of ^{1}H-NMR (500 MHz) of the nitrogen inversion of aziridine **1** are tabulated in Table 1. ^{1}H-NMR (500 MHz) spectrum of **1** in $CDCl_3$ at ambient temperature displays a sharp singlet of *tert*-butyl group (δ ppm. 1.16, 9H). The singlet was broadened (coalescence temperature at 242 K) and then split into two well-resolved singlets at δ = 1.20 and δ = 0.91 (Δν = 144.11 Hz, a mixture of two diastereomers with almost equal populations 1.00 and 1.24, respectively at 213 K. The coalescence temperature for the inversion of **1** in acetone is 238 K. It should be realized that all of the ^{1}H-NMR signals of **1** would split into two sets of signals. However, the peaks corresponding to *tert*-butyl group were utilized in our calculation due to large Δν and low complexity of the region.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

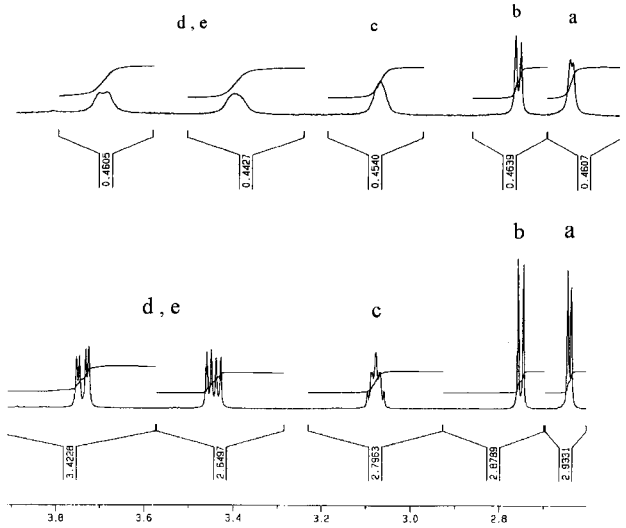


Fig. 1 ^{1}H-NMR (500 MHz) spectrum of **1** in $CDC1_3$ at 300 K (upper), at 340 K (lower).

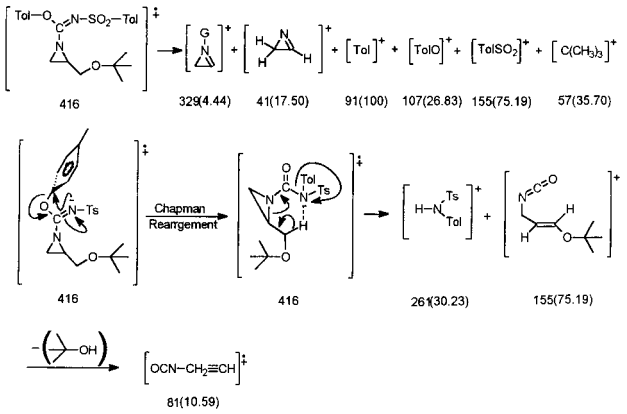
The rate constant, *k*, of the aziridine nitrogen inversion at coalescence temperature (T_c) for **1** was calculated from Gutowsky-Holm equation (1). Assuming the transmission coefficient, κ, to be unity, the free energy of activation ($\Delta G^{\ddagger}$) was calculated from Eyring equations (2).[2,16] Equation (1) is strictly valid for two states having equal populations, but the errors introduced by these deviations are small.[16,17]

$$k_c = \pi\Delta\nu/2^{-1.2} \qquad (1)$$

$$\Delta G^{\ddagger} = RT_c\,[InT_c - Ink_c + 23.76] \qquad (2)$$

Anet and co-workers have reported the effect of substitution on the rate of nitrogen inversion.[3] Furthermore they have demonstrated that in 1-acylaziridines nitrogen inversion is the prevalent rate process and not restricted rotation similar to what occurs with simple amides. In other words, the nitrogen atom will be strongly pyramidal. But conjugatively electron-withdrawing substituents stabilize the planar transition state and lower the energy barrier.

Of equal interest to the interconversion of nitrogen in imines is the *E/Z* isomerization of N-substituted-imines.[16–18] It is obvious from the literature that *E/Z* isomerization barrier will be much higher for most imines.[16–18] The extra conjugation of the aziridine nitrogen lone-pair with the oxygen of the tosyl group of the imidoyl was expected to increase the rotation about the imine C–N (more single bond in character) which in turn would lower the interconversion barrier. This was not, however, observed (the observed energy barrier was similar to conjugated imines). In other words, the mechanism for the interconversion of imine must be primarily through the inversion and not the rotation about the imine C–N. Above 403 K, in nitrobenzene there is a competition between the imine interconversion and the aziridine rearrangement.[19] The detailed investigations of the imine interconversion and the characterization of the new compound **1X** are now underway.



Scheme 2

Thus, we attribute the observed ^{1}H DNMR effect to nitrogen inversion of aziridine ring nitrogen.

Experimental

General: ^{1}H-NMR spectra were recorded by VARIAN EM390 (90 MHz), JEOL EX-90A (90 MHz) and BRUKER AVANACE DRX500 (500 MHz). ^{13}C-NMR spectra were recorded by BRUKER AVANACE DRX500 (500 MHz). The IR spectra were obtained on a SHIMADZU ZU435. Mass spectra were analysed by FISON TRIO 1000 instruments (70 e^v). Melting points were taken by the GALLENKAMP melting point apparatus and are uncorrected. Elemental analysis were performed using Heraeus CHN–O Rapid analyser by Tarbiat Modaress University Science Research Center, Tehran, Iran. All starting materials and solvents were purified with the proper purification techniques before use.[20] Variable temperature ^{1}H-NMR spectra were obtained on BRUKER AVANACE DRX500 (500 MHz) and JEOL EX-90A (90 MHz) spectrometer and temperature was measured at the probe (±0.1 °C). Samples were allowed to equilibrate for 10 min at each temperature before recording the spectra.

tert-*Butyl allyl ether* **(2)**. This compound was prepared from *tert*-butyl alcohol and allyl bromide by a procedure described by Kwart and coworkers.[11] Bp = 99–100°C, ^{1}H-NMR (90 MHz, CCl_4) δ ppm 1.20(s, 9H), 3.85 (d, 2H, *J* = 6Hz), 5–5.30 (m, 2H), 5.6–6.1 (m, 1H), IR (KBr); 2980 (s), 2900 (w), 2860 (w), 1624 (w), 1460 (w), 1360 (m), 1200 (m), 1120 (w), 1065 (m), 1022 (w), 985 (m) cm^{-1}. Mass spectrum: *m/z* (%) = 99 (13.64, $CH_2CHCH_2OC(CH_3)_2$, 57 (59.21, CH_2CHCH_2O, $C(CH_3)_3$), 41 (100, CH_2CHCH_2).

N′-(4-Methylbenzenesulfonyl) (4-methylphenoxy) imidoyl azide **(3)**: Azide **3** was prepared by the method previously reported from the reaction of 5-(4-methylphenoxy)tetrazole **6** and tosyl chloride **7**[4–6] (in anhydrous THF and 1.0 equivalent Et_3N) which was modified to give quantitative yields[13] in EtOAc and 1.3 equivalent Et_3N, mp 92 °C (dec.), ^{1}H-NMR (90 MHz, $CDCl_3$) δ ppm 2.36 (s, 3H), 2.42 (s, 3H), 6.64 (d, *J* = 9Hz, 2H), 7.15 (d, *J* = 9Hz, 2H), 7.25 (d, *J* = 7.8Hz, 2H), 7.72 (d, *J* = 7.8Hz, 2H). IR (KBr); 3050 (w), 3020 (w), 2900 (w), 2850 (w), 2175 (s), 2130 (s), 1540–1630 (vs), 1500 (s), 1330 (s), 1290 (s), 1150 (s), 1090 (s), 815 (s), 670 (m) cm^{-1}. Anal. calcd. for $C_{15}H_{14}N_4O_3S$; C, 54.53; H, 4.27; N, 16.96. Found: C, 53.10; H 4.20; N, 16.60%.

2-(tert-Butoxymethyl)-1-[N′-(4-methylbenzenesulfonyl) (4-methylphenoxy) imidoyl] aziridine **(1)**. A solution of azide **3** (6.61g, 20 mmol) and ether **2** (22.84g, 200mmol) was refluxed in 100 ml of acetonitrile under nitrogen atmosphere for 20 h. The excess solvent and **2** was recovered by distillation under reduced pressure. The residue was crystallized in ethyl acetate and cyclohexane and was allowed to stand over night. A brown precipitate was removed and the separated

Table 1 ^{1}H-NMR data for imidoyl aziridine **1**

Solvent	δ (ppm)	Isomers ratio	(Δν (Hz)	T_c, °C (K)	*k* (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
$CDCl_3$	1.20, 0.91	1:1.24[a]	144.11[a]	–31 (242)	320	11.30
Acetone-d_6	1.15,0.87	1:0.44[b]	148.76[b]	–35 (238)	308	11.11

[a]at 213 K; *i.e.* the lowest temperature reached.[b] At 193 K; *i.e.* the lowest temperature reached.

solution was added dropwise to cyclohexane until the solution become turbid and was allowed to stand overnight to produce 6.60 g of white crystals **1** (80% yield), mp = 110–115 °C. Recrystallization from chloroform and petroleum ether gave pure **1**, mp = 115–116 °C. IR (KBr); 2980 (s), 2900 (s), 2860 (m), 1640–1540 (vs), 1500 (m), 1450 (m), 1410 (s), 1350 (s), 1280 (s), 1220 (s), 1200 (s), 1150 (s), 1080 (s), 1100 (s), 1060 (m), 1020 (m), 980 (s), 910 (m), 880 (m), 820 (s), 750 (w), 730 (w), 710 (m), 670–700 (s) cm^{-1}. ^{1}H-NMR (90 MHz, $CDC1_3$) δ ppm 1.15 (s, 9H), 2.30 (s, 3H), 2.37 (s, 3H), 2.60–3.90 (m, 5H), 6.64 (d, *J* = 9Hz, 2H), 7.15, (d, *J* = 9Hz, 2H), 7.25 (d, *J* = 7.8Hz, 2H), 7.72, d, *J* = 7.8Hz, 2H). ^{1}H-NMR (500 MHz, $CDC1_3$, 300°K) δ ppm 1.160 (s, 9H), 2.325 (s, 3H), 2.378 (s, 3H), 2.636 (d, *J* = 3.41Hz, 2H), 2.753 (d, *J* = 5.93Hz, 1H), 3.0596 (br, 1H), 3.3840 (br, 1H), 3.675 (d, *J* = 7.92 Hz, 1H), 6.901 (d, *J* = 8.43 Hz, 2H), 7.107 (d, *J* = 8.4Hz, 2H), 7.196 (d, *J* = 8.1Hz, 2H), 7.708 (d, *J* = 8.12Hz, 2H). ^{1}H-NMR (500 MHz, $CDCl_3$, 340 K) δ ppm 1.180 (s, 9H), 2.327 (s, 3H), 2.377 (s, 3H), 2.642 (d, *J* = 4.07Hz, 1H), 2.752 (d, *J* = 6.0Hz, 1H), 3.060–3.097 (m, 1H), 3.443 (dd, *J* = 5.11, J = 10.61, 1H), 3.738 (dd, *J* = 3.325, *J* = 10.62, 1H), 6.921 (d, *J* = 8.42 Hz, 2H), 7.100 (d, *J* = 8.295Hz, 2H), 7.182 (d, *J* = 8.17Hz, 2H), 7.704 (d, *J* = 8.25HGz, 2H). ^{13}C-NMR (500 MHz, $CDCl_3$, 300 K) δ ppm 21.232, 21.869, 27.843, 32.798, 42.214, 60.161, 73.946, 121.372, 127.063, 129.428, 130.229, 136.257, 139.803, 142.972, 149.940, 163.503. Mass spectrum: *m/z* (%) = 329 (4.44, M^+ – $CH_2OC(CH_3)_3$), 262 (12.37, Tol–OTs, $TolNH_2Ts$), 261 (30.23 M^+ – Ts, Tol–NHTs), 156 (6.50, Tol–SO_2H), 155 (75.19, $OCNCH_2HC{=}CHOC(CH_3)_3$, $TolSO_2$), 108 (36.92, Tol–OH, Tol–NH_3), 107 (26.83, Tol–O, Tol–NH_2), 106 (12.84, Tol–NH), 91 (100, Tol), 81 (10.59, $OCNCH_2C{=}CH$), 77 (12.30, C_6H_5), 65 (15.58, C_5H_5), 57 (35.70, $C(CH_3)_3$), 41 (17.50). Analysis Calcd. For $C_{22}H_{28}N_2O_4S$: C, 63.43; H, 6.78; N, 6.73; Found; C, 63.46; H, 6.85, N, 6.74%.

This research was supported by the Isfahan University of Technology Graduate Council.

Received 15 February 2000, accepted 18 February 2000
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