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A Practical Synthesis of 2-Arylamino-6-alkylaminopurines from 2,6-Dichloropurine

Lech Ciszewski, Liladhar Waykole,* Mahavir Prashad, and Oljan Repić

Process R&D, Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Abstract:

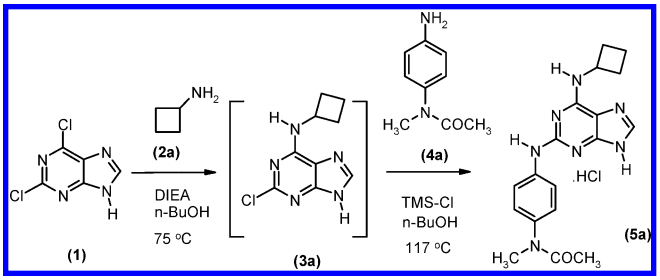
A practical synthesis of *N*-[4-(6-cyclobutylamino-*9H*-purin-2-ylamino)-phenyl]-*N*-methyl acetamide (QAB205, 5a), an anti-asthmatic agent, is described from 2,6-dichloropurine (1) by base-assisted substitution of the 6-chloro substituent with cyclobutylamine (2a) followed by a new trimethylsilyl chloride-catalyzed displacement of the 2-chloro group in intermediate 6-cycbutylamino-2-chloropurine (3a) with an aromatic amine. Both steps can also be carried out in one pot without isolating the intermediate 6-cyclobutylamino-2-chloropurine (3a). The general synthetic utility of this route is demonstrated by synthesizing several 2-arylamino-6-alkylaminopurines (5).

Introduction

Purines and aminopurines are a pharmaceutically important class of compounds. Recently, they have received a great deal of attention due to their important physiological and pharmacological properties.[1] They are reported to have potential as target nucleotide binding proteins that play a significant role in many biological processes.[2] They have been reported to possess antirhinovirus activity.[3] Also, purine scaffolds have been shown to have antitumor activity as kinase inhibitors.[4] Therefore, a large number of purine libraries have been synthesized using solid polymer supports or in solution.[5]

N-[4-(6-Cyclobutylamino-*9H*-purin-2-ylamino)-phenyl]-*N*-methyl acetamide (**5a**) is a potential antiasthmatic agent.[1] While the synthesis of **5a** was straightforward utilizing 2,6-dichloropurine (**1**) as the starting material (Scheme 1), it was necessary for us to optimize this synthesis for large-scale preparation. Our main goals were to improve the displacement of the 2-chloro substituent in intermediate (**3a**) with 4-*N*-methylacetanilidoaniline (**4a**) that required high temperature (130 °C) and to possibly develop a one-pot procedure from (**1**) to make the synthesis more efficient. In this paper we report a practical synthesis of **5a** from 2,6-dichloropurine (**1**) first by base-assisted substitution of the 6-chloro substituent with cyclobutylamine (**2a**), followed by a new trimethylsilyl chloride catalyzed displacement of the 2-chloro group in intermediate **3a** with **4a** in *n*-butanol at 117 °C. Both of the steps can also be carried out sequentially in one pot without isolating the intermediate **3a**. The general synthetic utility of this route is also demonstrated by synthesizing several 2-arylamino-6-alkylaminopurines (Scheme 2).

Scheme 1



Results and Discussion

Original conditions for the reaction of **1** with **2a** involved treatment of **1** (1 equiv) with **2a** (2.0 equiv) in *n*-butanol at 55 °C for 16 h to afford **3a** in 85% yield. Then, the reaction of the resulting **3a** with **4a** (2.7 equiv) in NMP at 130 °C over 6 h afforded the drug substance **5a** in 81% yield as a hemi-hydrochloride salt. These procedures suffered from shortcomings such as irreproducibility, very high reaction temperature, and difficult isolation and purification procedures due to the use of excess amounts of **2a** (2.0 equiv) and **4a** (2.7 equiv). Also the quality of the product was unsatisfactory due to its dark color and contamination with deacylated byproduct.

We focused on optimizing both the steps to achieve operational efficiency. In the first step, use of an excess amount (2 equiv) of the expensive cyclobutylamine **2a** was undesired. We found that the use of 1.1 equiv of **2a** was optimal when used with 1.1 equiv. of *N*,*N*-diisopropylethylamine (DIEA) as an acid scavenger. Also, the reaction time was shortened to 4.5 h when the reaction was carried out at 75 °C instead of 55 °C. Thus, to a mixture of **1** (1 equiv) and *N*,*N*-diisopropylethylamine (1.1 equiv) in *n*-butanol at 75 °C was added a solution of **2a** (1.1 equiv) in *n*-butanol over 1 h. After the addition of **2a**, the reaction mixture was stirred at 75 °C for an additional 3.5 h. The reaction proceeded smoothly and regioselectively as evidenced by

* Corresponding author: liladhar.waykole@novartis.com.

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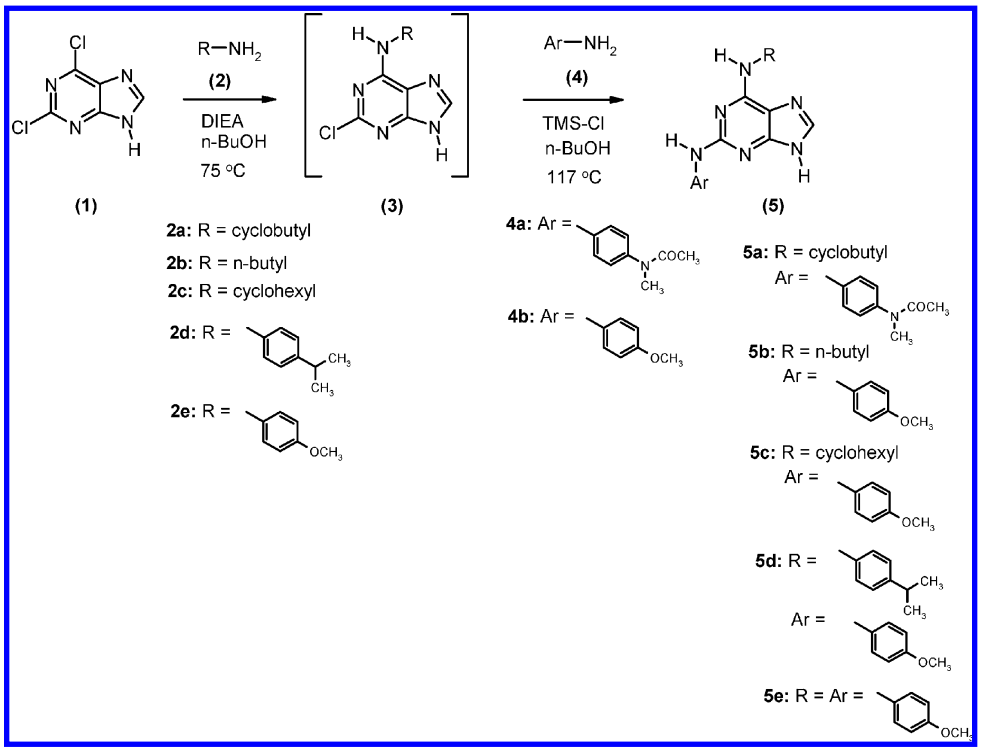
Scheme 2



HPLC analysis. The reaction mixture was cooled to 0−5 °C and was stirred for 1 h prior to the filtration of intermediate **3a**. Intermediate **3a** was isolated in 87% yield with >98% purity.

With a practical preparation of **3a** in hand we decided to investigate the displacement of relatively unreactive chlorine at the C-2 position of **3a** with **4a**. The unreactive nature generally shown by a C-2 chlorine in this case is reinforced by the inductive effect of the amino group introduced at C-6. The weaker nucleophilicity of the amino group of **4a** made this transformation even more challenging (higher temperature was needed). First, we lowered the amount of **4a** to 1.1 equiv from 2.7 equiv since the excess was complicating the isolation and purification of the drug substance **5a**. Use of DMF or DMSO instead of NMP at 130 °C for 12−14 h gave a dark-colored reaction mixture, whereas the use of *n*-butanol at 117 °C and *n*-pentanol at 130 °C gave a complete conversion in 30 and 15 h respectively, and the product **5a** was obtained as a beige solid. To have an optimum filtration rate of the product, *n*-butanol was selected as the solvent. However, the longer reaction time needed to be shortened. To this end we decided to explore catalytic conditions. Literature procedures either used the amines as solvent and/or elevated temperature.[6] Since **4a** is a solid it could not be used as a solvent, and elevated temperature was undesired for the scale-up. Use of sodium bicarbonate (1.2 equiv) and sodium hydroxide (1.2 equiv) in DMF at 130 °C gave no conversion over 10−12 h. Also, no reaction occurred in the presence of 1.1 equiv of *N*,*N*-diisopropylethylamine at 117 °C over 40 h.

After having no success with base catalysis we decided to explore acid catalysis. Our decision was based on the rationale that the protonation of either ring nitrogen N-3 or the 6-amino group would make the six-membered ring electron-deficient and facilitate the displacement of the 2-chloro substituent. To the best of our knowledge there are no reports of acid-catalyzed C-2 chlorine displacement of 2-chloropurine with an amine. The TFA (0.4−10 equiv)-catalyzed C-2 fluorine displacement of 6-alkyloxy 2-fluoro purine with an excess of amine in trifluoroethanol has been recently reported.[7] The use of an excess of TFA and a halogenated solvent were not preferred for scale-up. As our choice of solvent for both steps was *n*-butanol, after completion of the first step without isolation of **3a**, 0.5 equiv of aqueous hydrochloric acid (37%) was added to the reaction mixture at 117 °C, followed by addition of **4a** (1.25 equiv). The reaction was complete in 12 h. However, the isolated yield of **5a** was only 23%, and the filtration of product was very slow. Also the product contained ∼2% of the deacetylated byproduct. When **3a** was isolated and treated with **4a** in the presence of 0.1 equiv of 37% HCl, the product **5a** was obtained in 55% yield containing 1.8% of the deacylated byproduct. The lower yield due to deacylation of **5a**, slow filtration, and formation of deacylated byproduct were attributed to the presence of water in the reaction mixture. Water is not detrimental to the reaction itself, but the deacylation problem occurs in case of **5a** because of water. We also found that at least 0.1 equiv of aqueous hydrochloric acid (37%) was needed for completion of the reaction within 14 h. To improve the yield, minimize the byproduct formation, and improve the filtration, anhydrous hydrochloric

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Table 1. **Reaction of 1 with 2 and 3 with 4**[a]

entry	R−NH_2	time (h) with **1**	Ar−NH_2	time (h) with **3**	TMS-Cl (equiv) one-pot process	product and isolated yield[b] (%)
1	**2a**	4	**4a**	12	0.01 (two-step process)	**5a** 62
2	**2a**	4	**4a**	12	0	**5a** 0
3	**2b**	2	**4b**	9	1.3	**5b** 69
4	**2b**	2	**4b**	10	0	**5b** 0
5	**2c**	7	**4b**	10	1.3	**5c** 61
6	**2c**	7	**4b**	8	0	**5c** 0
7	**2d**	4	**4b**	8	1.3	**5d** 73
8	**2d**	4	**4b**	8	0	**5d** 0
9	**2e**	4	**4b**	12	1.3	**5e** 81
10	**2e**	4	**4b**	13	0	**5e** 0

[a] ***General procedure***: A mixture of (**1**) (1 equiv) and DIEA (1.1 equiv) in *n*-butanol was heated to 75 °C during 25 min with stirring. To the resulting solution was added a solution of **2** (1.1 equiv) in *n*-butanol maintaining the temperature at 75−77 °C. The reaction was monitored for completion (TLC or HPLC). After completion of the reaction, the mixture was cooled to 5 ± 3 °C over a period of 1 h. The suspension was filtered, and the filter cake was washed with *n*-butanol. The filter cake of **3** was collected and dried under vacuum. Then, to a stirred mixture of **3** (1 equiv) and **4** (1.1 equiv) in *n*-butanol at 25 °C TMSCl (0.02 equiv) was added, and the mixture was heated to 117 °C over 1 h. It was stirred at 117 °C until completion of the reaction monitored by TLC or HPLC (12−16 h). The reaction mixture was cooled to 50 ± 5 °C over a period of 2 h and stirred at this temperature for 1 h. The hot suspension was filtered, and the filter cake was washed three times, with warm (∼40 °C) *n*-butanol. The filter cake was collected and dried at 50 °C under vacuum to afford **5**. In a one-pot procedure after completion of the first step, to the suspension of **3** in *n*-butanol a solution of **4** (1.1 equiv) in *n*-butanol and TMSCl (0.5−1.3 equiv) was added. The mixture was heated to 117 °C and was stirred at 117 °C until completion of the reaction monitored by TLC or HPLC (12−16 h). [b] All the compounds gave satisfactory spectroscopy data.

acid was needed. Since the reaction solvent was *n*-butanol, this was easily achieved by adding TMS-Cl (1.5 equiv) to the reaction mixture at 117 °C instead of aqueous hydrochloric acid. However, this led to the formation of 18% of the deacetytlated byproduct. The amount of TMS-Cl needed was optimized to a minimum of 1 mol %. We found that the treatment of an isolated **3a** with **4a** (1.25 equiv) in *n*-butanol at 117 °C using 1 mol % of TMS-Cl in 12 h gave **5a** in 62% yield with >98% purity (0.8% byproduct). A two-step process was the preferred method to achieve higher yield and purity (minimum of deacylated byproduct) of drug substance **5a**. Thus, the process was carried out at a lower temperature, lowering the safety risks in these steps. Both of the steps worked equally well, yielding **5a** in 54% overall yield.

To explore the general applicability of these conditions, several 2-arylamino-6-alkylaminopurines and 2,6-diarylamino purines were synthesized (Scheme 2, Table 1).

All of the above preparations were carried out in *n*-butanol. The first step was carried out in the presence of *N*,*N*-diisopropylethylamine (1.1 equiv) at 75 °C and the second step at 117 °C either in the presence or absence of TMS-Cl. The amount of TMSCl required for the preparation of **5b**−**5e** in a one-pot process was 0.5−1.3 equiv and a minimum of 0.01 equiv in the two-step process. We found that either alkyl or arylamine (**2**−**2e)** could be used for the displacement of C-6 chlorine in **1**. In most cases the reaction was completed in 2−7 h. For the displacement of chlorine at C-2 in **3**, the presence of acid was essential, without which no displacement occurred. However, in the presence of acid the highly basic and nucleophilic alkylamine (**2**−**2c**) could not be used in this step as the protonated alkylamine failed to react. Thus, the TMS-Cl or acid-catalyzed C-2 substitution in **3** is limited to anilines. The 2,6-diaminopurines (**5a**−**5e)** were obtained in moderate to a good yields.

In summary, a highly efficient method for the preparation of 2,6-diaminopurine derivatives **5** has been developed.[8] Substitution at the 6-position of 2,6-dichloropurine (**1**) is a base-catalyzed and completely regiospecific process while substitution at the 2-position in **3** is found to be an acid-catalyzed process. No regeoisomers were detected at any step by HPLC analysis. The presence of aqueous hydrochloric acid (0.1−0.5 equiv) or trimethylsilyl chloride (0.01−0.5 equiv) is essential for the efficiency of second step, which is limited to aromatic amines. The use of aqueous hydrochloric acid was not preferred for the preparation of **5a** as it led to the formation of deacylated byproduct. The 2,6-disubstitution process in **1** with alkylamine and arylamine, respectively, can be carried out in two separate steps or sequentially in one-pot. The two-step procedure was applied for the preparation of **5a** to minimize the formation of deacylated impurity.

Experimental Section

^{1}H and ^{13}C NMR spectra were measured on a Bruker AVANCE DPX-300 MHz spectrometer in either $CDCl_3$ or DMSO-d_6. Analytical high performance liquid chromatography (HPLC) was carried out using Waters Alliance 2690 Separations module, a Waters 996 Photodiode ARRAY detector, and a C_{18} steel column, 5 μm particle size (4.6 mm × 250 mm). UV detection and mobile phase were varied, depending upon substrate. In-process control (TLC) was run using silica gel precoated plates with a 250-μm layer thickness. Plates were visualized with either 5% ethanolic phosphomolybdic acid solution and heat or 254 UV light, depending upon substrate.

Materials. The starting material (**1**) was purchased from a vendor (Borregaard, UK), and (**4a**) was purchased from L&L Technologies. All other reagents and solvents were purchased from various commercial sources and used without further purification. All of the isolated intermediates were analyzed as indicated above and used directly in subsequent steps. All reactions were run in an inert nitrogen atmosphere unless otherwise indicated.

2-Cyclobutylamino-6-chloropurine (3a). A 12-L, 4-necked, round-bottomed flask, equipped with a condenser, thermom-

(8) Ciszewski, L. A.; Waykole, L. M. (Novartis). U.S. Patent 6,897,307, May 24, 2005.

eter, and addition funnel under nitrogen atmosphere was charged with 492.9 g (2.61 mol) of 2,6-dichloro-9H-purine (**1**), 497.7 mL (2.87 mol) of *N*,*N*-diisopropylethylamine (DIEA), and 3.65 L of anhydrous *n*-butanol. The mixture was stirred and warmed to 75 °C during about 25 min. To the solution was added 244.9 mL (2.87 mol) of cyclobutylamine (**2a**) in 1.25 L of anhydrous *n*-butanol over 1 h at 75−77 °C. The reaction mixture was stirred at 75 °C for 4.5 h. The reaction was monitored by HPLC for completion. The mixture was cooled to 5 ± 3 °C over a period of 1 h. The suspension was filtered, and the filter cake was washed three times, with a total of 0.9 L of (∼5 °C) *n*-butanol. The filter cake was collected and dried at 75 °C/20 mm of Hg for 24 h to give 506.6 g of **3a** as a light-yellow crystalline solid: yield: 86.9% with purity 98%; mp 216-8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.03 (bs, 1H), 8.39 (bs, 1H), 8.12 (bs, 1 H), 4.60 (bs,1H), 2.24 (bs, 2H), 2.11 (b, s, 2 H), 1.6 (bs, 2H).

***N*-[4-(Cyclobutylamino-*9H*-purin-2-ylamino)-phenyl]-*N*-methyl-acetamide (5a).** A 5-L, 4-necked, round-bottomed flask, equipped with a condenser, thermometer, and addition funnel under nitrogen atmosphere was charged with 479.8 g (2.15 mol) of 2-chloro-*N*-cyclobutyl-9H-purin-6-amine (**3a**), 387.5 g (2.36 mol) of *N*-(4-aminophenyl)-*N*-methyl-acetamide (**4a**), and 3.6 L of dry *n*-butanol. The mixture was stirred at room temperature, and 2.72 mL (0.02 mol) of chlorotrimethylsilane was added to it. The reaction mixture was warmed to 117 °C over 50 min. It was stirred at 117 °C for 12.5 h. The reaction mixture solution was cooled to 50 ± 5 °C over a period of 2 h and stirred at this temperature for 1 h. The hot suspension was filtered, and the filter cake was washed three times, with a total of 1.2 L of warm (∼40 °C) *n*-butanol. The filter cake was collected and dried at 50 °C/20 mmHg for 24 h to yield 514.3 g of light-yellow crystalline solid **5a**; yield 61.8% with purity >98%; mp 270−2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (bs, 1H), 9.36 (bs, 1H), 8.72 (bs, 1H), 7.78−7.75 (bd, 2H), 7.29−7.26 (bd, 2H), 4.57 (bs, 1H), 3.12 (s, 3 H), 2.35 (m, 2H), 2.14−2.08 (m, 2 H), 2.08 (bs, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.5, 150.5, 149.07, 138.9, 138.67, 128.4, 128.2, 127.6, 122.1, 120. 6, 105.9, 60.7, 46.21, 36.9, 30.2, 22.5, 15.32; MS *m*/*z* 351.3 (M^+); Anal. Calcd for $C_{18}H_{22}ClN_7O$: C, 55.74; H, 5.72; N, 25.28. Found: C, 55.74; H, 5.86; N, 24.91; IR: 3422, 3279, 3123, 2985, 29847, 2870, 1560, 1476, 1431, 1394, 1337, 1318, 1250, 1176, 1145, 844, 782, 767, 727, 605, 562.

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