Articles

Reaction of Methyl (*E*)-2-Phenyl-1-azirine-3-acrylates with Hydrazines and Amidines. Synthetic and Mechanistic Implications

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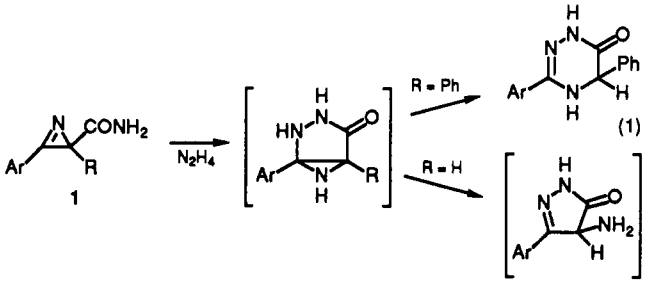
1-Azirines **2a–b** react with hydrazine in methanol to produce hexahydropyrrolo[3,2-*c*]pyrazol-5-ones **3a-b**. The process is suggested to involve intramolecular interception of an unstable 4-aminopyrazoline intermediate resulting from C=N bond cleavage. Reaction of **2a** with phenylhydrazine similarly affords **3c**. In dimethyl sulfoxide, on the other hand, formamidine, guanidine, and hydrazine afford imidazole **4**, pyrimidines **5a–b**, amino-*s*-triazine **6**, or triazole **9** as a consequence of C–C bond cleavage in aziridine intermediate **8**. The intermediacy of tautomers is proposed to account for the diversity of products in this case.

While the behavior of simple 1-azirines toward a variety of nucleophilic reagents has received considerable attention in the literature,[1] that of such systems containing additional electrophilic centers attached to the 3-position has been largely ignored. Reaction of 1-azirine-3-carboxamides (**1**) with hydrazine has been suggested to proceed through bicyclic aziridine intermediates with subsequent C–C or C–N bond cleavage to afford tetrahydro-1,2,4-triazin-6-ones or unstable 4-amino-2-pyrazolin-5-ones, depending upon the nature of the 3-substituent (eq 1).[2] Although this



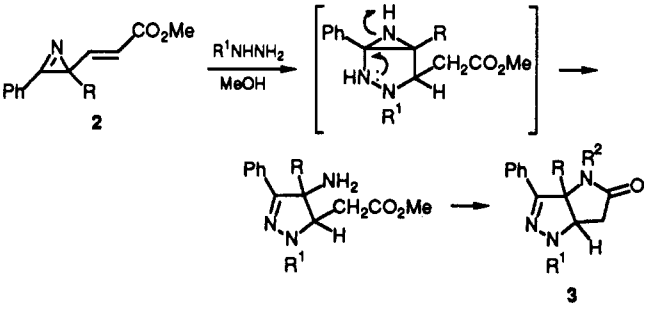
(1)

result would suggest a promising role for azirine systems containing three electrophilic centers (as in the readily available **2a**[3]) in the preparation of new heterocycles, no studies demonstrating this potential have appeared until now. In this work, we report our results concerning the reactivity of **2a–b** with hydrazines and amidines with emphasis on synthetic and mechanistic implications.

Results and Discussion

1-Azirines **2a** and **2b** were chosen as models for di- and trisubstituted systems, respectively, in as much as we had found that hydrazine reacts with methyl 2-phenyl-3-methyl-1-azirine-3-carboxylate to produce the corresponding tetrahydro-1,2,4-triazin-6-one.[4] This result

Table I. Bicyclics Formed in the Reactions of Azirines 2 with Hydrazines in Methanol



R	R^1	R^2	2	3	yield, %
H	H	H	**a**	**a**	43
Me	H	H	**b**	**b**	32
H	Ph	H	**a**	**c**	38
Me	Me	Me	–	**d**	44 (from **3b**)
H	Ph	Me	–	**e**	51 (from **3c**)

demonstrates that the electronic effect of the 3-phenyl group is not responsible for the C–C cleavage process depicted in eq 1. Reaction of **2a** with hydrazine in methanol (15 h at room temperature) afforded a colorless solid assigned structure **3a**[5] (Table I) on the basis of spectroscopic data. Thus, the presence of a CH_2CHCH fragment was suggested by the appearance, in the ^1H NMR spectrum, of 2 H and 1 H doublets with different *J* values, in addition to a 1 H multiplet. Similarly, **2b** produced **3b**, the reaction pathway being unaffected by the presence of a substituent other than hydrogen at the 3-position. The process may be represented as involving intramolecular interception in a C–N cleavage product derived from a bicyclic aziridine intermediate analogous to that depicted in eq 1. The absence of unsaturation adjacent to the aziridine portion of this intermediate should disfavor C–C bond cleavage. To address the question of initial nucleophilic attack at C-2 versus a Michael type at the 3-substituent, we examined the behavior of **2a** with phenylhydrazine. The ob-

(1) Eremeev, A.; Él'kinson, R. *Khim. Geterotsikl Soeden* **1984**, *6*, 723. Laurent, A. *Bull. Soc. Chim. Belg.* **1983**, *92*, 797. Nair, V.; Kim, K. *Heterocycles* **1977**, *7*, 353. Anderson, D.; Hassner, A. *Synthesis* **1975**, 483.
(2) Nishiwaki, T.; Saito, T. *J. Chem. Soc. C* **1971**, 2648.
(3) Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682.
(4) Nobre, C. M. M. S. Thesis, Universidade Estadual de Campinas, 1987.
(5) The crude reaction mixtures obtained in this study were all carefully analyzed by spectroscopic and chromatographic (thin layer and column) techniques. The products reported represent the only tractable material.

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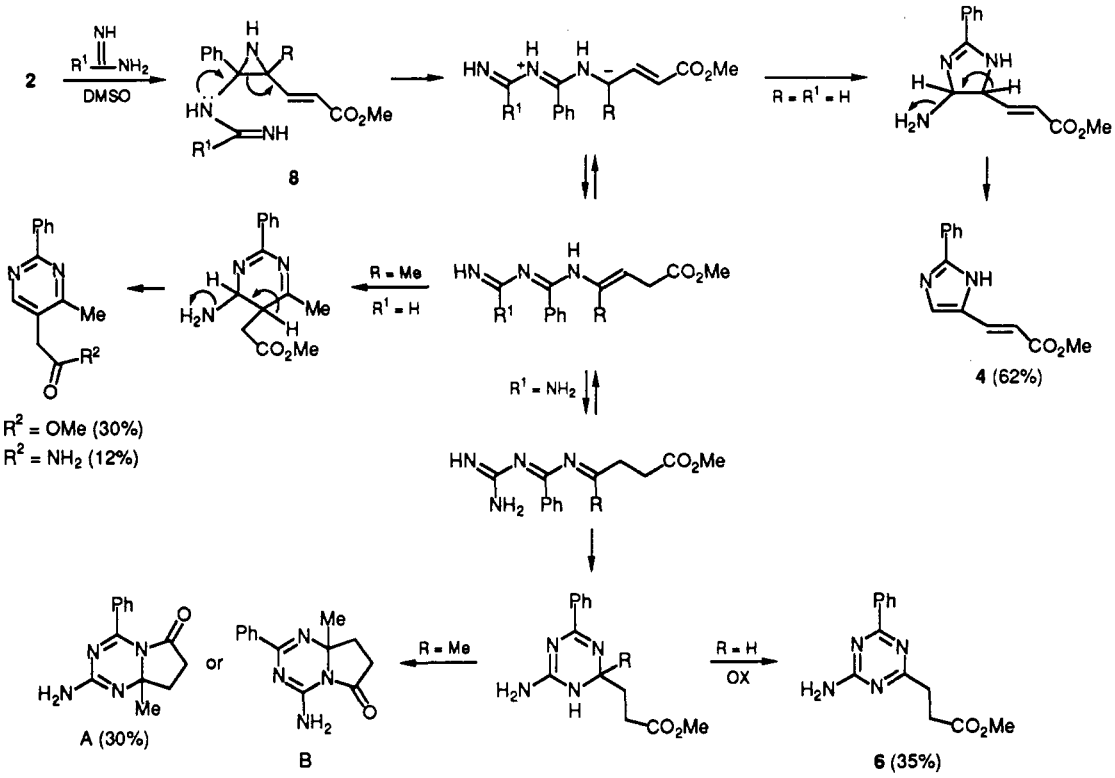
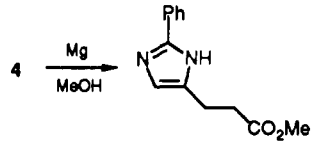
Scheme I. Products of the Reactions of Azirines 2 with Formamidine and Guanidine in Dimethyl Sulfoxide.

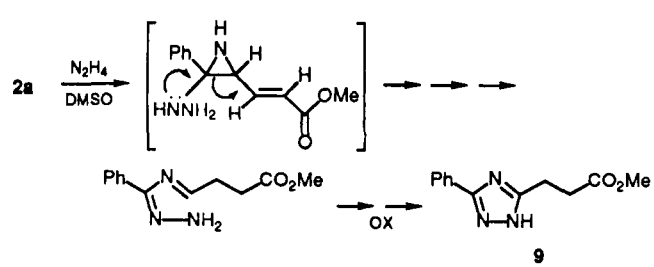


served formation of **3c** would suggest initial attack of the nucleophilic terminal nitrogen at C-2. The N-methylated derivatives **3d** and **3e** were obtained from **3b** and **3c**, respectively, upon treatment with KOH/CH_3I. The utilization of less polar solvents (benzene or CCl_4) in the above reaction produced mainly decomposition products containing trace quantities of **3**.

In an attempt to incorporate an additional carbon atom into the bicyclic products, reactions of **2** with formamidine and guanidine were studied. In methanol, only complex mixtures were obtained. Dimethyl sulfoxide, on the other hand, revealed an extraordinary solvent effect in these reactions (Scheme I). Thus, it was possible to observe the selective formation of imidazole **4**, pyrimidines **5a–b**, or amino-*s*-triazine **6**.[6] The ^1H NMR spectra of all compounds reveal a strong anisotropic deshielding effect on the phenyl ortho hydrogens (see the experimental section). The coplanarity required to produce such an effect rules out all other structures in as much as these would necessarily incorporate substituents adjacent to phenyl.[7] Although the products obtained here have not been described in the literature, the heteroaromatic nuclei contained therein have been well documented. Comparison of the ^1H NMR spectra of a variety of imidazoles[8] and pyrimidines[9] with those of **4** and **5** confirms the presence of hydrogen at the 4(5)-position in **4** and at the 6-position in **5**. Reduction of **4** (Mg/MeOH) afforded **7**, the ^1H NMR spectrum of which contained an A_2B_2 portion in addition to the $H_{4(5)}$ absorption at δ 6.80.

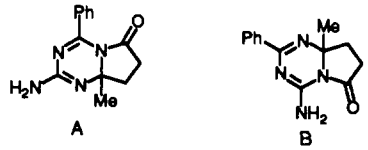


The reaction pathway reflects a strong directive effect of the 3-substituent on the azirine ring. This effect can be explained by considering that the reactions occur from different tautomers (Scheme I) resulting from C–C bond cleavage in aziridine intermediate **8**, wherein product formation is thermodynamically controlled. Interestingly, reaction of **2a** with hydrazine under these conditions produced the known 1,2,4-triazole **9**[7b] (35%) without any trace of **3a**. To the best of our knowledge, these results



represent the first example of a solvent-controlled C–N versus C–C bond cleavage process in the reactions of azirine derivatives.

(6) It was not possible to distinguish between structures A and B for the product (30% yield) from the reaction of **2b** with guanidine. The product was purified by column chromatography (florisil, benzene), mp 160–162 °C.



(7) (a) Olofson, R. A.; Kendall, R. V. *J. Org. Chem.* **1979**, *35*, 2246. (b) Buckler, R. T.; Hartzler, H. E.; Kurchacova, E.; Nichols, G.; Phillips, B. M. *J. Med. Chem.* **1978**, *21*, 1255.

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(9) Shkurko, O. P.; Mamaev, V. P. *Chem. Heterocycl. Comp. USSR (Engl. Transl.)* **1978**, *14*, 432 and 552.

Experimental Section[10]

The ^1H NMR spectra were recorded with a Varian T-60 or a Bruker AW-80 spectrometer using TMS as internal reference. Melting points, which are uncorrected, were obtained on a Reichert apparatus. Mass spectra were recorded with a Varian MAT-311A instrument.

Azirines **2a–b** were prepared according to the method described for **2a**.[3] The physical data for **2b** (obtained as a pale yellow oil in 42% overall yield from α-methylcinnamaldehyde) are as follows: IR (film) 1760, 1720, 1645 cm^{-1}; ^1H NMR (CCl_4) δ 1.60 (3 H, s), 3.65 (3 H, s), 5.80 (1 H, d, J = 16.0 Hz), 6.70 (1 H, d, J = 16.0 Hz), 7.60–8.00 (5 H, m).

Reactions of Azirines 2a-b with Hydrazines in Methanol. A solution containing **2** (1.00 mmol) and 95% hydrazine hydrate or phenylhydrazine (2.20 mmol) in methanol (10 mL) was allowed to stand at room temperature for 17 h. After evaporation of the solvent, the resulting pale yellow oil was triturated with ether to afford **3a–c** as colorless solids.

3a (from **2a** and hydrazine): mp 236–238 °C; IR (KBr) 3280, 1690 cm^{-1}; ^1H NMR (CF_3COOH) δ 3.42 (2 H, d, J = 6.0 Hz), 5.40 (1 H, m), 6.10 (1 H, d, J = 8.0 Hz), 7.40–8.00 (6 H, m), 8.60 (1 H, br); MS (m/e) 201 (M^+, 100).

3b (from **2b** and hydrazine): mp 221–223 °C; IR (KBr) 3300, 1680 cm^{-1}; ^1H NMR (CF_3COOH) δ 2.00 (3 H, s), 3.40 (2 H, d, J = 6.0 Hz), 4.90 (1 H, t, J = 6.0 Hz), 7.50 (6 H, m), 8.90 (1 H, br); MS (m/e) 215 (M^+, 93.3).

3c (from **2a** and phenylhydrazine): mp 253–255 °C; IR (KBr) 3200, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.00 (d, 2 H, J = 7.0 Hz), 4.80 (1 H, m), 5.40 (1 H, d, J = 10.0 Hz), 6.80–8.00 (10 H, m), 8.90 (1 H, br); MS (m/e) 277 (M^+, 100).

Methylation of Bicyclics 3b–c. To a solution of **3b** or **3c** (0.42 mmol) in dimethyl sulfoxide (2 mL) was added powdered potassium hydroxide (40 mg). After 10 min of stirring, methyl iodide (2.10 mmol) was added. After an additional 30 min of stirring, distilled water (10 mL) was added, and the resulting mixture was extracted with methylene chloride (3 × 10 mL). The organic layer was washed with distilled water (5 × 30 mL), dried over magnesium sulfate, and stripped of solvent to afford a yellow oil which was triturated with ether to produce **3d–e** as pale yellow solids.

3d (from **3b**): mp 100–102 °C; IR (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (3 H, s), 2.60 (5 H, m, CH_3 + CH_2), 3.00 (3 H, s), 3.40 (1 H, t, J = 6.0 Hz), 7.25–7.80 (5 H, m); MS (m/e) 243 (M^+, 100).

3e (from **3c**): mp 202–204 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (5 H, m, CH_3 + CH_2), 4.60 (1 H, m), 5.30 (1 H, d, J = 10.0 Hz), 6.80–8.00 (10 H, m); MS (m/e) 291 (M^+, 8.6).

Reactions of Azirines 2a–b with Formamidine in DMSO. To a solution of **2** (1.50 mmol) in DMSO (7 mL) were added formamidinium acetate (1.50 mmol) and potassium carbonate (415 mg). After 5 days of stirring, the reaction mixture was diluted with distilled water (15 mL) followed by extraction with methylene chloride (3 × 15 mL). The organic layer was washed with distilled water (5 × 30 mL), dried (magnesium sulfate), and stripped of solvent to afford a yellow oil which was submitted to column chromatography (florisil).

(10) All compounds gave satisfactory analytical data (±0.4% for C, H, N) (see the supplementary material).

4 (from **2a**, benzene as eluent): mp 163.5–165.5 °C; IR (KBr) 3040–3135, 1708, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (3 H, s), 6.42 (1 H, d, J = 16.0 Hz), 7.20–7.40 (4 H, m, $H_{4(5)}$ + meta,para-Ph), 7.59 (1 H, d, J = 16.0 Hz), 7.70–7.90 (2 H, m, ortho-Ph); MS (m/e) 228 (M^+, 100).

5a (from **2b**, benzene as eluent): oil; IR (film) 1740 cm^{-1}; ^1H NMR (CCl_4) δ 2.48 (3 H, s), 3.52 (2 H, s), 3.70 (3 H, s), 7.30–7.49 (3 H, m), 8.33–8.60 (3 H, m, H_6 + ortho-Ph); MS (m/e) 242 (M^+, 92.4).

5b (from **2b**, ether as eluent): mp 191.5–193 °C; IR (KBr) 3410, 3210, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (3 H, s), 3.53 (2 H, s), 7.24–7.60 (3 H, m), 8.30–8.56 (3 H, m, H_6 + ortho-Ph); MS (m/e) 227 (M^+, 75.0).

Reduction of 4 with Magnesium in Methanol. To a solution of **4** (30 mg, 0.13 mmol) in dry methanol (3 mL) was added magnesium turnings (128 mg). After 12 h of vigorous stirring, the resulting gray paste was treated with distilled water (10 mL) and neutralized with 10% HCl in an ice bath, followed by extraction with methylene chloride (3 × 5 mL). The organic layer was washed with distilled water (5 × 10 mL), dried (magnesium sulfate), and stripped of solvent to furnish a yellow oil which was triturated with isopropyl ether to afford **7** (19 mg, 60%) as a colorless solid: mp 116–118 °C; IR (KBr) 3060, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60–3.10 (4H, A_2B_2), 3.71 (3 H, s), 6.80 (1 H, s), 7.08–7.40 (3 H, m), 7.60–7.89 (2 H, m, ortho Ph); MS (m/e) 230 (M^+, 80.0).

Reaction of Azirine 2a with Guanidine in DMSO. To a solution of **2a** (340 mg, 1.69 mmol) in DMSO (8 mL) were added guanidine hydrochloride (170 mg, 1.78 mmol) and potassium carbonate (588 mg). After 5 days of stirring, the reaction mixture was diluted with distilled water (17 mL) followed by extraction with methylene chloride (3 × 20 mL). The organic layer was washed with distilled water (5 × 35 mL), dried (magnesium sulfate), and stripped of solvent to afford a yellow oil (250 mg), which was purified by column chromatography (florisil) to yield **6** (125 mg, 35%) as a colorless solid: mp 99.5–101 °C; IR (KBr) 3450, 3320, 3170, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (4 H, A_2B_2), 3.73 (3 H, s), 5.70 (2 H, br), 7.20–7.50 (3 H, m), 8.20–8.42 (2 H, m, ortho-Ph); MS (m/e) 258 (M^+, 52.3).

Reaction of 2a with Hydrazine in DMSO. A solution containing **2a** (362 mg, 1.8 mmol) and 95% hydrazine hydrate (0.11 mL) in DMSO (10 mL) was allowed to stand at room temperature for 12 h. Distilled water (20 mL) was added followed by extraction with methylene chloride (3 × 20 mL). The organic layer was dried (magnesium sulfate) and stripped of solvent to furnish a yellow oil which was triturated with isopropyl ether–hexane (1:1) to produce **9** (145 mg, 35%) as colorless prisms: mp 99–101 °C (lit.[7b] mp 117 °C; a sample prepared by us according to the literature procedure had a melting point and IR spectrum identical with that of **9**); IR (KBr) 3120, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (4 H, A_2B_2), 3.70 (3 H, s), 7.10–7.50 (3 H, m), 7.85–8.20 (2 H, m, ortho-Ph); MS (m/e) 231 (M^+, 24.0).

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Supplementary Material Available: Elemental analysis results for **3a–e**, **4**, **5a–b**, **6**, **7**, **9** (1 page). Ordering information is given on any current masthead page.