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Convenient synthesis of 2,9-disubstituted guanines mediated by solid-supported reagents

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Abstract

A novel application has been developed to separate regioisomers chemoselectively using a solid-supported reagent. An N7/N9 purine regioisomer mixture was purified using aluminum oxide/H^+ to provide the N9 isomer selectively as a parallel or high-throughput format (chemoselective high-throughput purification). 2,9-Disubstituted guanines were conveniently prepared by this new method in conjunction with solid-supported reagents. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: combinatorial chemistry; purines; supported reagents.

The guanine scaffold **1** has been of considerable interest because of its potent antiviral therapeutic activity.[1] Some analogs such as acyclovir, buciclovir, and gancyclovir have demonstrated antiherpes activity.[2] Several communications regarding high-throughput synthesis of 2,6-diaminopurines **2** or adenines **3** have been published;[3] however, no synthetic approach to the guanine scaffold using a combinatorial application has as yet been reported. During the course of exploring new synthetic strategies directed toward the purine scaffolds described in Fig. 1, we developed an effective high-throughput purification method to separate the N7/N9 regioisomers by solid-supported reagents (chemoselective high-throughput purification).[4a] This novel application using solid-supported reagents avoids laborious regioisomer separation and work-up steps and facilitates the library synthesis of diverse purines. Herein, we describe a convenient high-throughput purification method using solid-supported reagents to separate N7/N9 regioisomers of purines and its application to 2,9-disubstituted guanine synthesis.[4b]

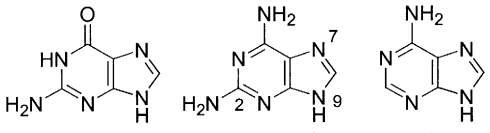

Fig. 1. The purine class and the numbering of the core structure

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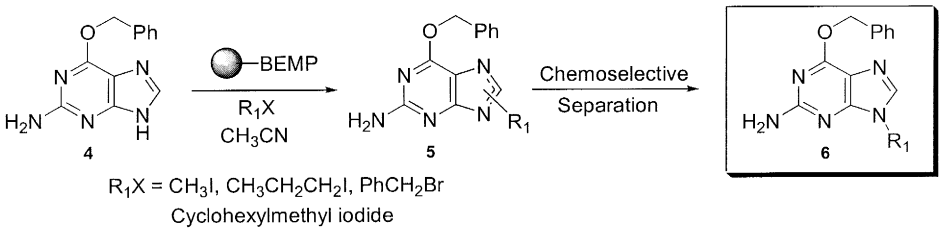
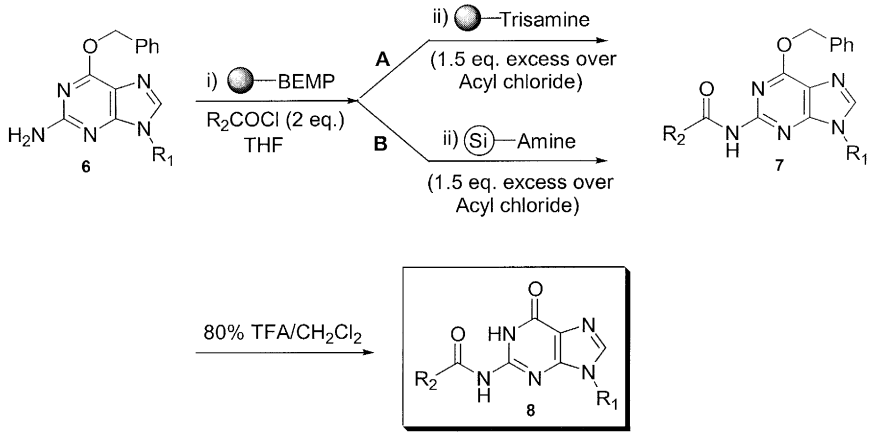
The guanine synthesis outlined in Scheme 1 started with the simple and direct alkylation of O^6-benzyl-2-aminopurine **4** with polymeric BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine).[5,6] This convenient alkylation approach using polymeric base was attempted in order to avoid the laborious Mitsunobu reaction introducing N9 substituents and tedious aqueous work-up steps. The alkylations of O^6-benzyl-2-aminopurine **4** proceeded smoothly in acetonitrile at room temperature to yield a mixture of N7 and N9 regioisomers **5**. The regioisomer ratio varying between 1:4 and 1:9 was determined by the integration of the C8 ^{1}H NMR signal.[7] Several inorganic-solid filtration pads and ion exchange resins were examined to explore an appropriate and convenient high-throughput method that could isolate the N9 isomer selectively from the mixture. Fortunately, aluminum oxide/H^+ proved to be the best filtration medium to obtain the N9 regioisomer **6** in moderate yields (30–75%) and high purity (>99%) without any N7 isomer contamination. The moderate yield of **6d** (R_1=cyclohexylmethyl) is partially attributed to incomplete *N*-alkylation, however, the unreactive **4** was also scavenged while the reaction mixture was passed through the alumina pad. The N7 isomer started to elute by washing the alumina pad with a 2 M solution of NH_3/MeOH.[8]



Scheme 1. Synthetic approach to purine analogs mediated by solid-supported reagents: isolated yield of the N9 isomers **6** after chemoselective purification employing an alumina/H^+ pad; **6a** (R_1=CH_3, 75%), **6b** (R_1=$CH_2CH_2CH_3$, 48%), **6c** (R_1=CH_2Ph, 56%), **6d** (R_1=cyclohexylmethyl, 30%)

Following the precedent method developed in our laboratory, subsequent acylation of **6** possessing a weakly nucleophilic amine at C2 proceeded successfully with polymeric BEMP (Scheme 2).[9] After completion of the reaction, polymer-bound trisamine treatment to remove the excess acyl chloride (scavenging pathway A) was followed by the deprotection of O^6-benzyl with 80% TFA/CH_2Cl_2 to provide several guanine core structures **8**.[10] Although the purities of final compounds determined by LC/MS (ELSD) are good overall, isolated yields are not satisfactory (Table 1).[11] To improve the isolated yield, amino-functionalized silica was tested to sequester the excess acyl chloride instead of the polystyrene-based trisamine resins.[12] The intrinsic advantages of silica such as no swelling and compatibility with various solvents were envisioned to affect the isolation of products in solution phase synthesis. After completing *N*-acylation, ultrapure amino-silica (Si–NH_2) was added and the mixture was shaken overnight (scavenging pathway B). Interestingly, the isolated yields increased from 10 to 40% with high purity. The increased yields were presumably attributed to the intrinsic physical properties of silica as described above. General synthetic procedures of 6,9-disubstituted guanine analogues **8** are described as follows: a solution of O^6-benzyl-2-aminopurine **4** (1.0 equiv.), polymer-bound BEMP (1.2 equiv.) and various alkylating reagents (1.2 equiv.), and anhydrous acetonitrile (0.2 M) was stirred overnight at room temperature. The mixture was passed through a pad of aluminum oxide/H^+ with a weight ratio of 1 g alumina per 1.0 mmol of **4** and then washed with anhydrous acetonitrile to provide diverse N9 alkylated purines **6**. For large-scale reactions, after passing through the alumina pad, the combined organic filtrates were evaporated in vacuo and the residue was triturated with 1:1 diethyl ether/hexane to provide highly pure N9 regioisomer (>99%). Subsequent acylation of **6** with polymer-supported BEMP (3.0 equiv.) and diverse acyl chlorides (5.0 equiv.) in THF was carried out overnight at

room temperature. Amino-silica gel (1.5-fold excess over acyl chloride) was added to the slurry in order to remove the excess acyl chloride from the mixture. After shaking overnight, the mixture was filtered and washed with THF. The combined filtrates were concentrated in vacuo. Treatment of the residue with 80% TFA/CH_2Cl_2 provided diverse guanine scaffolds **8** in moderate yield with high purity.[13] The isolated yield and purity of 2,9-disubstituted guanines **8** using two different sequestration methods are displayed in Table 1.



Scheme 2. The library synthesis of 2,9-disubstituted guanines

Table 1
Isolated yields and purity scores of guanines **8**

R_1 / R_2	Scavenging Method	Methyl	n-Propyl	Benzyl	Cyclohexylmethyl
H_3CO	A	34[a] (99)[b]	51 (86)	28 (99)	39 (99)
	B	68 (99)	75 (88)	37 (88)	55 (99)
Ph, Ph	A	68 (78)	69 (95)	63 (98)	49 (96)
	B	79 (91)	75 (99)	77 (98)	69 (93)
Ph O	A	34 (99)	60 (91)	32 (99)	42 (99)
	B	75 (99)	82 (99)	42 (99)	60 (99)
	A	57 (79)	70 (86)	53 (74)	76 (53)
	B	78 (75)	99 (97)	99 (99)	64 (99)

[a]Isolated yield, [b]Purity determined by LS/MS. The number reported in parenthesis is based on evaporative light scattering detector (ELSD) (see reference 11). Scavenging Method A done by polymeric trisamine, B by amino silica.

In summary, we report a novel application of solid-supported reagents that conveniently separates N7/N9 purine regioisomers in a high-throughput format or on a large scale. Using this method, 2,9-disubstituted guanines were prepared without any laborious regioisomer separation and tedious aqueous work-up. To the best of our knowledge, this is the first feasible high-throughput application of a solid-supported reagent used for regioisomer separation. In addition, the possibility of silica as a different solid-

supported reagent was examined for sequestration. Progress towards the library synthesis of different purine classes will be reported in due course utilizing these novel high-throughput purification and solid-supported reagents.

References

1. Kjellberg, J.; Johansson, N. G. *Nucleosides Nucleotides* **1989**, *8*, 225–256 and references cited therein.
2. Herdewijin, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 2131–2137.
3. (a) Norman, T.; Gray, N.; Koh, J.; Schultz, P. *J. Am. Chem. Soc.* **1996**, *118*, 7430–7431; (b) Gray, N.; Kwon, S.; Schultz, P. *Tetrahedron Lett.* **1997**, *38*, 1161–1164; (c) Nugiel, D.; Cornelius, L.; Corbett, J. *J. Org. Chem.* **1997**, *62*, 201–203; (d) Fiorini, M. T.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 1827–1830; (e) Chang, Y. T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Schultz, P. G. *Chem. Biol.* **1999**, *6*, 361–375.
4. (a) Kim, K.; McComas, W. Book of Abstracts, 218th ACS National Meeting, New Orleans, 22–26 August 1999, ORGN-597; (b) Kim, K.; McComas, W. Book of Abstracts, 218th ACS National Meeting, New Orleans, 22–26 August 1999, ORGN-359.
5. O^6-Benzyl-2-aminopurine **4** was prepared in large scale from commercially available 2-amino-6-chloropurine according to the precedent: Chae, M. Y.; McDougall, M. G.; Dolan, M. E.; Swenn, K.; Pegg, A. E.; Moschel, R. C. *J. Med. Chem.* **1994**, *37*, 342–347.
6. (a) Schwesinger, R. *Chimia* **1985**, *39*, 269–272; (b) Xu, W.; Mohan, R.; Morrissey, M. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1089–1092: polymer-supported BEMP is commercially available from Fluka.
7. The N7/N9 ratio was determined by the integration of the C-8 ^{1}H NMR signal, which for the N7 isomer appears slightly downfield from that of the N9 isomer: Raju, N.; Robins, R. K.; Vaghefi, M. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1769–1770 and references cited therein.
8. The purity of the N7 isomer determined by LC/MS (ELSD) varied between 60 and 96% depending on the alkylating reagents. Due to space limitations, more details will be provided in a full account of this work.
9. Kim, K.; Le, K. *Synlett* **1999**, *12*, 1957–1959.
10. Polymer-bound trisamine: Booth, R. J.; Hodges J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882–4886.
11. Purity was determined by a C18 reverse phase HPLC column, WR-C18 3u 120A (30×3.2 mm) of ES Industries in 10–90% CH_3CN/H_2O containing 0.02% TFA and monitored at 215 nm using a UV detector and by a SEDEX 55 evaporative light scattering detector (ELSD). Purity scores reported herein are based on ELSD.
12. Ultrapure amino silica gels are commercially available from SiliCycle, Inc., Quebec, Canada. Hewlett–Packard Co. now provides various functionalized silica as CombiZorb™.
13. The structures of four N9-alkylated purines **6** and 2,9-disubstituted guanines **8** were assigned by ^{1}H, ^{13}C NMR, and mass spectrometry (FAB).