

## A new and efficient preparation of 2-aminothiazole-5-carbamides: applications to the synthesis of the anti-cancer drug dasatinib

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Dedicated to Professor Franklin A Davis on his 70<sup>th</sup> birthday

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### Abstract

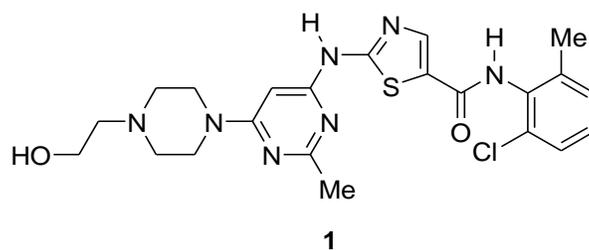
A new and efficient method has been developed for the synthesis of 2-amino-N-(2-chloro-6-methylphenyl)-thiazole-5-carboxamide. The new method involves a chemoselective  $\alpha$ -bromination of  $\beta$ -ethoxyacrylamide followed by a one-pot treatment with thiourea to give the desired 2-aminothiazole-5-carboxylamide in excellent yield. Application of this new method to the efficient synthesis of the anti-cancer drug dasatinib was demonstrated.

**Keywords:** Synthesis, 2-aminothiazole-5-carbamide, anti-cancer drug, dasatinib, SPRYCEL<sup>®</sup>

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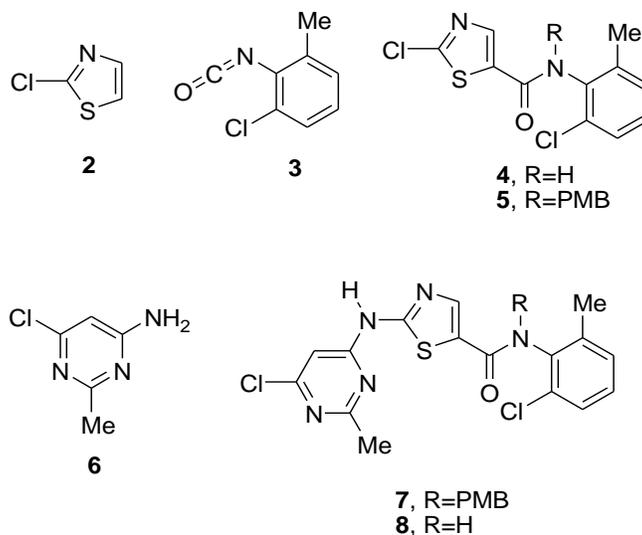
### Introduction

N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]-amino]-1,3-thiazole-5-carboxamide (BMS-354825, dasatinib, SPRYCEL<sup>®</sup>) is a novel multi-targeted kinase inhibitor recently approved in several countries for the treatment of chronic myelogenous leukemia (CML) as well as Philadelphia chromosome-positive acute lymphocytic leukemia (ALL). Dasatinib exhibits greater potency than imatinib mesylate (Gleevec<sup>®</sup>) and inhibits the majority of kinase mutations in imatinib-resistant CML.<sup>1-4</sup> Unlike imatinib, which binds to the inactive conformation of Bcr-Abl, dasatinib binds to the active form of the enzyme.<sup>1,5</sup> The ability to inhibit SRC-family kinases such as Hck and Lyn, in addition to binding to the active conformation of BCR-ABL, may both contribute to the effectiveness of dasatinib against imatinib-resistant tumors.<sup>6</sup>



**BMS-354825, Dasatinib, SPRYCEL®**

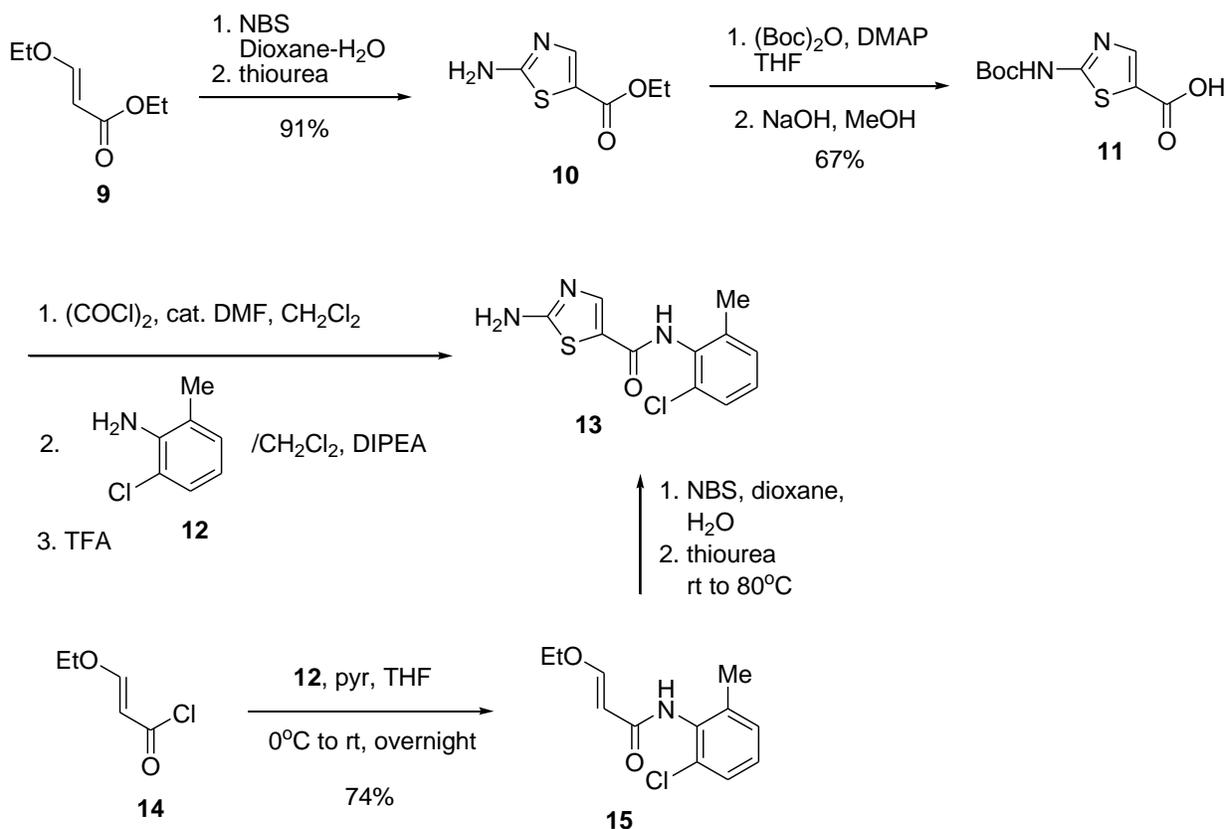
*N*-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-1,3-thiazole-5-carboxamide **1** was previously prepared from 2-chlorothiazole **2** via a sulfur directed ortho-lithiation and subsequent nucleophilic coupling with 2-chloro-6-methylphenyl isocyanate **3** to give the core intermediate, 2-chloro-*N*-(2-chloro-6-methylphenyl)-thiazole-5-carboxamide **4**.<sup>7</sup> Amide nitrogen protection of **4** with NaH and 4-methoxybenzyl chloride followed by another NaH mediated coupling of 4-amino-6-chloro-2-methyl pyrimidine **6** gave an advanced intermediate **7**. Deprotection of the PMB group of **7** afforded the penultimate intermediate, 2-(6-chloro-2-methylpyrimidin-4-ylamino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **8**, which was condensed with 1-(2-hydroxyethyl)piperazine to give final product **1**.<sup>7</sup>



## Results and Discussion

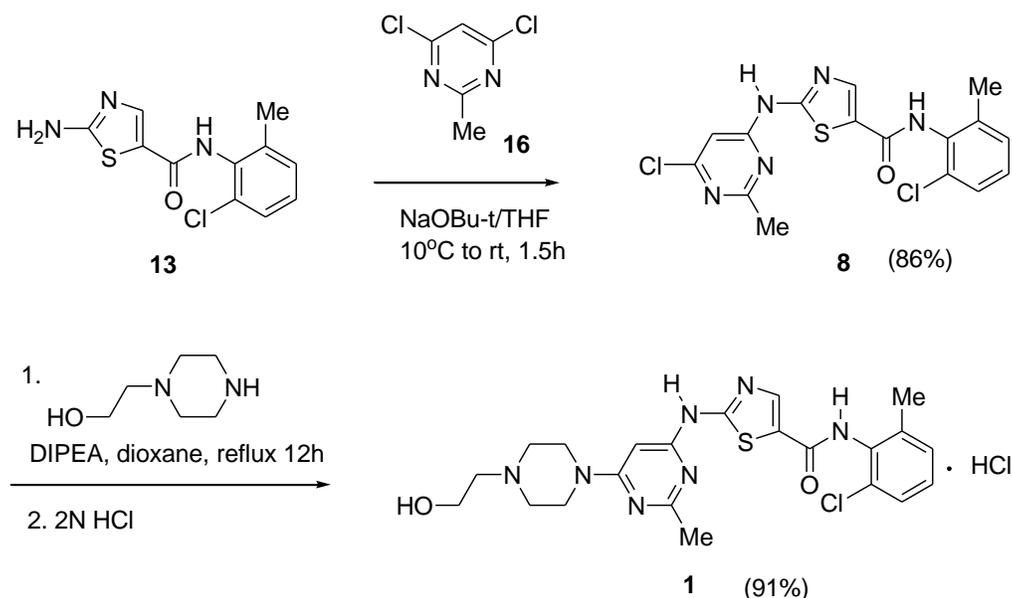
In a separate project, we required a facile method for the preparation of 2-aminothiazole-5-carboxamides to facilitate SAR studies which would also be amenable to large scale synthesis. Our initial focus was to use ethyl 2-aminothiazole-5-carboxylate **10** as core intermediate which

could be readily prepared in large scale using a process that was previously developed by us via electrophilic  $\alpha$ -bromination of ethyl  $\beta$ -ethoxyacrylate **9** followed by thiazole ring formation with thiourea.<sup>8</sup> N-Boc protection of ethyl 2-aminothiazole-5-carboxylate **10**, ester hydrolysis and carboxylic acid group activation followed by coupling with anilines gave the desired 2-N-Boc-aminothiazole-5-carboxamides **13** in fair to good overall yields with simple anilines, which were successfully used in our SAR studies.<sup>7</sup> However, coupling with 2-chloro-6-methylaniline **12** was unsatisfactory and not amenable for large scale synthesis of **1**, presumably due to the steric hindrance of the aniline. Thus, we decided to initially prepare  $\beta$ -ethoxyacrylamide **15** instead by coupling of the readily available  $\beta$ -ethoxy acryloyl chloride **14** with aniline **12**, followed by formation of the 2-aminothiazole-5-carboxamide **13** using an analogous protocol to the one developed for ethyl  $\beta$ -ethoxyacrylate **9**. The primary advantages of this new approach would be elimination of the protection and deprotection steps needed in the previous synthesis, in addition to elimination of the need for use and handling of n-BuLi and NaH on scale. The main concerns, however, were the potential competitive electrophilic bromination on the amide-nitrogen<sup>9</sup> and the phenyl ring<sup>10</sup> vs. the desired  $\alpha$ -bromination. Herein, we report our findings on the  $\alpha$ -bromination of  $\beta$ -ethoxyacrylamide **15**, subsequent thiazole ring formation and overall synthesis of dasatinib **1**.



Thus, treatment of  $\beta$ -ethoxy acryloyl chloride **14** 2-chloro-6-methylaniline **12** in THF using pyridine as base afforded *N*-(2-chloro-6-methylphenyl)  $\beta$ -ethoxy acrylamide **15** in 74% yields.<sup>11</sup> Next, we subjected  $\beta$ -ethoxy acrylamide **15** to the NBS mediated thiazole formation in a mixture of dioxane and water followed by addition of thiourea and heating to effect the ring closure. To our satisfaction, the desired 2-aminothiazole-5-carboxamide **13** was obtained in 95% yield. No *N*-bromination or phenyl ring bromination by-products were observed under these reaction conditions.

With an efficient method available for the large scale synthesis of 2-amino-*N*-(2-chloro-6-methylphenyl)-thiazole-5-carboxamide **13**, we next turned our attention to the direct coupling of **13** with 4,6-dichloro-2-methylpyrimidine **16**.<sup>12</sup> Using NaO-*t*Bu as base, the coupling reaction took place smoothly in THF from 10°C to room temperature. The reaction was complete in 1.5h affording the desired product, 2-(6-chloro-2-methylpyrimidin-4-ylamino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **8** in 86% isolated yield.<sup>7</sup> Coupling of **8** with 1-(2-hydroxyethyl)piperazine in dioxane and subsequent HCl salt formation following the previously reported conditions gave the final product, *N*-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazin-yl]]-2-methyl-4-pyrimidinyl]amino)-1,3-thiazole-5-carboxamide (**1**, dasatinib, SPRYCEL<sup>®</sup>), in 91% yield.<sup>7</sup>



## Conclusions

In summary, a new and efficient method has been developed for the synthesis of 2-aminothiazole-5-carboxamide **13**. The new method involved a chemoselective  $\alpha$ -bromination of  $\beta$ -ethoxyacrylamides followed by a one-pot treatment with thiourea to give the desired 2-aminothiazole-5-carboxamide excellent yields. Compared to previous methods for the

preparation of 2-aminothiazole-5-carboxylamides, this new approach not only avoids the generation and handling of air and moisture sensitive organometallic intermediates, the need for additional protection and deprotection steps, but also affords higher overall yields. Consequently, the new method is simpler in terms of experimental manipulation and operation and is shorter in overall synthetic sequence. Furthermore, the new method was successfully used in the scale synthesis of our newly developed anti-cancer drug dasatinib **1**. The application of this new method for the synthesis of other aminothiazole based biologically active compounds will be reported in due course.

## Experimental Section

**General.** Proton NMR spectra were recorded with a Bruker DRX-400 spectrometer using  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  as solvent and TMS as an internal standard. Chemical shifts ( $\delta$ ) are given from TMS (0 ppm) as internal standard for proton NMR. All other reagents and solvents were commercial products and were used as received unless otherwise noted. All reactions were monitored by HPLC using a Shimadzu LC-10AS system and YMS ODS-A S5 4.6x50mm column with linear gradient system of  $\text{H}_2\text{O-MeOH-H}_3\text{PO}_4$  90:10:0.2 to 10:90:0.2 over 4 min. and at a flow rate of 4 mL/min. All compounds were of >99% purity by analytical HPLC analyses. Melting points are uncorrected.

**(E)-N-(2-Chloro-6-methylphenyl)-3-ethoxyacrylamide 15.** To a cold stirring solution of 2-chloro-6-methylaniline (59.5 g 0.42 mol) and pyridine (68 mL, 0.63 mol) in tetrahydrofuran (600 mL) was added 3-ethoxyacryloyl chloride (84.7 g, 0.63 mol) slowly keeping the temp at 0-5°C. The mixture was then warmed and stirred 2 h. at 20°C. Hydrochloric acid (1N, 115 mL) was added at 0-10°C. The mixture was diluted with water (310 mL) and the resulting solution was concentrated under vacuum to a thick slurry. The slurry was diluted with toluene (275 mL) and stirred 15 min. at 20-22°C then 1 h at 0°C. The solid was collected by vacuum filtration, washed with water (2 x 75 mL) and dried to give 74.1 g (73.6 % yield) of (E)-N-(2-chloro-6-methylphenyl)-3-ethoxyacrylamide **15**.  $^1\text{H NMR}$  (400 Hz,  $\text{DMSO-d}_6$ )  $\delta$  1.26 (t, 3H, J= 7 Hz), 2.15 (s, 3H), 3.94 (q, 2H, J= 7 Hz), 5.58 (d, 1H, J=12.4 Hz), 7.10-7.27 (m, 2H, J=7.5 Hz), 7.27-7.37 (d, 1H, J=7.5 Hz), 7.45(d, 1H, J=12.4 Hz), 9.28 (s, 1H).

**2-Amino-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide 13.** To a mixture of (E)-N-(2-chloro-6-methylphenyl)-3-ethoxyacrylamide **15** (5.00 g 20.86 mmol) in 1,4-dioxane (27 mL) and water (27 mL) was added N-bromosuccinimide (4.08 g, 22.9 mmol) at -10 to 0°C. The slurry was warmed and stirred at 20-22°C for 3h. Thiourea (1.60g, 21 mmol) was added and the mixture heated to 80°C. After 2h, the resulting solution was cooled to 20-22° and conc. ammonium hydroxide (4.2 mL) was added dropwise. The resulting slurry was concentrated under vacuum to about half volume and cooled to 0-5°C. The solid was collected by vacuum filtration, washed with cold water (10 mL) and dried to give 5.3 g (94.9 % yield) of 2-amino-N-

(2-chloro-6-methylphenyl)thiazole-5-carboxamide **13**.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.19 (s, 3H), 7.09-7.29 (m, 2H,  $J=7.5$ ), 7.29-7.43 (d, 1H,  $J=7.5$ ), 7.61 (s, 2H), 7.85 (s, 1H), 9.63 (s, 1H).  $^{13}\text{C}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  172.47, 159.88, 144.08, 143.48, 139.19, 134.05, 132.81, 129.31, 127.31, 121.00, 18.66. Anal. Calcd for  $\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{OS}$ : C, 49.34; H, 3.76; N, 15.69; S, 11.97; Cl, 13.24. Found: C, 49.17; H, 3.37; N, 15.33; S, 11.96; Cl, 13.33.

**2-(6-Chloro-2-methylpyrimidin-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide 8**. To a stirring solution of 2-amino-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **13** (5.00 g, 18.67 mmole) and 4,6-dichloro-2-methylpyrimidine (3.65 g 22.4/mmol) in tetrahydrofuran (65 mL) was added a 30% wt. solution of sodium *t*-butoxide in tetrahydrofuran (21.1 g, 65.36 mmol) slowly with cooling to keep the temperature at 10-20°C. The mixture was stirred at room temperature for 1.5 h and cooled to 0-5°C. Hydrochloric acid, 2N (21.5 mL) was added slowly and the mixture stirred 1.75 h at 0-5°C. The solid was collected by vacuum filtration, washed with water (15 mL) and dried to give 6.63 g (86.4 % yield) of 2-(6-chloro-2-methylpyrimidin-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide **8**.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.24 (s, 3H), 2.59 (s, 3H), 6.95 (s, 1H), 7.26 (d,  $J = 7.7$  Hz, 1H), 7.30 (dd,  $J = 6.1, 6.7$  Hz, 1H), 7.41 (d,  $J = 7.7$  Hz, 1H), 8.32 (s, 1H), 10.02, (s, 1H), 12.24 (br s, 1H), identical by comparisons with literature data.<sup>7</sup>

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