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Synthesis of Pyridopyrazine-1,6-diones from 6-Hydroxypicolinic Acids via a One-Pot Coupling/Cyclization Reaction

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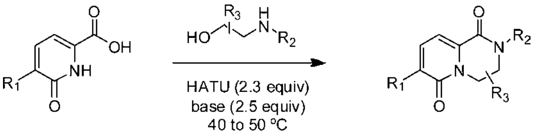
ABSTRACT



A facile one-pot synthesis of 3,4-dihydro-1*H*-pyrido[1,2-*a*]pyrazine-1,6(2*H*)-diones (pyridopyrazine-1,6-diones) has been developed which employs a sequential coupling/cyclization reaction of 6-hydroxypicolinic acids and β-hydroxylamines. The transformation proceeds in good yield under mild conditions using *O*-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to both carry out the amide formation and activate the hydroxyl group for intramolecular alkylation.

In the context of a recent medicinal chemistry program, we sought to convert a series of amides **1** into the corresponding conformationally restricted pyridopyrazine-1,6-dione derivatives **2** (Figure 1).[1] Introduction of conformational constraint is a common strategy in medicinal chemistry to improve potency by locking the molecule in its putative pharmacologically active conformation as well as to improve permeability and bioavailability by reducing the number of rotatable bonds.[2]

Several recent analyses have highlighted the importance of controlling physicochemical properties in drug design, in particular, reducing the lipophilicity of drug molecules.[3] High lipophilicity has been linked not only to increased risk of toxicity[4] but also to poor pharmacokinetic properties.[5,6] Therefore, given the increased polarity of pyridopyrazine-1,6-dione **2** relative to pyridyl amide **1**, this bicyclic ring system represents a potentially valuable structural motif in medicinal chemistry.

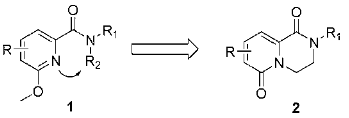


Figure 1. Genesis of the pyridopyrazine-1,6-dione ring system.

Surprisingly, a survey of the literature revealed only two distinct approaches related to this particular bicyclic system. Both methods start with a piperazinone intermediate onto which the aromatic portion is constructed and require

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(1) *Pfizer Inc.* WO12131539; 2012.

(2) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615–2623.

(3) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discovery* **2007**, *6*, 881–890.

(4) Hughes, J. D.; Blagg, J.; Price, D. A.; Bailey, S.; DeCrescenzo, G. A.; Devraj, R. V.; Ellsworth, E.; Fobian, Y. M.; Gibbs, M. E.; Gilles, R. W.; Greene, N.; Huang, E.; Krieger-Burke, T.; Loesel, J.; Wager, T.; Whiteley, L.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872–4875.

(5) Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, T. *ACS Chem. Neurosci.* **2010**, *1*, 420–434.

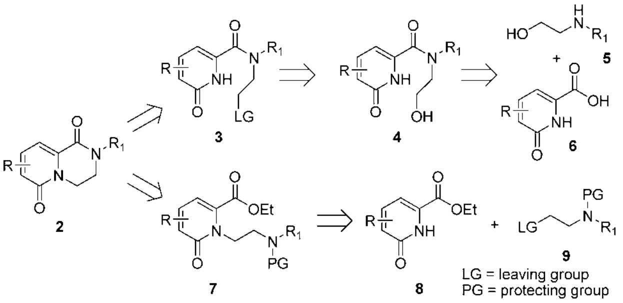
(6) Wager, T. T.; Hou, X.; Verhoest, P. R.; Villalobos, A. *ACS Chem. Neurosci.* **2010**, *1*, 435–449.

10.1021/ol303463e

multistep syntheses that proceed in low overall yield.[7,8] The lack of a general and efficient synthesis of the pyridopyrazine-1,6-dione scaffold provided an impetus for the development of a new synthetic approach to this potentially valuable but relatively unexplored heterocyclic ring system. Herein, we report a novel one-pot coupling/cyclization reaction for the efficient assembly of pyridopyrazine-1,6-diones **2**.

We envisioned two potential approaches to construct the pyridopyrazine-1,6-dione system starting from a series of readily available 6-hydroxypicolinic acids (e.g., **6**) that would allow access to a diverse set of these compounds (Scheme 1). Acids **6** proved to be versatile building blocks, as a number of these are commercially available or can be easily prepared by demethylation of the corresponding 6-methoxy-picolinic acids.[9] Thus, one approach would be to prepare amide-alcohol intermediate **4** via amide coupling of acid **6** with β-hydroxylamine **5**. Subsequently, conversion of the primary hydroxyl group to a suitable leaving group followed by intramolecular alkylative cyclization would provide product **2** in a manner similar to those reported in the syntheses of cytisine and protoberberines.[10,11] Alternatively, *N*-alkylation of pyridone **8** would give rise to intermediate **7**. Deprotection and intramolecular amidation would then theoretically afford the same product. We opted to focus our efforts on the former approach to avoid potential complications resulting from competitive *N*-/*O*-alkylation of ethyl picolinate **8**.

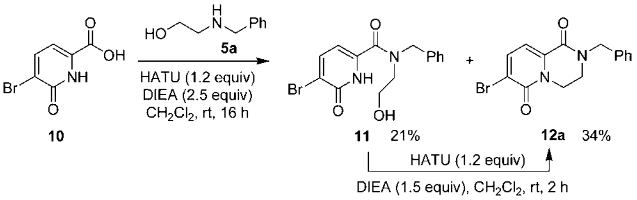
Scheme 1. Retrosynthesis of Pyridopyrazine-1,6-diones **2**



In our initial attempts to generate the amide-alcohol intermediate **11** (Scheme 2) utilizing standard peptide coupling protocols, we were surprised to find that using 1.2 equiv of the coupling reagent HATU and excess diisopropylethyl amine (DIEA) provided not only alcohol **11** but also the cyclized product **12a** along with unreacted acid **10**[12] in an approximately 1:2:2 ratio as indicated by LC/MS. Upon purification via column chromatography, intermediate **11** and pyridopyrazine-1,6-dione **12a** were isolated in 21% and 34% yield, respectively.

Formation of **12a** as a major product indicated that the cyclization step may in fact be promoted by the coupling reagent, and the observed distribution of products suggested that the initial amide coupling is likely the slowest step in the overall process. Consequently, we treated purified amide-alcohol **11** with HATU and DIEA and observed virtually complete conversion to the desired pyridopyrazine-1,6-dione **12a** as evidenced by TLC and LC/MS. It is important to note that the addition of DIEA is required for this transformation to proceed. The formation of **12a** under these reaction conditions was particularly interesting because to the best of our knowledge, there has been no report of *N*-alkylation of a heterocycle with an alcohol promoted by HATU or other peptide coupling reagents.[13] To firmly establish the role of HATU in the cyclization step, amide-alcohol **11** was subjected to a variety of conditions (thermal, acidic, basic, and exposure to silica) in the absence of HATU, and no formation of product **12a** was observed.

Scheme 2. Formation of Pyridopyrazine-1,6-dione **12a** via a One-Pot Coupling/Cyclization Reaction



These preliminary results inspired us to pursue a one-pot synthesis of the pyridopyrazine-1,6-diones directly from the acid **10**. Toward this end, the yield of the tandem coupling/cyclization reaction was improved to 55% by increasing the amount of HATU to 2.3 equiv. Further optimization revealed that warming the reaction mixture to reflux in methylene chloride resulted in complete consumption of acid **10** and increased the isolated yield of **12a** to 75%. Using these improved conditions, amide-alcohol **11** was not observed in any appreciable amount and was not recovered after column chromatography. With these optimized conditions in hand, we began to explore the

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(7) Kawahara, N.; Nakajima, T. *Heterocycles* **1983**, *20*, 1721–1725.

(8) Wai, J. S.; Kim, B.; Fisher, T. E.; Zhuang, L.; Embrey, M. W.; Williams, P. D.; Staas, D. D.; Culberson, C.; Lyly, T. A.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Schleif, W. A.; Gabryelski, L. J.; Jin, L.; Chen, I.-W.; Ellis, J. D.; Mallai, R.; Young, S. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5595–5599.

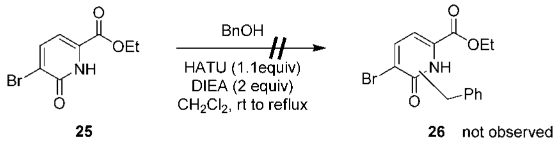
(9) Representative examples: (a) Leznoff, C. C.; Svirskaya, P. I.; Yedidia, V.; Miller, J. M. *J. Heterocycl. Chem.* **1985**, *22*, 145–147. (b) Ulbricht, T. L. V. *J. Chem. Soc.* **1961**, 3345–3348. (c) McElroy, W. T.; DeShong, P. *Tetrahedron* **2006**, *62*, 6945–6954.

(10) O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201–4204.

(11) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768–2772.

(12) While 2-pyridones and 2-hydroxypyridines exist as a tautomeric equilibrium in solution, the oxo-form predominates in polar solvents and in the solid state; see: Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645–1652.

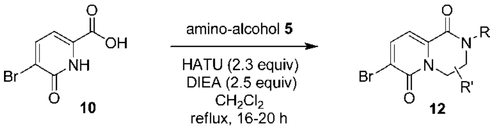
(13) The reaction below was attempted, but no alkylation product was observed.

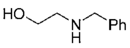
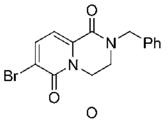
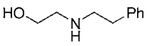
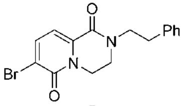
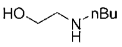
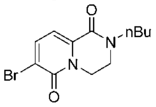
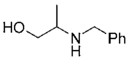
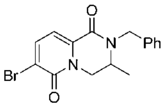
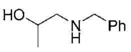
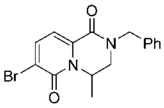
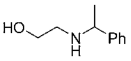
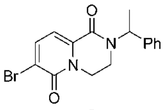
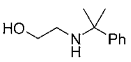
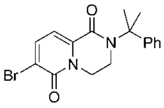


scope and limitations of this transformation, the results of which are presented in Table 1.

The tandem coupling/cyclization reaction was found to proceed in good to excellent yields when using unhindered amino alcohols (**12a**–**c**). However, substrates bearing substitution adjacent to the reacting moieties typically gave the corresponding products in lower yields, as highlighted by **12e** and **12f**. The presence of a methyl substituent at the carbon atom adjacent to the hydroxyl group reduced the yield from 75% to 29% (**12e**), while substitution near the amino group reduced the yield to 45% (**12f**). Interestingly, an α-methyl group on the ethylene linker adjacent to the nitrogen did not impede product formation as seen with **12d**, which was isolated in 69% yield. Not surprisingly, attempts to prepare **12g** from the corresponding amine **5g** did not afford any appreciable amount of the product by LC/MS and none could be isolated. Instead, the main identifiable side product was the ester arising from preferential coupling of the primary alcohol over the amino moiety (not isolated).

Table 1. Scope and Limitations of the One-Pot Pyridopyrazine-1,6-dione Synthesis



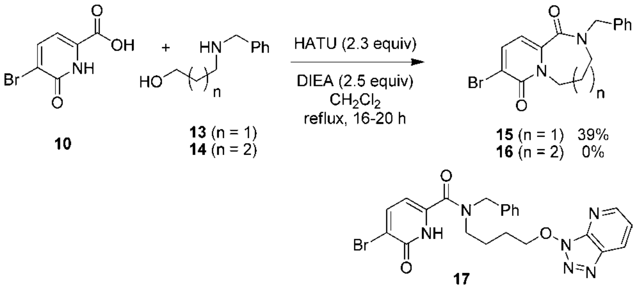
entry	amine 5a-f		product 12a-f		yield (%)
1		5a		12a	75[a]
2		5b		12b	69
3		5c		12c	82
4		5d		12d	69
5		5e		12e	29
6		5f		12f	45
7		5g		12g	0

[a] Reaction at rt gave the product in a 55% yield; TPTU gave a 46% yield.

In addition to HATU, we explored a select number of alternative peptide coupling reagents including *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI), 1,3-dicyclohexylcarbodiimide (DCC), 1-propanphosphoric acid cyclic anhydride (T3P), and *O*-(1,2-dihydro-2-oxo-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU). Among these reagents, only TPTU afforded the desired product **12a**, albeit in moderate yield (46%). This brief survey showed that HATU is clearly superior in the one-pot synthesis of pyridopyrazine-1,6-diones as compared to the other common coupling reagents that we examined.

We also sought to expand the scope of the coupling/cyclization reaction to include the formation of medium-sized rings. Thus, coupling of **10** with amino-alcohol **13** gave the seven-membered ring analogue **15** in 39% yield (Scheme 3). Intramolecular formation of seven-membered rings is typically not an efficient process, so, not surprisingly, this yield was reduced considerably as compared to **12a**. An attempt to expand to the eight-membered ring with our standard conditions failed to afford the desired product **16**, but rather gave **17** in 40% yield. This side product stems from activation of the primary hydroxyl group with the azabenzotriazole component of HATU. In fact, we were pleased to be able to isolate HOAt-ether **17**, as this provides further mechanistic support for the role of HATU in the cyclization step in this sequence.

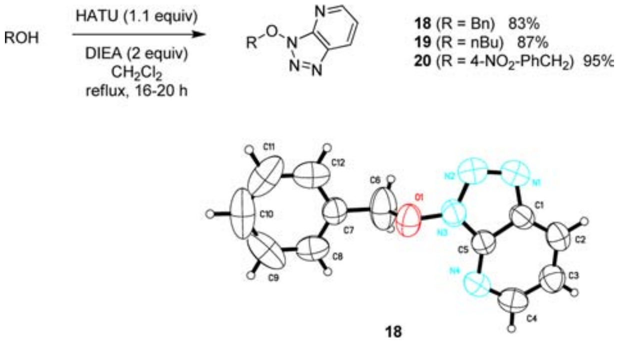
Scheme 3. Attempts To Form Medium-Size Rings



Discovery and isolation of **17** prompted us to examine the formation of HOAt-ethers by treating various alcohols with HATU and DIEA. Indeed, we were able to form the HOAt adducts **18**–**20** in high yields (Scheme 4). Additionally, single crystal X-ray analysis of **18** enabled unambiguous assignment of its regiochemistry. To the best of our knowledge, this transformation has not previously been reported.

While the initial reaction conditions for the coupling/cyclization reaction provided the 7-bromopyridopyrazine diones in good yields, inconsistent results were obtained in the synthesis of corresponding *des*-bromo analogues starting from acid **23**. Typically the intermediate amide-alcohols (analogous to **11**) were observed as the major products, whereas the desired pyridopyrazine diones were generally obtained in low yields. Postulating that the differences in pK_a's of the pyridone NH of picolinic acids **10** and **23** could be an important factor, we found that

Scheme 4. Formation of HOAt Adducts and ORTEP Diagram of X-ray Crystal Structure of **18**



substituting 1,5-diaza-bicyclo[4.3.0]-5-nonene (DBN), which has a conjugate acid pK_a of 13.5 and is more basic than DIEA (conjugate acid pK_a: 11.4), increased the yield of **24c** from 27% to 46% (Table 2).

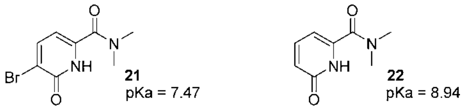
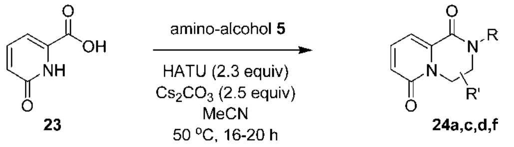


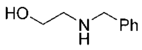
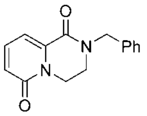
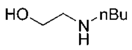
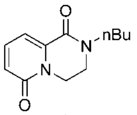
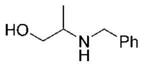
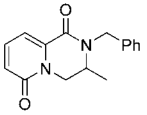
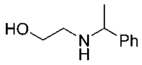
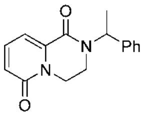
Figure 2. Effect of 5-substituent on pK_a.

To confirm the differences in pK_a as a result of the bromo substituent in the 5-position, we prepared the two standards shown in Figure 2 and measured their pK_a's according to a published procedure.[14] The pK_a's of compounds **21** and **22** were found to be 7.47 and 8.94, respectively, in an aqueous medium. Indeed, the presence of the bromide increases the acidity of the hydroxypicolinamide, lowering its pK_a by approximately 1.5 log units. As a result of this observation, a screen of various bases and solvents was undertaken.

Ultimately, cesium carbonate in acetonitrile at 50 °C gave results that were comparable to those obtained for the bromo-analogues **12a**–**f**. Using these optimized conditions, 7-H analogues **24a, 24c**, **24d**, and **24f** were obtained in good yields as shown in Table 2. Additionally, preparation of **12a** was repeated using these conditions and it was obtained in 67% yield. Thus, careful consideration of the pK_a of the starting material and selection of the suitable reaction conditions were crucial for successful optimization of this one-pot synthesis of pyridopyrazine-1,6-diones.

Table 2. Results with Cs_2CO_3/MeCN Condition



entry	amine **5a-f**		product **24a-f**		yield (%)
1		**5a**		**24a**	62
2		**5c**		**24c**	60[a]
3		**5d**		**24d**	78
4		**5f**		**24f**	47

[a] Reaction with DIEA/CH_2Cl_2/reflux gave product in 27% yield; DBN gave a 46% yield.

In conclusion, a new tandem coupling/cyclization approach to form 3,4-dihydro-1*H*-pyrido[1,2-*a*]pyrazine-1,6-(2*H*)diones starting from 6-hydroxypicolinic acids and β-hydroxyamines has been developed. Both steps in the one-pot process are mediated by HATU and proceed under mild reaction conditions to afford a series of pyridopyrazine-1,6-diones in good yields. Given the limited precedent for the construction of these bicyclic systems, our approach provides an efficient route to compounds of this class. Additionally, during these studies we discovered that alcohols readily form HOAt ethers by refluxing in CH_2Cl_2 in the presence of HATU and DIEA. Further results and applications in medicinal chemistry will be reported in due course.

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Supporting Information Available. Experimental details, ^1H and ^{13}C NMR spectra, and crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Shalaeva, M.; Kenseth, J.; Lombardo, F.; Bastin, A. *J. Pharm. Sci.* **2008**, *97*, 2581–2606.

The authors declare no competing financial interest.