ORGANIC LETTERS

2011
Vol. 13, No. 16
4204–4207

Discovery and Process Synthesis of Novel 2,7-Pyrrolo[2,1-*f*][1,2,4]triazines

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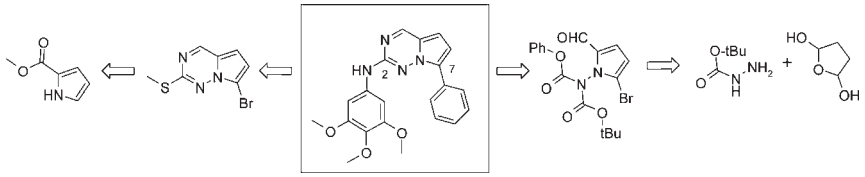
Received June 7, 2011

ABSTRACT



The synthesis of a new kinase inhibitor template 2-anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazine is described which includes a late stage orthogonally reactive key intermediate amenable to rapid diversification as well an optimized *in situ* triflate displacement to install the C2-aniline. Furthermore, an efficient scalable process approach will be highlighted which begins with *tert*-butyl carbazate to provide the key N−N bond and generates the pyrrolotriazine core through a stable bromoaldehyde intermediate followed by condensation with ammonium carbonate.

A unique bridgehead nitrogen heterocycle pyrrolo[2,1-*f*]-[1,2,4]triazine (Figure 1) was first reported by Neunhoeffer via addition/fragmentation of 1,2,4-triazines with dimethyl acetylenedicarboxylate to give **1**.[1] It was two years later that Migliara reported the synthesis of **2** via acid-mediated cyclization of a semicarbazone onto a pendant α-ketoester, followed by base-promoted cyclization.[2] More than a decade later Hayashi introduced C7-linked pyrrolotriazines to the medicinal chemistry field as novel C-nucleoside mimics (**3**), implementing similar chemistry to Migliara.[3] A novel pyrrole N-amination approach for formation of the key N−N bond, reported by Klein and co-workers, described syntheses of both C-nucleoside congeners[4] and minimally substituted pyrrolotriazines (**4**).[5] Limited new developments around this nucleus had been reported[6,7] until Hunt and co-workers described the design, synthesis, and utility of C4-substituted pyrrolotriazines (**5**) as quinazoline hinge-binding mimics in the discovery of ATP-competitive kinase inhibitors.[8] This discovery has had a profound impact on the kinase inhibitor field and has led to numerous candidates in late stages of clinical development. Further expansion of the utility of this heterocycle has led to the discovery of the clinical level IGF-1R inhibitor **6**.[9]

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10.1021/ol2015237
Published on Web 07/26/2011

The strategy to make these bioactive pyrrolotriazines has relied mainly on a pyrrole N-amination approach.[8]

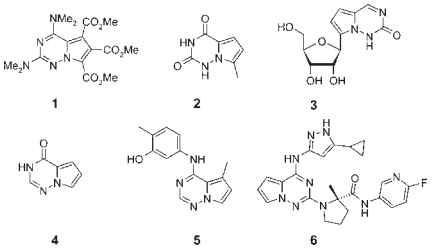


Figure 1. Pyrrolo[2,1-*f*][1,2,4]triazine derivatives.

Recently, we reported novel diaminopyrimidine ATP-competitive inhibitors of anaplastic lymphoma kinase (ALK).[10,11] In an effort to mimic the bioactive conformation we proposed constraining the diaminopyrimidine into a 2-anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazine (Figure 2) which, to the best of our knowledge, is a novel modification of this core template and a new kinase inhibitor platform.[12]

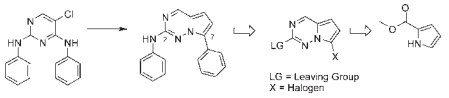


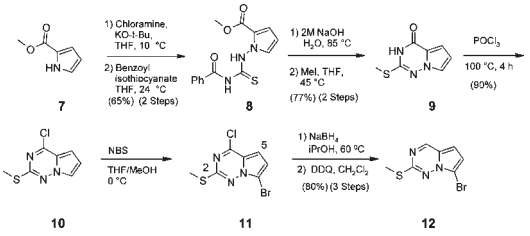
Figure 2. Initial design of novel 2-anilino-7-aryl-pyrrolo[2,1-*f*]-[1,2,4]triazines.

Herein, we describe the discovery synthesis of this new kinase inhibitor template which includes a late stage orthogonally substituted core structure amenable to rapid diversification as well as an optimized *in situ* triflate displacement to install the C2-aniline. Furthermore, an efficient scalable process approach will be described which begins with readily available *tert*-butyl carbazate and benefits from regioselective bromination and acylation culminating in the formation of the preferred 2-oxo derivative **16**.

The challenges associated with the initial synthesis included incorporating the appropriate oxidation state at C4 and installation of orthogonally reactive groups at C2 and C7 to support a late stage diversification strategy.

Relying on pyrrole N-amination[13] to install the key N–N bond, we were precluded from using the C2-aldehyde due to conversion to the nitrile during amination. Instead, we opted for the higher ester oxidation state; thus, methyl-2-pyrrole carboxylate (**7**, Scheme 1) was treated with chloramine and the crude material reacted with benzoylisothiocyanate to give **8**. Hydrolytic cyclization in 2 M NaOH followed by methylation afforded **9**. The choice of the thiomethyl moiety at C2 was central to providing both stability to the intermediates and latent reactivity. At this stage, we required a lower oxidation state at C4 and regioselective introduction of a halogen at C7. Attempted bromination of **9** was severely limited by solubility; however, if chlorination was effected first, bromination proceeded smoothly to give **11** and with reasonable regioselectivity for C7 vs C5 (ca. 5:1); the regioisomers were carried forward. Importantly, we had now clearly differentiated C2, C4, and C7 and could take advantage of the highly reactive C4 position. Interestingly, treatment of **11** with $NaBH_4$ resulted in reduction of not only the chloride but also the derived imine species. Fortunately, oxidation to restore aromaticity was quite mild and facile with DDQ to give the key intermediate **12** which was separated from the 5-Br regiomer at this stage by chromatography.

Scheme 1. Synthesis of Key 2,7-Substituted Intermediate



Intermediate **12** could be advanced to a target molecule (**15**, Scheme 2) via orthogonal approaches. Suzuki coupling to phenylboronic acid, followed by oxidation of the sulfide to sulfoxide **13**, provided an appropriate partner for S_NAr displacement with 3,4,5-trimethoxyaniline. Alternatively, **15** was arrived at *via* the reverse process where the phenyl group is installed in the final step. As we diversified our appendages, especially with regard to poorly nucleophilic and/or sterically demanding anilines, the sulfoxide displacement afforded poor yields with multiple side products. To circumvent this limitation, we focused on incorporating a more reactive nucleofuge at C2, namely a triflate or the like. Toward this end we converted the sulfoxide to the 2-oxo derivative **16**. The *in situ* **16** to **15** transformation could be carried out by triflate formation followed by S_NAr displacement with the aniline. The methodology offered significant advantages which included a one-pot triflate formation/displacement and milder reaction conditions (room temperature) and was amenable to a wide variety of anilines. Furthermore, **12** could also be converted to **14** using this chemistry.

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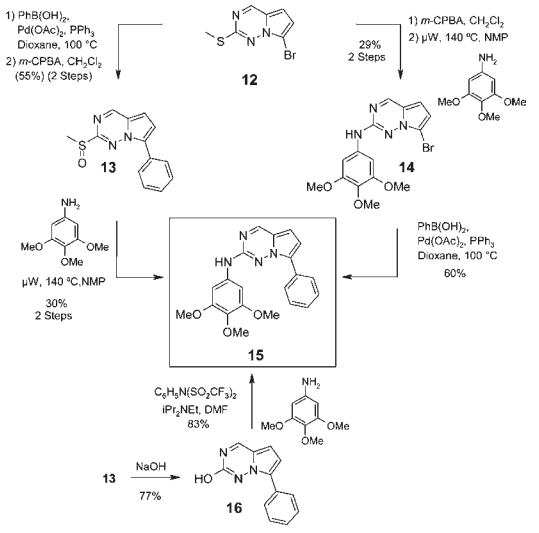
Scheme 2. End-Game Strategy for Synthesis of 2-Anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazines



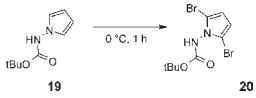
In an effort to develop a scalable process, we focused on the synthesis of an *N*-aminopyrrole containing a carbonyl at the desired aldehyde oxidation state. This would avoid the need to employ $POCl_3$, $NaBH_4$, and DDQ thus eliminating several steps. We also sought conditions which would regioselectively brominate exclusively at the 5-position of the pyrrole due to unsuccessful efforts to develop a crystallization to remove regioisomers from **11** and **12**. Separation was only achieved through chromatography. We also planned to avoid the less reactive sulfoxide **13** and form **16** directly, further providing a more succinct route to the final target.

Initial attempts focused on bromination of 1*H*-pyrrole-2-carboxaldehyde.[14] An extensive screen of common brominating conditions[15] provided the best result which employed pyridinium tribromide yielding a modest 39% area by HPLC of the 5-bromo-2-pyrrole carboxaldehyde. The dark unstable reaction mixture also contained starting material, a 4-bromo derivative, and overbrominated products, which together decomposed to tar on standing. Repeated attempts to apply the chloramine chemistry with 1*H*-pyrrole-2-carboxaldehyde resulted in consumption of the starting material with no desired product observed.

Unable to achieve a selective monobromination, we were encouraged by reports of the regioselective dibromination of Boc-protected pyrroles[16] and *N*-aminopyrroles.[17] Given the high cost and limited commercial availability of *N*-aminopyrrole, we were pleased to find a procedure to furnish Boc-*N*-aminopyrrole in one step utilizing the Clauson–Kaas reaction (Scheme 3).[18] Reported conditions[19] to synthesize **19** were optimized to allow for direct isolation from the reaction mixture in a single step by performing the reaction in NMP followed by addition of water to induce product crystallization. Fine tuning the amount of HCl along with the number of equivalents of **18** was critical to minimize side products providing the product in 55% isolated yield and 99.2 area % purity.

A screen of brominating reagents revealed several conditions which provided **20** with only trace amounts of overbromination or remaining starting material (Table 1). Both *N*-bromosuccinamide and 5,5-dimethyl-1,3-dibromohydantoin (DBH) demonstrated clean conversion with pyridinium tribromide providing slightly inferior results. Slightly higher reaction concentrations and different solvents were shown to be tolerated without significant overbromination. During scale-up, DBH was slow to dissolve in MTBE resulting in both conversion and selectivity issues. To mitigate these solubility problems, DBH was added as a solution in THF to **19** in NMP (entry 9). These conditions provided **20** in 87% yield with 98.6% purity after recrystallization.

Table 1. Dibromination Screening for the Synthesis of **20**



entry	reagent[a]	solvent	concn (mL/g)	**20** (A%)[b]
1	$Pyr\text{-}Br_3$	THF	40	88.6
2	NBS	DMF	40	95.2
3	DBH	DMF	40	98.4
4	DBH	THF	40	95.6
5	DBH	MTBE	40	97.5
6	DBH	NMP	40	95.6
7	DBH	NMP	20	96.7
8	DBH	NMP	10	86.4
9	**DBH**	**NMP/THF**[c]	**20/10**	**97.3**

[a] $Pyr\text{-}Br_3$: pyridinium tribromide. DBH: 1,3-dibromo-5,5-dimethylhydantoin. [b] Conversion based on HPLC area percent. [c] DBH added as a solution in 10 mL/g of THF to **19** dissolved in NMP.

With the desired dibrominated pyrrole **20** in hand, we sought conditions to effect a single, mild metal–halogen exchange which avoided cryogenic conditions. The

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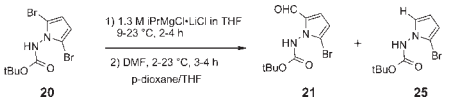
Table 2. Halogen−Metal Exchange Followed by Quenching with DMF



20 21 25

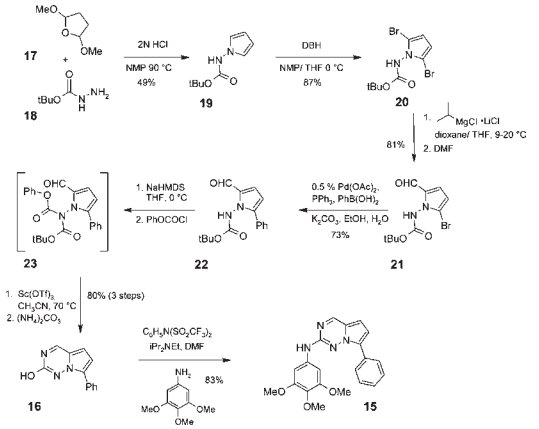
entry	*i*-PrMgCl•LiCl (equiv)	DMF (equiv)	**21** (A%)[a]	**25** (%)[b]
1	4.0	5.0	80.3	<1
2	2.5	5.0	91.4	3.5
3	2.5	1.6	90.8	ND[c]

[a] Conversion based on HPLC area percent. [b] Determined by ^{1}H NMR. [c] Not detected.

commercially available Knochel "Turbo Grignard" *i*-PrMgCl•LiCl[20] gave a clean monoexchange in 3−6 h at room temperature with negligible formation of reduced **25** (Table 2). Decreasing the amount of *i*-PrMgCl•LiCl resulted in a 10% increase in conversion. Reducing the amount of DMF had little effect on conversion but did allow for a single phase cut during workup. This allowed **21** to be isolated after simple extraction from an ethyl acetate/heptane recrystallization in 71−81% yield based on scale.

Suzuki coupling with **21** was straightforward requiring only 0.5% Pd catalyst loading in aqueous ethanol to cleanly provide **22** in 0.5 h at 80 °C. Crystallization from ethyl acetate/heptane furnished the product in 73% yield and 94 area % purity (Scheme 3).

Scheme 3. Process Route toward the Synthesis of 2-Anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazines



17 18 19 20 21 22 23 16 15

We now hoped to subject **22** to high pressure ammonia to allow for cyclization to give **16**. At 60 psi and 70 °C no product was noted, returning unreacted starting material along with some cleavage of the Boc group. It was next surmised that a more reactive carbamate was needed toward aminolysis. Treatment of **22** with NaHMDS in THF followed by addition of phenyl chloroformate resulted in 90−95% conversion to **23**. The crude reaction mixture when subjected to high pressure ammonia converted to **16** but in low yield. Encouraged by this result, Lewis acids were screened to activate **23** toward cyclization and it was discovered that both $Yb(OTf)_3$ and $Sc(OTf)_3$ catalyzed the formation of **16**.

Given the hindered rotation around the N−N bond and the large distance between the aldehyde and phenyl carbamate due to steric hindrance, the mechanism of the transformation was probed. Aware of a report[21] that LiBr in acetonitrile could selectively convert di-Boc protected amines into mono *tert*-butyl carbamates, control experiments in the absence of ammonia were performed which revealed that heating **23** with $Sc(OTf)_3$ or $Yb(OTf)_3$ allowed for the preferred removal of the Boc group while preserving the phenyl carbamate. No decomposition was noted during this transformation. LiBr however was not as selective toward removal of the Boc group, and significant amounts of **22** were observed. Upon removal of the *tert*-butyl carbamate, addition of ammonia gas or ammonium carbonate resulted in immediate formation of **16** as a precipitate from the reaction mixture. Addition of MTBE followed by filtration furnished the product in 80% yield and 99 area % purity for three steps. *In situ* conversion of **16** to the triflate followed by displacement with 3,4,5-trimethoxyaniline provided the target **15** in very good yield.

In summary, the synthesis of a new kinase inhibitor template, 2-anilino-7-aryl-pyrrolo[2,1-*f*][1,2,4]triazine, has been described which relies on a pyrrole N-amination followed by condensation/cyclization of an isothiocyanate to form the core ring structure. Chlorination at C4 and bromination at C7 set the stage for regioselective reduction to provide an orthogonally substituted key intermediate amenable for diversification via two routes to the desired target molecules. An optimized *in situ* triflate formation and aniline addition was also devised. Furthermore, a scalable process which avoids chromatography has been developed which benefits from a regioselective bromination at C7 and mild metal−halogen exchange. The sequence provides a stable intermediate **21** amenable to funtionalization and through novel, selective removal of a tert-butyl carbamate followed by addition of an ammonia source, provides a direct route to the important and preferred pyrrolotriazine core **16**.

Acknowledgment. The authors thank Profs. Bruce Lipshutz of the University of California, Santa Barbara and Amos B. Smith, III of the University of Pennsylvania for fruitful discussions as well as Drs. Mark Olsen and Kevin Wells-Knecht for analytical support.

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

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