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Synthesis of optically active phenylglycine derivatives from *Ss*-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide by using Lewis acids and *tert*-amines

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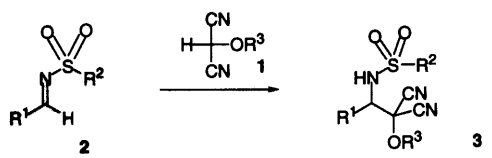
Abstract

Stereoselective synthesis of L- and D-phenylglycine derivatives was accomplished by the reaction of *Ss*-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide with 2-(*tert*-butyldimethylsiloxy)malononitrile (H-MAC-TBS) in the presence of Lewis acids and *tert*-amines.

Keywords: Acyl cyanides; Asymmetric synthesis; Phenylglycine; Amino acids and peptides; Peptides; Sulfinimines; Lewis acids

1. Introduction

Chemical synthesis of α-amino acids is one of the essential means for the supply of artificial, unnatural or rare α-amino acids and the peptides containing them. Based on the fact that *N*-protected-*C*-activated α-amino acids are useful synthetic intermediates for the synthesis of peptides, we have recently developed a method for the synthesis of the masked form of α-(*N*-sulfonylamino)acyl cyanide **3** [1] by the reaction of *N*-sulfonylimines **2** with MAC reagents **1** [2] (Scheme 1). The reaction proceeds within a short period at ambient temperature under mild conditions including, for example, a catalytic amount of triethylamine [1], palladium complex [3], or no catalyst under high-pressure [4].



Scheme 1.

We have applied this method to the asymmetric synthesis of α-amino acid derivatives by, respectively, using MAC reagent bearing asymmetric centers [5], optically active alkoxycarbonylated imines, and so on [6]. Typically, a mixture of diastereomers with low diastereoselectivity has been obtained. In this paper, however, we report a highly stereoselective synthesis of optically active phenylglycine derivatives **4** starting from the sulfinimine **5** [7] by using a MAC reagent **1a** (Scheme 2).

2. Results and discussions

2.1. Preliminary examinations of the reaction of sulfinimine with H-MAC-TBS

In the presence of various *tert*-amines such as pyridine, 2,6-lutidine, triethylamine, and diisopropylethylamine, the desired carbon-carbon bond formation reaction between **5** and **1a** was not observed. In the reaction, unidentified polar compounds were obtained probably because of self-condensation of the MAC reagent **1a**, but the sulfinimine **5** was quantitatively recovered. Therefore, trimethylsilyl triflate (TMSOTf) was added for the sake of the activation of **5**. In the presence of both TMSOTf and 2,6-lutidine [8], forma-

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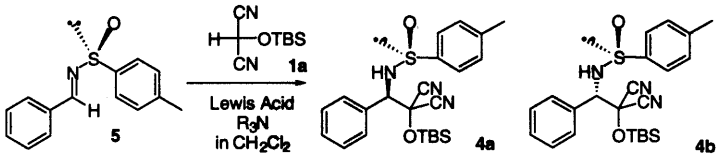


Scheme 2.

tion of the desired compounds **4** was observed. Therefore, we decided to carry out further optimization by the use of both Lewis acids and *tert*-amines.

2.2. The reactions of sulfinimine with H-MAC-TBS under various combinations of tert-amines and Lewis acids

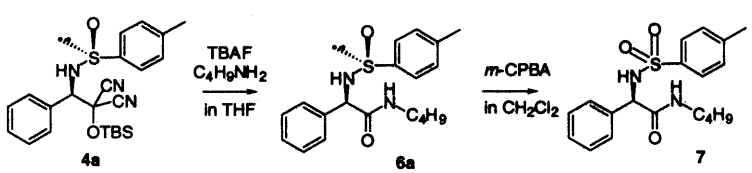
As shown in entries 1–3 in Table 1, we first carried out the reaction in the presence of trimethylsilyl triflate (TMSOTf) with 2,6-lutidine in CH_2Cl_2 at room temperature. A catalytic amount of the promoters gave a trace amount of the desired product **4**, and the sulfinimine **5** and **1a** were recovered in more than 90% yields (entry 1). By using two equivalents of TMSOTf and three equivalents of 2,6-lutidine, the desired compound **4** was obtained in 91% yield (entry 3). By using diisopropylethylamine (DIEA) instead of 2,6-lutidine, **4** was obtained in 86% isolated yield within 30 min (entry 4). We also examined several other Lewis acids (entries 5–9). No reaction occurred when $Sc(OTf)_3$ was used (entry 5). With titanium tetrachloride, the desired product **4** was not obtained and **5** was not recovered (entry 6). The desired product **4** was obtained in moderate yields with $BF_3{\cdot}OEt_2$, $ZnCl_2$, and $SnCl_4$, respectively (entries 7–9). In all cases shown in entries 1–9, the ***2R***-isomer **4a** was selectively produced and the best diastereoselectivity was observed when $BF_3 \cdot OEt_2$ was used (entry 7). In contrast, $Sn(OTf)_2$ gave the ***2S***-isomer **4b** with comparatively high stereoselectivity (entries 10 and 11).

2.3. The determination of the absolute configuration

A diastereomer **4a**, purified by using HPLC, was transformed at -40°C in THF with butylamine in the presence of tetrabutylammonium fluoride to the corresponding *N*-butyl amide **6a** in 92% yield along with a trace amount of the diastereomer **6b** (**6a**:**6b** = >98:2) (Scheme 3). After purification by recrystallization, **6a** was converted to the sulfonylamine **7** with 3-chloroperbenzoic acid in 99% yield. The authentic sample of ***2R*-7** was prepared from commercially available ***2R***-phenylglycine *via* sulfonylation and amide bond formation reactions with butylamine, according to the known procedure [9]. Measurement of the $[\alpha]_D^{22}$ proved that the synthetic **7** was a ***R***-isomer (synthetic: $[\alpha]_D^{22} = -109.7°$; authentic sample: $[\alpha]_D^{22} = -109.4°$). The absolute configuration of the benzylic position of **4a**, **4b**, and **6a** is therefore determined to be *R*, *S*, and *R*, respectively.

Table 1
The reaction of **1a** and **5** with Lewis acids and *tert*-amines

Entry	Lewis acid (equiv.)	Amine (equiv.)	Reaction period	Assumption of **5**	Yield of **4**	Ratio **4a**:**4b**
1	TMSOTf (0.1)	2,6-Lutidine (2.0)	2 h	trace		
2	TMSOTf (2.0)	2,6-Lutidine (2.0)	2 h	30	30	78:22
3	TMSOTf (2.0)	2,6-Lutidine (3.0)	1 h	94	91	78:22
4	TMSOTf (2.0)	DIEA (3.0)	30 min	100	86	74:26
5	$Sc(OTf)_3$ (2.0)	2,6-Lutidine (3.0)	5 h	0	0	
6	$TiCl_4$ (2.0)	DIEA (3.0)	8 h	100	0	
7	$BF_3{\cdot}OEt_2$ (2.0)	DIEA (3.0)	2 h	82	74	82:18
8	$Zn(OTf)_2$ (2.0)	DIEA (3.0)	2 h	57	56	56:44
9	$SnCl_4$ (2.0)	DIEA (3.0)	2 h	71	41	61:39
10	$Sn(OTf)_2$ (2.0)	DIEA (3.0)	5 min	63	81	5:95
11	$Sn(OTf)_2$ (3.0)	DIEA (3.0)	5 min	68	69	5:95



Scheme 3.

3. Conclusion

In conclusion, we have developed a method for the synthesis of an *N*-protected-C-activated phenylglycine in good to excellent yields. Each enantiomer can be selectively synthesized if the appropriate Lewis acid is used.

4. Experimental

4.1. General procedures

Melting points were determined using a Yanagimoto Micro Melting Point Apparatus and are uncorrected. IR spectra were measured on a JASCO FT-IR/420 Infrared Fourier Transfer Spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JMN-AL300 Spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$. Chemical shifts are described by δ value in ppm relative to tetramethylsilane as an internal standard. High Resolution Mass Spectra (HRMS) were measured on a JEOL JMS-SX102A. Elementary analyses were performed on a Yanagimoto CHN-Corder MT-3. 2,6-Lutidine and diisopropylethylamine were distilled over potassium hydroxide. Dichloromethane (CH_2Cl_2) was distilled over phosphorous pentoxide. All reactions were carried out under argon atmosphere unless otherwise noted. Preparation of (*S*)-(+)-*N*-Benzylidene-*p*-toluenesulfinamide (**5**) ($[\alpha]_D^{22} = +118.1°$ (*c* 1.73, $CHCl_3$)) was carried out by the known method [7] ($[\alpha]_D^{22} = +117.3°$ (*c*, 1.77, $CHCl_3$).

4.2. General procedure for the addition of H-MAC-TBS to (S)-(+)-N-benzylidene-p-toluenesulfinamide (5)

To a solution of **5** (243 mg, 1.0 mmol), and Lewis acid (0.1–2.0 eq.) in CH_2Cl_2 (5 ml) was added H-MAC-TBS (**1a**) (1.5–3.0 eq.), then *tert*-amine (1.0–3.0 eq.) was added in turn at room temperature. After being stirred for 5 min–8 h at room temperature, the reaction mixture was poured into saturated NH_4Claq, and extracted with three portions of CH_2Cl_2 (10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with silica gel column chromatography using hexane-ethyl acetate (6:1) as an eluent to give a mixture of **4a** and **4b** as a white solid. Each diastereomer was purified with HPLC [Rt = 34.8 min (**4a**), Rt = 31.2 min (**4b**), 7 ml min^{-1}, hexane/ethyl acetate = 10:1, Hibar column RT $^{\#}$250–10, LiChorsorb Si60, 10 mm id × 250 mm, Cica-Merck].

4.2.1. (Ss,3R)-2-[(tert-Butyldimethylsilyl)oxy]-2-cyano-3-[(4-methylphenyl)sulfinyl]amino -3-phenylpropionitrile (4a)

White powder, m.p. 63–65°C; $[\alpha]_D^{22}$ +118.6° (*c* 2.5, $CHCl_3$); FT-IR (KBr): 3173, 2934, 2244, 1596, 1463, 1262, 1151, 1050, 848 cm^{-1}; ^{1}H-NMR (300 MHz): 7.65 (d, *J* = 8.1 Hz, 2H), 7.41–7.32 (m, 5H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.96 (d, *J* = 7.5 Hz, 1H), 4.83 (brd, *J* = 7.5 Hz, −SONH, 1H), 2.4 (s, 3H), 0.83 (s, 9H), 0.31 (s, 3H), 0.20 (s, 3H); ^{13}C-NMR (75 MHz): 142.2, 141.3, 133.6, 129.9, 129.7, 128.8, 128.2, 125.4, 114.5, 113.9, 69.1, 66.0, 25.1, 21.4, 18.0, −4.6, −4.9; Anal. Calc. for $C_{23}H_{29}N_3O_2SSi$: C, 62.84; H, 6.65; N, 9.56. Found: C, 63.32; H, 7.01; N, 9.21%; EI-HRMS for M^+: 439.1750, Found: 439.1735.

4.2.2. (Ss,3S)-2-[(tert-Butyldimethylsilyl)oxy]-2-cyano-3-[(4-methylphenyl)sulfinyl]amino-3-phenylpropionitrile (4b)

Colorless crystals, m.p. 174–176°C; $[\alpha]_D^{22}$ +119.4° (*c* 1.6, $CHCl_3$); FT-IR (KBr): 3182, 2938, 2240, 1596, 1462, 1261, 1153, 1056, 849 cm^{-1}; ^{1}H-NMR (300 MHz): 7.64 (d, *J* = 8.0Hz, 2H), 7.60–7.52 (m, 2H), 7.52–7.42 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.83 (brd, *J* = 5.3 Hz, −SON*H*, 1H), 4.71 (d, *J* = 5.3 Hz, 1H), 2.45 (s, 3H), 0.84 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C-NMR (75 MHz): 142.3, 140.6, 131.6, 130.4, 129.9, 129.4, 128.8, 125.4, 113.5, 113.4, 68.1, 64.5, 25.1, 21.4, 18.0, −4.7, −4.8; Anal. Calc. for $C_{23}H_{29}N_3O_2SSi$: C, 62.84; H, 6.65; N, 9.56. Found: C, 62.58; H, 6.68; N, 9.45%.

4.2.3. (Ss,2R)-(−)-N-Butyl-2-[(4-methylphenyl)-sulfinyl]amino-2-phenylacetamide

To a solution of **4a** (32.8 mg, 0.075 mmol) and *n*-butylamine (11.2 mg, 15.1 μl, 0.153 mmol) in THF (1 ml) was added TBAF (1.0 M solution in THF) (90 μl, 0.09 mmol) at −40°C. The resultant mixture was stirred for an additional 1 h at −40°C, quenched with a saturated NH_4Cl solution (5 ml), and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified with silica gel column chromatography using hexane-ethyl acetate (1:1) as an eluent to give a mixture of **6a** along with a trace amount of **6b** (less than 2%) as a white solid (23.6 mg, 0.069 mmol, 92% yield), which was further purified by recrystallization from ethyl acetate-hexane.

Colorless crystals, m.p. 170–171°C; $[\alpha]_D^{22}$ −59.0° (*c* 2.3, $CHCl_3$); FT-IR (KBr): 3377, 3242, 2956, 2929, 1669, 1534, 1088, 1063, 809 cm^{-1}; ^{1}H-NMR (300 MHz): 7.38 (d, *J* = 8.1 Hz, 2H), 7.21–7.09 (m, 3H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.99–6.88 (m, 2H), 5.82 (brd, *J* = 4.5Hz, −SONH, 1H), 5.74 (br, −CONH, 1H), 4.80 (d, *J* = 4.5 Hz, 1H), 3.21 (dt, *J* = 6.6, 6.6 Hz, 2H), 2.30 (s, 3H), 1.46–1.33 (m, 2H), 1.30–1.15 (m, 2H),

0.85 (t, $J = 7.3$ Hz, 3H); ^{13}C-NMR (75 MHz): 170.4, 141.0, 139.8, 138.9, 129.0, 128.2, 127.4, 127.3, 126.0, 55.5, 39.5, 31.1, 21.1, 19.7, 13.5; Anal. Calc. for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.07; H, 7.08; N, 8.03%.

4.3. The preparation of (R)-(−)-N-n-Butyl-2-[(4-methylphenyl)sulfonyl]amino-2-phenylacetamide (7) from 6a

A mixture of **6a** (42.0 mg, 0.12 mmol) and *m*-chloroperbenzoic acid (33.0 mg, 70% purity, 0.13 mmol) in CH_2Cl_2 (1.5 ml) was stirred for 30 min at room temperature. The resulting mixture was purified with silica gel column chromatography using chloroform-ethyl acetate (3:1) as an eluent to give **7** as a white solid (43.7 mg, 0.12 mmol, 99% yield).

White powder, m.p. 158–159°C; $[\alpha]_D^{22}$ −109.7° (*c* 1.4, $CHCl_3$); FT-IR (KBr): 3326, 3264, 2957, 1648, 1554, 1453, 1344, 1327, 1162, 1093 cm^{-1}; ^{1}H-NMR (300 MHz): 7.59 (d, $J = 8.1$ Hz, 2H), 7.30–7.22 (m, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.16–7.10 (m, 3H), 5.88 (brd, $J = 4.7$ Hz, $-SO_2NH$, 1H), 5.61 (br, $-CONH$, 1H), 4.70 (d, $J = 4.7$ Hz, 1H), 3.15 (dt, $J = 6.7$, 6.7 Hz, 2H), 2.39 (s, 3H), 1.41–1.27 (m, 2H), 1.27–1.11 (m, 2H), 0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C-NMR (75 MHz): 168.9, 143.5, 136.8, 136.6, 129.5, 128.9, 128.5, 127.4, 127.2, 60.5, 39.7, 31.2, 21.5, 19.8, 13.6; Anal. Calc. for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.28; H, 6.89; N, 7.67%.

4.4. (R)-(−)-N-n-Butyl-2-[(4-methylphenyl)-sulfonyl]amino-2-phenylacetamide (7) from (R)-N-toluenesulfonyl-phenylglycine

A suspension of (*R*)-*N*-toluenesulfonyl-phenylglycine **9** (202 mg, 0.66 mmol) in CH_2Cl_2 was treated with $SOCl_2$ (0.5 ml). The mixture was refluxed with stirring for 1 h then evaporated to dryness *in vacuo*. The resultant acid chloride was dissolved in CH_2Cl_2 (6 ml), and butylamine (146 mg, 0.2 ml, 2.0 mmol) was added at 0°C. After being stirred for 10 min at 0°C, the reaction mixture was concentrated and the residue was purified with silica gel column chromatography using chloroform-ethyl acetate (3:1) as an eluent to give **7** as a white solid (204 mg, 0.57 mmol, 86% yield, $[\alpha]_D^{22}$ −102.1° (*c* 1.4, $CHCl_3$)), which was further purified by recrystallization from ethyl acetate (m.p. 159–160°C; $[\alpha]_D^{22}$ −109.4° (c 1.4, $CHCl_3$)).

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