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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 961–964

Stille coupling approaches for the synthesis of 8-aryl guanines

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Received 12 September 2006; revised 29 November 2006; accepted 7 December 2006

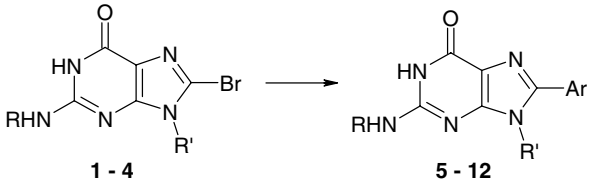
Abstract—The reaction of 8-bromoguanines with aryl and hetaryl stannanes in the presence of a palladium catalyst leads to the formation of the corresponding 8-aryl(hetaryl)guanines. It was found that the addition of triphenylarsine or triphenylbismuth strongly reduces the reaction time and increases product yields.

The purine skeleton is part of many naturally occurring ligands and the derivatives of purine nucleosides have been extensively studied as biological ligands involved in mediating metabolic processes and signaling pathways in all living organisms.[1] The interest in 8-substituted guanines stems from the fact that the introduction of an aryl substituent to position 8 of the guanine ring prevents its further oxidation in vivo.[2] According to the literature, 8-(*p*-substituted-aryl)-guanosines can be obtained by treating guanosine with an excess of the corresponding aryl diazonium salts but in low yields (20–32%).[3] The interaction between 8-bromoguanosine and pyren-1-yl boronic acid under palladium-catalyzed Suzuki–Miyaura cross-coupling conditions leads to the formation of 8-(pyren-1-yl)guanosine in moderate yield.[4] 8-Phenylguanine analogues were prepared by Stille coupling, which involved refluxing the initial 8-bromoguanines and trimethylphenylstannane for two days (67%).[5] Additionally, 8-(4-formylphenyl)[6] and 8-(4-dimethylamino)[7] guanosines have been prepared by Stille coupling through refluxing in toluene using $Pd(PPh_3)_4$ as the catalyst.

Our experience with the palladium-catalyzed Stille coupling[8] inspired us to investigate the incorporation of aryl and hetaryl groups at position 8 of the guanine core with the purpose of optimizing the conditions for the coupling.

Typically, the Stille coupling of aryl halides with aryl stannanes is performed under anhydrous conditions in aprotic solvents. Xylene is used as a solvent to allow increased reaction temperature and improve the solubility of the starting 8-bromo guanines. Our investigation started with the reaction of isobutyric acid 2-(8-bromo-2-isobutyrylamino-6-oxo-1,6-dihydropurin-9-ylmethoxy)-ethyl ester **1** previously dried in vacuo with *p*-(*i*-propoxy)phenyltrimethyl stannane using tetrakis(triphenylphosphino)palladium(0) as the catalyst (Scheme 1). The desired 8-*p*-(*i*-propoxy)phenyl guanine **5** [9] was obtained after 48 h heating at 130 °C in 75% yield in agreement with the literature data for similar couplings.[5–7] With the aim of reducing the reaction time and to activate the catalyst, a catalytic amount (5%) of triphenylarsine was added, due to the donor–acceptor As–Pd bond being longer than a P–Pd bond. The reaction on this occasion was complete only after 18 h of heating and the isolated yield of derivative **5** increased to 86%. Next, we replaced the triphenylarsine with triphenylbismuth. The reaction was now complete in 3 h and the target 8-*p*-(*i*-propoxy)phenyl guanine **5** was isolated in almost quantitative yield (96%) (Table 1).

The Stille coupling of 8-bromoguanine **1** with 2-(5-methylthienyl)tributyl stannane in the absence of activating ligand gave the expected product **6** in 24 h and 62% yield. Addition of triphenylarsine or bismuth significantly decreased the time of coupling to 4 h and



Scheme 1.

Keywords: Arsine; Bismuth; Guanine; Palladium; Stille coupling.
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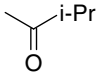
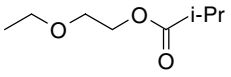
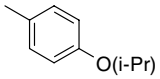
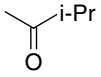
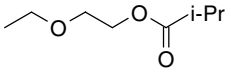
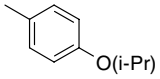
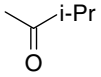
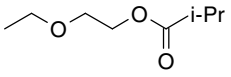
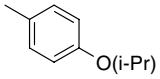
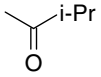
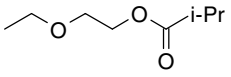
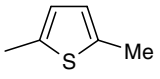
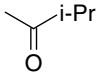
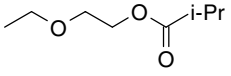
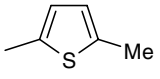
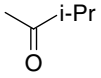
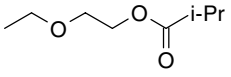
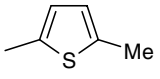
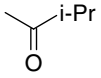
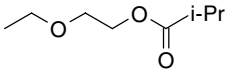
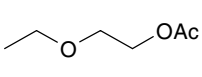
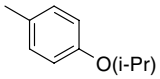
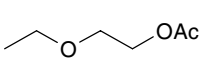
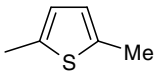
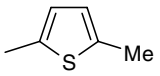
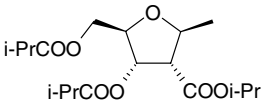
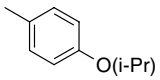
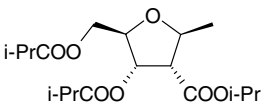
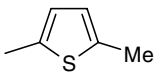
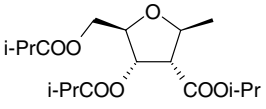
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.020

Table 1. Stille coupling of 8-bromo guanines with aryl or hetaryl stannanes

Entry	Reactant	R	R′	Ar	Ligand	Time (h)	Yield[a] (%)	Product
1	**1**				—	48	75	**5**
2	**1**				Ph_3As	18	86	**5**
3	**1**				Ph_3Bi	3	96	**5**
4	**1**				—	24	62	**6**
5	**1**				Ph_3As	4	74	**6**
6	**1**				Ph_3Bi	0.75	98	**6**
7	**1**				Ph_3Bi	1.5	82	**7**
8	**2**	Ac			Ph_3Bi	6	91	**8**
9	**2**	Ac			Ph_3Bi	3	99	**9**
10	**3**	Ac	H		Ph_3Bi	24	0	
11	**4**	H			Ph_3Bi	12	86	**10**
12	**4**	H			Ph_3Bi	1	96	**11**
13	**4**	H			Ph_3Bi	4	91	**12**

[a] Isolated yields.

45 min, respectively. It should be noted that the yield of isobutyric acid 2-[2-isobutyrylamino-8-(5-methylthiophen-2-yl)-6-oxo-1,6-dihydropurin-9-ylmethoxy]ethyl ester (**6**) was increased to 98% using Ph_3Bi as the catalyst activator. 8-(2-Pyridyl) analogue **7** was produced from 2-pyridyl trimethylstannane in 1.5 h using triphenylbismuth as the ligand in 82% yield.

The use of the diacetyl protected 8-bromoacyclovir derivative **2** as the starting material was also investigated. Under the same experimental conditions, more time was required for **2** to disappear (Table 1). This fact could be explained by the much lower solubility of **2** in xylene compared with the di(*i*-butyryl) protected analogue **1**. On the other hand, compound **2** was more easily accessible from a synthetic point of view.

Our attempts to convert N9-unprotected 8-bromo-2-acetylguanine (**3**) to the corresponding 8-(5-methylthiophen-2-yl) derivative failed due to very low solubility of

3 in xylene even at 150 °C. Conducting the reaction under microwave irradiation did not give a positive result.

The N2-unsubstituted sugar protected 8-bromoguanosine **4** readily reacted with aryl stannanes to yield the corresponding 8-aryl guanosines.[10–12] The time necessary for complete reaction depended on the activity of the stannane used. 8-(5-Methylthiophen-2-yl) guanosine **11** was obtained after just 1 h; however, the 2-pyridyl- **12** and *p*-(*i*-propoxy)phenyl **10** analogues required 4 h and 12 h, respectively, and were obtained in good to excellent yields.

Product **11** of the Stille coupling was unambiguously confirmed by X-ray diffraction. Crystals of isobutyric acid 5-[2-amino-8-(5-methylthiophen-2-yl)-6-oxo-1,6-dihydropurin-9-yl]-3,4-bis-isobutyryloxytetrahydrofuran-2-yl methyl ester (**11**) suitable for X-ray analysis were obtained by slow crystallization from ethanol. The ORTEP structure of **11** is shown in Figure 1.[10] Inspection of the molecular structure shows that the torsion angle between the purine heterocycle and the thiophene ring is 23.0(4)°, and that the sulfur and N(7) nitrogen atoms lie *syn* to each other. The presence of C=O and N–H groups plays an important role in the molecular packing of compound **11**. The crystal unit cell contains four molecules of guanosine **11** ($Z = 4$). The hydrogen of the N(10) amino group forms a strong intermolecular hydrogen bond (1.55 Å) with O(24) [N(10)H···O(24) = 2.555 Å]. Moreover, the second hydrogen atom of the N(10) amino group forms an intramolecular donor–acceptor bond with the O(11) oxygen of a second molecule of **11**; the bond length is equal to 1.82 Å [N(10)H···O(11) = 2.816 Å]. Also, the N(1)H hydrogen forms a H-bond with the N(7) nitrogen of another molecule of **11** (1.98 Å) [N(1)H···N(7) = 2.939 Å].

In summary, extremely convenient Stille coupling conditions [$Pd(PPh_3)_4$, Ph_3Bi, xylene, 130 °C] were developed for the arylation of 8-bromoguanine derivatives. Triphenylarsine can also be used. 8-Aryl and hetaryl analogues of acyclovir and guanosine were obtained in good to excellent yields.

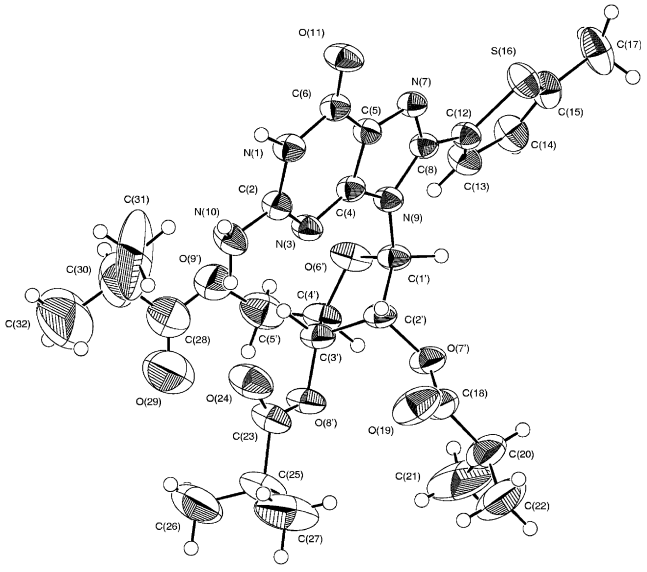


Figure 1. ORTEP crystal structure of isobutyric acid 5-[2-amino-8-(5-methylthiophen-2-yl)-6-oxo-1,6-dihydropurin-9-yl]-3,4-bis-isobutyryloxytetrahydrofuran-2-yl methyl ester (**11**).

Acknowledgment

Financial support of this work by the Latvian Council of Science (Grant No. 05.1757) is gratefully acknowledged.

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9. *General procedure*: A mixture of 8-bromo guanine (0.25 mmol), aryl stannane (0.3 mmol), tetrakis-(triphenylphosphino)palladium (14.4 mg, 0.0125 mmol), and triphenylbismuth (12.5 mg, 0.0125 mmol) in dry xylene (3 mL) was refluxed by TLC until the disappearance of the starting compound. The pure product was isolated by column chromatography on silica gel using chloroform/ethanol mixture 15:1 or 10:1 as eluent. The structures of compounds **5**–**12** were confirmed by ^{1}H (400 MHz, DMSO-d_6) and ^{13}C (100.6 MHz, DMSO-d_6) NMR, and ESI-MS data. (a) 2-[2-*iso*-Butyrylamino-8-(4-*iso*-propoxyphenyl)-6-oxo-1,6-dihydropurin-9-ylmethoxy]-ethyl ester (**5**) ^{1}H NMR: 1.00 (6H, d, $J = 6.8$ Hz), 1.14 (6H, d, $J = 6.8$ Hz), 1.31 (6H, d, $J = 6.8$ Hz), 2.44 (1H, septet, $J = 6.8$ Hz), 2.82 (1H, septet, $J = 6.8$ Hz), 3.81–3.83 (2H, m), 4.17–4.19 (2H, m), 4.73 (1H, septet, $J = 6.8$ Hz), 5.45 (2H, s), 7.06–7.08 (2H, m), 7.84–7.86 (2H, m), 11.72 (1H, br s), 12.17 (1H, br s). ^{13}C NMR: 19.1, 19.4, 22.2, 33.5, 35.2, 63.1, 67.2, 69.8, 72.3, 116.0, 119.9, 121.7, 130.6, 148.5, 149.6, 150.9, 155.2, 159.3, 176.5, 180.6. ESI-MS (MeCN): 501 [M+1]. (b) 2-[2-*iso*-Butyrylamino-8-(5-methylthiophen-2-yl)-6-oxo-1,6-dihydropurin-9-ylmethoxy]ethyl ester (**6**) ^{1}H NMR: 0.97 (6H, d, $J = 6.8$ Hz), 1.14 (6H, d, $J = 6.8$ Hz), 2.39 (1H, septet, $J = 6.8$ Hz), 2.50 (3H, s), 2.80 (1H, septet, $J = 6.8$ Hz), 3.76–3.78 (2H, m), 4.14–4.16 (2H, m), 5.55 (2H, s), 6.93 (1H, d, $J = 3.6$ Hz), 7.84–7.50 (1H, d, $J = 3.6$ Hz), 11.74 (1H, br s), 12.17 (1H, br s). ^{13}C NMR: 15.4, 19.0, 19.3, 33.5, 35.2, 63.0, 67.1, 72.2, 119.7, 127.2, 128.4, 129.7, 143.4, 144.1, 148.7, 150.9, 154.9, 176.4, 180.7. ESI-MS (MeCN): 462.9 [M+1]. (c) 2-[2-*iso*-Butyrylamino-8-(pyridin-2-yl)-6-oxo-1,6-dihydropurin-9-ylmethoxy]ethyl ester (**7**) ^{1}H NMR: 0.95 (6H, d,

$J = 6.8$ Hz), 1.14 (6H, d, $J = 6.8$ Hz), 2.38 (1H, septet, $J = 6.8$ Hz), 2.81 (1H, septet, $J = 6.8$ Hz), 3.67–3.70 (2H, m), 4.02–4.04 (2H, m), 6.17 (2H, s), 7.45–7.52 (1H, m), 7.97 (1H, ddd, $J = 1.6$ Hz, $J = 7.6$ Hz, $J = 7.8$ Hz), 8.22 (1H, d, $J = 7.8$ Hz), 8.65–8.68 (1H, m), 11.81 (1H, br s), 12.20 (1H, br s). ^{13}C NMR: 19.0, 19.3, 23.9, 33.4, 35.2, 63.1, 67.0, 73.2, 120.3, 123.6, 124.8, 138.0, 145.8, 149.1, 149.2, 149.6, 151.6, 155.2, 176.4, 180.8. ESI-MS (MeCN): 443 [M+1]. (d) 5-[2-Amino-8-(5-methylthiophen-2-yl)-6-oxo-1,6-dihydropurin-9-yl]-3,4-bis-isobutyryloxy-tetrahydrofuran-2-yl methyl ester (**11**) ^{1}H NMR: 0.98–1.11 (18H, three d, $J = 6.8$ Hz), 2.44–2.64 (3H, three septets, $J = 6.8$ Hz), 2.50 (3H, s), 4.17–4.44 (3H, m), 5.75 (1H, t, $J = 6.2$ Hz), 5.95 (1H, d, $J = 4.2$ Hz), 6.15 (1H, dd, $J = 3.8$ Hz, $J = 6.2$ Hz), 6.44 (2H, br s), 6.88 (1H, dd, $J = 1.2$ Hz, $J = 3.8$ Hz), 7.13 (1H, d, $J = 3.8$ Hz), 10.89 (1H, s). ^{13}C NMR: 12.9, 16.4, 16.5, 16.6, 16.6, 31.0, 31.1, 60.6, 68.1, 69.5, 77.1, 85.4, 114.7, 124.4, 125.9, 126.6, 138.8, 140.6, 149.8, 151.4, 154.3, 172.9, 173.0, 173.8. ESI-MS (MeCN): 591 [M+1].

10. Diffraction data were collected on a Nonius Kappa CCD diffractometer using graphite monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). The crystal structures of **11** were solved by direct methods[11] and refined by full-matrix least squares.[12] All nonhydrogen atoms were refined anisotropically. Crystal data for **11**: monoclinic; $a = 12.3585(2)$, $b = 13.2052(3)$, $c = 12.8097(3)$ Å, $\beta = 113.5346(9)°$; $V = 1916.61(7)$ Å^3, $Z = 4$, $\mu = 0.209$ mm^{-1}, $D_{calc} = 1.405$ g cm^{-1}; space group is $P2_1/a$. A total of 5569 reflection intensities were collected at room temperature. For structure refinement, 3695 independent reflections with $I \geqslant 2\cdot\sigma(I)$ were used. The final R-factor is 0.059. For further details, see crystallographic data for **11** deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 617349. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk].
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