Base-Catalyzed Elimination of Para-Substituted Thiophenoxides from 4-(Arylthio)azetidin-2-ones

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Introduction

Previously we postulated the $E1cB_R$ mechanism for reactions of 4-(aryloxy)azetidin-2-ones in aqueous alkali to give para-substituted phenoxide ions and 3-hydroxyacrylamide oxyanion.[1] Rate constants for the nucleofugic step can be obtained using this system, and we anticipated that with appropriate 4-substituted azetidin-2-ones we could rank several nucleofuges and possibly obtain a quantitative structure–activity relationship for them.[2] Here we report on the $E1cB_R$ reactions of 4-(arylthio)azetidin-2-ones **1–6** in aqueous alkali.

Experimental Section

A Durum D-110 stopped-flow spectrophotometer, interfaced with an Interactive Structures, Inc. Data Acquisition System A1 13 and an Apple IIe computer, was used. Other equipment were previously described.[1] Elemental analyses were performed by Atlantic Microlab, Inc. Melting points are uncorrected.

Compounds. 4-(Arylthio)azetidin-2-ones **1–6** and 3-piperidinoacrylamide, mp 145–146 °C (lit.[3] mp 146–147 °C), were synthesized by the methods of Clauss et al.[3] The following general method was used to synthesize **1–6**. To a stirred solution of the appropriate 4-substituted thiophenol (10 mmol) (Aldrich Chemical Co., Inc.) dissolved in 5 mL methanol in a 50-mL flask was added 10 mL of 1 N KOH (10 mmol). To this was added dropwise a solution of 1.29 g (10 mmol) of 4-acetoxyazetidin-2-one in 5 mL of water at room temperature. The reaction mixture was cooled to 0–10 °C and stirred for 30 min. Solvent was decanted from the first-formed solid or oil, and this was purified by crystallization.

4-(Phenylthio)azetidin-2-one (1): mp 72–73.5 °C (methanol) (lit.[3] mp 72 °C); ^{1}H NMR ($CDCl_3$) δ 6.5 (br, NH), 2.8–3.5 (m, CH_2), 5.1 (q, CH), 7.5 (s, 5 ArH). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.09. Found: C, 60.39; H, 5.09.

4-(*p*-Tolylthio)azetidin-2-one (2): mp 104.5–106 °C (ethyl acetate) (lit.[27] mp 104 °C); ^{1}H NMR ($CDCl_3$) δ 6.25 (br, NH), 2.7–3.5 (m, CH_2), 4.9 (q, CH), 2.4 (s, CH_3), 7.05–7.47 (m, ArH). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74. Found: C, 62.24; H, 5.78.

4-((*p*-Methoxyphenyl)thio)azetidin-2-one (3): mp 80–81.5 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 6.5 (br, H), 2.8–3.6 (m, CH_2), 5.1 (q, CH), 4 (s, CH_3), 7–7.7 (m, ArH). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.29. Found: C, 57.42; H, 5.32.

4-((*p*-Aminophenyl)thio)azetidin-2-one (4): mp 100–101 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 6.2 (br, NH), 2.7–3.4 (m, CH_2), 4.8 (q, CH), 6.6 (d, 2 ArH), 7.3 (d, 2 ArH). Anal. Calcd for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19. Found: C, 55.62; H, 5.25.

4-((*p*-Chlorophenyl)thio)azetidin-2-one (5): mp 103–104.5 °C (methanol) (lit.[27] mp 100 °C); ^{1}H NMR ($CDCl_3$) δ 6.4 (br, NH), 2.9–3.7 (m, CH_2), 5.25 (q, CH), 7.2–8.3 (m, ArH). Anal. Calcd for C_9H_8ClNOS: C, 50.59; H, 3.77. Found: C, 50.69; H, 3.79.

4-((*p*-Nitrophenyl)thio)azetidin-2-one (6): mp 131–133 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.4 (br, NH), 2.9–3.7 (m, CH_2), 5.15 (q, CH), 7.4 (t, 2 ArH), 8.2 (d, 2 ArH). Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60. Found: C, 48.28; H, 3.64.

Kinetics. Reactions were carried out in aqueous solution (calculated ionic strength 1.0 M, KCl) at 25 ± 0.1 °C and under pseudo-first-order conditions. Three-milliliter cuvettes were filled, stoppered, and allowed to equilibrate for 20 min in the thermostated sample chamber. Reactions were initiated by adding 10 μL of a solution of the appropriate compound **1–6** in methanol to the alkaline solution in the cuvette.

In the concentration range 0.01–1.0 M potassium hydroxide no additional buffers were used. Noncatalytic phosphate buffers were used to maintain pH for reactions of **6** using the Durrum model D-110. pH remained constant during runs. At low pH values the concentration of hydroxide ion was determined from the relationship $[OH^-] = (1.3 \pm 0.1)10^{(pH-14)}$ and the pH meter reading.

Production of thiophenolate ions and 3-hydroxyacrylamide oxyanion from **1–6** were followed spectrophotometrically at the wavelengths (nm) indicated: thiophenolate (255), *p*-chlorothiophenolate (270), *p*-nitrothiophenolate (420), *p*-aminothiophenolate (265), *p*-methoxythiophenolate (265), *p*-methylthiophenolate (265), and 3-hydroxyacrylamide oxyanion (265). As reactions proceeded, voltages proportional to absorbances and times were collected by the computer. A kinetics program gave the pseudo-first-order rate constants with standard errors, correlation coefficients and least squares plots of ln $(a - x)$ vs time. Plots were linear to at least 75% reaction and usually were linear to more than 90% reaction. Pseudo-first-order rate constants were generally reproducible to ca. 5%.

Products. The reactions of 4-((*p*-methoxyphenyl)thio)azetidin-2-one (**3**) (4.2×10^{-5} M) in 0.1 M KOH and 4-((*p*-chlorophenyl)thio)azetidin-2-one (**5**) (6.05×10^{-5} M) in 0.0033 M KOH were typical. The UV spectrum of the KOH solution containing the reaction products from **3** had a broad maximum at 265 nm ($\log \epsilon = 4.47$). When the reaction mixture was acidified with HCl (pH 2.06) the spectrum had λ_{max} 237 nm ($\log \epsilon = 3.91$). Absorbance at 265 nm was immediately regenerated when the acidic solution was rebasified. Under identical conditions the UV spectrum of *p*-methoxythiophenol had λ_{max} 264 nm ($\log \epsilon = 4.12$). Acidification (pH 2.06) gave λ_{max} 237 nm ($\log \epsilon = 3.88$). These data show that *p*-methoxythiophenol is a product and that there is another product with λ_{max} 265 nm ($\log \epsilon = 4.2$) that does not absorb in acidic solution. This compound is 3-hydroxyacrylamide oxyanion.[1] The UV spectrum of the KOH solution containing the reaction products from **5** had λ_{max} 267 nm ($\log \epsilon = 4.24$). Under identical conditions the UV spectrum of *p*-chlorothiophenol had λ_{max} 270 nm ($\log \epsilon = 4.2$). A difference spectrum had λ_{max} 265 nm ($\log \epsilon = 4.16$), which corresponds to 4-hydroxyacrylamide oxyanion.[1]

Reactions of 4-((*p*-chlorophenyl)thio)azetidin-2-one (**5**) in piperidine buffer, 0.1 M, pH 11.92, took a somewhat different course. The product spectrum had λ_{max} 280 nm ($\log \epsilon = 4.5$). This corresponds to a mixture of *p*-chlorothiophenoxide ions with λ_{max}

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Table I. Rate Data According to Eq 2 for Reactions of 1–6 in Dilute Potassium Hydroxide Solutions at 25 °C

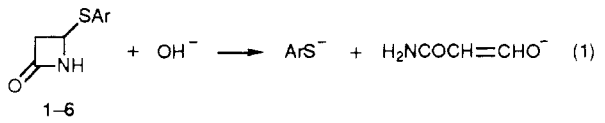
compd	intercept	slope	k_2, s^{-1}	pK_a	k_{obs}	$[OH^-]$
1 (H)	14.5 ± 1.36	3.13 ± 0.24	0.069	13.33	52	6
2 (CH_3)	25.9 ± 1.82	7.24 ± 0.33	0.039	13.45	48	7
3 (CH_3O)	26.6 ± 6.27	8.72 ± 0.89	0.038	13.52	22	8
4 (NH_2)	81.9 ± 3.30	28.9 ± 0.57	0.012	13.55	43	8
5 (Cl)	4.23 ± 2.51	0.97 ± 0.05	0.237	13.36	43	8
6 (NO_2)	0.35 ± 0.15	0.033 ± 0.0027	2.84	12.97	72	8
4 $(NH_2)_a$	105 ± 9.8	15.4 ± 1.43	0.0095	14.04	30	9

[a] Reactions were run in deuterium oxide, pK_a is for 4 N-^{2}H.

270 (log ϵ = 4.2) and 3-piperidinoacrylamide,[3] with λ_{max} 287 (log ϵ = 4.45). When the UV spectrum of *p*-chlorothiophenoxide was subtracted from the product spectrum, the difference spectrum had λ_{max} 287 (log ϵ = 4.38). The spectrum of the products from reaction of 4-acetoxyazetidin-2-one in 0.2 M piperidine buffer, pH 11.92, had λ_{max} 287 (log ϵ = 4.45), which corresponds to 3-piperidinoacrylamide. In aqueous piperidine (0.029 M) solution, the same product was obtained. Acidification of the reaction solution with HCl resulted in instantaneous loss of the 287-nm band. Basification with KOH gave a new band at 265 nm (log ϵ = 4.2), which is due to 3-hydroxyacrylamide oxyanion. After several hours, the spectrum of this latter solution had λ_{max} 287 (log ϵ = 4.5) and no 265-nm absorbance. 3-Piperidinoacrylamide was relatively stable in basic solutions but readily hydrolyzed to 3-hydroxyacrylamide in neutral and acidic solutions.[24-26] It was quite stable in piperidine buffers at high pH.

Results

In aqueous alkaline solution 4-arylthioazetidin-2-ones **1–6** give thiophenolate ions and 3-hydroxyacrylamide (eq 1). The pseudo-first-order rate constants (s^{-1}) for reactions



1–6 (1)

of **6** in (*N*,*N*-dimethylamino)ethanol buffer solutions (pH = 9.9, $[RNH_2]/[RNH_3^+]$ = 2) are 6.2×10^{-3} (0.05 M), 6.2×10^{-3} (0.1 M), and 5.5×10^{-3} (0.3 M). Similarly, pseudo-first-order rate constants (s^{-1}) for reactions **5** in piperidine buffer solutions (pH = 11.2, $[RNH_2]/[RNH_3]$ = 5) are 1.1×10^{-2} (0.04 M), 1.0×10^{-2} (0.12 M), and 8.8×10^{-3} (0.2 M). These data indicate no general acid–base catalysis by amine buffers.

In 0.01–1.0 M aqueous KOH, pseudo-first-order rate constants are related to acidity of solutions by eq 2, where

$$k_{obs} = k_2K_a/(K_a + [H^+]) = k_2[OH^-]/((K_w/K_a) + [OH^-]) \quad (2)$$

k_2 is a first order rate constant, K_a is the ionization constant for the amide groups of **1–6**, and K_w is the autoprotolysis constant for water at 25 °C. Least-squares plots[1] of $1/k_{obs}$ vs $1/[OH^-]$ (not shown) were linear and gave $1/k_2$ as intercept and K_w/k_2K_a as slope (Table I) from which k_2 and K_a values for **1–6** were calculated (Table I).

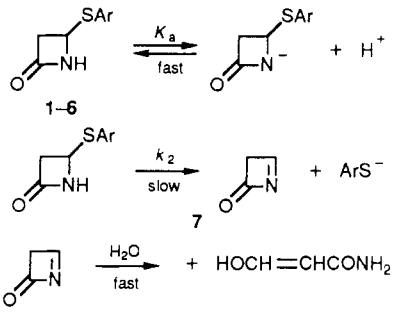
The deuterium solvent kinetic isotope effects for reactions of **4** are $k_2(H_2O)/k_2(^2H_2O)$ = 1.27 and $K_a(H_2O)/K_a(^2H_2O)$ = 3.1 (Table I).

The Hammett ρ = 2.08 ± 0.08 (r = 0.997). When σ° values[4] are used, ρ = 1.95 ± 0.03 (r = 0.9996). Regression of log k_2 on pK_a of thiophenols[5] gave β_{1g} = −0.89 ± 0.06 (r = 0.9976).

Discussion

The results from this study are consistent with the mechanism of Scheme I, which was suggested for reactions of 4-aryloxyazetidin-2-ones in aqueous potassium hydroxide.[1] According to Scheme I, the rate law is given by

Scheme I



eq 2, where k_2's (Table I) are for departure of leaving groups from conjugate bases of **1–6** and K_a's (Table I) are for ionizations of **1–6**.

Reactions of **6** in (*N*,*N*-dimethylamino)ethanol and of **5** in piperidine buffers are not catalyzed by amines, indicating no general acid–base catalysis as required by the proposed mechanism.

The deuterium solvent kinetic isotope effect, $k_2(H_2O)/k_2(^2H_2O)$, is 1.27 for **4**. For ionization of **4**, $K_a(H_2O)/K_a(^2H_2O)$ is 3.1. The isotope effect on k_2 is too small to convincingly support general acid–base catalysis but may reflect some more complicated reorganization of solvent[6,22,23] in the transition state for **4** than for 3,3-dimethyl-4-phenoxyazetidin-2-one, for which the deuterium solvent isotope effect is 1.[1] We speculate that the ether oxygen of (aryloxy)azetidin-2-one oxyanions should be more extensively hydrogen bonded with solvent than is sulfur in **4**. As the transition states are approached and as the negative charge on oxygen and sulfur becomes more developed, the increase and *change* in hydrogen bonded solvent structure around sulfur could be greater than the increase and *change* around oxygen. This could give rise to an isotope effect. Another contributing factor could be the different electron-releasing effects of *p*-^2H_2N vs *p*-H_2N and their relative abilities to stabilize the critical transition state. Deuterium is more electron donating than hydrogen[6] as is indicated by the 7% decrease in acidity of formic acid when CH is replaced by C^{2}H. Deuterium substitution in **4** should result in some transition-state destabilization. These or other interpretations of the isotope effect must be tempered by the errors in intercepts (Table I), which allow a range of 1.12–1.46 for the isotope effect. The isotope effect on K_a's is in the correct direction but is smaller than for 4-(aryloxy)azetidin-2-ones.[1]

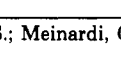
The mechanism of Scheme I features 1-azetin-4-one (**7**) as an intermediate on the reaction path. This compound has been postulated[7-12] to be an intermediate in substitution reactions of 4-acetoxyazetidin-2-one. Atrill et al.[7] were unsuccessful trapping **7** by Diels–Alder reaction with 2,4,6-trimethylbenzonitrile oxide of 4-(dimethylamino)-3-buten-2-one. However, Clauss et al.[3] showed that reaction of *trans*-10-((3-methyl-2-oxoazetidin-4-yl)sulfonyl)camphor with sodium thiophenolate in aqueous methanol gave *trans*-3-methyl-4-phenylthioazetidin-2-one. The stereochemical result supports elimination of camphor sulfinate

from the substituted camphor to give 7, which is attacked by thiophenoxide from the less hindered face to give trans product. Clauss et al.[3] also showed that 4-acetoxyacetidin-2-one reacts with 2 equiv of piperidine in the nonnucleophilic solvent acetonitrile to give 3-piperidinoacrylamide. It seemed probable that 7 was formed in this reaction too and that it was trapped by piperidine to give the product.

We extended this latter reaction to **5** in aqueous solutions of piperidine, reasoning that if 7 is an electrophilic intermediate in reactions of 1–6 (and other 4-substituted azetidin-2-ones) in aqueous solution, then added nucleophiles, e.g. piperidine, should compete with lyate species and trap it. When piperidine is the nucleophile, 3-piperidinoacrylamide should be the product. When reactions of **5** were carried out in piperidine buffer, pH 11.92, repetitive UV scans of the reaction mixture showed an increase in absorbance at λ_{max} 280 nm, consistent with formation of *p*-chlorothiophenolate ion and 3-piperidinoacrylamide (Experimental Section). The difference spectrum corresponded to that of 3-piperidinoacrylamide. This reaction was not catalyzed by piperidine (Results) and the pseudo-first-order rate constant was correctly predicted from eq 2, pH and the constants of Table I (Results). When 4-acetoxyazetidin-2-one was allowed to react in piperidine buffer solution, a single absorption at 287 nm characteristic of 3-piperidinoacrylamide was obtained. For 1–6 these results support the rate-determining formation of 7 (Scheme I), which may be quickly trapped by piperidine. 4-Acetoxyazetidin-2-one similarly reacts and it seems likely that other 4-substituted azetidin-2-ones also react to give 7 transiently.[28]

Stirling et al.[2,13,14] studied olefin-forming elimination reactions with leaving groups whose ranks spanned ca. 16 powers of 10 in reactivity, and they concluded that there is no correlation between leaving tendency and pK_a of conjugate acids of nucleofuges, except within a congeneric series such as 2-(aryloxy)ethyl phenyl sulfones for which $\beta_{lg} = -0.4$.[13] Similarly, there is no correlation between leaving tendency (log k_2) and pK_a of conjugate acids of leaving groups for reactions of 1–6 and 4-(aryloxy)azetidin-2-ones. However, within each series of compounds a good correlation exists. Thus for 1–6, $\beta_{lg} = -0.89$, which may be compared with values of −0.65 and −0.75 for similar reactions of 4-(para-substituted phenoxy)azetidin-2-ones and 4-(para-substituted phenoxy)-3,3-dimethylazetidin-2-ones, respectively.[1] For azetidinones, these measures of mechanism suggest that transition states for loss of thiophenoxide ions from anions of 1–6 appear later along the reaction coordinate than do those of comparable phenoxy derivatives. This is in accord with the lower ranks of thiophenoxides than phenoxides in elimination reactions of 1–6 and analogous phenoxy compounds, despite the fact that thiophenols are 2 to 3 orders of magnitude more acidic than phenols.[5,14] Thus phenoxides leave 4–7 times more quickly than thiophenoxides in this system.

In regard to the lower ranks of thiophenoxides than phenoxides, back bonding of an electron pair into sulfur's d orbitals has been invoked to account for transition state stabilization in reactions of thiolates with α,β-unsaturated compounds[16] and with carbonyl compounds.[17,18] For 1–6, such use of d orbitals could impart stability to ground states of the lactam anion



An alternative possibility for stabilization of ground states is suggested by results of ab initio SCF-MO calculations of thiomethyl anion, $HSCH_2^-$, that implicate polarization of sulfur rather than d orbital conjugation.[19] Van der Waals–London attraction[20] may also have a stabilizing role.

A comparison of ρ's for 1–6 (1.95) and 4-(para-substituted phenoxy)azetidin-2-ones (2.2)[1] indicates that 1–6 experience a slightly smaller change in charge than phenoxy compounds in the transition states for the nucleofugic step, k_2 (Scheme I). This result finds a parallel in ionization of thiophenols and phenols for which ρ's are 1.81[5] and 2.11,[15] respectively. Possibly, because of sulfur's large size and greater polarizability, sulfur in 1–6 carries a larger share of the charge in the transition state than does oxygen in analogous oxygen isosteres.

Our results show that phenoxides are higher ranked nucleofuges than analogous thiophenoxides and that a simple quantitative structure activity relationship, e.g. log k_2 vs pK_a, does not describe nucleofugality in these azetidin-2-ones. The possibility for developing such a QSAR seems small when the effect of replacing O or S by Se on reactivity is considered. Relative reactivity in the series is Se:O:S = 290:3.6:1.[21] For eliminations from 2-(arylseleno)-, 2-(aryloxy)-, and 2-(arylthio)ethyl phenyl sulfones,[2] the relative reactivities are 50:1.6:1.

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Registry No. 1, 31898-69-8; 2, 68960-59-8; 3, 129001-78-1; 4, 129287-21-4; 5, 68960-60-1; 6, 129287-22-5; $H_2NC(O)CH{=}CHO^-K^+$, 129314-70-1; D_2, 7782-39-0.

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Lipase-Catalyzed Stereoselective Thiotransesterification of Mercapto Esters

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Hydrolytic enzymes such as lipases, esterases, and proteases have been used extensively as catalysts in enantioselective and regioselective synthesis.[1] Many chiral synthons like alcohols,[2] amines,[3] and acids[4] have been prepared in high optical purity via enzymatic hydrolysis in water, or via esterification, transesterification, and aminolysis in organic solvents. Surprisingly, very little attention has been paid to the enzymatic resolution of thiols, in spite of their importance as chiral building blocks. In this work we report that lipases can be used for the preparation of optically active thiols. Acetyl thioesters **1** and **2** were chosen as model compounds, because they are versatile intermediates in the synthesis of antihypertensive agents[5] and other drugs of clinical interest.[6]

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