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A Practical One-Pot Synthesis of *trans*-4,5-Disubstituted 2-Pyrrolidinones and The Related Pyrrolidines

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Abstract: A practical and general method for the stereoselective synthesis of *trans*-4,5-disubstituted 2-pyrrolidinones was developed. Hydride reduction of these pyrrolidinones gave the corresponding pyrrolidines.
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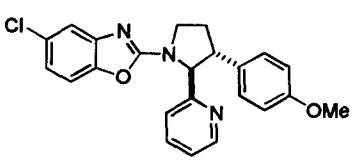
Substituted pyrrolidinone and pyrrolidine derivatives are attractive synthetic targets[1] because they possess a variety of biological activities and have been used for pharmaceutical purposes.[2] In our drug discovery program, the chiral 2-(1-pyrrolidino)-substituted benzoxazole 1 (BIRZ227)[3] was identified as an inhibitor of leukotriene biosynthesis and a potentially useful therapeutic agent for treating inflammatory disorders such as asthma, arthritis, inflammatory bowel disease, and psoriasis.



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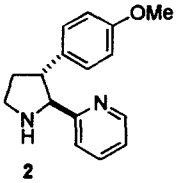
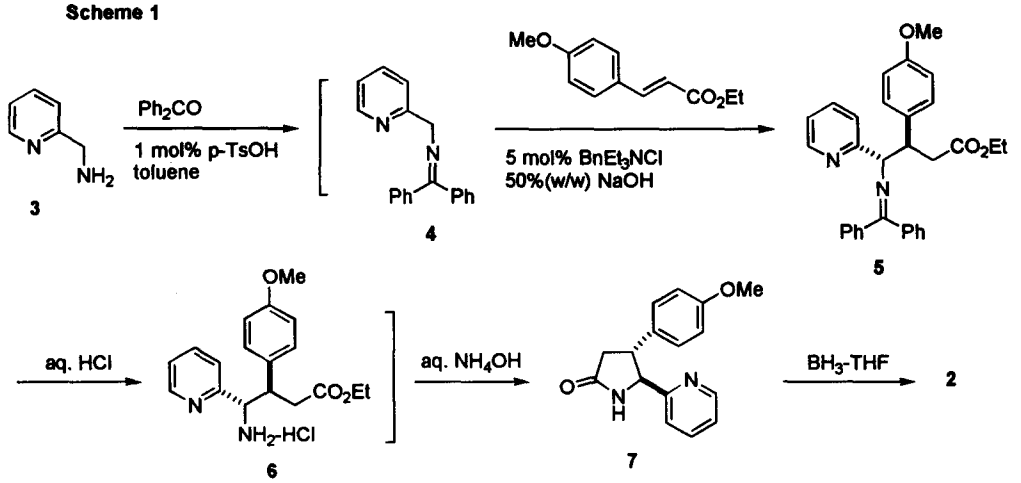


2

A multi-kilogram supply of **1** was needed to support the preclinical development studies. The reported synthesis of **1** involved the condensation of the resolved 2,3-disubstituted pyrrolidine (+)-**2** with 2,6-dichlorobenzoxazole, in which (±)-**2** was prepared by the [2+3]-cycloaddition of an azaallyl anion with 4-methoxystyrene at low temperature.[3,4] This method is not feasible for scale-up not only because of its poor reproducibility, but also owing to the required low temperature conditions (-78 °C) and the extensive chromatographic purification of the cycloaddition product. Therefore, a more practical alternative to **1** was required in order to satisfy the preclinical need. Herein we wish to report a practical, stereoselective synthesis of *trans*-4,5-disubstituted 2-pyrrolidinones and the following hydride reduction of the carbonyl group to give 2,3-disubstituted pyrrolidines related to **2**.

Phase transfer catalysis (PTC) is attractive for industrial processes due to its inherent experimental simplicity and efficiency.[5] Our synthetic approach to 2-pyrrolidinones is based on Michael addition of a Schiff base to a substituted cinnamate using the PTC conditions (Scheme I).[6,7] Condensation of 2-(aminomethyl)-pyridine (**3**) with benzophenone (1.0 M in toluene, 1 mol % *p*-TsOH, reflux, 16 h) using a Dean-Stark apparatus afforded the Schiff base **4**.[8] To this reaction mixture was directly added ethyl 4-methoxycinnamate, 5 mol % $BnEt_3NCl$, and 0.5 equivalent of aqueous 50% NaOH. This PTC reaction proceeded smoothly

Scheme 1



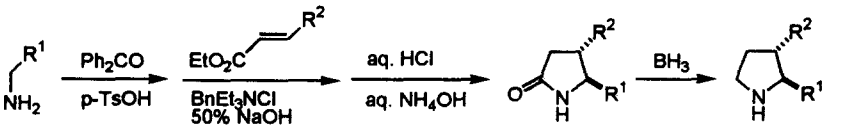
at room temperature overnight (15 h) to give Michael adduct **5**.[9] Acidic hydrolysis of **5** (3.5 eq. aq. 2.4 N HCl, rt, 16 h) afforded the HCl salt of aminoester **6**. At this point, the aqueous layer containing **6** was washed with toluene to remove all organic soluble materials, which consisted mainly of recovered Ph_2CO and a trace of unreacted unsaturated ester. The aqueous phase was then basified (4.5 eq. of conc. NH_4OH, toluene, rt, 15 h) in the two phase system. The desired 2-pyrrolidinone **7** was obtained in crystalline form in 72% overall yield from **3** (trans:cis = 93:7).[10] The trans and cis isomers of **7** can be easily distinguished by the characteristic chemical shifts of the C-5 methine proton; thus the ratio was determined by integration of the C-5 signals in the ^1H NMR spectrum of the crude product. For the trans isomer, the C-5 proton appears at δ 4.81 ppm (d, J = 6.6 Hz), whereas the corresponding proton in the cis isomer is at δ 5.13 ppm (d, J = 7.6 Hz). While consistent spectroscopic evidence was obtained to establish the trans/cis stereochemistry of **7** at this point, X-ray structures of the *p*-toluenesulfonamide of both corresponding trans and cis pyrrolidines **2** were determined to establish conclusively the relative and absolute stereochemistry.[4,11]

Borane reduction of **7** (1.0 M BH_3, THF, reflux) according to the standard protocol[12] afforded the 2,3-disubstituted pyrrolidine (±)-**2** in 87% yield. Attempted reduction by other reagents such as $LiAlH_4$ or Red-Al failed since the pyridine ring in **2** was also reduced.

The generality of this methodology was explored using a variety of substrates, and the results are summarized in Table 1. It appears the R^1 is limited to the substituents capable of stabilizing the transient anion of the Schiff base, while R^2 is more flexible and can be alkyl, aryl, or functional group such as CO_2R. In most cases, the pyrrolidinones and pyrrolidines were obtained in good yields.[13] The lower yield (47%) obtained for **11** (entry 5) is attributed to slow reaction and incomplete conversion in the PTC reaction even at the prolonged time (2 days), probably due to the steric hindrance by the i-Pr group.

In all cases (**7-16**), the trans pyrrolidinones were highly favored (90:10 - 98:2) over the cis isomers. The chemical shifts for the C-5 methine protons in the trans isomers generally appear at higher field ($\Delta\delta$ = 0.34 ppm) as doublets with smaller coupling constants (ΔJ = 0.6 Hz) compared to the corresponding cis isomers. Based on the results from deuterium-labeling control experiments,[14] the Michael addition step

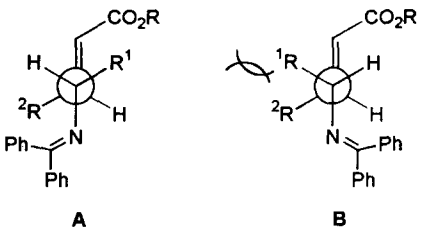
Table 1. Synthesis of 4,5-disubstituted pyrrolidinones (7-16) and their related pyrrolidines (2, 17-20)



			pyrrolidinones			pyrrolidines	
Entry	R^1	R^2	Product	Yield (%)[a]	trans:cis[b]	Product	Yield (%)
1	2-pyridyl	4-MeOPh	7	72	93:7	**2**	87
2	Ph[c]	Ph	**8**	64	96:4	**17**	90
3	Ph[c]	3-pyridyl	**9**	71	94:6	**18**	76
4	3-pyridyl	2-thienyl	**10**	79	94:6	**19**	68
5	3-pyridyl	i-Pr	**11**	47	98:2	**20**	74
6	3-pyridyl	4-MeOPh	**12**	85	95:5		
7	2-furyl[d]	4-MeOPh	**13**	66	94:6		
8	2-furyl[d]	3-pyridyl	**14**	70	90:10		
9	3-pyridyl	CO_2Et	**15**	91	94:6		
10	3-pyridyl	Me	**16**	86	90:10		

[a] Yields were determined after chromatography. [b] The trans:cis ratio was measured from the crude product prior to purification. [c] CH_2Cl_2 was added in the PTC reaction to avoid crystallization of the reactants. [d] aq. NH_2OH/EtOH was used for hydrolysis.

seems kinetically controlled and under the given reaction conditions neither base-induced equilibration nor a retro-Michael reaction should account for the observed diastereoselectivity. The diastereoselectivity in favor of the *syn* Michael adduct is rationalized by open transition states (TS's) as depicted in the following Newman projection **A** and **B**. The torsional strain between R^1 and R^2 in **B** favors transition state **A**.



In summary, a practical and general method for the stereoselective synthesis of *trans*-4,5-disubstituted 2-pyrrolidinones and related pyrrolidines has been developed. The synthetic route to 7 described in Scheme I clearly demonstrated its practicality and effectiveness. The simple one-pot operation, composed of the Schiff base formation, the PTC Michael addition, hydrolysis, and cyclization, is efficient. The four sequential transformations smoothly provide the desired product 7 in excellent yield and high diastereoselectivity. This process has been successfully carried out on >10 Kg scale in the pilot plant and similar results were obtained in terms of yield and stereoselectivity; in this case, the product 7 was directly crystallized from the reaction mixture. The resolution of the pyrrolidinone/pyrrolidine derivative and the synthesis of optically active **1** (BIRZ227) will be reported separately.

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8. ***trans*-4-(4-Methoxyphenyl)-5-(2-pyridyl)-2-pyrrolidinone (7). A representative procedure:** A solution of 2-(aminomethyl)pyridine (**3**, 1.62 g, 15.0 mmol), benzophenone (2.73 g, 15 mmol), and p-TsOH monohydrate (28.5 mg, 0.15 mmol) in 15 mL of toluene was heated at reflux using a Dean-Stark apparatus overnight (16 h). The reaction mixture was cooled to rt and ethyl 4-methoxycinnamate (3.09 g, 15 mmol), $BnEt_3NCl$ (171 mg, 0.75 mmol), and 50% (w/w) NaOH (0.39 mL, 7.5 mmol) were added. The resulting mixture was magnetically stirred at rt overnight (15 h). Hydrochloric acid (2.4 N, 22 mL, 52.8 mmol) was added. The two-phase mixture was stirred at rt overnight (16 h), and the layers were separated. The aqueous layer was washed with toluene (2x15 mL), mixed with toluene (20 mL), and basified with conc. NH_4OH (15 N, 4.5 mL, 67.5 mmol) at 0 °C. This two-phase mixture was stirred at rt overnight (15 h), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 3.46 g of the crude product **7** (trans:cis = 93:7). Purification by flash chromatography on silica gel (eluted with 5% MeOH in CH_2Cl_2) afforded 2.9 g (72%) of **7**. m.p. 118 - 119 °C; *trans*-**7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (d, J = 4.6 Hz, 1H), 7.64 (dt, J = 7.7 and 1.7 Hz, 1H), 7.22 - 7.25 (br. s, 1H), 7.19 (m, 1H), 7.17 - 7.15 (m, 3H), 6.86 (dd, J = 6.8 and 1.8 Hz, 2H), 4.81 (d, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.62 (q, J = 6.7 Hz, 1H), 2.86, 2.60 (ABq of d., J_{gem} = 17.0 Hz, J_{vic} = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 177.5, 160, 159.1, 150, 137.3, 133.6, 128.9, 123.3, 121.3, 114.6, 67.1, 55.6, 48.2, 39.1; *cis*-**7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J = 4.2 Hz, 1H), 7.40 (t, J = 1.7 Hz, 1H), 7.17 (br.s, 1H), 7.01 (dd, J = 6.8 and 4.6 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.76, 6.57 (ABq of d, J = 6.7 and 1.8 Hz, 4H), 5.13 (d, J = 7.6 Hz, 1H), 4.08 (q, J = 7.9 Hz, 1H), 3.67 (s, 3H), 2.82, 2.74 (ABq of d, J_{gem} = 16.7 Hz, J_{vic} = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 179.3, 158.6, 158.4, 149.2, 136.5, 130.7, 129.2, 122.7, 121.8, 113.7, 64.3, 55.5, 45.5, 36.7. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 5.97; N, 10.42.
9. Michael adduct **5** could be isolated by flash chromatography (syn:anti = 88:12 based on the integration of the C-2 methylene proton signals in ^{1}H NMR); *syn*-**5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 4.2 Hz, 1H), 7.74 (br. s, 1H), 7.59 (br. d, J = 8.4 Hz, 1H), 7.50 - 7.20 (m, 7H), 7.14 (br. s, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.82 - 6.69 (m, 1H), 6.70 (d, J = 8.7 Hz, 2H), 6.52 (br. s, 2H), 4.73 (br. s, 1H), 4.05 (dt, J = 5.1 and 5.1 Hz, 1H), 3.95 - 3.83 (m, 2H), 3.75 (s, 3H), 3.02, 2.78 (AMX, J = 15.6, 10.9, and 4.7 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H).
10. It was observed the *syn*-**6** cyclized at a faster rate than the corresponding *anti*-**6** under the given conditions, and hence the *trans:cis* ratio (93:7) of **7** was higher than the *syn:anti* ratio (88:12) of **5**.
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13. All new compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy.
14. Control experiments: a) the PTC reaction was carried out using the described procedure except 40% (w/w) NaOD/D_2O (from Aldrich) was used as base, A 37% deuterium incorporation was observed at the C-4 methine position of the Michael adduct **5**; b) the Michael adduct **5**, isolated by flash chromatography, was subjected to the PTC conditions (5% $BnEt_3NCl$, 40% NaOD/D_2O, toluene, rt, 14 h), no deuterium incorporation was observed at the C-4 methine position of **5**.

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