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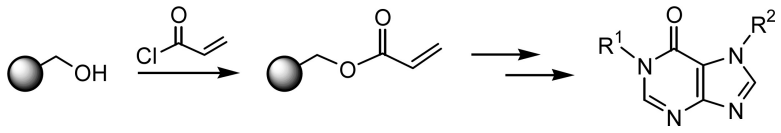

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Traceless Solid-Phase Synthesis of N1,N7-Disubstituted Purines

Han Fu and Yulin Lam*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

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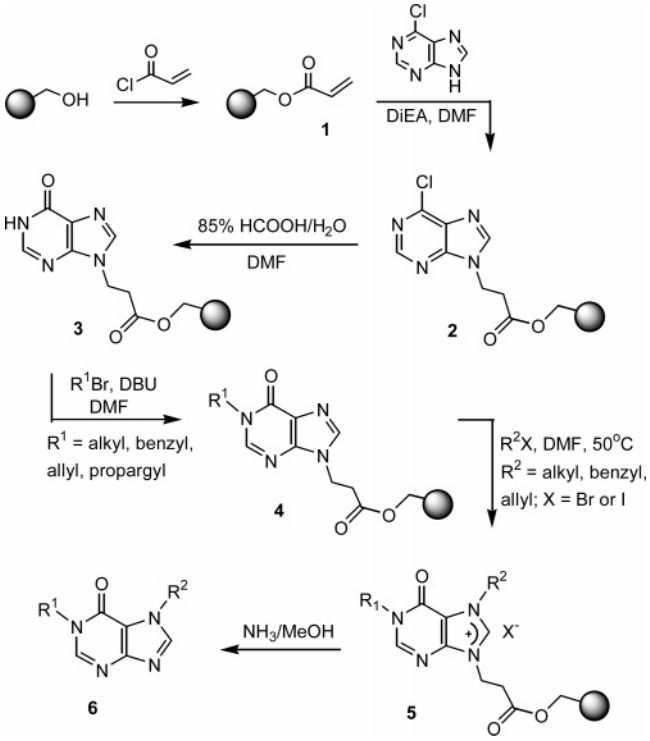
A highly regioselective and traceless solid-phase route to N1,N7-disubstituted purines has been developed. Key steps in the reaction strategy involves (i) coupling of 6-chloropurine to the REM resin (Michael addition), (ii) oxidation, (iii) N1-alkylation, (iv) quaternization, and (v) product release through Hofmann elimination. A library of 15 N1,N7-disubstituted purines was synthesized.

Introduction

Although N9-substituted purines are the natural nucleosides, in recent years, there has been much interest in the N7 regioisomers. These isomers have found applications as antiviral agents.[1] N7 guanines are also important DNA adducts formed as a result of exposure to electrophiles.[2] Consequently, 7-alkylguanines are the main types of DNA adducts excreted in urine and are therefore important markers for the development of diagnostic methods to detect and quantitate specific types of DNA damages.[3] Studies of N1,N7-disubstituted guanines have shown that they are capable of inhibiting telomerase activity and possess the ability to enhance the efficacy of other chemotherapeutic agents in the treatment of cancer.[4] Despite the abundance of work produced on purines, very few examples are known in the literature about their regioselective N7 alkylation.[1c,1d,5] Earlier studies have shown that, under kinetic control, alkylation of purines gives predominantly the N9 isomer.[6] Hence, selective N7 alkylation of purine is important for achieving high regioselectivity.

An important feature of solid-phase synthesis is the linker that attaches the compounds being synthesized onto the solid support.[7] Methods of immobilizing compounds to the solid phase for combinatorial synthesis initially rely upon traditional solid-phase peptide linkers, which resulted in the release of carboxylic acids, esters, or amides from the ester- or amide-bound substrate.[8] The presence of these appendages is acceptable if the final products embody these functional groups. However, complications may arise if these vestigial functionalities are redundant and affect the activities of the compounds. In this regard, development of novel traceless linkages for tethering compounds to solid supports such that the compounds do not contain the unwanted functional groups is an area of active investigation.[9] Herein, we describe a traceless solid-phase route for the synthesis of N1,N7-disubstituted purines. The linkage strategy involves the use of the REM resin which has been widely used in the synthesis of tertiary amines and involves a final Hofmann elimination step to release the target products.[10] Our synthetic route (Scheme 1) was designed such that the linker was anchored at the N9 position of the purine frame, leaving the N7 position as the steric priority to be alkylated to form a quaternary salt, thus allowing a highly regioselective N7 synthesis to be achieved.

Scheme 1. SPOS of N1,N7-Disubstituted Purines



Results and Discussion

Solution-Phase Synthesis of N1,N7-Disubstituted Purines. Prior to the solid-phase synthesis, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications required for solid-phase synthesis. In the first step, benzyl acrylate **7** was chosen to mimic the structure of the REM resin. Compound **7** was easily synthesized according to the standard procedure for the preparation of REM resin from the Wang resin.[10] Treatment of **7** with 6-chloropurine, in the presence of base, yielded **8** via Michael addition. A variety of bases were examined for this reaction. LiH gave no product at either

* To whom correspondence should be addressed. E-mail: chmlamyl@nus.edu.sg. Fax: (65)-6779-1691.

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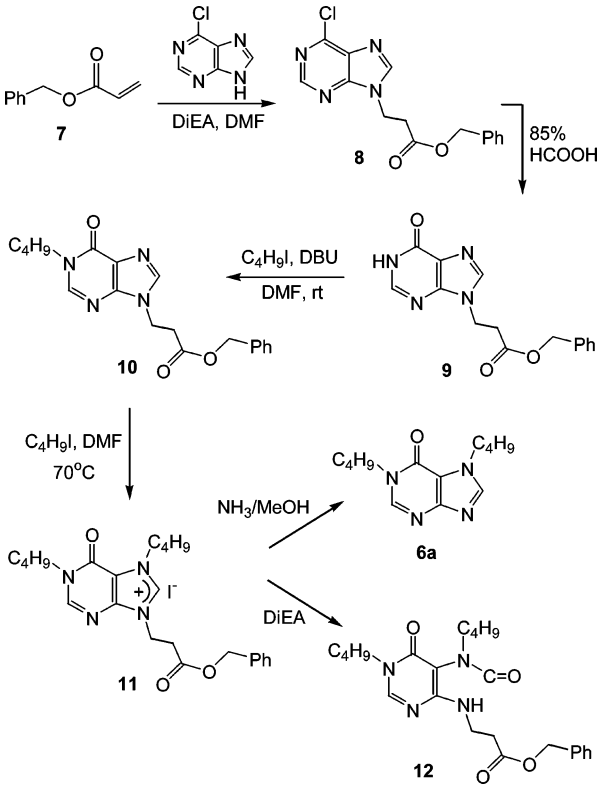
Scheme 2. Solution-Phase Study



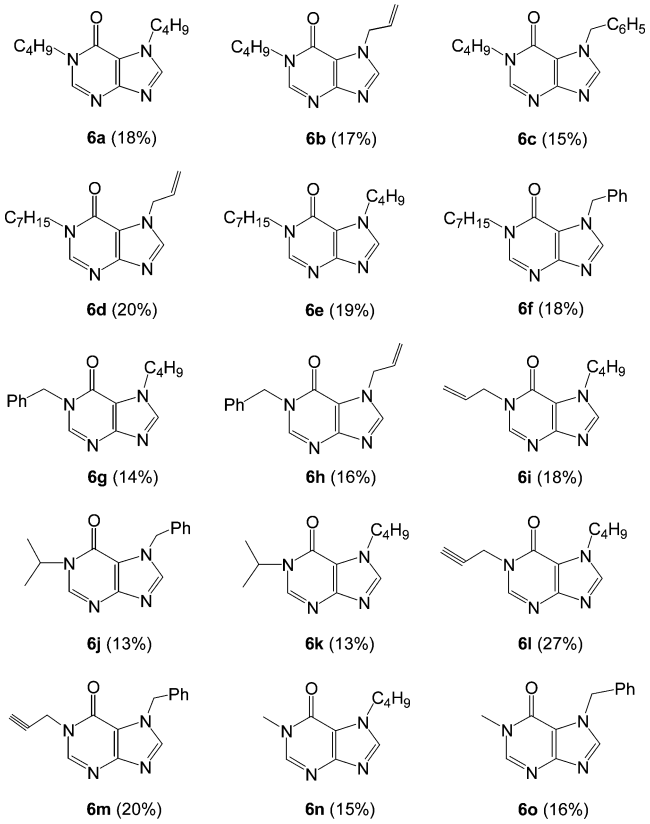


Figure 1. Library of **6**.

room temperature or elevated temperatures, while NaOMe gave 3-(6-chloro-purin-9-yl)-propionic acid, the ester hydrolysis product. Although reaction with K_2CO_3/DMF gave very low yield, it provided **8** in 60% yield when 18-crown-6 was included as a phase-transfer catalyst. Since our aim is to develop a procedure for solid-phase synthesis, it is necessary to choose a base that would solublize well in a solvent for which the resin had a good swelling effect. Hence, K_2CO_3/DMF/18-crown-6 was not an appropriate system for the solid-phase synthesis of **8**. Further investigation provided DiEA/DMF, which gave **8** in 74% yield when the reaction was carried out at room temperature (the yields were lower at higher temperatures and the N7 alkylated regioisomer was observed at temperatures above 90 °C). Subsequent acid-catalyzed hydrolysis of **8** with 85% formic acid afforded **9** in quantitative yield.

We next proceeded to N1-alkylate **9** with butyl iodide. The reaction could be carried out with DBU at room temperature or K_2CO_3/DMF at 90 °C to provide **10** in over 90% yields.[11] NOESY experiments clearly showed the *CH*$_2$N/*H*C2 interaction, which confirmed that the alkylation had occurred on the nitrogen instead of the oxygen at position 6. Quaternization of **10** with butyl iodide in DMF at 70 °C overnight proceeded smoothly to give **11** in quantitative yield. Subsequent treatment of **11** with TEA or DiEA was expected to give the final product **6a** via Hofmann elimination.[10] However, the yields obtained were very low (<20%) and the product isolated was identified as the imidazolium ring-opened compound **12** (Scheme 2). The formation of **12** may be attributed to the electron-deficient C8 which causes the imidazolium structure to be unstable under basic conditions.[2a] To effect the formation of **6a**, ammonia in methanol, a milder base, was chosen and upon stirring for 12 h, **6a** was obtained in 72% yield.

Solid-Phase Synthesis of N1,N7-Disubstituted Purines. With the solution-state pathway established, we proceeded to demonstrate the solid-phase route to these compounds. REM resin **1** was developed by treating the Wang resin with acryloyl chloride in the presence of DiEA.[10] The formation of **1** was amenable to KBr FTIR monitoring (i.e., appearance of carbonyl stretch at 1724 cm^{-1})**.** Subsequently, **1** was reacted with 6-chloropurine to give **2**, which was then hydrolyzed with 85% formic acid. DMF was added as a cosolvent in the acid-catalyzed hydrolysis step to facilitate resin swelling. The resin-bound intermediate **3** was alkylated at the N1 position under basic conditions followed by quaternization at N7 with different alkyl halides. When a bromide was used, the addition of sodium iodide to the quaternization mixture improved the efficiency of the alkylation. Our study also showed that lowering the temperature from 70 to 50 °C during quaternization gave fewer side products upon cleavage from the resin. The formations of **4** and **5** were monitored by HRMAS ^{13}C NMR for appearance of peaks corresponding to the alkyl groups. The final product **6** was released from the resin by an overnight treatment with 2 M ammonia in methanol.

To illustrate the versatility of this chemistry, a library of 15 compounds (**6a**−**6o**) was prepared (Figure 1). The overall yields obtained were 13−27% (purities of >95% by NMR), indicating an average yield of at least 70% for each step of the reaction. An X-ray crystal study of **6f** gives direct evidence that the regioselective alkylation had occurred at the N7 position rather than the N9 position.

In conclusion, we have demonstrated a novel traceless solid-phase synthetic route to N1,N7-disubstituted purines. The target compounds were obtained in high purity and good yields. To our knowledge, this is the first example of a highly regioselective synthesis of N7-substituted purines on the solid phase.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 Fourier Transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of tetramethylsilane (TMS). All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on a VG Micromass 7035 spectrometer under electron impact (EI). All chemical reagents were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh).

Acrylic Acid Benzyl Ester (7). DiEA (4.787 g, 37.04 mmol) and acryloyl chloride (3.352 g, 37.04 mmol) were added to a solution of benzyl alcohol (0.5 g, 4.63 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at room temperature for 4 h and then concentrated to dryness. The brown solid obtained was dissolved in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layer obtained was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:2) to give **7** as a colorless oil (0.688 g, 92%). ^{1}H NMR ($CDCl_3$): δ 5.17 (s, 2H, PhC**H**$_2$), 5.79 (dd, J = 1.2, 10.4 Hz, 1H, CHC**H**$_2$), 6.14 (dd, J = 10.5, 17.3 Hz, 1H, C**H**), 6.42 (dd, J = 1.2, 17.3 Hz, 1H, CHC**H**$_2$), 7.27−7.35 (m, 5H, C_6**H**$_5$). ^{13}C NMR ($CDCl_3$): δ 66.08, 128.04, 128.15, 128.37, 130.81, 135.75, 165.72. HRMS(EI): Calcd for $C_{10}H_{10}O_2$: 162.0681; found: 162.0680.

3-(6-Chloropurin-9-yl)propanoic Acid Benzyl Ester (8). Compound **7** (0.162 g, 1.0 mmol) and DiEA (0.142 g, 1.1 mmol) were added to a solution of 6-chloropurine (0.170 g, 1.1 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature for 48 h and then extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:2) to give **8** as a white solid (0.257 g, 74%). ^{1}H NMR ($CDCl_3$): δ 3.03 (t, J = 6.0 Hz, 2H, N9CH$_2$C**H**$_2$), 4.60 (t, 2H, J = 6.2 Hz, N9C**H**$_2$), 5.10 (s, 2H, PhC**H**$_2$), 7.24−7.36 (m, 5H, C_6**H**$_5$), 8.21 (s, 1H, C8**H**), 8.71 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 33.69, 39.89, 67.01, 128.28, 128.53, 131.52, 134.90, 145.90, 150.89, 151.56, 151.76, 170.30. HRMS(EI): Calcd for $C_{15}H_{13}ClN_4O_2$: 316.0727; found: 316.0723.

3-(6-Oxo-1,6-dihydro-purin-9-yl)propanoic Acid Benzyl Ester (9). Compound **8** (0.442 g, 1.4 mmol) was dissolved in 80% formic acid (13 mL) and the reaction mixture was stirred at 70 °C for 3 h and then evaporated to dryness. The white solid obtained was extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (methanol:CH_2Cl_2 = 1:8) to provide **9** as a white solid (0.4 g, 96%). ^{1}H NMR (DMSO-d_6): δ 3.02 (t, J = 6.8 Hz, 2H, N9CH$_2$C**H**$_2$), 4.40 (t, J = 6.8 Hz, 2H, N9C**H**$_2$), 5.07 (s, 2H, PhC**H**$_2$), 7.26−7.35 (m, 5H, C_6**H**$_5$), 8.02 (s, 1H, C8**H**), 8.04 (s, 1H, C2**H**), 12.26 (s, 1H, N1**H**). ^{13}C NMR ($CDCl_3$): δ 33.27, 65.34, 123.44, 127.46, 127.57, 127.89, 135.30, 139.81, 145.03, 147.82, 156.14, 169.86. HRMS(EI): Calcd for $C_{15}H_{14}N_4O_3$: 298.1066; found: 298.1079.

3-(1-Butyl-6-oxo-1,6-dihydro-purin-9-yl)propanoic Acid Benzyl Ester (10). 1-Bromobutane (47.4 mg, 0.346 mmol) and DBU (52.7 mg, 34.6 mmol) were added to the solution of **9** (86 mg, 0.289 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature overnight and then extracted with ethyl acetate and brine. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:1 followed by methanol:CH_2Cl_2 = 1:10) to provide **10** as a pale yellow oil (92.9 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.26−1.39 (m, 2H, C**H**$_2$CH$_3$), 1.65−1.75 (m, 2H, C**H**$_2$CH$_2$CH$_3$), 2.90 (t, J = 6.3 Hz, 2H, COC**H**$_2$), 3.99 (t, J = 7.3 Hz, 2H, N1C**H**$_2$), 4.42 (t, J = 6.4 Hz, 2H, N9C**H**$_2$), 5.05 (s, 2H, PhC**H**$_2$), 7.22−7.36 (m, 5H, C_6**H**$_5$), 7.78 (s, 1H, C8**H**), 7.99 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.44, 19.58, 31.62, 34.25, 39.41, 46.52, 66.78, 124.21, 128.21, 128.33, 128.44, 134.96, 140.25, 146.86, 147.33, 156.26, 170.19. HRMS(EI): Calcd for $C_{19}H_{22}N_4O_3$: 354.1692; found: 354.1675.

3-(1,7-Dibutyl-6-oxo-1,6-dihydro-purin-9-yl)propanoic Acid Phenyl Ester Salt (11). 1-Iodobutane (2.942 g, 16 mmol) was added to the solution of **10** (0.283 g, 0.8 mmol) in DMF (7 mL). The reaction mixture was stirred at 70 °C for 24 h and then evaporated to dryness. The residue was purified by column chromatography (methanol:CH_2Cl_2 = 1:15) to give **11** as a yellow solid (0.43 g, 100%). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 6H, C**H**$_3$), 1.37−1.47 (m, 4H, C**H**$_2$), 1.70−1.80 (m, 2H, C**H**$_2$), 1.94−2.05 (m, 2H, C**H**$_2$), 3.24 (t, J = 6.4 Hz, 2H, C**H**$_2$), 4.07 (t, J = 7.5 Hz, 2H, C**H**$_2$), 4.61 (t, J = 7.5 Hz, 2H, C**H**$_2$), 4.84 (t, J = 6.4 Hz, 2H, C**H**$_2$), 5.09 (s, 2H, PhC**H**$_2$), 7.31−7.32 (m, 5H, C_6**H**$_5$), 8.23 (s, 1H, C2**H**), 10.63 (s, 1H, C8**H**). ^{13}C NMR ($CDCl_3$): δ 13.34, 13.44, 19.41, 19.70, 31.44, 32.07, 33.15, 42.37, 47.52, 50.13, 67.08, 114.04, 128.42, 128.46, 128.54, 135.12, 141.46, 146.52, 150.83, 152.05, 169.84. HRMS(EI): Calcd for $C_{23}H_{31}N_4O_3$: 411.2396; found: 411.2391.

1,7-Dibutyl-1,7-dihydro-purin-6-one (6a). Compound **11** (123 mg, 0.23 mmol) was dissolved in the solution of 2 M ammonia in methanol (2.3 mL). The reaction mixture was stirred at room temperature for 24 h and then evaporated to dryness. The residue was purified by column chromatography (CH_3CN:CH_2Cl_2 = 1:1 followed by methanol:CH_2Cl_2 = 1:15) to give **6a** as a white solid (41 mg, 72%).

REM Resin (1). Wang resin (loading 1.47 mmol/g) was swollen in CH_2Cl_2. DiEA (8 equiv) and acryloyl chloride (8 equiv) were added and the reaction mixture was shaken at room temperature for 4 h. After which, the mixture was filtered and the resin washed sequentially with DMF (20 mL

× 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **1**.

Polymer-Supported 3-(6-Chloro-purin-9-yl)propanoic Acid Benzyl Ester (2). Resin **1** was swollen in DMF and 6-chloropurine (2 equiv) and DiEA (2 equiv) were added. The reaction mixture was shaken at room temperature for 48 h and then filtered and washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum. This procedure was repeated once to afford resin **2**.

Polymer-Supported 3-(6-oxo-1,6-dihydro-purin-9-yl)-propanoic Acid Benzyl Ester (3). Resin **2** was swollen in DMF for 30 min. 80% formic acid was added and the reaction mixture was stirred at 70 °C for 4 h. Then the resin was filtered and washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum at 40 °C to afford resin **3**.

General Procedure for the Preparation of Polymer-Bound 3-(1-Substituted-6-oxo-1,6-dihydro-purin-9-yl)propanoic Acid Benzyl Ester (4). Resin **3** was swollen in DMF for 30 min and the respective bromide (1.5 equiv) and DBU (2 equiv) were added. After the mixture was shaken at room temperature overnight, the resin was filtered and washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum. HRMAS ^{13}C NMR ($CDCl_3$): δ 13.39, 19.48, 33.49, 39.67, 53.24, 114.59, 127.27, 127.70, 128.09, 128.73, 129.02, 129.25, 129.96, 131.25, 144.96, 145.90, 150.50, 151.38, 158.88, 170.18.

General Procedure for the Preparation of Polymer-Bound 3-(1,7-Disubstituted-6-oxo-1,6-dihydro-purin-9-yl)-propanoic Acid Phenyl Ester Salt (5). Resin **4** was swollen in DMF for 30 min. The respective halide (20 equiv) was added and the mixture was stirred slowly at 50 °C for 24 h. After which, the resin was filtered and washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum. HRMAS ^{13}C NMR ($CDCl_3$): δ 13.52, 13.71, 19.01, 19.72, 53.40, 53.53, 65.46, 66.11, 69.95, 114.90, 127.51, 128.15, 128.39, 130.23, 130.98, 145.29, 159.09, 160.87, 166.05.

N1,N7-Disubstituted Purine (6). Resin **5** was swollen in CH_2Cl_2 for 30 min. 2 M ammonia in methanol (20 equiv) was added and the mixture was shaken at room temperature for 24 h. The resin was filtered and washed with methanol (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The washings were combined with the filtrate, concentrated to dryness, and purified by column chromatography.

1,7-Dibutyl-1,7-dihydro-purin-6-one (6a). ^{1}H NMR ($CDCl_3$): δ 0.90−0.96 (m, 6H, 2C**H**$_3$), 1.29−1.41 (m, 4H, C**H**$_2$), 1.68−1.78 (m, 2H, C**H**$_2$), 1.80−1.90 (m, 2H, C**H**$_2$), 3.99 (t, J = 7.3 Hz, 2H, C**H**$_2$), 4.35 (t, J = 7.3 Hz, 2H, C**H**$_2$), 7.80 (s, 1H, C8**H**), 7.98 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.42, 13.52, 19.50, 19.76, 31.82, 33.31, 46.26, 47.14, 115.10, 143.14, 146.31, 154.20, 156.95. HRMS(EI): Calcd for $C_{13}H_{20}N_4O$: 248.1637; found: 248.1636.

7-Allyl-1-butyl-1,7-dihydro-purin-6-one (6b). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.29−1.42 (m, 2H, C**H**$_2$), 1.66−1.76 (m, 2H, C**H**$_2$), 3.97 (t, J = 7.3 Hz, 2H, N1C**H**$_2$), 5.01 (d, J = 5.6 Hz, 2H, N7C**H**$_2$), 5.21 (dd, J = 10.5, 23.0 Hz, 2H, C**H**$_2$), 5.99−6.10 (m, 1H, C**H**), 7.82 (s, 1H, C8**H**), 7.97 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.48, 19.69, 31.75, 46.18, 49.12, 118.94, 132.41, 139.59, 143.01, 146.41, 154.19, 156.76. HRMS(EI**):** Calcd for $C_{12}H_{16}N_4O$: 232.1324; found: 232.1320.

7-Benzyl-1-butyl-1,7-dihydro-purin-6-one (6c). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.32−1.44 (m, 4H, C**H**$_2$), 1.68−1.78 (m, 2H, C**H**$_2$), 3.99 (t, J = 7.3 Hz, 2H, N1C**H**$_2$), 5.59 (s, 2H, PhC**H**$_2$), 7.29−7.36 (m, 5H, C_6**H**$_5$), 7.83 (s, 1H, C8**H**), 7.98 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.53, 19.76, 31.83, 46.25, 50.53, 115.11, 127.90, 128.45, 129.00, 135.66, 143.16, 146.48, 154.37, 156.87. HRMS(EI): Calcd for $C_{16}H_{18}N_4O$: 282.1481; found: 282.1478.

7-Allyl-1-heptyl-1,7-dihydro-purin-6-one (6d). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.22−1.31 (m, 8H, 4C**H**$_2$), 1.71−1.76 (m, 2H, C**H**$_2$), 3.98 (t, J = 7.3 Hz, 2H, N1C**H**$_2$), 5.04 (dd, J = 1.4 Hz, J = 5.9 Hz, 2H, N7C**H**$_2$), 5.24 (dd, J = 10.1 Hz, J = 20.2 Hz, 2H, CHC**H**$_2$), 5.99−6.11 (m, 1H, C**H**), 7.96 (s, 1H, C8**H**), 8.00 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.90, 22.41, 26.46, 28.70, 29.76, 31.53, 46.56, 49.30, 119.19, 132.30, 142.89, 146.69, 152.21, 154.13, 156.28. HRMS(EI): Calcd for $C_{15}H_{22}N_4O$: 274.1794; found: 274.1781.

7-Butyl-1-heptyl-1,7-dihydro-purin-6-one (6e). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J = 6.6 Hz, 3H, C**H**$_3$), 0.92−0.97 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.26−1.39 (m, 10H, 5C**H**$_2$), 1.73−1.92 (m, 4H, 2C**H**$_2$), 1.80−1.90 (m, 2H, C**H**$_2$), 4.00 (t, J = 7.5 Hz, 2H, N1C**H**$_2$), 4.38 (t, J = 7.3 Hz, 2H, N7C**H**$_2$), 7.90 (s, 1H, C8**H**), 8.00 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.45, 13.94, 19.55, 22.47, 26.54, 28.77, 29.85, 31.60, 33.33, 46.61, 47.30, 115.16, 143.06, 146.52, 154.18, 156.64. HRMS(EI): Calcd for $C_{16}H_{26}N_4O$: 290.2107; found: 290.2100.

7-Benzyl-1-heptyl-1,7-dihydro-purin-6-one (6f). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H, C**H**$_3$), 1.25−1.35 (m, 8H, 4C**H**$_2$), 1.75−1.79 (m, 2H, C**H**$_2$), 4.01 (t, J = 7.5 Hz, 2H, N1C**H**$_2$), 5.64 (s, 2H, PhC**H**$_2$), 7.35−7.36 (m, 5H, C_6**H**$_5$), 8.02 (s, 1H, C8**H**), 8.05 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.99, 22.51, 26.55, 28.80, 29.88, 31.63, 46.72, 50.91, 128.13, 128.70, 129.14, 142.77, 147.03. HRMS(EI): Calcd for $C_{19}H_{24}N_4O$: 324.1950; found: 324.1947.

1-Benzyl-7-butyl-1,7-dihydro-purin-6-one (6g). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.5 Hz, 3H, C**H**$_3$), 1.23−1.33 (m, 2H, C**H**$_2$), 1.75−1.85 (m, 2H, C**H**$_2$), 4.30 (t, J = 7.3 Hz, 2H, N7C**H**$_2$), 5.14 (s, 2H, PhC**H**$_2$), 7.21−7.26 (m, 5H, C_6**H**$_5$), 7.78 (s, 1H, C8**H**), 8.07 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.24, 19.27, 33.04, 46.92, 48.77, 114.87, 127.57, 127.93, 128.69, 135.71, 143.13, 146.24, 153.94, 156.71. HRMS(EI): Calcd for $C_{16}H_{18}N_4O$: 282.1481; found: 282.1479.

7-Allyl-1-benzyl-1,7-dihydro-purin-6-one (6h). ^{1}H NMR ($CDCl_3$): δ 5.04 (dd, J = 1.4, 5.9 Hz, 2H, N7C**H**$_2$), 5.19 (dd, J = 1.0, 10.5 Hz, 2H, CHC**H**$_2$), 5.16 (s, 2H, PhC**H**$_2$), 5.93−6.06 (m, 1H, C**H**), 7.21−7.26 (m, 5H, C_6**H**$_5$), 7.81 (s, 1H, C8**H**), 8.08 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 48.79, 48.96, 114.78, 118.81, 127.58, 127.96, 128.70, 132.23, 135.65, 143.03, 146.35, 153.98, 156.59. HRMS(EI): Calcd for $C_{15}H_{14}N_4O$: 266.1168; found: 266.1164.

1-Allyl-7-butyl-1,7-dihydro-purin-6-one (6i). ^{1}H NMR ($CDCl_3$): δ 0.83 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.20−1.33 (m,

2H, C**H**$_2$), 1.71−1.81 (m, 2H,C**H**$_2$), 4.28 (t, J = 7.2 Hz, 2H, N7C**H**$_2$), 4.55 (d, J = 6.0 Hz, 2H, N1C**H**$_2$), 5.13 (dd, J = 10.4, 13.7 Hz, 2H, C**H**$_2$), 5.83−5.92 (m, 1H C**H**), 7.77 (s, 1H, C8**H**), 7.92 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.16, 19.21, 33.01, 46.89, 47.46, 114.70, 118.32, 131.88, 143.11, 146.01, 153.66, 156.67. HRMS(EI): Calcd for $C_{12}H_{16}N_4O$: 232.1324; found: 232.1321.

7-Benzyl-1-isopropyl-1,7-dihydro-purin-6-one (6j). ^{1}H NMR ($CDCl_3$): δ 1.47 (d, J = 6.9 Hz, 6H, 2C**H**$_3$), 5.15−5.24 (m, 1H, N1C**H**), 5.60 (s, 2H, PhC**H**$_2$), 7.30−7.35 (m, 5H, C$_6$**H**$_5$), 7.85 (s, 1H, C8**H**), 8.09 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 22.46, 45.51, 50.53, 127.97, 128.50, 129.06, 135.68, 143.28, 143.61, 154.22, 156.34. HRMS(EI): Calcd for $C_{15}H_{16}N_4O$: 268.1324; found: 268.1356.

7-Butyl-1-isopropyl-1,7-dihydro-purin-6-one (6k). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.29−1.36 (m, 2H, C**H**$_2$), 1.45 (d, J = 6.9 Hz, 6H, 2C**H**$_3$), 1.79−1.89 (m, 2H, C**H**$_2$), 4.35 (t, J = 7.3 Hz, 2H, N7C**H**$_2$), 5.10−5.24 (m, 1H, N1C**H**), 7.82 (s, 1H, C8**H**), 8.06 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.39, 19.49, 22.40, 33.28, 45.43, 47.10, 114.78, 143.19, 143.41, 153.96, 156.31. HRMS(EI): Calcd for $C_{12}H_{18}N_4O$: 234.1481; found: 234.1475.

7-Butyl-1-prop-2-ynyl-1,7-dihydro-purin-6-one (6l). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.19−1.27 (m, 2H, C**H**$_2$), 1.71−1.81 (m, 2H, C**H**$_2$), 2.43−2.45 (m, 1H, C**H**), 4.27 (t, J = 7.3 Hz, 2H, N7C**H**$_2$), 4.74 (dd, J = 1.0, 2.8 Hz, 2H, N1C**H**$_2$), 7.77 (s, 1H, C8**H**), 8.19 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.19, 19.23, 32.98, 34.51, 46.95, 74.70, 114.45, 139.85, 143.27, 145.18, 153.22, 156.74. HRMS(EI): Calcd for $C_{12}H_{14}N_4O$: 230.1168; found: 232.1162.

7-Benzyl-1-prop-2-ynyl-1,7-dihydro-purin-6-one (6m). ^{1}H NMR ($CDCl_3$): δ 2.46−2.48 (m, 1H, C**H**), 4.77 (d, J = 2.4 Hz, 2H, N1C**H**$_2$), 5.55 (s, 2H, PhC**H**$_2$), 7.27−7.31 (m, 5H, C$_6$**H**$_5$), 7.86 (s, 1H, C8**H**), 8.24 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 34.62, 50.48, 74.97, 114.63, 127.80, 128.39, 128.91, 135.44, 143.40, 145.39, 153.53, 156.86. HRMS(EI): Calcd for $C_{15}H_{12}N_4O$: 264.1011; found: 264.1011.

7-Butyl-1-methyl-1,7-dihydro-purin-6-one (6n). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H, C**H**$_3$), 1.20−1.28 (m, 2H, C**H**$_2$), 1.72−1.82 (m, 2H, C**H**$_2$), 3.52 (s, 3H, N1C**H**$_3$), 4.28 (t, J = 7.1 Hz, 2H, N7C**H**$_2$), 7.75 (s, 1H, C8**H**), 7.97 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 13.24, 19.28, 33.09, 33.40, 46.96, 114.76, 143.06, 146.46, 154.39, 156.94. HRMS(EI): Calcd for $C_{10}H_{14}N_4O$: 206.1168; found: 206.1167.

7-Benzyl-1-methyl-1,7-dihydro-purin-6-one (6o). ^{1}H NMR ($CDCl_3$): δ 3.57 (s, 3H, N1C**H**$_3$), 5.57 (s, 2H, PhC**H**$_2$), 7.30 (m, 5H, C$_6$**H**$_5$), 7.85 (s, 1H, C8**H**), 8.01 (s, 1H, C2**H**). ^{13}C NMR ($CDCl_3$): δ 33.51, 50.51, 114.96, 127.82, 128.42, 128.96, 135.65, 143.19, 146.69, 154.70, 157.07. HRMS(EI): Calcd for $C_{13}H_{12}N_4O$: 240.1011; found: 240.1013.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of all compounds and crystallographic data in CIF format of **6f** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Reaction with K_2CO_3 in refluxing methanol enabled both N1-alkylation and transesterification to occur. This was evidenced by the quaternized product, 3-(1,7-dibutyl-6-oxo-1,6-dihydro-purin-9-yl)-propionic acid methyl ester salt, **13** obtained.

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