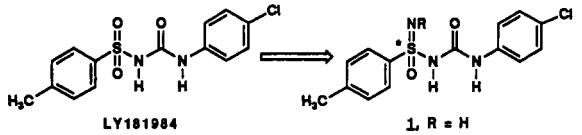
Synthesis and Resolution of Sulfonimidamide Analogs of Sulfonylureas

John E. Toth,* James Ray, and Jack Deeter†

Cancer Research Division and Chemistry and Biotechnology Research Division, Lilly Research Laboratories, Eli Lilly & Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Received January 26, 1993

Sulfonylureas have maintained an important position in medicinal chemistry since the discovery of their hypoglycemic activity and their weed-growth inhibiting properties.[1,2] A recent report from these laboratories detailed the antitumor activity of certain diarylsulfonylureas, exemplified by LY181984.[3] In regard to extending the structure–activity relationship within this diarylsulfonylurea series, certain structure-inherent characteristics were considered. Sulfonylureas are acidic compounds ($3 < pK_a < 7$) and are susceptible to hydrolysis in solution in the acid form. Substitution at the sulfonyl nitrogen atom, which prevents sulfonylurea ionization, also decreases structure stability. Thus, structural modifications are limited to the alkyl/aryl domains at the termini of the molecule. We postulated that the substitution of a nitrogen atom for an oxygen atom of the sulfonyl function might extend the SAR of this series by providing another terminus for modification in addition to creating a stereogenic center. This O → N modification had indeed

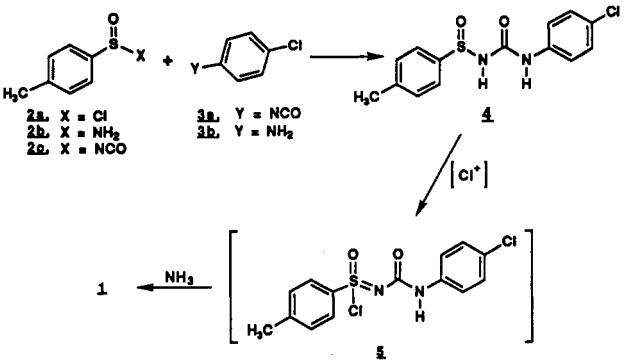


LY181984 1, R = H

been applied to the sulfonylurea hypoglycemic tolbutamide[4] and to the sulfonylurea herbicides,[5] although little information regarding the properties of the analogs was reported. This paper details the synthesis and the resolution of these sulfonimidamide analogs and an interesting rearrangement observed during their synthesis.

The Synthesis. We first attempted the synthesis of sulfonimidamide **1** through the chlorination/amination of sulfinylurea **4**, as reported by Johnson (Scheme I).[4] To this end, *p*-toluenesulfinamide **2b** in THF was treated with potassium *tert*-butoxide followed by *p*-chlorophenylisocyanate **3a** to provide the sulfinylurea **4**, contaminated by substantial amounts of another urea.[6] The purification

Scheme I



of **4** was complicated by its poor solubility in common organic solvents and its tendency to fragment when dissolved in polar solvents (e.g., DMF, DMSO).

The methodology of Jänchen and Westphal[7] provided the requisite sulfinylurea **4** in a convenient manner (Scheme I). Treatment of *p*-toluenesulfinyl chloride **2a**[8] with a slight excess of silver cyanate in ethyl ether produced the sulfinyl isocyanate **2c**, which was isolated as an ether solution by simple filtration of the precipitated silver salts. Addition of an ethereal solution of *p*-chloroaniline to the isocyanate solution produced the sulfinylurea **4** as an analytically pure precipitate in 70–80% yields. This sequence has been scaled to 1.0 mol with no difficulty.

With the source of sulfinylurea **4** established, the chlorination/amination of **4** was investigated and proceeded as reported.[4] Treatment of a suspension of **4** in THF (0.1–0.3 M) with 1 equiv of *N*-chlorobenzotriazole,[9] or *tert*-butyl hypochlorite, rapidly produced a solution of **5** which was added dropwise to an excess of ammonia at −76 °C. Evaporation of the volatiles produced a crude solid which was slurried in water, collected, and dried to give the desired sulfonimidamide **1**, as an analytically pure amorphous solid, in 70–80% yield from **4**.

The Rearrangement. In the course of preparing the *N*-(*n*-propyl)sulfonimidamide **6** by the same synthetic route, flash chromatography of the crude reaction product yielded two isomeric sulfonimidamides, **A** and **B**, in 62% combined yield (~2:1 ratio by NMR). The most distinguishing physical chemical characteristic of **A** and **B** was observed in their UV spectra. **A** exhibited a λ_{max} = 250 nm (ϵ = 25 000) and **B** a λ_{max} = 235 nm (ϵ = 20 000). On the basis of λ_{max} analogy to **1**, product **A** was assigned structure **6**. The structure of **B** was deduced by single-crystal X-ray analysis to be the rearranged sulfonimidamide **8**.[10]

Mechanistically, this process appeared to be proceeding through two competing pathways, one involving a direct intermolecular displacement of chloride by *n*-propylamine to produce **6** and another operating through intermediate **7** to deliver the aniline in an intramolecular displacement reaction to produce **8**.[11] The formation of **8** could be

† Chemstry and Biotechnology Research Division.

(1) Larner, J. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th ed.; Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; Macmillan Publishing Co., Inc.: New York, 1980, p 1510. See also: Ferner, R. E.; Alberti, K. G. M. M. *Quart. J. Med., New Ser.* **1989**, *73*(271), 987.

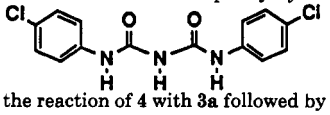
(2) Levitt, G. *ACS Symp. Ser.* **1991**, *443*, 17.

(3) Howbert, J. J.; Grossman, C. S.; Crowell, T. A.; Reider, B. J.; Harper, R. W.; Kramer, K. K.; Tao, E. V.; Aikens, J.; Poore, G. A.; Rinzel, S. M.; Grindey, G. B.; Shaw, W. N.; Todd, G. C. *J. Med. Chem.* **1990**, *33*, 2393.

(4) Johnson, C. R.; Jonsson, E. U.; Bacon, C. C. *J. Org. Chem.* **1979**, *44*, 2055. Johnson, C. R.; Wambsgans, A. *J. Org. Chem.* **1979**, *44*, 2278.

(5) Hillemann, C. L. (Du Pont) US Patent 4,666,506, 1987.

(6) The suggested structure of this impurity by FDMS is



presumably from the reaction of **4** with **3a** followed by sulfinyl cleavage.

(7) Jähnchen, G.; Westphal, G. *Z. Chem.* **1969**, *8*, 305.

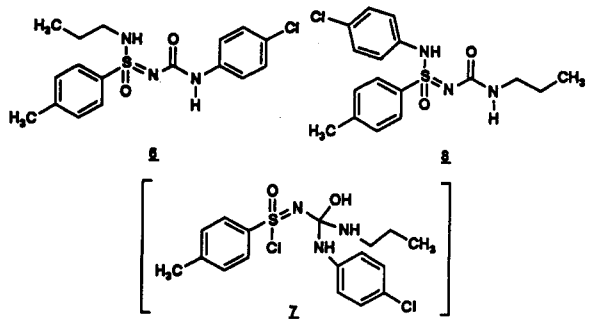
(8) Kurzer, F. *Organic Syntheses*; John Wiley & Sons, Inc.; New York, 1963; Collect. Vol. IV, p 937.

(9) Rees, C. W.; Storr, R. C. *J. Chem Soc C* **1969**, 1474.

(10) X-ray data has been filed with the Cambridge Crystallographic Data Center.

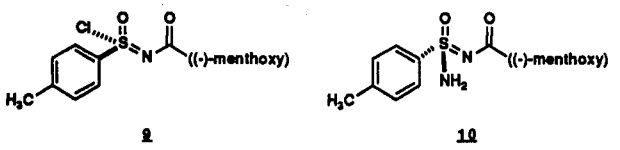
(11) In a competition experiment, **5** was added to a mixture of *n*-propylamine (4.0 equiv, 0.8 M in THF) and 4-bromoaniline (1.0 equiv, 0.2 M in THF) at 0 °C. NMR (300 MHz) and FDMS analysis showed the crude product consisted of **6** and **8** (1.3:1) and no bromoaniline-containing sulfonimidamide products.

0022-3263/93/1958-3469$04.00/0



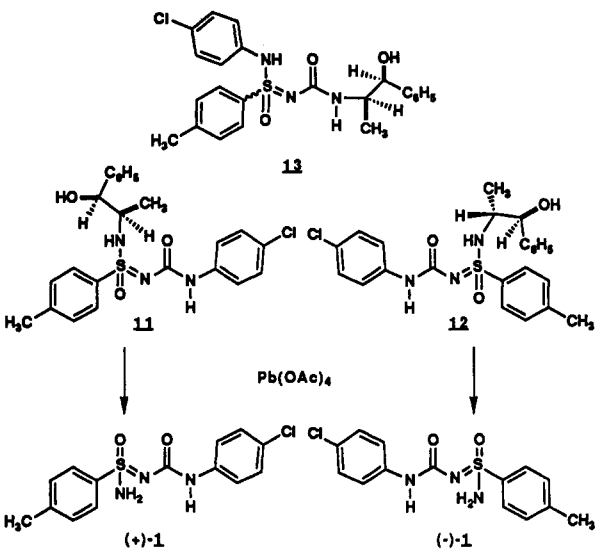
surpressed by initiating the reaction at −76 °C and by using a large excess of *n*-propylamine.[12]

The Resolution. The resolution of sulfonimidamide **1** proved to be more difficult than expected. The obvious strategy of reacting a chiral amine with sulfonimidoyl chloride **5** failed to produce a chromatographically resolvable mixture of the diastereomeric sulfonimidamides in the case of (*R*)-(+)-α-methylbenzylamine and with the amino acid esters of L-phenylalanine and L-alanine.[13] Separation of these crude reaction mixtures was also complicated by the presence of variable amounts of rearranged diastereomeric sulfonimidamides. Cram reported the synthesis of (+)-sulfonimidoyl chloride **9** and reported its conversion, with probable inversion of configuration, to the sulfonimidamide **10**.[14]



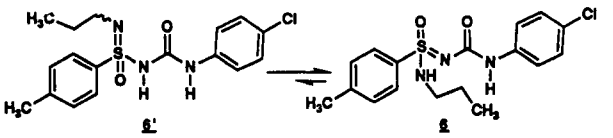
To test this approach, we attempted to exchange the (−)-menthoxy group of a mixture of **10** and its sulfur diastereomer, with *p*-chloroaniline, with no success. In rethinking the failure of auxiliary amines (*vide supra*) to provide chromatographically resolvable diastereomeric mixtures with minimal rearrangement, we postulated that an amine possessing a vicinally disposed polar functional group might facilitate such a separation. Our efforts turned to the recently reported $Pb(OAc)_4$ cleavage of carbamate-protected serine derivatives.[15] In fact, the reaction of **5** with (1*S*,2*R*)-norephedrine produced a mixture of the desired diastereomers **11** and **12** and the rearranged sulfonimidamide diastereomers **13**, the relative ratio of which was dependent on the number of equivalents of (1*S*,2*R*)-norephedrine and the reaction temperature employed (Scheme II).[16] Treatment of **11** and **12**, readily separated by silica gel flash chromatography, with $Pb(OAc)_4$ in ethyl acetate directly provided (+)-**1**, $[\alpha]^{30}_D$ = +58.8° (*c* = 1.0, methanol) and (−)-**1**, $[\alpha]^{30}_D$ = −58.9° (*c* = 1.0, methanol) in 55–60% yield. The absolute configurations of (+)-**1** and (−)-**1** have not been determined.

Scheme II



Discussion

These sulfonimidamide analogs exhibited several interesting physical characteristics in comparison to their sulfonylurea counterparts. Their ^{1}H-NMR spectra (300 MHz, d_6-DMSO) showed a proton–proton coupling pattern consistent with a structure that is best represented by, for example, the tautomer **6** rather than **6′** in polar solution (δ 7.61, t, 1H, exchanged with D_2O, $-CH_2NH$). Compound **1** has a pK_a of 10.5 vs 6.1 for LY181984 when titrated in aqueous DMF, and the former shows better hydrolytic stability to aqueous acids.[17] A single-crystal X-ray analysis of **1** confirmed the connectivity of the sulfonimidamide linkage.[10] It has been reported that sulfonimidoyl chlorides react with alcohols to produce the corresponding sulfonamide.[4] It is interesting to note that, in the reaction of (1*S*,2*R*)-norephedrine with **5**, no LY181984 was observed.



Summary. This note has demonstrated a convenient method for the preparation of sulfonimidamide analogs of sulfonylureas. The methodology is complicated, however, by the tendency of sulfonimidoyl chloride **5** to react with certain amines in an unexpected rearrangement pathway. Although this rearrangement pathway was not studied, its contribution to the product distribution was reduced under conditions of low temperature and excess amine, such that moderate yields of the desired products were obtained. In addition, the methodology was used to resolve racemic **1** in quantities large enough to permit the evaluation of the antitumor activities of the individual enantiomers. These will be reported in due course.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR

(12) In a competition experiment, **5** was added to a mixture of *n*-propylamine (10 equiv, 1.33 M in THF) and 4-bromoaniline (10 equiv, 1.33 M in THF) at −76 °C → rt. NMR (300 MHz) and HPLC analysis (system A) showed that only sulfonimidamide **6** was produced.

(13) For the use of amino acids as surrogate nitrogen chiral auxiliaries, see: Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468.

(14) Jones, M. R.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 2183.

(15) Apitz, G.; Steglich, W. *Tetrahedron Lett.* **1991**, *32*, 3163.

(16) In practice, 10 equiv of (1*S*,2*R*)-norephedrine (1.15 M in THF) at −76 °C → rt, gave an 11,12:13 ratio of 2.0:1.0 by NMR (300 MHz).

(17) LY181984 and **1** were individually dissolved in a mixture of 5.0 mL of aqueous H_3PO_4 solution (pH = 2.0) and 5.0 mL of acetonitrile and the solutions stored at rt.; hydrolysis, as monitored by HPLC (system A) over 22 h, was not observed for **1**, while <40% of the LY181984 remained intact.

spectra were acquired on a GE QE-300 spectrometer at 300 MHz (proton) and 75 MHz (carbon). Heteroatom–proton assignments were made on the basis of D_2O exchange. Coupling constants are reported in Hz. TLC was performed on silica gel 60 F_{254} plates from E. Merck. Flash chromatography was carried out on EM Science silica gel 60 (230–400-mesh ASTM). HPLC was performed on a Waters 600E system with the following: system A, Radial-Pak 8NVC18 (8 mm × 100 mm, 4 μm) with C18 precolumn and employing a gradient solvent program utilizing 25% acetonitrile/0.025 M pH 7.0 $NaPO_4$ buffer at 1.5 mL/min flow rate for 5 min followed by linear change to 60% acetonitrile over 5 min, a 5 min hold, another 5 min linear change to 25% acetonitrile, and a 5 min hold; system B, tandem Radial-Pak 8NVC18 (8 mm × 100 mm, 4 μm) with C18 precolumn and employing isocratic elution with 25% (1% aqueous acetic acid)/75% acetonitrile at a 2.0 mL/min flow rate. All UV detection was at 254 nm. All solvents and chemicals were used as purchased without further purification. *tert*-Butyl hypochlorite was obtained from TCI America. Reactions were run under nitrogen. Reported concentrations refer to final reaction concentrations.

***N*-(4-Methylbenzenesulfinyl)-*N*'-(4-chlorophenyl)urea (4).** A dry 250-mL three-neck round-bottom flask fitted with a mechanical stirrer, addition funnel, and nitrogen line was charged with silver cyanate (20.8 g, 138.6 mmol) and 70 mL of ether. This mixture was cooled to 0 °C and the addition funnel charged with a solution of crude *p*-toluenesulfinyl chloride[8] (16.95 g, 97.05 mmol) in 70 mL of ether; the sulfinyl chloride solution was added dropwise to the cyanate mixture with vigorous stirring over 30 min, keeping the temperature at 0 °C. After the cooling bath was removed and the mixture stirred at room temperature for 2 h, the suspended silver chloride was removed by filtration and the yellow sulfinyl isocyanate solution was transferred to a dry 1-L three-neck flask. A solution of **3b** (11.2 g, 87.8 mmol) in 200 mL of ether was added dropwise to the ice-cold sulfinyl isocyanate solution over 15 min. After being warmed to room temperature and stirred overnight, the resulting solid was collected by filtration and rinsed with 1 L of ether. Vacuum drying at 40 °C for 4 h gave 20.93 g (77%) of **4** as a white to light purple solid: mp 163–164 °C; R_f (10/1 EtOAc/HOAc) = 0.63; ^{1}H NMR (d_6-DMSO) δ 2.38 (s, 3H, CH_3), 7.33 (d, 2H, J = 8.8, Ar-*H*), 7.41–7.46 (m, 4H, Ar-*H*), 7.63 (d, 2H, J = 8.1, Ar-*H*), 8.83 (s, 1H, N*H*) and 9.56 (s, 1H, SON*H*); ^{13}C NMR (d_6-DMSO) δ 21.3, 120.8, 125.2, 127.0, 129.2, 130.2, 137.9, 141.6, 142.0, and 153.2; IR (KBr) 3274, 3158, 1698, 1247, 1207, 1178 and 1096 cm^{-1}; FDMS (DMSO) *m/e* 308, 310 (M^+). Anal. Calcd for $C_{14}H_{13}Cl_1N_2O_2S_1$: C, 54.46; H, 4.24; N, 9.07. Found: C, 54.34; H, 4.32; N, 8.91.

***N*-[[(4-Chlorophenyl)amino]carbonyl]-4-methylbenzenesulfonimidamide (1).** Compound **4** (1.85 g, 6.0 mmol) was suspended in 50 mL of THF under nitrogen and treated with *N*-chlorobenzotriazole[9] (968 mg, 6.3 mmol) in one portion. The mixture became homogeneous and yellow after 10 min and was stirred another 25 min. This solution was added dropwise over 10 min to 25 mL of ammonia at −76 °C. After being stirred for 15 min the mixture was allowed to warm to rt for 2 h. The volatiles were removed under vacuum, and the residue was diluted with 50 mL of water. The resulting slurry of white solid, after being stirred for 15 min, was collected by filtration and rinsed with water (20 mL) and ether (50 mL). Vacuum drying overnight at 50 °C yielded 1.43 g (74%) of **1** as a white solid: mp 171–172 °C; R_f (1/9 MeOH/$CHCl_3$) = 0.48; pK_a = 10.5 (DMF/H_2O (2/1)); ^{1}H NMR (d_6-NMR) δ 2.36 (s, 3H, CH_3), 7.18 (d, 2H, J = 8.8, Ar-*H*), 7.37 (d, 2H, J = 8.0, Ar-*H*), 7.45–7.48 (d overlapping s, 4H, 2Ar-*H* + NH_2), 7.76 (d, 2H, J = 8.2, Ar-*H*) and 9.24 (s, 1H, N*H*); ^{13}C NMR (d_6-DMSO) δ 21.4, 119.9, 125.2, 127.0, 128.6, 129.6, 140.2, 141.0, 142.8 and 157.2; IR (KBr) 3429, 3401, 3279, 3056, 1651, 1618, 1591, 1521, 1273, 1222, 1175, and 1114 cm^{-1}; UV (EtOH) λ_{max} (ε) 205.2 (34 293), 254.4 (29 327) nm; FDMS (DMSO) *m/e* 323,325 (M^+). Anal. Calcd for $C_{14}H_{14}Cl_1N_3O_2S_1$: C, 51.93; H, 4.36; N, 12.98. Found: C, 51.67; H, 4.47; N, 12.68.

The Reaction of 5 with *n*-Propylamine. The method for the preparation of **1** was followed using **4** (12.4 g, 40.2 mmol), *N*-chlorobenzotriazole[9] (6.7 g, 44 mmol), and *n*-propylamine (9 mL, 110 mmol, 0.33 M in THF) at 0 °C. The crude product (16.3 g) was purified by Prep 500 silica gel chromatography (toluene/EtOAc) to give two fractions, 6.35 and 2.65 g. The larger fraction was recrystallized from 50 mL of ether/hexane (1:1) to yield 4.04 g (27%) of **6** as a white solid: mp 118–119.5 °C; R_f (1/1 EtOAc/hexane) = 0.62; ^{1}H NMR (d_6-DMSO) δ 0.7–0.8 (m, 3H, $CH_2CH_2CH_3$), 1.35–1.42 (m, 2H, $CH_2CH_2CH_3$), 2.37 (s, 3H, CH_3), 2.68–2.74 (m, 2H, $CH_2CH_2CH_3$), 7.20 (d, 2H, J = 8.8, Ar-*H*), 7.38 (d, 2H, J = 8.1, Ar-*H*), 7.48 (d, 2H, J = 8.8, Ar-*H*), 7.61 (t, 1H, J = 5, N*H*), 9.29 (bs, 1H, N*H*); IR (KBr) 3299, 32529, 2975, 1645, 1549, 1533, 1275, 1231, 1179, and 1137 cm^{-1}; UV (EtOH) λ_{max} (ε) 206.0 (33 591) and 254.8 (29 371) nm; FDMS (DMSO) *m/e* 365, 367 (M^+). Anal. Calcd for $C_{17}H_{20}Cl_1N_3O_2S_1$: C, 55.81; H, 5.51; N, 11.49. Found: C, 55.96; H, 5.64; N, 11.21.

The smaller fraction was recrystallized from 10 mL of ether to give 2.21 g (15%) of **8** as a white solid: mp 134–135.5 °C; R_f (1/1 EtOAc/hexane) = 0.54; ^{1}H NMR (d_6-DMSO) δ 0.7–0.8 (m, 3H, $CH_2CH_2CH_3$), 1.30–1.38 (m, 2H, $CH_2CH_2CH_3$), 2.31 (s, 3H, CH_3), 2.84–2.90 (m, 2H, $CH_2CH_2CH_3$), 6.94 (bs, 1H, N*H*), 7.05 (d, 2H, J = 8.7, Ar-*H*), 7.23 (d, 2H, J = 8.7, Ar-*H*), 7.32 (d, 2H, J = 8.0, Ar-*H*), 7.67 (broad d, 2H, J = 7.2, Ar-*H*), 10.2 (bs, 1H, N*H*); IR (KBr) 3394, 3130, 2963, 2926, 1617, 1529, 1288, 1271, 1219, and 1175 cm^{-1}; UV (EtOH) λ_{max} (ε) 206.0 (28 758) and 233.4 (23 158) nm; FDMS (DMSO) *m/e* 365, 367 (M^+). Anal. Calcd for $C_{17}H_{20}Cl_1N_3O_2S_1$: C, 55.81; H, 5.51; N, 11.49. Found: C, 56.07; H, 5.40; N, 11.33.

The Reaction of 5 with (1*S*,2*R*)-Norephedrine. A suspension of **4** (7.14 g, 23.2 mmol) in THF (95 mL) at rt under nitrogen was treated with *tert*-butyl hypochlorite (2.76 mL, 23.2 mmol) and stirred for 30 min. The resulting solution was added dropwise over 1 h to a solution of (1*S*,2*R*)-norephedrine (35.0 g, 231.5 mmol) in 110 mL of THF cooled in a dry ice/2-propanol bath. After being stirred for an additional hour at −76 °C, the cooling bath was removed, and after an additional 1.5 h, the reaction mixture was poured into 1 N HCl solution (500 mL) and extracted with EtOAc (2 × 250 mL). The combined extract was washed with water and brine and dried (Na_2SO_4); filtration and evaporation gave a foam which, by NMR analysis, had the content **11**,**12**:**13** = 2.0:1.0. Silica gel flash chromatography (EtOAc/hexane) of the crude reaction product provided 3.14 g (30%) of **11**, 3.35 g (32%) of **12**, and 3.45 g (33%) of **13**:

11: foam from CCl_4; R_f (1/1 EtOAc/hexane) = 0.44; $[\alpha]^{30}_D$ = +29.8° (c = 1.0, methanol); pK_a = 11.9 (DMF/H_2O (2/1)); de >200:1 (HPLC system A);[18] ^{1}H NMR (d_6-DMSO) δ 0.72 (d, 3H, J = 6.7, NCHCH_3), 2.35 (s, 3H, CH_3), 3.41 (m, 1 H, HNC*H*−), 4.68 (t, 1H, J = 4.2, CHC*H*OH), 5.44 (d, 1H, J = 4.7, CHO*H*), 7.12–7.28 (m, 9H, Ar*H*), 7.34 (d, 2H, J = 8.2, Ar*H*), 7.50 (d, 2H, J = 8.9, Ar*H*), 7.74 (d, 2H, J = 8.1, Ar*H*), 7.75 (d, 1H, J = 7.3, CHN*H*), 9.32 (s, 1H, ArN*H*); IR (KBr) 3291, 1637, 1270, 1228 and 1122 cm^{-1}; UV(EtOH) λ_{max}(ε) 204.4 (45 390) and 254.2 (28 340) nm; FDMS (DMSO) *m/e* 457, 459 (M^+). Anal. Calcd for $C_{23}H_{24}Cl_1N_3O_3S_1$·0.14$CCl_4$: C, 57.96; H, 5.21; N, 8.76. Found: C, 57.91; H, 5.21; N, 8.71.

12: foam from CCl_4; R_f (1/1 EtOAc/hexane) = 0.38; $[\alpha]^{30}_D$ = −36.9° (c = 1.0, methanol); pK_a = 11.8 (DMF/H_2O (2/1)); de not available;[19] ^{1}H NMR (d_6-DMSO) δ 0.90 (d, 3H, J = 6.6, NCHCH_3), 2.35 (s, 3H, CH_3), 3.38 (m, 1H, HNC*H*− obscured by HOD peak), 4.49 (t, 1H, J = 4.3, CHC*H*OH), 5.43 (d, 1H, J = 4.6, CHO*H*), 7.09–7.26 (m, 7H, Ar*H*), 7.29 (d, 2H, J = 8.2, Ar*H*), 7.52 (d, 2H, J = 8.9, Ar*H*), 7.64 (d, 2H, J = 8.2, Ar*H*), 7.71 (d, 1H, J = 8.4, CHN*H*), 9.37 (s, 1H, ArN*H*); IR (KBr) 3408, 1636, 1276, 1230 and 1123 cm^{-1}; UV (EtOH) λ_{max} (ε) 204.8 (26 683) and 258.0 (25 646) nm; FDMS (DMSO) *m/e* 457, 459 (M^+). Anal. Calcd for $C_{23}H_{24}Cl_1N_3O_3S_1$: C, 60.32; H, 5.28; N, 9.17. Found: C, 60.26; H, 5.44; N, 9.22.

13: crystals from THF/hexane, diastereomeric composition not determined; mp 180–181 °C; R_f (1/1 EtOAc/hexane) = 0.23; IR (KBr) 3284, 1620, 1296, 1251, and 1182 cm^{-1}; UV (EtOH) λ_{max} (ε) 204.4 (42 483) and 232.2 (22 029) nm; FDMS (DMSO) *m/e* 457, 459 (M^+). Anal. Calcd for $C_{23}H_{24}Cl_1N_3O_3S_1$: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.56; H, 5.28; N, 9.44.

The Reaction of 11 and 12 with Pb(OAc)$_4$. A solution of **11** (2.50 g, 5.47 mmol) in EtOAc (50 mL) at rt was treated with $Pb(OAc)_4$ solid (3.40 g, 7.66 mmol) in one portion. Twenty min

(18) This was determined on the basis of integrator area % comparisons at 254 nm.

(19) Although **12** was homogeneous by 300-MHz NMR, a firm de was not determined. In view of the stereochemically clean conversion of **11** to (−)-**1**, one may infer that the de of **12** was 39:1.

later, the reaction was filtered through a Celite pad into 100 mL of 20% aqueous citric acid solution. The pad was washed with 50 mL of THF and the filtrate also added to the 20% aqueous citric acid solution. After being stirred for 10 min, the organic phase was separated and the aqueous extracted with EtOAc/THF (100 mL, 1:1). The combined organic phase was dried ($MgSO_4$), filtered, and evaporated to yield the crude product contaminated by citric acid and benzaldehyde. Silica gel flash chromatography of this crude product provided 0.96 g (54%) of (−)-1; mp 168–169 °C; R_f (1/9 MeOH/$CHCl_3$) = 0.48; $[\alpha]^{30}_D$ = −58.9° (c = 1.0, methanol); 99% ee; ^{1}H NMR (d_6-DMSO) same as (±)-(1); FDMS (DMSO) m/e 323, 325 (M^+). Anal. Calcd for $C_{14}H_{14}Cl_1N_3O_2S_1$: C, 51.93; H, 4.36; N, 12.98. Found: C, 51.63; H, 4.21; N, 12.81. In a similar manner, **12** (2.50 g, 5.47 mmol) provided 1.05 g (59%) of (+)-1; mp 167–168 °C; R_f (1/9 MeOH/$CHCl_3$) = 0.48; $[\alpha]^{30}_D$ = +58.8° (c = 1.0, methanol); 95% ee; ^{1}H NMR (d_6-DMSO) same as (±)-(1); FDMS (DMSO) m/e 323, 325 (M^+). Anal. Calcd for $C_{14}H_{14}Cl_1N_3O_2S_1$: C, 51.93; H, 4.36; N, 12.98. Found: C, 52.23; H, 4.20; N, 12.73. The enantiomeric purity of these samples was determined by their individual conversion (DMAP, Et_3N, and (−)-menthoxyacetyl chloride in CH_2Cl_2) to the diastereomeric amides, which were assayed by HPLC (system B) in duplicate. Chromatographic peak assignments were verified by doping experiments with the diastereomeric amides produced from racemic **1**.[19]

Acknowledgment. The authors wish to express their appreciation for the analytical services provided by the Chemistry and Biotechnology Research Division and for the quantities of **4** provided by Bennie Foster, Dave Hunden, and Elizabeth Aaron.

Additions and Corrections

Vol. 56, 1991

Derrick L. J. Clive,* Chengzhi Zhang, K. S. Keshava Murthy, William D. Hayward, and Sylvain Daigneault. New Low-Valent Titanium Reagents for Dicarbonyl Coupling and Their Use in a General Method of Annulation.

Page 6451, Table III. Entries o to s should refer to titanium tetrachloride and not to titanium trichloride.

Vol. 57, 1992

Scott McN. Sieburth* and Louis Fensterbank. An Intramolecular Diels-Alder Reaction of Vinylsilanes.

Page 5281. The following note was inadvertently omitted.

Note Added in Proof. After submission of this manuscript, we learned of a contribution by the Stork group in this area (Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578–7579). We would like to thank Professor Stork for sharing his manuscript prior to publication.

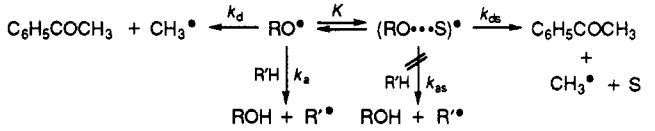
Vol. 58, 1993

Sung Soo Kim,* Sung Yeon Kim, Seung Sin Ryou, Choon Seung Lee, and Kwang Hee Yoo. Solvent Effects in the Hydrogen Abstractions by *tert*-Butoxy Radical: Veracity of the Reactivity/Selectivity Principle.

Pages 192–196. Solvent effects on hydrogen abstractions by cumyloxyl radical have been recently investigated (Avila, D. V.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466). The rate constants for the β-scission become larger with increasing solvent polarity, while those of hydrogen abstractions from cyclohexane stay essentially constant.

Those observations can be eminently rationalized by assuming equilibration between solvent-free and solvated cumyloxyl radicals, where the former either abstracts hydrogen from cyclohexane or experiences homolytic fragmentation while the latter solely undergoes β-scission as with Scheme I. The ratio of the products, i.e., 2-phenyl-2-propanol and acetophenone, can be equated with eq 1.

Scheme I[a]



[a] Key: RO•, cumyloxyl radical; (RO···S)•, solvated cumyloxyl radical; S, solvent; R′H, cyclohexane; ROH, 2-phenyl-2-propanol; K, equilibrium constant; k_a and k_{as}, rate constants for the abstractions by solvent-free and solvated cumyloxyl radicals, respectively, with k_{as} negligibly small; k_d and k_{ds}, rate constants for β-scission with solvent-free and solvated cumyloxyl radicals, respectively.

$$\frac{\Delta[\mathrm{ROH}]}{\Delta[\mathrm{C_6H_5COCH_3}]} = \frac{k_a[\mathrm{RO^\bullet}][\mathrm{R'H}]}{k_d[\mathrm{RO^\bullet}] + k_{ds}[(\mathrm{RO\cdots S})^\bullet]} \quad (1)$$

Strong solvation of cumyloxyl radical could render $k_{ds} \gg k_d$ and $[(RO\cdots S)^\bullet] \gg [RO^\bullet]$, whereby eq 1 could be approximated to eq 2. Yield of the alcohol is then also controlled by an equilibrium constant K which may be variable with solvents to disclose vigorous solvent interactions with the hydrogen abstractions. The rate constant for the abstraction involved with product ratio studies by Walling and Wagner may correspond thereby to k_a/K in eq 2.

$$\frac{\Delta[\mathrm{ROH}]}{\Delta[\mathrm{C_6H_5COCH_3}]} = \frac{k_a[\mathrm{RO^\bullet}]}{k_{ds}[(\mathrm{RO\cdots S})^\bullet]}[\mathrm{R'H}] = \frac{k_a}{k_{ds}}\frac{1}{K}[\mathrm{R'H}] \quad (2)$$

They proposed that only weakly solvated *tert*-butoxy radical should be capable of hydrogen abstraction at the slower rate, which must be kinetically equivalent to the previous equilibration regulating concentration of solvent-free *tert*-butoxy radical, the sole hydrogen abstractor.