Organic Process Research & Development

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Development of a Practical Synthesis of a Functionalized Pyrrolo[2,1-f][1,2,4]triazine Nucleus

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ABSTRACT: Functionalized pyrrolotriazine **1b** is a key heterocyclic building block in the synthesis of BMS-690514, a potent anticancer agent. Described herein are our development activities that led to the efficient preparation of **1b** on a large scale. The key transformations include a selective C-alkylation of an oxalacetate salt with a hydrazonyl bromide to form a 2-hydrazonoethyl-3-oxosuccinate, followed by cyclodehydration to an aminopyrrole. Subsequent deprotection and condensation with formamidine afforded the pyrrolotriazine scaffold. Further elaboration of this core provided the desired pyrrolotriazinyl amine.

INTRODUCTION

Drug candidates containing the pyrrolotriazine core have shown efficacy for multiple therapeutic targets, including VEGFR-2 and EGFR/pan-Her.[1,2] BMS-690514 (Figure 1)

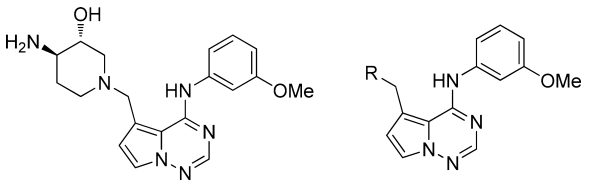


Figure 1. Structures of BMS-690514 and pyrrolotriazine core **1**.

was identified as a potent kinase inhibitor for several solid tumor malignancies.[1] Functionalized pyrrolotriazines **1a** and **1b** (Figure 1) are advanced intermediates utilized in the preparation of BMS-690514. Due to the need for significant quantities of BMS-690514, a practical synthesis suitable for the large-scale production of pyrrolotriazine **1b** was desired.

Our initial campaign was a subtle modification[3] of the strategy developed by our colleagues in Discovery Chemistry[1b,4] and delivered 2 kg of key intermediate **1a** (Scheme 1). While this process had the advantage of sharing a common intermediate (**6**) with other programs,[5] further modification of the pyrrole substitution pattern was required (steps f and g). Several aspects of the synthesis are problematic for long-term manufacture, including the lengthy synthesis (11 linear steps to intermediate **1a**), the requirement of chromatography to isolate chloride **9**, and up to 13% of competing ring-brominated side products in intermediates **10**, **11**, and **1a**. These shortcomings prompted us to develop an alternative, more efficient synthesis of this key intermediate.

We reasoned target **1b** (Scheme 2) could be derived from pyrrolotriazine **12** via a known chlorination/amination sequence[5,6] and subsequent reduction of the ethyl ester.[7] Since annulations of *N*-amino pyrrole-dicarboxylates (e.g., **13**) to pyrrolotriazine esters (e.g., **12**) are generally reliable processes,[5,6] the viability of this route depended on the availability of **13**. Although **13** appears to be a relatively simple structure, few methods exist for the preparation of *N*-amino pyrrole-2,3-dicarboxylates.[8] Recently, a general method for the *N*-amination of pyrroles[3d,e] using *O*-(4-nitrobenzoyl)-hydroxylamine was developed by researchers at Bristol-Myers Squibb (used to prepare compound **5**, Scheme 1). However, we desired an approach that would generate the *N*-aminopyrrole directly without the necessity for use of large quantities of an aminating agent on scale.

In 1979, Sprio[9] reported that chlorohydrazone **16** underwent alkylation with the anion of oxosuccinate to produce intermediate **17**, which was poised for cyclodehydration to the corresponding amino pyrrole **18** (Scheme 3). If hydrazonyl halide **15** were to be substituted for the alkylating agent **16**, the resulting dicarboxylate **14** should analogously cyclize to the protected amino pyrrole **13**. This would represent a considerably shorter synthesis of the *N*-amino pyrrole with the desired substitution pattern when compared to the original synthesis and offered several synthetic options for further elaboration. In addition, implementation of this route would circumvent the need for *N*-amination and ester removal (steps d, f, and g, Scheme 1). Following this strategy, we now wish to report the results of our development efforts that led to the preparation of 125 kg of functionalized pyrrolotriazine **1b**.

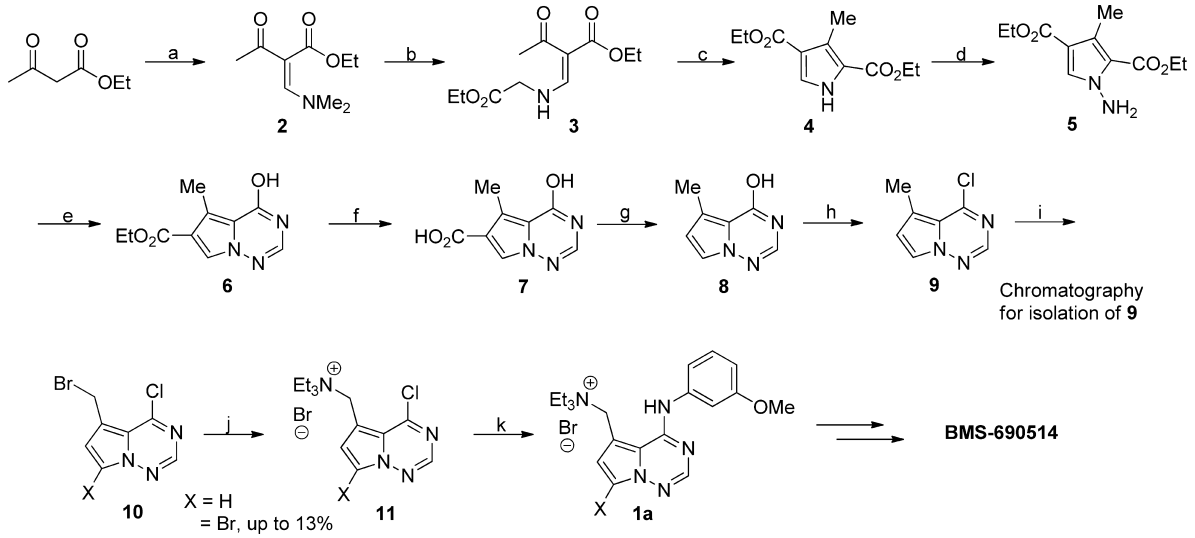
RESULTS AND DISCUSSIONS

Bromohydrazone 20. The alternate synthesis (Scheme 4) commenced with the condensation of commercially available bromoacetal **19** and Cbz-hydrazine under acidic conditions to produce hydrazonyl bromide **20**.[10] The Cbz-protecting group was selected due to its demonstrated stability to the downstream chemistry, while still allowing facile deprotection under mild conditions. Different acids, including various concentrations of HCl and H_3PO_4, H_2SO_4, acetic acid, trifluoroacetic acid, methanesulfonic acid (MSA), and 4-methylbenzenesulfonic acid (pTSA), were screened for their ability to facilitate the condensation reaction. The results

Received: September 10, 2012
Published: October 15, 2012

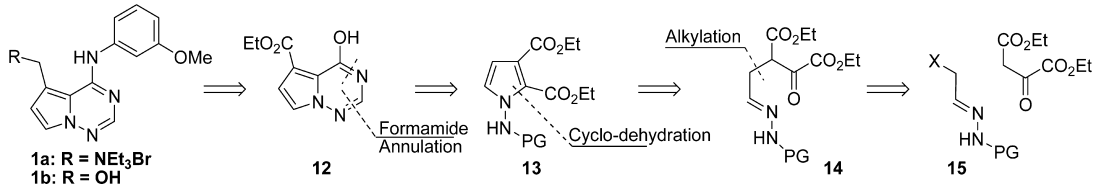
   dx.doi.org/10.1021/op300252n | *Org. Process Res. Dev.* 2012, 16, 1846–1853

Scheme 1. Synthesis of Pyrrolotriazine 1a via Modification of the Discovery Chemistry Route[a]

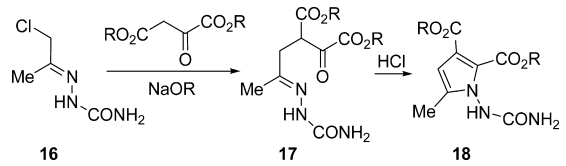


[a]Reagents and conditions: (a) *N*,*N*-Dimethylformamide dimethylacetal, pTSA 5%, neat, 55 °C. (b) Glycine ethyl ester hydrochloride, EtOH, 50 °C, 78% for two steps. (c) NaOEt/EtOH, 60 °C, 65%. (d) KO^{t}Bu, *O*-(4-nitrobenzoyl)hydrozylamine, 25 °C, NMP. (e) Formamide, H_3PO_4, 120 °C, 79% for two steps. (f) NaOH, EtOH, 60 °C, 94%. (g) H_3PO_4, 125 °C, 78%. (h) $POCl_3$, *i*-Pr_2NEt, toluene, 100 °C, 80%. (i) NBS, AIBN, PhCl, 80 °C. (j) Et_3N, CH_2Cl_2, 63% for two steps. (k) *m*-Anisidine, toluene, 55 °C, 94%.

Scheme 2. Retrosynthetic Analysis of Pyrrolotriazine 1



Scheme 3. Literature Precedent for the Preparation of Pyrrole Dicarboxylates



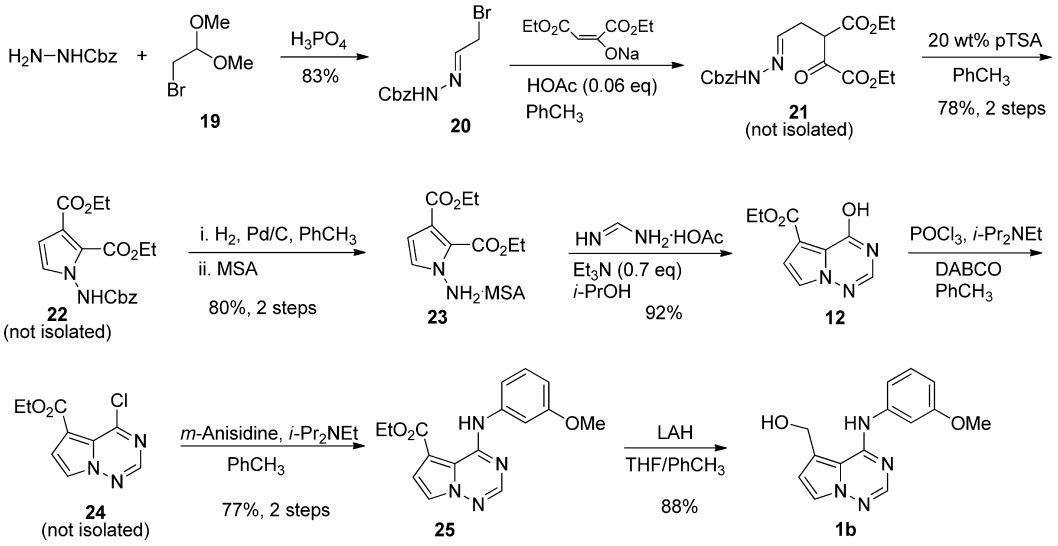
indicated that concentrated H_3PO_4 afforded the fastest condensation reaction and the cleanest reaction profile. Advantageously, hydrazone **20** precipitated as the reaction progressed, allowing isolation by simple filtration. However, the cake required sufficient washing with a considerable amount of water (a total of 40 L/kg of benzyl carbazate) to increase the pH of the final filtrate to 3−4. A wet cake whose filtrate was more acidic required extended drying times, possibly due to the presence of residual H_3PO_4, which also increased the risk of decomposition. Further concerns regarding the drying protocol were raised by chemical safety evaluation of hydrazone **20**. Compound **20** has a relatively strong decomposition exotherm of 900 J/g at ∼100 °C, and as a result it is recommended that this compound be handled below 50 °C. Other process parameters, including reaction temperature and solvent volume, were optimized, and this process was used to generate 550 kg of bromide **20** over five batches.[11]

Alkylation and Cyclodehydration to Protected Pyrrole Dicarboxylate 22. The next transformation in the synthesis involved alkylation of sodium diethyl oxalacetate with bromohydrazone **20** to afford intermediate **21**. Initial alkylation attempts were based on literature examples[9] and utilized alcoholic solvents, providing **21** in modest yields (∼35%). This low yield was attributed to the formation of significant amounts of both bis and *O*-alkylated side product (Figure 2). Performing the reaction at lower temperature (0 vs 21 °C) did not improve the impurity profile. Further evaluation of the reaction revealed that the use of less polar solvents afforded the product in higher yields, as the level of the bisalkylated impurity was significantly reduced with only a slight increase of the *O*-alkylated side product (Table 1, entries 3−10). The use of DMF resulted in the highest level of the bisalkylated impurity, and dichloromethane did not offer any improvement (Table 1, entries 11 and 12). Among the solvents investigated, toluene provided the best in-process impurity profile of keto ester **21**.[12]

Upon performing the alkylation procedure on a slightly larger scale (10 g), it was found that the yield was not reproducible, ranging from 35 to 60%. In an attempt to further improve the selectivity and obtain a more consistent yield, additives, including water, DMF, LiCl, and triethylamine (TEA), were evaluated. This initial screening (Table 2, entries 1−5) did not reveal any promising options, and unsurprisingly, the addition of base (TEA) increased the amount of bisalkyl impurity (entry 4). This result suggested to us that excess base may be detrimental to the reaction. Examination of the sodium oxalacetate bottle label indicated that the reagent contains ∼1% sodium hydroxide,[13] which prompted us to investigate the impact of acidic additives on the reaction. Indeed, catalytic amounts of acid effectively decreased the levels of both the O-

dx.doi.org/10.1021/op300252n | *Org. Process Res. Dev.* 2012, 16, 1846−1853

Scheme 4. Synthesis of Pyrrolotriazine 1b



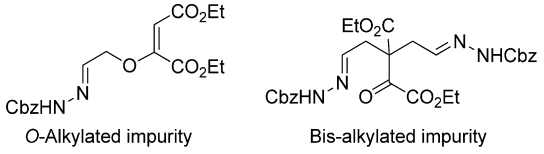


Figure 2. Impurities formed in the alkylation of oxalacetate.

Table 1. Results of Alkylation Reaction to Form Oxosuccinate 21 in Various Solvents

		HPLC area percent[a]		
entry	solvent	**21**	O-alkylated	bisalkylated
1	EtOH	39	1.8	37
2	^{i}PrOH	41	2.1	35
3	MeCN	48	2.6	30
4	THF	65	3.6	19
5	MeTHF	67	3.5	20
6	EtOAc	66	3.7	22
7	^{i}PrOAc	67	4.1	18
8	toluene	75	5.1	8.5
9	$C_6H_5CF_3$	71	4.7	13
10	anisole	68	3.9	16
11	DMF	17	1.2	32
12	DCM	52	2.2	23

[a]Reactions were carried out with 0.50 mmol of bromide **20** and 1.1 equiv of sodium oxalacetate in 3 mL of the solvent at ambient temperature. The reactions were analyzed by HPLC after 6 h.

alkylated and bisalkylated impurities (Table 2, entries 7–9) and significantly increased the yield of **21**. These results indicated that an acidic additive reduced levels of O-alkylated impurity and consumed excess base that potentially caused the bisalkylation. The detrimental base hypothesis could also explain the higher levels of the bisalkylated impurity observed in the reactions utilizing polar solvents (Table 1, entries 1, 2, and 11) since residual solid NaOH in the oxalacetate reagent would be more soluble. Optimally, 0.06–0.15 equiv of acetic acid afforded the cleanest monoalkylation profile along with the highest solution yield. In practice, consistent and high yields of **21** were achieved by the addition of bromide **20** to a slurry of sodium oxalacetate and acetic acid at 20 °C.[14]

Table 2. Impact of Additives on the Alkylation Reaction to Oxosuccinate 21

		HPLC area percent[a]			
entry	additive, equiv	**21**	O-alkylated	bisalkylated	**21**, solution yield,[b] %
1	none	74.8	5.1	8.5	66
2	water, 2.0	77.7	4.4	9.3	65
3	DMF, 2.0	66.4	3.3	17.0	–[c]
4	TEA, 2.0	64.6	3.1	18.6	–[c]
5	LiCl, 2.0	74.0	4.3	12.7	–[c]
6	KH_2PO_4, 0.10	77.3	4.5	8.8	–[c]
7	pTSA, 0.06	81.2	3.8	3.5	75
8	HOAc, 0.06	83.1	4.2	3.7	81
9	HOAc, 0.20	82.1	4.2	1.4	79

[a]Reactions were carried out with 0.53 mmol of sodium oxalacetate and designated additives in 3 mL of toluene, and then bromide **20** (0.50 mmol) was added at ambient temperature. The samples were taken for HPLC analysis after 4–6 h. [b]Obtained by quantitative HPLC analysis against the calibration curve of the reference standard. [c]Undetermined.

Although keto ester **21** in pure form is a white solid (mp 92 °C), attempts to crystallize it directly from the crude workup solution were unsuccessful.[15] Instead, the process stream containing **21**[16] was used to prepare pyrrole **22** via a pTSA-catalyzed cyclodehydration.[17] It should be noted that no work up of the reaction to form **21** was required. Addition of pTSA (0.3 equiv) to the slurry of **21** followed by warming to 40–45 °C gave a stream of the desired protected aminopyrrole **22**. After completion of the cyclization to pyrrole **22** and an aqueous workup, a stable solution of **22** in toluene was obtained (78% yield for the two steps). The crude reaction stream performed satisfactorily in the subsequent hydrogenolysis to remove the Cbz group and was thus used without purification.

Removal of the Cbz Group and Formation of MSA Salt 23. Hydrogenolysis of the Cbz group of **22** to provide amino pyrrole **23** proceeded smoothly and was typically complete in 6 h using 10% Pd/C and 30 psig of hydrogen at 25 °C. However, free base **23** was found to be unstable at ambient temperature due to an intermolecular reaction between the ethyl ester and the unprotected hydrazine (up to 5% over the

dx.doi.org/10.1021/op300252n | Org. Process Res. Dev. 2012, 16, 1846–1853

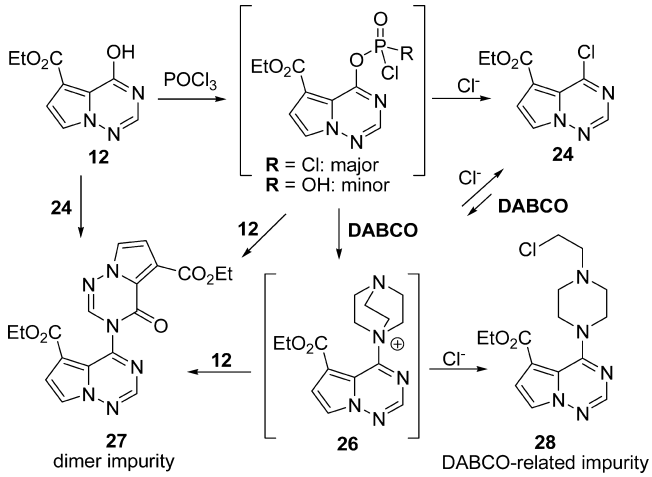
course of 7 days). To circumvent this unwanted side reaction, we investigated the conversion of **23** to a salt. It was reasoned that salt formation should increase the stability of the compound in neat form and provide the additional benefit of streamlining isolation. Among the acids studied, only sulfonic acids such as MSA and pTSA produced crystalline solids with **23**. MSA proved to be superior to pTSA, affording the MSA salt of **23** in higher yield and better purity upon crystallization (toluene/isopropanol, 6:4 v/v). After three consecutive through-process reactions (steps 2−4), aminopyrrole **23** was isolated as a crystalline MSA salt in 62% overall yield. This crystallization effectively removed the impurities that had accumulated from the preceding three steps, affording **23** in >99% HPLC purity. In addition, residual Pd was found to be less than 10 ppm, and isopropyl methanesulfonate, a genotoxic impurity that could have potentially formed, was not detected (<10 ppm) in the isolated MSA salt **23**.[18]

Annulation to Pyrrolotriazine Ester 12. The original procedure[5] for annulation of pyrrole dicarboxylate **23** consisted of heating in formamide, which served as both a reagent and solvent. This procedure required high temperatures and extended reaction times (10−16 h at 140 °C) to achieve reaction completion. An additional liability with this process was the propensity of product **12** to form a highly stable formamide solvate, which performed poorly in the subsequent chlorination as the reaction stalled at low conversions.

Formamidine acetate[19] was shown to be a viable alternative to formamide in this reaction. A solvent screen revealed that isopropanol in conjunction with formamidine acetate (1.7 equiv) gave complete conversion in 8−12 h at a much lower temperature (78−82 °C). A further reduction in reaction time to 5 h was achieved when TEA (0.7 equiv) was added to partially neutralize MSA.[20] This modified process provided **12** in 92% yield and >99.5% HPLC purity without formation of formamide solvate.[21] This represented a substantial improvement in yield and efficiency over the original formamide process (76% yield). At this stage we have successfully prepared the desired pyrrolotriazine core, and functionalization of the periphery was all that stood between us and our intended target **1b**.

Chlorination and Amination to 4-Aminopyrrolotriazine 25. Initial studies on the conversion of pyrrolotriazine **12** to chloride **24** employed the standard method of phosphoryl chloride ($POCl_3$) and *i*-Pr_2NEt in toluene.[5,6] However, the chlorination required high temperatures (105 °C) and extended reaction times (15−24 h) and provided a moderate in-process yield (65%) of chloride **24** due to formation of multiple impurities. The major impurity was identified as the condensate **27** (up to 10%, Scheme 5). Addition of catalytic DABCO[22] significantly increased the rate of conversion while suppressing the formation of **27**, resulting in an improved yield of chloride **24** (90% in-process yield). Mechanistic studies indicated that multiple phosphoryl intermediates rapidly formed in the first stage of the reaction. The subsequent chloride displacement required elevated temperatures to reach completion and was thus rate-limiting. Impurity **27** was generated from the condensation of unreacted **12** and chloride **24** (or one of the phosphoryl intermediates),[23] and the rate of formation increased at higher temperatures. Operationally, to minimize impurity **27**, the reaction was initially held at a lower temperature (45−75 °C) to convert near all of **12** (>90%) to chloride **24** or one of the phosphoryl intermediates. The temperature was then increased to 95 °C to complete the

Scheme 5. Chlorination of Pyrrolotriazine 12



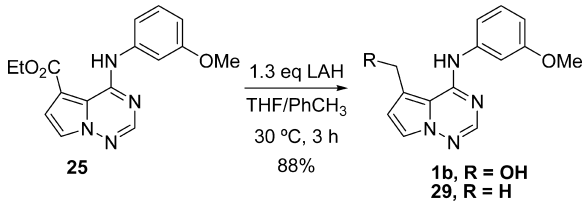
displacement of the phosphoryl intermediates with chloride and form **24** (see procedure for details).[24] The other significant byproduct **28** was derived from attack of the chloride ion at one of the three α-carbons of the activated DABCO intermediate **26** (Scheme 5).[25] Our optimized conditions employed 1.3 equiv of *i*-Pr_2NEt and $POCl_3$ and 0.1 equiv of DABCO, which minimized the levels of both the condensate impurity **27** (<3%) and the DABCO-related impurity **28** (<1%).[26]

Following completion of the chlorination and aqueous workup, the toluene stream[27] of **24** was allowed to react with *m*-anisidine in the presence of *i*-Pr_2NEt to afford **25**.[28] Product **25** precipitated during its formation, and addition of isopropanol at the end of the reaction allowed for the isolation of **25** in high yield by filtration. The addition of isopropanol was important as it facilitated the removal of impurities during the crystallization of **25**, including **27** and **28** from the chlorination reaction. Overall, the telescoped sequence from pyrrolotriazine **12** provided amine **25** in 77% yield over the two steps with >99.5% HPLC purity.

Reduction to Pyrrolotriazine 1b. To complete the synthesis of **1b**, pyrrolotriazine ester **25** was reduced to the corresponding alcohol with lithium aluminum hydride (LAH). During optimization of this step, it was found that the addition of toluene as a cosolvent increased the rate of the reduction.[29] Thus, addition of a 2.0 M LAH in THF (1.3 equiv) to a suspension of **25** in toluene led to complete conversion in 3 h at 30 °C, while the reaction required 5−8 h at 40 °C in THF alone. Crystallization from isopropanol/toluene reproducibly provided **1b** in 88% yield and >99.5% HPLC purity.

The major impurity observed in this process was methyl derivative **29** (Scheme 6), resulting from over reduction. Maintaining the temperature at 30 °C was an important process control (0.5−1% of **29**) as at higher temperatures the level of the over-reduction impurity increased. Other reducing reagents

Scheme 6. Reduction of Ester 25 to Pyrrolotriazine 1b



dx.doi.org/10.1021/op300252n | Org. Process Res. Dev. 2012, 16, 1846−1853

were examined, but led to either poor conversion ($NaBH_4$) or to more side reactions (Red-Al).

CONCLUSIONS

A new and efficient process for the synthesis of pyrrolotriazine **1b** has been developed and implemented on scale, affording over 125 kg of the target compound. Operational efficiency was built into the process by the inclusion of four telescoped steps which minimized the number of isolations to five. The key transformations include a selective C-alkylation of sodium oxalacetate, followed by cyclodehydration to directly form the *N*-aminopyrrole diester **22**. Subsequent annulation of aminopyrrole diester **22** with formamidine provided the pyrrolotriazine core **12**. Elaboration of **12** by the addition of *m*-anisidine and ester reduction produced **1b** in 9 steps, 33% overall yield from bromoacetal **19**, and excellent quality (99.2 wt %). This methodology provides access to key pharmacophores such as **1b** and is a substantial improvement over previous procedures (11 steps, 14% overall yield). Our further process development studies utilizing **1b** for the production of drug candidate BMS-690514 will be reported in a separate paper.[30]

EXPERIMENTAL SECTION

General. Starting materials, solvents, and reagents were purchased from commercial sources and were used as received without purification. Reactions were monitored by reverse-phase HPLC on a Shimazu chromatograph. HPLC purity refers to chromatographic area percentage. Quoted yields are for isolated materials or calculated solution yields and were corrected for potency using an external standard. NMR spectra were recorded on a Bruker 400 spectrometer, and the chemical shifts were reported in ppm with the solvent resonance as the internal standard (^{1}H, $CDCl_3$: 7.26; DMSO-d_6: 2.50. ^{13}C, $CDCl_3$: 77.0, DMSO-d_6: 39.5).

The processes described below are taken from the laboratory process descriptions, which provided the basis for the operations at our contract manufacturing site. The scales on which these processes were executed at the contract manufacturing site are given for each stage.

Benzyl 2-(2-Bromoethylidene)hydrazinecarboxylate (20). To a slurry of benzyl carbazate (500 g, 2.92 mol) in water (4.0 L) was added 2-bromo-1,1-dimethoxy ethane (519 g, 2.98 mol) at 21 °C. Phosphoric acid (85%, 1.5 L) was charged over 30 min while maintaining the batch temperature at 21−45 °C. The resulting thin slurry was heated to 45 °C and stirred until complete consumption (12−18 h) of benzyl carbazate (≤1.0%) by HPLC analysis. The reaction mixture was then filtered, and the product cake was washed sequentially with water (2.0 L), aqueous K_2HPO_4 (5%, 2.5 kg), and water (2.5 L). The wet cake was dried under vacuum at 40−45 °C until a KF of ≤0.6% was achieved, providing bromide **20** (728 g, 92% yield; 99.5% HPLC purity) as an off-white solid. (**Caution**: This compound is Ames positive, an eye irritant, and a sensitizer, which also has a decomposition exotherm of 900 J/g at ∼100 °C. It is recommended that this compound be handled at lower than 50 °C.) This process was successfully implemented at our contract manufacturing site (five batches, 75 kg input of benzyl carbazate), providing 563 kg of the product with >99% HPLC purity: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.2 (s, br, 1H), 7.43−7.32 (m, 6 H), 5.14 (s, 2 H), 4.18 (d, J = 6.3 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 153.1, 141.9, 136.3, 128.4, 128.1, 128.0, 66.0, 31.5; IR (KBr, cm^{-1}) 3273, 1720, 1539, 1369, 1245, 1027, 933, 750, 693; HRMS calcd for $C_{10}H_{12}BrN_2O_2$ 271.0077 [M + H]; found 271.0070 [M + H].

Diethyl 1-(Benzyloxycarbonylamino)-1*H*-pyrrole-2,3-dicarboxylate (22). To a slurry of sodium diethyl oxalacetate (516 g, 2.33 mol) in toluene (8.0 L) was added glacial acetic acid (7.4 mL, 0.13 mol) at 20 °C. The resulting slurry was agitated for 30 min. Bromide **20** (590 g, 2.15 mol) was added into the slurry in four equal portions over 1 h. After completion of the addition, toluene (850 mL) was charged as a rinse. The reaction progress was monitored by HPLC until consumption (5−6 h) of bromide **20** (≤0.5%). *p*-Toluenesulfonic acid monohydrate (118 g, 0.621 mol) was charged, and the slurry was warmed to 40−45 °C. The cyclodehydration reaction was monitored by HPLC until ketoester **21** was ≤0.5% (4−6 h). The slurry was then cooled to 15−20 °C, and an aqueous solution of 5% K_2HPO_4 (2.36 kg) was charged. After agitation for 30 min, the separated organic phase was washed twice with water (4.0 and 2.0 L) and polish-filtered, providing a solution of protected aminopyrrole **22** in toluene (9.5 L, KF = 750 ppm). The solution contained 608 g (78% for two steps) of **22**, as calculated by HPLC quantification, and was used in the next transformation without further purification. The process was successfully executed over six batches using an input of 80 kg of **20** (473 kg of **22** obtained as a solution in toluene). Intermediate **22** (after chromatographic purification): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, br, 1H), 7.30−7.43 (m, 5 H), 6.86 (d, J = 3.2 Hz, 1 H), 6.49 (d, J = 2.9 Hz, 1 H), 5.21 (s, 2 H), 4.30 (q, J = 7.2 Hz, 2 H), 4.26 (q, J = 6.9 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.29 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 160.1, 155.7, 135.1, 128.6, 128.5, 128.3, 126.7, 122.8, 120.5, 108.8, 68.4, 61.3, 60.8, 14.2, 13.9; IR (KBr, cm^{-1}) 3237, 2987, 1725, 1704, 1528, 1417, 1278, 1253, 1173, 1104, 1027, 768, 738. Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.01; H, 5.43; N, 7.72.

Diethyl 1-Amino-1*H*-pyrrole-2,3-dicarboxylate Methanesulfonate (23). To the process stream of crude Cbz pyrrole **22** in toluene (64 g/L, 4.4 L, 0.78 mol) was added Pd/C (80.0 g, 10 wt % dry basis). The reactor was purged twice with nitrogen and three times with hydrogen. The agitation was set at 400 rpm, the temperature at 25 °C, and the hydrogen pressure at 30 psig. The reaction progress was monitored by hydrogen uptake, and reaction completion (3−5 h) was confirmed by HPLC (pyrrole **22**, ≤0.5%). After completion of the reaction, the system was purged twice with nitrogen. The reaction mixture was then filtered to remove the catalyst. Toluene (250 mL) was used to rinse the reactor and the filter. The combined filtrate and rinse (4.5 L) contained 171 g (96% yield) of pyrrole **23**, as determined by HPLC quantification.

The stream of crude pyrrole **23** in toluene (4.5 L, 38 g/L) was concentrated under vacuum at 45 °C until the volume reached 650 mL. The concentrated solution was cooled to 20 °C, and isopropanol (320 mL) was added, followed by MSA (55 mL, 0.85 mol) over 15 min. A slurry was formed within 5 min, which was stirred at 20 °C for 3 h, then cooled to ∼3 °C. The slurry was held for 3 h at ∼3 °C and then filtered. The product cake was rinsed with cold IPA/toluene (3−10 °C; 4:6 v/v, 2 × 350 mL) and toluene (200 mL). The wet cake was dried under vacuum at ∼45 °C for 6 h to afford 210 g of MSA salt **23** as a white solid (80% yield based on calculated amount of pyrrole **22** input). The process was successfully implemented over six batches using an input of 78 kg of **22** (295 kg of MSA

dx.doi.org/10.1021/op300252n | Org. Process Res. Dev. 2012, 16, 1846−1853

salt **23** obtained): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.47 (s, br, 1H), 6.86 (d, J = 2.8 Hz, 1 H), 6.30 (d, J = 2.8 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 4.15 (q, J = 6.9 Hz, 2 H), 2.39 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.2, 160.9, 125.4, 124.8, 114.8, 107.0, 60.9, 59.7, 14.1, 13.9; IR (KBr, cm^{-1}) 3127, 2907, 2666, 1724, 1700, 1526, 1431, 1306, 1249, 1171, 1107, 1024, 777, 747. Anal. Calcd for $C_{11}H_{18}N_2O_7S$: C, 40.99; H, 5.63; N, 8.69. Found: C, 41.17; H, 5.51; N, 8.61.

Ethyl 4-Hydroxypyrrolo[1,2-f][1,2,4]triazine-5-carboxylate (12). To a slurry of MSA salt **23** (150 g, 0.467 mol) in isopropanol (380 mL) was charged formamidine acetate (85.9 g, 0.817 mol) and TEA (45.5 mL, 0.327 mol). The resulting slurry became a clear solution upon heating to 78−83 °C, and the solution remained clear for ∼1.5 h before the product started to precipitate. The reaction progress was monitored by HPLC until the starting material was consumed (≤0.5%; 5−8 h). Water (750 mL) was then added to the reaction slurry, resulting in a decrease of the reaction temperature from 83 to 60 °C. The slurry was further cooled to 21 °C over 1 h and then was held for 3−16 h and filtered. The product cake was washed with water (3 × 300 mL). The wet cake was dried under vacuum at 40−50 °C to afford **12** (89.1 g, 92% yield; 99.6% HPLC purity) as a white solid. The process was successfully executed over two batches using an input of 130 kg of **23** (140 kg of **12** obtained): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.3 (s, br, 1 H), 7.95 (s, 1 H), 7.41 (d, J = 2.2 Hz, 1 H), 7.07 (d, J = 2.2 Hz, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 154.3, 138.8, 121.5, 120.1, 116.3, 114.0, 60.8, 14.3; IR (KBr, cm^{-1}) 3244, 3107, 2992, 1756, 1721, 1644, 1541, 1372, 1285, 1225, 1173, 1142, 1081, 1040, 794, 748, 734. Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.22; H, 4.23; N, 20.33.

Ethyl 4-(3-Methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazine-5-carboxylate (25). To a slurry of pyrrolotriazine **12** (250 g, 1.21 mol) in toluene (3.0 L) was added DABCO (13.8 g, 0.12 mol) and i-Pr$_2$NEt (274 mL, 1.57 mol). The mixture was stirred for 5 min, and $POCl_3$ (146 mL, 1.57 mol) was added at <35 °C. The reaction mixture was heated to 45 °C over 60 min and held 45 °C for 45 min. The temperature was then increased to 75 °C over 60 min and held at 75 °C for 45 min. Finally, the mixture was heated to 95 °C over 35 min and held at 95 °C until starting material **12** and the related phosphoryl intermediates were ≤1% by HPLC analysis (2−3 h). The batch was cooled to ambient temperature and quenched by the slow addition of aqueous K_2HPO_4 solution (20 wt %, 2.0 L) at <40 °C. The separated rich organic layer was washed with aqueous K_2HPO_4 solution (20 wt %, 1.0 L). The separated organic phase was polish-filtered, and the resulting filtrate was held at ambient temperature and used in the subsequent m-anisidine displacement. Quantitative HPLC analysis indicated that the filtrate contained 248 g (91%) of chloride **24** (3.2 L, KF 0.12%), and no potency loss was observed for the solution after standing for a week at ambient temperature.

The process stream of chloride **24** in toluene (77.5 g/L, 3.2 L, 1.10 mol) was cooled to 15 °C, and i-Pr$_2$NEt (209 mL, 1.20 mol) was added, followed by m-anisidine (135 mL, 1.20 mol) over a period of 15 min at <30 °C (**Caution**: m-anisindine is Ames positive and a GTI). The reaction mixture became a slurry within 0.5 h as the product formed and precipitated along with i-Pr$_2$NEt HCl salt. The mixture was stirred at 25−30 °C until chloride **24** was ≤1.0% by HPLC analysis (3−5 h). Isopropanol (3.0 L) was added, which not only reduced the solubility of the product, but also dissolved i-Pr$_2$NEt HCl salt. The resulting slurry was cooled to 0−5 °C and held at this temperature for 2 h. The slurry was filtered, and the product cake was washed with isopropanol (2 × 500 mL). The wet cake was dried under vacuum at 45 °C to afford the title compound as a white solid (291 g, 77% for two steps from **12**; 99.6% HPLC purity). A modified process, utilizing 0.1 equiv of N-methyl morpholine in place of DABCO in the chlorinating step, was successfully performed in four batches using an input of 28 kg of **12** (166 kg of **25** obtained). The modification improved the impurity profile by eliminating the DABCO-related impurity **28** with a comparable yield of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.1 (s, br, 1 H) 8.12 (s, 1 H), 7.70 (dd, J = 2.2, 2.2 Hz, 1 H), 7.49 (d, J = 3.2 Hz, 1 H), 7.39−7.37 (m, 1 H), 7.19 (d, J = 3.2 Hz, 1 H), 6.73−6.68 (m, 1 H), 4.43 (q, J = 7.2 Hz, 2 H), 3.87 (s, 3 H), 1.44 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 160.1, 152.2, 149.0, 139.4, 129.6, 119.2, 118.1, 114.2, 113.8, 109.7, 107.5, 107.2, 61.4, 55.4, 14.3; IR (KBr, cm^{-1}) 3244, 3107, 2992, 1756, 1721, 1372, 1285, 1225, 1040, 748. Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.93. Found: C, 61.47; H, 5.07; N, 17.85.

(4-(3-Methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazin-5-yl)methanol (1b). A solution of LAH (2.0 M in THF, 40 mL, 80 mmol) was added over 20 min to the slurry of ester **25** (20 g, 64 mmol) in toluene (80 mL) at <40 °C (**Caution**: exothermic reaction!). The reaction mixture was stirred at 28−35 °C until completion (1−3 h) of the reduction by HPLC analysis (starting material ≤0.5%) and then cooled to 10 °C. Acetone (18.8 mL) was slowly added to the reaction mixture at <35 °C (**Caution**: exothermic quench and hydrogen gas evolved!). The resulting mixture was stirred for 30 min and then was added into a mixture of THF (40 mL) and aqueous potassium sodium tartrate solution (25 wt %, 192 g), resulting in a white slurry. The reaction vessel was rinsed with a mixture of THF (40 mL) and water (20 mL), and the rinse was added to the batch. The resulting slurry was stirred for 15 min and filtered. The organic layer was separated from the biphasic filtrate and washed with water (100 mL), followed by concentration at 50−80 °C in vacuo to ∼100 mL. Isopropanol (150 mL) was added into the concentrated solution, and the resulting mixture was concentrated under vacuum. The isopropanol solvent swap was repeated until residual toluene was ≤5% v/v by GC analysis. The mixture was heated to 68−75 °C to dissolve the solids that had precipitated during the solvent swap and then was cooled to 0−3 °C over 2 h. The resulting slurry was agitated at 0−3 °C for >1 h prior to filtration. The product cake was rinsed with IPA−heptane (1:2 v/v, 60 mL) and dried under vacuum at 45−50 °C to give **1b** (15.3 g, 89% yield; 99.6% HPLC purity) as an off-white solid. The process was successfully implemented in four batches using an input of 40 kg of **25** (125 kg of **1b** obtained): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.96 (s, br, 1 H), 7.91 (s, 1 H), 7.44 (s, 1 H), 7.34 (d, J = 2.2 Hz, 1 H), 7.24−7.13 (m, 2 H), 6.64−6.61 (m, 1 H), 6.40 (d, J = 2.2 Hz, 1 H), 4.88 (d, J = 5.1 Hz, 2 H), 3.81 (s, 3 H), 1.41 (t, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 152.3, 147.5, 139.7, 129.5, 117, 4, 115.7, 113.7, 113.3, 110.3, 109.2, 107.1, 59.3, 55.3; IR (KBr, cm^{-1}) 3127, 3066, 2993, 2839, 1652, 1595, 1495, 1261, 1203, 1035, 943, 835, 746. Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.12; H, 5.22; N, 20.72.

dx.doi.org/10.1021/op300252n | Org. Process Res. Dev. 2012, 16, 1846−1853

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Su Pan for developing the HPLC analytical methods and Dr. Simon Leung for the chemical safety evaluation of compound **20**. We also acknowledge Drs. Thomas Razler, Ian Young, Adrian Ortiz, and Jaan Pesti for helpful discussions, together with Chemical Development senior management for support during the preparation of the manuscript.

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(11) Compound **20** is Ames positive, an eye irritant, and a sensitizer and should be handled with caution.

(12) It has been reported that protic solvents favored C-alkylation, and O-alkylated products were the major product in polar aprotic solvents for the alkyation of cyclopentan-1,3-diones. See: Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* **1982**, *38*, 1279−1283. In our case, the protic solvents provided slightly higher (∼20:1) selectivity of the desired C-alkylation over O-alkylation, but product **21** was formed in lower yield due to the increased formation of the bisalkyl impurity (Table 1, entries 1 and 2).

(13) Per the Sigma-Aldrich product label.

(14) We discovered that the source and quality of sodium diethyloxalacetate had an impact on the impurity profile and reaction yield. To distinguish between different lots, the pH of an aqueous solution (1.0 g of the salt in 25 mL of water) of sodium diethyloxalacetate was measured. Batches of sodium diethyloxalacetate that produced an aqueous solution with pH > 9.5 led to higher levels of the bisalkyl impurity and lower yields. These batches required additional acetic acid (>0.12 equiv) to produce levels of the bisalkyl impurity and yields similar to batches of diethyloxalacetate that provided aqueous solutions with a pH < 9.5.

(15) The proton NMR analysis of **21** (after chromatographic purification) clearly reveals that it is a keto form, not an enol, as a double doublet pattern of the α-proton of the ketone **21** at δ 3.1 ppm (see the Experimental Section). In addition, only one peak was observed for **21** in the HPLC chromatogram.

(16) Less than 1% potency loss of **21** was observed after holding the reaction stream for 48 h at room temperature. No potency loss of **22** in the toluene stream after aqueous workup was observed after one week at ambient temperature. However, the reaction stream of **22** without aqueous workup shows about 1% loss of product potency after 19 h at ambient temperature and 6% loss after 4 days.

(17) Upon scaling this protocol, an emulsion layer was observed which needed to be set aside and further processed to recover the product pyrrole. Additional lab development work on this step determined that replacing toluene with isopropyl acetate as the solvent in the telescoped sequence eliminated the formation of the emulsion.

(18) When utilizing **22** in the isopropyl acetate stream, we found that water content played an important role. When the KF was >3 wt %, the hydrogenolysis was complete within 2 h with no impact on the impurity profile. The use of isopropyl acetate removed the periodic venting that was necessary with toluene. Once complete, the solution was filtered, concentrated, and azetropically dried to obtain a water concentration of <1 wt %. This was crucial for the crystallization of MSA salt of **23** as with >1.5 wt % water oiling occurred which fouled the isolation.

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(20) Addition of 1 equiv of TEA, which fully neutralized the MSA, slowed the acid-catalyzed annulation.

(21) During a stress test of the reaction in isopropanol, the isopropyl derivative of **12**, resulting from the ester exchange, was observed at <0.1 HPLC AP after holding the mixture at 80 °C for 12 h. For a

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(24) Compound **24**, a dermal sensitizer (not Ames positive), was not isolated, and its stream was used directly in the subsequent amination.
(25) Impurity **28** was seen in increased levels when higher equivalents of DABCO were used.
(26) A study performed after our development work revealed that replacing DABCO with *N*-methyl morpholine eliminated the impurity **28** and provided comparable yield of product **24**.
(27) After aqueous workup, the solution of chloride **24** in toluene is stable. No potency loss was observed after standing for 3 days at ambient temperature.
(28) An amide impurity resulting from the reaction of *m*-anisidine with the ethyl ester of **25** was consistently observed at <1% in the reaction mixture.
(29) Reduction of an amide to the corresponding amine was reported to proceed faster and cleaner with the LAH·2THF complex in toluene than that with LAH in THF, see: Watson, T. J.; Ayers, T. A.; Shah, N.; Wenstrup, D.; Webster, M.; Freund, D.; Horgan, S.; Carey, J. P. *Org. Process Res. Dev.* **2003**, *7*, 521−532.
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