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Selective Amidation of 2,6-Dihalogenopurines: Application to the Synthesis of New 2,6,9-Trisubstituted Purines

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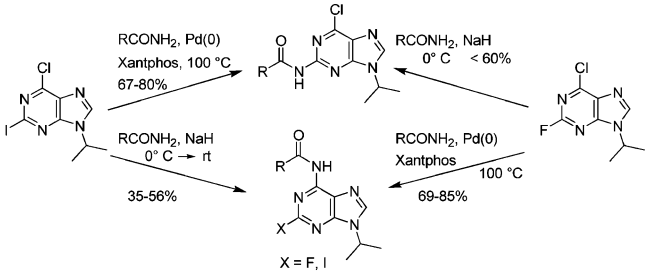
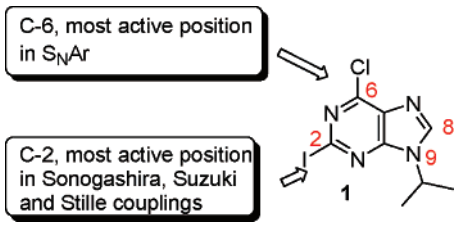


We report herein the palladium(0)/Xantphos-catalyzed cross-coupling of various amides with 2,6-dihalogenopurines, with substituent-dependent regioselectivity. Furthermore, subjecting the same 2,6-dihalogenopurines to S_NAr conditions with amide/NaH in DMF leads to inverted regioselectivity albeit in lower yield. These methodologies allow the two-step synthesis of new 2,6,9-trisubstituted purines from readily available 2,6-dihalogenopurines.

A great variety of di-, tri-, or tetrasubstituted purines so far described in the literature have been found to be potent inhibitors of chaperone HSP90, protein kinases (MAP, Src, and Cdk), sulfotransferases, phosphodiesterases, and microtubule assembly, inducers of interferon and (de)differenciation, antagonists of adenosine receptors, and corticotropin-releasing hormone receptors.[1] This wide range of biological activities displayed by purines is confered by the diversity of the substituents that can be combined on the C-2, C-6, C-8, and N-9 centers (Scheme 1). It is therefore of great interest to explore new types of substituents on the purine ring of which introduction of an amide function at positions 2 and/or 6 is particularly pertinent since known inhibitors of various protein kinases have been improved in this way.[2,3] Whereas many 2,6-diaminopurine derivatives (roscovitine, purvalanol)[1] exhibit potent biological activities,

SCHEME 1. Structure of the Purine Ring



6-amido-2-aminopurines have not yet been explored and, therefore, could find new applications in biology.

Following our previous efforts to synthesize 2-amidopurines from 6-amino-2-iodopurines,[4] the goal of the present work was to synthesize purine derivatives bearing the alternative combination of an amide at the 6-position and an amine at position 2 from a readily available 2,6-dihalogenopurine such as **1**[1] (Schemes 1 and 2). However, according to the literature (Scheme 1), an initial amination step (S_NAr) of **1** would occur at position 6.[5−8] Thus, to prepare a 6-amidopurine from **1**, the amidation step must be carried out first. While 6-amidopurines can be synthesized in two steps from 2,6-dihalogenopurine (amination followed by acylation[9−11]), a more straightforward method would be a direct amidation of 2,6-dihalogenopurine **1**. Although Pd(0)-catalyzed amidations of 6-bromo-[12] and 6-chloropurine[13] have been described during the progress of our work, the regioselectivity in amidations of 2,6-dihalogenopurines has not yet been studied. Therefore, this paper reports the first examples of regioselective amidation of 2,6-dihalogenopurines via an efficient Pd(0)-catalyzed reaction using Buchwald conditions.[14]

Palladium-catalyzed reactions on purines can be performed by taking advantage of the well-known regioselectivity between the 6 and 2 positions in Suzuki,[15] Sonogashira,[16,17] and Stille[18] reactions. For example, Pd(0)-catalyzed alkyne cross-coupling with **1**, at room temperature, provides the 2-alkynyl derivative

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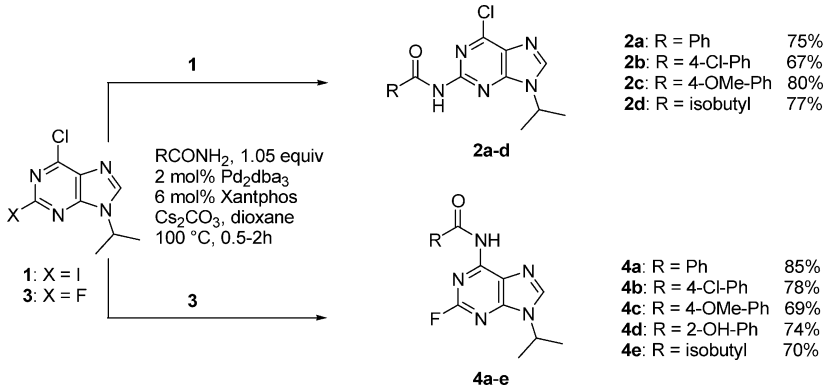
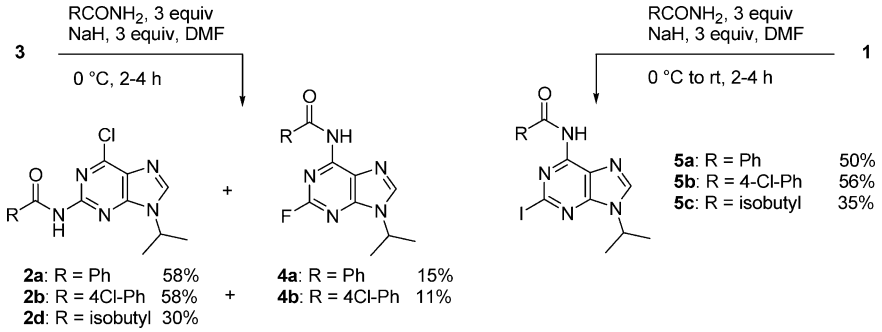
SCHEME 2. Palladium-Catalyzed Amidation of 2,6-Dihalogenopurines



SCHEME 3. Synthesis of 2-Amido- or 6-Amidopurines Using Amide/NaH



in high yield. In this context, we first investigated the cross-coupling of 1.05 equiv of different amides (aryl or alkyl) and 6-chloro-2-iodopurine **1**, in the presence of 2 mol % of Pd_2dba_3, 6 mol % of Xantphos, and 1.4 equiv of Cs_2CO_3 in anhydrous dioxane at 100 °C, according to the conditions described by Buchwald.[14] These conditions led to the regioselective formation of 2-amidopurines **2a**−**d** in 67−80% yield (Scheme 2). As proof of the regioselectivity, ^{13}C NMR experiments revealed the disappearence of the characteristic signal of the C-2-I of **1** (δ = 116.4 ppm) and appearance of a new signal for C-2-NHCOR (δ = 151−153 ppm). In addition, the structure of compounds **2a**−**d** was also confirmed by their mass spectra, which showed the presence of the two isotopes of the chlorine atom in a 3/1 ratio. This regioselectivity is comparable to that observed in Sonogashira or Suzuki coupling when applied to the same dihalogenopurine **1**. Interestingly, Buchwald amidation of **1** was significantly faster than the previously reported amidation of various aryl halides (2 h vs 18−24 h).[14] We found that reaction of more than 1 equiv of amide led to trace amounts of 2,6-diamidopurines, while no reaction occurred in the absence of palladium catalyst.

When Buchwald amidation conditions where applied to 6-chloro-2-fluoropurine[19] **3** (Scheme 2), a different regioselectivity was observed giving exclusively the 6-amido substituted purines **4a**−**e** in good yield (69−85%). The structure of these compounds (**4a**−**e**) was unambiguously confirmed by ^{13}C NMR experiments showing the characteristic splitting of C-2 (d, J_{C-F} = 200 Hz) and C-4 and C-6 (d, $J_{C-F} \approx$ 18 Hz) due to the large coupling with the adjacent fluorine atom. No reaction occurred at room temperature, and incomplete conversion was observed below 100 °C.

As an alternative to the Pd(0)-catalyzed cross-coupling of amides to 2,6-dihalogenopurines, a mixture of amide and NaH[20] was reacted with **1** in anhydrous DMF to give the 6-substituted purines **5** as the sole products in moderate yield (35−56%) (Scheme 3). Lower yields were observed with less than 3 equiv of amide/NaH. Interestingly, the regioselectivity of this typical S_NAr-type reaction was inverted as compared to the palladium-catalyzed amidation of **1** (Scheme 2). When the 6-chloro-2-fluoropurine **3** was subjected to the same reaction conditions, 2-substituted purines (**2a**,**b**,**d**) were obtained as the main products as well as a small amount of 6-substituted purine (**4a**,**b**) (Scheme 3). This substrate-dependent regioselectivity, although incomplete, is particularly noteworthy as it allows access to 2-amido-6-aminopurines of biological interest.[4]

With the goal in mind of synthesizing 6-amido-2-aminopurines, we focused our attention on 6-amido-2-fluoropurines **4a**−**d** (Scheme 4). Substitution at position 2 of 6-amido-2-iodopurine **5** with various amines would involve prolonged reaction time (>24 h) and high temperature (>120 °C), which may be deleterious to the amide at 6. However, a palladium-catalyzed amination[21−24] may be used to overcome the low reactivity of the iodine atom at position 2 in **5** toward S_NAr. Therefore, since

(19) Compound **3** was prepared from commercially available 2-amino-6-chloropurine and sodium nitrite in aqueous tetrafluoroboric acid as described by: Gray, N. S.; Kwon, S.; Schultz, P. G. *Tetrahedron Lett.* **1997**, *38*, 1161. This was followed by a Mitsunobu reaction with isopropyl alcohol, according to a modification of ref 5. See the Supporting Information for the preparation of **3**.

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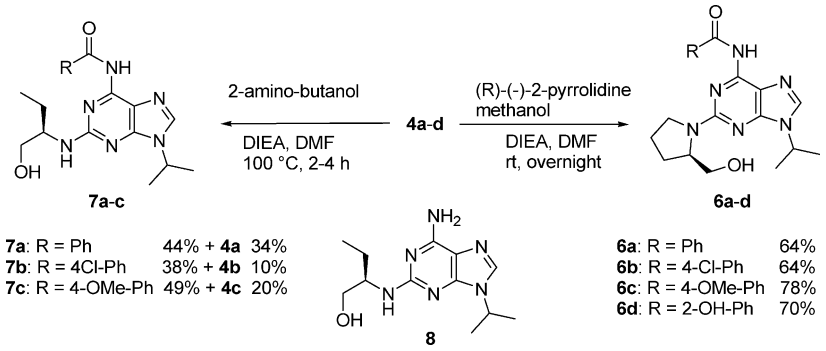
SCHEME 4. Synthesis of 2-Amino-6-amidopurines



the fluorine atom is more reactive than iodine toward S_NAr conditions, 6-amido-2-fluoropurines **4** (Scheme 2) are valuable intermediates that can be subjected to an additional S_NAr with various amines to provide interesting analogues of known inhibitors of biological targets such as Cdk's.

Thus, substitution of the fluorine atom in **4a**−**d** (Scheme 4) with (*R*)-(−)-2-pyrrolidine methanol in DMF was achieved at room temperature and gave the corresponding trisubstituted purines **6a**−**d** in good yield, whereas substitution of the fluorine atom using a stoichiometric amount of primary amine ((*R*)-(−)-2-aminobutanol) required heating to 100 °C and led to **7a**−**c** in moderate yield.

Fluorine substitution with excess amine and prolonged reaction times led to decreased yields of the desired products and the formation of significant amounts of 6-aminopurine **8** (Scheme 4) and *N*-(1-hydroxymethylpropyl)benzamide (not shown). In each case, these products were isolated by chromatography and could be rationalized by attack by the amine at the amide carbonyl of **4a**−**c**.

In conclusion, the regioselectivity of the amidation of 2,6-dihalogenopurines strongly depends on the reaction conditions (Pd(0) versus S_NAr) and opens an easy access to 2- or 6-amidopurines from the same precursor. Overall, the methods of amidation reported in the present paper are straightforward using readily available starting materials. We have shown that Buchwald amidation (Pd_2dba_3, Xantphos, and Cs_2CO_3 in dioxane at 100 °C) of 6-chloro-2-fluoropurine **3** is regioselective at position 6. In contrast, when an iodine atom is present at position 2 (as in **1**), the 2-amido-6-chloropurine derivative **2** is obtained regioselectively. An alternative method using $RCONH_2$/NaH in DMF (S_NAr) allowed us to achieve the inverted regioselective amidation at position 6 in the presence of an iodine atom at position 2. Interestingly, this reaction was performed at 0 °C, but in lower yield as compared to the Pd(0) cross-coupling amidation. This S_NAr-type reaction of 6-chloro-2-fluoropurine derivative **3** gave selectively the 2-amido-substituted purine **2** and a small amount of the 6-amido-substituted purine **4**. In addition, in order to obtain the desired 6-amido-2-aminopurines, the 6-chloro-2-fluoropurine **3** is the molecule of choice to perform Pd(0)-catalyzed amidation at position 6, followed by S_NAr at position 2 with various amines.

The synthesis of several new trisubstituted purines (**6a**−**d**, **7a**−**c**) bearing an amine at position 2 and an amide at position 6 highlights the potential of our strategy from intermediate **3**. The biological activity of these new purine derivatives is under investigation and will be reported in a separate article.

Experimental Section

General Procedure for Pd-Catalyzed Couplings of 2,6-Dihalogenopurines and Amides As Illustrated by the Synthesis of *N*-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)-3-methylbutyramide (2d). A Schlenk tube was charged with 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1**[6] (198 mg, 0.61 mmol), isovaleramide (66 mg, 0.65 mmol), cesium carbonate (280 mg, 0.86 mmol), Pd_2dba_3 (12.4 mg, 0.013 mmol), and Xantphos (21.2 mg, 0.036 mmol). The Schlenk tube was fitted with a condenser, capped with a rubber septum, evacuated, and backfilled with argon. This evacuation/backfill was repeated twice. Then 1,4-dioxane (4 mL) was added through the septum. The mixture was stirred for 1 h at 100 °C. The reaction mixture was then cooled to room temperature and partitioned between H_2O/CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The yellow solid was purified by flash chromatography on silica gel (0−3% EtOH/CH_2Cl_2) to afford the title compound **2d** (140 mg, 77%) as a pale yellow amorphous solid: mp 175−177 °C. An analytical sample was obtained by trituration with Et_2O as a white solid (72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05, (d, J = 6.7 Hz, 6H),1.64 (d, J = 6.8 Hz, 6H), 2.27 (sept, J = 6.7 Hz, 1H), 2.65 (bd, J = 6.7 Hz, 2H), 4.85 (sept, J = 6.8 Hz, 1H), 8.05 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 22.5, 25.5, 46.3, 47.9, 128.3, 142.3, 150.9, 151.5, 152.2, 171.9; MS (electrospray) *m*/*z* 296.1 (45) $[M + H]^+$, 298.1 (10) $[M + H]^+$, 318.1 (100) $[M + Na]^+$, 320.1 (30) $[M + Na]^+$. Anal. Calcd for $C_{13}H_{18}ClN_5O$: C, 52.79; H, 6.13; N, 23.68. Found: C, 52.69; H, 6.33; N, 23.59.

***N*-(2-Fluoro-9-isopropyl-9*H*-purin-6-yl)-3-methylbutyramide (4e).** The same procedure as above was followed with 6-chloro-2-fluoro-9-isopropyl-9*H*-purine **3**[19] (198 mg, 0.920 mmol), isovaleramide (101 mg, 1 mmol), cesium carbonate (421 mg, 1.29 mmol), Pd_2dba_3 (17.5 mg, 0.019 mmol), Xantphos (32.1 mg, 0.055 mmol), and dioxane (5.5 mL). The residue was purified by flash chromatography on silica gel (1% EtOH/CH_2Cl_2) to afford the title compound **4e** (181 mg, 70%) as a yellow solid. An analytical sample was obtained by recrystallization from hot heptane as off-white crystals: mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05, (d, J = 6.7 Hz, 6H), 1.62 (d, J = 6.8 Hz, 6H), 2.28 (m, 1H), 2.83 (bd, J = 6.7 Hz, 2H), 4.81 (sept, J = 6.8 Hz, 1H), 8.07 (s, 1H), 8.97 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 22.5, 25.5, 46.6, 47.89, 120.2, 141.1, 150.7 (d, J = 19 Hz), 152.6 (d, J = 18 Hz), 157.8 (d, J = 212 Hz), 172.9; MS (electrospray) *m*/*z* 302 (100) $[M + Na]^+$, 280 (30) $[M + H]^+$. Anal. Calcd for $C_{13}H_{18}FN_5O$: C, 55.90; H, 6.50; N, 25.07. Found: C, 55.53; H, 6.35; N, 25.06.

General Procedure for Amidation of 2,6-Dihalogenopurines with Amides Using NaH As Illustrated by the Synthesis of *N*-(2-Iodo-9-isopropyl-9*H*-purin-6-yl)benzamide (5a). To a suspension of NaH (60% in mineral oil, 42 mg, 1 mmol) in anhydrous DMF (2.5 mL) was added at once benzamide (115 mg, 0.95 mmol), and the mixture was stirred at room temperature for 1.5 h. To the resultant thick white suspension cooled to 0 °C was added dropwise

a solution of 6-chloro-2-iodo-9-isopropyl-9*H*-purine **1** (102 mg, 0.32 mmol) in anhydrous DMF (1.1 mL). The reaction mixture was allowed to warm to room temperature overnight. The DMF was evaporated off after quenching with a few drops of water. The resulting crude mixture was partitioned between H_2O/CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The yellow solid was purified by flash chromatography on silica gel (0−1% EtOH/CH_2Cl_2) to afford the title compound **5** (69 mg, 50%) as a yellow amorphous solid. An analytical sample was obtained by trituration with Et_2O as a white solid (53%): mp 181−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, J = 6.6 Hz, 6H), 4.93 (sept, J = 6.6 Hz, 1H), 7.52 (m, 2H), 7.60 (m, 1H), 8 (m, 3H), 8.74 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23, 47.9, 118, 124.1, 128.4, 129.2, 133.3, 133.4, 141.1, 149.5, 153.6, 164.8; MS (electrospray) *m*/*z* 408.3 (70) $[M + H]^+$, 430.3 (100) $[M + Na]^+$. Anal. Calcd for $C_{15}H_{14}IN_5O$, H_2O: C, 42.37; H, 3.79; N, 16.47. Found: C, 42.77; H, 3.56; N, 16.61.

General Procedure for Couplings of Compounds 4a−d and (R)-(−)-2-pyrrolidinemethanol As Illustrated by the Synthesis of 2-Hydroxy-*N*-[2-((*R*)-(−)-2-hydroxymethylpyrrolidin-1-yl)-9-isopropyl-9*H*-purin-6-yl]benzamide (6d). To a solution of compound **4d** (129.5 mg, 0.41 mmol) in anhydrous DMF (2 mL) were successively added *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol) and (*R*)-(−)-2-pyrrolidinemethanol (85 μL, 0.92 mmol). The mixture was stirred overnight at room temperature. The DMF was then evaporated off, and the residue was purified by flash chromatography on silica gel (1−2% MeOH/CH_2Cl_2) to give a white solid which was further triturated with Et_2O to afford the title compound **6d** (114 mg, 70%) as a yellow solid: mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, J = 6.7 Hz, 6H), 1.81 (m, 1H), 1.99−2.19 (m, 3H), 3.68−3.90 (m, 4H), 4.41 (m, 1H), 4.68 (sept, J = 6.7 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.74 (s, 1H), 7.86 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.2, 24, 29.4, 47, 48.5, 61, 69, 116.1, 117, 117.9, 118.9, 128.9, 134.6, 137.9, 150, 152.9, 160.8; MS (electrospray) *m*/*z* 397.2 (45) $[M + H]^+$, 419.2 (100) $[M + Na]^+$. Anal. Calcd for $C_{20}H_{24}N_6O_3$: C, 60.59; H, 6.10; N, 21.20. Found: C, 60.36; H, 6.07; N, 21.25.

General Procedure for Couplings of Compounds 4a−c and (*R*)-(−)-2-aminobutan-1-ol As Illustrated by the Synthesis of *N*-[2-((*R*)-(−)-1-Hydroxymethylpropylamino)-9-isopropyl-9*H*-purin-6-yl]benzamide (7a). To a solution of compound **4a** (70 mg, 0.234 mmol) in anhydrous DMF (1.5 mL) were successively added *N*,*N*-diisopropylethylamine (110 μL, 0.631 mmol) and (*R*)-(−)-2-aminobutan-1-ol (25 μL, 0.264 mmol). The mixture was stirred for 6 h at 110 °C. The DMF was then evaporated off, and the residue was purified by flash chromatography on silica gel (1−3% EtOH/CH_2Cl_2) to give the title compound **7a** (38 mg, 44%) as a yellow pale oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1 (t, J = 7.5 Hz, 3H), 1.53−1.67 (m, 8H), 3.64−3.89 (m, 2H), 4 (m, 1H), 4.65 (sept, J = 6.7 Hz, 1H), 5.59 (bs, 1H), 7.46 (m, 2H), 7.55 (m, 1H), 7.70 (s, 1H), 7.99 (d, J = 7.3 Hz, 2H), 9.3 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 22.1, 22.2, 24.7, 46.8, 55.4, 66, 116.4, 127.8, 128.5, 132.3, 134, 137.2, 149.6, 153, 159.3, 165.2; HRMS (ESI) calcd for $C_{19}H_{24}N_6O_2Na$ $[(M + Na)^+]$ 391.1853, found 391.1859.

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Supporting Information Available: ^{1}H and ^{13}C NMR and MS data for compounds **2a−d**, **4a−e**, **5a−c**, **6a−d**, **7a−c**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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