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A Short Asymmetric Synthesis of 2,5-Disubstituted Pyrrolidines

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Abstract: A novel approach to chiral 2,5-disubstituted pyrrolidines, starting from chiral 2-phenylglycinol, 1,5-dimethoxytetrahydrofuran, and benzotriazole, involves the diastereoselective substitution by Grignard reagents of a benzotriazolyl group in a crystalline intermediate obtained in high yield.

Chiral 2,5-disubstituted pyrrolidine alkaloids possess important biological activity, and the synthesis of alkaloids of this type is of considerable current interest. Higashiyama and co-workers reported an asymmetric synthesis of (*R,R*)-2,5-bis(aryl)pyrrolidines by the diastereoselective addition of Grignard reagents to chiral aromatic imines,[1] but this method is apparently restricted to the preparation of 2-aryl- and 2,5-diarylpyrrolidines. Rapoport *et al.* prepared chiral 2,5-disubstituted pyrrolidines from glutamic acid,[2] in a synthesis requiring ten or more steps. Oppolzer *et al.* synthesized 2,5-disubstituted pyrrolidines *via* 2-carbonylsultam, 5-alkyl-*N*-hydroxypyrrolines as chiral intermediates.[3] Kibayashi *et al.* made 2,5-disubstituted pyrrolidines in seven steps starting with *D*-mannitol.[4] Husson and co-workers synthesized 8-phenyl-2-cyano-oxazolopyrrolidine as a chiral synthon for the preparation of chiral 2-alkylpyrrolidines.[5,6]

Here we report an efficient general method to prepare chiral 2,5-disubstituted pyrrolidines from (4*S*,5*R*)-5-(benzotriazol-1-yl)-4-phenyl-[1,2-*a*]oxazolopyrrolidine (**2**), which is easily obtained from benzotriazole, 2,5-dimethoxytetrahydrofuran and (*S*)-phenylglycinol. Crystalline intermediate **2** was prepared in 80% yield {$[\alpha]_D^{20}$ 88.95, c, 0.57, EtOH} from succindialdehyde (hydrolyzed 2,5-dimethoxytetrahydrofuran), (*S*)-phenylglycinol and benzotriazole (Scheme 1).[7] Both ^1H and ^{13}C NMR spectra of the crude product showed that only one diastereoisomer was obtained. The detailed structure of **2** was demonstrated by X-ray crystallography to be that shown in Figure 1.[8] The formation of **2** is expected, based on previous benzotriazole synthetic methodology.[9]

Treatment of intermediate **2** with 1 equivalent of Grignard reagent at 0 °C gave a mixture of *cis*- **5** and *trans*-2,5-disubstituted pyrrolidine **6**, along with a large amount of recovered starting material **2**, instead of the expected monosubstituted product **3**. Addition of a Lewis acid such as $ZnBr_2$ to the reaction mixture, expected to assist the departure of the benzotriazolyl group by coordination with the 3-position nitrogen, gave only elimination product **4**. Lowering the reaction temperature and the speed of Grignard reagent

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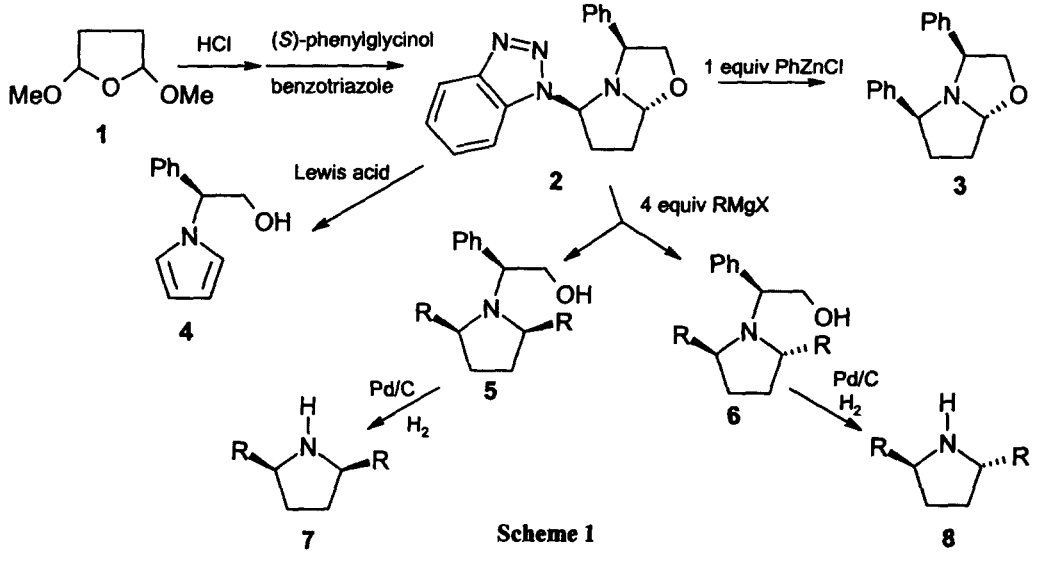
addition did not yield the expected monosubstituted **3**, indicating that the two reaction centers have similar reactivity towards the Grignard reagent. Organozinc reagent (1 equivalent) when applied in the above reaction instead of Grignard reagent, did furnish the monosubstituted product **3**, but in very low yield (10%) and mixed with disubstituted products **5** and **6**, elimination product **4** and recovered starting material **2**. With organolithium reagent, no reaction occurred at -78 °C, an elimination took place at 20 °C.

When 4 equivalent of Grignard reagent was reacted with intermediate **2** at 0 °C, the reactions gave mixtures of *cis*-products **5a-e** and *trans*-products **6a-e** in excellent total yields. Diastereoisomeric pairs **5** and **6** were separated by column chromatography. The structures of compounds **5a** and **6a** were identified by comparison of both ^{1}H and ^{13}C NMR data with those reported in the literature[1] and structure **6b** was confirmed by X-ray crystallography (Figure 2).[10]



Scheme 1

Table 1. Preparation of Compounds **5** and **6**.[11]

Entry	R	yield **5** (%)	yield **6** (%)	Total yield (%)	Ratio **5**:**6**	$[\alpha]_D^{20}$ of **5** (c, g/mL, EtOH)	$[\alpha]_D^{20}$ of **6** (c, g/mL, EtOH)
a	Ph	45	45	90	1:1	-17.6 (0.72)	-3.12 (0.48)
b	Me	57	19	76	3:1	+30.1(0.93)	-23.0(0.87)
c	*n*-Pr	55	22	77	5:2	+20.3(1.48)	-36.7(0.82)
d	*n*-Pentyl	53	17	70	3:1	+14.6(1.28)	-42.9(0.62)
e	$PhCH_2CH_2$	60	30	90	2:1	+8.2(4.51)	-25.5(1.37)[a]

[a] Solvent: $CHCl_3$.

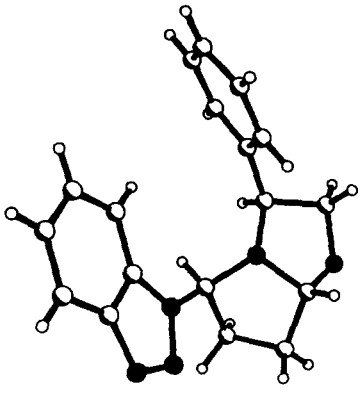


Fig.1. The X-ray structure of **2**

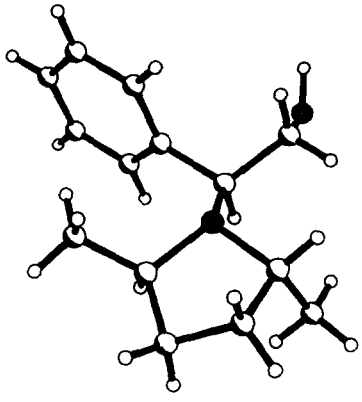


Fig. 2. The X-ray structure of **6b**

As shown in Table 1, both aryl and alkyl Grignard reagents reacted with intermediate **2** to give *cis*- and *trans*- products **5** and **6**. When phenylmagnesium bromide reacted with **2**, the reaction gave **5a** and **6a** in the ratio of 1:1. However, methylmagnesium bromide in this reaction gave **5b** and **6b** in a ratio of 3:1. Similarly, other alkyl Grignard reagents reacted with **2**, to afford **5** and **6** in ratios of about 3:1.

Hydrogenation of **5b-e** and **6b-e** in the presence of Pd/C catalyst gave the corresponding *cis*- and *trans*-2,5-disubstituted pyrrolidines **7b-e** and **8b-e** in excellent yields. The products were isolated as their hydrochloride salts. Compounds **5a** and **6a** were not suitable for hydrogenation; however, their conversion into the corresponding **7a** and **8a** has already been reported.[1] As expected, compounds **8b-e** show optical rotations, but **7b-e** do not. The results of the hydrogenations are listed in Table 2. Structures **5a-e**, **7b-e**, **6a-e** and **8b-e** were supported by their ^{1}H, ^{13}C NMR spectra and elemental analyses.

Table 2. Preparation of Compounds **7** and **8**.[12]

Compound	R	Yield (%)	Mp (°C)	$[\alpha]_D^{20}$ (c, g/ml EtOH)
7b	Me	90	213-215	< ±0.01 (0.94)
7c	*n*-Pr	95	168-170	< ±0.01 (1.03)
7d	*n*-Pentyl	92	148-150	< ±0.01 (1.40)
7e	$PhCH_2CH_2$	89	153-154	< ±0.01 (0.88)
8b	Me	87	164-166	+0.76 (1.19)
8c	*n*-Pr	84	133-135	+0.32 (0.94)
8d	*n*-Pentyl	80	123-125	+0.44 (1.21)
8e	$PhCH_2CH_2$	76	137-138	-7.70 (0.61)

In conclusion, key intermediate (4*S*,5*R*)-5-(benzotriazol-1-yl)-4-phenyl[1,2-*a*]oxazolopyrrolidine (**2**) was obtained in 80% yield from benzotriazole, 2,5-dimethoxytetrahydrofuran and (*S*)-phenylglycinol. Reactions of **2** with Grignard reagents gave chiral 2,5-disubstituted pyrrolidines **5** and **6**. Their separation followed by hydrogenation provides a simple and general method to prepare chiral *trans*-2,5-disubstituted pyrrolidines **8a-e**.

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6. Huang, P. Q.; Arseniyadis, S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 547.
7. Preparation of compound **2**: A mixture of 2,5-dimethoxytetrahydrofuran (1.3 mL, 10 mmol) and HCl aqueous solution (40 mL, 0.1 N) was refluxed for one hour, then cooled to rt. A solution of benzotriazole (1.19 g, 10 mmol) and (*S*)-phenylglycinol (1.37 g, 10 mL) in methylene chloride (100 mL) was added and stirred overnight. The reaction mixture was washed with NaOH aqueous solution (2 N, 3x30 mL) and water (2x30 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from ethyl acetate to give crystalline product **2** in 80% yield; mp 139-140 °C, $[\alpha]_D^{20}$ = +89.0 (c, 0.57, EtOH), ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 2.27-2.32 (m, 1H), 2.57-2.67 (m, 3H), 3.68-3.75 (m, 1H), 4.48-4.55 (m, 2H), 5.23-5.24 (m, 1H), 5.98-6.01 (m, 1H), 7.05-7.20 (m, 5H), 7.26-7.35 (m, 2H), 7.53 (d, 1H, J = 7.1 Hz), 7.97-8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 29.6, 30.0, 68.5, 73.2, 82.4, 97.6, 111.0, 111.1, 119.8, 123.8, 126.1, 127.2, 128.4, 131.6, 140.6, 146.8. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.55; H, 5.93; N, 18.30. Found: C, 70.16; H, 6.18; N, 18.23.
8. Crystal data for **2** at -132 °C: $C_{18}H_{18}N_4O$, M 306.36, orthorhombic, $P2_12_12_1$, a = 5.6900 (1), b = 9.3343 (2), c = 27.1700 (5) Å, V = 1511.53 (5) Å^3, Z = 4, λ (MoKα) = 0.71073 Å, F (000) = 648, D_c = 1.346 gcm^{-3}, μ = 0.087 mm^{-1}, 3082 reflections, 209 parameters, R = 0.0331, wR = 0.0763 for all data.
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10. Crystal data for **6b** at 23 °C: $C_{14}H_{21}NO$, M 219.32, monoclinic, $P2_1$, a = 8.3271 (6), b = 8.2785 (5), c = 10.1973 (7) Å, β = 106.761 (2)°, V = 673.10 (8) Å^3, Z = 2, λ (MoKα) = 0.71073 Å, F (000) = 240, D_c = 1.082 gcm^{-3}, μ = 0.067 mm^{-1}, 1246 reflections, 149 parameters, R = 0.0385, wR = 0.1038 for all data.
11. General procedure for **5** and **6**: To a cold solution (ice water bath) of 5-(benzotriazol-1-yl)-4-phenyl [1,2-*a*]-oxazolopyrrolidine (1.53 g, 5 mmol) in dry THF (100 mL), Grignard reagent (20 mmol) was added dropwise under nitrogen. The reaction mixture was warmed to rt and stirred overnight. Then, the mixture was washed with NaOH (2 N, 3x30 mL) and water (2x30 mL) and extracted with ethyl ether. The organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel, eluent: hexane/ethyl acetate = 10/1), to give pure products **5** and **6**.
12. General procedure for **7** and **8**: A solution of compound **5** or **6** (2 mmol) and 10% Pd/C (50 mg) in methanol (60 mL) was charged with hydrogen at a pressure of 40 psi at rt for 24 hours. After filtration of the catalyst, the filtrate was treated with concentrated HCl (2 mL) and stirred at rt for 30 min. The solvent was evaporated under vacuum, and the residue was washed with ethyl ether to provide products **7** or **8** as white solids. Recrystallization from $CHCl_3$ and hexane gave crystalline products.