to the vacuum space (5), the Teflon sleeve was sliced, leading to a gap approximately 0.5-mm wide. The vacuum space is formed by a Cajon vacuum union (6), the o-rings (7) of which seal against the glass parts of the cell. A vacuum port (8), soldered to the union (6), is connected to a liquid nitrogen trapped mechanical vacuum pump. The temperature in the source chamber (1) and the cold finger (2) is controlled to within 0.5 °C through silicone oil circulating from two independent thermostated baths. Heat transfer between these two parts is minimized by a vacuum jacket surrounding the cold finger. Thus a relatively steep temperature gradient is established in the vapor at the flat end of the cold finger, which restricts nucleation and growth of the crystals to this limited region.

The leak from the growth chamber serves two purposes. First, at room temperature and during heat-up to growth temperature the leak allows for the thorough in situ drying and outgassing of the starting material and cell interior. This feature proved particularly useful for the ortho betaine, which had adsorbed water present from its synthesis. Second, and even more important, the continuous efflux of gaseous components from the cell at growth temperatures maximizes the transport rate.[24] This, in turn, is particularly important for growth of crystals with limited thermal stability, since it allows for significant transport at low vapor pressures; i.e., low temperatures.

Nucleation and growth on the flat face of the cold finger were monitored through a long focal length microscope (30×). Exploratory runs showed that the growth of the well-faceted crystals, i.e., attainment of sufficient surface mobility of adatoms,[26] required growth temperatures of 120 °C. The onset of nucleation, within a few hours after an increase of the source temperature above that of the cold finger, typically required temperature differences of 60 °C. As soon as nucleation of 1–5 crystallites was observed, this temperature difference was reduced to around 10 °C to promote growth without further nucleation. The growth of 2–3-mm sized crystals typically required 3–5 days, during which the temperature of the ortho betaine source material was slowly increased by a total of 2–4 deg. After growth, the crystals were cooled down from the growth temperature within a few hours.

Crystal Structure Determination. A crystal of the ortho betaine was mounted on a glass fiber in air using epoxy cement. Weissenberg photographs revealed the crystal to be orthorhombic P_{bca}. The density was measured by flotation in hexane/Freon 112, $D_m = 1.217$ (1) g/cm^3, $D_x = 1.219$ g/cm^3. Data were collected at room temperature on a CAD-4 X-ray diffractometer using Cu K radiation. Accurate cell dimensions and orientation matrix were obtained by centering 25 reflections with $2\theta > 40°$; $a = 11.723$ (1), $b = 22.264$ (2), and $c = 17.853$ (2) Å; $Z = 8$. Intensity data were collected in $\omega/2\theta$ scan mode for 2894 reflections. Intensity checks on three standards indicated no decay during data collection. Absorption corrections were not applied. The structure was solved by direct methods using the crystallographic computer package XTAL2.2.[27] The structure was refined by full-matrix least-squares methods with anisotropic temperature factors for all nonhydrogen atoms. All hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters refined. The final conventional R index was 0.057; the final difference map contained no significant unaccounted density. The list of final atomic coordinates, atomic thermal parameters, and molecular dimensions have been deposited as supplementary material.

Registry No. 2, 120712-61-0; 2,4,6-triphenylpyrylium tetrafluoroborate, 448-61-3; 2,4-dimethyl-6-aminophenol, 41458-65-5; sodium acetate, 127-09-3; fluoroboric acid, 16872-11-0.

Supplementary Material Available: Tables of non-hydrogen atom coordinates, hydrogen atom parameters, non-hydrogen thermal parameters, and bond lengths (4 pages). Ordering information is given on any current masthead page.

(26) Rosenberger, F. In *Interfacial Aspects of Phase Transformations*; Mataftschiev, B., Ed.; Reidel: Dordrecht, 1982; pp 315–364.

(27) Hall, S. R.; Stewart, J. M. *XTAL2.2 Users Manual*; University of W. Australia and University of Maryland, 1987.

Alkyltransferase Model Reactions: Synthesis of Sulfonium and Ammonium Compounds Containing Neighboring Nucleophiles. Kinetic Studies of the Intramolecular Reaction of Amino, Hydroxy, Phenoxy, and Mercapto Onium Salts

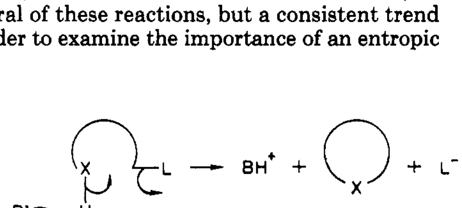
Robert J. Miller, Athan Kuliopulos, and James K. Coward*,†

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Received November 28, 1988

The synthesis of a series of sulfonium and ammonium salts containing a variety of neighboring nucleophiles is described. Several of these molecules undergo facile cyclization reactions with rate enhancements of ca. 10^5 over the corresponding intermolecular reaction. Investigation of the reaction kinetics showed that these intramolecular nucleophilic reactions obey the Brønsted relation with $\beta = 0.34$ for the sulfonium series and $\beta \geq 0.49$ for the ammonium series. Buffer catalysis is observed in several of these reactions, but a consistent trend is not apparent. Activation parameters have been determined in order to examine the importance of an entropic driving force in intramolecular reactions.

As part of our research on the mechanism of enzyme-catalyzed alkyl transfer reactions, we wished to extend our previous observations[1–3] on the possible role of general catalysis in these reactions. In order to probe the structural requirements in the reaction shown in eq 1, the synthesis of molecules containing a variety of appropriately positioned nucleophiles (X) and leaving groups (L) was required. To this end we have developed methods for the synthesis of substituted thioanisoles and N-methylanilines



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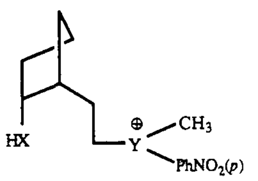
† Present address: Departments of Chemistry and Medicinal Chemistry, The University of Michigan, Ann Arbor, MI 48109.

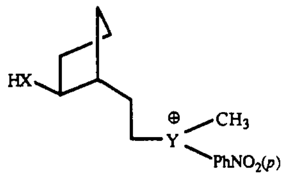
(1) Coward, J. K.; Lok, R.; Takagi, O. *J. Am. Chem. Soc.* **1976**, *98*, 1057–1059.

containing tethered nucleophilic groups of interest. Methylation of the aryl sulfide or aniline followed by, in most cases, removal of a protecting group reveals the neighboring nucleophile, which then is capable of undergoing the reaction shown in eq 1. In this paper we describe the syntheses of 1–4 for use as substrates for kinetics investigations. In addition, we present our findings from investigations of the reaction kinetics and our interpretation of the results, particularly in terms of possible general catalysis of nucleophilic attack at sp^3 carbon.



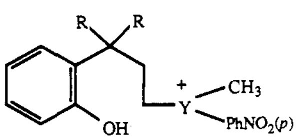
1

a, X = O, Y = S
b, X = NH, Y = S
c, X = NH, Y = NCH_3
d, X = O, Y = NCH_3
e, X = S, Y = NCH_3



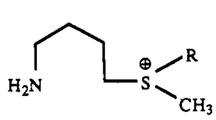
2

a, X = O, Y = S
b, X = NH, Y = S
c, X = NH, Y = NCH_3
d, X = O, Y = NCH_3



3

a, R = H, Y = S
b, R = CH_3, Y = S
c, R = CH_3, Y = NCH_3

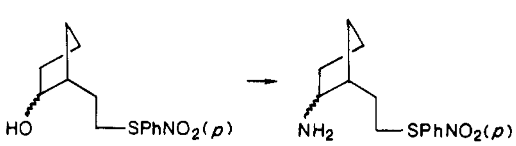


4

a, R = p-$NO_2C_6H_4$
b, R = C_6H_{11}

Results

Synthesis. A. Synthesis of *cis*- and *trans*-(2-Aminocyclopentyl)ethyl Sulfonium Salts (1b and 2b). Initially, we attempted to use appropriate 2-substituted cyclopentanols[2] as synthetic precursors (eq 2). In the case

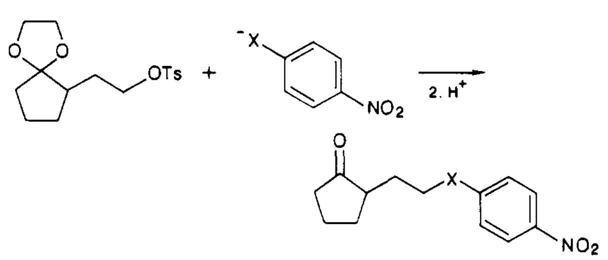


(2)

of the *trans*-alcohol, application of the Mitsunobu reaction[4] with phthalimide led to the *cis*-phthalimido derivative in only modest (42%) yield (Scheme I). Mesylation of the *trans*-alcohol, followed by displacement of the mesyl group with potassium phthalimide resulted in a low (28%) yield of the desired *cis*-phthalimido derivative accompanied by products of elimination reactions. Hydrazinolysis of the *cis*-phthalimide led to the desired *cis*-amine, 6, in good (78%) yield. Use of a less basic and less bulky nucleophile, N_3^-, led to formation of the desired *cis*-azide in nearly quantitative yield. Unfortunately, specific reduction of the azide function in the presence of the nitrophenyl substituent, using such reagents as triphenylphosphine–pyridine[5] or 1,3-dithiopropane–Et_3N,[6] resulted in very low (0–12%) yields of the desired *cis*-amine. Even less promising results were obtained in attempting to convert the *cis*-alcohol to the *trans*-amine (eq 2). Thus, attempted use of the Mitsunobu reaction or displacement of the mesyl group with phthalimide anion led to none of the desired *trans*-amine precursor, although displacement with N_3^- led to the *trans*-azide in high (84%) yield. However, selective reduction of the azide function using triphenylphosphine–pyridine again failed to yield the corresponding amine.

A more satisfactory synthesis of the amine sulfonium salts, **1b** and **2b**, is shown in Scheme I. The 2-substituted cyclopentanone, **5**,[2] was converted to the *O*-methyl oxime, followed by reduction to the *cis*-amine, **6**, using $Na(CF_3COO)BH_3$ according to Umino et al.[7] The *cis*-amine was protected as a benzyl carbamate, **7**, after which methylation at sulfur followed by removal of the protecting group afforded the desired *cis*-aminosulfonium salt, **1b**. Similarly, the known *trans*-(2-aminocyclopentyl)ethanol, **8**,[8] was protected at the amine function as a benzyl carbamate, **9**, which then was converted to the *p*-nitrophenyl thioether, **10**, via the intermediate tosylate. Methylation at sulfur followed by removal of the protecting group afforded the desired *trans*-aminosulfonium salt, **2b**.

B. Synthesis of *cis*- and *trans*-[(2-Aminocyclopentyl)ethyl]ammonium Salts (1c and 2c). The synthesis of 2-substituted cyclopentylethyl *p*-nitrophenyl thioethers, as precursors of **1a,b** and **2a,b**, utilized the 2-substituted cyclopentanone, **5**, as a key intermediate.[2] This, in turn, was prepared from the appropriate ketal tosylate, as shown in eq 3 (X = S). We attempted to use



(3)

5, X = S
11, X = NCH_3

a similar approach in the synthesis of **11**, but found that the *p*-nitroaniline anion failed to react with the ketal tosylate shown in eq 3 (X = NCH_3) under a variety of reaction conditions. Only when methyl tosylate was the electrophilic component did we observe any alkylation of the aniline anion. Therefore, we investigated the synthesis of **11** by the route shown in Scheme II. The known 2-(2-hydroxyethyl)cyclopentanone ethylene ketal, **12**,[2] was converted to the phthalimide derivative by the method of Mitsunobu et al.,[4] followed by hydrazinolysis to afford the free amine, **13**. Arylation of the amine with *p*-nitrofluorobenzene to give **14** was effected by the method of Taylor and Stocknicki.[9] Methylation at nitrogen followed by removal of the ketal gave the key intermediate **11**. Conversion of this intermediate to the *cis*- and *trans*-amino ammonium salts, **1c** and **2c**, was accomplished in a manner

(2) Knipe, J. O.; Coward, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4339–4348.
(3) Knipe, J. O.; Vasquez, P. J.; Coward, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3202–3209.
(4) Mitsunobu, O. *Synthesis* **1981**, 1–28 and references therein.
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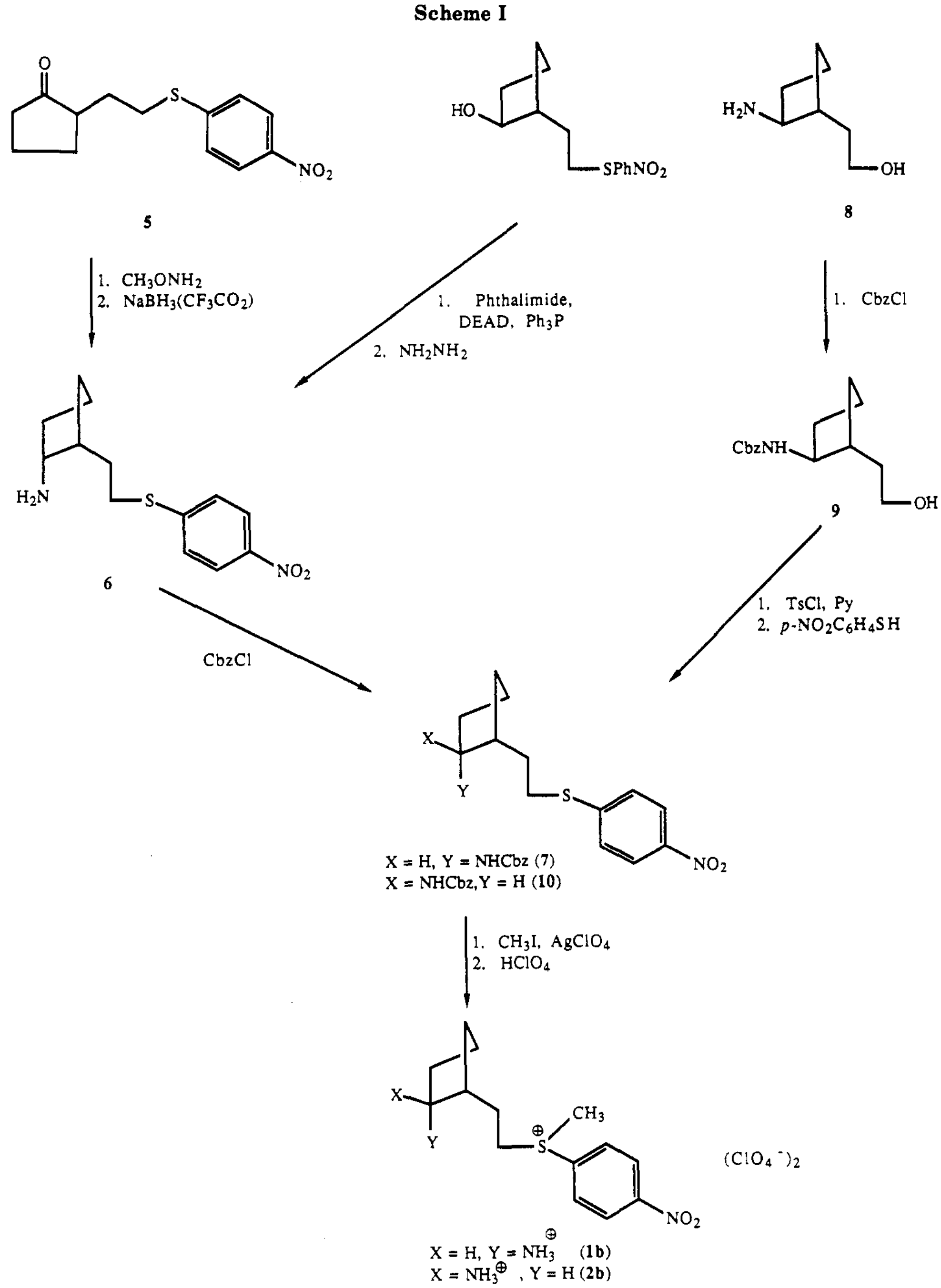
(6) Bayley, H.; Standring, D. N.; Knowles, J. *Tetrahedron Lett.* **1978**, 3633–3634.
(7) Umino, N.; Iwakuma, T.; Ikezaki, M.; Itoh, N. *Chem. Pharm. Bull.* **1978**, *26*, 2897–2898.
(8) Booth, H.; King, F. E.; Mason, K. G.; Parrick, J.; Whitehead, R. L. St. D. *J. Chem. Soc.* **1959**, 1050–1054.
(9) Taylor, E. E.; Stocknicki, J. S. *Synthesis* **1981**, 606–608.

Scheme I

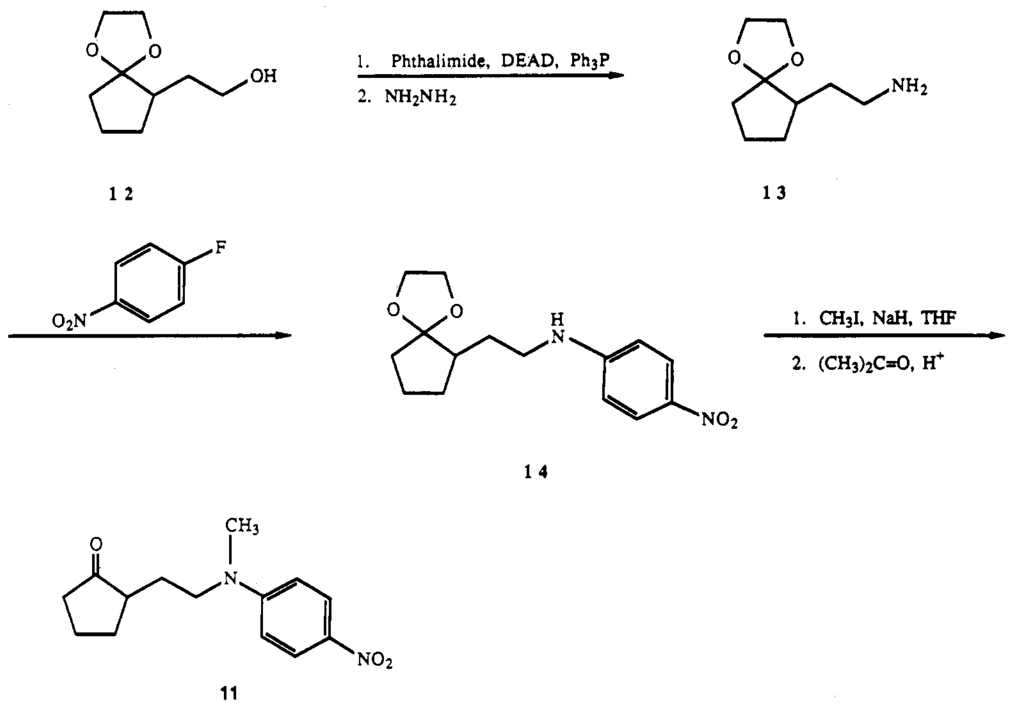


similar to that described for the synthesis of **1b** and **2b**. As depicted in Scheme III, the 2-substituted cyclopentanone, **11**, was converted to the *O*-methyl oxime, **15**, which was reduced to a 1:1 mixture of the *cis*- and *trans*-amines (**16a** and **16b**). This result is in contrast to the isolation of only the *cis*-amine, **6**, on reduction of the oxime derived from **5** under identical conditions (Scheme I). Reaction of the mixture of isomeric amines with benzyl chloroformate led to a mixture of *cis*- and *trans*-benzyl carbamates, which could be separated by preparative TLC to afford the pure cis (**17a**) and trans (**17b**) isomers. Methylation at the anilino nitrogen followed by acid hydrolysis of the benzyl carbamate gave **1c** and **2c** from **17a** and **17b**, respectively.

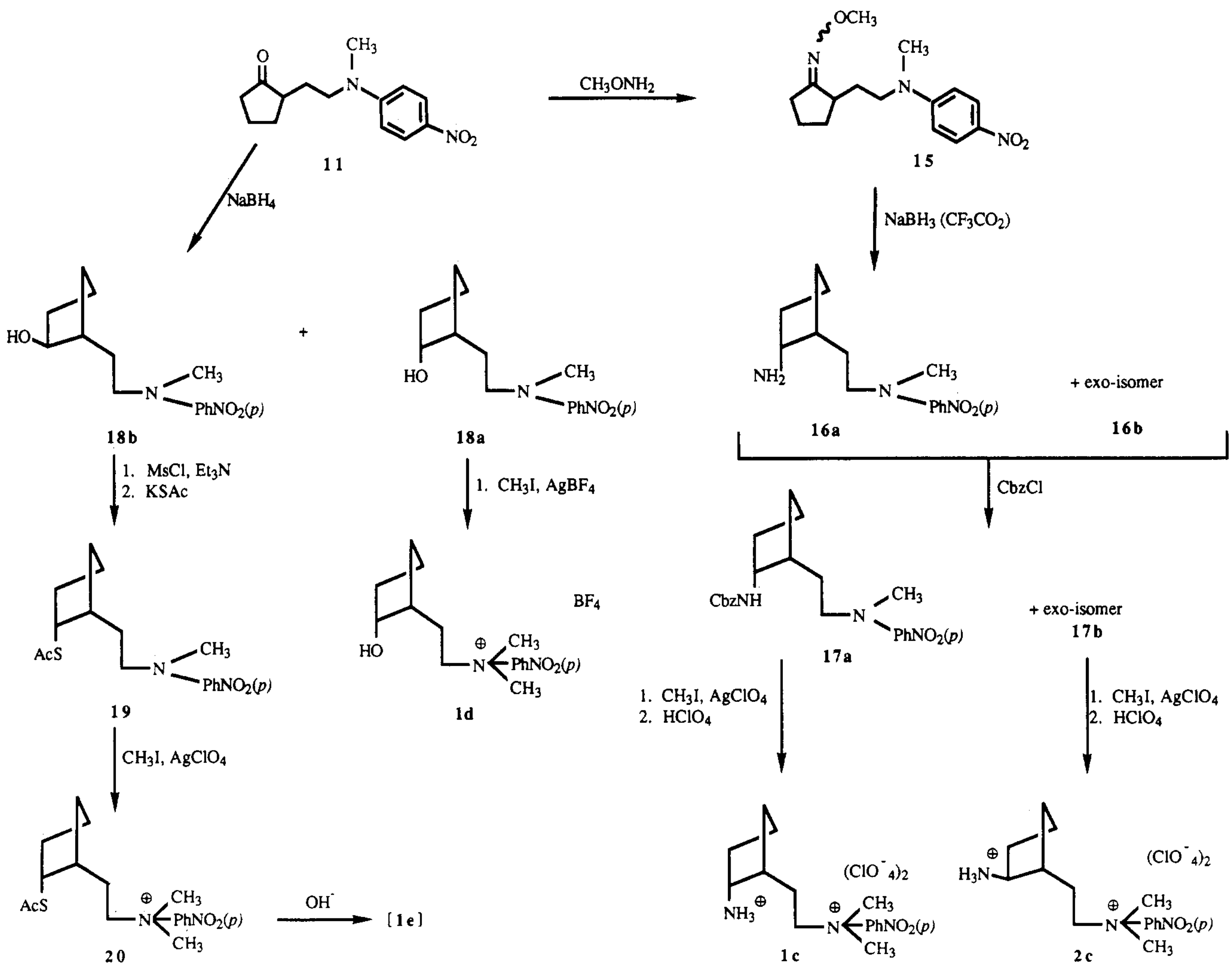
C. Synthesis of *cis*-[(2-Hydroxycyclopentyl)ethyl]ammonium Salt (1d). In a manner similar to that described previously for the reduction of **5**,[2] reaction of **11** with $NaBH_4$ gave a mixture of the *cis*- and *trans*-[(2-hydroxycyclopentyl)ethyl]-*p*-nitro-*N*-methylanilines, **18a** and **18b**, in which the cis isomer predominated by a ratio of ca. 4:1. This is the converse of that observed in an earlier reduction of the related 2-substituted cyclopentanone, **5**, by $NaBH_4$.[2] After separation of the isomeric alcohols by preparative TLC, the cis isomer, **18a**, was converted to the desired anilinium salt, **1d**, by reaction in toluene–CH_2Cl_2 (3:1) with CH_3I in the presence of soluble $AgBF_4$. In contrast, the use of $AgClO_4$, which is insoluble in the CH_2Cl_2 reaction solvent, led to O-methylation of **18a**.

D. Synthesis of *cis*-[(2-Mercaptocyclopentyl)ethyl]ammonium salt (1e). The *trans*-alcohol, **18b**, was converted to the corresponding mesylate under standard conditions. Reaction of the mesylate with KSAc in DMF at 60 °C led to a mixture of three products in a ratio of 1:1:2. The desired *cis*-thioacetate, **19**, could be separated from the other two components by preparative TLC. Methylation at nitrogen gave the S-protected anilinium salt, **20**. This thioester could not be cleaved to the free thiol, **1e**, by 2 N HBr in HOAc. Reaction with 37% HBr

Scheme II

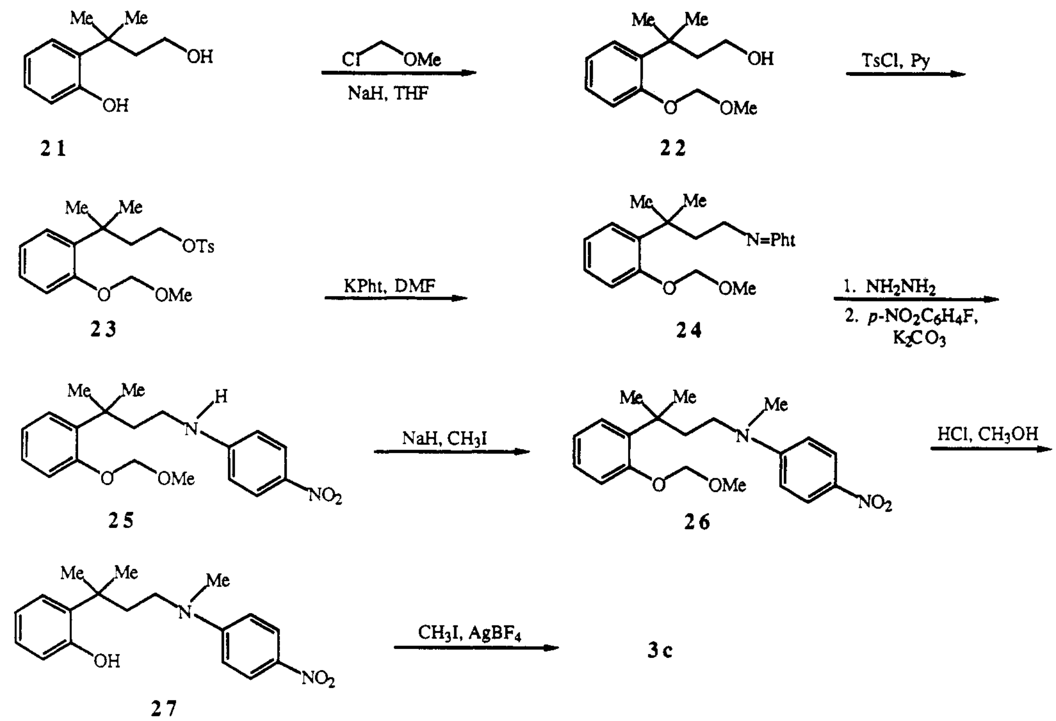


Scheme III



in HOAc led to the undesired disulfide even when carried out in an argon atmosphere and in the presence of the Br_2 scavenger, anisole. Base hydrolysis of **20** gave the desired thiol, **1e**, which immediately cyclized as expected. Therefore, **20** was utilized as a stable precursor of **1e**, and **1e** was generated in situ for kinetic studies.

Scheme IV



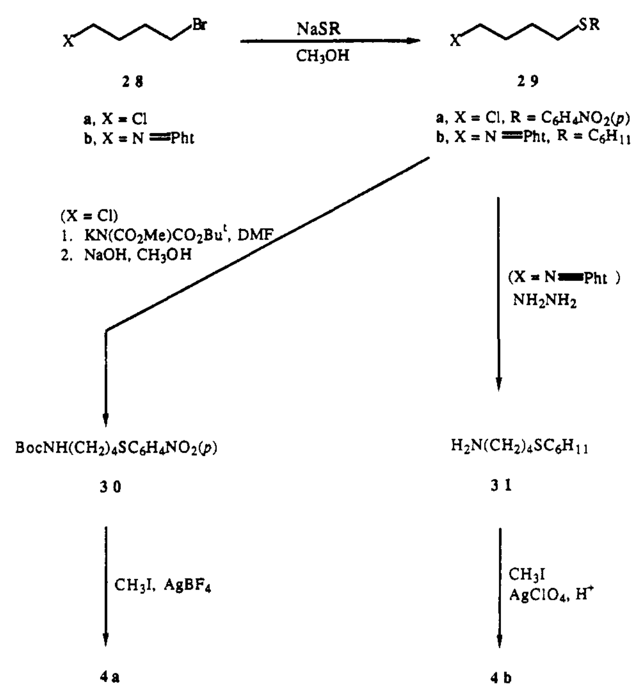
E. Synthesis of [(o-Hydroxyphenyl)propyl]ammonium Salt (3c). Synthesis of the appropriately substituted phenol ammonium salt (Scheme IV) followed the general strategy employed in the synthesis of related phenol sulfonium salts.[3] Thus, 3-(2-hydroxyphenyl)-3,3-dimethyl-1-propanol (21)[10] was selectively protected at the phenolic hydroxyl group as a methoxymethyl (MOM) ether (22). Introduction of the amine functionality was accomplished by reaction of potassium phthalimide with the tosylate (23) derived from 22. Hydrazinolysis of the phthalimide, 24, followed by arylation of the intermediate primary amine with p-nitrofluorobenzene[9] gave 25. Methylation of the aniline anion derived from 25 led to 26, following which the MOM group was removed by methanolic HCl to give 27. The desired phenol ammonium salt, 3c, was then obtained by methylation of 27 with CH_3I in the presence of $AgBF_4$.

F. Synthesis of (4-Aminobutyl)sulfonium Salts (4a,b). Synthesis of the acyclic sulfonium salts followed the same general procedure as outlined above for the synthesis of **1b**. Displacement of bromide in 1-bromo-4-chlorobutane by p-nitrothiophenol or in N-(4-bromobutyl)phthalimide by cyclohexylmercaptan gave the corresponding thioethers. These compounds could be converted to the corresponding amine sulfonium salts by standard methods (see Scheme V and the supplementary material).

Kinetics. The reactions of substrates **1**–**4** have been studied in aqueous buffers over a wide range of pH and, with the exceptions noted below, have been shown to react as shown in eq 1.[1-3] Thus, the cis-aminosulfonium salt, **1b**, and the cis-aminoammonium salt, **1c**, react in a buffer-dependent manner according to the rate expression given by eq 4. Plots of the pH–rate profiles (log k_o vs pH) for **1b** (25 °C) and **1c** (40 °C) are shown in Figure 1. The

$$k_{obsd} = k_o + k_{B_t}[B_t] \qquad (4)$$

Scheme V



solid line in each plot is the best fit of the experimental data to the rate expression shown in eq 5.[11] Each kinetic

$$k_o = k_{RNH_2}\left(\frac{K_a}{K_a + a_H}\right) \qquad (5)$$

run was analyzed as described in the Experimental Section, and the results of these analyses are summarized in Scheme VI. In the case of both **1b** and **1c**, preparative reactions were carried out on a ca. 0.25-mmol scale at high

(10) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166–9174.

(11) (a) Bruice, T. C.; Benkovic, S. J. *Bioorganic Chemistry*; W. A. Benjamin: New York, 1966. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.

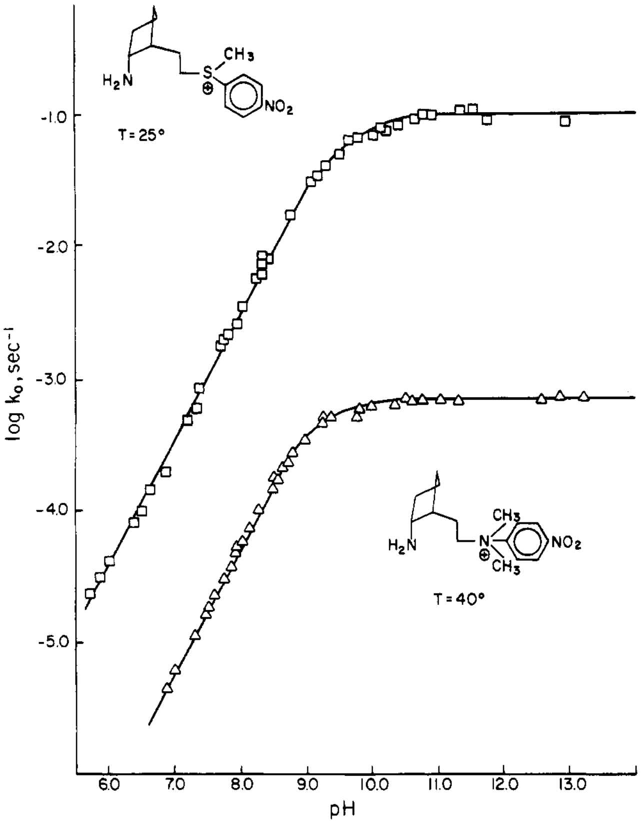


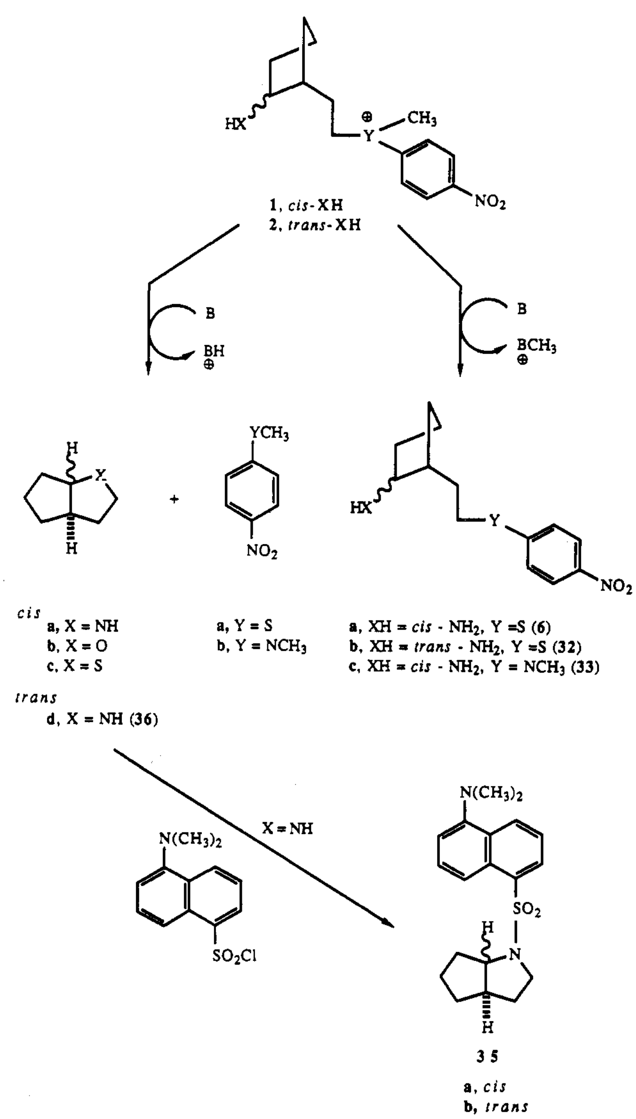
Figure 1. pH–rate profile for the reaction of **1b** (T = 25 °C) and **1c** (T = 40 °C). The points are experimental values and the line represents the best fit of the data to eq 5.

pH (0.1 M OH^-) under conditions of temperature and ionic strength which were identical with those employed in the routine kinetics investigations. In both cases, equimolar amounts of the cyclized amine, *cis*-cyclopentano[*b*]pyrrolidine, and either *p*-nitrothioanisole (from **1b**) or *N,N*-dimethyl-*p*-nitroaniline (from **1c**) were isolated in 85–95% yield. Thus, the reaction of **1b** and **1c** with lyate species at high pH leads only to products arising from the cyclization reaction of interest. At lower pH, buffer-mediated reactions are observed which involve either proton or methyl transfer to the basic buffer species, B. These results are qualitatively the same as previously observed in this laboratory with the *cis*-hydroxy sulfonium salt, **1a**.[2]

In earlier work the *trans*-hydroxy sulfonium salt, **2a**, was shown to be inert under the reaction conditions employed.[2] However, in the current work the *trans*-amino sulfonium salt, **2b**, cyclized to the trans bicyclic amine and *p*-nitrothioanisole, albeit with k_{RNH_2} = ca. 0.1% that of **1b**. In order to obtain an estimate of the rate enhancement obtained by using the cis 2-substituted cyclopentyl system, **1**, the reaction of an acyclic analogue **4a**, was studied, and the products were analyzed as described for **1b** and **1c**. The intramolecular reaction of **4a** to form pyrrolidine and *p*-nitrothioanisole obeyed the rate expression of eq 5 (data not shown) with k_{RNH_2} = ca. 20% that of **1b**. In addition, comparison of the first-order rate constant observed in the intermolecular reaction of cyclopentylamine and diethyl-*p*-nitrophenylsulfonium perchlorate at 40 °C leads to an effective molarity[11] for **1b** of ca. 2×10^5 M. A similar comparison between **1c** and *N,N,N*-trimethyl-*p*-nitroanilium perchlorate could not be made because of the low reactivity of the latter compound with cyclopentylamine.

The *cis*-hydroxy ammonium salt, **1d**, failed to undergo the cyclization reaction of eq 1 at pH <10 and temperatures up to 60 °C. This result precluded the ability to obtain any rate data for **1d** other than an upper limit

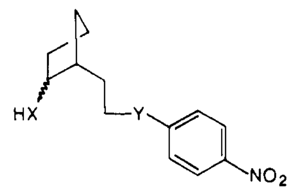
Scheme VI



estimate for k_{ROH}. The pK_{app} for **1d** was estimated to have a value of −2, as previously estimated for **1a**.[3] Given the uncertainty of this datum point on the Brønsted plot (Figure 3), only a lower limit estimate of β could be obtained for the ammonium compounds. At higher pH, formation of *p*-nitrophenol was observed even at 40 °C as a result of hydroxide-mediated displacement of the *N*-methylamine derivative. Similar reactions of hydroxide ion on (*p*-nitrophenyl)sulfonium salts have been observed in earlier work from this laboratory.[2,12] The *cis*-mercapto ammonium salt, **1e**, was generated in situ by basic hydrolysis of the *S*-acetyl derivative, **20**. The rate constant, k_{RS^-}, for the intramolecular cyclization reaction of **1e** to give *p*-nitrothioanisole and, presumably, the *cis*-cyclopentano[*b*]tetrahydrothiophene, could not be determined with great accuracy because of the complex reaction kinetics seen with this compound. The observed lag in the appearance of *p*-nitrothioanisole may be due to a slow hydrolysis of the thiol ester[13] followed by a more rapid cyclization of the thiolate (eq 1). A summary of intramolecular rate constants, k_{RXH} and k_{RX^-}, for the reactions of **1** and **2** discussed above is given in Table I.

(12) Coward, J. K.; Sweet, W. D. *J. Org. Chem.* **1971**, *36*, 2337–2346.
(13) Tarbell, D. S.; Cameron, D. P. *J. Am. Chem. Soc.* **1956**, *78*, 2731–2735.

Table I. Rate Constants for Cyclization of 1 and 2



compd	X	Y	T, °C	k_{RXH}, s^{-1}	k_{RX^-}, s^{-1}	pK_{app}	ref
cis							
1a	O	S	25	5.00×10^{-6}	8.63	16.57	2
1a	O	S	40	3.59×10^{-5}	31.23	16.13	2
1b	NH	S	25	9.28×10^{-2}	–	9.46	*d*
1b	NH	S	40	3.71×10^{-1}	–	9.15[e]	*d*
1c	NH	NCH_3	30	2.00×10^{-4}	–	nd	*d*
1c	NH	NCH_3	40	7.38×10^{-4}	–	9.15	*d*
1d	O	NCH_3	40	$\leq 2.00 \times 10^{-8}$ [a]	nd[b,c]	nd	*d*
trans							
2a	O	S	25	$\leq 2.00 \times 10^{-8}$ [a]	nd[c]	nd	2
2b	NH	S	25	1.22×10^{-4}	–	nd	*d*
2c	NH	NCH_3	40	$\leq 2.00 \times 10^{-8}$ [a]	–	nd	*d*

[a] Temperature range 25–40 °C (**2a**, **2c**) or 25–60 °C (**1d**) → no reaction ($k_{obsd} \leq 2 \times 10^{-8}$ s^{-1}). [b] nd = not determined. [c] Only the slow formation of *p*-nitrophenol was observed. [d] This work. [e] Not determined directly; based on pK_{app} obtained directly at 40 °C for **1c**.

The phenol ammonium salt, **3c**, also was found to react in a buffer-dependent manner according to the rate expression of eq 4. A plot of the pH–rate profile (T = 40 °C) for **3c** is shown in Figure 2, together with data previously obtained in this laboratory for **3b**.[3] The solid line in each plot is the best fit of the experimental data to the rate expression shown in eq 6.[11] Each kinetic run was analyzed

$$k_o = k_{ROH}\left(\frac{a_H}{K_a + a_H}\right) + k_{RO^-}\left(\frac{K_a}{K_a + a_H}\right) \quad (6)$$

for products as described in the Experimental Section, and the results of these analyses are similar to those summarized above for the reactions of **1** and **2**. The data of Figure 2 lead to values of pK_{app} = 11.16 and $k_{RO^-} = 7.16 \times 10^{-3}$ s^{-1} for the reaction of **3c**. The pK_{app} for **3b** cannot be obtained directly from our kinetics data[3] (Figure 2). A value of pK_{app} = 11.16 has been used for **3b** based on the value obtained for **3c** (Figure 2). These values are similar to pK_a = 11.35 reported for *o-tert*-butylphenol.[14] Together with similar data for **1** and **2** (Table I), discussed above, the data for **3b** and **3c** obtained at T = 40 °C are presented in graphical form as a Brønsted plot[11] in Figure 3.

As noted in the Experimental Section, the pH–rate profiles shown in Figures 1 and 2 are based on data obtained by extrapolating buffer-catalyzed reactions to zero buffer concentration to give a buffer-independent rate, k_o. Unfortunately, quantitative analysis of the buffer dependence has not led to a consistent pattern with the amine nucleophiles (**1b** and **1c**) as was observed previously[2,3] with oxygen nucleophiles (**1a**, **3a**, and **3b**). An exception to this statement is the effect of imidazole buffer on the reaction of **1b** (Figure 4) in which the rate of cyclization is clearly catalyzed by the basic buffer species, imidazole. This is in contrast to the buffer effects observed with **1a** in which imidazole was singularly ineffective in catalyzing the cyclization reaction.[2]

The temperature dependence of the reactions of selected substrates at high pH (0.1 M OH^-) was studied over a temperature range of 25–40 °C. Activation parameters obtained from Arrhenius plots of these rate data are given in Table II, together with values obtained in previous studies from this laboratory.[2,3]

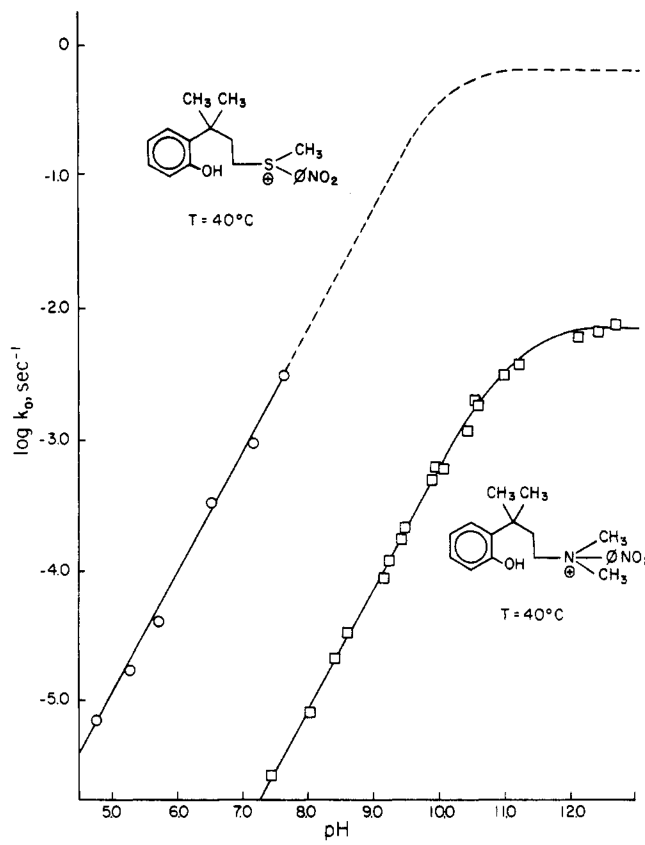


Figure 2. pH–rate profile for the reaction of **3b** and **3c** at T = 40 °C. The points are experimental values and the line represents the best fit of the data to eq 6.

Discussion

The synthetic routes described in this paper (Schemes I–IV) lead to the stereospecific positioning of nucleophilic centers in close proximity to sp^3 carbon adjacent to an onium pole. As such, the resulting molecules, **1**–**4**, are able to undergo cyclization reactions of the type indicated in eq 1. Evidence for the assigned stereochemistry is provided by the NMR data given in the Experimental Section for each new compound. However, the 2-position bearing the

(14) Pliev, T. N. *Dokl. Akad. Nauk. SSSR* **1969**, *184*, 1113–1116.

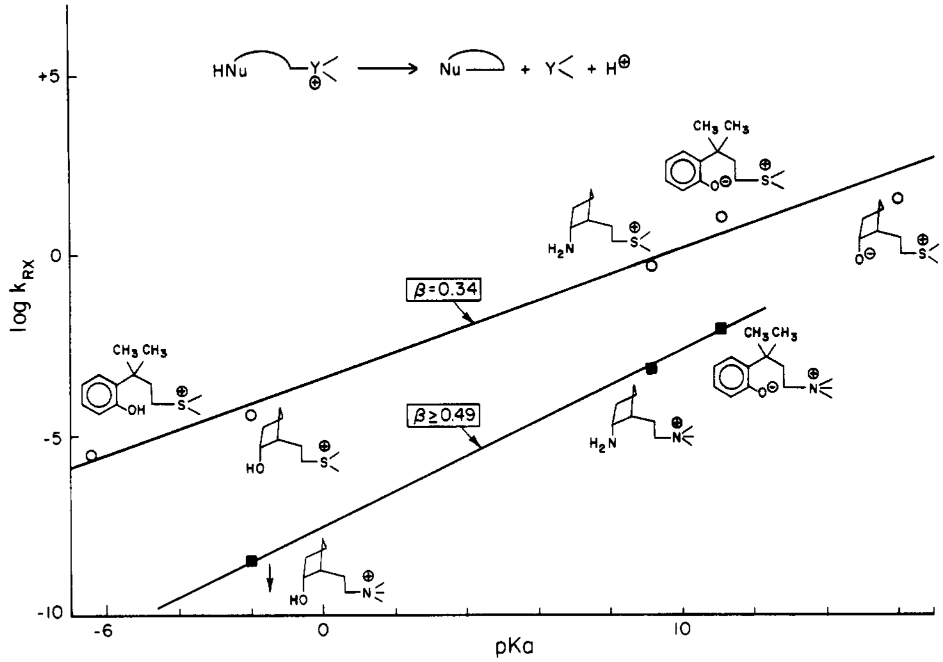


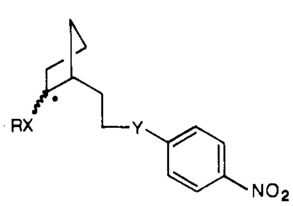
Figure 3. Brønsted plot of log k_{RXH} or k_{RX^-} vs pK_a of the conjugate acid for a series of sulfonium compounds (**1a**, **1b**, **3b**) and ammonium compounds (**1c**, **1d**, **3c**) at T = 40 °C. The line (slope = β) represents the least-squares fit of the data.

Table II. Activation Parameters of k_{RXH} or k_{RX^-} of Selected Substrates

compd	k	$\Delta G^{\ddagger\,a}$	$\Delta H^{\ddagger\,a}$	$\Delta S^{\ddagger\,b}$	ref
1a	ROH	27.0	22.5	−15	2
1a	RO^-	16.1	15.1	−3.7	2
1b	RNH_2	18.9 ± 3.0	16.2 ± 2.6	−9.2 ± 1.5	this work
1c	RNH_2	22.9 ± 0.2	22.7 ± 0.2	−0.7	this work
3a	RO^-	21.5	25.6	13.6	3
3c	RO^-	21.5 ± 0.8	22.5 ± 0.8	3.2 ± 0.1	this work
4a	RNH_2	19.8 ± 0.8	14.8 ± 0.6	−16.9 ± 0.7	this work

[a] Kilocalories/mole. [b] Calories/degree mole.

Table III. NMR Resonances of Stereochemically Diagnostic Shifts for Model Compounds



compound	X	Y	R	δ, α-methine (·), ppm ¹H	¹³C
7	NH (*cis*)	S	Cbz	4.20	–
10	NH (*trans*)	S	Cbz	3.69	–
17a	NH (*cis*)	NCH_3	Cbz	4.21	54.22
17b	NH (*trans*)	NCH_3	Cbz	3.69	58.00
desMe-**1a**[a]	O (*cis*)	S	H	4.21	–
desMe-**2a**[a]	O (*trans*)	S	H	3.83	–
18a	O (*cis*)	NCH_3	H	4.20	74.48
18b	O (*trans*)	NCH_3	H	3.88	82.77
19	S (*cis*)	NCH_3	Ac	4.00	48.31
endo-norbornamine[b]				3.69	23.3
exo-norbornamine[b]				2.79	25.3
endo-norborneol[c]				3.98	42.4
exo-norborneol[c]				3.70	44.3

[a] Reference 2. [b] Reference 15. [c] Reference 16.

nucleophilic group in the cyclopentyl series, **1** and **2**, is most sensitive to changes in the relative stereochemistry of interest in this work. In Table III are found ¹H and ¹³C chemical shift data for this methine CH, together with data from the literature on the endo and exo isomers of norbornamine[15] and norborneol.[16] From these data it is clear that the change in chemical shift (upfield for ¹H, downfield for ¹³C) observed in the *exo*- vs *endo*-norbornyl compounds

(15) Wilson, N. K.; Stothers, J. B. In *Topics of Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley & Sons: New York, 1974; Vol. 8, p 43.

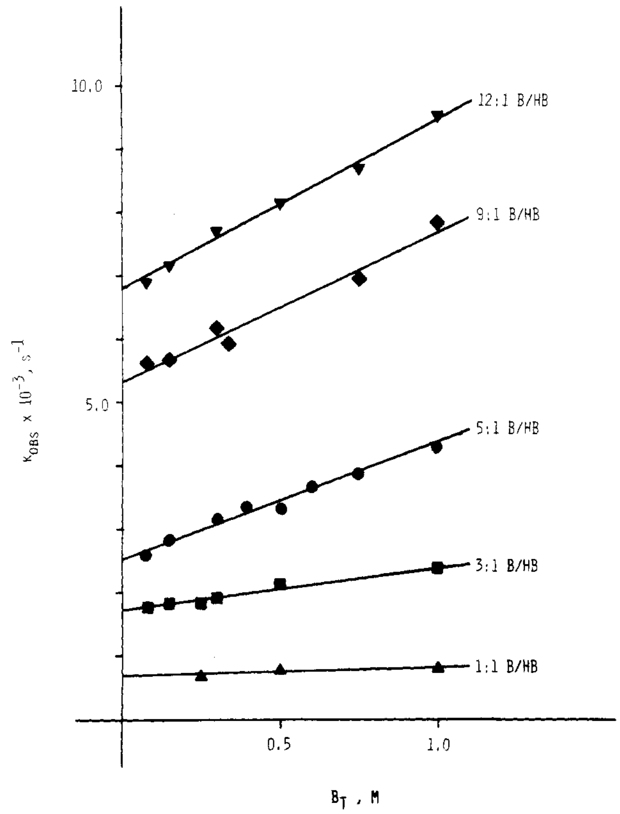


Figure 4. Buffer dependence of observed rate of reaction (k_{obsd}) of **1b** in imidazole buffer (T = 25 °C).

is observed in the *trans*- vs *cis*-1,2-disubstituted cyclopentyl derivatives studied in this work and in previous work from this laboratory.[2] These data, together with the large difference in the rate of cyclization in 1 vs 2 (Table I) provide strong support for the assigned stereochemistry.

The kinetics data summarized in Table I and Figure 3 not only show a correlation between rate and nucleophilicity (Brønsted relation), but also one between rate and nucleofugality. As is expected, each sulfonium compound has a higher value of k_{RXH} and k_{RX^-} for a given intramolecular nucleophile than does the corresponding ammonium compound. In addition, the fact that *N,N*-dimethyl-*p*-nitroaniline is a poorer leaving group than *p*-nitrothioanisole should result in a later transition state for reactions involving the ammonium compounds vs the sulfonium compounds according to the Hammond postulate.[17] This is borne out by the values of $\beta = 0.34$ vs $\beta \geq 0.49$ for sulfonium salts vs the ammonium salts. Unfortunately, the low reactivity of several of the ammonium compounds (i.e., **1d** and **3c**) precluded obtaining as extensive a set of data for the ammonium series as had been possible for the sulfonium series. It should be noted that the most reactive ammonium salt, **1e**, has a value of k_{RX} much higher than would be predicted based on its pK_a value. This positive deviation from the Brønsted relation is presumably due to the known enhanced reactivity of soft nucleophiles with soft electrophiles.[18] Due to concerns about its accuracy (see Results), the rate constant, k_{RX}, obtained for **1e** was not included in the correlation to determine the value of $\beta \geq 0.49$ for the ammonium series.

Limited temperature-dependence studies were carried out and led to the activation parameters presented in Table II. It is tempting to explain this type of data in terms of subtle changes in transition state structure. However, the data of Table II do not allow us to draw such conclusions with any degree of confidence. Of interest in terms of recent discussions on the origin of rate enhancements in intramolecular reactions[19] is the wide range of $\Delta S^{\ddagger}$ shown in the data. There is no apparent correlation between enhanced reactivity and a positive $\Delta S^{\ddagger}$. The compounds containing intramolecular oxygen nucleophiles for which sufficient rate data are available (**1a**, **3a**, and **3c**) show more positive $\Delta S^{\ddagger}$ values for the oxyanions than for the neutral amine or alcohol/phenol species. This may be due to an extensively solvated oxyanion, which must be desolvated before the reaction of interest can occur.

Compounds of the type reported in this paper should allow for probing the molecular features required for general base catalysis of nucleophilic reactions at sp^3 carbon.[1-3,20] At this point, one can say only that general catalysis of nucleophilic reactions at sp^3 carbon depends on the nucleophile, the leaving group, and the buffer. Such catalysis has been observed in a limited number of cases in this research (e.g., Figure 4) and previously.[1-3,20] This indicates that further studies along these lines would suggest mechanisms by which this type of catalysis might be involved in enzyme-catalyzed reactions of *S*-adenosylmethionine and 5-methyltetrahydrofolate.

Experimental Section

All reaction solvents as well as organic buffers were purified by known methods.[21] All reactions were under a positive pressure of nitrogen. Analytical thin-layer chromatography was carried out on the following sorbents: silica gel (EM Reagents 5775), cellulose (Eastman 13254), Neutral alumina (EM Reagents 5581), reverse phase (Analtech, 250 µm). Preparative thin-layer chromatography was performed on silica gel plates (Analtech 1000, 1500, and 2000 µm thickness). Flash column chromatography[22] (40–63 µm silica gel, EM Reagents 9385), and preparative high-performance liquid chromatography (HPLC) (Waters 500 A with silica column) were also employed. Analytical HPLC analyses were done on a modular system incorporating an Altex 100A pump (isocratic elution), a Rheodyne injection port (200 µL loop), and either a Whatman Partisil PXS 10/25 ODS-2 or an Altex Ultrasphere ODS column. Sample detection was accomplished on a Gilson Holochrome and Hewlett-Packard 3390A integrator. Routine variable-wavelength UV scans were carried out on a Perkin-Elmer 552 spectrophotometer with a Hitachi X-Y recorder. ^{1}H NMR spectroscopy was done using either a Varian T-60, a Perkin Elmer R-600, or a Varian XL-200 spectrometer. ^{13}C NMR (broad band decoupled) was performed on either a Bruker WB-100 or a Varian XL-200 spectrometer. All resonances are reporter as ppm (δ) versus internal standards: TMS for organic solvents and TSP for D_2O. Samples for IR spectroscopy were analyzed as Nujol mulls, KBr pellets, or as films on NaCl plates. Melting points were taken on a Mel-Temp device and are uncorrected.

Reaction kinetics were monitored by a Gilford 2400 spectrophotometer with a water-jacketed four-position cuvette holder, and calculations were performed on a IBM CS 9000 laboratory computer using the GILRUN program.[23] Alternatively, reaction kinetics were studied by use of a Beckman DU-7 spectrophotometer interfaced to an IBM CS 9000 computer with either the KINESTAT or KINECONT programs.[23] Reaction temperatures for the kinetic studies were maintained within ±0.05 °C by either a Haake FE-2 water bath or a Haake E-2 immersion heater/circulator. Determination of pH was accomplished with a Radiometer Model 26 meter equipped with a Radiometer Ag/AgCl electrode (GK2402 B) with sample immersion in a 10-gal water

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(17) Reference 11b, pp 193–199.
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(19) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128–134.
(20) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 340–344.
(21) Perrin, D. D.; Armarego, W. L.; Perrin, D. R. *Purification of Laboratory Compounds*, 2nd ed.; Pergamon Press: New York, 1980.
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(23) Miller, R. J. Ph.D. Thesis, Rensselaer Polytechnic Institute, Troy, NY, 1985.

bath which had been equilibrated to the desired temperature with a Braun Thermomix II immersion heater/circulator.

2-(2′-Oxocyclopentyl)ethyl *p*-Nitrophenyl Thioether, Oxime *O*-Methyl Ether. 1-(2-Oxocyclopentyl)-2-[(*p*-nitrophenyl)thio]ethane, **5**,[2] (200 mg, 0.85 mmol) was dissolved in absolute ethanol (1 mL) and pyridine (1 mL) and placed in a 10-mL round-bottom flask. To this was added *O*-methylhydroxylamine hydrochloride (104.6 mg, 1.26 mmol), and the resulting solution was heated at reflux temperature for 16 h, at which point a white precipitate had formed (presumably pyridinium hydrochloride). The solvent then was evaporated in vacuo, and the resulting residue was dissolved in $CHCl_3$ (15 mL). The $CHCl_3$ solution was washed with H_2O (3 × 10 mL), 10% H_2SO_4 (3 × 10 mL), and brine (3 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo to yield a yellow oil (185 mg, 84%). The syn and anti ketoximes were resolved on preparative TLC (silica gel, hexane–EtOAc (2:1)) to give two bands of R_f = 0.51 (28 mg, 13%) and R_f = 0.66 (139 mg, 47%). The ^{1}H and ^{13}C NMR spectrum of the two isomers were in agreement with previously reported ^{1}H data[24] and ^{13}C[25] data for *O*-methyl oximes of 2-substituted cyclopentanones. Inspection of these data allowed the assignment of the syn (R_f = 0.51) and anti isomer (R_f = 0.66). Syn: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03, 7.23 (dd, *J* = 8.0 Hz, 2, aromatic), 3.7 (s, 3, OCH_3), 2.93 (t, *J* = 7.4 Hz, 2, CH_2S), 2.55–0.4 (m, 9, CH_2 and CH); ^{13}C NMR (40 MHz, $CDCl_3$) 166.86 (C=N), 147.67 (C-4 of phenyl), 144.96 (C-1 of phenyl), 126.17 (C-3, C-4 of phenyl), 123.93 (C-2, C-6 of phenyl), 61.44 (OMe), 39.23 (CH_2S), 31.11 (methine), 30.95 (CH_2C=N), 30.29 (CH_2C), 30.16 (CH_2CH_2=N), 23.09 ppm (CH_2CH_2S). Anti: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02, 7.32 (dd, *J* = 9.0 Hz, 4, aromatic), 3.82 (s, 3, OCH_3), 3.4–3.0 (m, 2, CH_2S), 2.6–1.0 (m, 9, CH_2 and CH); ^{13}C NMR (40 MHz, $CDCl_3$) 166.96 (C=N), 147.88 (C-4 of phenyl), 144.81 (C-1 of phenyl), 125.99 (C-3, C-5 of phenyl), 61.56 (OCH_3), 39.23 (CH_2S), 31.82 (methine), 31.38 (CH_2C=N), 29.68 (CH_2C), 27.65 (CH_2CH_2C=N), 22.60 ppm (CH_2CH_2S). Anal. Calcd for $C_{14}H_{18}N_2O_3S$ (anti): C, 57.12; H, 6.16; N, 9.52. Found: C, 57.09; H, 6.19; N, 9.38.

***cis*-2-(2′-Aminocyclopentyl)ethyl *p*-Nitrophenyl Thioether (6). Method A.** The reduction of the ketoxime prepared above was performed according to the procedure of Umino and co-workers.[7] The ketoxime (100 mg, 0.38 mmol) was dissolved in dry distilled THF (1.6 mL) and placed in a 10-mL pressure-equalized addition funnel which was affixed to a three-neck 50-mL round-bottom flask fitted with a rubber septum and reflux condenser. Sodium borohydride (64.6 mg, 1.71 mmol) in THF (1.6 mL) was added to the round-bottom flask, followed by syringe addition of trifluoroacetic acid (131 μL, 1.71 mmol). After the cessation of H_2 evolution, the ketoxime was added dropwise over 15 min, followed by stirring at ambient temperature for 2 h and then 16 h at reflux. The resulting reaction mixture was quenched with H_2O (1.5 mL) and concentrated in vacuo. The residue was dissolved in methylene chloride (15 mL), washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and evaporated in vacuo to give a yellow oil. The oil was dissolved in diethyl ether (10 mL) followed by bubbling with dry HCl gas. The green solid that formed was recrystallized twice from MeOH–ether to give the HCl salt of **6** as dark brown rods (50 mg, 48%, mp 143–145 °C): ^{1}H NMR (60 MHz on free amine, $CDCl_3$) δ 8.02, 7.22 (dd, *J* = 8 Hz, 4, aromatic), 3.9–3.5 (m, 1, CHN), 3.21–2.6 (t, *J* = 9.0 Hz, 2, CH_2S), 2.3–0.5 (m, 12, CH_2 and CH); IR (film, cm^{-1}) 3360 (w, NH), 2942 (m, alip CH), 1592, 1570 (s, aromatic), 1510 (s, N=O), 1335 (s, C–N).

Method B. *trans*-2-(2′-Hydroxycyclopentyl)ethyl *p*-nitrophenyl thioether[2] was converted to the corresponding *cis*-2′-*N*-phthaloyl derivative by the procedure of Mitsunobu et al.[4] and involved the addition of triphenylphosphine (221.1 mg, 0.84 mmol) and phthalimide (124 mg, 0.84 mmol) in THF (5 mL) to a solution of the trans alcohol (225 mg, 0.84 mmol) and diethyl azodicarboxylate (DEAD) in THF (30 mL). The reaction solution was allowed to stir for 72 h after which the solvent was removed in vacuo. The residual yellow solid was purified by preparative TLC (hexanes–EtOAc, 3:1) to give 137 mg (42%) of the *N*-phthaloyl derivative as a yellow oil. This material (0.35 mmol) was dissolved in 95% EtOH (15 mL) containing 85% NH_2NH_2·H_2O (0.3 mL, 5.25 mmol) and heated at reflux temperature for 6 h. The reaction solution was cooled, added to H_2O (50 mL), and acidified to pH 4.0 with glacial HOAc, and the resulting mixture was then filtered. Concentration of the filtrate in vacuo gave 73 mg (78%) of a yellow oil. A solution of this material in diethyl ether (10 mL) was treated with HCl(g) to provide a crude HCl salt, which was crystallized from MeOH–ether to give 70 mg (66%) of **6**·HCl, mp 143–145 °C. The spectral properties of **6**·HCl prepared by method B were identical with the material prepared by method A. Anal. Calcd for $C_{13}H_{19}N_2O_2SCl$: C, 51.56; H, 6.32; N, 9.25; S, 10.59. Found: C, 51.65: H, 6.36; N, 9.25: S, 10.60.

***cis*-2-[2′-[*N*-(Carbobenzyloxy)amino]cyclopentyl]ethyl *p*-Nitrophenyl Thioether (7).** To 1 N NaOH (5 mL) and diethyl ether (5 mL) was added **6** (283 mg, 0.28 mmol) in a 25-mL three-neck round-bottom flask equipped with gas-inlet adapter, rubber septum, and pressure-equalized addition funnel. Benzyl chloroformate (204.1 mg, 1.20 mmol) in diethyl ether (5 mL) was added to the above mixture via the addition funnel over 0.5 h, followed by stirring at ambient temperature for 18 h. The aqueous phase was removed and extracted with diethyl ether (3 × 10 mL). The ethereal phases were pooled, washed with H_2O (3 × 10 mL) and brine (3 × 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **7** as a yellow solid. Crystallization from MeOH–H_2O yielded **7** as yellow plates (279 mg, 66%, mp 98–99 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15, 7.35 (dd, *J* = 9.0 Hz, 4, aromatic), 7.39 (s, 5, aromatic), 5.15 (s, 2, benzyl), 4.65 (d, *J* = 8.9 Hz, 1, NH), 4.4–4.0 (m, 1, CHN), 3.28–2.85 (t, *J* = 8.0 Hz, 2, CH_2S), 2.38–0.95 (m, 9, CH_2 and CH). Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.89; S, 8.00. Found: C, 62.90; H, 6.09; N, 6.89; S, 7.84.

***trans*-2-[2′-[*N*-(Carbobenzyloxy)amino]cyclopentyl]ethanol (9).** *trans*-2-(2′-Hydroxyethyl)cyclopentylamine, **8**[8] (68 mg, 0.53 mmol), was dissolved in diethyl ether (2.5 mL) and 1 M NaOH (2.5 mL). To this was added benzyl chloroformate (120.0 mg, 0.60 mmol) followed by stirring at ambient temperature for 16 h. The aqueous phase was removed and extracted with diethyl ether (3 × 5 mL). The ether phases were pooled, dried over $MgSO_4$, and evaporated in vacuo to give a clear colorless oil, which solidified upon standing (132 mg, 94%, mp 65–68 °C). An analytical sample was obtained by preparative TLC on silica gel (hexanes–EtOAc (2:1)) to provide **9** in 69% yield as white needles, mp 72–74 °C. Larger scale purification was accomplished by flash chromatography using hexanes–EtOAc (2:1) followed by 2-propanol–EtOAc (1:1) as the mobile phase: ^{1}H NMR 60 MHz ($CDCl_3$) δ 7.30 (s, 5, aromatic), 5.06 (s, 2, benzyl), 3.8–3.4 (m, 4, OH, NH, CH_2O), 2.2–0.9 (m, 9, CH_2 and CH). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 68.40; H, 8.04; N, 5.57. Found: C, 68.36; H, 8.04; N, 5.30.

***trans*-2-[2′-[*N*-(Carbobenzyloxy)amino]cyclopentyl]ethyl Tosylate.** To a solution of **9** (132 mg, 0.50 mmol) in pyridine (1 mL) was added recrystallized (from hexanes) tosyl chloride (107.7 mg, 0.56 mmol) followed by stirring for 16 h at 4 °C. The reaction mixture then was poured into H_2O (10 mL) and extracted with diethyl ether (3 × 10 mL). The ethereal fractions were pooled and washed with 5% H_2SO_4 (3 × 10 mL) and brine (3 × 10 mL), dried over Mg_2SO_4, and evaporated in vacuo to give the tosylate as a clear oil (167 mg, 80%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.7, 7.2 (dd, *J* = 7.4 Hz, 4, aromatic), 7.30 (s, 5, phenyl), 5.1 (s, 2, benzyl), 4.9–4.4 (m, 1, NH), 4.1 (t, *J* = 5.0 Hz, 2, $CH_2OS(=O)_2$), 3.9–3.3 (m, 1, CHN), 2.4 (s, 3, CH_3), 2.3–0.90 (m, 9, CH_2 and CH).

***trans*-2-[2′-[*N*-(Carbobenzyloxy)amino]cyclopentyl]ethyl *p*-Nitrophenyl Thioether (10).** *p*-Nitrothiophenol (70 mg, 0.45 mmol) and sodium methoxide (24 mg, 0.45 mmol) were added to a solution of the tosylate prepared above (160 mg, 0.39 mmol) in dry methanol (2 mL). The reaction solution then was heated to 60 °C for 16 h. The solvent was evaporated in vacuo, and the residue was dissolved in diethyl ether (35 mL). The ether was washed with 5% Na_2CO_3 (5 × 35 mL), H_2O (3 × 30 mL), and brine (3 × 30 mL), dried over Mg_2SO_4, and evaporated in vacuo to yield a yellow solid. Crystallization from MeOH gave **10** as yellow needles (75 mg, 75%, mp 115–116 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12, 7.30 (dd, *J* = 8.0 Hz, 4, aromatic), 7.35 (s, 5, phenyl), 5.08 (s, 2, benzyl), 4.71 (d, *J* = 6.0 Hz, 1, NH), 3.8–3.58 (q, 1, CHN), 3.2–2.9 (m, 2, CH_2S), 2.2–1.2 (m, 9, CH_2 and CH). An analytical

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(25) Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017–1028. See also Fraser, R. R.; Dhawan, K. L. *J. Chem. Soc., Chem. Commun.* **1976**, 674–675.

sample was obtained by a recrystallization from MeOH, mp 119–122 °C. Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99; S, 8.00. Found: C, 62.97; H, 6.05; N, 6.96; S, 8.14.

2-(2′-Oxocyclopentyl)ethylamine, Ethylene Ketal (13). The preparation of the intermediate phthalimide was in accord with the method of Mitsunobu and co-workers[4] in which 2-(2′-oxocyclopentyl)ethanol ethylene ketal, **12**[2] (5.61 g, 32.76 mmol), and DEAD (5.70 g, 32.76 mmol) were dissolved in dry distilled THF (150 mL) and placed in a dry 500-mL three-neck round-bottom flask equipped with a 125-mL addition funnel and two rubber septa. To the addition funnel was added a solution of phthalimide (4.82 g, 32.8 mmol) and triphenylphosphine (8.59 g, 32.8 mmol) in THF (75 mL). The apparatus was thoroughly flushed of air with N_2, and the contents of the addition funnel were added to the rest of the mixture over a 1-h period, followed by stirring at ambient temperature for 48 h. The solvent then was concentrated in vacuo to give a thick yellow semisolid. This material was dissolved in methanol (165 mL) and 85% hydrazine hydrate (2.5 mL, 65.5 mmol), followed by heating at reflux temperature for 16 h. The solvent was cooled and removed under reduced pressure. The resulting solid was partially dissolved in pH 4.0 aqueous acetic acid (100 mL) and filtered. The fitrate then was brought to pH 12.0 with solid KOH and extracted with $CHCl_3$ (3 × 300 mL). The organic fractions were pooled, dried over Mg_2SO_4, and concentrated in vacuo to give a brown solid. Trituration of this solid with $CHCl_3$ followed by cooling (−20 °C) of the $CHCl_3$ solution overnight, and finally removal by filtration of additional solid from the cold $CHCl_3$ extract, led to 3.28 g of crude amine upon evaporation of the $CHCl_3$ in vacuo. This material was sufficiently pure for use in the arylation reaction to provide **14**. Additional crude material (ca. 2.0 g) could be obtained by continuous extraction of the aqueous layer (pH 12.0) with $CHCl_3$. Kugelrohr distillation (56 °C pot temperature (0.050 nmHg)) of a 2.0-g portion of the crude product gave **13** as a clear white liquid (763 mg, 36%): ^1H NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 4, OCH_2CH_2O), 2.72 (t, J = 7.2 Hz, 2, CH_2N), 2.25–0.90 (m, 11, CH_2, CH, and NH); IR (film, cm^{-1}) 3360 (w, N–H), 1585 (w, N–H), 1110 (m, C–N), 1038 (m, C–N). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 61.81; H, 9.92; N, 8.06.

***N*-[2-(2′-Oxocyclopentyl)ethyl]-*p*-nitroaniline, Ethylene Ketal (14).** The arylation of **13** was done according to the procedure of Taylor and Stocknicki[9] in which **13** (81 mg, 0.47 mmol) was dissolved in dry acetonitrile (5 mL). To this was added finely powdered K_2CO_3 (65 mg, 0.47 mmol) and 1-fluoro-4-nitrobenzene (50 μL, 0.47 mmol) followed by heating at reflux temperature for 24 h. The reaction solution gradually turned from colorless to an intense yellow. After cooling, the reaction solution was poured into H_2O (50 mL) and extracted with methylene chloride (3 × 20 mL). The organic fractions were pooled, washed with brine (3 × 50 mL), dried over Mg_2SO_4, and evaporated in vacuo to give a yellow oil (104 mg, 77%). This oil was purified by preparative TLC (2000 μm silica, hexanes–EtOAc (3:1)) to give a bright yellow band (R_f = 0.19), which upon removal and extraction gave **14** as a yellow crystalline solid (72 mg, 52%, mp (iPrOH) 90–92 °C): ^1H NMR (60 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 2, aromatic), 6.5 (d, J = 9.0 Hz, 2, aromatic), 4.05–4.52 (m, 1, NH), 3.95 (s, 4, OCH_2CH_2O), 3.25 (t, J = 6.0 Hz, 2, CHN), 2.20–1.0 (m, 9, CH_2 and CH); mass spectrum (EI, 70 eV), m/e (rel intensity) 99 (100), 141 (93.87), 177 (26.04), 219 (19.69), 231 (21.71), 247 (24.95), 263 (16.47), 292 (40.80). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.64; H, 6.84; N, 9.59. Found: C, 61.56; H, 6.92; N, 9.56.

***N*-[2-(2′-Oxocyclopentyl)ethyl]-*N*-methyl-*p*-nitroaniline, Ethylene Ketal.** To a 15-mL flame-dried flask and magnetic stir bar were added sodium hydride (20 mg, 0.34 mmol) (50% oil emulsion) and freshly distilled THF (6 mL), followed by **14** (100 mg, 0.34 mmol) in THF (5 mL). Upon addition of **14**, the solution turned a deep blue-green with the concomitant evolution of gas (presumably H_2). At this point, methyl tosylate (70 mg, 0.46 mmol) was added. After 16 h of stirring at ambient temperature, the reaction solution was poured into H_2O (60 mL) and extracted with diethyl ether (3 × 10 mL). The ethereal fractions were combined, washed with H_2O (3 × 30 mL), 5% $NaHCO_3$ (3 × 30 mL), and brine (1 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo to yield a yellow oil. The product was purified via preparative TLC (2 × 1000 μm silica gel, eluted once with hexanes–EtOAc (3:1)) to give a yellow band (R_f = 0.35), which, when removed and extracted, gave the desired compound as an oil (89 mg, 85%): ^1H NMR (60 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 2, aromatic), 6.5 (d, J = 9.0 Hz, 2, aromatic), 3.85 (s, 4, OCH_2CH_2O), 3.37 (t, J = 7.6 Hz, 2, CH_2N), 3.00 (s, 3, NMe), 2.20–1.03 (m, 9, CH_2 and CH). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.54; H, 7.27; N, 9.12.

***N*-[2-(2′-Oxocyclopentyl)ethyl]-*N*-methyl-*p*-nitroaniline (11).** To a solution of the ketal prepared above (89 mg, 0.29 mmol) in dry acetone (3.5 mL) was added *p*-toluenesulfonic acid monohydrate (25 mg, 0.14 mmol) followed by heating at reflux temperature for 16 h. The solvent then was removed in vacuo, and the resulting residue was dissolved in diethyl ether (50 mL), washed with 10% Na_2CO_3 (3 × 30 mL), H_2O (3 × 30 mL), and brine (1 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo to give a yellow oil. Crystallization from 2-propanol gave **11** as yellow plates (65 mg, 83%, mp 61–63 °C): ^1H NMR (60 MHz, $CDCl_3$) δ 8.09 (J = 9.0 Hz, 2, aromatic), 6.62 (d, J = 9.0 Hz, 2, aromatic), 3.55 (t, J = 6.0 Hz, 2, CH_2N), 3.08 (s, 3, NCH_3), 2.5–0.7 (m, 9, CH_2 and CH); IR (KBr, cm^{-1}) 1750 (s, C=O). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.05; H, 6.95; N, 10.66.

***N*-[2-(2′-Oxocyclopentyl)ethyl]-*N*-methyl-*p*-nitroaniline, Oxime *O*-Methyl Ether (15).** To pyridine (3 mL) and ethanol (3 mL) were added **11** (348 mg, 1.32 mmol) and *O*-methylhydroxylamine hydrochloride (Fisher) (165.5 mg, 1.98 mmol), followed by heating at reflux temperature for 18 h. The reaction mixture then was cooled to ambient temperature, poured into H_2O (15 mL), and extracted with diethyl ether (3 × 75 mL). The organic fractions were combined, washed with 2% $CuCl_2$ (3 × 100 mL), H_2O, (3 × 100 mL), and brine (1 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo to give 380 mg of a yellow solid. A portion (118 mg) of this crude product was purified by preparative TLC (2 × 2000 μm silica gel, eluted once with hexanes–EtOAc (3:1)) to give two major bands. Removal and extraction gave both the syn and anti isomers of the oxime, **15**, as oils. (R_f = 0.30, 31 mg, 26%; R_f = 0.37, 40 mg, 45%). Analysis of these compounds gave spectral data that were consistent with the previously described oxime precursor of **6**. In this case, the lower band (R_f = 0.31) was determined to be the syn and the upper band (R_f = 0.37) the anti isomer. Syn: ^1H NMR (200 MHz, $CDCl_3$) δ 8.12 (d, J = 9.46 Hz, 2, aromatic), 6.61 (d, J = 9.52, 2, aromatic), 3.84 (s, 3, OCH_3O), 3.46 (t, J = 7.69 Hz, 2, CH_2N), 3.071 (s, 3, NCH_3), 2.26–1.5 (m, 9, CH_2 and CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) 166.80 (C=N), 155.65 (C-4 of aromatic), 128.38 (C-1 of aromatic), 126.56 (C-3, C-5 of aromatic), 110.75 (C-2, C-6 of aromatic), 62.10 (OCH_3), 51.84 (CH_2N), 41.32 (NCH_3), 38.05 (CH on cyclopentyl ring), 33.50 (CH_2C=N), 30.26 (CH_2CH), 28.16 (CH_2CH_2C=N), 23.51 ppm (CH_2CH_2N). Anti: ^1H NMR (200 MHz, ($CDCl_3$) δ 8.12 (d, J = 9.48 Hz, 2, aromatic), 6.70 (d, J = 9.49 Hz, 2, aromatic), 3.90 (s, 3, OCH_3), 4.01–0.39 (m, 2, CH_2N), 3.09 (s, 3, NCH_3), 2.64–1.09 (m, 9, CH_2 and CH); ^{13}C NMR (40 MHz, $CDCl_3$) 167.25 (C=N), 153.44 (C-4 of aromatic), 128.35 (C-1 of aromatic), 126.26 (C-3, C-5 of aromatic), 110.25 (C-2, C-6 of aromatic), 61.83 (OCH_3), 50.91 (CH_2N), 40.73 (NCH_3), 38.48 (CH on cyclopentyl ring), 32.28 (CH_2C=N), 29.29 (CH_2CH), 27.65 (CH_2CH_2C=N), 22.76 ppm (CH_2CH_2N). Anal. Calcd for $C_{15}H_{21}N_3O_3$ (anti): C, 61.84; H, 7.26; N, 14.42. Found: C, 61.63; H, 7.32; N, 14.34.

***cis*- and *trans*-*N*-[2-[2′-[*N*′-(Carbobenzyloxy)amino]cyclopentyl]ethyl]-*N*-methyl-*p*-nitroaniline (17a and 17b).** The same procedure employed in the reduction of the ketoxime precursor of **6** was used and involved suspending sodium borohydride (233 mg, 4.15 mmol) in THF (4.0 mL) with trifluoroacetic acid (319 μL, 4.15 mmol). To this was added **15** (243 mg, 0.83 mmol) in THF (4.0 mL) followed by heating to reflux for 18 h. The excess borohydride reagent was destroyed by the addition of H_2O (10 mL), and the product was extracted into diethyl ether (3 × 80 mL). The ethereal phases were pooled and washed with H_2O (3 × 60 mL) and 5% HCl(aq) (3 × 5 mL). The acid fractions were combined and lyophylized to give a yellow solid. This solid was added to 1 M NaOH (30 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic fractions were pooled, dried over $MgSO_4$, and evaporated in vacuo to give a red oil (100 mg). A portion of this oil (63 mg, 0.24 mmo) was dissolved in diethyl ether (5 mL), followed by 5 mL of 1 M NaOH. To this mixture was added benzyl chloroformate (43 μL, 0.30 mmol) followed by stirring at ambient temperature for 18 h. The ether was transferred to a separatory funnel with the aid of additional ether, washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo to give a yellow oil. Purification by preparative TLC (1500 μm, eluted thrice with hexanes–EtOAc (3:1)) gave two major bands as oils (R_f = 0.43, 30 mg, 15% overall from oxime; R_f = 0.58, 35 mg, 17% overall from oxime). Spectral analysis of these two compounds revealed that the upper band (R_f = 0.58) was the cis isomer, **17a**, while the lower band (R_f = 0.43) was the trans isomer, **17b**. Cis (**17a**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.12 (d, J = 9.50 Hz, 2, aniline), 7.35 (s, 5, phenyl), 6.65 (d, J = 9.5 Hz, 2, aniline), 5.14 (s, 2, benzyl), 4.74 (d, J = 8.8 Hz, 1, NH), 4.35–4.07 (m, 1, CHN), 3.47 (t, J = 8.0 Hz, 2, CH_2N), 3.01 (s, 3, NCH_3), 2.30–0.73 (m, 9, CH_2 and CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) 156.11 (C=O), 153.36 (C-4 of aniline), 136.76 (C-1 of aniline), 136.42 (C-1 of phenyl), 128.60, 128.27, 128.18 (o, m, p C's of phenyl), 126.26 (C-3, C-5 of aniline to nitro), 110.11 (C-2, C-6 of aniline), 66.89 (CH_2OC=O), 54.22 (CHN), 51.65 (CH_2N), 41.21 (NCH_3), 38.38 (CH on cyclopentyl ring), 30.61 (CH_2CHN), 29.68 (CH_2CH_2N), 26.64 (CH_2CHCHN), 21.46 ppm (CH_2CH_2C-HN). Trans (**17b**): ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.09 (d, J = 9.60 Hz, 2, aniline), 7.33 (s, 2, phenyl), 6.58 (d, J = 9.60 Hz, 2, aniline), 5.10 (s, 2, benzyl), 4.68 (d, J = 8.8 Hz, 1, NH), 3.88–3.5 (m, 1, CHN), 3.46 (t, J = 8.0 Hz, 2, CH_2N), 3.04 (s, 3, NCH_3), 2.43–0.63 (m, 9, CH_2 and CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) dm 156.09 (C=O), 153.36 (C-4 of aniline), 136.87 (C-1 of aniline), 136.51 (C-1 of phenyl), 128.57, 128.13, 127.69 (o, m, p of phenyl), 126.28 (C-3, C-5 of aniline), 110.14 (C-2, C-6 of aniline), 66.80 (CH_2OC=O), 58.00 (CHN on cyclopentyl ring), 51.25 (CH_2N), 44.57 (NCH_3), 38.40 (CH on cyclopentyl ring), 32.87 (CH_2CHN), 30.65 (CH_2C-H_2N), 30.38 (CH_2CHCHN), 22.15 ppm (CH_2CH_2CHN). Anal. Calcd for $C_{22}H_{27}N_3O_4$ (cis): C, 66.48; H, 6.85; N, 10.57. Found: C, 66.31; H, 7.12; N, 10.19.

***cis*- and *trans*-*N*-[2-(2′-Hydroxycyclopentyl)ethyl]-*N*-methyl-*p*-nitroaniline (18a and 18b).** To a 100-mL round-bottom flask containing absolute methanol (21 mL) and dry THF (30 mL) chilled to 0 °C were added *N*-[2-(2′-oxocyclopentyl)-ethyl]-*N*-methyl-*p*-nitroaniline, **11** (755 mg, 2.87 mmol), and sodium borohydride (150 mg, 4.00 mmol). The reaction solution turned a deep orange and was allowed to stir at ambient temperature for 18 h. The solvent then was removed in vacuo, and the resulting residue was partioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The organic fraction was removed, washed with H_2O (3 × 50 mL) and brine (1 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by preparative TLC (5 × 2000 μm silica, eluted thrice with hexanes–EtOAc (3:1)) gave two major bands, which upon removal and inspection yielded the cis (R_f = 0.29, 141 mg, 18%) and trans (R_f = 0.18, 526 mg, 69%, mp 70–71 °C after recrystallization from *i*-PrOH) alcohols, **18a** and **18b**. Cis (**18a**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11, 6.63 (dd, J = 9.52, 4, aromatic), 4.26–4.15 (m, 1, CHO), 3.66–3.32 (m, 2, CH_2N), 3.06 (s, 3, NCH_3), 2.05–1.1 (m, 9, CH_2 and CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) 153.09 (C-4 of aromatic), 136.77 (C-1 of aromatic), 126.31 (C-3, C-5 of aromatic), 110.21 (C-2, C-6 of aromatic), 74.48 (CHOH), 51.93 (CH_2N), 43.01 (CH_3N), 38.56 (CH on cyclopentyl), 35.64 (CH_2-CHOH), 29.20 (CH_2CH), 26.49 (CH_2CH_2CH), 21.88 (CH_2CH_2N). Trans (**18b**): ^{1}H NMR (200 MHz, ($CDCl_3$) δ 8.12, 6.60 (dd, J = 9.48, 4, aromatic), 3.88 (q, J = 6.03, CHO), 3.50 (t, J = 7.99, 2, CH_2N), 3.08 (s, 3, CH_3N), 2.2–1.75 (m, 9, CH_2 and CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) 156.96 (C-4 of aromatic), 140.05 (C-1 of aromatic), 129.77 (C-3, C-5 of aromatic), 113.65 (C-2, C-6 or aromatic), 82.77 (CHOH), 55.05 (CH_2N), 49.08 (CH_3N), 42.05 (CH on cyclopentyl), 38.29 (CH_2CHOH), 34.35 (CH_2CH), 33.57 (CH_2CH_2-CHOH), 25.26 (CH_2CH_2N); IR (neat, cm^{-1}) 3300 (O–H). Anal. Calcd for $C_{14}H_{20}N_2O_3$ (trans): C, 63.62; H, 7.64; N, 10.60. Found: C, 63.59; H, 7.65; N, 10.55.

***trans*-*N*-[2-(2′-Hydroxycyclopentyl)ethyl]-*N*-methyl-*p*-nitrophenylaniline, *O*-Methanesulfonate.** Mesylation of the alcohol in **18b** was done in accord with the method of Crossland and Servis[26] and involved dissolving **18b** (222 mg, 0.84 mmol), triethylamine (235 μL, 1.68 mmol), and mesylchloride (85 μL, 1.10 mmol) in dry methylene chloride (6 mL) cooled to 0 °C. The reaction solution was allowed to stir at 4 °C for 18 h. The compound was isolated in an identical manner with the literature method[26] except 5% HAc was substituted for 5% H_2SO_4 in the acid wash. The procedure yielded the mesylate as a yellow oil (257 mg, 89%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.01, 6.61 (dd, J = 9.5 Hz, 4 aromatic), 4.85–4.57 (m, 1, CHOS(=O)$_2$), 3.49 (t, J = 7.0 Hz, CH_2N), 3.07 (s, 3, CH_3S(=O)$_2$), 3.01 (s, 3, CH_3N), 2.35–1.20 (m, 9, CH_2 and CH).

***cis*-*N*-[2-[2′-(Thioacetoxy)cyclopentyl]ethyl]-*N*-methyl-*p*-nitroaniline (19).** The *cis*-thioacetyl compound, **19**, was prepared by thioacetate displacement of the *trans*-mesylate prepared directly above and entailed dissolving the mesylate (203 mg, 0.59 mmol) in DMF (5 mL) with purified potassium thioacetate (101 mg, 0.89 mmol) (Kodak). This mixture was heated to 50 °C for 18 h. The reaction mixture was then poured into H_2O (75 mL) and extracted with diethyl ether (3 × 30 mL). The ether fractions were pooled, washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil. This material was purified by preparative TLC (2 × 1500 μm silica eluted once with hexanes–EtOAc (3:1)). Three bands were evident, of which one (R_f = 0.52) was the desired compound, **19** (40 mg, 21%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11, 6.59 (dd, J = 9.0 Hz, 4, aromatic), 4.08–3.95 (m, 1, CHS), 3.41 (t, J = 7.9, 2, CH_2N), 3.053 (s, 3, CH_3N), 2.36 (s, 3, CH_3C(=O)), 2.2-1.2 (m, 9, CH_2 and CH); IR (neat, cm^{-1}) 1683 (C=O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 195.70 (C=O), 150.48 (C-4 of aromatic), 136.23 (C-1 of aromatic), 126.38 (C-3, C-5 of aromatic), 110.30 (C-2, C-6 of aromatic), 51.88 (CH_2N), 48.31 (CHS), 41.49 (CH_3N), 38.65 (CH on cyclopentyl), 33.83 (CH_2CHS), 31.41 (CH_3C(=O)), 30.83 (CH_2CH), 28.69 (CH_2C-H_2CHS), 22.32 ppm (CH_2CH_2N).

3-[2-*O*-(Methoxymethyl)-2-hydroxyphenyl]-3,3-dimethyl-1-propanol (22). The selective protection of the phenolic group was done in accord with the procedure Corey and coworkers.[27] To a two-neck round-bottom flask equipped with a pressure-equalized addition funnel and septum was added sodium hydride (50% oil emulsion) (266.3 mg, 5.55 mmol) suspended in freshly distilled THF (30 mL). To the attached addition funnel was added 3-(2-hydroxyphenyl)-3,3-dimethylpropanol, **21**[3,10] (1.00 g, 5.55 mmol), in distilled THF (20 mL). The reaction flask was chilled to 0 °C, and the contents of the addition funnel were added dropwise over 30 min. Chloromethyl methyl ether (446.8 mg, 5.55 mmol) was added, followed by a gradual warming of the reaction mixture to ambient temperature over 6 h. The reaction was poured into H_2O (200 mL) and extracted into diethyl ether (3 × 80 mL). The ether fractions were pooled, washed with H_2O (2 × 100 mL) and brine (1 × 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil in quantitative yield: ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.26–6.42 (m, 4, aromatic), 5.06 (s, 2, OCH_2O), 3.32 (t, J = 7.0 Hz, 3, CH_2O), 3.37 (s, 3, OCH_3), 2.04 (t, J = 7.0 Hz, CH_2), 3.31 (s, 6, CH_3); IR (neat, cm^{-1}) 3350 (s, OH). An analytical sample was obtained by preparative TLC on silica gel in EtOAc, followed by crystallization of the resulting yellow oil from pentane to give white cubic crystals, mp 48.5–49.0 °C. Anal. Calcd for $C_{13}H_{20}O_3$: C, 71.61; H, 8.99. Found: C, 71.35; H, 8.90.

3-[2-*O*-(Methoxymethyl)-2-hydroxyphenyl]-3,3-dimethyl-1-propyl Tosylate (23). To a 100-mL round-bottom flask charged with pyridine (50 mL) was added **22** (1.41 g, 5.51 mmol) followed by cooling to 0 °C. Tosyl chloride (1.21 g, 6.34 mmol) was added in one portion, and the reaction flask was allowed to stir at 4.0 °C for 18 h. The reaction mixture was poured into H_2O (200 mL) and extracted with diethyl ether (3 × 100 mL). The ethereal fractions were combined, washed with 2% $CuCl_2$ (3 × 100 mL), H_2O (3 × 100 mL), and brine (3 × 100 mL), dried over $MgSO_4$, and evaporated in vacuo to give a quantitative yield of **23** as a clear, white oil. This material was carried on to the next step without further purification: ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.43, 7.08 (dd, J = 8.0 Hz, 4, tosyl), 7.14–6.32 (m, 4, phenyl), 4.92 (s, 2, OCH_2O), 3.62 (t, J = 7.0 Hz, CH_2OS(=O)$_2$), 3.22 (s, 3, OCH_3), 2.22 (s, 3, CH_3 on tosyl), 2.10 (t, J = 7.0 Hz, CH_2), 1.17 (s, 5, CH_3); IR (neat, cm^{-1}) no OH stretch, 1357 (S=O).

3-[2-*O*-(Methoxymethyl)-2-hydroxyphenyl]-3,3-dimethyl-1-propylphthalimide (24). To a 100-mL round-bottom

(26) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.

(27) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, C. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034.

Table IV. Synthesis and Properties of Onium Salts 1-4

compd	anion	precursor	yield, %	λ_{max}
1b	ClO_4^-	**7**	25	252
2b	ClO_4^-	**10**	48	248
1c	ClO_4^-	**17a**	74	237
2c	ClO_4^-	**17b**	83	237
1d	BF_4^-	**18a**	32[a]	250
1e (20)	ClO_4^-	**19**	62	-
3c	BF_4^-	**27**	nd	241
4a	BF_4^-	**30**	64	250
4b	ClO_4^-	**31**	67	220

[a] Yield calculated based on ϵ = 10980 (determined for solution of N,N,N-trimethyl-p-nitroanilinium perchlorate (Zaki, A.; Fahim, H. J. *J. Chem. Soc.* **1942**, 270–272) in H_2O).

flask equipped with reflux condenser were added[23] (2.15 g, 5.50 mmol) and potassium phthalimide (1.11 g, 6.00 mmol) in dry DMF (60 mL). This mixture was heated to 60 °C for 18 h. The solvent was cooled, poured into H_2O (500 mL), and extracted with diethyl ether (3 × 200 mL). The ethereal phases were pooled, washed with H_2O (5 × 200 mL) and brine (2 × 200 mL), dried over $MgSO_4$, and evaporated in vacuo to give a semisolid emerald-green oil (1.80 g, 90%) sufficiently pure for conversion to **25**. Purification of another sample by preparative TLC (1500 μm silica, eluted once with hexanes–EtOAc (3:1)) yielded **24** (R_f = 0.53) as a clear, colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (dm, J = 10 Hz, 4, aromatic phthalimide), 7.40–6.65 (m, 4, phenol aromatic), 5.22 (s, 2, OCH_2O), 3.50 (s, 3, OCH_3), 3.43 (t, J = 8.0 Hz, CH_2N), 2.24 (t, J = 8.0 Hz, CH_2), 1.41 (s, 6, CH_3); IR (film, cm^{-1}) 1762, 1700 (N(C=O)). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.26; H, 7.17; N, 3.14.

***N*-[3-[2-*O*-(Methoxymethyl)-2-hydroxyphenyl]-3,3-dimethyl-1-propyl]-*p*-nitroaniline (25).** To a 100-mL round-bottom flask charged with 95% ethanol (50 mL) and 85% hydrazine hydrate (2.5 mL, 45 mmol) was dissolved **24** (1.80 g, 5.50 mmol). The solvent then was heated to reflux for 18 h. The reaction was cooled to ambient temperature and filtered, and solvent removed in vacuo to give the intermediate amine as a white solid (1.33 g, 100%). This material was dissolved in acetonitrile (60 mL) and placed in a round-bottom flask equipped with reflux condenser. To this solution was added potassium carbonate (760 mg, 5.50 mmol) and 1-fluoro-4-nitrobenzene (776 mg, 5.50 mmol), followed by heating at reflux temperature for 18 h. During this time period, the reactin mixture turned from a turbid white to a bright cloudy yellow. The solvent was removed under reduced pressure, and the resulting residue was partitioned between methylene chloride and H_2O. The organic phase was separated, washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo to give a red oil. Purification by flash column chromatography (200 g silica, eluted with hexanes–EtOAc (3:1), 50-mL fraction volume) yielded the major component eluting at fractions 11–22. Pooling of these fractions and evaporation in vacuo gave **25** as a yellow-crystalline solid (437 mg, 22%, mp 114–116 °C): ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2, aniline), 7.45–6.80 (m, 4, phenol), 6.25 (d, J = 9.0 Hz, 2, aniline), 5.15 (s, 2, OCH_2O), 4.40–4.0 (m, 1, NH), 3.43 (s, 3, OCH_3), 3.26–2.75 (m, 2, CH_2N), 2.20 (t, J = 8.0 Hz, 2, CH_2), 1.45 (s, 6, CH_3). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.20; H, 7.02; N, 8.13. Found: C, 65.66; N, 7.01; N, 7.84.

***N*-[3-[2-*O*-(Methoxymethyl)-2-hydroxyphenyl]-3,3-dimethyl-1-propyl]-*N*-methyl-*p*-nitroaniline (26).** To a flame-dried 100-mL round-bottom flask was placed sodium hydride (65 mg, 1.30 mmol) (50% oil emulsion) in freshly distilled THF (60 mL) followed by **23** (437 mg, 1.22 mmol), the addition of which caused effervescence. When this outgassing had ceased, CH_3I (80 μL, 1.30 mmol) was added, followed by stirring at ambient temperature for 18 h. The solvent was concentrated under reduced pressure to yield a yellow semisolid residue. This material was partitioned between H_2O (100 mL) and diethyl ether (100 mL). The ether phase was removed, washed with H_2O (3 × 75 mL) and brine (3 × 75 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. Purification by preparative TLC (4 × 1500 μm silica eluted twice with hexanes–EtOAc (3:1)) gave one major band (R_f = 0.70), which upon removal and extraction gave **26** as a yellow oil, which crystallized upon standing (307 mg, 66%, mp 83.5–85 °C): ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.0 (d, J = 9.0 Hz, 2, aniline), 7.40–6.75 (m, 4, phenol), 6.35 (d, J = 9.0 Hz, 2, aniline), 5.16 (s, 2, OCH_2O), 3.42 (s, 3, OCH_3), 3.43–2.95 (m, 2, CH_2N), 2.85 (s, 3, NCH_3), 2.37–2.02 (m, 2, CH_2), 1.43 (s, 6, CH_3). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.32; N, 7.82. Found: C, 66.87; H, 7.34; N, 7.75.

***N*-[3-(2-Hydroxyphenyl)-3,3-dimethyl-1-propyl]-*N*-methyl-*p*-nitroaniline (27).** Removal of the methoxymethyl protecting group was accomplished by the method of Fieser and Fieser,[28] in which **26** (72 mg, 0.20 mmol) was dissolved in absolute methanol (10 mL) with two drops of concentrated hydrochloric acid. This solution was placed in a 25-mL round-bottom flask equipped with a reflux condenser and heated at reflux temperature for 1 h. The solvent was removed in vacuo, and the resulting residue was dissolved in methylene chloride (15 mL). The organic phase was washed with H_2O (3 × 20 mL) and brine (3 × 30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow, crystalline solid. Recrystallization from petroleum ether gave **27** as yellow needles (60 mg, 93%, mp 155–157 °C dec): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (d, J = 9.60 Hz, aniline), 7.30–7.09 (m, 2, phenol), 6.98–6.78 (m, 2, phenol), 6.48 (d, J = 9.60 Hz, aniline), 5.75 (s, 1, OH), 3.20–3.06 (m, 2, CH_2N), 2.95 (s, 3, CH_3N), 2.28–2.12 (m, 2, CH_2), 1.46 (s, 6, CH_3). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.16; H, 7.02; N, 8.78.

General Procedure for Synthesis of Onium Salts 1–4. The thioether or amine (ca. 0.1 mmol) to be methylated was dissolved in CH_2Cl_2 (5–10 mL), to which $AgClO_4$ (1.1 equiv) and CH_3I (1.1 equiv) were added. The reaction solution was allowed to stir in the dark for 1–2 h. The reaction mixture was then filtered through a 0.45-μm Zetapor (AMF) filter, and the filtrate was evaporated in vacuo. The residue was triturated with diethyl ether or toluene in order to remove any unreacted organic starting materials. In the case of the non-amine onium salts (i.e., **1d** and **3c**), the residue was dissolved in H_2O and filtered to provide a stock solution for use in kinetics studies. In the case of the amine onium salts (i.e., **1b**, **2b**, **1c**, and **2c**) derived from Cbz-protected precursors, the Cbz group was removed by dissolving the filtrate residue in 70% $HClO_4$ (ca. 0.5 mL) and heating the solution on a steam bath for 15 min. After cooling, the amine onium salts were precipitated by addition of diethyl ether. The resulting precipitate was collected on a filter, dissolved in H_2O, and filtered, and the aqueous filtrate was lyophilized to give the desired onium salts as highly deliquescent solids. Stock solutions for use in kinetics studies were obtained by dissolving these solids in H_2O. Yield and λ_{max} data for onium salts 1–4 are summarized in Table IV.

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Supplementary Material Available: Details on the synthesis of thioether precursors of **4** and several compounds (**31–37**) used for product analysis studies, in addition to HPLC procedures used for product analysis (Table V) and kinetics determinations (8 pages). Ordering information is given on any current masthead page.

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