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A Novel Approach to Substituted 2*H*-Azirines

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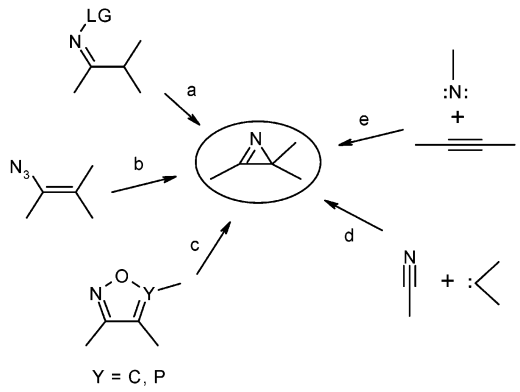
Abstract: 2-(Benzotriazol-1-yl)-2*H*-azirines **4a**−**c**, obtained by treatment of oximes **2a**−**c** with tosyl chloride and aqueous KOH, were reacted with benzylmagnesium bromide or 4-methylbenzylmagnesium bromide in the presence of zinc chloride to give 2-benzyl-2*H*-azirines **5a**−**f**. Potassium phthalimide and sodium salt of benzenethiol converted 2-(benzotriazol-1-yl)-2*H*-azirines **4a**−**c** into novel 2*H*-azirines **6a**−**c** and **7** in good yields.

2*H*-Azirines are important for their versatile chemical and biological behavior.[1] 2*H*-Azirines are naturally occurring antibiotics.[2] Substituted and functionalized azirines are versatile precursors for the preparation of functionalized aziridines.[1a,3] Azirines with phosphorus substituents regulate many important biological functions.[4]

2*H*-Azirines were first reported by Neber et al.[5] Existing synthetic protocols can be categorized[6] as the following: (i) intramolecular reactions of *N*-functionalized imines, vinyl azides, isoxazoles, and oxazaphospholes (routes a, b, and c of Scheme 1) and (ii) intermolecular reactions between nitriles and carbenes or nitrenes and acetylenes (routes d and e of Scheme 1). The Neber reaction (route a), the most extensively used, is facilitated by electron-withdrawing groups at the α-position to *N*-functionalized imines. Asymmetric syntheses of 2*H*-azirines containing a carboxylic ester group[3c] or a phosphorus substituent[3d,7] by this methodology have been reported.

SCHEME 1



Recently, 2-halo-2*H*-azirines[8] have been used for halide displacement by reacting with nucleophiles. However, reported successful halide displacements of 2-halo-2*H*-azirines are limited to some *N*-nucleophiles, specifically potassium phthalimide. A reaction with aniline gave the expected substitution product in 11% yield.

Benzotriazole can be used in place of a halogen as a leaving group in many reactions;[9] indeed, the combination of a 2*H*-azirine ring and a benzotriazole group can enhance 2*H*-azirine chemistry as is now demonstrated.

Synthesis of 2-(Benzotriazol-1-yl)-2*H*-azirines 4a−c. Starting *N*-acylmethylbenzotriazoles **1a**−**c** were obtained either by reaction of 1-(trimethylsilylmethyl)-benzotriazole and acyl chlorides[10] or by treatment of benzotriazole with 2-chloroacetophenone in toluene under reflux.[11] Compounds **1a**−**c** with hydroxylamine hydrochloride provided oximes **2a**−**c** (≥90%) as single isomers, which with tosyl chloride and aqueous KOH in a mixture of chloroform and ethyl ether at 0 °C in the presence of tetra-*n*-butylammonium hydrogen sulfate (as a phase-transfer catalyst) provided 2-(benzotriazol-1-yl)-2*H*-azirines **4a**−**c** (Scheme 2, Table 1). The concentration and amount of aqueous KOH and the reaction time significantly affected product yields. Optimal conditions were found to be 10 equiv of 10% aqueous KOH and 5−6 h of reaction time at 0 °C; this avoided any isolation of oxime tosylates **3**. NMR spectra and elementary analysis supported the structures of **4a**−**c** (Table 1). The ^{13}C NMR spectra of **4a**−**c** displayed the expected signals charac-

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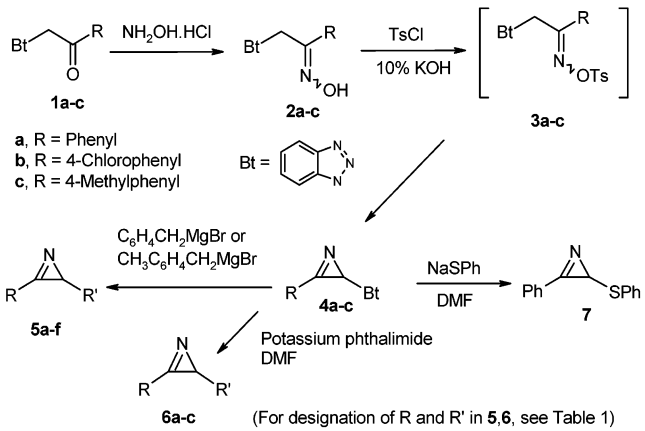
SCHEME 2



teristic of benzotriazolyl at δ ca. 146 and 110, and of the sp^3 carbon (C-2) and the sp^2 carbon (C-3) of the 2*H*-azirine ring at δ ca. 42 and 164, respectively.

Substitution Reactions of 2-(Benzotriazol-1-yl)-2*H*-azirines. Most documented reactions of 2*H*-azirines with nucleophiles involve nucleophilic addition to the imine bond.[1,12] No previous nucleophilic replacement of a 2-substituent of 2*H*-azirines with a *C*-nucleophile has been documented. Reported successful halide displacements of 2-halo-2*H*-azirines with nucleophiles have all involved an additional electron-withdrawing group, e.g. carboxylate, at the 2-position.[8]

We studied the reactivity of 2-(benzotriazol-1-yl)-2*H*-azirines using organometallic reagents, phthalimide anion, and benzenethiol anion as nucleophiles. Treatment of 2-(benzotriazol-1-yl)-2*H*-azirines **4a**−**c** with benzylmagnesium chloride or 4-methylbenzylmagnesium bromide in the presence of zinc chloride gave the desired products **5a**−**f** in moderate to good yields (Scheme 2, Table 1). Except for **5a**−**f**, no other products were observed in each case. Compared with 2*H*-azirines **4a**−**c**, the ^{13}C NMR spectra of **5a**−**f** displayed the disappearance of benzotriazole moiety signals, and the appearance of signals characteristic of benzyl at δ ca. 33.2−33.6. The spectra data of **5a** are also consistent with those reported.[13] In the presence of zinc chloride, unfortunately, reactions of **4a**−**c** with other Grignard reagents, both aryl (e.g. phenyl, *p*-chlorophenyl, *p*-tolyl) and alkyl (e.g. phenylethyl, pentyl), failed. In some cases, the reactions did not proceed but allowed for the recovery of the starting 2-(benzotriazol-1-yl)-2*H*-azirines, while in other cases, the disappearance of the starting 2-(benzotriazol-1-yl)-2*H*-azirines resulted in a complicated mixture.

Following a procedure previously used for substitution of 2-halo-2*H*-azirines,[8b] treatment of 2-(benzotriazol-1-yl)-2*H*-azirines **4a**−**c** with potassium phthalimide at room temperature in DMF led to the synthesis of novel 2*H*-azirine derivatives **6a**−**c** in good yield (Scheme 2, Table 1). Reaction with the sodium salt of benzenethiol was less successful: **4a** gave an oil that consisted largely of **7**, a compound that decomposed at 20 °C and could not be completely purified.

In conclusion, we have developed a methodology for the synthesis of 2-(benzotriazol-1-yl)-2*H*-azirines under mild conditions, and have disclosed the first example of nucleophilic substitution reactions of 2*H*-azirines with organometallic reagents. Novel 2*H*-azirine derivatives were thus obtained.

Experimental Section

General. Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ (unless stated otherwise) with tetramethylsilane as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C (75 MHz). All anhydrous solvents were distilled from sodium under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon or nitrogen atmosphere.

General Procedure for the Oximes 2a−c. To a solution of hydroxylamine hydrochloride (30 mmol) in water (50 mL) was added a solution of benzotriazolylmethyl ketone **1** (15 mmol) in ethanol (50 mL) followed by dropwise addition of 10% NaOH (30 mmol) solution at room temperature. After addition, the yellow or off-white colored mixture was stirred under reflux overnight. Upon cooling to room temperature, white crystals of the product formed and were collected by filtration with no further purification necessary.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenyl-1-ethanone-oxime (2a). White prisms (93%), mp 234−236 °C (lit.[14] mp 223−225 °C, 56%); ^1H NMR (DMSO-d_6) 12.2 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.73−7.70 (m, 2H), 7.55 (dd, J = 7.2, 7.9 Hz, 1H), 7.40−7.32 (m, 4H), 6.09 (s, 2H); ^{13}C NMR (DMSO-d_6) 151.2, 145.3, 134.4, 133.3, 129.6, 128.8, 127.9, 126.7, 124.5, 119.6, 110.9, 41.5.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-chlorophenyl)-1-ethanoneoxime (2b). White needles (91%), mp 226−227 °C; ^1H NMR (DMSO-d_6) 12.33 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 7.8, 7.0 Hz, 1H), 7.43−7.37 (m, 3H), 6.10 (s, 2H); ^{13}C NMR (DMSO-d_6) 149.9, 144.8, 134.0, 132.8, 128.4, 128.0, 127.4, 124.0, 119.1, 110.4, 41.0. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.31; N, 21.04. Found: C, 67.43; H, 5.47; N, 21.02.

2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)-1-ethanoneoxime (2c). White microcrystals (92%), mp 185−188 °C; ^1H NMR (DMSO-d_6) 12.11 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.62−7.53 (m, 3H), 7.37 (dd, J = 8.0, 7.3 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.07 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6) 150.6, 144.9, 138.8, 132.8, 131.1, 128.9, 127.4, 126.2, 124.0, 119.1, 110.4, 41.0, 20.7. Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.47; H, 3.92; N, 19.49.

General Procedure for 2-(Benzotriazol-1-yl)-2*H*-azirines 4a−c. To a solution of oxime **2** (20 mmol) in a mixture of ethyl ether (150 mL) and chloroform (50 mL) was added dropwise aqueous KOH (11.2 g of KOH dissolved in 50 mL of water) at 0 °C. After the addition of the base solution, the mixture was stirred vigorously at this temperature for 30 min, and then a catalytic amount of Bu_4NHSO_4 was added. A solution of *p*-toluenesulfonyl chloride (TsCl) in Et_2O (50 mL) was added dropwise at 0 °C. After this addition, the final mixture was stirred at 0−5 °C for 6 h until the solid reactants disappeared. The reaction mixture was transferred into a separatory funnel and extracted with ethyl ether. The combined organic layer was washed with water and dried over $MgSO_4$. The residue on removal of solvents was purified by column (hexanes−ethyl acetate) to give the desired products **4a**−**c**.

1-(3-Phenyl-2*H*-aziren-2-yl)-1*H*-1,2,3-benzotriazole (4a). White needles (40%), mp 99−100 °C; ^1H NMR δ 8.15 (d, J = 6.7

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TABLE 1. 2*H*-Azirines 4 and Their Derivatives 5, 6, and 7

entry	R	R′	yield (%)	mp (°C)	^{13}C NMR	
4a	Ph		60	99−100	42.6 (C-2)	164.6 (C-3)
4b	4-ClC_6H_4		58	158−160	42.4 (C-2)	163.8 (C-3)
4c	4-MeC_6H_4		66	101−102	42.6 (C-2)	164.1 (C-3)
5a	Ph	$C_6H_5CH_2$	66	oil	40.1 (C-2)	171.6 (C-3)
5b	Ph	4-Me$C_6H_4CH_2$	53	oil	39.7 (C-2)	171.3 (C-3)
5c	4-ClC_6H_4	$C_6H_5CH_2$	44	oil	40.0 (C-2)	170.9 (C-3)
5d	4-ClC_6H_4	4-Me$C_6H_4CH_2$	66	93−95	39.6 (C-2)	171.0 (C-3)
5e	4-MeC_6H_4	$C_6H_5CH_2$	71	oil	40.2 (C-2)	171.1 (C-3)
5f	4-MeC_6H_4	4-Me$C_6H_4CH_2$	50	oil	39.9 (C-2)	171.3 (C-3)
6a	Ph	phthalimido	71	139−140	35.6 (C-2)	165.3 (C-3)
6b	4-ClC_6H_4	phthalimido	57	182.5−184.5	35.7 (C-2)	164.7 (C-3)
6c	4-MeC_6H_4	phthalimido	79	145−146	35.5 (C-2)	164.8 (C-3)
7	Ph	PhS	60	oil	37.6 (C-2)	166.4 (C-3)

Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.73−7.62 (m, 4H), 7.50 (t, J = 7.6 Hz, 1H), 7.37 (dd, J = 7.9, 7.3 Hz, 1H), 5.19 (s, 1H); ^{13}C NMR δ 164.6, 146.1, 134.4, 132.8, 130.5, 129.5, 127.8, 124.2, 123.0, 120.1, 109.8, 42.7. Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.81; H, 4.39; N, 23.92.

1-[3-(4-Chlorophenyl)-2*H*-aziren-2-yl]-1*H*-1,2,3-benzotriazole (4b). Yellow prism (58%), mp 158−160 °C; ^{1}H NMR δ 8.10 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.39 (dd, J = 8.0, 7.3 Hz, 1H), 5.17 (s, 1H); ^{13}C NMR δ 163.8, 146.2, 140.9, 132.9, 131.7, 130.0, 127.9, 124.3, 121.6, 120.2, 109.7, 42.4. Anal. Calcd for $C_{14}H_9ClN_4$: C, 62.58; H, 3.38; N, 20.85. Found: C, 62.81; H, 3.34; N, 20.84.

1-[3-(4-Methylphenyl)-2*H*-aziren-2-yl]-1*H*-1,2,3-benzotriazole (4c). Yellow microcrystals (66%), mp 101−102 °C; ^{1}H NMR δ 8.07−8.02 (m, 3H), 7.69 (d, J = 8.2 Hz, 1H), 7.50−7.44 (m, 3H), 7.37 (dd, J = 7.8, 7.4 Hz, 1H), 5.18 (s, 1H), 2.5 (s, 3H); ^{13}C NMR δ 164.1, 146.1, 145.6, 132.8, 130.6, 130.2, 127.7, 124.2, 120.3, 120.1, 109.9, 42.6, 22.0. Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.63; H, 4.96; N, 24.46.

General Procedure for 2*H*-Azirines 5a−f. Under N_2, activated Mg powder (2 mmol) was added into a dried two-necked flask equipped with a condenser and magnetic stirrer. Then 5 mL of Et_2O was added. With the starting of the stirrer, 3−4 drops of a solution of the bromide (2 mmol) in 5 mL of Et_2O was added by syringe, and several minutes later, the remaining bromide solution was added dropwise. The mixture was heated and refluxed slowly for 1h. Upon cooling to −18 °C (ice−salt bath), $ZnCl_2$ solution (1.0 M, 2.0 mL) was added, and 30−40 min later, a solution of starting 2*H*-azirine **4** (0.5 mmol) in 5 mL of toluene was added at this temperature. After these additions, the final mixture was stirred at −18 °C to room temperature overnight (around 24 h). TLC showed almost no starting material. The reaction was quenched with water, and the reaction mixture was diluted with Et_2O, washed with water, and dried over $MgSO_4$. The residue on removal of solvents was purified by column (hexanes−ethyl acetate) to give the desired products **5a**−**f**.

2-Benzyl-3-phenyl-2*H*-azirine (5a). Oil (70%);[13] ^{1}H NMR δ 7.77−7.75 (m, 2H), 7.55−7.47 (m, 3H), 7.31−7.21 (m, 5H), 3.06 (dd, J = 14.6, 5.1, 1H), 2.76 (dd, J = 14.6, 5.1 Hz, 1H), 2.51 (t, J = 5.1 Hz, 1H); ^{13}C NMR δ 171.6, 139.3, 132.8, 129.3, 129.0, 128.9, 128.5, 126.3, 125.5, 40.1, 33.2.

2-(4-Methylbenzyl)-3-phenyl-2*H*-azirine (5b). Oil (70%); ^{1}H NMR δ 7.86−7.83 (m, 2H), 7.65−7.55 (m, 3H), 7.25 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 3.08 (dd, J = 14.6 4.9 Hz, 1H), 2.77 (dd, J = 14.6, 5.3 Hz, 1H), 2.55 (t, J = 5.1 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR δ 171.7, 136.2, 135.8, 132.8, 129.4, 129.2, 129.0, 128.8, 125.6, 39.7, 33.4, 21.0. Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.53; H, 7.24; N, 6.20.

2-Benzyl-3-(4-chlorophenyl)-2*H*-azirine (5c). Oil (70%); ^{1}H NMR δ 7.67 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.33−7.20 (m, 5H), 3.09 (dd, J = 14.6, 4.9 Hz, 1H), 2.73 (dd, J = 14.6, 5.1 Hz, 1H), 2.54 (t, J = 5.1 Hz, 1H); ^{13}C NMR δ 170.9, 139.1, 139.0, 130.5, 129.5, 128.9, 128.6, 126.4, 124.0, 40.0, 33.5. Anal. Calcd for $C_{15}H_{12}ClN$: C, 74.53; H, 5.00; N, 5.79. Found: C, 74.55; H, 5.37; N, 5.76.

3-(4-Chlorophenyl)-2-(4-methylbenzyl)-2*H*-azirine (5d). White prism (80%), mp 93−95 °C; ^{1}H NMR δ 7.69 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.17−7.09 (m, 4H), 3.05 (dd, J = 14.6, 4.8 Hz, 1H), 2.68 (dd, J = 14.6, 5.4 Hz, 1H), 2.51 (dd, J = 5.1, 4.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR δ 171.0, 139.0, 136.0, 135.9, 130.5, 129.5, 129.2, 128.8, 124.1, 39.6, 33.6, 21.0. Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.18; H, 5.65; N, 5.32.

2-Benzyl-3-(4-methylphenyl)-2*H*-azirine (5e). Oil (71%); ^{1}H NMR δ 7.57 (d, J = 7.8 Hz, 2H), 7.24−7.14 (m, 7H), 2.97 (dd, J = 14.6, 5.1 Hz, 1H), 2.65 (dd, J = 14.6, 5.1 Hz, 1H), 2.40 (t, J = 5.1 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR δ 171.1, 143.6, 139.5, 129.7, 129.4, 128.9, 128.5, 126.2, 122.7, 40.2, 32.9, 21.8. Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.67; H, 7.23; N, 6.02.

2-(4-Methylbenzyl)-3-(4-methylphenyl)-2*H*-azirine (5f). Oil (50%); ^{1}H NMR δ 7.67 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 3.01 (dd, J = 14.6, 4.9 Hz, 1H), 2.68 (dd, J = 14.6, 5.4 Hz, 1H), 2.46−2.44 (m, 4H), 2.34 (s, 3H); ^{13}C NMR δ 171.3, 143.6, 136.4, 135.7, 129.8, 129.4, 129.2, 128.8, 122.9, 39.9, 33.1, 21.8, 21.0. HRMS (FAB) Calcd for $C_{17}H_{17}N_1$ [M^+] 235.1361. Found 235.1359.

General Procedure for 2*H*-Azirines 6a−c. To a solution of potassium phthalimide (0.5 mmol) in DMF (5 mL) was added dropwise a solution of starting 2*H*-azirine **4** (0.5 mmol) in DMF (5 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature overnight (around 18 h). Crushed ice was added to quench the reaction, then the mixture was transferred to a separatory funnel and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. The residue on the removal of Et_2O was purified by column to give a yellow oil. Recrystallization was carried out in hexane/ethyl acetate.

2-(3-Phenyl-2*H*-aziren-2-yl)-1*H*-isoindole-1,3(2*H*)-dione (6a). Yellow microcrystals (70%), mp 139−140 °C; ^{1}H NMR 8.10−8.07 (m, 2H), 7.82−7.80 (m, 2H), 7.72−7.70 (m, 2H), 7.66−7.58 (m, 3H), 4.27 (s, 1H); ^{13}C NMR 167.9, 165.3, 134.3, 133.4, 131.7, 130.2, 128.9, 124.7, 123.3, 35.6. Anal. Calcd for $C_{16}H_{10}N_2O$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.16; H, 3.83; N, 10.58.

2-[3-(4-Chlorophenyl)-2*H*-aziren-2-yl]-1*H*-isoindole-1,3-(2*H*)-dione (6b). Yellow needles (57%), mp 182.5−184.5 °C; ^{1}H NMR δ 8.03 (d, J = 8.4 Hz, 2H), 7.85−7.81 (m, 2H), 7.75−7.72 (m, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.27 (s, 1H). ^{13}C NMR δ 167.9, 164.7, 139.9, 134.4, 131.8, 131.5, 129.5, 123.5, 123.3, 35.7. HRMS (FAB) calcd for $C_{16}H_9N_2O_2$ [M^+] 296.0353. Found 296.0351.

2-[3-(4-Methylphenyl)-2*H*-aziren-2-yl]-1*H*-isoindole-1,3-(2*H*)-dione (6c). Yellow needles (79%), mp 145−146 °C; ^{1}H NMR δ 7.97 (d, J = 8.1 Hz, 2H), 7.83−7.79 (m, 2H), 7.72−7.70 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.24 (s, 1H), 2.48 (s. 3H); ^{13}C NMR δ 168.0, 164.8, 144.4, 134.3, 131.8, 130.3, 129.7, 123.4, 122.0, 35.5, 21.9. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.79; H, 4.21; N, 10.10.

The Procedure for 2*H*-Azirine 7. To a solution of the sodium salt of benzenethiol (0.5 mmol) in DMF (5 mL), cooled at 0 °C, was added dropwise a solution of starting 2*H*-azirine **4a** (0.5 mmol) in DMF (5 mL). After addition, the reaction

mixture quickly turned purple and was stirred at 0 °C for 1 h. Crushed ice was added to quench the reaction, then the mixture was transferred to a separatory funnel and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. The residue on the removal of Et_2O was purified by column to give green oil. This compound is not stable at room temperature.

Phenyl 3-Phenyl-2*H*-aziren-2-ylsulfide (7). Green oil (70%); ^{1}H NMR 7.87 (d, J = 8.4 Hz, 2H), 7.67−7.55 (m, 5H), 7.36−7.24 (m, 3H), 3.84 (s, 1H); ^{13}C NMR 166.4, 136.3, 133.6, 130.1, 129.8, 129.2, 129.0, 126.8, 124.0, 37.6. HRMS (FAB) calcd for $C_{14}H_{11}NS$ [M + 2H] 227.0769. Found 227.0764.

Supporting Information Available: General procedure and characterization data for compounds **2a**−**c**, **4a**−**c, 5a**−**f, 6a**−**c**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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