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Efficient synthesis of an androgen receptor modulator

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Abstract

An efficient synthesis of the androgen receptor modulator (***R***)-**4a** having an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one skeleton is described. Synthesis of this ring system, not readily accessible by classical Knorr cyclization methodology, was accomplished by an *ortho*-metallation strategy. Thus, lithiation of a pivaloyl-protected 7-amino-3,4-dihydro-1,4-benzoxazine using *n*-butyllithium allowed the introduction of a trifluoroacetyl group regioselectively at the 8-position. Subsequent Wittig reaction and acid catalyzed cyclization afforded the desired 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (***R***)-**4a** in very good overall yield from the corresponding benzoxazine.

Successful development of selective estrogen receptor modulators (SERMs) in hormone therapy has strengthened the growing notion among endocrinologists that orally available, selective, and non-steroidal androgens[1] that do not suffer from the liabilities of testosterone treatments[2] offer potentially safer hormone therapies for the treatment of debilitating conditions such as muscle wasting and osteoporosis. Our medicinal chemistry group has identified over the years a number of selective, non-steroidal classes of selective androgen receptor modulators (SARMs).[3] A particularly interesting structural template was 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-ones **3**.[4] In some instances, during the synthesis of these compounds, regioisomer **4** was observed in minute quantities (1–3%). This side product arose during the Knorr cyclization involving 7-aminobenzoxazine **1** and ketoester **2** (Scheme 1). In a multi-gram scale-up synthesis of **3a**, chromatographic purification and recrystallization also yielded angular regioisomer **4a**. These compounds, derived from 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-ones, proved to be potent SARMs.[5]

The interest in **4** presented us with the synthetic challenge of how to prepare this class of molecules efficiently in the gram quantities needed for in vivo pharmacological studies. Herein, we describe an efficient synthesis of **4a** in excellent enantiopurity and in very good overall yield employing a regioselective metallation strategy.

An efficient, scaleable synthesis of aminobenzoxazine **1** in enantiopure form has been developed for the preparation of **3a**.[4] Thus, the focus of our strategy toward **4a** was centered on this key intermediate as the starting point.

Our initial efforts focused on altering the regiochemical bias in the Knorr cyclization[6] toward the desired angular quinolinone regioisomer. The two-step sequence in this synthesis involves initial formation of anilide **5** followed by electrophilic cyclodehydration catalyzed by strong acids such as sulfuric and polyphosphoric acid at elevated temperatures. Cyclodehydration has also been known to be catalyzed by Lewis acids.[3b] We were intrigued by the possibility of driving the reaction toward the angular quinolinones by using a bidentate Lewis acid through a potential template effect by chelating to both the carbonyl and the *O*-alkyl group (Scheme 2).[7] A number of Lewis acids were

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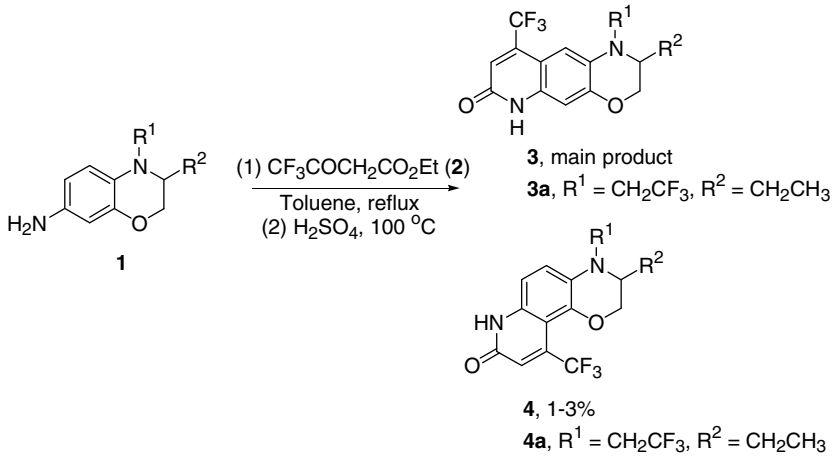
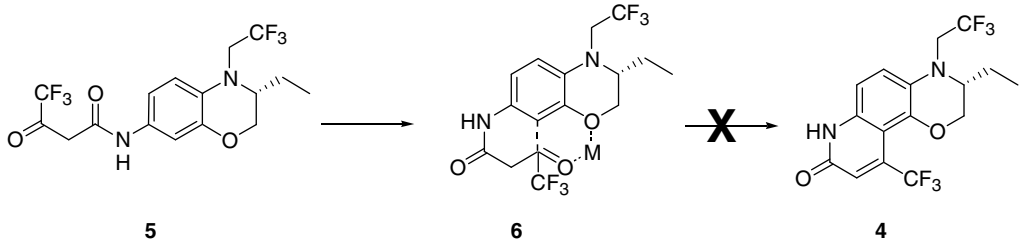


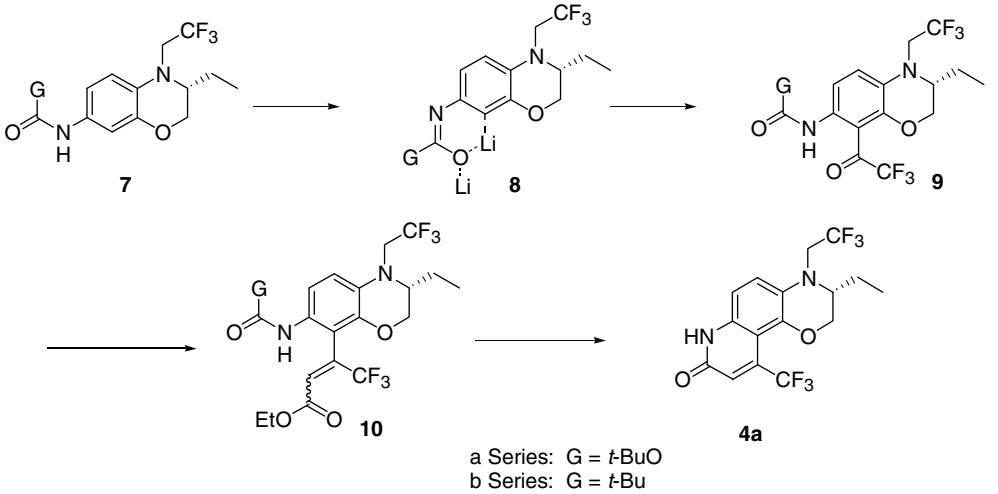
Scheme 1.



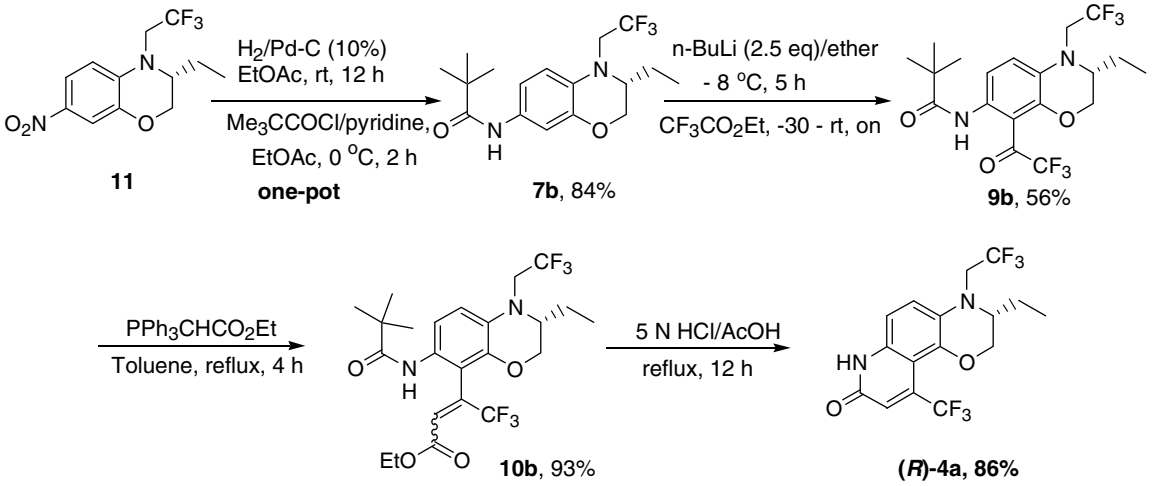
Scheme 2.

examined as catalysts such as $ZnCl_2$, $MgCl_2$, $Cu(OTf)_2$, and $Yb(OTf)_3$. To our disappointment, none of the reactions produced any noticeable selectivity for the angular isomer.

Our unsuccessful attempts in reversing the regioselectivity in the electrophilic cyclization forced our attention to functionalizing the aromatic ring by *ortho*-metallation. Directed lithiation of *t*-butylcarbamates[8] and pivalamides[9] of anilines is well known. We reasoned that the combined *ortho*-directing influence of carbamate/amide and benzoxazine oxygens should direct the protophilic attack *ortho* to the benzoxazine oxygen. Treatment of the resulting dianion with a trifluoroacetate electrophile should afford the trifluoroacetyl derivative. We further envisaged a Wittig reaction strategy to elaborate this intermediate to the desired quinolinone **4a** (Scheme 3).[10] Recently Schlosser and co-workers[10b] have reported a similar strategy for the preparation of substituted quinolinones.



Scheme 3.



Scheme 4.

Due to the ease of removal, we initially chose the *t*-butyl carbamate of **7a** for our lithiation strategy. Thus, the treatment of carbamate **7a** with a slight excess (2.4 equiv) of *t*-BuLi in ether at −20 °C for 3 h, followed by quenching with ethyl trifluoroacetate furnished the desired acetyl derivative **9a** in 25% yield. Attempts to improve the yield by varying temperature (0–20 °C), reaction time (2–8 h), metallating agent (*t*-BuLi, *sec*-BuLi), solvent (THF, ether, TBME), and additives (TMEDA) showed only marginal improvement. Poor yields and the need to use pyrophoric *t*-butyllithium[8b] prompted us to consider the pivaloylamide for lithiation. Thus, metallation of pivalamide **7b** with *n*-butyllithium at −8 °C in diethyl ether, we were pleased to find, went smoothly affording the trifluoroacetyl derivative **9b** in 50% isolated yield.

With a practical protocol to **9b** now secured, we proceeded to develop an efficient scaleable synthesis of **4a** starting from the nitrobenzoxazine **11**. As outlined in Scheme 4, reduction of **11** by catalytic hydrogenation followed by treatment with pivaloyl chloride in a one-pot operation furnished pivalamide **7b** in very good overall yields. Lithiation of **7b** with *n*-butyllithum in diethyl ether followed by quenching with ethyl trifluoroacetate furnished the trifluoroacetyl derivative in 56% isolated yield on a 50 g scale reaction. Wittig reaction using carbethoxymethylene triphenylphosphorane in refluxing toluene furnished the cinnamate **10b** in 93%, as predominently the trans isomer (cis/trans 1/9). Hydrolysis of the crude pivalamide and concomitant cyclization to the quinolinone was accomplished by heating with 5 N HCl in acetic acid to afford (*R*)-**4a** in 86% isolated yield.

In conclusion, an efficient synthesis of **4a** is described. Our synthesis demonstrates the utility of *ortho*-metallation as an excellent practical strategy toward the preparation of isomeric carbostyrils that are not accessible by the traditional Knorr cyclization. In our SARM program, this method has proved useful for the large-scale preparation of analogues for in vivo studies.

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