A Short Synthesis of a Pyrrole Derivative Having a Chiral Substituent

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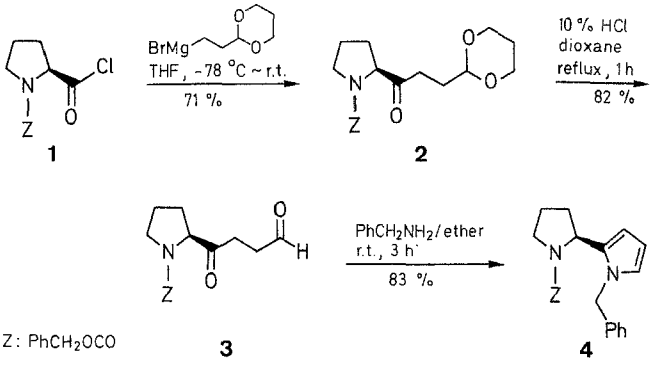
Optically active pyrrole derivative **4** with a pyrrolidinyl group derived from L-proline has been prepared by a three-step sequence in 48% overall yield from *N*-benzyloxycarbonyl-L-prolyl chloride (**1**).

Synthesis of new optically active ligands is necessary for some organic reactions related to metal carbonyl complexes leading to effective asymmetric reactions. Recently, the study of metal carbonyl complexes coordinated with pyrrole has received much attention.[1] Some fruitful organic reactions can be expected by using metal carbonyl complex having chiral pyrroles as an asymmetric catalyst. Based on this idea, we have started the synthesis of chiral pyrroles and reported here a general preparative method to obtain a representative of this class of compounds.

A three carbon system needed for our synthesis was found in the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane and magnesium, which has been reported[2] to be more stable than the 1,3-dioxolane derivative.[3] The condensation of the Grignard reagent and *N*-benzyloxycarbonyl-L-prolyl chloride (**1**),[4] prepared from *N*-benzyloxycarbonyl-L-proline and thionyl chloride, was carried out by slowly adding the Grignard reagent to the acyl chloride **1** in tetrahydrofuran at −78 °C. (2*S*)-1-Benzyloxycarbonyl-2-[3-(1,3-dioxan-2-yl)propanoyl]pyrrolidine (**2**) was obtained in 71% yield after column chromatography. Deprotection of **2** smoothly proceeded in 10% hydrochloric acid/dioxane solution to give (2*S*)-1-benzyloxycarbonyl-2-(4-oxobutanoyl)pyrrolidine (**3**) in 82% yield. The condensation of dicarbonyl compound **3** and benzylamine was easily carried out in ether to afford the pyrrole derivative; (2*S*)-1-benzyloxycarbonyl-2-(1-benzyl-2-pyrrol-yl)pyrrolidine (**4**) in 83% yield.[4]



1 **2** **3** **4**

In summary, a short and convenient synthesis with good overall yield of the pyrrole derivative **4** (48% starting from **1**), having a chiral moiety is reported.

Unless otherwise noted, chemicals were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone, immediately prior to use. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. For TLC Merck silica gel 60 on aluminum sheets was used. Melting points are uncorrected. IR spectra were taken with JASCO A-302 IR spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL MH-100 spectrometer. Optical rotations were recorded on Union Giken PM-101 polarimeter.

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(2*S*)-1-Benzyloxycarbonyl-2-[3-(1,3-dioxan-2-yl)propanoyl]pyrrolidine (2):

To a solution of *N*-benzyloxycarbonyl-L-prolyl chloride (**1**; 10.2 g, 38.1 mmol) in THF (100 mL) is added at −78 °C under argon the Grignard reagent prepared freshly from 2-(2-bromoethyl)-1,3-dioxane[2] (10.7 g, 5.5 mmol) and Mg (1.6 g, 6.7 mmol) in THF (50 mL). After addition, the mixture is allowed to warm to room temperature and then stirred overnight. Water (30 mL) is added, and THF is removed using a rotary evaporator. The residue is extracted with ether (3 × 50 mL), washed with sat. aq. solution of Na_2CO_3 (20 mL), and dried ($MgSO_4$). After removal of the solvent, a pale yellow oil is obtained, which is purified by flash column chromatography [silica gel (300 g), eluent: 20% EtOAc in hexane] to give **2** as an oil; yield: 9.40 g (71%); The thin layer chromatography of **2** showed a spot; R_f 0.37, (50% EtOAc in hexane); $[\alpha]_D^{22}$ −41.40° (*c* = 1.07, $CHCl_3$).

$C_{19}H_{25}NO_5$	calc.	C 65.69	H 7.25	N 4.03
(347.4)	found	65.72	7.23	4.08

IR (neat): ν = 1700, 1125 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.13–1.45 (m, 2H); 1.53–2.36 (m, 6H); 2.36–2.91 (m, 2H); 3.40–3.93 (m, 4H); 3.39–4.22 (m, 2H); 4.26–4.73 (m, 2H); 5.16 (s, 2H); 7.46 (s, 5H).

(2*S*)-1-Benzyloxycarbonyl-2-(4-oxo-1-butanoyl)pyrrolidine (3):

A solution of **2** (1.1 g, 3.2 mmol) in 10% HCl (5 mL) and dioxane (5 mL) is refluxed with stirring for 20 min. After cooled to room temperature, the resulting mixture is extracted with ether (3 × 10 mL). The organic layer is washed with a sat. aq. solution of Na_2CO_3 (5 mL) and dried ($MgSO_4$). The solvent is removed with a rotary evaporator and the residual colored oil is purified by flash column chromatography [silica gel (30 g) with 15% EtOAc in hexane] to give **3**; yield: 0.76 g (82%); R_f 0.36 (50% EtOAc in hexane).

$C_{16}H_{19}NO_4$	calc.	C 66.42	H 6.62	N 4.84
(289.3)	found	66.51	6.59	4.88

IR (neat): ν = 1710, 1690 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.48–2.20 (m, 4H); 2.40–2.70 (m, 4H); 3.4 (t, 2H, *J* = 6 Hz); 4.12–4.32 (m, 1H); 4.96 (s, 2H); 7.19 (s, 5H); 9.45 (d, 1H, *J* = 7 Hz).

(2*S*)-1-Benzyloxycarbonyl-2-(1-benzyl-2-pyrrol-yl)pyrrolidine (4):

To a solution of **3** (5.23 g, 18 mmol) in ether (100 mL) is added freshly distilled benzylamine (2.15 g, 20 mmol). The resulting solution is stirred for 3 h at room temperature under N_2 and then quenched with brine (10 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed with a rotary evaporator to give a colored oil which was purified by flash column chromatography (silica gel (200 g) with 10% EtOAc in hexane) to give compound **4** as a white solid; yield 5.41 g (83%); R_f 0.39 (30% EtOAc in hexane); mp 48–49 °C; $[\alpha]_D^{19}$ + 6.22° (*c* = 0.933, $CHCl_3$).

$C_{23}H_{24}N_2O_2$	calc.	C 76.64	H 6.71	N 7.77
(360.4)	found	76.58	6.77	7.80

IR (Nujol): ν = 1680 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.40–2.04 (m, 4H); 3.25–3.63 (m, 2H); 4.40–5.19 (m, 5H); 5.64–6.00 (m, 2H); 6.33 (t, 1H, *J* = 2 Hz); 6.55–7.29 (m, 10H).

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(1) Kershner, D.L., Basolo, F. *J. Am. Chem. Soc.* **1987**, *109*, 7396, and references cited therein.
(2) Stowell, J.C. *J. Org. Chem.* **1976**, *41*, 560.
(3) Sato, T., Kawara, T., Sakata, K., Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 505.
(4) Starting from *N*-(*p*-toluenesulfonyl)prolyl chloride and carrying out the same sequence of reactions as for the preparation of **4**, we have also synthesized (2*S*)-1-*p*-toluenesulfonyl-2-(1-benzylpyrrol-2-yl) pyrrolidine; yield: 51% (overall); white needles; mp 150–151 °C; $[\alpha]_D^{16}$ −46.10° (*c* = 1.00, $CHCl_3$).

$C_{22}H_{24}N_2O_2S$	calc.	C 69.45	H 6.36	N 7.36
(380.5)	found	69.52	6.72	7.41

IR (Nujol): ν = 1340, 1160 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ = 1.52–1.79 (m, 4H); 2.38 (s, 3H); 3.42 (m, 2H); 4.76 (t, 1H, *J* = 6 Hz); 5.25 (AB q, 2H, *J* = 16, 28 Hz); 6.02–6.12 (m, 2H); 6.68 (t, 1H, *J* = 2 Hz); 7.05–7.42 (m, 9H).

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