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Direct B-Alkyl Suzuki−Miyaura Cross-Coupling of 2-Halopurines. Practical Synthesis of ST1535, a Potent Adenosine A_{2A} Receptor Antagonist

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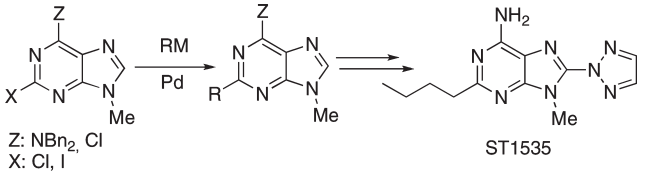

The scope and limitations of using palladium-catalyzed cross-coupling reactions of diverse butyl metal species with two different 2-halopurines were evaluated. While tributylboranes reacted readily and regioselectively with both 2-chloro-6-dibenzylaminopurines and 2-iodo-6-chloropurines, all the other alkyl metal species were much less reactive and gave very poor yield and/or selectivity of the desired product. This protocol was applied to the synthesis of an important adenosine A_{2A} receptor antagonist, ST1535.

The biological importance of purine bases has long been recognized.[1] Furthermore, substituted purines are important structural elements of drug molecules and have been demonstrated to provide high-affinity ligands for a variety of proteins/receptors and enzymes.[2−4] In particular, purines bearing alkyl substituents attached to ring carbon atoms dramatically influence their base-pairing ability, selective binding to target cells, and stability toward enzymatic degradation/metabolism. Thus, efficient and selective ways to introduce an alkyl chain on the purine core are highly desirable. As a part of our research in the field of adenosine A_{2A} receptor antagonists as attractive nondopaminergic anti-Parkinson's agents, we designed and synthesized new scaffolds containing the purine core as the binding motif to adenosine A_{2A} receptors.[5] In particular, we focused our attention on 2-alkyl-6-amino-8-triazolpurines with ST1535 being the most potent and adenosine selective of a series of analogues currently in phase II clinical trials.[6] The presence of a nonfunctionalized alkyl chain in position 2 of the heterocyclic ring makes the structure synthetically challenging to prepare (Figure 1).

Classical methods for the preparation of 2-alkylpurines are based on ring-closure reactions/heterocyclization of appropriately substituted pyrimidines or imidazoles with carboxylic acid equivalents and usually involve multistep procedures and proceed with moderate to low yields.[7] More recently, transition metal-catalyzed cross-coupling reactions involving sp^2-hybridized carbon nucleophiles and aryl and vinyl halides have altered organic synthesis enormously[8] and many highly efficient and mild protocols for C−C bond construction have emerged and can be considered excellent alternatives. Yet, few comprehensive studies have been published concerning the analogous cross-coupling of C(sp^3)-hybridized organometallics with aryl halides.[9] Perhaps the most utilized C−C bond forming cross-coupling reactions when an sp^3 carbon in the coupling event is involved are the B-alkyl Suzuki−Miyaura, Stille, and Negishi reactions. Among them, the Suzuki coupling has gained significant attention due to its mildness, versatility, and reduced environmental impact. Our interest in selective adenosine A_{2A} receptor antagonists as new anti-Parkinson's agents has focused attention on C2-alkyl-substituted purine derivatives having a C6-free amino group and a triazole heterocycle in position 8. A focused library of potential A_{2A} antagonists has been designed and the Stille reaction

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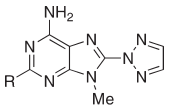

FIGURE 1. General structure of A_{2A} antagonist and ST1535.

has been used to introduce different alkyl chains.[5a] Despite the fact that the Stille reaction was very useful to introduce alkyl chains in the less reactive 2-position of the purine, it had several drawbacks, including toxicity of the reagents and byproduct, low turnover number (TON) and turnover frequency (TOF), harsh reaction conditions, and problematic final purification. Herein, we report on the scope and limitations of the utilization of different butyl metal reagents in the synthesis of 2-butyl-substituted purines as an alternative synthetic methodology to the Stille reaction and its application in the synthesis of ST1535.[10] First, we tried to optimize the catalytic system and reaction conditions of 6-dibenzylamino-2-chloro-9-methylpurine, previously reported by us, with different butyl metal species. Results of the cross-coupling reactions are reported in Table 1.

Although there are several reports of Negishi couplings on 2-halopurines[11] and it is probably the most convenient way to introduce alkyl groups onto N-alkylated purines, no reaction occurred on **1** using commercially available 1 M BuZnBr in THF under standard reaction conditions (entry 2). Butyl zinc bromide generated from BuLi or BuMgBr and $ZnBr_2$ with Pd(dppf)Cl_2 also did not afford the coupling reaction (entry 3). We then turned our attention to stable and commercially available alkyl boron derivates such as butyl boronic acid and butyl trifluoroborates.[12] Because of their unique reactivity and benign features, both of these seemed to be promising reagents for the direct introduction of alkyl groups to the C2 position of purines. Unfortunately, only trace amounts of product were found with both reagents (entries 4−9). Only in the case of trifluoroborate using the best conditions reported by Molander[13] was 11% of the product obtained (entry 10). The small success of the B-alkyl Suzuki−Miyaura reactions with potassium alkyltrifluoroborates and alkyl boronic acids did not discourage us to test other alkyl metal reagents based on boron. Normally, B-alkyl-9BBNs are used but must be prepared and used in situ.

Moreover, the preparation of B-alkyl-9BBNs bearing lower alkyl groups is inconvenient as it involves hydroboration of volatile alkenes (in our case butene) or other tedious operations. On the other hand, some tri-*n*-alkylboranes are commercially available or conveniently prepared from Grignard reagents and have been reported in a few cross-coupling reactions.[14] Gratifyingly, when commercially available tri-*n*-butylborane with 2 mol % Pd(dppf)Cl_2, Cs_2CO_3 (2 equiv), and chloropurine **1** was used, satisfactory conversion and yield of the desired product **2a** was obtained (entry 11). Optimization of the reaction conditions in terms of catalyst loading, base, and solvent (data not shown) achieved complete conversion and very good yield (entry 12). Variation of the organoborane was also carried out, using tri-*n*-ethylborane, which gave the desired product **2b** in comparable yield (entry 13). Thus, this procedure can replace the Stille coupling in the synthesis of ST1535 that can be obtained by using the sequence already reported.[5a] The existing synthesis of ST1535 presents some limitations other than the C−C bond formation, however, such as the use of very expensive 2,6-dichloropurine as the starting material, the need to first introduce the protected amino group in the more reactive C6 position, and, consequently, the problematic final deprotection with triflic acid.

To further improve the overall efficiency of the synthesis of ST1535 and explore the scope and limitations of this B-alkyl Suzuki coupling with trialkylborane, the more challenging and readily available substrate 6-chloro-2-iodo-9-methylpurine was chosen, since regioselectivity in the alkylation step had to be taken into account.[15] According to the literature,[16] the C2 position should be the most reactive position in palladium-catalyzed cross-coupling reactions, whereas the C6 position should be the most reactive position in nucleophilic substitution reactions. Thus, the C−C coupling must be carried out first, which opens the possibility of further derivatization of such compounds at the 6-position to give biologically relevant compounds. As expected by using the optimal conditions reported above, the reaction proceeded with high regioselectivity and afforded 2-butyl-6-chloro-9-methylpurine in good yield (Table 2, entry 1). Only trace amounts of bis-alkylated product (< 3%) were found. Decreasing the catalyst loading or the amount of organoborane led to lower conversion and poor yields (entries 2 and 3). As expected, variation of the nucleophile with tri-*n*-ethylborane gave coupling product **4b** in excellent yield (entry 13). Notably, B-alkyl Suzuki coupling also on this substrate with use of conventional butylboronic acid and butyltrifluoroborate provided very low yields under different conditions (entries 4−7). No highly toxic thallium compounds (TlOH or Tl_2CO_3) or other additives were utilized for the reaction. The Negishi cross-coupling with BuZnBr did not proceed in a satisfactory manner and low conversions in different experimental conditions were found (entries 10−12). However, the use of highly reactive alkylzinc reagents with aryl or heteroaryl halides has been reported.[17] Thus, we cannot exclude that further optimization of the reaction conditions and/or in situ generation of the air- and moisture-sensitive zinc reagents could improve the yield of the cross-coupling product. On the contrary, the Stille coupling with a toxic stannane

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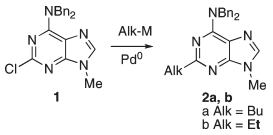
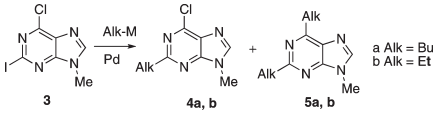
TABLE 1. Cross Coupling of 1 with Different Alkyl Metal Species



entry	alkyl-M (2 equiv)	reaction conditions	conversion (%)[a]	yield (%)[b]
1	Bu_4Sn	$Pd(PPh_3)_4$ (20%), NMP, 120 °C, 48 h	100	79
2	BuZnBr	$Pd(PPh_3)_4$ (20%), THF, 60 °C, 20 h	NR[c]	
3	BuLi or $BuMgBr/ZnBr_2$	$Pd(dppf)Cl_2$ (20%), THF, 60 °C, 20 h	NR[c]	
4	$BuB(OH)_2$	$Pd(PPh_3)_4$ (10%), K_3PO_4, dioxane, 100 °C, 20 h	trace	
5	$BuB(OH)_2$	$Pd_2(dba)_3$ (1.5%), Cs_2CO_3, IPr·HCl (3%), dioxane, 80 °C, 20 h	NR[c]	
6	$BuB(OH)_2$	$Pd_2(dba)_3$ (1.5%), Cs_2CO_3, L (3%),[d] dioxane, 80 °C, 24 h	trace	
7	$BuB(OH)_2$	$Pd(PPh_3)_4$ (5%), Na_2CO_3, EtOH/DME/H_2O, 45 W, 80 °C, 4 min	NR[c]	
8	$BuB(OH)_2$	$Pd(OAc)_2$ (0.4%), Na_2CO_3, TBAB, H_2O/DME, 100 W, 160 °C, 5 min	trace	
9	$BuBF_3K$	$PdCl_2(dppf)$ (10%), Cs_2CO_3, THF, H_2O, 60 °C, 20 h	15	10
10	$BuBF_3K$	$Pd(OAc)_2$ (10%), RuPhos, K_2CO_3, 10:1 toluene/H_2O, 80 °C, 20 h	17	11
11	Bu_3B	$PdCl_2(dppf)$ (2%), Cs_2CO_3, THF, 60 °C, 20 h	80	63
12	Bu_3B	$PdCl_2(dppf)$ (6%), Cs_2CO_3, THF, 60 °C, 16 h	100	85
13	Et_3B	$PdCl_2(dppf)$ (6%), Cs_2CO_3, THF, 60 °C, 16 h	100	87

[a]Determined by HPLC. [b]Yield of isolated product (average of two experiments). [c]No reaction. [d]L = 2-(di-*tert*-butylphosphino)biphenyl.

TABLE 2. Cross Coupling of 3 with Different Alkyl Metal Species



entry	alkyl-M	reaction conditions	conversion (%)[a]	yield (%) (**4a**,**b**)[b]
1	Bu_3B (2 equiv)	$PdCl_2(dppf)$ (6%), Cs_2CO_3, THF, 60 °C, 6 h	100	66
2	Bu_3B (2 equiv)	$PdCl_2(dppf)$ (2%), Cs_2CO_3, THF, 60 °C, 20 h	66	48
3	Bu_3B (1.1 equiv)	$PdCl_2(dppf)$ (6%), Cs_2CO_3, THF, 60 °C, 20 h	40	27
4	$BuB(OH)_2$ (1.1 equiv)	$Pd_2(dba)_3$ (2%), P(*t*-Bu)$_3$, Cs_2CO_3, dioxane, 100 °C, 24 h	NR[e]	
5	$BuB(OH)_2$ (1.2 equiv)	$Pd(OAc)_2$ (4%), XPhos, Cs_2CO_3, toluene, 100 °C, 24 h	NR[e]	
6	$BuB(OH)_2$ (1.5 equiv)	$Pd(OAc)_2$ (4%), XPhos, K_3PO_4, toluene, 100 °C, 24 h	NR[e]	
7	$BuBF_3K$ (1.1 equiv)	$PdCl_2(dppf)$ (10%), Cs_2CO_3, THF, H_2O, 60 °C, 20 h	5	3
8[c]	Bu_4Sn (2 equiv)	$Pd(PPh_3)_4$ (20%), NMP, 90 °C, 48 h	100	51[c]
9	Bu_4Sn (1.1 equiv)	$Pd(PPh_3)_4$ (20%), NMP, 90 °C, 48 h	60	41
10	BuZnBr (1.2 equiv)	$Pd(PPh_3)_4$ (5%), THF, 50 °C, 20 h	56	44
11	BuZnBr (1.2 equiv)	$Pd(OAc)_2$ (5%), XPhos, THF, 50 °C, 20 h	27	ND[d]
12	BuZnBr (1.2 equiv)	$PdCl_2(PPh_3)_2$ (5%), XPhos, THF, 50 °C, 20 h	NR[e]	
13	Et_3B (1.1 equiv)	$PdCl_2(dppf)$ (6%), Cs_2CO_3, THF, 60 °C, 3 h	100	77

[a]Determined by HPLC. [b]Yield of isolated product (average of two experiments). [c]Formation of **5** (29%). [d]Not determined. [e]No reaction; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

reagent worked very well; however, a large amount of the bis-alkylated product **5** was obtained (entry 8).

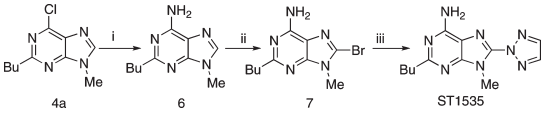
Thus, with coupling product **4a** in our hands, an easy, simple, protecting group free synthesis of ST1535 was accomplished via a simple three-step sequence: (i) amination with aqueous ammonia, (ii) regioselective bromination of C8, and (iii) bromide displacement with triazole to afford ST1535 in good overall yield without using hazardous reagents and protecting groups (Scheme 1).

In summary, tributylborane was found to be an excellent reagent for cross-coupling reactions with two different 2-halopurines under Pd catalysis. This protocol, to the best of our knowledge, is the first direct, mild, and regioselective B-alkyl-Suzuki−Miyaura cross coupling of 2-halopurines, which are well-known challenging substrates in Pd-mediated cross-coupling chemistry. Thus, it is especially useful for the incorporation of lower *n*-alkyl chains to the less reactive C2 position of 2-halopurine. The reasonable catalyst loading, relatively short reaction time, as well as the commercially available starting material are additional advantages. Application of the protocol allowed a novel, practical, protecting-group-free synthesis of ST1535, a promising molecule for the treatment of Parkinson's disease.

Experimental Section

General Procedure. To a mixture of the appropiate 2-halopurine (1.0 mmol), Cs_2CO_3 (977 mg, 3.0 mmol), and Pd (dppf)Cl_2·CH_2Cl_2 (49 mg, 6 mol %) in a Schlenk tube under Ar atmosphere was added freshly distilled THF (2.0 mL). To the stirred suspension was added tributylborane (1 M solution in THF) or triethylborane (1 M solution in hexane) in one portion, and the mixture was refluxed for the appropriate time. To the cooled reaction mixture was added 50% aq HOAc (2 mL) and the whole was refluxed for 1 h. The cooled solution was basified with a saturated solution of $NaHCO_3$ and then extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed successively with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (dichloromethane/MeOH, 99:1).

SCHEME 1. Novel Synthesis of ST1535[a]



[a]Reagents: (i) NH_3(aq)/dioxane, 70 °C 16 h; (ii) Br_2 acetate buffer pH 4, 10 min; (iii) 1*H*-1,2,3-triazole, Cs_2CO_3, DMF, 80 °C 16 h.

Dibenzyl(2-*n*-butyl-9-methyl-9*H*-purin-6-yl)amine (2a): yield 85%; mp 72−73 °C; MS (ESI) 386 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 8.0 Hz, 3H), 1.33−1.44 (m, 2H), 1.76−1.84 (m, 2H), 2.88 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H), 5.11−5.82 (br, 4H), 7.30 (s, 10H), 7.65 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 22.6, 29.8, 31.0, 39.3, 49.46, 49.48, 117.7, 127.1, 128.1, 128.5, 138.4, 138.7, 152.4, 154.5, 165.3. Anal. Calcd for $C_{24}H_{27}N_5$ (385.23): C, 74.77; H, 7.06; N, 18.17. Found: C, 74.89; H, 7.02; N, 18.26.

Dibenzyl(2-*n*-ethyl-9-methyl-9*H*-purin-6-yl)amine (2b): yield 87%; MS (ESI) 358 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 8.0 Hz, 2H), 2.88 (q, J = 8.0 Hz, 2H), 3.82 (s, 3H), 5.14−5.47 (br, 4H), 7.31 (s, 10H), 7.66 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.1, 29.7, 32.7, 49.1, 49.4, 117.8, 127.1, 128.1, 128.5, 138.4, 138.7, 152.4, 154.5, 166.1. Anal. Calcd for $C_{22}H_{23}N_5$ (357.20): C, 73.92; H, 6.49; N, 19.59. Found: C, 73.88; H, 6.60; N, 19.72.

2-*n*-Butyl-6-chloro-9-methyl-9*H*-purine (4a): yield 66%; mp 53−54 °C; MS (ESI) 225−227 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.33−1.48 (m, 2H), 1.77−1.88 (m, 2H), 3.02 (t, J = 7.7 Hz, 2H), 3.91 (s, 3H), 8.02 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 22.5, 30.1, 31.2, 38.9, 116.7, 129.3, 150.5, 152.7, 166.3. Anal. Calcd for $C_{10}H_{13}ClN_4$ (224.08): C, 53.45; H, 5.83; N, 24.94. Found: C, 53.32; H, 5.67; N, 24.99.

2-*n*-Ethyl-6-chloro-9-methyl-9*H*-purine (4b): yield 77%; mp 100−101 °C; MS (ESI) 197−199 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, J = 8.0 Hz, 3H), 3.05 (q, J = 8.0 Hz, 2H), 3.91 (s, 3H), 8.03 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.1, 30.1, 32.4, 129.3, 145.0, 150.5, 152.7, 167.0. Anal. Calcd for $C_8H_9ClN_4$ (196.05): C, 48.86; H, 4.61; N, 28.49. Found: C, 48.91; H, 4.55; N, 28.38.

2-Butyl-9-methyl-9*H*-purin-6-amine (6): To a solution of **4a** (174 mg, 0.85 mmol) in dioxane (1.3 mL) was added 30% w/w water solution of ammonia (2.6 mL). The reaction mixture was stirred overnight in an autoclave at 70 °C. The solution was evaporated at atmospheric pressure at 50 °C and then under reduced pressure. The residue was purified by flash chromatography (gradient dichloromethane−methanol 98:2 and 93:7). Yield 72%; mp 146−148 °C; MS (ESI) 206 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.37−1.49 (m, 2H), 1.72−1.84 (m, 2H), 2.82 (t, J = 8.0 Hz, 2H), 3.82 (s, 3H), 7.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.7, 29.8, 31.4, 36.2, 117.7, 140.7, 151.2, 154.8, 165.9. Anal. Calcd for $C_{10}H_{15}N_5$ (205.13): C, 58.51; H, 7.37; N, 34.12. Found: C, 58.63; H, 7.25; N, 34.08.

8-Bromo-2-butyl-9-methyl-9*H*-purin-6-amine (7): Bromine (300 μL, 5.8 mmol) was added dropwise, at −15 °C, to **6** (123 mg, 0.6 mmol) dissolved in a mixture of MeOH (1.6 mL), THF (1.6 mL), and acetate buffer pH 4 (1.6 mL) (obtained by dissolving 4 g of sodium acetate in 100 mL of water and by adjusting to pH 4 with glacial acetic acid). The reaction was stirred at −15 °C for 10 min and at room temperature for 30 min. An excess of bromine was eliminated with sodium metabisulfite and the reaction was brought to pH 8 by addition of a saturated solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane. The organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, in order to give a residue (yield 80%) that was used for the following reaction without further purification.

2-Butyl-9-methyl-8-(2*H*-1,2,3-triazol-2-yl)-9*H*-purin-6-amine (ST1535): To a solution of **7** (34 mg, 0.12 mmol) in anhydrous DMF (1 mL) were added Cs_2CO_3 (59 mg, 0.18 mmol) and then 1*H*-1,2,3-triazole (10 μL, 0.18 mmol). The mixture was stirred overnight at 90 °C. The solvent was evaporated under reduced pressure and the residue obtained was suspended in water and extracted with dichloromethane (4 × 50 mL). The combined organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, to give a residue that was purified by flash chromatography (dichloromethane−methanol 95:5). The solid obtained was crystallized by ethanol. Yield 30%; mp 182 °C; MS (ESI) 273 (M + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, J = 7.25 Hz, 3H), 1.3−1.5 (m, 2H), 1.7−1.9 (m, 2H), 2.85 (t, J = 7.9 Hz, 2H), 4.07 (s, 3H), 5.56 (br, 2H), 8.00 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.6, 31.1, 31.2, 39.3, 115.2, 136.9, 141.9, 151.4, 155.1, 166.8. Anal. Calcd for $C_{12}H_{16}N_8$ (272.15): C, 52.93; H, 5.92; N, 41.15. Found: C, 52.87; H, 6.03; N, 41.02.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.