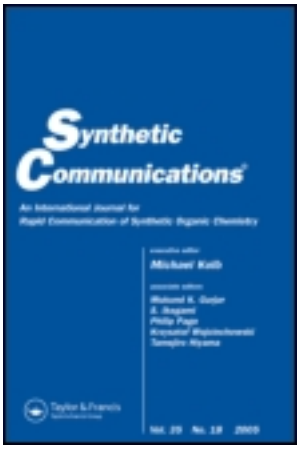

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Superoxide-Mediated Synthesis of N-Aminoaziridines from N-Aminoheterocycles and Olefins

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Superoxide-Mediated Synthesis of *N*-Aminoaziridines from *N*-Aminoheterocycles and Olefins

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Abstract: Oxidation of 3-amino-2-methyl-4(3H)-quinazolone and *N*-aminophthalimide by superoxide ion generated in situ in the presence of olefinic substrates gives rise to the formation of *N*-aminoaziridine derivatives.

Keywords: *N*-Aminoaziridines, 18-crown-6 ether, olefins, superoxide

Aziridines have attracted considerable attention in recent years because of their easy conversion into high polymers, their use as aminoalkylating agents, and their powerful physiological actions.[1–3] There exists a family of heterocyclic compounds, aminated on nitrogen, whose oxidation in the presence of alkenes gives *N*-aminoaziridines.[4] The reactive intermediates in these oxidations have been assumed to be aminonitrenes.[4] The *N*-aminoaziridines are of high synthetic importance because they could provide a new route to α-hydrazino acids, which are natural constituents of peptide antibiotics.[5–7] They also act as inhibitors of enzymes that metabolize the corresponding α-amino acids.[8,9]

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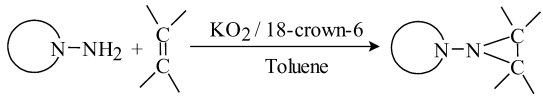
Certain aminonitrenes are capable of adding to olefins to yield *N*-amino-aziridines. However, there exist only a few useful syntheses of *N*-amino-aziridines. The present study has been undertaken with an objective to assess the role of superoxide ion[10] and to develop a new synthetic route to *N*-aminoaziridines (Scheme 1).

During the present course of reaction, superoxide ion was generated in situ by the phase-transfer reaction of KO_2 with 18-crown-6 ether in sodium-dried toluene and allowed to react with the substrates, 3-amino-2-methyl-4(3H)-quinazolone (**1**) and *N*-aminophthalimide (**2**), in the presence of olefins. As a result, the substrate **1** reacted with cyclohexene, styrene, and indene to afford 7-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-7-azabicyclo [4.1.0] heptane (**1a**); 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-phenyl-aziridine (**1b**); and 2,3-benzo-6-(3,4-dihydro-2-methyl-4-oxoquinazoline-3-yl)-6-azabicyclo [3.1.0] hexane (**1c**), respectively, whereas the substrate **2** reacted with cyclohexene, styrene, 2,2,4-trimethylpent-2-ene, and mesityl oxide to provide 7-phthalimido-7-azabicyclo [4.1.0] heptane (**2a**); 2-phenyl-1-phthalimido-aziridine (**2b**); 3-t-butyl-2,2-dimethyl-1-phthalimidoaziridine (**2c**); and 3-acetyl-2,2-dimethyl-1-phthalimidoaziridine (**2d**), respectively, albeit in low yields (Table 1).

The isolated yields reported in Table 1 were achieved by the use of a 4.0-fold molar excess of KO_2 and a 2.0-fold molar excess of 18-crown-6 over the substrate **1**/**2** in toluene. The optimum molar ratio of *N*-amino compound **1**/**2** and olefin was 1 : 5. Use of larger amounts of olefin did not improve the yield, but use of smaller amounts caused a decrease in the yield. Usually the reaction was conducted for 6–10 h at room temperature under a dry nitrogen atmosphere. The mixture was then quenched and worked up to furnish the product (**1a–c** and **2a–d**). Each reaction was monitored on TLC to check the completion of the reaction. The products were identified based on their physical and spectroscopic data.

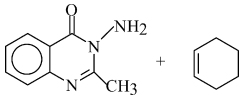
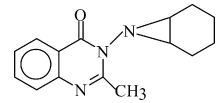
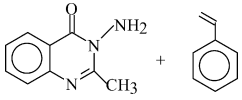
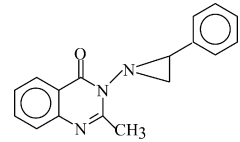
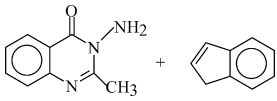
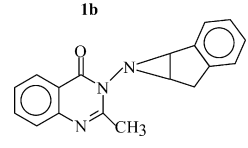
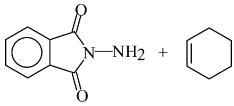
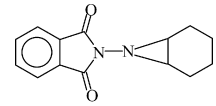
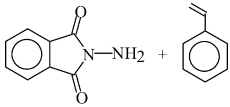
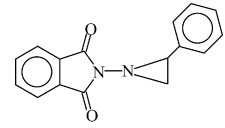
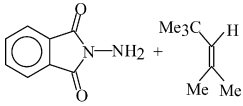
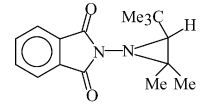
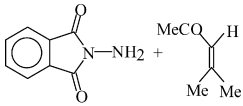
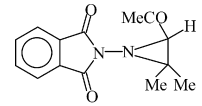
EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL FT-NMR spectrometer FX-90Q and the chemical shifts are expressed as δ/ppm, using TMS as internal reference.



Scheme 1.

Table 1. Reaction of KO_2 with *N*-amino compounds **1**/**2** in the presence of olefins

Reactant	Product	Yields[a] (%)
 **1**	 **1a**	43
 **1**	 **1b**	48
 **1**	 **1c**	37
 **2**	 **2a**	32
 **2**	 **2b**	39
 **2**	 **2c**	55
 **2**	 **2d**	68

[a]Isolated mass yields are based on *N*-amino compounds **1**/**2**.

Potassium superoxide and 18-crown-6 were procured from E. Merck and were used as received. Dry DMF (Aldrich) was stored over molecular sieves (4°A) prior to use. The substrate 3-amino-2-methyl-4(3H)-quinazolone (**1**) was prepared in two steps using literature procedures.[11,12] *N*-Aminophthalimide (**2**) was obtained by the reaction of phthalimide and 96% hydrazine hydrate in ethyl alcohol.[13] Cyclohexene was prepared from cyclohexanone using an established method.[14]

Reaction of Superoxide Ion Generated in situ with *N*-Amino Compounds (1/2) in the Presence of Olefins: General Procedure

Sodium-dried toluene (80 ml) was placed into a three-necked, round-bottom flask fitted with a dropping funnel, an inlet nitrogen bubbler, a magnetic stirrer, and a Liebig condenser guarded with a calcium chloride tube. Potassium superoxide (0.68 g, 0.0096 mol) and 18-crown-6 ether (1.27 g, 0.0048 mol) were weighed under nitrogen atmosphere using an atmosbag and were transferred into the flask. The olefin (0.012 mol) and *N*-amino compound **1/2** (0.0024 mol) were added to the stirred reaction mixture. Nitrogen was bubbled continuously, and the reaction mixture was stirred magnetically for 6–10 h at room temperature until the starting material was consumed as indicated by TLC. The solvent was removed with a rotary evaporator, and the residue was treated with dichloromethane. It was filtered, and the filtrate was dried over anhydrous sodium sulphate. Evaporation of the solvent furnished a residue, which was recrystallized or passed through a column to get the pure aziridine derivative.

Physical and Spectral Data

1a: mp 127–129°C. CHN analysis (%): $C_{15}H_{17}N_3O$(255) calcd. C, 70.59; H, 6.66; N, 16.47. Found C, 70.55; H, 6.61; N, 16.45. IR (KBr, cm^{-1}): 778, 1595, and 1668; ^{1}H NMR (90 MHz, $CDCl_3$): 1.40 (m, 4H, CH_2); 2.18 (m, 4H, CH_2); 2.60 (m, 5H, $CH_3 + CH$); 7.50 (m, 3H, ArH); 8.10 (d, 1H, ArH).

1b: mp 123°C. CHN analysis (%): $C_{17}H_{15}N_3O$(277) calcd. C, 73.64; H, 5.41; N, 15.16. Found C, 73.60; H, 5.41; N, 15.13. IR (KBr, cm^{-1}): 778, 1592, and 1668; ^{1}H NMR (90 MHz, $CDCl_3$): 2.65 (s, 3H, CH_3); 2.88 (dd, 1H); 3.10 (dd, 1H); 3.70 (dd, 1H); 7.45 (s, 5H, ArH); 7.6 (m, 3H, ArH); 8.12 (m, 1H, ArH).

1c: mp 182°C. CHN analysis (%): $C_{18}H_{15}N_3O$(289) calcd. C, 74.74; H, 5.19; N, 15.53. Found C, 74.48; H, 5.24; N, 15.39. IR (KBr, cm^{-1}): 781, 1698, and 1668; ^{1}H-NMR (90 MHz, $CDCl_3$): 2.72 (s, 3H, CH_3); 3.48 (d, 2H, CH_2); 3.74 (m, 1H); 4.24 (d, 1H); 7.36 (m, 4H, ArH); 7.64 (m, 3H, ArH); 8.18 (m, 1H, ArH).

2a: mp 136–137°C. CHN analysis (%): $C_{14}H_{14}N_2O_2$ (242) calcd. C, 69.42; H, 5.78; N, 11.57. Found C, 69.40; H, 5.73; N, 11.54. IR (KBr, cm^{-1}): 710, 720, 890, 992, 1155, 1710 (br), 1765, and 1780; ^{1}H NMR (90 MHz, $CDCl_3$): 1.35 (m, 4H, CH_2); 2.10 (m, 4H, CH_2); 2.72 (m, 2H); 7.7 (m, 4H, ArH).

2b: mp 150°C. CHN analysis (%): $C_{16}H_{12}N_2O_2$ (264) calcd. C, 72.72; H, 4.54; N, 10.60. Found C, 72.70; H, 4.50; N, 10.55. IR (KBr, cm^{-1}): 700, 748, 885, 980, 1150, 1712 (br), 1765, and 1780; ^{1}H NMR (90 MHz, $CDCl_3$): 2.75 (dd, 1H); 2.85 (dd, 1H); 3.5–3.7 (dd, 1H); 7.45 (m, 5H, ArH); 7.70 (m, 4H, ArH).

2c: mp 75°C. CHN analysis (%): $C_{16}H_{20}N_2O$ (272) Calcd. C, 70.58; H, 7.35; N, 10.29. Found C, 70.46; H, 7.41; N, 10.35. IR (KBr, cm^{-1}): 700, 778, 888, 980, 1076, 1150, 1725 (br), and 1770; ^1H NMR (90 MHz, $CDCl_3$): 1.18 (s, 9H, 3 × CH_3); 1.28 (s, 3H, CH_3); 1.60 (s, 3H, CH_3); 2.78 (s, 1H); 7.76 (m, 4H, ArH).

2d: mp 68°C. CHN analysis (%): $C_{14}H_{14}N_2O_3$ (258) calcd. C, 65.12; H, 5.43; N, 10.85. Found C, 65.20; H, 5.36; N, 10.88. IR (KBr, cm^{-1}): 708, 788, 880, 980, 1070, 1150, 1712 (br), and 1779; ^1H NMR (90 MHz, CCl_4): 1.40 (s, 6H, 2 × CH_3); 2.28 (s, 3H, CH_3CO); 3.10 (1H, CH); 7.78 (m, 4H, ArH).

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