The Use of 2-Oxazolidinones as Latent Aziridine Equivalents. 2. Aminoethylation of Aromatic Amines, Phenols, and Thiophenols†,[1]

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The utility of 2-oxazolidinones 1 as latent, carboxylated aziridine functionalities was examined. Reaction of 2-oxazolidinone (**1a**), 3-methyl-2-oxazolidinone (**1b**), 3-(phenylmethyl)-2-oxazolidinone (**1c**), 3-phenyl-2-oxazolidinone (**1d**), 4,4-dimethyl-2-oxazolidinone (**1e**), and 5-ethyl-2-oxazolidinone (**1f**) with aromatic amine salts, phenol, or thiophenols at elevated temperatures (>130 °C) afforded aminoethylated adducts. The aminoethylation occurred with concomitant loss of carbon dioxide to furnish variously substituted N-aryl-1,2-ethanediamines **4**, 1-(2-phenoxyethyl)-2-imidazolidinone (**8**), or 2-(arylthio)ethanamines **9** on reactions of 1 with aromatic amine salts, phenol, and thiophenols, respectively. Imidazolidinone 8 is believed to be a secondary reaction product resulting from the condensation of the initially formed 2-phenoxyethanamine with starting oxazolidinone **1a**. The aminoethylation reaction did not proceed with aliphatic amine hydrochlorides or alkyl mercaptans. Preliminary mechanistic pathways for these ring openings were also investigated employing a specific, C-5 deuterium-labeled oxazolidinone **1b**-d_2. Ring-opening experiments of **1b**-d_2 with *N*-methylaniline hydrochloride suggest reaction can occur through either a dioxazolinium **5** and/or an aziridinium **6** intermediate. In contrast, reaction of **1b**-d_2 with thiophenol suggests ring-opening to proceed only via the dioxazolinium pathway.

Introduction

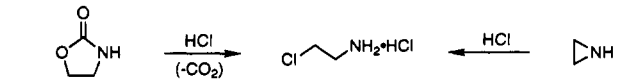
Aminoethylation transformations with amines constitute a fundamental preparative approach to myriad substituted ethylenediamine (1,2-ethanediamine) intermediates in organic synthesis.[3] These intermediates are typically prepared through use of variously substituted aziridine or substituted aziridine salts. However, over the past several decades, increasing evidence has accumulated on the toxic and carcinogenic properties of aziridines and aziridine salts which has severely limited their use for these applications.[4] We wish to describe the continuation of our efforts at the utilization of substituted 2-oxazolidinones for specific aminoethylation applications.[1,5]

The aminoethylation potential of 2-oxazolidinone was first described by Nemirowsky in 1885.[6] He reported that treatment of 2-oxazolidinone (**1a**) with HCl afforded 2-chloroethylamine hydrochloride and CO_2 (Scheme I). This result was followed by Gabriel's observation three years later that aziridine also furnished the same aminoethylation product on reaction with HCl.[7] As a probable result from Gabriel's findings with aziridine, the general utility of the oxazolidinone transformation lay dormant for over 65 years. Later investigators eventually corroborated Nemirowsky's earlier findings by employing other mineral acids and other oxazolidinones.[8] Similarly, more recent work has shown that 2-oxazolidinones can undergo decarboxylative ring-openings with carboxylic and sulfonic acids,[9] carboxylic acid chlorides,[1] and, under appropriate conditions, aromatic amines[10] and π-rich aromatics[11] to afford a wide variety of aminoethylated adducts.

In contrast to the ring opening of oxazolidinones at the C-5 position under electrophilic conditions, nucleophiles react exclusively at the C-2 position to give carbonyl addition products.[12] For example, reaction of oxazolidinones 1 with aliphatic or aromatic amines afford *N*-(2-hydroxyethyl)ureas **2**[13] and imidazolidinones **3**[14] via attack at the C-2 ring carbonyl position. Imidazolidinones **3** are observed only when aromatic amines are employed as a consequence of the higher temperatures which are required to promote the initial ring opening with 1. These higher temperatures subsequently promote the dehydration of **2** to **3** (Scheme II).

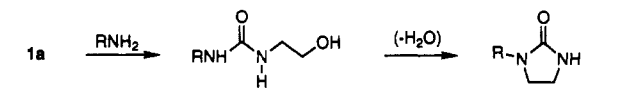
We wish to report in this account our findings on the general reaction of variously substituted 2-oxazolidinones

Scheme I



2-Oxazolidinone (**1a**) Aziridine

Scheme II



2 (R=aliphatic) **3** (R=aromatic)

1 with aromatic amines salts, phenols, and thiophenols to afford the corresponding 1,2-ethanediamine,[15] imidazolidinone, and 2-(arylthio)ethanamine products.[16] These

† Dedicated to Professor A. I. Meyers on the occasion of his sixtieth birthday.

(1) For the preceding paper in this series see: Poindexter, G. S. *J. Heterocycl. Chem.* **1983**, *20*, 1431.
(2) Central Research, Dow Chemical Co., Midland, MI 06498.
(3) Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969; pp 260–262 and references cited therein.
(4) (a) Fishbein, L. J. *Toxicol. Environ. Health (U.S.A.)* **1980**, *6*, 1133. (b) Hata, Y.; Watanabe, M.; Shiratori, O.; and Takase, S. *Biochem. Biophys. Res. Commun.* **1978**, *80*, 911.
(5) Poindexter, G. S. *U.S. Patent* **1983**, 4,381,401.
(6) Nemirowsky, J. J. *J. Prakt. Chem.* **1885**, *31*, 179.
(7) Gabriel, S. *Chem. Ber.* **1888**, *21*, 1049.
(8) (a) McKay, A. F.; Braun, R. O. *J. Org. Chem.* **1951**, *16*, 1829. (b) Viard, M. J. *Brit. Patent*, **1953**, *693*, 325. (c) Jones, J. I. *Chem. Ind.* **1956**, 1454. (d) Piper, J. R.; Elliot, R. D.; Stringfellow, C. R.; Johnson, T. P. *Ibid.* **1966**, 2010. (e) Suto, M. J.; Stier, M. A.; Werbel, L. M. *J. Med. Chem.* **1991**, *34*, 1207.
(9) (a) Najar, H.; Chambrier, P.; Guidicelli, R.; Menin, J. *Bull. Soc. Chim. Fr.* **1957**, 1069. (b) Hsieh, H. H. *U.S. Patent* **1984**, 4,444,694.
(10) (a) Yamanaka, T.; Shimizo, S. and Ikeda, S. *Jpn. Kokai Tokyo Koho* **1975**, 75,111,089; *Chem. Abstr.* **1976**, *84*, 44,207m. (b) Shimizu, S.; Yamanka, T. *Jpn. Kokai Tokyo Koho* **1975**, 101, 373; *Chem. Abstr.* **1976**, *84*, 59,593h.
(11) Jouitteau, C.; Le Perchec, P.; Forestiere, A.; Sillion, B. *Tetrahedron Lett.* **1980**, *21*, 1719.
(12) (a) Dyen, M. E.; Swern, D. *Chem. Rev.* **1966**, *67*, 197. (b) Cornforth, J. W. *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley and Sons: New York, 1957; Vol. 5, pp 396–403.
(13) Najar, H.; Chambrier, P.; Guidicelli, R.; Menin, J.; Duchemin, J. *Bull. Soc. Chim. Fr.* **1959**, 1841.
(14) Gabriel, S.; Eschenbach, G. *Chem. Ber.* **1987**, *30*, 2494.
(15) Analogous products have been reported for the reaction of aromatic amine salts and aziridine. For example, see: Spaenig, H.; Dokner, T.; Karn, H.; Frank, A. *Ger. Offen.* **1972**, 2,057,744; *Chem. Abstr.* **1972**, *77*, 61,523j.
(16) (a) Tomalia, D. A. in *Functional Monomers*; Yocum, R. H., Nyquist, E. B., Eds.; Marcel Dekker: New York, 1974; Vol. 2, Chapter 1, pp 58–71. (b) Pankratov, V. A.; Frenkel, Ts. M.; Fainleib, A. M. *Uspekhi Khimii.* **1983**, *52*, 1018; English translation, *Russian Chem. Rev.* **1983**, *52*, 576.

0022-3263/92/1957-6257$03.00/0

Table I. Solvent and Temperature Dependence on the Reaction of 2-Oxazolidinone (1a) with Aniline Hydrochloride To Yield 4a[a]

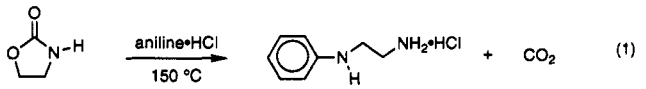
entry	solvent	temp[b] (°C)	time (h)	% yield 4a[c]
1	water	105	16	0
2	*n*-butanol	118	24	0
3	*n*-hexanol	156	72	85
4	2-(2-methoxyethoxy)ethanol	170	3	78
5	neat[d]	170	5	38

[a] All reactions were carried out using 0.10 mol quantities of 1a and aniline hydrochloride in 35 mL of the indicated solvents. [b] Experimentally determined reaction temperature. [c] Isolated crude yields. [d] Solid mixture became a partial melt at 160 °C.

results support those earlier findings of Nemirowsky's which demonstrate that under certain conditions 2-oxazolidinones can function as carboxylated aziridine equivalents.

Results and Discussion

We initially observed that the reaction of 2-oxazolidinone (1a) with 1 equiv of aniline hydrochloride at 160 °C resulted in ring opening of 1a with concomitant evolution of CO_2. After basic workup, *N*-phenyl-1,2-ethanediamine (4a) was obtained as the only product in a 78% distilled yield. Products resulting from C-2 carbonyl addition (2 or 3) were not observed as was previously reported for the reaction of 1a with aniline.[12] Thus, the use of an amine salt in place of a free amine altered the course of the reaction and furnished an aminoethylated product instead of a urea or imidazolidinone (vide supra).

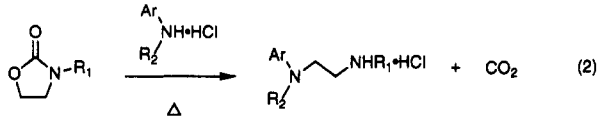


1a 4a

In order to assess the generality of the reaction, the effects of temperature and solvent were investigated. The results of these studies are summarized in Table I. The influence of reaction temperature on the ring-opening is shown in entries 1–4. No reaction occurred on heating equimolar quantities of 1a and aniline hydrochloride in either refluxing H_2O or *n*-BuOH. However, use of the higher boiling *n*-hexanol (156 °C) and 2-(2-methoxyethoxy)ethanol (170 °C) solvents promoted the ring-opening to give diamine 4a and CO_2. By incremental heating of 1a and aniline hydrochloride in *n*-hexanol, CO_2 evolution was initially observed at approximately 130 °C. Thus, this temperature probably represents the minimal temperature which is needed to initiate the reaction.

Reaction rate was also influenced by increasing the reaction temperature. Diamine 4a was obtained in an 85% yield after 72 h in refluxing *n*-hexanol (156 °C, entry 3). A 78% yield of 4a could be obtained after 3 h at 170 °C in the higher boiling 2-(2-methoxyethoxy)ethanol (entry 4). Neat reaction of 1a and aniline hydrochloride at 170 °C only gave diamine 4a in a 38% yield after 5 h. The lower reaction rate and yield observed in this latter case were probably due to inadequate mixing of the reactants since a homogeneous melt between the two reactants was not achieved.

The scope of the reaction was subsequently studied using variously substituted aromatic amine salts and other 2-substituted oxazolidinones 1. The results of these investigations are summarized in Table II. The reactions



1a, R_1=H
1b, R_1=Me
1c, R_1=CH_2Ph
1d, R_1=Ph

4

were carried out either at 170 °C in 2-(2-methoxyethoxy)ethanol solvent (method A) or at 160 °C as neat melts (method B). The progress of the ring-opening reactions could be conveniently monitored by observing carbon

Table II. 1,2-Ethanediamines 4 from Reaction of Oxazolidinones 1 with Aromatic Amine Hydrochloride Salts

entry	oxazolidinone	ArNHR′·HCl	method	product[b]	% yield[c]	mp/bp (°C (mmHg))
1	1a, R = H	$PhNH_2$	A	4a, $PhNHCH_2CH_2NH_2$[d]	78	95 (10 mm)
2	1a, R = H	$PhNH_2$	B	4a, $PhNHCH_2CH_2NH_2$[d]	38	95 (10 mm)
3	1a, R = H	4-$MePhNH_2$	A	4b, 4-$MePhNHCH_2CH_2NH_2$[e]	76	110 (1.5 mm)
4	1a, R = H	2-$ClPhNH_2$	A	4c, 2-$ClPhNHCH_2CH_2NH_2$[f]	50	90 (0.5 mm)
5	1a, R = H	3-$ClPhNH_2$	B	4d, 3-$ClPhNHCH_2CH_2NH_2$[f]	80	201–202[i]
6	1a, R = H	4-$MeOPhNH_2$	A	4e, 4-$MeOPhNHCH_2CH_2NH_2$[e]	45	130 (1 mm)
7	1a, R = H	4-$MeSPhNH_2$	A	4f, 4-$MeSPhNHCH_2CH_2NH_2$[f]	58	95 (0.1 mm)
8	1a, R = H	4-EtO_2CPhNH_2	A	4g, 4-$EtO_2CPhNHCH_2CH_2NH_2$[g]	61	130 (1 mm)
9	1a, R = H	3-O_2NPhNH_2	A	4h, 3-$O_2NPhNHCH_2CH_2NH_2$[h]	72	245 dec[i]
10	1a, R = H	4-H_2NPhNH_2	A	4i, 4-$H_2NPhNHCH_2CH_2NH_2$[f]	29	160 (0.1 mm)
11	1a, R = H	PhNHMe	A	4j, $PhN(Me)CH_2CH_2NH_2$[k]	79	95 (0.5 mm)
12	1a, R = H	PhNHMe	B	4j, $PhN(Me)CH_2CH_2NH_2$[k]	90	214–215[i]
13	1b, R = Me	$PhNH_2$	A	4k, $PhNHCH_2CH_2NHMe$[l]	81	105 (0.4 mm)
14	1b, R = Me	$PhNH_2$	B	4k, $PhNHCH_2CH_2NHMe$[l]	68	160–162[i]
15	1b, R = Me	PhNHMe	B	4l, $PhN(Me)CH_2CH_2NHMe$[m]	89	149–150[i]
16	1b, R = Me	$PhNHCH_2Ph$	B	4m, $PhN(CH_2Ph)CH_2CH_2NHMe$[n]	22	157–159[i]
17	1c, R = CH_2Ph	$PhNH_2$	B	4n, $PhNHCH_2NHCH_2Ph$[l]	63	172–178[i]
18	1c, R = CH_2Ph	PhNHMe	B	4o, $PhN(Me)CH_2CH_2NHCH_2Ph$	56	169–170[i]
19	1d, R = Ph	3-$MePhNH_2$	A	4p, 3-$MePHNHCH_2CH_2NHPh$	28	172–175[p]

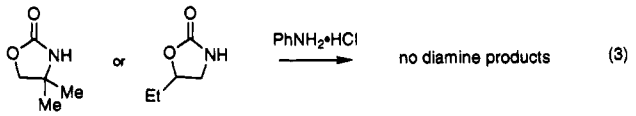
[a] All reactions were carried out as described in the Experimental Section. Method A: 2-(2-methoxyethoxy)ethanol used as solvent. Method B: reactions carried out as neat melts. [b] All products displayed spectral properties (^1H NMR and ^{13}C NMR) which were consistent with the assigned structure. [c] Isolated yield. [d] Seto, E.; Kise, M.; Morita, I. Jpn. Kokai Tokkyo Koho 78 65,845, 1978; *Chem. Abstr.* **1978**, *89*, P197,174b. [e] Fauran, C.; Douzon, C.; Raynaud, G.; Bailly, Y. Fr. Demande 2,204,407, 1974; *Chem. Abstr.* **1974**, *81*, P169,539r. [f] Hiltman, R.; Wollweber, H.; Herman, G. Ger. Offen. 2,140,405, 1973; *Chem. Abstr.* **1973**, *78*, 136,299x. [g] Reference 21b. [h] Lehman, D.; Femmer, K.; Faust, G. Ger. Offen. 2,844,497, 1979; *Chem. Abstr.* **1979**, *91*, P123,552t. [i] Monohydrochloride salt. [j] Wotiz, J. H.; Kleopfer, R. D.; Barelski, P. M.; Hinckley, C. C.; Koster, D. F. *J. Org. Chem.* **1972**, *37*, 1758. [k] Chapuis, C.; Gauverau, A.; Klaebe, A.; Lattes, A.; Perie, J. J.; Tran Le Tran; D'All, A. *Bull. Soc. Chim. Fr.* **1973**, 977. [l] Kliegel, W.; Franckenstein, G. H. *Liebigs Ann. Chem.* **1977**, 956. [m] Kametani, T.; Kigasawa, K.; Hiiragi, M.; Aoyama, T. *J. Org. Chem.* **1972** *37*, 1450. [n] Van der Brink, F. G.; Lien, E. J. *Hand. Exp. Pharmacol.* (Histamine, Anti-Histaminics, Part 2), **1978**, *18*, 333. [o] *n*-Hexanol used as solvent. [p] Dihydrochloride salt.

dioxide evolution or by TLC analysis. In contrast to the results obtained with aniline hydrochloride, good yields of diamines could be obtained by reaction of 1 and the amine hydrochlorides as neat mixtures (entries 5, 12, 14, 15, and 17). In these instances homogeneous melts were realized on heating. In general, if homogeneous melts were not obtained after heating, addition of a small amount of 2-(2-methoxyethoxy)ethanol led to dissolution of the reactants and subsequently higher yields of diamines 4.[17]

There was a casual relationship between relative amine salt acidities and yields of isolated products using the salts of π-deficient and π-rich aromatic amines. In general, the more acidic, π-deficient, amine salts gave higher isolated yields of diamine products as shown in Table II. For example, yields of aminoethylation products resulting from the reaction of **1a** with the hydrochloride salts of 3-chloroaniline (entry 5), 3-nitroaniline (entry 9), or aniline itself (entry 1) were greater than those from the reaction of the more basic salts of 4-anisidine (entry 6), 4-(methylthio)aniline (entry 7), or 1,4-phenylenediamine (entry 10).

Steric interactions of both the oxazolidinone and amine salt were also examined. Addition of an *N*-methyl group to either the amine salt (entries 1 vs 11) or the oxazolidinone (entries 12 vs 15) had little effect on yield of isolated product. However, addition of the larger *N*-benzyl substituent to either oxazolidinone or amine salt (entries 15 vs 16, and 15 vs 18) dramatically lowered the isolated yields of product diamines 4 in comparison to the less sterically demanding methyl congeners. Debenzylation of **1c** under the acidic conditions might also explain lowered product formation in the former example. *N*-Phenyl substitution also adversely affected yields with amine salts. Only low isolated yields of diamine product **4p** were observed on the reaction of *m*-toluidine with 3-phenyl-2-oxazolidinone (**1d**, entry 19).

A more profound example of steric interactions adversely influencing the outcome of the ring-opening reaction was observed with use of either 4,4-dimethyl-2-oxazolidinone (**1e**) or 5-ethyl-2-oxazolidinone (**1f**). No ring-opening of either oxazolidinone with aniline hydrochloride could be detected to give any diamine products. It appears that in the ring openings with amines the oxazolidinone must be unsubstituted at the reacting or adjacent centers. Alkyl ring substituents at either the C-4 or C-5 positions of the oxazolidinone ring critically alters reactivity to preclude aminoethylation chemistry with aniline salts.

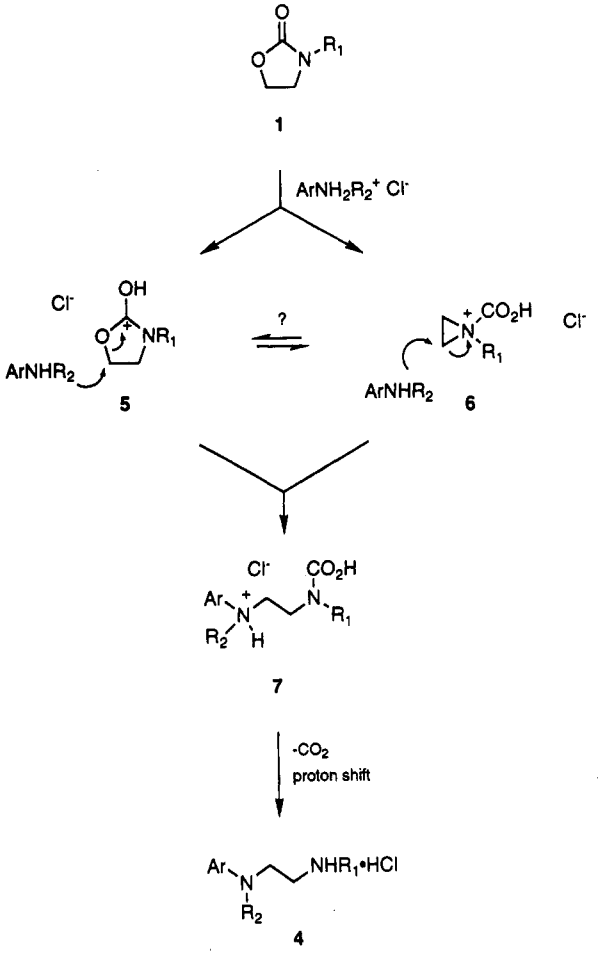


(3)

1e **1f**

The ring-opening reaction did not proceed using the hydrochloride salts of aliphatic amines. Reaction of **1a** and *n*-$BuNH_2$·HCl in 2-(2-methoxyethoxy)ethanol at 160 °C failed to give any diamine product after 12 h. Starting amine and oxazolidinone **1a** were recovered unchanged. The ability of aromatic amine salts and reluctance of of aliphatic amine salts to promote ring-opening can presumably be explained as a function of the relative acidities of their respective conjugate acids. Aromatic amine salts (pK_a's 5) appear to be sufficiently acidic to promote the ring-opening reaction. In contrast, aliphatic amine salts

Scheme III



(pK_a's 10) are considerably less acidic than their aromatic counterpoints and presumably not strong enough acids to initiate the reaction.

Although little is known about the mechanism of this amine salt mediated ring-opening, the results above are consistent with and support reaction through ionic intermediate **5** and/or **6** (Scheme III). Protonation of **1a** by the amine salt at high temperatures could lead directly to ambident dioxazolinium intermediate **5**. Ring-opening by nucleophilic attack at C-5 with aniline would furnish the carbamic acid **7**.[18] Loss of CO_2 and prototropic shift to the more basic aliphatic nitrogen would afford the observed diamine product **4**. Alternatively, ring-opening could perhaps occur through an aziridinium species such as **6**. Nucleophilic attack at the C-2 position of **6** would furnish the carbamic acid **7** and ultimately diamine **4** after decarboxylation and prototropic shift. Whether the diazonium species is preceded by the formation of dioxazolinium intermediate **5** or is formed directly from starting oxazolidinone **1** is unknown at this time.

The mechanism is also attractive since it explains the absence of any polyaminoethylated amine and/or carbonyl addition products. Polyaminoethylated adducts (tri- and tetramines, etc.) are not formed since the primary aliphatic amine salts **4** are not sufficiently acidic to promote further

(17) In one particular instance, large-scale preparation of *N*-methyldiamine **4k** using aniline–HCl and oxazolidinone **1b** and employing 2-(2-methoxyethoxy)ethanol as solvent resulted in substantial formation of the *N,N'*-dimethyldiamine **4l**. **4l** was believed to result from secondary reaction of **4k** with the solvent at 170 °C under acidic conditions.

(18) Similar ambident species have been demonstrated to undergo nucleophilic attack at C-5. See: Hunig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 548.

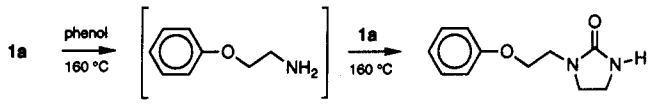
(19) (a) Oda, R.; Miyanoki, M.; Okano, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1910. (b) Oda, R.; Miyanoki, M.; Okano, M. *Ibid.* **1962**, *35*, 1309. (c) Bald, G.; Kretzschmer, K.; Markert, M.; Wimmer, M. *Angew. Makromol Chem.* **1975**, *44*, 151. (d) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; Thomson, D. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 961.

Table III. Arylthioethanamines 9 from Reaction of Oxazolidinones 1 with ArSH[a]

entry	oxazolidinone	ArSH	product[b]	% yield[c]	mp/bp (°C (mmHg))
1	1a, R = H	PhSH	9a, $PhSCH_2CH_2NH_2$[d]	60	130 (0.3 mm)
2	1a, R = H	2-H_2NPhSH	9b, 2-H_2NPhS$CH_2CH_2NH_2$[e]	66	130 (0.2 mm)
3	1a, R = H	4-*t*-Bu-2-MePhSH	9c, 4-*t*-Bu-2-MePhS$CH_2CH_2NH_2$	27	118 (0.2 mm)
4	1b, R = Me	PhSH	9d, $PhSHCH_2CH_2NHMe$[f]	86	95 (0.3 mm)
5	1b, R = Me	2-MeOPhSH	9e, 2-MeOPhSCH_2CH_2NHMe	78	101–103[g]
6	1b, R = Me	2-MePhSH	9f, 2-MePhSCH_2CH_2NHMe	82	103–104[g]
7	1b, R = Me	3-MePhSH	9g, 3-MePhSCH_2CH_2NHMe	70	56–57[g]
8	1b, R = Me	4-MePhSH	9h, 4-MePhSCH_2CH_2NHMe	76	104–106
9	1b, R = Me	4-HOPhSH	9i, 4-HOPhSCH_2CH_2NHMe	55	75–77
10	1b, R = Me	4-H_2NPhSH	9j, 4-H_2NPhSCH_2CH_2NHMe	94	212–215 dec[h]
11	1b, R = Me	4-t-Bu-2-MePhSH	9k, 4-*t*-Bu-2-MePhSHCH_2CH_2NHMe	76	115 (0.9 mm)
12	1c, R = CH_2Ph	PhSH	9l, $PhSCH_2CH_2NHCH_2Ph$[i]	75	120 (0.1 mm)
13	1d, R = Ph	PhSH	9m, $PhSCH_2CH_2NHPh$[j]	93	125 (0.1 mm)
14	1d, R = Ph	4-HO-3,5-(*t*-Bu)$_2$PhSH	9n, 4-HO-3,5-(*t*-Bu)$_2$PhSCH_2CH_2NHPh	63	138–140[k]
15	1e, (4,4-dimethyl)	PhSH	9o, $PhSCH_2C(Me)_2NH_2$[l]	64	159–160[g]
16	1e, (4,4-dimethyl)	2-MePhSH	9p, 2-MePh$CH_2C(Me)_2NH_2$	65	85 (0.4 mm)
17	1e, (4,4-dimethyl)	4-t-Bu-2-MePhSH	9q, 4-*t*-Bu-2-MePhS$CH_2C(Me)_2NH_2$	63	149–150[g]

[a] All reactions were carried out as neat solutions as described in the Experimental Section. [b] All products displayed spectral properties (^1H and ^{13}C NMR) which were consistent with assigned structure. [c] Isolated yield. [d] Reference 24. [e] Pagani, G.; Borgna, P.; Baruffini, A. *Farmaco. Ed. Sci.* **1967**, *22*, 519; *Chem. Abstr.* **1968**, *68*, 39,259v. [f] Wehrmeister, H. L. *J. Org. Chem.* **1963**, *28*, 2589. [g] Monohydrochloride salt. [h] Dihydrochloride salt. [i] Brookes, R. F.; Godson, D. H.; Hams, A. F.; Weighton, D. M.; Wells, W. H. Aus. Patent 491,880, 1978; *Chem. Abstr.* **1978**, *89*, 163,572q. [j] Grillot, G. F.; Schaffrath, R. E. *J. Org. Chem.* **1959**, *24*, 1035. [k] Oxalate salt. [l] Meguerian, G.; Clapp, L. B. *J. Am. Chem. Soc.* **1951**, *73*, 2121.

Scheme IV



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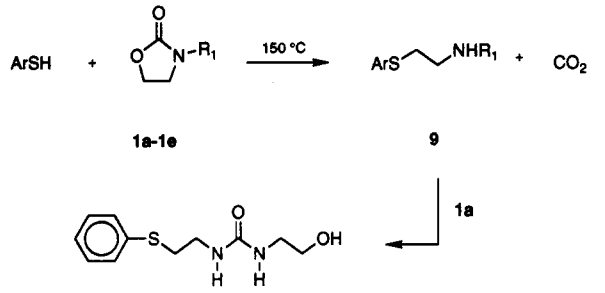
Scheme V



ring-opening with **1**. Carbonyl addition products (**2** and/or **3**) are not observed since the primary diamines **4** are initially formed as their hydrochloride salts and thus precluded from secondary carbonyl additions with the oxazolidinone.

In contrast to the reaction of aromatic amine hydrochlorides with oxazolidinones, the reaction of phenol with **1a** was sluggish and did not afford the desired 2-phenoxyethanamine. Treatment of oxazolidinone **1a** with 1 equiv of phenol at 160 °C afforded a viscous oil. Workup and purification of the oil yielded a small amount (10% yield) of a crystalline material as the only isolable product. Analysis of this material revealed it be imidazolidinone **8** (Scheme IV). Imidazolidinone **8** is the probable result of the reaction of the desired product 2-phenoxyethanamine with **1a** at these elevated temperatures. The predominant products of the reaction were unreacted phenol and a polymeric material assumed to be polyethylenimine.[16a] No further attempts at optimizing the aminoethylation conditions were attempted.

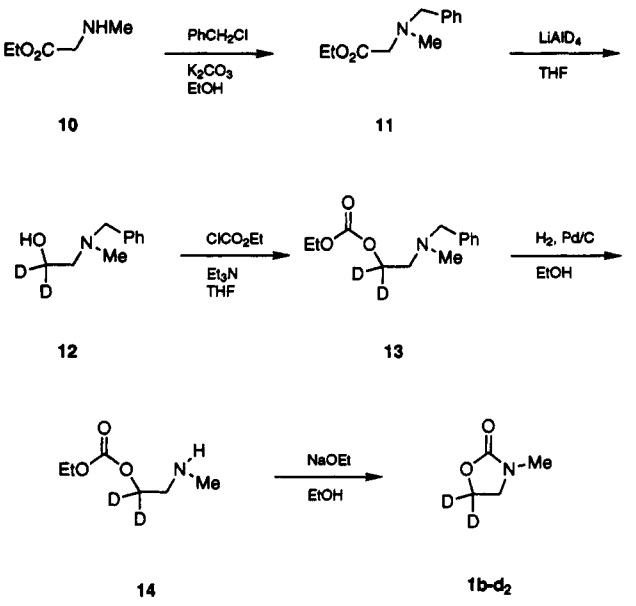
The reaction of oxazolidinones with thiophenols was also examined. In contrast to the reaction described above with phenols, thiophenols promote rapid reaction with oxazolidinones to give aminoethylated adducts in good yields. Treatment of **1a** with 1 equiv of thiophenol in a 130 °C oil bath resulted in a vigorous evolution of CO_2. After 1 h the neat reaction mixture was cooled to ambient temperature where it solidified to a colorless solid. The solid was found to be a 5:1 mixture of the desired 2-(phenylthio)ethanamine (**9a**) and the urea **2a**. Distillation afforded the pure amine **9a** in 60% yield (Scheme V). Control reactions demonstrated that urea **2a** was a secondary product from the condensation of amine **9a** with unreacted **1a**.

Other oxazolidinones and thiophenols were examined in this ring-opening reaction and the results summarized in Table III. No attempts were made to isolate any products other than the desired amines from these reactions. However, it can be seen that when other N-substituted oxazolidinones were used in the ring-opening process, the yields of the desired aminoethylation products **9** increased. Urea formation was only a problem when the N-unsubstituted 2-oxazolidinones (**1a** and **1e**) were employed to give the more reactive primary amines (entries 1–3 and 15–17).

Yields of the desired 2-(arylthio)ethanamines **9** were very high when N-substituted 2-oxazolidinones were used. With the exception of entry 9, isolated yields of amines ranged from 70 to 94% for reaction with oxazolidinones **1b**, **1c**, and **1d**. Thus reaction of thiophenol with *N*-methyl-, *N*-benzyl-, or *N*-phenyl-substituted oxazolidinones efficiently afforded the corresponding N-substituted amines **9d**, **9l**, and **9m** in yields of 86%, 75%, and 93%, respectively. It was observed that some of the more sterically hindered thiophenols having substituents in the ortho position required longer reaction periods for the ring opening to go to completion. However, these examples still provided the desired amines in relatively high yield (entries 5, 6, 11, 16, and 17).

There was little influence of thiophenol acidity on ring-opening. For example, treatment of thiophenol (entry 4) or 4-aminothiophenol (entry 10) with *N*-methyloxazolidinone (**1b**) had little effect on product yields (86% yield for **9d** vs 94% yield for **9j**). The low isolated yield of amine **9i** (entry 9) was probably the result of the chromatography which was required for isolation and purification. In contrast with the aromatic amines, ring-

Scheme VI



opening of the 4,4-dimethyloxazolidinone (**1e**) was easily accomplished to afford 2-(arylthio)propanamines **9o**, **9p**, and **9q** in moderate yields (entries 15–17). Aminoethylations using oxazolidinone **1e** generally required longer reaction times for completion due to the steric effect of the adjacent quaternary position on the ring. No reaction was observed with oxazolidinone **1f**.

Aliphatic mercaptans did not promote the ring opening. Treatment of **1b** with octanethiol at 160 °C for 8 h afforded no aminoethylation products. The oxazolidinone was recovered unchanged. This result is not surprising considering aliphatic amine salts also fail to effect ring opening. In this latter instance aliphatic mercaptans also appear too weakly acidic to promote the reaction.

In comparison to the analogous reactions of oxazolidinones with either amines or phenols, the use of thiophenols generally afforded higher yields of the desired amines as well as requiring shorter reaction times for completion. It appears thiophenols are sufficiently acidic to promote protonation while at the same time better nucleophiles than anilines or phenol to affect ring-opening. The mechanism of the ring opening can be envisioned to proceed through the same intermediates as illustrated in Scheme III with aromatic amines. Both a dioxazolinium intermediate **5** and/or an aziridinium species **6** can be postulated in this reaction. In order to distinguish between these possible modes of ring opening through either dioxazolinium intermediate **5** and/or aziridinium intermediate **6**, we prepared the specifically labeled oxazolidinone **1b**-d_2 to study deuterium distribution in the resulting diamine product. Ring-opening would either be expected to yield a specific C-2 labeled amine from reaction at the C-5 position of **5** or an amine product with both a C-1 and C-2 deuterium distribution pattern by virtue of ring-opening at the degenerate ring positions of aziridinium **6**.

The preparation of 3-methyl-2-oxazolidinone **1b**-d_2 having perdeuterio substitution at C-5 is depicted is Scheme VI. Treatment of ethyl sarcosine (**10**) with benzyl chloride gave the *N*-benzyl adduct **11** in a 72% yield. Reduction of **11** with $LiAlD_4$ in dry THF furnished amino alcohol **12** in quantitative yield. Direct reduction of **10** was precluded due to the appreciable water solubility and consequent low isolated yields of the resulting *N*-methylamino alcohol. High-field ^1H and ^{13}C NMR analysis of **12** revealed complete deuterium incorporation at the reduced position. Reaction of amino alcohol **12** with $ClCO_2Et$ gave carbonate **13** which was subsequently debenzylated on hydrogenolysis to yield amino carbonate **14** in an 80% overall yield. ^1H NMR analysis of **14** indicated no deuterium scrambling had occurred on debenzylation. Ring closure to oxazolidinone **1b**-d_2 was accomplished by treatment with NaOEt in EtOH in a quantitative yield.

The integrity of the deuterium labeling in **1b**-d_2 was proven by NMR analysis. The ^1H NMR spectrum of **1b**-d_2 revealed no C-5 methylene absorption at 4.31 ppm indicating complete deuterium incorporation.[20] This was further supported by ^{13}C NMR analysis of the material which showed a small pentuplet for C-5 at 61.5 ppm which is also consistent for perdeuterio substitution at this position.

Ring-opening of oxazolidinone **1b**-d_2 was carried out by reaction with *N*-methylaniline hydrochloride in the absence of solvent and at temperatures between 140 to 170 °C. The melts were maintained at those temperatures for 18 h to assure completeness of reaction. The deuterium substitution pattern in the product diamine **15a**:**16a** ratios were determined by high-field ^1H NMR analysis (see Experimental Section). The results from these ring openings to yield either diamine **15a** and/or **16a** are summarized in Table IV.

Table IV. Deuterium Labeling Results from the Reaction of Oxazolidinone 1b-d_2 with *N*-Methylaniline Hydrochloride[a]

entry	temp (°C)	time (h)	% yield	15a:16a[b]
1	140	18	27	91:9
2	150	18	31	78:22
3	170	18	24	66:34

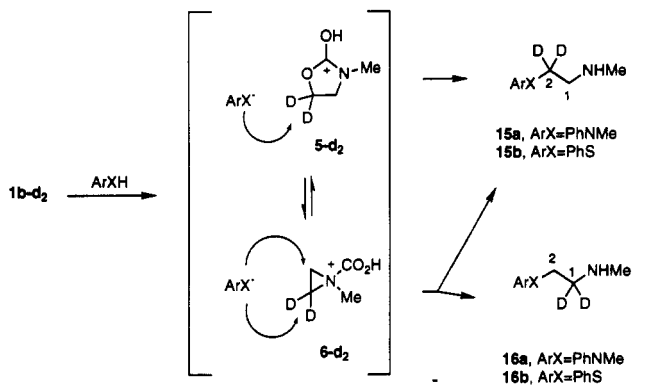
[a] Reactions were carried out on a 5 mmol scale described in the Experimental Section. [b] Deuterium distribution ratios determined by ^1H NMR analysis using a Bruker AM-300 spectrometer and are accurate to within ±5%.

Reaction of **1b**-d_2 with *N*-methylaniline hydrochloride at 140 °C for 18 h gave the deuterium-substituted diamine in a 27% yield. ^1H NMR analysis showed a **15a**:**16a** ratio of 91:9 (entry 1). This result suggests nucleophilic ring-opening proceeds in a greater than 80% fashion via dioxazolinium intermediate **5**-d_2. The ratio, however, was not constant with reaction temperature. If the same reaction was carried out at 150 °C for 18 h, a 31% yield of diamine was isolated and found to have a **15a**:**16a** ratio of 78:22 (entry 2). This temperature effect of lowering the **15a**:**16a** ratio was further manifested on conducting the ring-opening reaction at 170 °C. In this manner the diamine was obtained in a 24% yield and found to have a **15a**:**16a** ratio of 66:34. Control experiments using a **15a**:**16a** hydrochloride salt mixture indicated no thermally-induced, secondary deuterium scrambling occurred on heating. The **15a**:**16a** ratio of 91:9 was unchanged after this mixture was heated at 160 °C for 18 h. Additionally, the integrity of the deuterium positioning in starting oxazolidinone **1b**-d_2 was maintained after heating at 170 °C for 18 h.

These results indicate that reaction temperature has an effect on the deuterium distribution ratios and suggest ring opening can occur through either of the postulated intermediates (Scheme VII). Lower temperatures promote reaction through dioxazolinium species **5**-d_2 while higher temperatures lead to increasing ring-opening by way of aziridinum **6**-d_2. Since the isotopic integrity of oxazoli-

(20) NMR spectral data and assignments for oxazolidinone **1b**: ^1H NMR ($CDCl_3$) δ 4.31 (m, 2 H, CH_2O), 3.60 (m, 2 H, CH_2N), and 2.86 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 158.8 (C-2), 61.7 (C-5), 46.8 (C-4), and 30.9 ppm (C-methyl).

Scheme VII



dinone **1b**-d_2 and product diamines were not secondarily affected at these elevated temperatures, the results can possibly be explained by way of a thermally-induced **5**-d_2 to **6**-d_2 transformation. Oxazolidinone to aziridine rearrangements and the reverse have been reported to occur at elevated temperatures (>200 °C).[19] Under the electrophilic conditions reported here employing aniline salts, it appears this transformation can proceed at substantially lower temperatures (ca. 140 °C).

Reaction of **1b**-d_2 with thiophenol at 140 °C for 5 h gave 2-(phenylthio)ethanamine **15b** in an 82% yield after chromatography. ^{1}H NMR analysis of the free base revealed the C-2 methylene absorption 3.00 ppm was not present. Moreover, the ^{13}C NMR spectrum displayed a pentuplet at the C-2 position (33.2 ppm). None of the isomeric, C-1 deuterium-substituted product **16b** was observed. The same reaction was also carried out at higher temperatures to determine whether any products resulting from the aziridinium pathway could be observed. Reaction of **1b**-d_2 with thiophenol at 170 °C gave **15b** in low yield after chromatography. Again none of the isomeric deuterium pattern in **16b** was observed. In contrast to the aromatic amine hydrochlorides, it appears temperature has no influence on the ring-opening pathway with thiophenols.

In conclusion, appropriately substituted 2-oxazolidinones can function as latent carboxylated aziridine equivalents on reaction with aniline salts and thiophenols. This methodology allows the preparation of a wide variety of *N*-aryl-1,2-ethanediamines and 2-(arylthio)ethanamines. Phenols give only poor yields of aminoethylation products with oxazolidinones. In comparison to other aminoethylation methodologies using oxazolines[21] and/or aziridines,[3] the oxazolidinone method will not yield aminoethylation products with aliphatic amines or alkyl mercaptans. However, this oxazolidinone methodology can be conducted without the need for secondary hydrolysis as in the case of oxazolines or require the use of special equipment necessary for the handling of noxious and toxic aziridine intermediates. Carbon dioxide is the only biproduct. We are currently exploring reactions of oxazolidinones with other electrophiles and are attempting to extend the general methodology to other cyclic carbamates.

Experimental Section

General Methods. Distillations were performed using an Aldrich Kugelrohr oven (bulb-to-bulb), and thus the boiling points reported in Tables II and III are only approximate. Unless otherwise indicated, the aromatic amine hydrochlorides and thiophenols were obtained from commercial sources. If the salts were not commercially available, the free bases were converted to their hydrochloride salts by treatment with ethanolic HCl, collected by filtration, and then air dried. Starting 2-oxazolidinone (**1a**), 3-methyl-2-oxazolidinone (**2b**), and ethyl sarcosine (**10**) were purchased from Aldrich Chemical Co., Milwaukee, WI. 3-Phenyl-2-oxazolidinone (**1d**, mp 121–122 °C), 4,4-dimethyl-2-oxazolidinone (**1e**, mp 54–56 °C), and 5-ethyl-2-oxazolidinone [**1f**, bp 116 °C (0.3 mm)] were prepared following literature procedures.[22]

3-(Phenylmethyl)-2-oxazolidinone (1c). To a stirred, cold (ice-bath), N_2-blanketed suspension of NaH (28.0 g, 0.55 mol, 60% in mineral oil, hexane washed) in 100 mL of dry THF was slowly added by dropping funnel a solution of oxazolidinone **1a** (43.6 g, 0.500 mol) dissolved in 500 mL of 10:1 THF/DMF. After the addition was complete (ca. 30 min) the resulting gray suspension was allowed to warm to ambient temperature and stir for 24 h. Benzyl bromide (66 mL, 0.56 mol) was then added to the white suspension via syringe and the mixture stirred for 24 h. H_2O (25 mL) was then carefully introduced and the resulting solution reduced in vacuo to approximately 200 mL and poured into 500 mL of H_2O. The aqueous mixture was extracted with three portions of CH_2Cl_2, and then the combined organic layers were washed with H_2O and brine and dried over $MgSO_4$. After filtration, the solution was concentrated in vacuo and the resulting yellow oil purified by Kugelrohr distillation [bp 110 °C (0.1 mm)] to furnish 81.1 g (92% yield) of **1c** as a clear oil which solidified on standing at room temperature to a colorless solid: mp 76–78 °C (lit.[23] mp 80–81 °C); ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 5 H), 4.37 (s, 2 H), 4.21 (m, 2 H), and 3.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) 158.5, 135.9, 128.8, 128.1, 127.0, 61.8, 43.3, and 44.0 ppm. Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.02; H, 6.30; N, 8.03.

General Method for the Preparation of 1,2-Ethanediamines 4. Method A. Equimolar quantities (0.20 mol) of the requisite 2-oxazolidinone **1** and aromatic amine hydrochloride were taken up in 35 mL of 2-(2-methoxyethoxy)ethanol and then heated while being stirred in a 160–170 °C oil bath. During this time the mixture generally became homogeneous and CO_2 evolution began. After 4–24 h, the CO_2 evolution had ceased, the heating bath was removed, and the dark reaction solution was allowed to cool to room temperature. In some instances, the diamine hydrochloride **4** crystallized on standing and was collected by filtration and ether wash. When crystallization did not occur, the solution was concentrated in vacuo and the resulting dark residue dissolved into 100 mL of 10% aqueous NaOH (wt/vol) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and then dried over anhydrous K_2CO_3. After filtration the solvent was removed in vacuo to furnish the crude diamines as dark liquids. Kugelrohr distillation at reduced pressures or use of flash chromatography afforded the purified products as pale yellow liquids or low-melting solids (Table II).

Method B. Equimolar quantities (0.10 mol) of the requisite 2-oxazolidinone **1** and aromatic amine hydrochloride were heated neat while being stirred to 150–165 °C for 5–24 h or until all CO_2 evolution had ceased. The dark mixtures were then cooled to room temperature and recrystallized from EtOH/Et_2O (Table II). By these procedures the following novel diamines were obtained.

***N*-[4-(Methylthio)phenyl]-1,2-ethanediamine hydrochloride (4f)** was obtained as a yellow oil (method A). The free base was then converted to its hydrochloride salt by treatment with 6.5 N ethanolic HCl and collected as a colorless white solid: mp 231–232 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.34 (br s, 3 H), 7.12 (m, 2 H), 6.60 (m, 2 H), 6.08 (br s, 1 H), 3.34 (m, 2 H), 2.95 (t, 2 H, J = 6.0 Hz), and 2.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) 146.8, 130.6, 122.5, 113.0, 40.3, 37.9, and 18.1 ppm. Anal. Calcd for $C_9H_{14}N_2S$·HCl: C, 49.42; H, 6.91; N, 12.81. Found: C, 49.22; H, 6.93; N, 12.86.

***N*-Methyl-*N*-phenyl-*N'*-(phenylmethyl)-1,2-ethanediamine monohydrochloride (4o)** was isolated as a creamy white solid (method B): mp 169–170 °C; ^{1}H NMR (DMSO-d_6) δ 9.90 (br s,

(21) (a) Fazio, M. J. *J. Org. Chem.* **1984**, *49*, 4889; (b) Poindexter, G. S. *Synthesis* **1981**, 541. (c) Seelinger, W.; Aufdehaar, E.; Diepers, W.; Feinauer, R.; Nehring, R.; Thier, W.; Hellman, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 875. (d) Kormendy, K.; Sohar, P.; Vorford, J. *Ann. Univ. Sci. Budap. Rolando Eotvos Nominatae, Sect. Chim.* **1962**, *4*, 61; *Chem. Abstr.* **1962**, *59*, 12,805f.

(22) Homeyer, A. H. *U.S. Patent* **1946**, 2,399,118.

(23) Maillard, J.; Vincent, M.; Rapin, M.; VanTri, V.; Remond, G. *Bull. Soc. Chim. Fr.* **1967**, 2110.

2 H), 7.66 (m, 2 H), 7.35 (m, 3 H), 7.18 (m, 2 H), 6.75 (m, 3 H), 4.17 (s, 2 H), 3.80 (m, 2 H), 3.04 (m, 2 H), and 2.86 (s, 3 H); ^{13}C NMR (DMSO-d_6) 148.4, 132.0, 130.1, 129.0, 128.4, 116.3, 112.2, 50.0, 47.7, 42.7, and 37.9 ppm. Anal. Calcd for $C_{16}H_{20}N_2$·HCl: C, 69.43; H, 7.65; N, 10.12. Found: C, 69.48; H, 7.66; N, 10.21.

***N*-(3-Methylphenyl)-*N'*-phenyl-1,2-ethanediamine dihydrochloride (4p)** was obtained as a yellow oil after purification by flash chromatography (SiO_2: EtOAc/hexane). The free base was converted to the hydrochloride salt and the salt isolated as a white crystalline solid after recrystallization from *i*-PrOH/H_2O: mp 172–175 °C; ^{1}H NMR (DMSO-d_6) δ 8.59 (br s, 2 H), 7.28 (m, 3 H), 7.07 (m, 6 H), 3.45 (s, 4 H), and 2.27 (s, 3 H); ^{13}C NMR (DMSO-d_6) 142.3, 140.1, 139.1, 129.5, 129.3, 125.3, 122.6, 119.7, 117.5, 116.4, 45.4, 43.7, and 21.1 ppm. Anal. Calcd for $C_{15}H_{18}N_2$·1.9 HCl: C, 60.95; H, 6.79; N, 9.48. Found: C, 60.69; H, 6.78; N, 9.36.

Reaction of 2-Oxazolidinone (1a) with Phenol. A mixture of phenol (9.60 g, 0.100 mol) and 2-oxazolidinone (**1a**, 8.70 g, 0.100 mol) was heated in a 160 °C oil bath for 3 h. After the mixture was cooled to room temperature, 250 mL of 10% aqueous NaOH (wt/vol) was added to the oil and the resulting solution extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine and dried over $MgSO_4$. After filtration, the volatiles were removed in vacuo to give a colorless residue. The residue was taken up in *i*-PrOH and recrystallized to give 3.59 g (10.2 mmol, 10% yield) of 1-(2-phenoxyethyl)-2-imidazolidinone (**8**) as a colorless solid: mp 109–110 °C; IR (Nujol) 1695 and 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2 H), 6.85 (m, 3 H), 5.58 (br s, 1 H), 4.05 (m, 2 H), and 3.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) 163.1, 158.6, 129.5, 121.0, 114.6, 67.3, 46.7, 43.4, and 38.4 ppm. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 65.87; H, 6.85; N, 13.32.

Reaction of 2-Oxazolidinone (1a) with Thiophenol. A mixture of thiophenol (13.2 g, 0.120 mol), **1a** (8.71 g, 0.100 mol), and 0.45 g of LiCl was purged under N_2 for 5 min and then heated under N_2 for 1 h in a 130 °C oil bath. After cooling to ambient temperature, the resulting white solid was taken up in 10% aqueous HCl and heated on a steam bath for several min. The mixture was filtered, and the resulting solid was washed with H_2O. After recrystallization from EtOAc, 2.91 g (12.1 mmol, 12% yield) of the colorless white solid *N*-(2-hydroxyethyl)-*N'*-[2-(phenylthio)ethyl]urea (**2a**) was collected by filtration: mp 112–113 °C; IR (KBr) 1620, and 1590 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.33 (m, 5 H), 6.26 (t, 1 H, J = 5.7 Hz), 6.06 (t, 1 H, J = 5.5 Hz), 4.69 (br s, 1 H), 3.39 (m, 2 H), 3.20 (q, 2 H, J = 6.6 Hz), 3.10 (q, 2 H, J = 5.7 Hz), and 2.99 (t, 2 H, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) 158.0, 135.9, 128.9, 128.0, 125.5, 60.8, 42.1, 39.0, and 32.7 ppm. Anal. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.72; N, 11.66. Found: C, 54.70; H, 6.80; N, 11.35.

The above filtrate was made basic to pH 10 with solid NaOH and then extracted with CH_2Cl_2. The combined extracts were washed with H_2O and brine and dried over K_2CO_3. After filtration and concentration in vacuo, Kugelrohr distillation (130 °C (0.3 mm)) gave 9.18 g (60.0 mmol, 60% yield) of 2-(phenylthio)-ethanamine (**9a**)[24] as a clear oil. The oil was treated with ethanolic HCl to give the salt as a colorless solid after trituration from Et_2O: mp 106–110 °C (sintered); ^{1}H NMR (DMSO-d_6) δ 8.41 (br s, 3 H), 7.28 (m, 5 H), 3.27 (t, 2 H, J = 7.0 Hz), and 2.94 (t, 2 H, J = 7.0 Hz). Anal. Calcd for $C_8H_{11}NS$·HCl: C, 50.66; H, 6.38; N, 7.39. Found: C, 50.59; H, 6.54; N, 7.66.

General Method for the Preparation of 2-(Arylthio)-ethanamines 9. Equimolar amounts (0.1 mol) of the appropriate oxazolidinone **1** and thiophenol (0.1 mol) were heated together while stirring under N_2 in a 130–150 °C oil bath. The stirred reaction mixtures were maintained at these temperatures for several h or until all CO_2 evolution had ceased. Generally small amounts (ca. 10 mg) of LiCl were added to reduce reaction times. The crude reaction mixtures were then cooled to room temperature and the resulting amines purified by either distillation, flash chromatography, or conversion to their hydrochloride salts and recrystallized. The following novel amines reported in Table III were obtained using this procedure.

2-[[4-(1,1-Dimethylethyl)-2-methylphenyl]thio]ethanamine (9c) was obtained as a pale yellow oil after distillation: ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 3 H), 2.87 (m, 4), 2.40 (s, 3 H), 1.50 (br s, 2 H), and 1.27 (s, 9 H); ^{13}C NMR ($CDCl_3$) 148.9, 137.5, 131.6, 129.1, 127.1, 123.3, 41.1, 37.5, 34.1, 31.2, and 20.7 ppm. Anal. Calcd for $C_{13}H_{21}NS$·0.10 H_2O: C, 69.35; H, 9.49; N, 6.23; H_2O, 0.80. Found: C, 69.43; H, 9.68; N, 6.17; H_2O, 1.10.

2-[(2-Methoxyphenyl)thio]-*N*-methylethanamine hydrochloride (9e) was obtained as a pale tan solid after recrystallization from EtOH/Et_2O: ^{1}H NMR (DMSO-d_6) δ 9.50 (br s, 2 H), 7.46 (m, 1 H), 7.22 (m, 1 H), 7.05 (m, 2 H), 3.84 (s, 3 H), 3.30 (m, 2 H), 3.06 (m, 2 H), and 2.54 (s, 3 H); ^{13}C NMR (DMSO-d_6) 156.7, 128.5, 127.5, 122.1, 121.1, 111.1, 55.8, 47.2, 32.2, and 26.0 ppm. Anal. Calcd for $C_{10}H_{15}NOS$·HCl: C, 51.38; H, 6.90; N, 5.99. Found: C, 51.18; H, 6.96; N, 6.16.

***N*-Methyl-2-[(2-methylphenyl)thio]ethanamine hydrochloride (9f)** was isolated as a colorless solid after recrystallization from EtOH/Et_2O: ^{1}H NMR (DMSO-d_6) δ 9.64 (br s, 2 H), 7.53 (m, 1 H), 7.22 (m, 3 H), 3.42 (m, 2 H), 3.10 (m, 2 H), 2.62 (s, 3 H), and 2.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) 136.7, 133.3, 130.2, 127.5, 126.7, 126.0, 47.1, 32.1, 26.8, and 19.8 ppm. Anal. Calcd for $C_{10}H_{15}NS$·HCl: C, 55.16; H, 7.41; N, 6.43. Found: C, 55.51; H, 7.54; N, 6.38.

***N*-Methyl-2-[(3-methylphenyl)thio]ethanamine hydrochloride (9g)** was obtained as a colorless, low-melting solid after trituration from Et_2O: ^{1}H NMR ($CDCl_3$) δ 2.31 (br s, 2 H), 7.24 (m, 3 H), 7.05 (m, 1 H), 3.38 (m, 2 H), 3.11 (m, 2 H), 2.68 (s, 3 H), and 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) 139.2, 133.1, 130.9, 129.2, 128.1, 127.3, 48.5, 33.1, 29.2, and 21.3 ppm. Anal. Calcd for $C_{10}H_{15}NS$·HCl: C, 55.16; H, 7.41; N, 6.43. Found: C, 55.28; H, 7.34; N, 6.37.

***N*-Methyl-2-[(4-methylphenyl)thio]ethanamine hydrochloride (9h)** was collected as a colorless solid after recrystallization from from EtOH/Et_2O: ^{1}H NMR (DMSO-d_6) δ 9.60 (br s, 2 H), 7.40 (d, 2 H, J = 8.2 Hz), 7.18 (d, 2 H, J = 8.2 Hz), 3.38 (m, 2 H), 3.09 (m, 2 H), 2.60 (s, 3 H), and 2.30 (s, 3 H); ^{13}C NMR (DMSO-d_6) 136.0, 130.3, 129.9, 129.3, 47.3, 32.1, 28.1, and 20.5 ppm. Anal. Calcd for $C_{10}H_{15}NS$·HCl: C, 55.16; H, 7.41; N, 6.43. Found: C, 55.26; H, 7.47; N, 6.49.

4-[[2-(Methylamino)ethyl]thio]phenol hydrochloride (9i) was obtained as a colorless white solid after purification by flash chromatography (SiO_2: MeOH/$CHCl_3$) and conversion to the HCl salt: ^{1}H NMR (DMSO-d_6) δ 9.82 (br s, 1 H), 9.26 (br s, 2 H), 7.32 (d, 2 H, J = 8.5 Hz), 6.84 (d, 2 H, J = 8.5 Hz), 3.13 (m, 2 H), 2.99 (m, 2 H), and 2.54 (s, 3 H); ^{13}C NMR (DMSO-d_6) 157.3, 133.4, 121.1, 116.3, 47.3, 32.1, and 30.2 ppm. Anal. Calcd for $C_9H_{13}NOS$·HCl·0.20 H_2O: C, 48.41; H, 6.50; N, 6.27; H_2O, 1.61. Found: C, 48.41; H, 6.45; N, 6.24; H_2O, 1.48.

4-[[2-(Methylamino)ethyl]thio]benzenamine dihydrochloride (9j) was obtained as a brown solid after recrystallization from EtOH/Et_2O: ^{1}H NMR (DMSO-d_6) δ 10.18 (br s, 2 H), 9.40 (br s, 3 H), 7.56 (d, 2 H, J = 8.6 Hz), 7.39 (d, 2 H, J = 8.6 Hz), 3.64 (m, 2 H), 3.07 (m, 2 H), and 2.57 (s, 3 H); ^{13}C NMR (DMSO-d_6) 133.3, 130.7, 129.3, 123.6, 46.9, 32.1, and 27.4 ppm. Anal. Calcd for $C_9H_{14}N_2S$·HCl: C, 42.36; H, 6.32; N, 10.98. Found: C, 42.25; H, 6.10; N, 10.73.

2-[[4-(1,1-Dimethylethyl)-2-methylphenyl]thio]-*N*-methylethanamine (9k) was isolated as a pale yellow liquid after Kugelrohr distillation: ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 3 H), 3.00 (m, 2 H), 2.80 (m, 2 H), 2.42 (s, 3 H), 2.39 (s, 3 H), 1.42 (br s, 1 H), and 1.29 (s, 9 H); ^{13}C NMR ($CDCl_3$) 149.1, 137.6, 131.7, 129.0, 127.2, 123.4, 50.4, 36.0, 34.2, 33.5, 31.3, and 20.7 ppm. Anal. Calcd for $C_{14}H_{23}NS$: C, 70.83; H, 9.77; N, 5.90. Found: C, 70.77; H, 9.78; N, 5.68.

2,6-Bis(1,1-Dimethylethyl)-4-[[2-(phenylamino)ethyl]-thio]phenol oxalate (9n) was obtained as a brown oil after purification by flash chromatography (SiO_2: EtOAc/hexane). The free base was subsequently converted to the oxalate salt to afford a white amorphous solid after recrystallization from EtOAc/hexane: ^{1}H NMR (DMSO-d_6) δ 7.15 (s, 2 H), 7.00 (t, 2 H, J = 4.0 Hz), 6.49 (t, 1 H, J = 7.3 Hz), 6.45 (t, 2 H, J = 7.8 Hz), 3.15 (t, 2 H, J = 5.7 Hz), 2.92 (t, 2 H, J = 6.4 Hz), and 1.35 (s, 18 H); ^{13}C NMR (DMSO-d_6) 160.9, 153.4, 148.2, 140.2, 128.9, 127.9, 124.6, 115.9, 111.9, 42.5, 34.6, 33.9, and 30.2 ppm. Anal. Calcd for $C_{22}H_{31}NSO$·0.55 $C_2H_2O_4$: C, 68.16; H, 7.95; N, 3.44. Found: C, 68.14; H, 7.92; N, 3.72.

(24) Gabriel, S.; Colman, J. *Chem. Ber.* **1911**, *44*, 3628.

1-[(2-Methylphenyl)thio]-2-methyl-2-propanamine (9p) was obtained as a pale yellow liquid after Kugelrohr distillation: ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1 H, J = 7.0 Hz), 7.10 (m, 3 H), 2.94 (s, 2 H), 2.39 (s, 3 H), 1.45 (br s, 2 H), and 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) 137.6, 136.6, 130.2, 128.6, 126.3, 125.7, 50.5, 49.3, 29.8, and 20.5 ppm. Anal. Calcd for $C_{11}H_{17}NS$·0.10 H_2O: C, 67.03; H, 8.80; N, 7.11; H_2O, 0.91. Found: C, 66.76; H, 8.80; N, 7.03; H_2O, 1.15.

1-[[4-(1,1-Dimethylethyl)-2-methylphenyl]thio]-2-methyl-2-propanamine hydrochloride (9q) was isolated as a colorless white solid after trituration from Et_2O: ^{1}H NMR (DMSO-d_6) δ 8.58 (br s, 3 H), 7.25 (m, 3 H), 3.28 (s, 2 H), 2.37 (s, 3 H), 1.35 (s, 6 H), and 1.25 (s, 9 H); ^{13}C NMR (DMSO-d_6) 149.0, 136.9, 131.3, 129.1, 127.2, 123.5, 54.5, 42.1, 34.0, 31.0, 24.3, and 20.5 ppm. Anal. Calcd for $C_{15}H_{25}NS$·HCl: C, 62.58; H, 9.10; N, 4.87. Found: C, 62.48; H, 9.05; N, 5.00.

Preparation of Deuterium-Labeled Oxazolidinone 1b-d_2. Ethyl *N*-Methyl-*N*-(phenylmethyl)glycine (11).[25] A mixture of sarcosine ethyl ester (**10**, 50.0 g, 0.326 mol), benzyl chloride (49.9 g, 0.390 mol), micropulverized K_2CO_3 (53.8 g, 0.390 mol), and a catalytic amount (ca. 700 mg) of NaI in 150 mL of absolute EtOH was refluxed under N_2 for 20 h. The resulting mixture was cooled to room temperature and filtered and the filtrate concentrated in vacuo to give a crude oil. The oil was purified by flash chromatography (SiO_2: $CHCl_3$) to yield 48.8 g (72% yield) of 11 as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 4.17 (q, 2 H, J = 7.5 Hz), 3.68 (s, 2 H), 3.25 (s, 3 H), 2.38 (s, 3 H), and 1.24 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) 170.6, 138.5, 129.0, 128.3, 127.2, 61.0, 57.5, 42.0, and 14.3 ppm. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 68.22; H, 9.06; N, 6.63. Found: C, 67.95; H, 8.99; N, 6.42.

Ethyl [*N*-Methyl-*N*-(phenylmethyl)amino]ethanol-*1,1*-d_2 (12). To a stirred, room-temperature, N_2-atm suspension of $LiAlD_4$ (5.00 g, 0.150 mol) in 150 mL of THF was added a solution of 11 (30.5 g, 0.150 mol) in 150 mL of THF. The mixture was stirred for 20 h at ambient temperatures, and then H_2O (5 mL), 15% aqueous NaOH (5 mL, wt/vol), and H_2O (15 mL) were successively added. After filtration, the filtrate was concentrated in vacuo to yield 18.1 g (74% yield) of **12** as a colorless oil. A small portion of the oil was treated with oxalic acid to give the salt as a colorless solid: mp 109–111 °C; ^{1}H (DMSO-d_6) δ 10.0 (br s, 3 H), 7.58 (br s, 2 H), 7.44 (br s, 3 H), 4.37 (s, 2 H), and 2.75 (s, 3 H); ^{13}C NMR (DMSO-d_6) 165.3, 131.0, 130.4, 129.2, 128.6, 58.9, 56.2, 55.0 (CD_2), and 39.5 ppm. Anal. Calcd for $C_{10}H_{13}D_2NO$·$C_2H_2O_4$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.06; H, 6.66; N, 5.36.

Ethyl [*N*-Methyl-*N*-(phenylmethyl)amino]ethyl-*1,1*-d_2 Carbonate (13). A solution of **12** (8.10 g, 50.0 mmol), Et_3N (5.60 g, 55.0 mmol), and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) in 100 mL of dry THF was cooled to ice-bath temperatures and stirred under N_2. $ClCO_2Et$ (6.00 g, 55.0 mmol) in 100 mL of THF was added and the resulting solution warmed to room temperature and then refluxed for 20 h. After the solvent was removed under reduced pressure, the residue was subjected to flash chromatography (SiO_2: $CHCl_3$) to give 9.4 g (80%) of **13** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 4.16 (q, 2 H, J = 7.1 Hz), 3.54 (s, 2 H), 2.66 (s, 2 H), 2.25 (s, 3 H), and 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) 155.1, 138.7, 128.8, 128.3, 127.0, 65.4 (CD_2), 63.8, 62.4, 55.2, 42.5 and 14.3 ppm. Anal. Calcd for $C_{13}H_{17}D_2NO_3$: C, 64.71; H, 8.77; N, 5.81. Found: C, 64.39; H, 8.71; N, 5.66.

Ethyl 2-(*N*-Methylamino)ethyl-*1,1*-d_2 Carbonate (14). A solution of **13** (12.0 g, 50.0 mmol) in 150 mL of absolute EtOH containing 1.0 g of 10% Pd on C was shaken under 60 psi of H_2 on a Parr hydrogenation apparatus for 20 h. The catalyst was removed by filtration through Celite and the filtrate concentrated to yield 7.50 g (quantitative) of **14** as as a clear oil. A small portion of the oil was converted to the HCl salt by treatment with ethanolic HCl and isolated as a colorless white solid: mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 9.26 (br s, 2 H), 4.25 (q, 2 H, J = 7.1 Hz), 3.38 (s, 2 H), 2.81 (s, 3 H), and 1.31 (q, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) 154.5, 64.7, 62.8 (CD_2), 47.6, 33.6, and 14.2 ppm. Anal. Calcd for $C_6H_{11}D_2NO_3$·HCl: C, 39.25; H, 7.69; N, 7.63. Found: C, 38.96; H, 7.60; N, 7.35.

3-Methyl-2-oxazolidinone-*5,5*-d_2 (1b-d_2). A solution of **14** (2.90 g, 20.0 mmol) in 75 mL of absolute EtOH containing a catalytic amount of NaOEt was refluxed 1 h under N_2. Removal of the volatiles in vacuo gave a crude residue which was purified by flash chromatography (SiO_2: $CHCl_3$) to furnish 2.0 g (quantitative yield) of oxazolidinone **1b-d_2** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 2 H) and 2.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) 158.8, 61.1 (p, CD_2, J = 21.6 Hz), 46.6, and 31.8 ppm. Anal. Calcd for $C_4H_5D_2NO_2$: C, 45.70; H, 8.63; N, 13.33. Found: C, 45.92; H, 8.89; N, 12.99.

Reactions of Oxazolidinone 1b-d_2 with N-Methylaniline Hydrochloride. A mixture of **1b-d_2** (500 mg, 4.85 mmol) and *N*-methylaniline hydrochloride (650 mg, 4.51 mmol) were heated in an oil bath for 18 h at the indicated temperatures (Table IV). The usually dark reaction mixtures were cooled to room temperature and then made basic by the addition of 50 mL of 1 N aqueous NaOH solution. After extraction of the basic solution with CH_2Cl_2, the combined organic portions were dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo to yield crude diamine product. Final purification was accomplished by flash chromatography (SiO_2: MeOH/$CHCl_3$) to furnish the diamines **15a** and **16a** as a clear oil. Deuterium positioning in **15a**:**16a** was determined by careful ^{1}H NMR analysis at 300 MHz in $CDCl_3$. The C-1 methylene absorption at δ 2.80 was integrated against the C-2 methylene absorption at δ 3.45 to determine relative amounts of **15a** and/or **16a** as indicated in Table IV. These proton assignments were based on a substituent effect study using diamine **4l** and its corresponding trifluoroacetamide derivative [300-MHz ^{1}H NMR spectrum for **4l** free base: ($CDCl_3$) δ 7.21 (m, 2 H), 6.74 (m, 3 H), 3.45 (t, J = 6.5 Hz), 2.95 (s, 3 H), 2.80 (t, 2 H, J = 6.5 Hz), 2.46 (s, 3 H), and 1.28 (br s, 1 H)]. The C-1 methylene absorption of **4l** at 2.80 ppm was shifted downfield to 3.58 ppm after formation as the trifluoroacetamide derivative. The C-2 methylene absorption was only slightly affected on derivatization (3.45–3.56 ppm).

Reaction of Oxazolidinone 1b-d_2 with Thiophenol. A mixture of thiophenol (1.10 g, 10.0 mmol), oxazolidinone **1b-d_2** (1.00 g, 9.90 mmol), and 10 mg of LiCl was heated under N_2 in a 140 °C oil bath for 5 h. After being cooled to room temperature, the yellow residue was taken up in $CHCl_3$ and purified by flash chromatography (SiO_2: MeOH/$CHCl_3$) to give 1.37 g (8.11 mmol, 82% yield) of *N*-methyl-2-(phenylthio)ethanamine-*2,2*-d_2 (**16b**) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 2.81 (s, 2 H), 2.43 (s, 3 H), and 2.00 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 136.0, 129.4, 128.3, 126.8, 58.1, 36.0, and 33.2 (p, CD_2, J = 22.6 Hz) ppm. The deuterium positioning in **16b** was determined by the lack of any C-2 methylene ^{1}H NMR absorption of **9d**. Both the C-1 and C-2 methylene signals were assigned after conversion of **9d** to its corresponding trifluoroacetamide derivative [300-MHz ^{1}H NMR spectrum of **9d** free base: ($CDCl_3$) δ 7.34 (m, 2 H), 7.25 (m, 2 H), 7.17 (m, 1 H), 3.04 (m, 2 H), 2.80 (m, 2 H), 2.41 (s, 3 H), and 1.32 (br s, 1 H)]. The C-1 methylene absorption of **9d** at 2.80 ppm was shifted downfield to 3.56 ppm on derivatization. The C-2 methylene was only slightly affected after derivatization (3.04–3.09 ppm).

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Registry No. **1a**, 497-25-6; **1b**, 19836-78-3; **1b-d_2**, 143745-73-7; **1c**, 2510-33-0; **1d**, 703-56-0; **1e**, 26654-39-7; **1f**, 25664-78-2; **2a**, 66923-49-7; **4a**, 108445-06-3; **4b**, 143745-52-2; **4c**, 53673-09-9; **4d**, 143745-53-3; **4e**, 143745-54-4; **4f**, 143745-55-5; **4g**, 143745-56-6; **4h**, 84035-89-2; **4i**, 143745-57-7; **4j**, 141832-98-6; **4k**, 138374-03-5; **4l**, 33905-42-9; **4m**, 143745-58-8; **4n**, 143745-59-9; **4o**, 143745-60-2; **4p**, 143745-61-3; **9a**, 2014-75-7; **9b**, 60116-14-5; **9c**, 143745-62-4; **9d**, 2014-78-0; **9e**, 143745-63-5; **9f**, 115335-00-7; **9g**, 115335-01-8; **9h**, 115335-16-5; **9i**, 143745-64-6; **9j**, 143745-65-7; **9k**, 114458-75-2; **9l**, 67747-34-6; **9m**, 92249-42-8; **9n**, 143745-67-9; **9o**, 56216-03-6;

(25) Maier, R.; Weitum, E.; Wetzel, B.; Reuter, W.; Goeth, H.; Lechner, U. *Ger. Offen.* **1976**, 2,515,076.

9p, 143745-68-0; **9q**, 143745-69-1; **10**, 13200-60-7; **11**, 62004-76-6; **12**, 143745-70-4; **13**, 143745-71-5; **14**, 143745-72-6; **15a**, 143745-74-8; **15b**, 143745-75-9; **16a**, 143745-76-0; **16b**, 143745-77-1; $PhNH_2$, 142-04-1; 4-$MePhNH_2$, 540-23-8; 2-$ClPhNH_2$, 137-04-2; 3-$ClPhNH_2$, 141-85-5; 4-$MeOPhNH_2$, 20265-97-8; 4-$MeSPhNH_2$, 39870-00-3; 4-EtO_2CPhNH_2, 23239-88-5; 3-O_2NPhNH_2, 33240-96-9; 4-H_2NPhNH_2, 55972-71-9; PhNHMe, 2739-12-0; $PhNHCH_2Ph$, 2290-89-3; 3-$MePhNH_2$, 638-03-9; PhSH, 12385-08-9; 2-H_2NPhSH, 137-07-5; 4-*t*-Bu-2-MePhSH, 15570-10-2; 2-MeOPhSH, 7217-59-6; 2-MePhSH, 137-06-4; 3-MePhSH, 108-40-7; 4-MePhSH, 106-45-6; 4-HOPhSH, 637-89-8; 4-H_2NPhSH, 1193-02-8; 4-HO-3,5-(*t*-$Bu)_2PhSH$, 950-59-4.

An Asymmetric Route to Enantiomerically Pure 1,2,3-Trisubstituted Cyclopropanes

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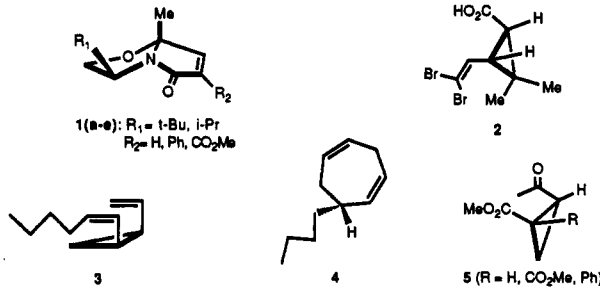
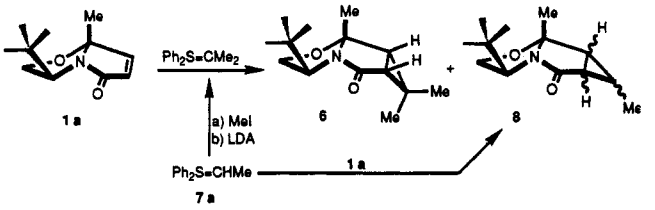
Cycloaddition of various sulfur ylides to the chiral unsaturated lactams **1a**, **1b** led to cyclopropanated products containing a monosubstituted appendage. The stereochemical outcome is such that all the products are mainly (or exclusively) the kinetically controlled *endo-syn*-**8**, -**9**, or *endo-anti*-**10**. The latter occurs by virtue of an epimerization to the thermodynamically favored product. Removal of the chiral auxiliary following Wittig reaction on the intermediate carbinol amines (**11**, **15**) gave chiral, nonracemic 1,2,3-trisubstituted cyclopropanes containing various functionalities (**13**, **16**).

Earlier cyclopropanations of unsaturated bicyclic lactams **1** have provided access to the potent insecticide precursor, *cis*-(1*S*,3*R*)-deltamethrinic acid (**2**), dictyopterene C (**3**), a proposed biogenic precursor to dictyopterene C′ (**4**), the potent seaweed sperm attractant, and various other enantiomerically pure cyclopropanes **5**.[1] It

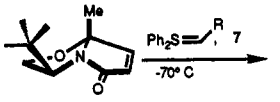


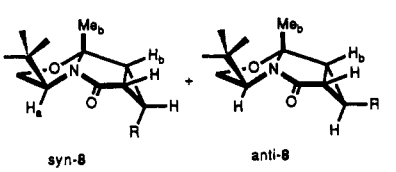
is obvious from their structures that these cyclopropyl systems possess only two stereogenic centers. We now wish to disclose extensions of this chiral cyclopropanation methodology which afford absolute stereocontrol of three centers leading to enantiomerically pure 1,2,3-trisubstituted cyclopropanes.[2]

In our earlier effort directed toward the asymmetric synthesis of deltamethrinic acid, **2**, cyclopropanation of the unsaturated lactam **1a** with diphenylsulfonium isopropylide gave mixtures of the desired *gem*-dimethylcyclopropane **6** and two diastereomeric monomethylcyclopropanes **8**. The isopropylide was generated in situ and, as a result of incomplete alkylation of the ylide **7a**, varying amounts of monomethylcyclopropanes **8** were produced. Interestingly, of the four possible stereoisomers (endo/exo and syn/anti) monomethylcyclopropanes, only two were produced, and more importantly they were produced in unequal amounts.



These findings prompted an investigation of cyclopropanation of the unsaturated lactam **1a** with diphenylsulfonium ethylide **7** (R = Me).[3] When the reaction with **1a** was performed at −70 °C followed by warming to −20 °C, the two *syn*- and *anti*-cyclopropyl adducts **8a** were obtained in 95% yield as a 3.0:1 mixture as determined by VPC analysis. The diastereomeric ratio of **8a** could be improved to 4.6:1 by maintaining the reaction temperature between −70 °C and −60 °C.





	syn	anti
8a, R = Me	4.6	1
8b, R = CH = CH_2	31.0	1
8c, R = Ph	7.0	1

The major diastereomer was determined to be the endo–syn adduct **8a** by NOE experiments which showed

(1) For earlier studies on chiral bicyclic lactams, including cyclopropanation, see a review on this subject: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *46*, 9503–9569.

(2) For recent reports of cyclopropanations providing tri- and tetrasubstituted, enantiomerically pure cyclopropanes, see: (a) Winkler, J. D.; Gretler, E. A. *Tetrahedron Lett.* **1991**, *41*, 5733. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *50*, 7373. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (d) Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367.

(3) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.

0022-3263/92/1957-6265$03.00/0