ORGANIC LETTERS

2012
Vol. 14, No. 13
3546–3549

N−N Bond-Forming Cyclization for the One-Pot Synthesis of *N*-Aryl[3,4-*d*]-pyrazolopyrimidines

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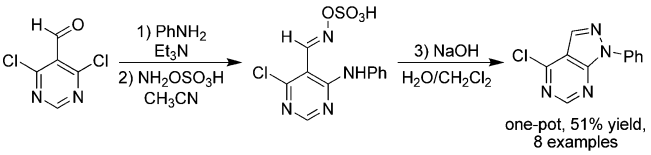
Received June 6, 2012

ABSTRACT



An efficient one-pot synthesis of *N*-aryl[3,4-*d*]pyrazolopyrimidines in good yield and under mild reaction conditions is described. By exploiting electron-deficient hydroxylamines, the substituted oxime products were formed with very high *E*-diastereoselectivity. The key step utilizes a cyclization reaction upon an oxime derived from hydroxylamine-*O*-sulfonic acid to form the N−N bond of the product.

The discovery of ATP-competitive inhibitors of protein kinases and ATPases has become one of the most active areas of research in medicinal chemistry and the pharmaceutical industry.[1] [3,4-*d*]Pyrazolopyrimidines are important scaffolds in this respect because of their ability to closely mimic the purine ring of adenosine in ATP while imparting changes to the electronic properties of the ring system and creating novel vectors for substitution. The [3,4-*d*]pyrazolopyrimidine scaffold has been used in potent inhibitors of various protein kinases and ATPases, which has led to a greater understanding of the role of these enzymes in disease and to the development of novel therapeutics.[2]

An important factor in a successful drug discovery program is the ability to synthesize a large number of structural analogues in a rapid and efficient manner, in order to establish structure−activity relationships and modify physicochemical properties of compounds. A number of approaches to the synthesis of [3,4-*d*]pyrazolopyrimidine libraries have previously been described which focused on the cyclization of hydrazine derivatives with an appropriate electrophile to incorporate the N−N bond of the ring system.[3] However, utilizing hydrazines has a number of disadvantages, including lengthy synthetic sequences, the synthesis and handling of hydrazine derivatives, low overall yields, and harsh reaction conditions. These synthetic drawbacks have so far limited the application of the pyrazolopyrimidine scaffold in medicinal chemistry.

During a recent project investigating the function of chaperonin ATPases in cancer,[4] we required the rapid synthesis of a library of ATP-mimics based on the [3,4-*d*]-pyrazolopyrimidine scaffold. To achieve this, we developed

(1) (a) Cohen, P. *Nat. Rev. Drug Discov.* **2002**, *1*, 309. (b) Zhang, J.; Yang, P. L.; Gray, N. S. *Nat. Rev. Cancer* **2009**, *9*, 28. (c) Chène, P. *Nat. Rev. Drug Discov.* **2002**, *1*, 665.

(2) (a) Staerk, J.; Lyssiotis, C. A.; Medeiro, L. A.; Bollong, M.; Foreman, R. K.; Zhu, S.; Garcia, M.; Gao, Q.; Bouchez, L. C.; Lairson, L. L.; Charette, B. D.; Supekova, L.; Janes, J.; Brinker, A.; Cho, C. Y.; Jaenisch, R.; Schultz, P. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5734. (b) Smalley, T. L., Jr.; Peat, A. J.; Boucheron, J. A.; Dickerson, S.; Garrido, D.; Preugschat, F.; Schweiker, S. L.; Thomson, S. A.; Wang, T. Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2091. (c) Honigberg, L. A.; Smith, A. M; Sirisawad, M.; Verner, E.; Loury, D.; Chang, B.; Li, S.; Pan, Z.; Thamm, D. H.; Miller, R. A.; Buggy, J. J. *Proc. Nat. Sci.* **2010**, *107*, 13075.

(3) (a) Slavish, P. J.; Price, J. E.; Hanumesh, P.; Webb, T. R. *J. Comb. Chem.* **2010**, *12*, 807. (b) Hanefeld, U.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1545. (c) Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H; Hiestand, P.; Manning, U.; Neumann, U.; Rucklin, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 262. (d) Baraldi, P. G.; Bovero, A.; Fruttarolo, F.; Romagnoli, R.; Tabrizi, M. A.; Preti, D.; Varani, K.; Borea, P. A.; Moorman, A. R. *Bioorg. Med. Chem.* **2003**, *11*, 4161. (e) Chapman, E.; Farr, G. W.; Furtak, K.; Horwich, A. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 811. (f) Boyd, S.; Campbell, L.; Liao, W.; Meng, Q.; Peng, Z.; Wang, X.; Waring, M. J. *Tetrahedron Lett.* **2008**, *49*, 7395. (g) Tan, T. M. C.; Yang, F.; Fu, H.; Raghavendra, M. S.; Lam, Y. *J. Comb. Chem.* **207**, *9*, 210.

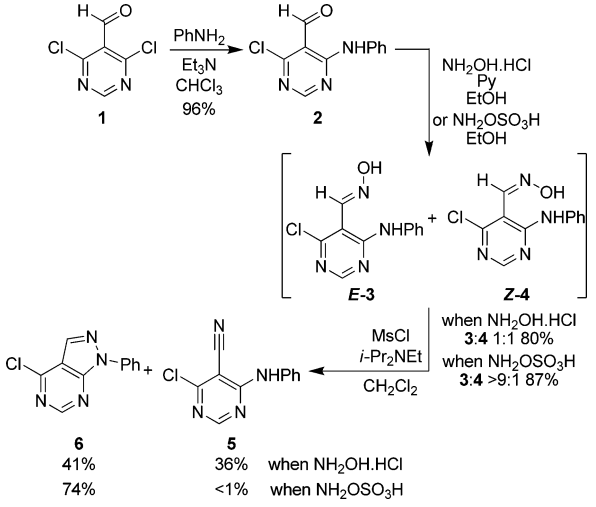
(4) For a review of the function of chaperonins, see: Horwich, A. L.; Farr, G. W.; Fenton, W. A. *Chem. Rev.* **2006**, *106*, 1917.

10.1021/ol301561a
Published on Web 06/26/2012

a novel one-pot synthesis that is readily applicable to producing analogues using commercially available starting materials and does not require metal-based catalysts or hydrazines.

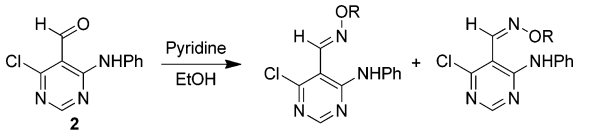
Rather than incorporating the N−N bond of the aromatic heterocycle as a preformed unit prior to cyclization, this functionality can be introduced in the key synthetic step via a cyclization reaction using an appropriately activated nitrogen source.[5] This approach negates the requirement for the synthesis and handling of hydrazines and exploits the greater number of commercially available amine derivatives, expanding the diversity of pyrazolopyrimidine libraries that could be used in drug discovery. A related N−N bond-forming cyclization reaction was previously observed by Fenniri and co-workers during their attempted *syn*-elimination of an *E*-oxime derivative to give a nitrile.[6] The undesired pyrazolopyrimidine byproduct was isolated in 28% yield.

Scheme 1. Stepwise Pyrazolopyrimidine Synthesis



We began our synthesis with a nucleophilic substitution reaction on the commercially available dichloropyrimidine aldehyde **1** with aniline to give **2** in 96% yield under standard conditions (Scheme 1).[7] No products resulting from imine formation at the aldehyde functionality were observed. The resulting pyrimidine **2** was then treated with hydroxylamine hydrochloride in ethanol to give oximes **3** and **4** as a 1:1 mixture of *E*- and *Z*-isomers.[8] Owing to decomposition during attempted chromatographic separation, the mixture was taken on to the next step without further purification.[9] Treatment of oximes **3** and **4** with mesyl chloride and *N,N*-diisopropylethylamine gave the desired pyrazolopyrimidine **6** in 41% isolated yield. It has previously been reported that only *E*-oximes can undergo N−N bond-forming cyclizations with amines to give 5-membered aromatic rings.[10] The nitrile byproduct **5** was isolated in 36% yield, presumably as a result of elimination of the *O*-mesyl-*Z*-oxime isomer intermediate, since this isomer could not undergo cyclization to form the desired product.[11]

Table 1. Substituted Hydroxylamines

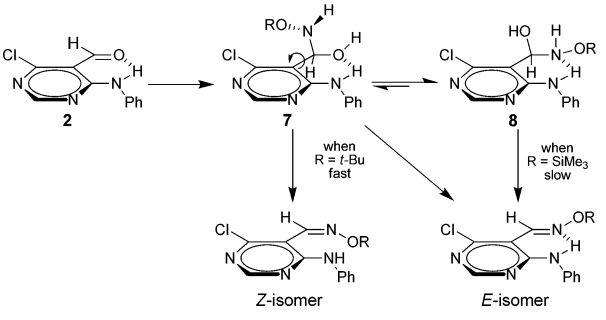


entry	hydroxylamine	*E*:*Z* ratio[b]
1	$NH_2OH \cdot HCl$	1:1
2	$NH_2OBn \cdot HCl$	1:1
3	$NH_2Ot\text{-}Bu \cdot HCl$	2:3
4	NH_2OTMS[a]	4:1

[a] Product observed as free oxime. [b] Determined by examination of crude ^1H NMR spectrum.

To improve the overall yield of the cyclization strategy it was necessary to synthesize the *E*-oxime **3** with high diastereoselectivity. The stereoselectivity of oxime formation can be difficult to control for aromatic aldehydes, with results often depending on catalyst and temperature.[12] However, in this case, changes to the reaction conditions gave little improvement in diastereoselectivity of this reaction. It had previously been proposed that *E*-oxime diastereoselectivity could be improved by increasing the steric hindrance of the *O*-substituent on the hydroxylamine.[13] To investigate this rationale, a number of oxime derivatives were generated using substituted hydroxylamines (Table 1).

Scheme 2. Oxime Stereoselectivity



(5) For examples of N−N bond formation in the synthesis of aromatic heterocycles, see: (a) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576. (b) Clayton, K. A.; Black, D. StC.; Harper, J. B. *Tetrahedron* **2008**, *64*, 3183. (c) Sugimoto, T.; Itagaki, K.; Irie, K. *Bioorg. Med. Chem.* **2008**, *16*, 650. (d) O'Dell, D. K.; Nicholas, K. M. *Heterocycles* **2004**, *63*, 373. (e) Reddy, A. C. S.; Narsaiah, B.; Venkataratnam, R. V. *Synth. Commun.* **1997**, *27*, 2217. (f) Buscemi, S.; Vivona, N.; Caronna, T. *J. Org. Chem.* **1996**, *61*, 8397. (g) Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 2501.

(6) Beingessner, R. L.; Deng, B. L.; Fanwick, P. E.; Fenniri, H. *J. Org. Chem.* **2008**, *73*, 931.

(7) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889.

(8) Diastereomeric ratio was determined by examination of the crude ^1H NMR spectrum. Configuration was determined by NOE correlation; see: Heinisch, G.; Holzer, W. *Tetrahedron Lett.* **1990**, *31*, 3109.

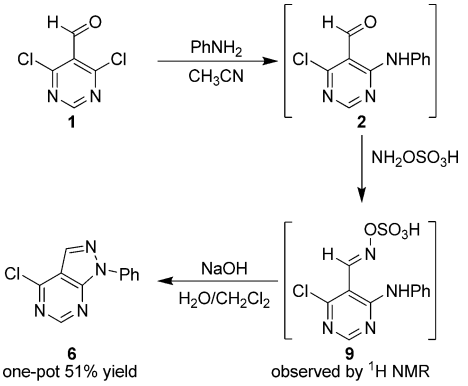
(9) All attempts at chromatographic separation resulted in decomposition. The yield refers to recovered mass and reflects a clean ^1H NMR spectrum of crude product.

It was clear from our screen that the diastereoselectivity of oxime formation was not determined by the relative steric hindrance of the *O*-hydroxylamine substituent. Increasing steric hindrance from hydroxylamine to *O*-*tert*-butylhydroxylamine actually resulted in a small preference for the formation of the *Z*-diastereomer.[14] In contrast, *O*-TMS-hydroxylamine gave increased diastereoselectivity for the desired *E*-oxime isomer. To explain the observed stereoselectivity, we proposed that the electron-withdrawing nature of the silicon substituent in *O*-TMS-hydroxylamine[15] slowed the stereodefining elimination step of oxime formation (Scheme 2). This allowed intermediate **7** to rearrange to the more stable conformer **8**, which contains an intramolecular NHN-hydrogen bond and the OR group in a pseudoequatorial conformation.[16] Conformational change prior to elimination forces the hydroxylamine derivative away from the aromatic ring so that the elimination step occurs with high *E*-stereoselectivity.

We were able to exploit this observation by utilizing the commercially available hydroxylamine-*O*-sulfonic acid as an electron-deficient hydroxylamine equivalent. Treatment of aldehyde **2** with hydroxylamine-*O*-sulfonic acid in ethanol resulted in the formation of *E*-oxime **3**, in 87% yield and $>9{:}1$ dr (Scheme 1).[17] The intermediate *O*-sulfonic acid oxime was not observed, presumably due to ethanolysis under the reaction conditions. Reaction of *E*-oxime **3** with mesyl chloride and *N*,*N*-diisopropylethylamine resulted in clean cyclization to give the desired pyrazolopyrimidine **6** in 74% yield (Scheme 1).[18]

Hydroxylamine-*O*-sulfonic acid has previously been exploited as a source of electrophilic nitrogen to synthesize N−N and N−O bonds.[19] Under our reaction conditions, no spontaneous cyclization of the *O*-sulfonic acid oxime intermediate **9** was observed. When the oxime synthesis was carried out in acetonitrile, intermediate **9** was sufficiently stable to be observed by ^{1}H NMR spectroscopy, confirming the high diastereoselectivity of the reaction (the minor isomer could not be observed by ^{1}H NMR analysis, see the Supporting Information). Unfortunately, treatment of intermediate **9** under both acidic and basic conditions in various organic solvents either led to *syn*-elimination to give nitrile **5** or a complex mixture of products through decomposition.

Scheme 3. One-Pot Synthesis



In Kemp and Woodward's seminal publication on the use of hydroxylamine-*O*-sulfonic acid for the synthesis of benzisoxazole, biphasic reaction conditions were employed to facilitate the cyclization reaction.[20] Presumably, aqueous conditions stabilize the highly charged sulfonate leaving group, promoting the cyclization process. A solution of intermediate **9** in acetonitrile was therefore diluted with dichloromethane and aqueous 1 M sodium hydroxide solution. Clean cyclization proceeded to give the desired pyrazolopyrimidine **6** in 59% yield from **2**, and no nitrile byproduct **5** was observed. Finally, we were able to combine all three steps of this synthesis into a one-pot procedure by carrying out the nucleophilic substitution reaction of **1** with aniline in acetonitrile. Hydroxylamine-*O*-sulfonic acid was then added followed by dilution with dichloromethane and aqueous 1 M sodium hydroxide solution to give a biphasic mixture, which resulted in the formation of the desired pyrazolopyrimidine **6** in 51% yield from **1** (Scheme 3).

To explore the scope of our one-pot pyrazolopyrimidine synthesis, several analogues were synthesized incorporating both electron-donating and -withdrawing groups on the aromatic ring (Table 2). The targets were produced in good yield from this three-step, one-pot protocol. Of note are the mild reaction conditions used which allow for potentially sensitive functionality, labile protecting groups, and unprotected groups to be used while still affording good yields. Unfortunately, the use of aliphatic amines failed to induce formation of the desired pyrazolopyrimidine **17**, despite the success of the first two steps of this protocol.[21] Treatment of the *O*-sulfonic acid oxime

(10) The stereochemical requirement of this type of N−N bond-forming cyclization reaction has previously been described: Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021.

(11) *E*-Oxime mesyl ethers can also undergo *syn*-elimination to give nitriles: Al-Awadi, N. A.; Elnagdi, M. H.; Kaul, K.; Ilingovan, S.; El-Dusouqui, O. M. E. *Tetrahedron* **1998**, *54*, 4633.

(12) Sharghi, H.; Sarvari, M. H. *Synlett* **2001**, 99.

(13) Emami, S.; Falahati, M.; Banifatemi, A.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 5881.

(14) The configuration of isolated *O*-substituted oximes could be determined by HN-HMBC NMR spectroscopy; see: (a) Huang, X. S.; Liu, X.; Constantine, K. L.; Leet, J. E.; Roongta, V. *Magn. Reson. Chem.* **2007**, *45*, 447. (b) Jansma, A.; Zhang, Q.; Li, B.; Ding, Q.; Uno, T.; Bursulaya, B.; Liu, Y.; Furet, P.; Gray, N. S.; Geierstanger, B. H. *J. Med. Chem.* **2007**, *50*, 5875.

(15) For a discussion of the SiON motif as an electron-withdrawing group, see: Mitzel, N. W.; Blake, A. J.; Rankin, D. W. H. *J. Am. Chem. Soc.* **1997**, *119*, 4143.

(16) For a discussion on the stability of this type of intramolecular hydrogen bond, see: Kuhn, B.; Mohr, P.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 2601.

(17) This ratio was found to vary between 9:1 and 19:1 depending on the dryness of the ethanol used.

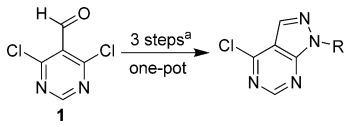
(18) The base used in the cyclization of the *E*-oxime **3** had a significant effect on the yield of this reaction. Triethylamine gave much lower yields of pyrazolopyrimidine **6** and larger amounts of nitrile **5**.

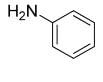
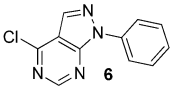
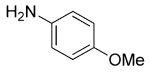
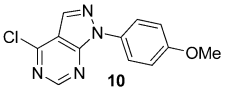
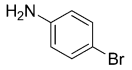
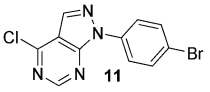
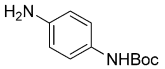
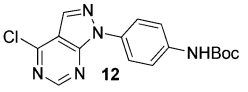
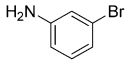
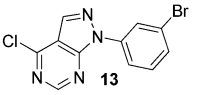
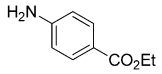
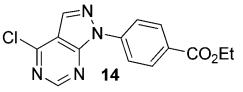
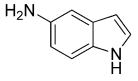
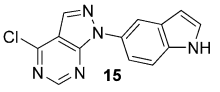
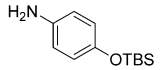
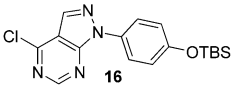
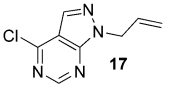
(19) For a review of *O*-sulfonic acid hydroxylamine, see: Wallace, R. G. *Aldrichimica Acta* **1980**, *13*, 3.

(20) Kemp, D. S.; Woodward, R. B. *Tetrahedron* **1965**, *21*, 3019.

(21) Under the conditions reported, a variety of aliphatic amines failed to give the desired pyrazolopyrimidine product and resulted in decompostition of starting material.

Table 2. Three-Step One-Pot Pyrazolopyrimidine Synthesis



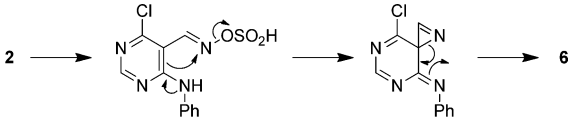
entry	amine	pyrazolopyrimidine	yield
1		 **6**	51%
2		 **10**	59%
3		 **11**	52%
4		 **12**	69%
5		 **13**	34%
6		 **14**	30%
7		 **15**	38%
8		 **16**	56%
9		 **17**	0%

[a] Key: (i) amine, NEt_3, MeCN, −15 °C to rt, 1−16 h; (ii) NH_2O-SO_3H, rt, 16 h; (iii) DCM, 1 M NaOH, 6 h.

intermediate derived from allylamine with base resulted only in a complex mixture of products.

Although the mechanism of this unusual N−N bond-forming reaction is unclear, a plausable mechanism is shown in Scheme 4.[22] This resembles the mechanism of the Neber reaction used to synthesize indoles.[23] A further discussion of possible mechanisms is presented in the Supporting Information.

Scheme 4. Plausable Mechanism



In summary, we have described a novel one-pot synthesis of *N*-aryl[3,4-*d*]pyrazolopyrimidines in good yield and under mild reaction conditions. By exploiting electron-deficient hydroxylamines the oxime product was formed with very high *E*-diastereoselectivity. The key step utilizes a hydroxylamine-*O*-sulfonic acid derived oxime in a cyclization reaction to form the N−N bond of the pyrazolopyrimidine ring. Carrying out the reaction under biphasic aqueous conditions promoted clean ring closure to afford the pyrazolopyrimidines with a range of functionality in good yield. We believe our one-pot protocol is a significant addition to the methodologies available for the synthesis of these important pharmaceutical compounds.

Acknowledgment. We thank Cancer Research UK (grant no. C309/A11566) and The Wellcome Trust for funding. We also thank Dr Maggie Liu of The Institute of Cancer Research for assistance with NMR analysis.

Supporting Information Available. Detailed spectroscopic data for new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Greszler, S.; Stevens, K. L. *Org. Synth.* **2009**, *86*, 17.
(23) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7641.

The authors declare no competing financial interest.