An Efficient and General Synthesis of 5-Substituted Pyrrolidinones

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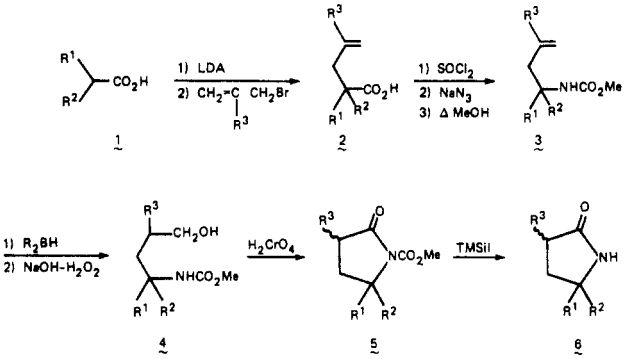
2-Pyrrolidinone derivatives are widespread materials of considerable laboratory and commercial importance. In spite of this, there is no generally useful synthesis of either symmetrically or unsymmetrically 5,5-disubstituted derivatives. This is particularly true for those cases bearing aryl substituents. We describe here an effective and general synthesis of 5-mono- and disubstituted 2-pyrrolidinones (including aryl and spiro substituents) from readily available precursors. The flexibility of the reaction sequence should also readily permit the simultaneous introduction of additional substituents at other ring positions. The overall success of the procedure results from the discovery of a novel oxidative cyclization reaction of acyclic hydroxyurethane precursors.

In connection with another investigation, a series of 2-pyrrolidinone derivatives with a variety of substituent groups primarily in position 5 were needed. Since many of the desired compounds were unsymmetrically 5,5-disubstituted, often incorporating at least one aryl group, the common literature techniques were not generally applicable.[1] For this reason, we decided to construct the 2-pyrrolidinone ring system from fragments (see Scheme I), thus maintaining maximum flexibility for substituent incorporation. We describe here the results of this study.

The alkylation of the acid dianions, generated with 2 mol of lithium diisopropylamide (LDA),[2] was uneventful and the desired products were isolated in high yield. In most cases, the production of the urethane derivatives was accomplished by standard techniques (i.e., conversion to the acid chloride, formation of the acyl azide with sodium azide, and subsequent thermolysis).[3] However, some difficulty with competing lactonization was encountered with the preparation of the acid chloride from **2d**. In this particular case, the use of diphenylphosphoryl azide[4] and triethylamine, resulting in the situ formation of the isocyanate, was advantageous. This procedure proved so convenient that it was frequently substituted for the classical technique in subsequent lactam syntheses. The addition of alcohol subsequent to the isocyanate formation prevented concomitant esterification of the acid[5,6] which often led to purification problems.

A number of hydroborating reagents (BH_3·THF, BH_3·DMS, disiamylborane, 9-BBN) were surveyed for the conversion of the urethanes **3** to the corresponding alcohol **4**. Of these, disiamylborane represented the best compromise between regioselectivity in the hydroboration and ease of product isolation. This regioselectivity is particularly critical in the transformation of **3f** where specific reduction of the monosubstituted double bond was desired. This technique ultimately permitted the construction of spirocyclic lactam derivatives which were differentially functionalized within the carbocyclic ring. Systems of this type are useful intermediates for the synthesis of a number of spirocyclic natural products.[8]

Scheme I



	R^1	R^2	R^3
a	Ph	H	H
b	Ph	Ph	H
c	Ph	Me	H
d	Ph	H	CH_3
e		$-(CH_2)_5-$	H
f		$-CH_2CH{=}CH(CH_2)_2-$	H

The oxidative cyclization of the acyclic alcohols **4** to the desired *N*-carbomethoxy lactams **5** was accomplished simply and effectively by the use of Jones reagent. Presumably, this reaction proceeds by initial oxidation to the corresponding aldehyde, followed by acid-catalyzed cyclization on nitrogen[9] and subsequent oxidation to **5**. As expected, the oxidation of **4d** resulted in a stereoisomeric mixture of the *N*-carbomethoxy lactams which were easily separated on a preparative scale by short-column chromatography. The desired 2-pyrrolidinones were generated from the corresponding *N*-carbomethoxy derivatives by selective decarboxymethylation using trimethylsilyl iodide[10] in chloroform.

This procedure represents an effective and general synthesis of 5-substituted 2-pyrrolidinones (including aryl and spiro substituents) from readily available starting materials with overall yields which ranged from 50–75%. Although five steps are involved, most yields are high and intermediates rarely require extensive purification.

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Chemical studies of these and other substituted pyrrolidinones are in progress.

Experimental Section

All solvents were routinely dried and distilled before use. ^1H NMR spectra were recorded on a Varian HA-100, using tetramethylsilane as an internal standard. Infrared spectra were taken on a Perkin-Elmer 297 instrument. GLC analyses were accomplished with a Hewlett-Packard 5750 instrument by using a glass column (0.25 in. × 6 ft) packed with 10% SE-30 on Gas Chrom Q. Flash chromatographic purifications were performed as described by Still and co-workers.[11]

General Procedure for Prepartion of 2-Pyrrolidinones 6a–f. Preparation of Acids 2a–f. A solution containing 20 mmol of the substituted acetic acid in 10 mL of dry THF was added to 50 mmol of lithium diisopropylamide (LDA) in 50 mL of THF at 0 °C. The suspension was stirred for 1 h at 25 °C and 0.5 h at 60 °C. After the mixture was cooled to 0 °C, 50 mmol of allyl bromide was added and the reaction stirred for 16 h at 25 °C. At this point, the mixture was quenched with saturated ammonium chloride solution and acidified with 2 N H_2SO_4. The aqueous layer was extracted with ether and washed with 20% K_2CO_3 solution. The aqueous layer was then acidified with 6 N H_2SO_4 and reextracted with ether. The crude product was pumped down to 0.05 mm to remove any remaining solvent and carried on to the next step without further purification.

2a: 78%; ^1H NMR ($CDCl_3$) δ 7.19 (s, 5 H), 5.44–5.86 (m, 1 H), 4.84–5.12 (m, 2 H), 3.58 (t, J = 7 Hz, 1 H), 2.20–2.97 (m, 2 H).

2b: 75%; ^1H NMR ($CDCl_3$) δ 7.06–7.29 (m, 10 H), 5.30–5.78 (m, 1 H), 4.70–4.96 (m, 2 H), 3.12 (d, J = 7 Hz, 2 H).

2c: 88%; ^1H NMR ($CDCl_3$) δ 7.03–7.47 (m, 5 H), 5.36–5.80 (m, 1 H), 4.87–5.14 (m, 2 H), 2.72 (m, 2 H), 1.54 (s, 3 H).

2d: 92%; ^1H NMR ($CDCl_3$) δ 7.00–7.40 (m, 5 H), 4.63 (m, 2 H), 3.72 (t, J = 7 Hz, 1 H), 2.20–2.90 (m, 2 H), 1.6 (s, 3 H).

2e: 72%; ^1H NMR ($CDCl_3$) δ 5.49–5.93 (m, 1 H), 4.81–5.13 (m, 2 H), 2.25 (d, J = 7 Hz, 2 H), 1.10–2.50 (m, 10 H).

2f: 75%; ^1H NMR ($CDCl_3$) δ 5.50–6.00 (m, 3 H), 4.90–5.20 (m, 2 H), 1.50–2.80 (m, 8 H).

Preparation of Urethanes 3a–f. Procedure A. The crude acids **2a–c,e-f** (30 mmol) were stirred for 1 h at 25 °C with 10 mL of thionyl chloride. The volatile materials were removed by distillation at 50 mm. The residue which remained was transferred by Kugelrohr distillation (0.1 mm, 110 °C) to furnish the pure acid chloride. A solution of 30 mmol of the acid chloride in 100 mL of dry acetone was added to 0.3 mol of sodium azide in 200 mL of water at 0 °C over 1 h. After 2 h at 25 °C, the mixture was poured into ice water and extracted with ether. The organic phase was washed with brine and dried over $MgSO_4$. The crude acid azide was isolated by evaporation of the solvent and used without purification.

The crude acid azide from above was dissolved in 50 mL of benzene and added over 0.5 h to 50 mL of refluxing benzene. The benzene was removed by distillation and the resulting isocyanate dissolved in 50 mL of methanol and refluxed for 48 h. After evaporation of the solvent, the products were separated by short column chromatography over silica gel, using ether/hexane (1:1). The urethanes could be further purified by recrystallization or by Kugelrohr distillation (0.05 mm, 110 °C).

3a: 96%; mp 72 °C; IR (KBr) 3320 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 5 H), 5.40–5.83 (m, 1 H), 4.90–5.16 (m, 3 H), 4.71 (m, 1 H), 3.58 (s, 3 H), 2.49 (m, 2 H); high-resolution mass spectrum, m/e 204.102 (calcd 204.103). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 70.22; H, 7.36. Found: C, 70.24; H, 7.36.

3b: 98%; mp 72 °C; IR (KBr) 3310, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 10 H), 5.28–5.94 (m, 2 H), 4.88–5.14 (m, 2 H), 3.47 (s, 3 H), 3.26 (d, J = 6 Hz, 2 H); high-resolution mass spectrum, m/e 281.139 (calcd 281.142).

3c: 93%; mp 87 °C; IR (KBr) 3320, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14–7.35 (m, 5 H), 5.32–5.76 (m, 1 H), 4.92–5.16 (m, 3 H), 3.52 (s, 3 H), 2.61 (m, 2 H), 1.67 (s, 3 H); high-resolution mass spectrum, m/e 219.127 (calcd 219.126).

3e: 90%; IR (neat) 3320, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50–5.92 (m, 1 H), 4.86–5.11 (m, 2 H), 4.25–4.50 (br s, 1 H), 3.57 (s, 3 H), 2.44 (d, J = 7 Hz, 2 H), 1.10–2.05 (m, 10 H); high-resolution mass spectrum, m/e 197.141 (calcd 197.142).

3f: 84%; IR (neat) 3345, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32–5.94 (m, 3 H), 4.84–5.22 (m, 2 H), 4.40–4.65 (br s, 1 H), 3.53 (s, 3 H), 1.88–2.73 (m, 6 H), 1.41–1.72 (m, 2 H); high-resolution mass spectrum, m/e 195.124 (calcd 195.126).

Preparation of 3d. Procedure B. A solution containing 5.71 g, 30 mmol, of **2d**, 9.08 g, 33 mmol, of diphenylphosphoryl azide (DPPA), and 3.54 g, 35 mmol, of triethylamine in 100 mL of benzene was refluxed for 3 h. The benzene was removed and the residue dissolved in 50 mL of methanol. This solution was refluxed for 48 h and the solvent evaporated. The crude mixture was dissolved in 40 mL of a 1:1 mixture of methanol and 10% sodium hydroxide and refluxed for 30 min. After dilution with 50 mL of water, the aqueous layer was extracted with ether. The ether was dried over $MgSO_4$ and evaporated. The crude product was chromatographed over silica gel as described above and distilled, using a Kugelrohr (0.05 mm, 120 °C), to give **3d**, 5.9 g (90%).

3d: IR (neat) 3325, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (s, 5 H), 3.25–4.98 (br s, 1 H), 4.62–5.10 (m, 3 H), 3.55 (s, 3 H), 2.38 (m, 2 H), 1.69 (s, 3 H); high-resolution mass spectrum, m/e 219.128 (calcd 219.126).

Preparation of 4a–e. To a solution containing 5 mmol of the olefins **3a–f** in 20 mL of THF at 0 °C was added 20 mL of a 0.5 M solution of disiamylborane in THF. The reaction mixture was stirred for 0.5 h (25 °C) before 1 mL of water was carefully added. At this point, 3 mL of 3 M sodium hydroxide and 2 mL of 30% H_2O_2 was added at 0 °C. After the mixture was stirred at 50 °C for 1 h, 40 mL of a 1:1 ether–water mixture was added and the aqueous phase saturated with solid potassium chloride. The combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography over silica gel (ether) and used directly in the next step.

Preparation of *N*-(Carbomethoxy)-2-pyrrolidinones 5a–f. To a solution containing the alcohols **4a–e** in 100 mL of acetone at 25 °C was added enough Jones reagent such that the solution above the green precipitate remained orange for at least 10 min. The solvent was then evaporated and the residue dissolved in 100 mL of water. The aqueous phase was extracted with ether, washed with 10% $NaHCO_3$ solution, and dried over $MgSO_4$. Evaporation of the ether yielded the crude products **5a–f**. In the case of **5d**, the isomers were subsequently separated by careful short-column chromatography over silica gel (ether–hexane, 1:1).

5a: mp 107 °C; 65%; IR (KBr) 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04–7.34 (m, 5 H), 5.12–5.28 (m, 1 H), 3.68 (s, 3 H), 2.32–2.79 (m, 3 H), 1.12–1.70 (m, 1 H); high-resolution mass spectrum, m/e 219.090 (calcd 219.088). Anal. Calcd for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98. Found: C, 65.62; H, 5.85.

5b: mp 134 °C; 80%; IR (KBr) 1776, 1752, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (br s, 10 H), 3.45 (s, 3 H), 2.60–2.80 (m, 2 H), 2.30–2.52 (m, 2 H); high-resultion mass spectrum, m/e 295.120 (calcd 295.121). Anal. Calcd for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80. Found: C, 72.82; H, 5.75.

5c: mp 80 °C; 87%; IR (KBr) 1750, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (s, 5 H), 3.65 (s, 3 H), 2.36–2.59 (m, 2 H), 1.96–2.20 (m, 2 H), 1.89 (s, 3 H); high-resolution mass spectrum, m/e 233.115 (calcd 233.116).

5d (cis):[12] 41%; IR (neat) 1785, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98–7.36 (m, 5 H), 5.12 (t, J = 7 Hz, 1 H), 3.68 (s, 3 H), 2.46–2.82 (m, 1 H), 1.98–2.20 (m, 2 H), 1.17 (d, J = 7 Hz, 3 H); high-resolution mass spectrum, m/e 233.115 (calcd 233.116).

5d (trans):[12] 23%; IR (neat) 1785, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02–7.40 (m, 5 H), 4.96 (t, J = 7 Hz, 1 H), 3.64 (s, 3 H), 2.42–2.92 (m, 2 H), 1.32–1.78 (m, 1 H), 1.25 (d, J = 7 Hz, 3 H).

5e: mp 74 °C; 65%; IR (KBr) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 2.30–2.56 (m, 2 H), 1.80–2.06 (m, 2 H), 1.12–1.80 (m, 10 H); high-resolution mass spectrum, m/e 211.123 (calcd 211.121). Anal. Calcd for $C_{11}H_{17}O_3N$: C, 62.53; H, 8.11. Found: C, 62.43; H, 8.08.

5f: mp 86 °C; 60%; IR (KBr) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42–5.74 (m, 2 H), 3.80 (s, 3 H), 1.38–3.10 (m, 10 H); high-resolution mass spectrum, m/e 209.106 (calcd 209.105). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.20; H, 7.22.

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Preparation of 2-Pyrrolidinones 6a-f. The *N*-(carbomethoxy)-2-pyrrolidinones **5a-f** (5 mmol) in 10 mL of ethanol-free chloroform and 6 mmol of distilled trimethylsilyl iodide were stirred at 60 °C for 15 h. At this point, the solvent was evaporated and the residue dissolved in 20 mL of a 1:1 ether-water mixture. The ether was removed to yield the crude lactams **6a-f** which were purified by sublimation (0.1 mm) or recrystallization.

6a: mp 107 °C (lit. mp 103-105 °C); 96%; IR (KBr) 3180, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05-7.35 (m, 5 H), 7.50-7.80 (br s, 1 H), 4.67 (m, 1 H), 2.27-2.68 (m, 3 H), 1.75-2.13 (m, 1 H); high-resolution mass spectrum, *m/e* 161.083 (calcd 161.084). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88. Found: C, 74.42; H, 6.88.

6b: mp 194 °C; 92%; IR (KBr) 3160, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64-7.84 (br s, 1 H), 7.20 (s, 10 H), 2.62-2.86 (m, 2 H), 2.29-2.52 (m, 2 H); high-resolution mass spectrum, *m/e* 237.115 (calcd 237.115). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.64; H, 6.24.

6c: mp 114 °C; 98%; IR (KBr) 3170, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.60 (br s, 1 H), 7.00-7.35 (m, 5 H), 2.07-2.50 (m, 4 H), 1.61 (s, 3 H); high-resolution mass spectrum, *m/e* 175.101 (calcd 175.100).

6d (cis):[12] mp 113 °C; 86%; IR (KBr) 3205, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (br s, 5 H), 6.47 (br s, 1 H), 4.64 (t, J = 6 Hz, 1 H), 2.42-2.72 (m, 1 H), 1.05-1.30 (m, 2 H), 1.22 (d, J = 7 Hz, 3 H); high-resolution mass spectrum, *m/e* 175.101 (calcd 175.100). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.50; H, 7.37.

6d (trans):[12] mp 127 °C; 85%; IR (KBr) 3200, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (br s, 5 H), 6.04 (br s, 1 H), 4.50 (m, 1 H), 2.30-2.80 (m, 2 H), 1.35-1.70 (m, 1 H), 1.18 (d, J = 6 Hz, 3 H); high-resolution mass spectrum, *m/e* 175.100 (calcd 175.100).

6e: mp 127 °C (lit.[13] mp 132 °C); 90%; IR (KBr) 3190, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-7.90 (br s, 1 H), 2.24-2.49 (m, 2 H), 1.70-1.95 (m, 2 H), 1.20-1.70 (m, 10 H); high-resolution mass spectrum, *m/e* 153.116 (calcd 153.115). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.60; H, 9.02.

6f: mp 92 °C; 90%; IR (KBr) 3190, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40-6.90 (br s, 1 H), 5.32-5.68 (m, 2 H), 1.52-2.54 (m, 10 H); high-resolution mass spectrum, *m/e* 151.102 (calcd 151.100).

Registry No. 1a, 103-82-2; **1b**, 117-34-0; **1c**, 492-37-5; **1e**, 98-89-5; **1f**, 4771-80-6; **2a**, 1575-70-8; **2a** acid chloride, 76403-12-8; **2a** acid azide, 76403-13-9; **2a** isocyanate, 76403-14-0; **2b**, 6966-03-6; **2b** acid chloride, 50790-27-7; **2b** acid azide, 76403-15-1; **2b** isocyanate, 76403-16-2; **2c**, 76403-17-3; **2c** acid chloride, 76403-18-4; **2c** acid azide, 76403-19-5; **2c** isocyanate, 76403-20-8; **2d**, 76403-21-9; **2d** acid chloride, 76403-22-0; **2d** acid azide, 76403-23-1; **2d** isocyanate, 76403-24-2; **2e**, 72335-50-3; **2e** acid chloride, 72335-83-2; **2e** acid azide, 76403-25-3; **2e** isocyanate, 76403-26-4; **2f**, 76403-27-5; **2f** acid chloride, 76403-28-6; **2f** acid azide, 76403-29-7; **2f** isocyanate, 76403-30-0; **3a**, 76403-31-1; **3b**, 76403-32-2; **3c**, 76403-33-3; **3d**, 76403-34-4; **3e**, 76403-35-5; **3f**, 76403-36-6; **4a**, 76403-37-7; **4b**, 76403-38-8; **4c**, 76403-39-9; **4d**, 76403-40-2; **4e**, 76403-41-3; **4f**, 76403-41-3; **5a**, 76403-42-4; **5b**, 76403-43-5; **5c**, 76403-44-6; *cis*-**5d**, 76403-45-7; *trans*-**5d**, 76403-46-8; **5e**, 76403-47-9; **5f**, 76403-48-0; **6a**, 22050-10-8; **6b**, 40052-79-7; **6c**, 5578-98-3; *cis*-**6d**, 76403-49-1; *trans*-**6d**, 76403-50-4; **6e**, 5498-74-8; **6f**, 76403-51-5; allyl bromide, 106-95-6; 2-methylallyl bromide, 1458-98-6.

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Thiono-Thiolo Rearrangement and Solvolysis of the Secondary Alkyl Phosphorothionates. 3[1a]

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The protic acid catalyzed thiono-thiolo (O→S) migration of secondary alkyl groups in trialkyl phosphorothionates **1** occurs in a complex fashion. Analysis of product distribution, stereochemistry, and deuterium incorporation experiments supports an ion-pair-type intermediate, **7**, as being responsible for the entire process. Nucleophilic attack by **1** on **7** initiates the chain reaction leading to **2**. In trifluoroacetic acid medium inversion of configuration (96%) at the carbon atom of the migration *sec*-butyl group was observed. A high concentration of **1** promotes this mode of rearrangement. However, the overall stereospecificity of *sec*-butyl migration is much lower due to an elimination process leading to the dialkyl hydrogen phosphorothioate **3** and an intermediate olefin which after protonation in acidic medium returns to the ion pair **7**. The latter process is responsible for the non-stereospecific formation of part of the rearrangement product **2** and contributes to the lower stereospecificity of the trifluoroacetolysis process. The role of reaction-medium acidity is discussed.

An attempt to apply the protic acid catalyzed thiono-thiolo rearrangement of O-alkyl esters of phosphorothioic acids to the stereospecific conversion of the alcohols into alkanethiols[1a] demonstrated that the mechanism of this rearrangement is complex. It has been shown that this process depends on the nature of the migrating alkyl group R, the chemical environment of the phosphorus atom, and the solvating properties of the reaction medium.[1] The stereochemical results of the rearrangement of optically active 2-[(α-methylbenzyl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (**1f**) in CF_3COOH and $(CF_3)_2CHOH$ (comparable ionizing powers[2] but different dielectric constants) are very similar while a large difference occurs in the stereochemical course between TFA and AcOH solutions (different ionizing powers, comparable dielectric constants, and a strongly emphasized difference in their acidities[3]). These differences have been discussed in terms of a dissociative mechanism involving ion-pair intermediates. Recombination within the internal ion pair (low acidity and low ionizing power, e.g., AcOH) affords the *S*-alkyl product with retention at the α-carbon atom in the

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