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A New Strategy for the Construction of the Imidazo[1,5-*a*]quinoxalin-4-one Ring System and Its Application to the Efficient Synthesis of BMS-238497, a Novel and Potent Lck Inhibitor

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Abstract: A new efficient strategy was developed for the construction of the imidazo[1,5-*a*]quinoxalin-4-one ring system. The new method involves condensation of *o*-nitroaniline with glyoxylate in methanol followed by treatment of the resulting α-(*o*-nitroanilino)-α-methoxy acetate with tosylmethyl isocyanide (TosMIC) reagent to give 1-(*o*-nitrophenyl)-imidazole-5-carboxylate. Reductive cyclization of the nitro imidazole carboxylate afforded imidazo[1,5-*a*]quinoxalin-4-one in three steps and 60% overall yield. The new method was successfully applied to the synthesis of BMS-238497, a novel and potent Lck inhibitor.

Imidazo[1,5-*a*]quinoxalines and related imidazo[1,5-*a*]-quinoxalin-4-ones are important heterocycles in the synthesis of a variety of biologically important and medicinally useful agents. For example, they were used in the synthesis of GABA/benzodiazepine receptor agonists/antagonists,[1] cAMP and cGMP phosphodiesterase inhibitors,[2] and A_1- and A_{2a}-adenosine receptor agonists,[3] in addition to many other pharmacologically active compounds.[4−7] More recently, 4-(2-chloro-6-methylphenylamino)-7,8-dimethoxyimidazo[1,5-*a*]quinoxaline (**1**; BMS-238497) emerged as a novel and potent inhibitor of Src-family kinase $p56^{Lck}$.[8,9] BMS-238497 displays excellent enzymatic activity against Lck (IC_{50} = 2 nM) and good potency in blocking T cell proliferation (IC_{50} = 0.67 μM).[8,9] To support further characterization and SAR study on this compound, we required ready access to a large amount of compound **1** as well as its precursor, 7,8-dimethoxyimidazo[1,5-*a*]quinoxalin-4-one (**2**) (Figure 1).

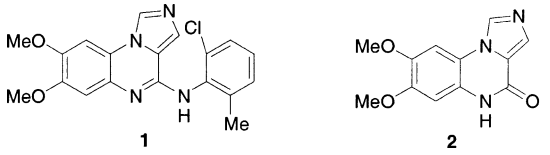

FIGURE 1.

Previously, two approaches have been reported for the construction of the imidazo[1,5-a]quinoxalin-4-one ring system.[8,10] The first approach starts with phenylene-1,2-diamines **3** and is featured by a tosylmethyl isocyanide (TosMIC) mediated imidazole ring formation of the *N*-protected quinoxalin-2-one **5**. While useful for the preparation of certain imidazo[1,5-*a*]quinoxalin-4-ones, this approach suffers a number of drawbacks such as the poor regioselectivity encountered in the formation of quinoxalin-2-ones **4** when unsymmetrical phenylene-1,2-diamines are used, the lack of control of chemoselectivity of *N*-protection vs *O*-protection during the protection step, and the difficulty in separating the regioisomers, in addition to the air sensitivity of the electron-rich phenylene-1,2-diamines **3**.

The second approach reported uses 2-fluoroanilines **9** as the starting materials and involves an intramolecular nucleophilic aromatic substitution and cyclization of 2-fluoranilino amides of imidazole-5-carboxylic acid **11**.[12] This approach is much more efficient compared with the previous one. However, this approach is not without limitations. It was found that the intramolecular nucleophilic aromatic substitution and ring closure failed with electron-rich fluoroanilines (e.g. R = OMe).

To address the above-mentioned problems and to develop a potentially more general method amenable for large-scale synthesis of imidazo[1,5-*a*]quinoxalines and related compounds, a new approach was investigated that differs strategically from the previous methods in term of the order and the way the heterocylic rings are constructed. Herein, we describe a new efficient method for the construction of such ring systems which is featured by a preformation of the 1-(2-nitroaryl)-5-ethoxycarbonylimidazole ring **14** via reaction of α-(*o*-nitroanilino)-α-methoxy acetate **13** with TosMIC reagent followed by a reductive ring closure of the nitro ester **14** to form the desired compounds (Scheme 2).

Thus, treatment of 2-nitro-4,5-dimethoxyaniline **12** with ethyl glyoxylate in methanol under reflux overnight afforded a novel compound, ethyl α-methoxy-α-(2-nitro-4,5-dimethoxy)anilino acetate **13**.[13] After the solution was cooled to room temperature, the crystalline compound **13**

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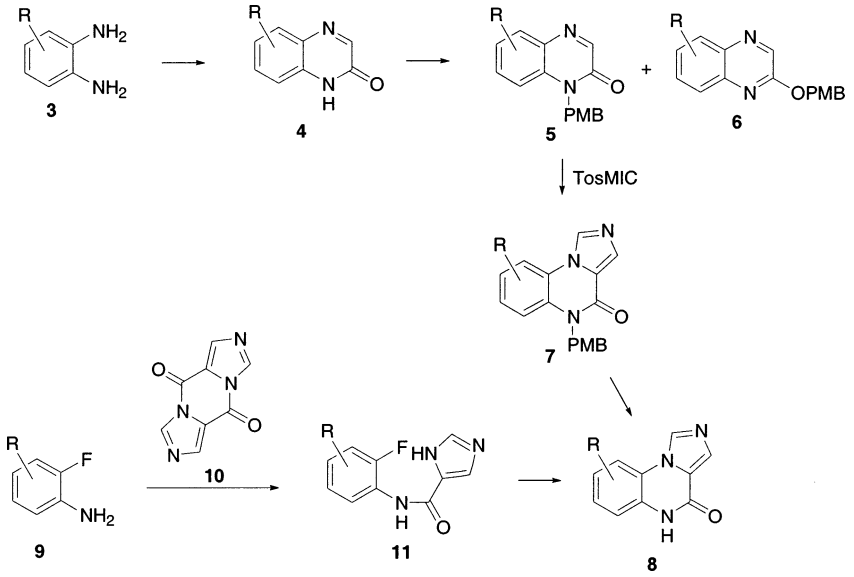
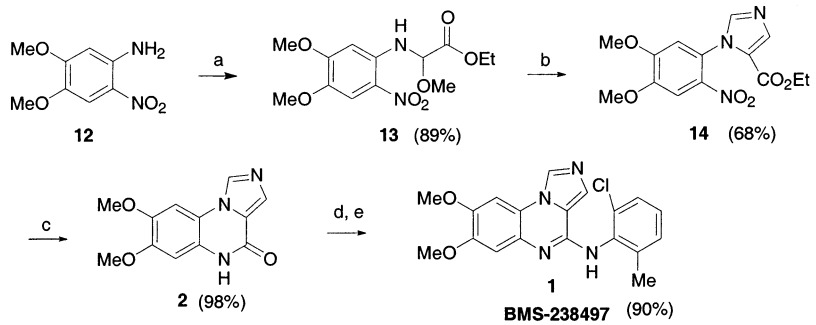
SCHEME 1



SCHEME 2[a]



[a] Reagents and conditions: (a) $OHCCO_2Et$/MeOH, 17 h; (b) TosMIC/K_2CO_3, EtOH, 50 °C, 4 h; (c) $Na_2S_2O_4$, HOAc/H_2O, 105 °C, 6 h; (d) $POCl_3$, Et_3N, reflux; (e) 2-Cl-6-$MeC_6H_3NH_2$/NaHMDS, THF, 70 °C.

was isolated by filtration in 89% yield. Reaction of **13** with TosMIC reagent[14] in ethanol and with potassium carbonate at 50 °C for 4 h gave smoothly 1-(2-nitro-4,5-dimethoxyphenyl)imidazole-5-carboxylate **14** that was isolated by filtration in 68% after the reaction was quenched with water.[13]

Reductive cyclization of **14** to the corresponding imidazo[1,5-*a*]quinoxalin-4-one **2** was initially attempted with use of hydrogenation conditions. Treatment of **14** with formic acid and catalytic amount of palladium on charcoal in ethanol overnight gave a complex mixture of products, from which none of the desired compound **2** or its precyclized aniline intermediate was observed by LC/MS. Reduction with iron powder in acetic acid was next investigated.[15] Refluxing **14** in acetic acid in the presence of 5 equiv of iron powder for half an hour afforded cleanly the desired compound **2**; however, difficulty was encountered in isolation of product **2** from the reaction mixture due to the contamination of inorganic salts.

Finally, it was found that the combination of sodium dithionite[16] in acetic acid was the condition of choice for conducting the reductive cyclization of **14** to **2**. Treatment of **14** with 4 equiv of sodium dithionite in a mixture of acetic acid and water at 105 °C for 6 h afforded exclusively compound **2**, which was isolated by filtration in 98% yield after the reaction mixture was cooled and diluted with water. The resulting imidazo[1,5-*a*]quinoxalin-4-one **2** was next converted to the desired BMS-238497 following the reported conditions.[8]

In summary, a new efficient method has been developed for the construction of the imidazo[1,5-*a*]quinoxalin-4-one ring system. The new method involves condensation of *o*-nitroaniline with glyoxylate to give an α-(*o*-nitroanilino)-α-methoxy acetate followed by treatment with TosMIC reagent to afford 1-(*o*-nitrophenyl)imidazole-5-carboxylate. Reductive cyclization of the nitro imidazole carboxylate affords imidazo[1,5-*a*]quinoxalin-4-one in three steps and 60% overall yield. The new process was readily scaled up and no chromatographic separation of products was involved. The new method has also been successfully applied to the large-scale synthesis of the novel Lck inhibitor, BMS-238497, and related compounds.

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Experimental Section

α-(4,5-Dimethoxy-2-nitrophenylamino)-α-methoxyacetic acid ethyl ester (13): In a 2-L round-bottomed flask equipped with a magnetic stirrer was placed 4,5-dimethoxy-2-nitroaniline[17] (**12**, 59.0 g, 297 mmol) and methanol (1 L). The mixture was stirred at room temperature under argon. Ethyl glyoxylate (270 mL, 50% in toluene) was added. The reaction mixture was stirred at 65 °C for 17 h and cooled to room temperature. The resulting slurry was filtered and washed with methanol (100 mL) and heptane (100 mL). The cake was dried under vacuum at 45 °C overnight to give α-(4,5-dimethoxy-2-nitrophenylamino)-α-methoxyacetic acid ethyl ester (**13**), 83.3 g (89%). Mp 118−119 °C. ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 3.34 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 5.35 (d, J = 5.8 Hz, 1H), 6.59 (s, 1H), 7.67 (s, 1H), 9.13 (d, J = 5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.4, 55.8, 56.7, 56.8, 62.7, 82.2, 106.9, 107.9, 140.4, 142.1, 142.3, 157.3, 167.8. Anal. Calcd for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.52; H, 5.59; N, 8.91.

3-(4,5-Dimethoxy-2-nitrophenyl)imidazole-4-carboxylic acid ethyl ester (14): To a 2-L round-bottom flask equipped with a magnetic stirrer was added α-(4,5-dimethoxy-2-nitrophenylamino)-α-methoxyacetic acid ethyl ester (**13**, 32.95 g, 104.84 mmol), tosylmethyl isocyanide (27.04 g (138.50 mmol), and absolute ethanol (1.44 L). The reaction mixture was stirred under argon and potassium carbonate (36.15 g, 261.56 mmol) was added. The suspension was heated to ∼50 °C and stirred for 4 h. The reaction mixture was then concentrated under reduced pressure at ∼50 °C. The resulting residue was slurried in water. The suspended solids were isolated by filtration and washed with water. The wet cake was slurried in 2-propanol (50 mL) and then heptane (100 mL). The wet cake was dried at 45 °C to give 3-(4,5-dimethoxy-2-nitrophenyl)imidazole-4-carboxylic acid ethyl ester (**14**), 23.00 g (68%). Mp 139−140 °C. ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 6.80 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 14.5, 57.1, 57.2, 61.6, 107.8, 108.4, 112.0, 125.0, 137.5, 138.5, 141.8, 149.8, 153.6, 159.9. Anal. Calcd for $C_{14}H_{15}N_3O_6$: C, 52.34; H, 4.71; N, 13.08. Found: C, 52.26; H, 4.59; N, 12.84.

7,8-Dimethoxyimidazoquinoxalin-4-one (2): To a 1-L round-bottom flask equipped with a magnetic stirrer was added 3-(4,5-dimethoxy-2-nitrophenyl)imidazole-4-carboxylic acid ethyl ester (**14**, 19.36 g, 60.26 mmol), glacial acetic acid (100 mL), and water (100 mL). The mixture was stirred to give a slurry and sodium dithionite (41.97 g, 241.03 mmol) was added. The reaction mixture was heated to 105 °C and stirred for 6 h under nitrogen. Water (500 mL) was added and the slurry was cooled to room temperature. After 2 h of stirring, the slurry was filtered. The cake was washed with water (3 × 50 mL) and dried in a vacuum oven at 45 °C for 42 h to give 7,8-dimethoxyimidazoquinoxalin-4-one (**2**), 14.43 g (98%). Mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H), 3.87 (s, 3H), 6.90 (s, 1H), 7.79 (s, 1H), 7.81 (s, 1H), 9,02 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 56.0, 56.8, 100.3, 100.5, 113.5, 122.6, 122.7, 130.8, 133.0, 145.4, 148.5, 154.0. Anal. Calcd for $C_{12}H_{11}N_3O_3 \cdot 0.2H_2O$: C, 57.92; H, 4.62; N, 16.89. Found: C, 57.80; H, 4.55; N, 16.60.

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