Vol. 36, No. 39 25 September 1995 ISSN 0040-4039

Tetrahedron Letters

The International Journal for the Rapid Publication of Preliminary Communications in Organic Chemistry

Contents

[*Continued on outside back cover*]

Pergamon

Tetrahedron Letters, Vol. 36, No. 39, pp. 7011-7014, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

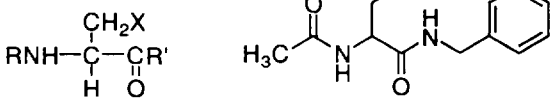
0040-4039(95)01451-9

Trimethylsilyl Halides: Effective Reagents for the Synthesis of β-Halo Amino Acid Derivatives

Daeock Choi and Harold Kohn*
Department of Chemistry, University of Houston, Houston, Texas 77204-5641

Abstract: β-Halogen alanine derivatives are prepared in moderate yields in one step from the corresponding serine compound and trimethylsilyl halide.

β-Halogen-substituted amino acid derivatives 1a-c have been used as irreversible inactivators of enzymatic processes[1,2] and are reagents for the construction of functionalized unnatural amino acids.[3-5] Most current methods for the synthesis of 1a-c proceed through the corresponding serine analogue 1d, thereby generating optically pure derivatives.[3] Established routes for the synthesis of β-chloro adduct 1a include treatment of 1d with either phosphorous pentachloride[3,6] or triphenylphosphine and carbon tetrachloride,[1,7,8] whereas the reaction of 1d with triphenylphosphine and carbon tetrabromide produces 1b.[1,8] The most common synthesis for β-iodo adduct 1c requires initial conversion of the serine hydroxy group to the tosylate (mesylate) 1e, then displacement with NaI.[3,9,10] In this letter we report a one-step, versatile method for the synthesis of β-halogen amino acid derivatives. The method has been shown to proceed without racemization and effectively introduces a β-halogen substituent into peptides.

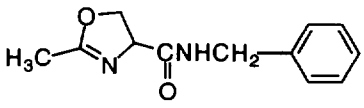


1a X = Cl
b X = Br
c X = I
d X = OH
e X = OTs

2a X = Cl
b X = Br
c X = I
d X = OH
e X = F

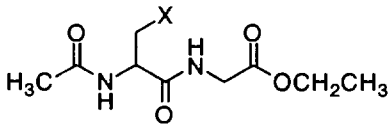
For an ongoing project to prepare bioactive amino acid derivatives,[11] we needed the β-halogen compounds 2a-2c. Jung and coworkers[12,13] have advanced trimethylsilyl bromide and iodide[14] as effective reagents for the conversion of primary alcohols to bromides and iodides, respectively. Use of trimethylsilyl chloride in their procedure did not afford the alkyl chloride. Recently, Snyder reported that dimethyl sulfoxide catalyzed the trimethylsilyl chloride conversion of 1° and 3° alcohols to the corresponding

chlorides.[15] Employing the Jung protocol and commercially available trimethylsilyl halides, (*R*,*S*)-*N*-acetylserine-*N*-benzylamide[16] (2d) was converted to 2a-2c in acetonitrile.[17,18] Attempts to convert 2d to β-fluoro 2e with trimethylsilyl fluoride were unsuccessful (room temperature, 24 h) and gave dihydrooxazole 3 in a 46% yield.[19]

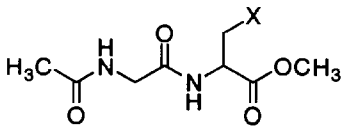


3

The trimethylsilyl halide reactions were accomplished within 8 h at reflux temperatures. The isolated yields were from 74% for 2a to 20% for 2c. These decreased yields have been attributed in part to the sensitivity of the β-halogen product to the reflux conditions. Significantly, the hydroxy to chloride interchange within the serine derivative 2d proceeded without apparent racemization. Treatment of (*R*)-2d with trimethylsilyl chloride in acetonitrile gave only (*R*)-2a (NMR analysis).[20] The utility of this procedure for the introduction of β-halogen substituents within peptides was demonstrated by the conversion of dipeptides 4a and 5a to β-chloro aducts 4b[21] and 5b,[22] respectively, in 40-52% yields.



4a X = OH
b X = Cl



5a X = OH
b X = Cl

In conclusion, trimethylsilyl halides are effective reagents for the installation of β-halo substituents within *N*-acyl serine containing peptides. The reaction proceeds in one step and in moderate yields. The respective conversion of serine derivatives 2d, 4a, and 5a to β-chloro derivatives 2a, 4b, and 5b with trimethylsilyl chloride in the absence of dimethyl sulfoxide was unexpected.[12,13,15] The mechanism for this transformation is under investigation.

Acknowledgments. This work was funded, in part, by the Robert A. Welch Foundation and the State of Texas Advanced Technology Program.

REFERENCES AND NOTES

1. Silverman, R.B.; Levy, M.A. *J. Org. Chem.* **1980**, *45*, 815.
2. Schirlin, D.; Ducep, J.B.; Baltzer, S.; Bey, P.; Piriou, F.; Wagner, J.; Hornsperger, J.M.; Heydt, J.G.; Jung, M.J.; Danzin, C.; Weiss, R.; Fischer, J.; Mitschler, A.; De Cian, A. J. *Chem. Soc. Perkin Trans.* **1992**, *1*, 1053.

3. Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987, pp 127-145.
4. Dunn, M.J.; Jackson, R.F.W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.
5. Bajgrowicz, J.A.; El Hallaoui, A.; Jacquier, R.; Pigière, C.; Viallefont, P. *Tetrahedron Lett.* **1984**, *25*, 2759.
6. Miller, M.J.; Mattingly, P.G.; Morrison, M.A.; Kerwin, Jr., J.F. *J. Am. Chem. Soc* **1980**, *102*, 7026.
7. Snyder, E.I. *J. Org. Chem.* **1972**, *37*, 1466.
8. Gruber, L.; Tömösközi, I; Radics, L. *Synthesis* **1975**, 708.
9. Butera, J.; Rini, J.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 3676.
10. Itaya, T.; Mizutani, A. *Tetrahedron Lett.* **1985**, *26*, 347.
11. Kohn, H.; Sawhney, K.N.; Bardel, P.; Robertson, D.W.; Leander, J.D. *J. Med. Chem.* **1993**, *36*, 3350.
12. Jung, M.E.; Ornstein, P.L. *Tetrahedron Lett.* **1977**, *18*, 2659.
13. Jung, M.E.; Hatfield, G.L. *Tetrahedron Lett.* **1978**, *19*, 4483.
14. Schmidt, A.H. *Aldrichimica Acta.* **1981**, *14*, 31.
15. Snyder, D.C. *J. Org. Chem.* **1995**, *60*, 2638.
16. LeGall, P. M.S. Thesis, University of Houston, 1982.
17. Satisfactory spectral data (^{1}H and ^{13}C NMR, IR, low and high resolution MS) were obtained for all new compounds.
18. General Procedures for the Preparation of 2a-2c:

To a CH_3CN suspension of 2d (1 mmol) (20 mL/mmol of 2d) was added trimethylsilyl halide (2.5 mmol) under N_2. The reaction mixture was heated at reflux (2-8 h) and then the solvent was removed under reduced pressure. The residue was dissolved in a 1:1 mixture of $CHCl_3$ and H_2O, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was triturated with Et_2O to give the desired product.

2a: mp 143-144 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, C(O)C**H**$_3$), 3.72 (dd, J = 6.3, 11.1 Hz, C**H**H'Cl), 3.94 (dd, J = 6.3, 11.1 Hz, CH**H'**Cl), 4.48 (d, J = 5.7 Hz, NHC**H**$_2$), 4.72-4.81 (m, C**H**), 6.36 (br d, J = 6.3 Hz, N**H**), 6.49 (br s, N**H**), 7.22-7.35 (m, 5 Ph**H**); ^{13}C NMR (DMSO-d_6) 22.45 (C(O)**C**H$_3$), 42.16 (**C**H$_2$N or **C**H$_2$Cl), 44.62 (**C**H$_2$N or **C**H$_2$Cl), 53.89 (**C**H), 126.70 (**C$_{4'}$**), 127.03 (**2C$_{2'}$** or **2C$_{3'}$**), 128.16 (**2C$_{2'}$** or **2C$_{3'}$**), 138.39 (**C$_{1'}$**), 168.38 (**C**(O)CH$_3$ or **C**(O)NH), 169.52 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) 257 (M^++1, 28), 255 (M^++1, 81) 222 (100); M_r (+CI) 255.090 85 [M^++1] (calcd for $C_{12}H_{16}ClN_2O_2$ 255.090 03).

2b: mp 123-125 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C(O)C**H**$_3$), 3.59 (dd, J = 4.8, 10.5 Hz, C**H**H'Br), 3.74 (dd, J = 4.8, 10.5 Hz, CH**H'**Br), 4.47 (d, J = 5.7 Hz, NHC**H**$_2$), 4.79-4.83 (m, C**H**), 6.42 (br d, J = 6.6 Hz, N**H**), 6.47 (br s, N**H**), 7.29-7.37 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 23.07 (C(O)**C**H$_3$), 32.19 (**C**H$_2$Br), 43.79 (**C**H$_2$N), 53.57 (**C**H), 127.62 (**C$_{4'}$**), 127.71 (**2C$_{2'}$** or **2C$_{3'}$**), 128.70 (**2C$_{2'}$** or **2C$_{3'}$**), 137.37 (**C$_{1'}$**), 168.58 (**C**(O)CH$_3$ or **C**(O)NH), 170.37 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) 301 [M^++1, 5], 299 [M^++1, 5], 220 (72), 219 (100); M_r (+CI) 299.039 22 [M^++1] (calcd for $C_{12}H_{16}BrN_2O_2$ 299.039 51).

2c: mp 169-170 °C (dec); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, C(O)C**H$_3$**), 4.38-4.51 (m, C**H$_2$**I), 4.48 (d, *J* = 5.7 Hz, NHC**H$_2$**), 4.63-4.70 (m, C**H**), 6.52 (br d, *J* = 7.2 Hz, N**H**), 6.87 (br s, N**H**), 7.30-7.35 (m, 5 Ph**H**); ^{13}C NMR ($CDCl_3$) 4.83 (**C**H$_2$I), 22.75 (C(O)**C**H$_3$), 43.44 (**C**H$_2$N), 53.31 (**C**H), 127.29 (**C$_{4'}$**), 127.42 (**2C$_{2'}$** or **2C$_{3'}$**), 128.33 (**2C$_{2'}$** or **2C$_{3'}$**), 136.87 (**C$_{1'}$**), 168.39 (**C**(O)CH$_3$ or **C**(O)NH), 169.80 (**C**(O)CH$_3$ or **C**(O)NH) ppm; MS (+CI) m/e (rel intensity) 220 (20), 219 (100); M_r (+CI) 347.025 81 [M$^+$+1] (calcd for $C_{12}H_{16}IN_2O_2$ 347.025 65).

19. Compound 3: mp 129-130 °C; ^{1}H NMR (DMSO-d_6) δ 1.93 (s, C**H$_3$**), 4.21-4.38 (m, NHC**H$_2$**, OC**H$_2$**CH), 4.55-4.61 (m, C**H**), 7.22-7.33 (m, 5 Ph**H**), 8.43 (t, *J* = 5.7 Hz, N**H**); ^{13}C NMR (CD_3OD) 13.64 (**C**H$_3$), 44.12 (NHCH$_2$), 69.67 (**C**H), 71.87 (OCH$_2$CH), 128.32 (**C$_{4'}$**), 128.60 (**2C$_{2'}$** or **2C$_{3'}$**), 129.56(**2C$_{2'}$** or **2C$_{3'}$**), 139.60 (**C$_{1'}$**), 170.65 (**C**(N)O or **C**(O)), 173.66 (**C**(N)O or CO)) ppm; MS CI(+) (rel intensity) 219 (M$^+$+1, 100), 141 (41); M_r (+CI) 219.112 64 [M$^+$+1] (calcd for $C_{12}H_{15}N_2O_2$ 219.113 35).

20. Addition of a saturated $CDCl_3$ solution containing (*R*)-(-)- mandelic acid to (*R*)-2a gave only one signal in the ^{1}H NMR spectrum for the acetyl methyl protons, while the corresponding racemate gave two peaks of equal height. For the previous use of this method for the assessment of enantiomeric purity, see reference 11.

21. Compound 4b: mp 107-108 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, *J* = 6.9 Hz, OCH$_2$C**H$_3$**), 1.88 (s, C(O)C**H$_3$**), 3.67 (dd, *J* = 7.1, 11.1 Hz, CH**H**'Cl), 3.77 (dd, *J* = 5.1, 11.1 Hz, CH**H**'Cl), 3.83 (d, *J* = 6.0 Hz, NHC**H$_2$**), 4.07 (q, *J* = 6.9 Hz, OC**H$_2$**CH$_3$), 4.61-4.68 (m, C**H**), 8.31 (d, *J* = 8.4 Hz, N**H**), 8.58 (t, *J* = 6.0 Hz, N**H**); ^{13}C NMR (DMSO-d_6) 14.02 (OCH$_2$**C**H$_3$), 22.45 (C(O)**C**H$_3$), 40.82 (NH**C**H$_2$ or **C**H$_2$Cl), 44.55 (NH**C**H$_2$ or **C**H$_2$Cl), 53.57 (**C**H), 60.43 (O**C**H$_2$CH$_3$), 169.01, 169.33, 169.53 (**C**(O)CH$_3$, **C**(O)NH, **C**(O)OCH$_2$CH$_3$) ppm; MS CI(+) (rel intensity) 253 (M$^+$+1, 57), 251 (M$^+$+1, 100), 215 (41); M_r (+CI) 251.080 55 [M$^+$+1] (calcd for $C_9H_{16}ClN_2O_4$ 251.079 86).

22. Compound 5b: mp 133-134 °C; ^{1}H NMR (DMSO-d_6) δ 1.84 (s, C(O)C**H$_3$**), 3.67 (s, OC**H$_3$**), 3.75 (d, *J* = 5.9 Hz, NHC**H$_2$**), 3.81-3.91 (m, C**H$_2$**Cl), 4.71-4.77 (m, C**H**), 8.12 (t, *J* = 5.9 Hz, N**H**), 8.50 (d, *J* = 7.8 Hz, N**H**); ^{13}C NMR (CD_3OD) 22.38 (C(O)**C**H$_3$), 43.26 (NH**C**H$_2$ or **C**H$_2$Cl), 44.97 (NH**C**H$_2$ or **C**H$_2$Cl), 53.21 (**C**H), 55.02 (O**C**H$_3$), 170.58, 171.65, 173.80 (**C**(O)CH$_3$, **C**(O)NH, **C**(O)OCH$_3$) ppm; MS CI(+) (rel intensity) 239 (M$^+$+1, 41), 237 (M$^+$+1, 100); M_r (+CI) 237.064 37 [M$^+$+1] (calcd for $C_8H_{14}ClN_2O_4$ 237.064 21).

(*Received in USA* 30 *June* 1995; *accepted* 28 *July* 1995)