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Design of Thermally Stable Versions of the Burgess Reagent: Stability and Reactivity Study[1]

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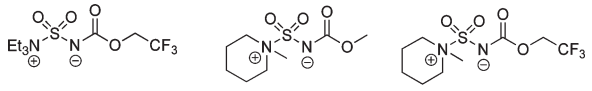

Three new versions of the Burgess reagent were synthesized and their thermal stability investigated by NMR. The new reagents exhibited improved reactivity toward epoxides, diols, and vinyl oxiranes as compared with the original version.

The Burgess reagent, discovered in 1968[2] and employed as a mild dehydrating agent for primary and secondary alcohols, has recently come to focus in a variety of new reaction schemes. Several reviews highlighting the reactive options of this reagent were published[3] and its use was featured in the total syntheses of quite a few natural products.[4] As recently as a decade ago it was assumed that epoxides were inert to the action of the Burgess reagent. However, in 2003 we published a report on the conversion of oxiranes to cis-fused cyclic sulfamidates.[5] Nicolaou reported the synthesis of sulfamidates[6] by the reaction of the Burgess reagent with 1,2-diols or epoxy alcohols and we have investigated mechanistic similarities of the two pathways. In 2006 we reported the synthesis of a chiral auxiliary version of the Burgess reagent by reacting the chlorosulfonylisocyanate with (−)-menthol.[7] Reactions of this version of the Burgess reagent with various oxiranes allowed isolation of diastereomeric sulfamidates that could be hydrolyzed to yield protected *cis*-1,2-amino alcohols in both enatiomeric configurations following the removal of the menthyl auxiliary. In addition, as the sulfamidates mimic the reactivity of cyclic sulfates, *trans*-1,2-amino alcohols were obtained following the opening of the sulfamidates with ammonium benzoate. Thus all isomers of 1,2-amino alcohols in both enantiomeric series became easily accessible. A concise application of this protocol was expressed in the enantiodivergent formal total synthesis of (+)- and (−)-balanol.[8] In addition, a serendipidous discovery allowed for a high yield preparation of disulfides from thiols by the action of the Burgess reagent.[9] Details of the synthetic, mechanistic, and computational studies, including modeling by Density Functional Theory and suggestions of possible transition states for the epoxide opening, were published in a recent full paper.[10] Herein we report the synthesis of new versions of the Burgess reagent and their thermal stability profile along with a comparison of their reactivity with the original methyl carbamate compound.

During our studies of the reactivity of the Burgess reagent with various cyclic and acyclic oxiranes we were disappointed with rather modest yields of the sulfamidates. Furthermore, we found that the reactions with epoxides led to cis-fused sulfamidates in a process that required 2 equiv of the Burgess reagent, in analogy with Nicolaou's observations of similar requirements for the conversion of 1,2-diols to sulfamidates. The nucleophilic opening of strained rings is energetically more demanding than the relatively facile sulfonation of alcohols that operates in the dehydration protocols or in the reactions with 1,2-diols. We have observed that both the original Burgess reagent **1** and its chiral auxiliary version **2** were not particularly stable at the temperature of refluxing THF, conditions frequently necessary for the nucleophilic opening of oxiranes. As the yields of sulfamidates from oxiranes rarely exceeded 40%, we set out to design several versions that would increase the stability of either the anionic or the cationic portion of the zwitterions. The new reagents shown in Figure 1 were easily prepared from their components by the usual procedures (see the Experimental Section for details).

To determine the thermal stability of the reagents we chose to follow their decomposition in THF-d_8 at 50 °C and at reflux by monitoring the content of the sample by ^{13}C NMR.

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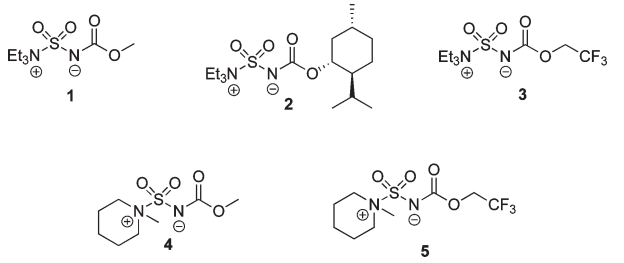


FIGURE 1. New versions of the Burgess reagent.

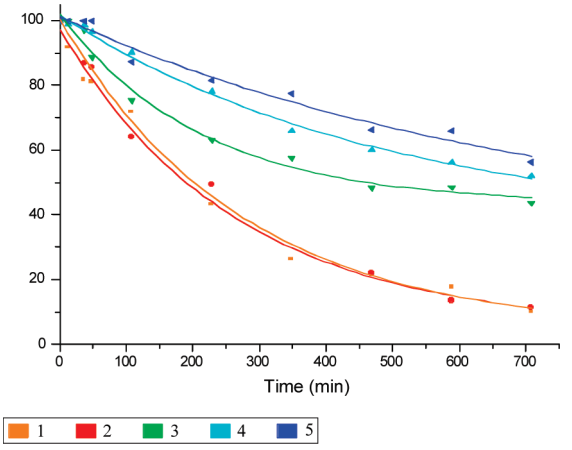


FIGURE 2. Decomposition of Burgess reagents as a function of time at 50 °C.

A timed series of $^{13}C\{^{1}H\}$ NMR spectra were recorded for each reagent. For each spectrum the peak area of the carbamate ^{13}C signal (around 157 ppm) was determined by direct integration and calibration against solvent ^{13}C signal corresponding to THF-d_8 at 64.6 ppm. The magnitude of the carbamate ^{13}C signal in the first spectrum was set at 100%.

The results are shown in Figures 2 and 3 and are compared with those obtained for the original Burgess reagent as well as its menthyl chiral auxiliary version. [The plots shown are the actual decays with percent content illustrated on the left.]

We were surprised how unstable both the original Burgess reagent **1** and its chiral auxiliary version **2** were at higher temperature. The half-life of **1** and **2** at 50 °C is 216 and 198 min, respectively. At reflux, the corresponding half-lives are even shorter, determined at 19 min for **1** and 13 min for **2**. The Burgess reagent as well as the menthyl chiral auxiliary version completely decompose in less than an hour at 78 °C. These observations explain why the yields of sulfamidates from oxiranes were modest, in contrast to the yields reported for sulfamidate production from 1,2-diols. Major improvements in stability were noticed with the new reagents **3**, **4**, and **5**, as shown in Figures 2 and 3. The reagents derived from *N*-methylpiperidine are essentially completely stable even at refluxing temperatures for 3 h or more. The reactivity of the new reagents was examined for simple dehydration as well as nucleophilic opening of oxiranes and the synthesis of sulfamidates from 1,2-styrene diol, as shown in Figure 4. The results are compared in terms of yields to those obtained with the original Burgess reagent **1** and the chiral auxiliary version **2**.

From the results in Figure 4 it is clear that the best compromise between stability and reactivity is attained with either trifluoroethyl version **3** or the *N*-methyl piperidine

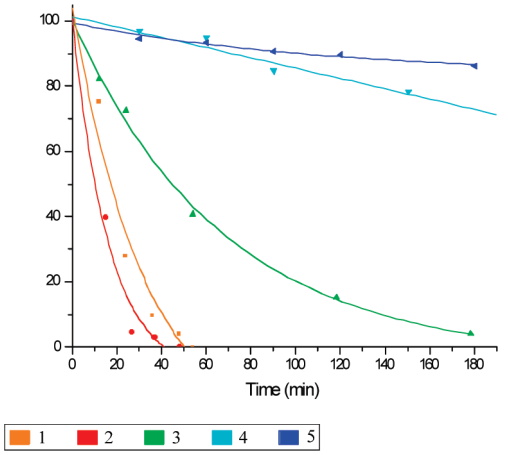
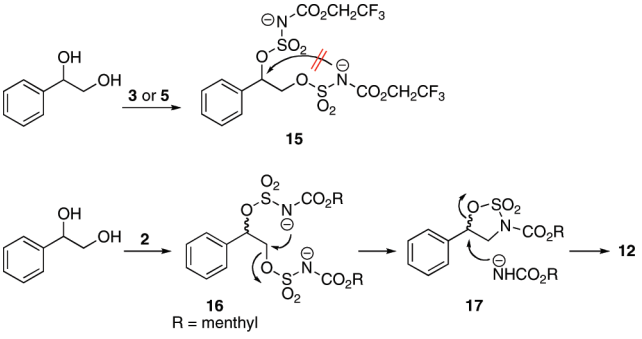


FIGURE 3. Decomposition of Burgess reagents as a function of time at 78 °C.

version **4**. The increased stability of reagent **5** does not offer additional advantages in its reactivity, at least in the cases involving the oxiranes. The reaction of the Burgess reagents **3** and **5** with 1,2-styrene diol did not produce the sulfamidates under the reaction conditions used for the other reagents. Only bis-sulfonation was observed and this would be consistent with the mechanism proposed by Nicolaou and tested by our group for the formation of sulfamidates from diols. The inductive effect of the trifluoromethyl group decreases the nucleophilicity of the carbamate anion in both reagents containing this group and hence the rate of displacement to form the sulfamidates is greatly reduced in the intermediates such as **15**. The isolation of the protected diamine **12** from the reaction of the menthyl Burgess reagent **2** with styrene diol was surprising. However, its formation may be rationalized by invoking the bis-sulfonated intermediate **16**, which, for steric reasons, may not undergo the intramolecular displacement at the benzylic position to yield the expected sulfamidate of type **8**. Instead the alternate, less sterically demanding, process may yield sulfamidate **17**, whose further displacement at the benzylic position with the carbamate anion (generated upon the departure of the second equivalent of the Burgess reagent from **16**) provides the protected diamine **12**, as shown.



The suggested mechanism for the conversion of styrene diol to **12** is in agreement with the results reported by Burgess in 1973 on the conversion of cyclohexanol and benzyl alcohol to the corresponding *N*-hexyl- and *N*-benzylcarbamates by S_N2 displacement of the sulfonylated intermediates such as **16**.[11]

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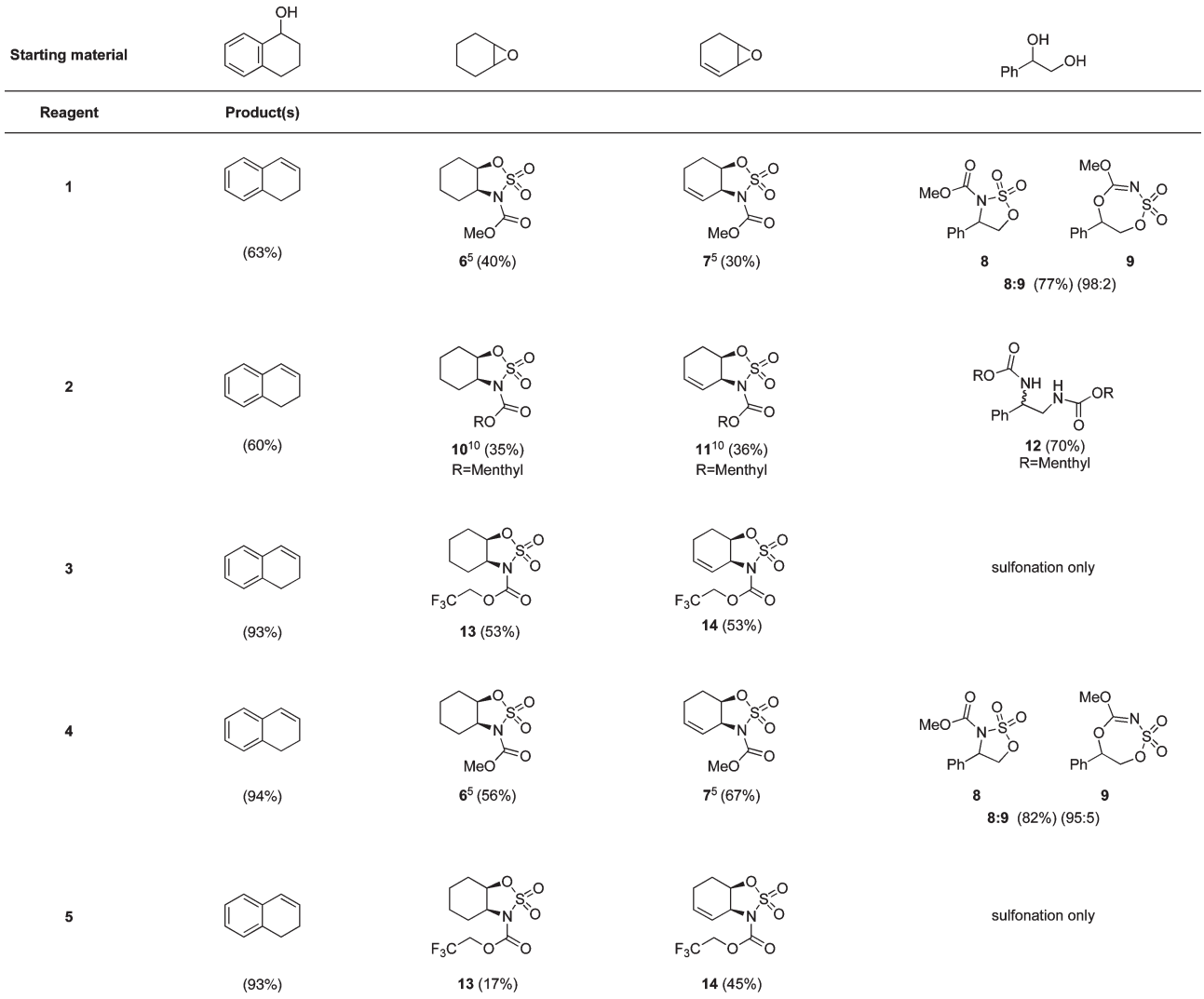

FIGURE 4. Reactivity trends of the new Burgess reagents in dehydration, reactions with oxiranes, and with styrene diol. The reactions were carried out in refluxing THF at ~80 °C.

The full assignment of structures was performed by 2D HSQC and 2D COSY NMR spectroscopy for all compounds and is shown for all H- and C-atoms in the Supporting Information. For the assignment of **12** 2D HMBC NMR spectroscopy was also performed.

In conclusion, we have shown that the stability as well as the reactivity of the original Burgess reagent can be improved by addressing the electronic quality of both portions of the zwitterion. The best results in terms of yield improvements were achieved with reagent **4**.

Experimental Section

General. All reactions were performed in flame-dried glassware under argon atmosphere. THF and benzene were freshly distilled from sodium/benzophenone. All Burgess reagents were recrystallized twice from dry THF prior to use.

***N,N*-Diethyl-*N*-{[(2,2,2-trifluoroethyloxycarbonyl)amino]sulfonyl}-ethanaminium, Inner Salt (3).** 2,2,2-Trifluoroethanol (3.36 mL, 46 mmol) in dry benzene (10 mL) was added dropwise to chlorosulfonyl isocyanate (4.0 mL, 46 mmol) in 15 mL of dry benzene at room temperature. When the addition was complete, the reaction mixture was stirred for 30 min. The product, 2,2,2-trifluoroethyl chlorosulfonylcarbamate, was precipitated with cold hexanes as white crystals, 10.25 g (42 mmol, 92%); mp 80−82 °C (C_6H_6); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (m, 1H), 4.66 (q, J = 7.9 Hz, 2H); ^{13}C NMR1483.9, 1396.8, 1166.0 cm^{-1}; LRMS (FAB+ NBA matrix) m/z 242, 149 (18.9), 99 (41.3), 73 (25.9), 59 (80.8), 49 (100.0); HRMS calcd for $C_3H_4ClNF_3O_4$ 241.9423, found 241.9496.

2,2,2-Trifluoroethyl chlorosulfonylcarbamate (2.0 g, 8.3 mmol) in 50 mL of dry THF was added dropwise to triethylamine (2.90 mL, 20.75 mmol) in 20 mL of dry THF in an ice bath, then the reaction mixture was stirred for 2 h. Triethylammonium chloride was filtered and the solvent removed in vacuo. The product (**3**) was recrystallized twice from dry THF, 1.91 g (6.2 mmol, 75%); mp 77−79 °C (THF); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.45 (dq, J = 8.6, 3.7 Hz, 2H) 3.46 (dq, J = 7.3, 2.9 Hz, 6H) 1.41 (dt, J = 7.2, 3.7 Hz, 9H); ^{13}C NMR (THF-d_8, 150 MHz) δ 155.4, 123.8 (q, J = 277.4 Hz), 60.1 (q, J = 35.8 Hz), 50.6, 8.5; IR (KBr) ν 3167.6, 2986.1, 2931.6, 2676.8, 2637.9, 2107.9, 1750.3, 1691.2 cm^{-1}; LRMS (FAB + NBA matrix) m/z 307, 239 (30.8), 102 (100.0), 86 (20.0); HRMS calcd for $C_9H_{17}F_3N_2O_4S$ 306.0851, found 307.0930 ($M^+ + H$).

***N*-Methyl-*N*-{[(methyloxycarbonyl)amino]sulfonyl}piperidinaminium, Inner Salt (4).** Methyl chlorosulfonylcarbamate (6.83 g, 39 mmol) in benzene (30 mL) was added dropwise to *N*-methylpiperidine in benzene (20 mL) at 0 °C. The reaction mixture was stirred for an additional 2 h. After removal of *N*-methylpiperidinium

chloride by filtration, the solvent was removed in vacuo. The product was recrystallized twice from dry THF to yield **4**, 6.6 g (28 mmol, 71%); mp 87−90 °C (THF); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 3.60 (m, 2H), 3.45 (m, 2H), 3.14 (s, 3H), 1.50−2.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 76.6, 54.7, 53.3, 40.1, 21.6, 20.6; IR (KBr) ν 3206.4, 2951.4, 2869.3, 2686.4, 2110.2, 1704.5, 1470.7 cm^{-1}; LRMS (FAB + NBA matrix) m/z 237, 205 (34.3), 100 (100.0), 70 (11.2).

***N*-Methyl-*N*-{[(2,2,2-trifluoroethyloxycarbonyl) amino]sulfonyl}-piperidinaminium, Inner Salt (5).** 2,2,2-Trifluoroethyl chlorosulfonylcarbamate (4.0 g, 17 mmol) in 30 mL of dry THF was added dropwise to *N*-methylpiperidine (3.80 g, 38 mmol) in 20 mL of dry THF at 0 °C. The reaction mixture was stirred for 2 h. *N*-Methylpiperidinium chloride was removed by filtration and the solvent was removed in vacuo. The product was recrystallized twice from dry THF to yield **5**, 2.4 g (7.9 mmol, 48%); mp 79−81 °C (THF); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.48 (q, J = 8.5 Hz, 2H), 3.63 (m, 2H), 3.45 (m, 2H), 3.15 (s, 3H), 1.82−1.99 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.1, 123.2 (q, J = 277.8 Hz), 61.7 (q, J = 36.0 Hz), 54.8, 40.2, 21.4, 20.6; IR (KBr) ν 3425.3, 2964.1, 2872.7, 2716.4, 2127.0, 1712.9, 1470.3 cm^{-1}; LRMS (FAB + NBA matrix) m/z 305, 205 (26.7), 137 (3.9), 100 (100.00); HRMS calcd for $C_9H_{15}F_3N_2O_4S$ 305.0783, found 305.0764.

Methyl *cis*-Tetrahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-Dioxide (7). Eluent hexanes−ethyl acetate, 4:1; R_f 0.42 (2:1 hexanes−ethyl acetate); mp 145−147 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.12 (m, 1H), 5.81 (d, 10.32 Hz, 1H), 5.21 (s, 1H), 4.80 (s, 1H), 3.93 (s, 3H), 2.35 (m, 1H), 2.30 (m, 1H), 2.15 (m, 1H), 1.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.5, 131.6, 120.7, 77.8, 55.5, 54.6, 24.0, 18.5; IR (KBr) ν 3438.9, 3010.2, 2963.5, 2853.3, 2544.9, 1725.9 cm^{-1}; LRMS (FAB + NBA matrix) m/z 234, 214 (13.5), 156 (27.4), 79 (40.3); HRMS calcd for $C_8H_{11}NO_4S$ 233.0358, found 234.0394 (M^+ + H). Anal. Calcd for $C_8H_{11}NO_5S$: C 41.20, H 4.75. Found: C 41.32, H 4.75.

2,2,2-Trifluoroethyl *cis*-Hexahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-Dioxide (13). Eluent hexanes−ethyl acetate, 2:1; R_f 0.45 (2:1 hexanes−ethyl acetate); mp 83−85 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.07 (d, J = 3.1 Hz, 1H), 4.69 (m, 1H), 4.61 (m, 1H), 4.27 (m, 1H), 2.38 (m, 1H), 2.33 (m, 1H), 1.90 (m, 1H), 1.81 (m, 2H), 1.69 (m, 1H), 1.55 (m, 1H), 1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 148.3, 122.3 (q, J = 278.8 Hz), 80.0, 62.5 (q, J = 37.6 Hz), 58.4, 27.1, 26.9, 21.8, 18.8; IR (KBr) ν 3031.7, 2947.2, 2871.5, 1755.5, 1623.1 cm^{-1}; LRMS (FAB + NBA matrix) m/z 304, 258 (5.5), 224 (43.3), 136 (30.7), 81 (100.0); HRMS calcd for $C_9H_{13}F_3NO_5S$ 304.0467, found 304.0512. Anal. Calcd for $C_9H_{12}F_3NO_5S$: C 35.65, H 3.99. Found: C 35.74, H 3.98.

2,2,2-Trifluoroethyl *cis*-Tetrahydro-3*H*-1,2,3-benzoxathiazole-3-carboxylate 2,2-Dioxide (14). Eluent hexanes−ethyl acetate, 2:1; R_f 0.46 (2:1 hexanes−ethyl acetate); mp 70−72 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15 (m, 1H), 5.79 (d, J = 10.2 Hz, 1H), 5.24 (s, 1H), 4.85 (s, 1H), 4.65 (m, 2H), 2.29 (m, 2H), 2.09 (m, 1H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.6, 132.3, 122.3 (q, J = 277.7 Hz), 120.1, 78.1, 62.5 (q, J = 37.6 Hz), 55.7, 27.1, 23.9, 18.5; IR (KBr) ν 3492.1, 3044.8, 2982.3, 2933.8, 2853.8, 1766.9 cm^{-1}; LRMS (EI) m/z 301, 221 (33.5), 220 (18.4), 216 (14.2), 120 (21.5), 94 (30.0), 78 (100.0); HRMS calcd for $C_9H_{10}F_3NO_5S$ 301.0232, found 301.0229. Anal. Calcd for $C_9H_{10}F_3NO_5S$: C 35.88, H 3.35. Found: C 35.98, H 3.24.

Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 1-Phenylethane-1,2-diyldicarbamate (12). R_f 0.75 (1:1 hexanes−ethyl acetate); mp 173−75 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 2H), 7.29 (m, 3H), 5.72 (m, 1H), 4.82 (m, 2H), 4.56 (m, 2H), 3.52 (s, 2H), 2.01 (m, 4H), 1.69 (m, 5H), 1.51 (s, 3H), 1.32 (m, 2H), 0.75−1.20 (m, 24H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 128.7, 127.7, 126.3, 75.0, 74.8, 56.4, 47.3, 41.4, 34.3, 31.4, 26.3, 23.5, 22.0, 20.9, 16.4; IR (KBr) ν 1015.2, 1148.8, 1291.1, 1455.0, 1533.1, 1685.8, 2956.1, 3364.2 cm^{-1}; LRMS (FAB + NBA matrix) m/z, 501(11.3), 319 (22.1), 225 (24.3), 181 (69.9), 120 (38.0), 83 (100.0); HRMS calcd for $C_{30}H_{49}N_2O_4$ 501.3692, found 501.3691. Anal. Calcd for $C_{30}H_{48}N_2O_4$: C 71.96, H 9.66, N 5.59. Found: C 71.70, H 9.78, N 5.60.

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Supporting Information Available: NMR data collection protocol, procedure for decomposition study of Burgess reagents at 50 and 78 °C, general procedures for dehydration of 1,2,3,4-tetrahydro-1-naphthol and for reactions with oxiranes and diols, and ^{1}H and ^{13}C NMR spectra of new Burgess reagents and sulfamidates. This material is available free of charge via the Internet at http://pubs.acs.org.