Simple, mild, and practical esterification, thioesterification, and amide formation utilizing *p*-toluenesulfonyl chloride and *N*-methylimidazole

Kazunori Wakasugi, Akira Iida, Tomonori Misaki, Yoshinori Nishii, Yoo Tanabe*

Supporting Information

A PDF file of five ^{1}H NMR spectra are attached for an ^{1}H-NMR monitoring study using 3-phenylpropanoic acid analogs **3**, **4**, **5**, **8**, and **9**.

A typical procedure using Et_3N and cat. DMAP instead of *N*-methylimidazole (2)

TsCl (**1**; 229 mg, 1.2 mmol) in CH_3CN (1.0 mL) was added to a stirred solution of 3-phenylpropanoic acid (**3**; 150 mg, 1.0 mmol), Et_3N (303 mg, 3.0 mmol), and DMAP (12 mg, 0.1 mmol) in CH_3CN (1.0 mL) at 0 - 5 ℃ under an Ar atmosphere, and the mixture was stirred for 30 min. To the stirred mixture, 2-octanol (**6**; 130 mg, 1.0 mmol) in CH_3CN (1.0 mL) was added at 0 - 5 ℃, which was stirred at 20-25 ℃ for 2 h. Water was added to the stirred mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : ether = 40 : 1) to gave 2-octyl 3-phenylpropanonate (104 mg, 40%).

***N*-Carbobenzyloxy-*l*-proline methyl ester**[23]

TsCl (**1**; 229 mg, 1.2 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of *N*-Cbz-*l*-proline (**11**; 249 mg, 1.0 mmol) and *N*-methylimidazole (**2**; 246 mg, 3.0 mmol) in CH_2Cl_2 (1.0 mL) at -40 to -35 ℃ under an Ar atmosphere, and the mixture was stirred for 30 min. To the mixture CH_3OH

(32 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added at -40 – -35 ℃, followed by stirring at the same temp. for 2 h. The reaction mixture was poured into the stirred ice-water (reverse quench), which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : EtOAc = 4 : 1) to give the desired product (240 mg, 90%).

>99% ee by HPLC analysis [flow rate 1.00 ml / min, solvent: *n*-hexane / 2-propanol = 80 / 20, t_R (racemic) = 3.89 min and 7.06 min respectively, t_R (*N*-Carbobenzyloxy-*l*-proline methyl ester) = 6.95 min]

Colorless oil; $[\alpha]_D^{23}$ -57.0 (*c* 1.01, CH_3OH) [lit. $[\alpha]_D^{20}$ -57.3 (*c* 1.0, CH_3OH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.82-2.06 (3H, m), 2.13-2.29 (1H, m), 3.44-3.67 (2H, m), 3.58 (3H x 1/2, s), 3.74 (3H x 1/2, s), 4.34 (1H x 1/2, dd, *J* = 3.7 Hz, 8.5 Hz), 4.40 (1H x 1/2, dd, *J* = 3.6 Hz, 8.8 Hz), 5.05 (1H x 1/2, d, *Jgem* = 12.4 Hz), 5.11 (1H x 1/2, d, *Jgem* = 12.4 Hz), 5.19 (1H x 1/2, d, *Jgem* = 12.4 Hz), 5.19 (1H x 1/2, d, *Jgem* = 12.4 Hz), 7.27-7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.46, 24.24, 29.83, 30.85, 46.35, 46.84, 51.96, 52.14, 58.78, 59.10, 66.86, 66.93, 127.70, 127.79, 127.83, 127.88, 128.31, 128.37, 136.56, 136.65, 154.20, 154.80, 173.04, 173.20; IR (neat) ν = 2955, 1748, 1709, 1416, 1354, 1202, 1119 cm^{-1}.

(3*S*,4*S*)-4-[(1*R*)-1-Benzyloxycarbonylethyl]-1-(*tert*-butoxycarbonylmethyl)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone[13]

TsCl (**1**; 114 mg, 0.60 mmol) in CH_3CN (0.5 mL) was added to a stirred solution of (3*S*,4*S*)-1-(*tert*-butoxycarbonylmethyl)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-1-carboxyethyl]-2-azetidinone (**12**; 208 mg, 0.50 mmol) and *N*-methylimidazole (**2**; 123 mg, 1.5 mmol) in CH_3CN (0.5 mL) at 20 – 25 ℃ under an Ar atmosphere, and the mixture was stirred for 30 min. To

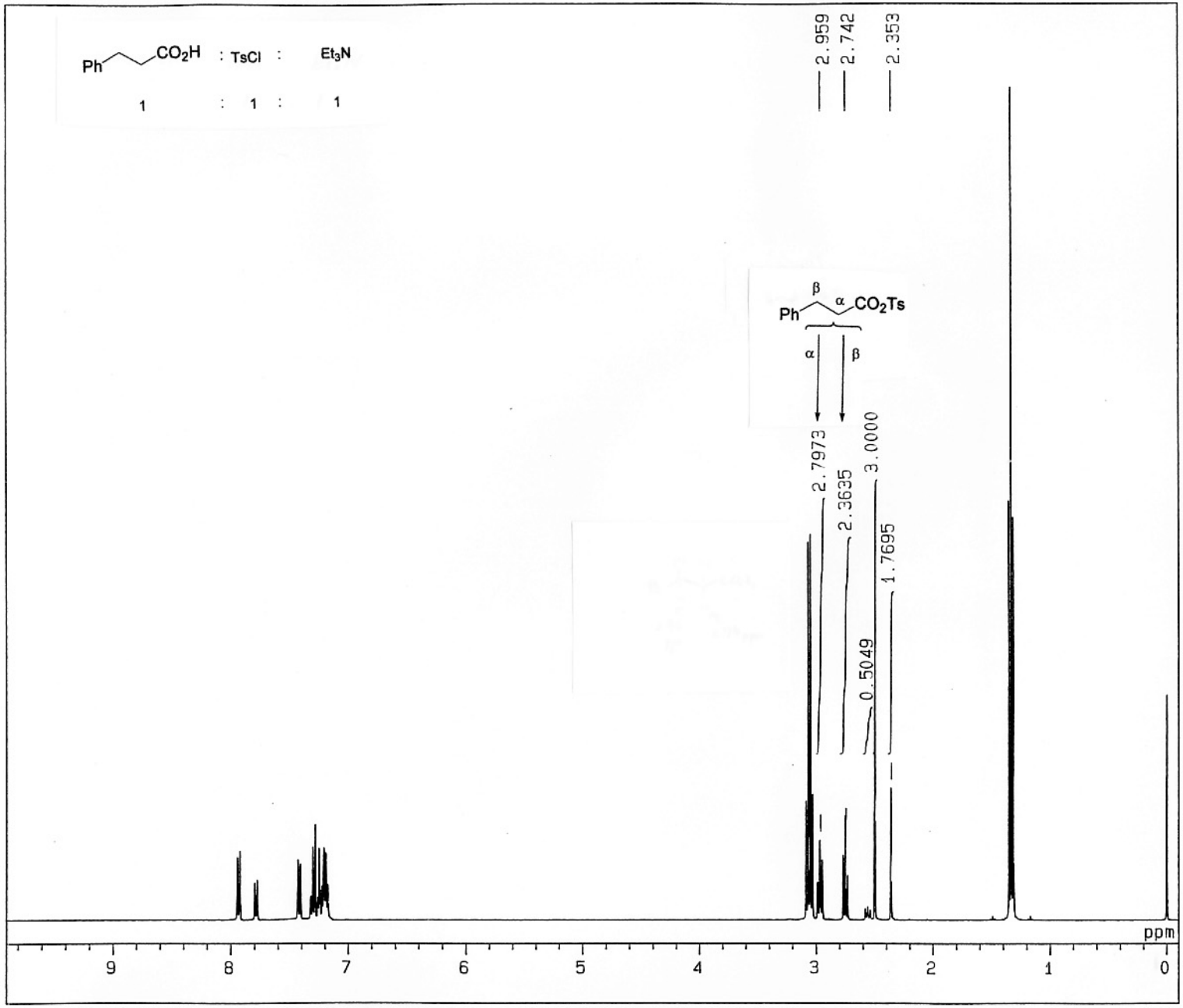
the mixture benzyl alcohol (54 mg, 0.50 mmol) in CH_3CN (0.5 mL) was added at 20 – 25 ℃, followed by stirring at the same temp. for 2 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : EtOAc = 7 : 1) to give the desired product (240 mg, 95%).

Colorless oil; $[\alpha]_D^{23}$ -15.2 (*c* 0.20, $CHCl_3$) [lit. $[\alpha]_D^{24}$ -14.7 (*c* 0.202, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 1.23 (3H, d, *J* = 6.3 Hz), 1.24 (3H, d, *J* = 7.1 Hz), 1.45 (9H, s), 2.90 (1H, dq, *J* = 3.4 Hz, 7.1 Hz), 3.00 (1H, dd, *J* = 2.2 Hz, 6.6 Hz), 3.64 (1H, d, *Jgem* = 17.8 Hz), 4.02 (1H, d, *Jgem* = 17.8 Hz), 4.13 (1H, dd *J* = 2.2 Hz, 3.4 Hz), 4.16 (1H, dd, *J* = 6.3 Hz, 6.6 Hz), 5.08 (1H, d, *Jgem* = 12.2 Hz), 5.13 (1H, *Jgem* = 12.2 Hz), 7.31-7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.84, -4.30, 11.78, 17.86, 22.73, 25.74, 28.02, 40.62, 43.08, 57.16, 60.74, 66.35, 66.70, 81.90, 128.34, 128.40, 128.61, 135.52, 167.28, 167.88, 173.97; IR (neat) ν = 2932, 2888 1767, 1740, 1460, 1370, 1157 cm^{-1}.

(1*S*)-2-Methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl (1*R*,3*R*)-chrysanthemate[14]

TsCl (**1**; 114 mg, 0.60 mmol) in CH_3CN (0.5 mL) was added to a stirred solution of (1*R*,3*R*)-chrysanthemic acid (**13**; 84 mg, 0.50 mmol) and *N*-methylimidazole (**2**; 123 mg, 1.5 mmol) in CH_3CN (0.5 mL) at 20 – 25 ℃ under an Ar atmosphere, and the mixture was stirred for 30 min. To the mixture (*S*)-4-hydroxy-3-methyl-2-(2-propynyl)cyclopent-2-en-1-one (**14**; 75 mg, 0.50 mmol) in CH_3CN (0.5 mL) was added at 20 – 25 ℃, followed by stirring at the same temp. for 2 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : EtOAc = 7 : 1) to give the desired product (137 mg, 91%).

Colorless oil; $[\alpha]_D^{23}$ -11.6 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.15 (3H, s), 1.27 (3H, s), 1.42 (1H, d, *J* = 5.4 Hz), 1.72 (3H, s), 1.73 (3H, s), 1.99 (1H, dd, *J* = 2.0 Hz, 6.4 Hz), 2.10 (1H, dd, *J* = 5.4 Hz, 6.2 Hz), 2.17 (3H, s), 2.26 (1H, dd, *J* = 2.0 Hz, *Jgem* = 18.8 Hz), 2.90 (1H dd, *J* = 6.4 Hz, *Jgem* = 18.8 Hz), 3.16 (2H, d, *J* = 7.8 Hz), 4.91 (1H, t, *J* = 7.8 Hz), 5.69 (1H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.45, 14.21, 18.48, 20.39, 22.07, 25.53, 29.19, 33.03, 34.48, 41.80, 68.96, 72.76, 79.36, 120.72, 135.96, 138.22, 167.05, 172.22; IR (neat) ν = 3291, 2926, 1719, 1659, 1422, 1383, 1194, 1154, 1115 cm^{-1}.



8-OCT-2002 15: 26: 31.28

DFILE :
SFILE :

COMNT :
EXMOD : SINGL
IRMOD : NON
POINT : 32768
FREQU : 7993.61 Hz
SCANS : 8
DUMMY : 4
ACQTM : 4.0993 sec
PD : 2.9007 sec
RGAIN : 17

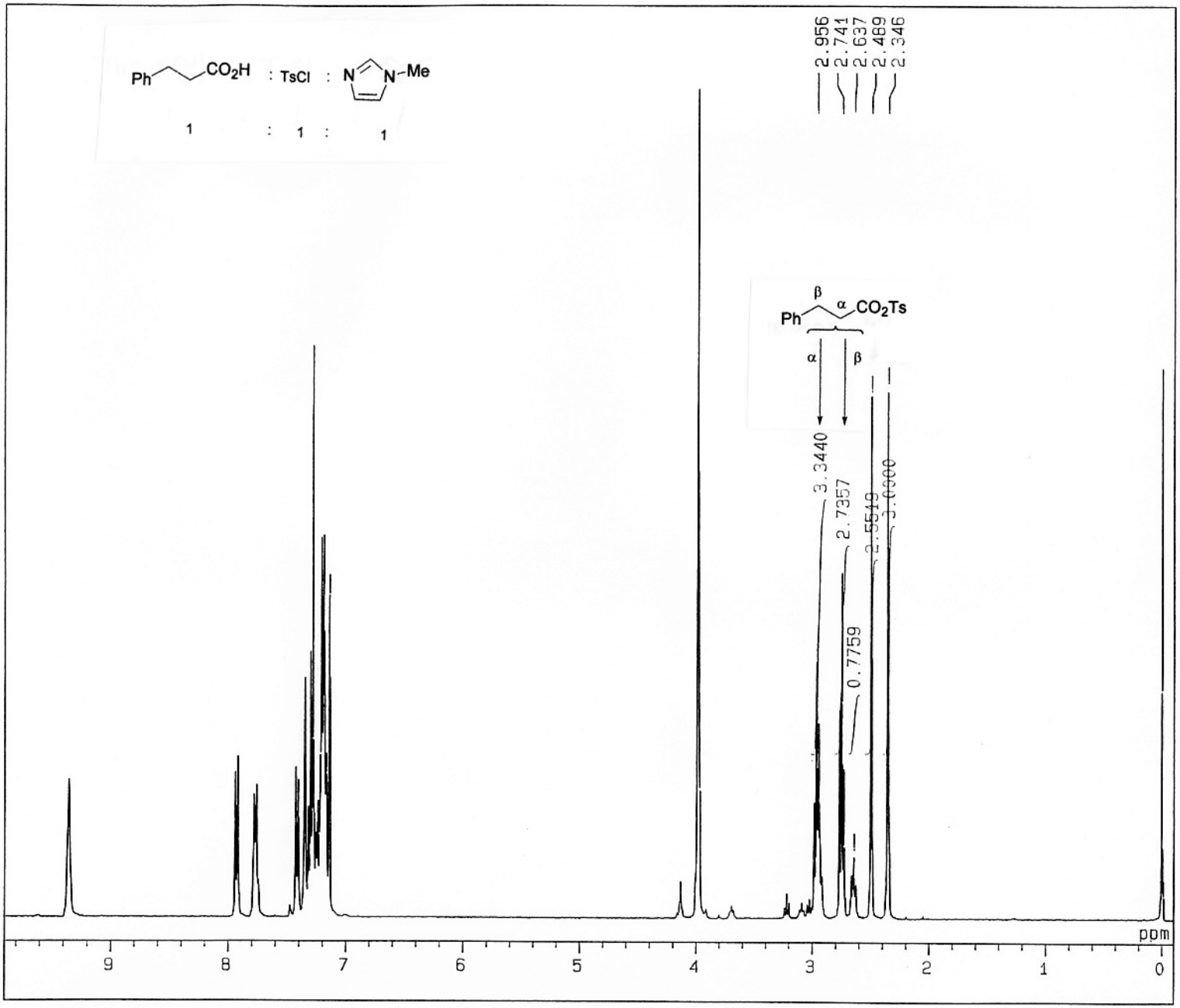
PW1 : 5.50 usec

OBNUC : 1H
OBFRQ : 399.65 MHz
OBSET : 134500.00 Hz

IRNUC : 1H
IRFRQ : 399.65 MHz
IRSET : 134500.00 Hz
IRATN : 511
IRRPW : 50.0 usec
IRBP1 : 27
IRBP2 : 6
IRRNS : 0

ADBIT : 16
CTEMP : 26.0 c
CSPED : 12 Hz
SLVNT : CDCL3

RESOL : 0.24 Hz
BF : 0.01 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 0.00 ppm
XE : 3997.53 Hz
XS : 38.91 Hz
operator



15-OCT-2002 19: 16: 38.95

DFILE :
SFILE :

COMNT :
EXMOD : SINGL
IRMOD : NON
POINT : 32768
FREQU : 7993.61 Hz
SCANS : 8
DUMMY : 4
ACQTM : 4.0993 sec
PD : 2.9007 sec
RGAIN : 18

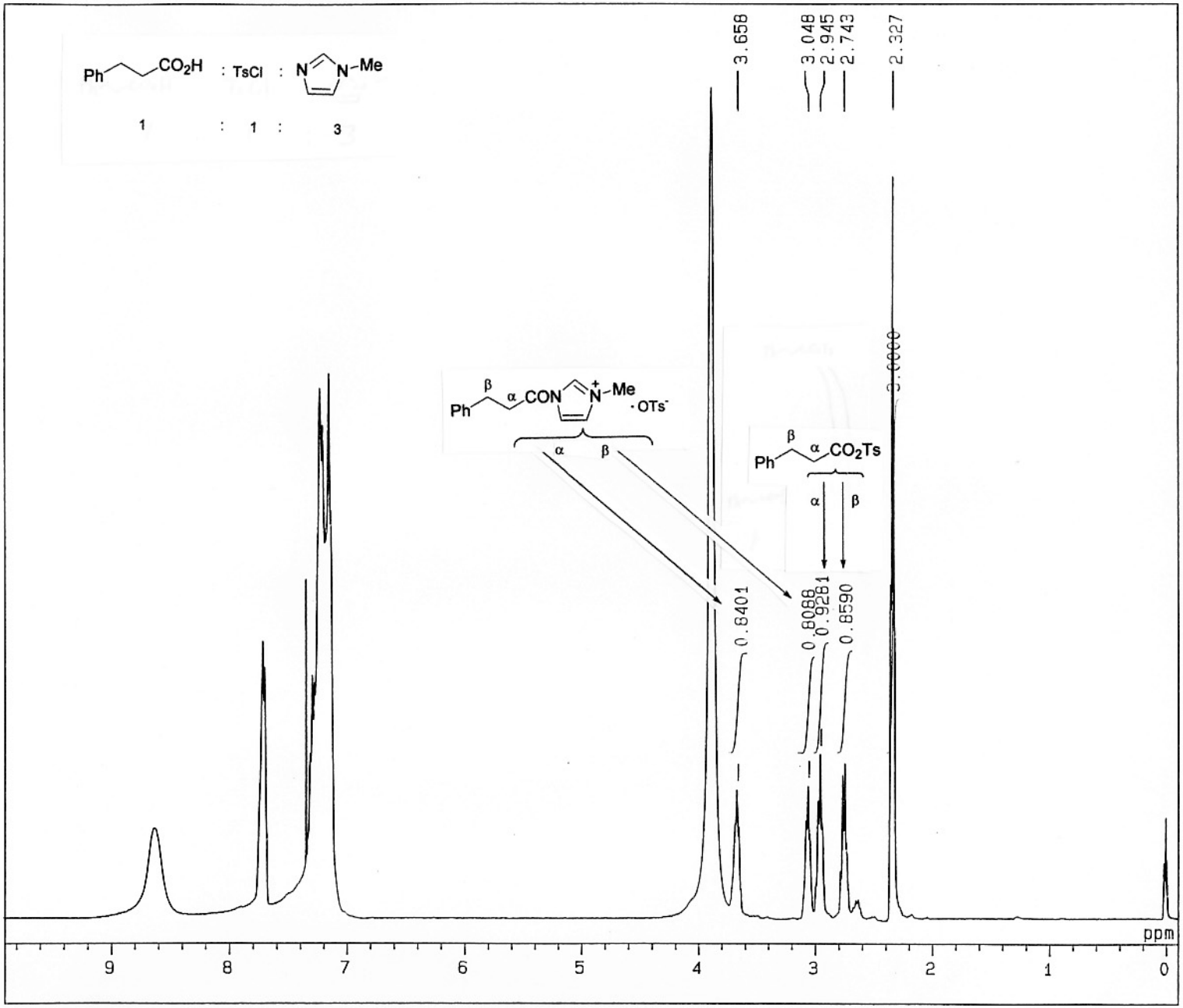
PW1 : 5.50 usec

OBNUC : 1H
OBFRQ : 399.65 MHz
OBSET : 134500.00 Hz

IRNUC : 1H
IRFRQ : 399.65 MHz
IRSET : 134500.00 Hz
IRATN : 511
IRRPW : 50.0 usec
IRBP1 : 27
IRBP2 : 6
IRRNS : 0

ADBIT : 16
CTEMP : 25.9 c
CSPED : 10 Hz
SLVNT : CDCL3

RESOL : 0.24 Hz
BF : 0.01 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 0.00 ppm
XE : 3997.53 Hz
XS : 38.42 Hz
operator



15-OCT-2002 14:28:26.04

DFILE :
SFILE :

COMNT :
EXMOD : SINGL
IRMOD : NON
POINT : 32768
FREQU : 7993.61 Hz
SCANS : 8
DUMMY : 4
ACQTM : 4.0993 sec
PD : 2.9007 sec
RGAIN : 14

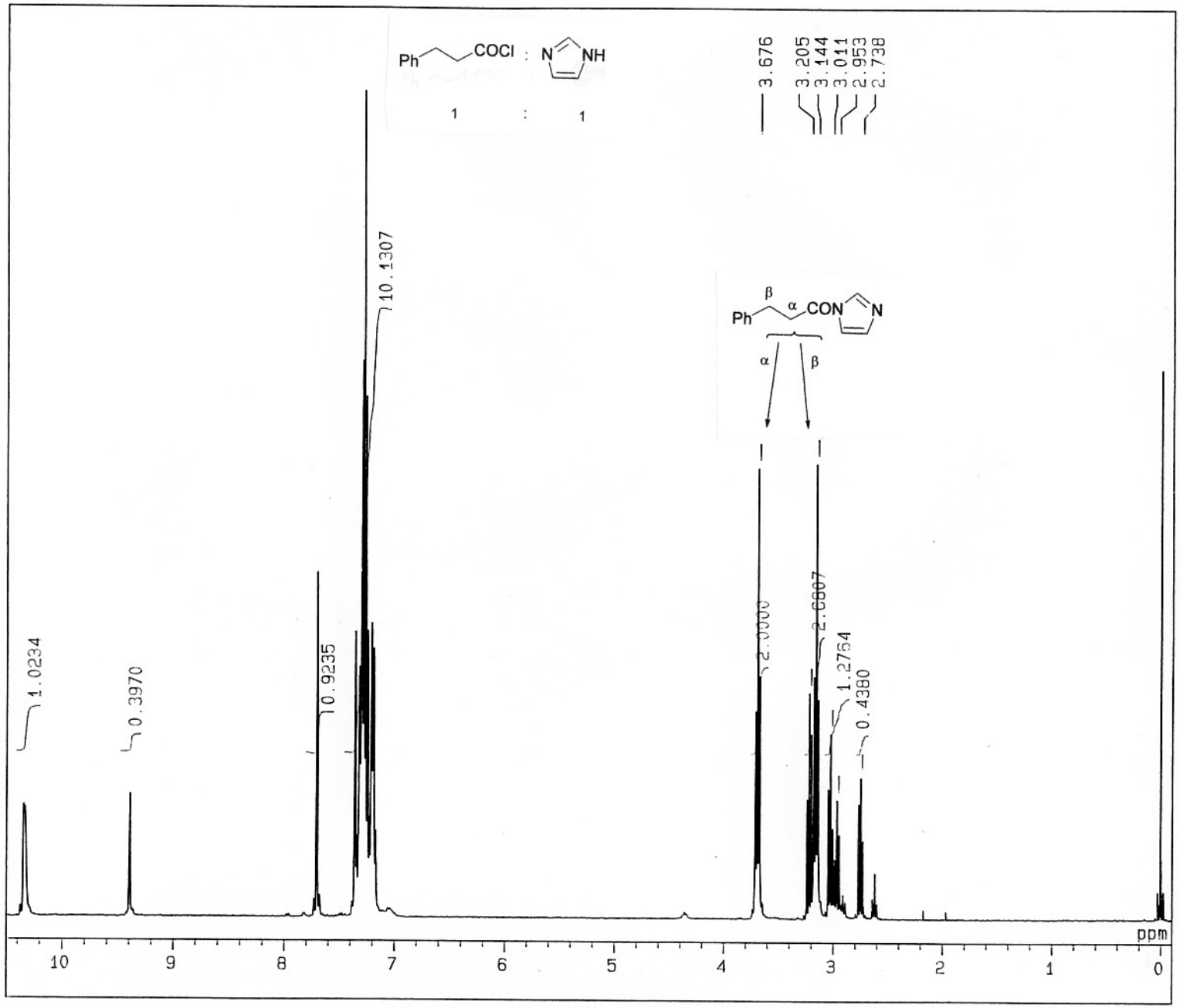
PW1 : 5.50 usec

OBNUC : 1H
OBFRQ : 399.65 MHz
OBSET : 134500.00 Hz

IRNUC : 1H
IRFRQ : 399.65 MHz
IRSET : 134500.00 Hz
IRATN : 511
IRRPW : 50.0 usec
IRBP1 : 27
IRBP2 : 6
IRRNS : 0

ADBIT : 16
CTEMP : 25.9 c
CSPED : 11 Hz
SLVNT : CDCL3

RESOL : 0.24 Hz
BF : 0.01 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 0.00 ppm
XE : 3997.53 Hz
XS : 64.52 Hz
operator



5-NOV-2002 13: 11: 20.43

DFILE :
SFILE :

COMNT :
EXMOD : SINGL
IRMOD : NON
POINT : 32768
FREQU : 7993.61 Hz
SCANS : 8
DUMMY : 4
ACQTM : 4.0993 sec
PD : 2.9007 sec
RGAIN : 17

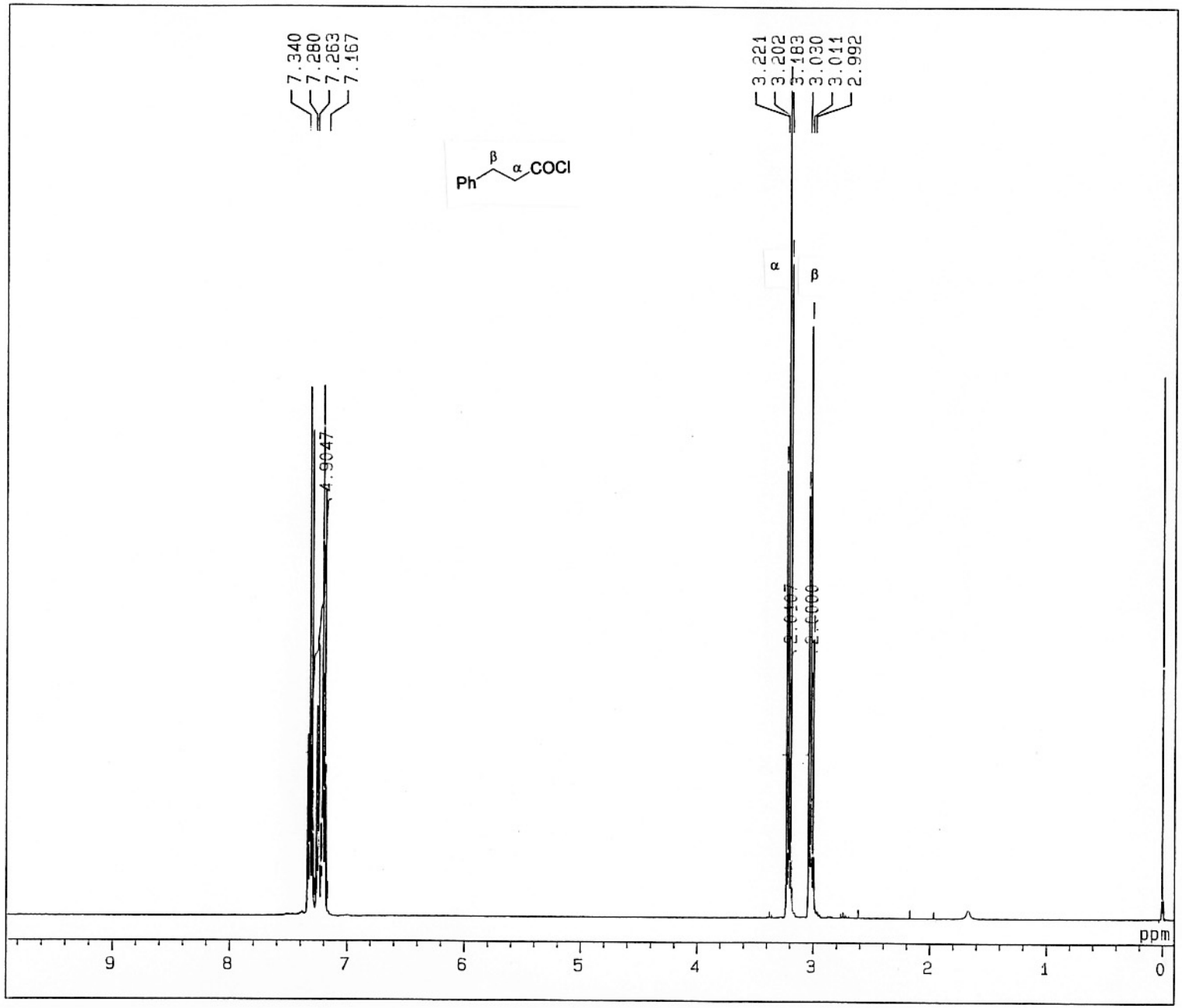
PW1 : 5.50 usec

OBNUC : 1H
OBFRQ : 399.65 MHz
OBSET : 134500.00 Hz

IRNUC : 1H
IRFRQ : 399.65 MHz
IRSET : 134500.00 Hz
IRATN : 511
IRRPW : 50.0 usec
IRBP1 : 27
IRBP2 : 6
IRRNS : 0

ADBIT : 16
CTEMP : 26.2 c
CSPED : 10 Hz
SLVNT : CDCL3

RESOL : 0.24 Hz
BF : 0.01 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 0.00 ppm
XE : 4237.33 Hz
XS : -83.19 Hz
operator



16-JAN-2003 17: 17: 15.92

DFILE :
SFILE :

COMNT :
EXMOD : SINGL
IRMOD : NON
POINT : 32768
FREQU : 7993.61 Hz
SCANS : 8
DUMMY : 4
ACQTM : 4.0993 sec
PD : 2.9007 sec
RGAIN : 16

PW1 : 5.50 usec

OBNUC : 1H
OBFRQ : 399.65 MHz
OBSET : 134500.00 Hz

IRNUC : 1H
IRFRQ : 399.65 MHz
IRSET : 134500.00 Hz
IRATN : 511
IRRPW : 50.0 usec
IRBP1 : 27
IRBP2 : 6
IRRNS : 0

ADBIT : 16
CTEMP : 25.9 c
CSPED : 14 Hz
SLVNT : CDCL3

RESOL : 0.24 Hz
BF : 0.01 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 0.00 ppm
XE : 3997.53 Hz
XS : 27.69 Hz
operator