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Synthesis of unsymmetrical and regio-defined 2,3,6-quinoxaline and 2,3,7-pyridopyrazine derivatives

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Abstract—Differential reactivity of the amine functionality in a number of common 1,2-diamine starting materials is exploited to undertake an expedient synthesis of unsymmetrical 2,3,6-trisubstituted quinoxaline and unsymmetrical 2,3,7-trisubstituted pyridopyrazine derivatives.

The quinoxaline and pyridopyrazine nuclei have been a source of great interest to organic, medicinal, and materials scientists over many years.[1] For example, recent reports in the area of medicinal chemistry have described quinoxalines, or pyridopyrazines, as inhibitors of cyclophilin A,[2] JSP-1,[3] AMPA,[4] ACE,[5] PKB/Akt,[6] CCR4,[7] and EGF/PDGF[8] amongst others. Unsymmetrical 2,3-disubstituted versions of both quinoxaline and pyridopyrazine heterocycles, in which a substituent is also present on the benzenoid or pyridinoid ring, have been described less in the literature. This is in part because few methods have been described to make these compounds in a regio-defined manner.[9] As part of an internal drug discovery program, we required an expedient synthesis of such molecules (e.g. **1**, Fig. 1). [10] Thus, in this Letter, we would like to detail a method to prepare a number of regio-defined 2,3,6-trisubstituted quinoxaline and 2,3,7-trisubstituted pyridinopyrazine derivatives.

Our approach to the synthesis of quinoxaline derivatives employed 4-nitrobenzene-1,2-diamine **3** as the starting material. The use of this compound allowed us to establish differential reactivity between the two amino-groups by the presence of an electron-withdrawing 4-nitro substituent. Compound **3** could be selectively reacted with acetic anhydride to provide the mono-acylated adduct in 95% yield and with complete control of regiochemistry. Carbodiimide-mediated coupling with the α-keto acid, thiophene-2-glyoxylic acid, next gave diamide **4**. Thiophene-2-glyoxylic acid was chosen as a representative α-keto acid for this synthesis as the thiophene moiety was a key part of an emerging pharmacophore for molecules with kinase inhibitor activity. Intermediate **4** was then cyclized to the desired quinoxaline **5** by the action of 1 M hydrochloric acid in refluxing methanol (Scheme 1). Product purification consisted of allowing the reaction mixture to cool to room temperature and filtering to afford **5** as one pure regioisomer.[11]

The differential reactivity present in 4-nitrobenzene-1,2-diamine **3** allowed us to selectively prepare a complementary regioisomer **6**, by reaction with the acid

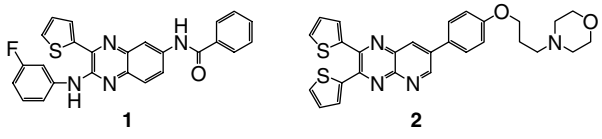
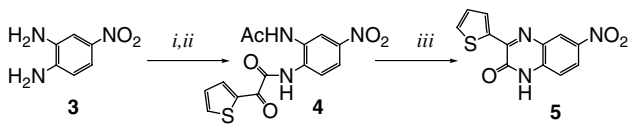


Figure 1. Unsymmetrical quinoxaline and lead pyridopyrazine.



Scheme 1. Reagents and conditions: (i) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to rt (95%); (ii) 2-thiophene-glyoxylic acid, EDCI, Et_3N, CH_2Cl_2, rt; (iii) 1 M HCl, MeOH, reflux (70% over two steps).

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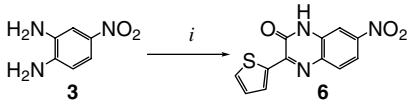
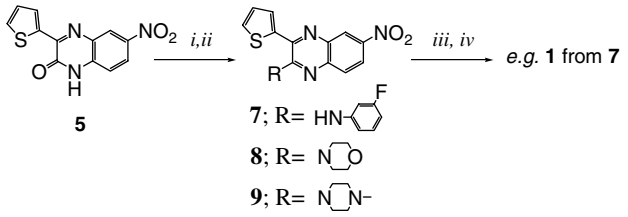


Scheme 2. Reagents and conditions: (i) 2-oxo-2-(thiophen-2-yl)acetyl chloride, Et_3N, CH_2Cl_2, 0 °C to reflux (70%).

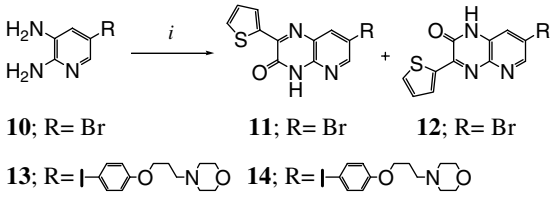


Scheme 3. Reagents and condtions: (i) $POCl_3$, DMF 110 °C (95%); (ii) $RNHR_1$, ^{i}PrOH, 100 °C (ca. 90%); (iii) H_2, Pd(C), MeOH, 40 °C (89%); (iv) R_2COCl, Et_3N, CH_2Cl_2 (70%).

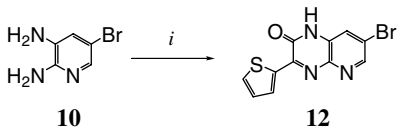
chloride of thiophene glyoxylic acid (Scheme 2). The reaction proceeded with excellent regioselectivity to provide **6** as one pure regioisomer in high yield.

Lactams **5** and **6** could be chlorinated and displaced with amines or anilines to provide regio-defined unsymmetrical quinoxaline derivatives (for clarity, only reactions with compound **5** are shown; yields are comparable with the other regioisomer). After displacement, the nitro group could then be reduced and the resulting aniline coupled with various acid chlorides to afford a range of amide final compounds (Scheme 3). For example, compound **1** was prepared from intermediate **7**.[10]

Our synthesis of regio-defined 2,3,7-trisubstituted pyridopyrazines used a similar concept to the quinoxaline derivatives above, starting from commercially available 5-bromo-2,3-diaminopyridine **10**. It was reasoned that the presence of an electron-withdrawing pyridyl nitrogen would lead to differential reactivity between the two amino-substituents in **10**, thus allowing an ability to construct compounds in a regioselective manner. To our delight, this hypothesis was confirmed by the reaction of **10** with 1 equiv of 2-thiopheneglyoxylic acid in refluxing ethanol to provide an 85:15 mixture of pyridopyrazones **11** and **12** as judged by proton nuclear magnetic resonance (NMR) spectroscopy (Scheme 4). Although **11** and **12** could be separated at this stage by repeated filtration from hot ethanol (**12** was less



Scheme 4. Reagents and condtions: (i) 2-thiopheneglyoxylic acid, EtOH, reflux (when R = Br, **11**:**12** formed in 85:15 ratio).



Scheme 5. Reagents and condtions: (i) 2-oxo-2-(thiophen-2-yl)acetyl chloride, Et_3N, CH_2Cl_2, 0 °C to reflux (60–70%).

soluble), it was more convenient to perform additional transformations on the regioisomeric mixture. Separation was easily accomplished later by standard column chromatography. Interestingly, an analogous reaction with a 5-aryl starting material **13** gave pyridopyrazone **14** as one pure regioisomer, albeit in ca. 30% yield. The reduced efficiency of this transformation is likely due to the formation of a salt between the coupling partners.

In an analogous fashion as to that described for the synthesis of quinoxalines above, the reaction of **10** with the acid chloride of 2-thiophene glyoxylic acid gave the pyridopyrazone regioisomer **12** as one pure compound (Scheme 5).

The structure of compounds **5** and **6** was confirmed by NMR spectroscopy. The presence of a nuclear Overhauser effect (NOE) between distinguishable aromatic protons and the lactam NH enabled the structure to be definitively assigned. Similarly, the structure of compound **12** was confirmed by a positive NOE, while compound **11** lacked an NOE correlation upon irradiation of the lactam NH (Fig. 2).

To prepare a large set of unsymmetrical derivatives, compound **14** was reacted with Vilsmeir's reagent ($[Me_2N{=}CHCl]^+Cl^-$) in a mixture of DMF and 1,2-dichloroethane at 80 °C to give the chloro-derivative **15** in 40–58% yield.[12] A range of transformations were then investigated to gain access to a diverse array of 2,3,7-unsymmetrical derivatives (Scheme 6). For instance, **15** could participate in a number of cross-coupling reactions providing entry into the regio-defined 2,3,7-triaryl or 3-alkyl-2,7-diaryl derivatives. For example, a Suzuki reaction with 5-formyl-thiophene-2-boronic acid gave a product (**16**), in which a formyl group was regioselectively introduced into lead structure **2**.[13] The formation of 3-alkyl-2,7-diaryl derivatives, such as **17** and **18**, was accomplished using an iron-mediated coupling with a Grignard reagent.[14] A palladium-catalyzed coupling with $Pd(Ph_3P)_4$ (30 mol %) and 10 equiv

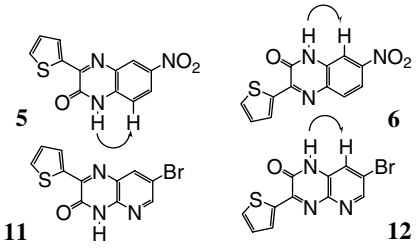
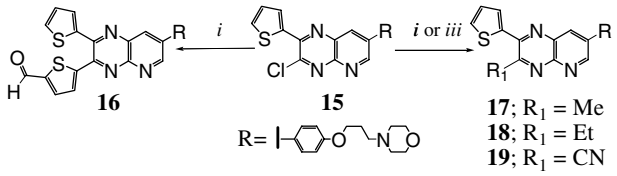


Figure 2. Use of NOE studies to determine the structure.



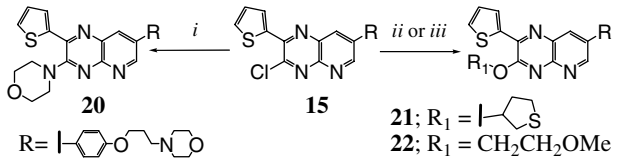
Scheme 6. Reagents and condtions: (i) 5-formyl-2-thiopheneboronic acid, $PdCl_2(dppf)$, K_2CO_3, H_2O, 1,4-dioxane, reflux (or microwave at 110 °C); (ii) RMgI, $Fe(acac)_3$, THF, NMP, rt (low yield); (iii) $Pd(Ph_3P)_4$, $Zn(CN)_2$, DMF, 100 °C, microwave (50–60%).

of $Zn(CN)_2$ was used to incorporate a nitrile group, giving **19** in good yield. Other methods for nitrile formation, such as displacement with NaCN, KCN, or CuCN, did not yield any product. Indeed, the choice of catalyst for this reaction proved to be of crucial importance, as $PdCl_2(dppf)_2$ failed to yield any of the desired nitrile **19** upon reaction with $Zn(CN)_2$.

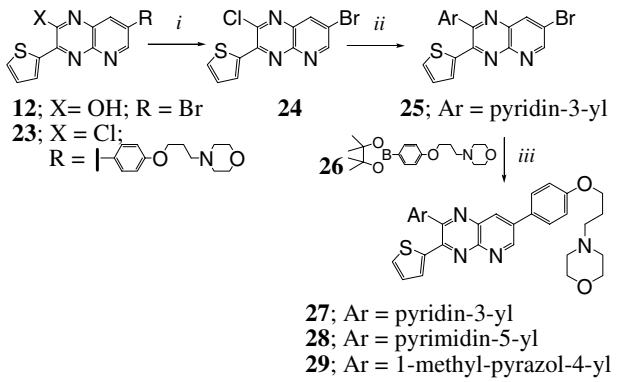
Displacement reactions of **15**, using either nitrogen or oxygen nucleophiles, were also successful (Scheme 7). The latter were reacted via their DBU salts[15] when displaced with a secondary alcohol, such as tetrahydrothiophen-3-ol,[16] to give **21**. Reaction with primary alcohols to give adducts such as **22** was accomplished using a Pd(0)-mediated coupling[17] in toluene as a solvent.[18]

Preparation of regioisomeric analogues proved to be more of a challenge as all attempts to synthesize **23** failed. Instead, a three-step procedure from lactam **12** was devised (Scheme 8). First, **12** was reacted with $POCl_3$ to give chloride **24**. A series of Suzuki reactions were then undertaken to prepare the desired regioisomeric pyridopyrazines. For example, **24** was cross-coupled with pyrdine-3-boronic acid to give the mono-pyridyl adduct **25** in moderate yield (30–40%). The bromide in **25** was then coupled further using boronic ester **26** to give the final 2,3,7-triaryl derivative **27**. The same general strategy was also used to prepare related regio-defined 2,3,7-triaryl derivatives **28** and **29** using an identical reaction sequence.

In conclusion, we have shown that differential reactivity between two amino groups in an aromatic 1,2-diamine starting material can be exploited to obtain a number of regio-defined unsymmetrical 2,3,6-quinoxaline, or 2,3,7-pyridopyrazine derivatives. Our approach to 2,3,7-pyridopyrazines is particularly noteworthy, as the use of palladium- and iron-mediated cross-coupling



Scheme 7. Reagents and condtions: (i) morpholine, ^{i}PrOH, 100 °C (ca. 70%); (ii) (a) DBU, DMSO, rt, (b) NaH, tetrahydrothiophen-3-ol, THF, 0 °C to reflux (ca. 30%); (iii) $HOCH_2CH_2OMe$, $Pd(OAc)_2$, Cs_2CO_3, 2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, toluene, 70 °C, microwave (ca. 50%).



Scheme 8. Reagents and condtions: (i) $POCl_3$ (30%); (ii) $ArB(OH)_2$ or boronic ester, $PdCl_2(dppf)_2$, K_2CO_3, H_2O, 1,4-dioxane, microwave at 110 °C (30–40%); (iii) **26**, $PdCl_2(dppf)_2$, K_2CO_3, 1,4-dioxane, microwave at 110 °C (60%).

reactions could be utilized to obtain isomerically pure 2,3,7-triaryl or 3-alkyl-2,7-diaryl compounds, respectively. The general approach outlined in this Letter will likely be of interest to those working in the fields of medicinal or materials chemistry, where the quinoxaline and pyridopyrazine nuclei have demonstrated usefulness.

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11. *Data for compound* **5**: ^{1}H NMR (300 MHz; DMSO-d_6) δ 13.15 (1H, s), 8.52 (1H, d, $J = 2.4$ Hz), 8.45 (1H, dd, $J = 3.9$, 1.2 Hz), 8.34 (1H, dd, $J = 9.0$, 2.4 Hz), 7.94 (1H, dd, $J = 4.8$, 1.2 Hz), 7.48 (1H, d, $J = 9.0$ Hz), 7.28 (1H, dd, $J = 5.1$, 3.9 Hz). $m/z = 274$ (M+1).
12. This reaction proved to be particularly capricious. Careful control of temperature, concentration and the ratio of DMF: 1,2-DCE proved to be crucial for a successful outcome.
13. Other Suzuki couplings with **15** were performed using the following boronic acids or esters to give coupled products in 30–50% yield: phenyl, 3-furyl, 3-pyridyl, 4-pyridyl, 5-pyrimidyl, isoxazol-4-yl, 3,5-dimethyloxazol-4-yl and 1-methylpyrazol-4-yl. Reaction with imidazole-4-boronic acid resulted in hydrolysis of the starting material.
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18. The importance of the palladium catalyst for this transformation was not investigated as the corresponding reaction conducted in the absence of $Pd(OAc)_2$, or ligand, was not performed. However, previous efforts to directly displace the chloro-group from compound **15** using either an alcohol or an alkoxide were unsuccessful.