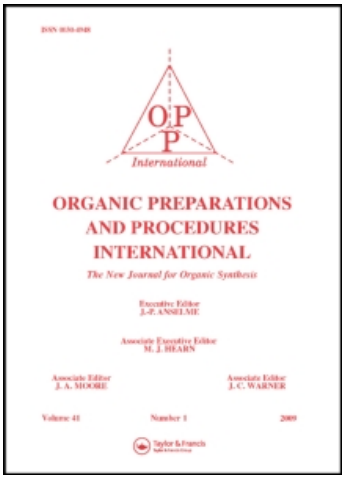


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# A CONVENIENT PROCEDURE FOR THE PREPARATION OF *t*-BUTYLDIMETHYLSILYL ETHERS OF HYDROXYAMINO ACIDS

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# A CONVENIENT PROCEDURE FOR THE PREPARATION OF t-BUTYLDIMETHYLSILYL ETHERS OF HYDROXYAMINO ACIDS

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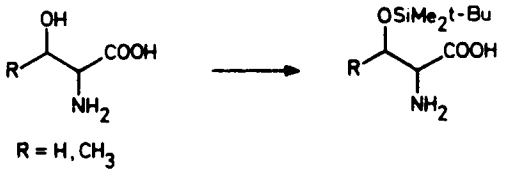
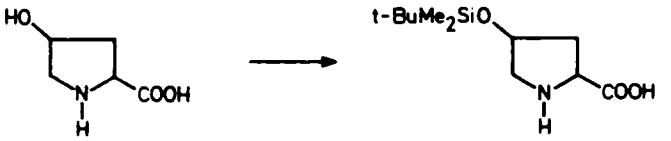
In the course of a synthetic project devoted to the synthesis of heterocyclic compounds via 1,3-dipolar cycloadditions,[1] we found it necessary to protect the hydroxyl group of hydroxyamino acids to avoid dehydration products. The required protective group should combine stability under the conditions used yet be easily removable by a specific reagent. The t-butyldimethylsilyl group was considered the reagent of choice because it has received much attention during recent years in organic synthesis and is one of the most useful silyl derivatives for a wide range of alcohols.[2] However, to our knowledge, t-butyldimethylsilyl ethers of hydroxy aminoacids have not yet been described. This paper reports a simple and mild procedure




for the preparation of t-butyldimethylsilyl ethers of hydroxyamino acids in acetonitrile in the presence of variable amounts of t-butyldimethylsilyl chloride and 1,8-diazabicyclo[5.4.0] undec-7-ene.

An initial experiment using the conventional procedure for the preparation of t-butyldimethylsilyl ethers (t-butyldimethylsilyl chloride, imidazole in dimethylformamide) was unsuccessful. An alternative effective procedure for the introduction of t-butyldimethylsilyl

group in a variety of substrates uses t-butyldimethylsilyl chloride with 1,8-diazabicyclo [5.4.0]undec-7-ene as a base.[3] This procedure is reported to give high yields for carboxylic acids as well as for primary and secondary amines. It was found that the use of a slight excess (1.2-1.5 equiv.) of t-butyldimethylsilyl chloride in a volume of acetonitrile such that the silyl ether precipitates from the solution, gave good yields of O-t-butyldimethylsilylserine, O-t-butyldimethylsilylthreonine, O-t-butyldimethylsilyl-cis-4-hydroxy-D-proline (Table 1.) The products were isolated by simple filtration.

With trans-4-hydroxy-L-proline, a three-fold excess of t-butyldimethylsilyl chloride must be used to obtain the corresponding silyl ether. In this case, a mixture of silylated compounds is obtained, O-t-butyldimethylsilyl-trans-4-hydroxy-L-proline being the main product. Hydrolysis of the reaction mixture with aqueous sodium hydroxide or aqueous potassium carbonate in methanol/tetrahydrofuran solution afforded the O-t-butyldimethylsilyl ether in good yields. As either cis-4-hydroxy-D-proline or trans-4-hydroxy-L-proline affords a single diastereoisomer, there was no racemization at C-2. Nevertheless, we adduced further evidence that neither partial nor complete racemization occurred in the reaction with t-butyldimethylsilyl chloride and 1,8-diazabicyclo[5.4.7]undec-7-ene or when an excess of the reagents is used in the subsequent hydrolytic step; the enantiomeric purity of O-t-butyldimethylsilyl ethers of L-serine and L-threonine was tested by the method developed for



TABLE 1. Preparation of t-Butyldimethylsilyl Ethers of Hydroxyamino Acids

| Substrate | Time (hrs) | Reagents[a] | Yields (%) |
|---|---|---|---|
| L-Serine | 21 | 1.5 | 74 |
| L-Threonine | 23 | 1.2 | 78 |
| trans-4-Hydroxy L-proline | 24 | 3.5 | 60 |
| cis-4-Hydroxy-D-proline | 48 | 1.5 | 70 |

a) molar excess

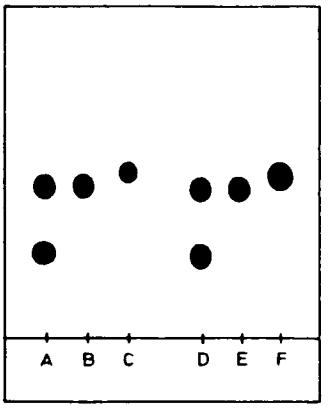



Figure 1

the direct enantiomeric resolution of D,L-amino acids and/or their derivatives through ligand exchange on thin-layer chromatographic plates,[4] or by checking the enantiomeric purity of L-serine and L-threonine obtained from O-t-butyldimethylsilyl-L-serine and O-t-butyldimethylsilyl-L-threonine by hydrolysis with acetic acid. Fig. 1 reproduces the thin-layer chromatogram [eluent MeOH-$H_2O$-$CH_3CN$ (5:5:9)] of O-t-butyldimethylsilyl-D,L-serine (A),

O-t-butyldimethylsilyl-L-serine (B), D,L-Serine (C), O-t-butyldimethylsilyl-D,L-threonine (D), O-t-butyldimethylsilyl-L-threonine (E), D,L-threonine (F).

## EXPERIMENTAL SECTION

IR spectra were determined on a Perkin Elmer 681 spectrophotometer. Mass spectra were recorded on a VG 7070 EQ spectrometer (direct inlet, 70 eV). $^1$H-NMR and $^{13}$C-NMR spectra were obtained on a Brucker WP-80 in $CD_3OD$ solution. Chemical shifts are reported in ppm (δ) from internal TMS. The microanalyses for the new compounds were determined on a Perkin Elmer 240 Elemental Analyzer. Melting points are uncorrected. Tetrahydrofuran (C. Erba) was distilled from lithium aluminum hydride. Acetonitrile from Merck was used without further purification. t-Butyldimethylsilyl chloride (97%), 1,8-diazabicyclo[5.4.0]undec-7-ene (96%), cis-4-hydroxy-D-proline, trans-4-hydroxy-L-proline, DL-serine, L-serine, DL-threonine and L-threonine were supplied by Aldrich Chem. Co and used without further treatment. Chiral plates were supplied by Macherey-Nagel GmbH &Co. KG (West Germany).

Typical Procedure.- L-Serine (0.70 g, 6.66 mmol) was added to a solution of t-butyldimethylsilyl chloride (1.47 g, 9.76 mmol) in acetonitrile (7 ml). The suspension was cooled to 0° and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.48 ml, 9.89 mmol) was added. The reaction mixture was stirred for 24 hrs at room temperature under a nitrogen atmosphere, then filtered. The precipitate crystallized from MeOH/$CH_3CN$ and afforded pure O-t-butyldimethylsilyl-L-serine (1.08 g, 74% yield), mp. 179-180° (water). $[\alpha]_D^{25}$ = -7.54 (c = 2.5; MeOH); IR (Nujol) 3390, 1620, 1260 cm$^{-1}$; $^1$H NMR ($CD_3OD$): δ 4.03 (d, 2H, J = 5.0 Hz), 3.61 (t, 1H, J = 5.0 Hz), 0.95 (s, 9H), 0.10 (s, 6H). $^{13}$C NMR ($CD_3OD$): δ 171.00 (s), 62.98 (t), 57.42 (d), 25.78 (q), 18.63 (s), -5.95 (q). MS m/e: 204 ($M^+$ -$CH_3$), 189 (204-$CH_3$), 174 ($M^+$ -COOH), 162 ($M^+$ -$CMe_3$).

Anal. Calcd for $C_9H_{21}NO_3Si$: C, 49.31; H, 9.59; N, 6.39

Found: C, 49.13; H, 9.52; N, 6.45

O-t-Butyldimethylsilyl-L-threonine (78% yield), mp. 173-174° (water); $[\alpha]_D^{25}$ = -28.26 (c = 2.9; MeOH). IR (Nujol): 3580-3380, 1625, 1260, 1060 cm$^{-1}$.$^1$H NMR ($CD_3OD$): δ 4.63 (dq, 1H, J = 6.7 and 3.0 Hz), 3.4 (d, 1H, J = 3.0 Hz), 1.32 (d, 3H, J = 6.7 Hz), 0.95 (s, 9H), 0.10 (s, 6H). $^{13}$C NMR ($CD_3OD$): δ 172.02 (s), 68.01 (d), 60.67 (d), 25.75 (q), 21.53 (q), 18.21 (s), -5.22 (q). MS m/e: 188 ($M^+$-$CO_2H$), 176 ($M^+$ -$C(CH_3)_3$), 159 (188-$CHNH_2$).

Anal. Calcd for $C_{10}H_{23}NO_3Si$: C, 51.50; H, 9.87; N, 6.00

Found: C, 51.45; H, 9.94; N, 5.95

cis-O-t-Butyldimethylsilyl-4-hydroxy-D-proline (70% yield), mp. 198° (dec.), from water. $[\alpha]_D^{25}$ = +23.3 (c = 2.97; MeOH). IR (Nujol): 3140, 1600, 1250, 1090 cm$^{-1}$. $^1$H NMR ($CD_3OD$): δ 4.66 (m, 1H), 4.21 (dd, 1H, J = 8.0 and 10.0 Hz), 3.35 (m, 2H), 2.22 (m, 2H), 0.93 (s, 9H), 0.15 (s, 6H). $^{13}$C-NMR ($CD_3OD$): δ 174.03 (s), 72.01 (d), 68.04 (d), 55.29 (t), 39.33 (t), 26.14 (q), 18.68 (s), 1.40 (q). MS m/e: 230 ($M^+$ -$CH_3$), 200 ($M^+$ -COOH).

Anal. Calcd for $C_{11}H_{23}NO_3Si$: C, 53.87; H, 9.39; N, 5.71

Found: C, 53.73; H, 9.28; N, 5.59

O-t-Butyldimethylsilyl-trans-4-hydroxy-L-proline.- To a solution of t-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) was dissolved in acetonitrile (3 ml), was added with trans-4-hydroxy-L-proline (0.393 g, 3.0 mmol). After cooling to 0°, 1,8-diazabicyclo[5.4.0]undec-7-ene (1.66 ml, 11 mmol) was added and the mixture was stirred for 24 hrs at room temperature and then extracted with n-pentane. The combined organic extracts were evaporated under vacuum. The residue was dissolved in methanol (8 ml), tetrahydrofuran (4 ml), water, (4 ml) and then treated with aqueous sodium hydroxide (2N, 6 ml). The reaction mixture was stirred for 1.5 hr at room temperature, adjusted to pH = 6 with 1N HCl (12 ml), concentrated and filtered. The precipitate obtained was crystallized from water and afforded pure O-t-butyldimethylsilyl-trans-4-hydroxy-L-proline (0.441 g, 60%), mp. 147-151° (dec.) from water. $[\alpha]_D^{25}$ = -32.0 (c = 1.8; MeOH). IR ($CHCl_3$): 3400 sh, 3100 1625, 1260, 1095 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 60°): δ 8.2 (broad signal, 2H), 4.66 (m, 1H), 4.21 (dd, 1H, J = 8.0, 7.5 Hz), 3.32 (m, 2H), 2.18 (m, 2H), 0.95 (s, 9H), 0.10 (s, 6H). $^{13}C$ NMR ($CD_3OD$): δ 174.94 (s), 74.24 (d), 62.74 (d), 56.11 (t), 41.30 (t), 27.52 (q), 20.13 (d), 1.41 (q). MS m/e: 200 ($M^+$ -COOH).

Anal. Calcd for $C_{11}H_{23}NO_3Si$: C, 53.87; H, 9.39; N, 5.71

Found: C, 53.75; H, 9.30; N, 5.62

Procedure for the Direct Determination of the Enantiomeric Purity of Silyl Ethers and Aminoacids.- A 1% solution of the compound to be analyzed was applied to a commercially available chiral plate and developed (30-90 min) with the eluent mentioned earlier. After drying, the spots were made visible by spraying with 0.1% ninhydrin reagent.

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