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A Highly Efficient Synthesis of RWJ 47639: A Novel, Orally Active Angiotensin II Receptor Antagonist.

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Abstract: RWJ 47639 (**1**), a new, potent and orally active angiotensin II receptor antagonist was synthesized by an efficient three-step process utilizing addition of a substituted phenyllithium to an *ortho*-fluorophenyloxazoline as the key step.

As part of our search for novel heterocyclic agents which possess angiotensin II receptor activity[1] we have identified RWJ 47639 (**1**) as a potent, orally active angiotensin II receptor antagonist. Interestingly, **1** was found to be much more potent orally than would be predicted based on *in vitro* activity. RWJ 47639 (**1**) has a pA_2 of 6.9 and showed maximal activity when compared to enalapril[2a] and losartan[2b] in the spontaneously hypertensive rat (SHR) preparation.[3] Each of these compounds reduced blood pressure in the SHR from a normal level of ~185 mm Hg to 140 mm Hg.[4] RWJ 47639 (**1**) demonstrated a fast onset of action (15 minutes) and duration of >12 hours. The fast onset of action is an indication that metabolic activation is probably not occurring.

Our initial synthesis of **1** utilized previously reported intermediates and is outlined in Scheme I.[2b,5] While this is a straightforward synthesis, it required seven steps to generate **1**. We required a more efficient sequence to generate larger quantities of **1** for extended biological evaluation. Herein, we report an efficient, novel three-step synthesis of RWJ 47639 that is suitable for scale-up.

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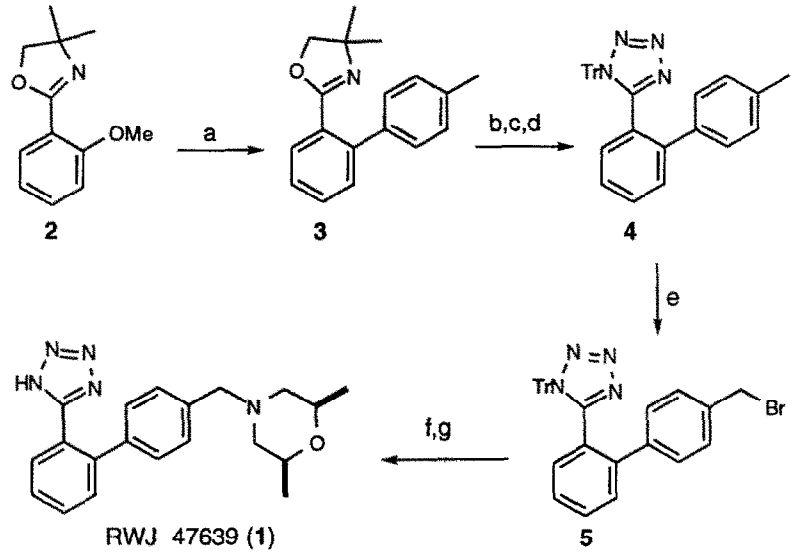
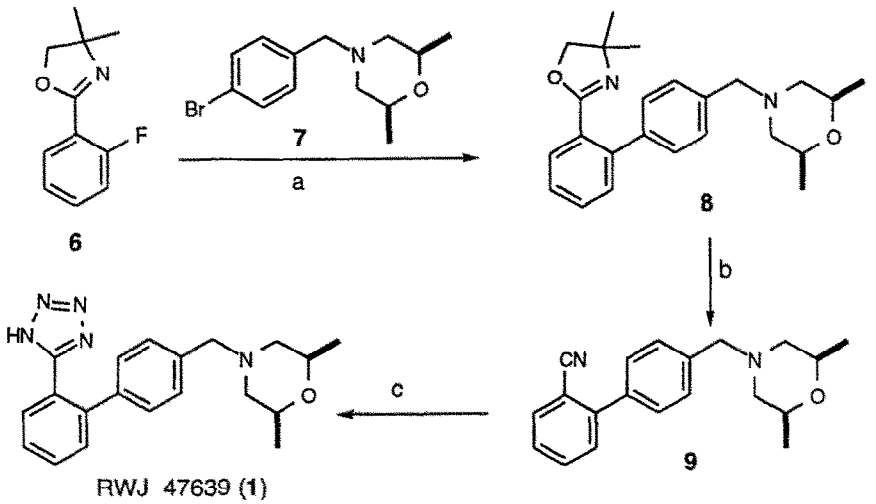
Scheme I

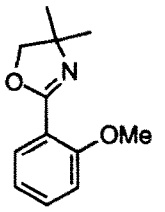


a) *p*-tolylmagnesium bromide, THF, 96%; b) $POCl_3$, pyridine, 90%; c) Bu_3SnCl, NaN_3, xylenes, 82%; d) trityl chloride, Et_3N, CH_2Cl_2, 79%; e) NBS, AIBN, CCl_4, 76%; f) 2,6-dimethylmorpholine, K_2CO_3, CH_3CN, 73%; g) 3N HCl, THF, 62%.

Scheme II



a) **7**, s-BuLi, THF, 65 °C, 67%; b) $POCl_3$, pyridine, 83%; c) Bu_3SnCl, NaN_3, xylenes, reflux, acidic work-up, 77%.



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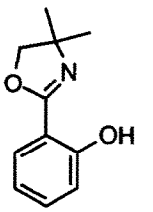

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Our improved synthesis, shown in Scheme II, begins with fluorophenyloxazoline **6**[6] and bromide **7**, which is readily available from 4-bromobenzyl bromide and 2,6-dimethylmorpholine.[7] In a slight modification of the Meyers protocol,[6] **7** was converted to the corresponding organolithium by treatment with *sec*-butyllithium. Reaction of this organolithium with **6** in refluxing THF gave the coupled biphenyloxazoline **8** in 67% yield.[8] Reaction in refluxing THF gave higher isolated yields than at room temperature. Improved yields have been previously obtained in Grignard additions to methoxyphenyloxazolines when the reaction temperature was increased from room temperature to reflux in THF.[9] It should be noted that reaction of the corresponding Grignard reagent of **7** with 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline (**2**) gave large amounts of cleavage product, the corresponding phenol **10.** Side reactions of this type have also been reported by Meyers.[10]

Conversion of **8** to RWJ 47639 (**1**) was accomplished in a straightforward manner.[2b] Treatment of **8** with phosphorus oxychloride gave **9** in 83% yield. Reaction of **9** with tributyltin azide (generated from tributyltin chloride and sodium azide) in xylenes gave RWJ 47639 (**1**) in 77% yield.

In conclusion, we have described a highly efficient three-step synthesis of RWJ 47639, a new, potent, orally active angiotensin II receptor antagonist, in 43% overall yield. The synthesis utilized a Meyers coupling reaction to form the biphenyl system. It is the first reported example of the coupling of an *ortho*-fluorophenyloxazoline and an organolithium reagent incorporating a morpholino unit within it.

Acknowledgement: We wish to thank Dr. Ronald Russell for helpful discussions.

References and Notes

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4. Doses tested were 10 and 30 mg/kg po. A maximal blood pressure reduction for angiotensin inhibition in this preparation is between 45 and 50 mm Hg.

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7. The *cis*- and *trans*-dimethyl isomers of 1-(4-bromophenylmethyl)-3,5-dimethylmorpholine are easily separable by silica gel flash column chromatography. The *cis*-dimethyl stereochemistry of RWJ 47639 was confirmed by x-ray analysis of biphenylnitrile **9**. All compounds gave satisfactory ^{1}H NMR, IR, MS, and CHN analyses.

8. Preparation of biphenyloxazoline **8**: To a solution of bromide **7** (0.840 g, 2.96 mmol) in 6.0 mL of THF at -78 °C was added 4.00 mL of a 1.3M solution of *sec*-butyllithium in cyclohexane. The mixture was warmed to -65 °C over 60 min whereupon a solution of fluorophenyloxazoline **6** (0.520 g, 2.69 mmol) in 5.0 mL of THF was added. The mixture was stirred 3.5 h at room temperature then was heated 22 h at reflux. After cooling to room temperature, the mixture was quenched with 10 mL of saturated $NaHCO_3$ solution and was extracted (3x15 mL) with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hexanes:EtOAc, 1:1 to 3:7) gave biphenyloxazoline **8** (0.683 g, 67%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, 6H, J=6.3 Hz); 1.27 (s, 6H); 1.76 (t, 2H, J=11.1 Hz); 2.72 (d, 2H, J=10.4 Hz); 3.52 (s, 2H); 3.70 (m, 2H); 3.80 (s, 2H); 7.34 (m, 6H); 7.47 (d, 1H, J=7.2 Hz); 7.70 (d, 1H, J=7.5 Hz). IR (cm^{-1}): 2970, 2932, 2869, 1657, 1351, 1314, 1084, 760. MS(DCI): m/z 379 (MH^+). Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.80; H, 7.98; N, 7.25.

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