mmol), chlorotrimethylsilane (83 mg, 0.76 mmol) and NaI (114 mg, 0.76 mmol) gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 111 mg (95%) of (-)-**1f**: amorphous white solid; crystallization attempts were unsuccessful; R_f 0.36 ($CHCl_3$/MeOH, 93/7, v/v); $[\alpha]^{22}_D$ -76.6° (c = 2.7, methanol); CIMS (100 eV) m/z (relative intensity) 306 ($[M + 1]^+$, 13), 276 (37), 232 (100), 216 ($[C_{12}H_{12}N_2O_2]^+$, 19), 201 (49), 200 ($[C_{12}H_{12}N_2O]^+$, 22), 199 (20), 174 (30); ^1H NMR (400 MHz) δ 8.22 (br s, 1 H, NH), 7.19 (d, 1 H, J = 9.0 Hz, C(12)H), 6.92-6.76 (m, 2 H, C(9)H and C(11)H), 4.93 and 4.81 (AB spectrum, 2 H, ^2J = 9.0 Hz, C(4)H_2), 4.06 (br s, 1 H, C(13b)H), 3.83 (s, 3 H, OCH_3), 3.56 (m, 1 H, C(7)H), 3.42 (m, 1 H, C(1)H), 3.27 (m, 1 H, C(2)H), 3.09 (m, 1 H, C(7)H), 2.95 (m, 1 H, C(8)H), 2.83 (dd, 1 H, C(2)H), 2.81 (m, 1 H, C(8)H), 1.87 (br s, 2 H, NH_2).

(1*S*,13b*R*)-1-Amino-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2',3':1,2]pyrido[3,4-*b*]indole (43). Via the same procedure as described for **38a** with **41** (110 mg, 0.27 mmol), chlorotrimethylsilane (59 mg, 0.54 mmol) and NaI (81 mg, 0.54 mmol) gave after column chromatography (EtOAc/*n*-hexane, 40/60, v/v) 65 mg (78%) of **43**: crystallized from CH_2Cl_2/*n*-hexane; mp 104-105 °C; R_f 0.24 ($CHCl_3$/MeOH, 93/7, v/v); $[\alpha]^{22}_D$ +3° (c = 2.0, methanol); CIMS (100 eV) m/z (relative intensity) 306 ($[M + 1]^+$, 48), 262 (30), 233 (38), 232 (54), 216 ($[C_{12}H_{12}N_2O_2]^+$, 100), 201 (95), 200 ($[C_{12}H_{12}N_2O]^+$, 51), 199 (35); ^1H NMR (400 MHz) δ 9.87 (br s, 1 H, NH), 7.23 (d, 1 H, J = 9.0 Hz, C(12)H)), 6.94-6.73 (m, 2 H, C(9)H and C(11)H), 4.94 (br s, 2 H, C(4)H_2), 3.87 (s, 3 H, OCH_3), 3.77-3.51 (br m, 3 H, C(13b)H, C(1)H, and C(7)H), 3.13-2.77 (m, 5 H, C(2)H_2, C(7)H, and C(8)H_2), 1.69 (br s, 2 H, NH_2).

Acknowledgment. We thank Ad Swolfs for taking the 400-MHz ^{13}C and ^1H NMR spectra of the cyclized products, as well as the low-temperature 400-MHz ^1H NMR spectrum of **42a**. This work was supported by the Technology Foundation of the Netherlands (STW).

Registry No. (-)-**1e**, 110597-53-0; (+)-**1e**, 120330-76-9; (-)-**1f**, 126645-51-0; **7**, 16620-52-3; **9**, 68935-49-9; **11**, 126645-25-8; **12**, 126645-26-9; **12** (R_2 = OH), 2766-43-0; **13**, 126645-27-0; **13** (R_2 = OH), 88050-18-4; **14**, 126645-28-1; **14** ((+)-MTPA ester), 126663-64-7; **15**, 126645-29-2; **16**, 126645-30-5; **17**, 126645-31-6; **18**, 126645-32-7; **19**, 126645-33-8; **20**, 126645-34-9; **21**, 126645-35-0; **22**, 126645-36-1; **23**, 126645-37-2; **24a**, 56926-94-4; **24b**, 126645-21-4; **24b** (R_3 = OH), 95715-85-8; **25a**, 126645-38-3; **25b**, 126645-22-5; **26a**, 126645-39-4; **26b**, 126645-23-6; **27**, 125109-08-2; **28**, 126645-40-7; **29**, 126645-41-8; **30a**, 126645-42-9; **30b**, 126645-24-7; **31**, 126645-43-0; **32**, 126645-44-1; **33a**, 126645-45-2; **33b**, 126645-47-4; **33b**, 126645-47-4; **34**, 126645-46-3; **35**, 55477-80-0; **35** (isomer 1), 126645-48-5; **36** (isomer 2), 126645-49-6; **38a**, 126722-18-7; **38b**, 126722-19-8; **39a**, 120296-29-9; **39b**, 120330-77-0; **40**, 126645-50-9; **41**, 126722-20-1; **42a**, 126783-64-0; **42b**, 126722-21-2; **43**, 126722-22-3.

Repetitive Imidazole Synthesis Using an Immobilized Imidazole Template

Darshan Ranganathan,* Ramesh Rathi, and Shashi Sharma

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

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A model representing the chemical simulation of the ATP-imidazole cycle programmed to continuous production of the daughter imidazoles from the immobilized parent imidazole template is presented. 6-Chloropurine was anchored to polystyrene by reaction with Ⓟ-CH_2Cl. Hydrolysis of the product purine followed by alkylation with phenacyl bromide afforded 1-phenacyl-9-polymer-bound hypoxanthine, which on treatment with benzylamine and *p*-TsOH produced the expected daughter molecule, 1-benzyl-5-phenylimidazole in 30% yield and the polymer-bound 5-amino-4-(benzylcarbamoyl)imidazole, which, in turn, was transformed to the template 9-polymer-bound hypoxanthine by treatment with MsOH followed by formamide. To prove the concept of the continuous generation of the daughter molecule, the regenerated parent template was processed through a second cycle using the same protocol when the expected daughter product 1-benzyl-5-phenylimidazole was obtained in 14% yield. Polymer-bound adenine when subjected to a similar protocol failed to yield any daughter molecule. Endeavours to prepare polymer-linked 4-oxoquinazoline and anthranilic acid are also reported here.

The ATP-imidazole cycle associated with the biosynthesis of ATP, GTP, and histidine exemplifies a unique synthetic strategy of Nature, wherein a daughter imidazole is produced from a mobile parent imidazole template in a cyclic pathway.[1] We have recently[2] shown that the salient features of the ATP-imidazole cycle could be demonstrated using either hypoxanthine or adenine as the carrier molecule. It was also demonstrated that the operating part of the cycle, namely, the vicinal disposition of an amino and a carboxyl group, could be transplanted onto a more amenable anchor. Thus, anthranilic acid via transformation to 4-oxoquinazoline performed as an excellent template for the production of N-protected 5-substituted imidazoles.

It could be readily perceived that were such parent templates to be linked to a polymer backbone, the daughter product alone would be in the mobile phase, thus making continuous use of the immobilized template possible. In the present work we have endeavored to anchor the already established templates, hypoxanthine, adenine, and 4-oxoquinazoline, to a polymer support and to demonstrate the capability of these systems in generating daughter molecules.

Macroporous polystyrene crosslinked with 2% divinylbenzene was chloromethylated with chloromethyl methyl ether in the presence of catalytic amounts of $SnCl_4$.[3] The extent of incorporation of the functional group was, in this case, estimated on the basis of weight

(1) Greenberg, D. M. *Metabolic Pathways*; Academic Press: New York, 1969; Vol. III, p 268. Ranganathan, D.; Ranganathan, S. *Art in Biosynthesis*; Academic Press: New York, 1976; p 82.

(2) Ranganathan, D.; Farooqi, F. *Tetrahedron Lett.* **1984**, 5701. Ranganathan, D.; Farooqi, F.; Bhattacharyya, D. *Tetrahedron Lett.* **1985**, 2905. Ranganathan, D.; Farooqi, F.; Bhattacharyya, D.; Mehrotra, S.; Kesavan, K. *Tetrahedron* **1986**, *42*, 4481.

(3) Frechet, J. M. J.; de Smet, M. D.; Farall, M. J. *J. Org. Chem.* **1979**, *44*, 1774.

increase and expressed in terms of the degree of functionalization (DF)[4] and the number of milliequilivalents of the desired compound present per gram of the polymer (mequiv/g).[5]

Chloromethylated polystyrene was reacted with 6-chloropurine[6] in DMSO in the presence of anhydrous K_2CO_3. After the reaction, the beads were filtered, washed successively with hot water, dioxane, acetone, and ether, and then dried to constant weight in vacuo at 60 °C.

The DF and milliequivalents/gram of the Ⓟ-CH_2-6-chloropurine thus obtained and all other samples described below were based on nitrogen analysis.[7]

In the transformation of chloromethylated polystyrene to polymer-bound 6-chloropurine, the nitrogen analysis is reliable, since in this step the polymer reagent having 0% nitrogen content can be theoretically transformed to one having a maximum of 20.7% nitrogen content/unit. A noteworthy point in these studies is that the properties of the polymer-bound template and other polymer-bound intermediates derived from it would have IR properties very similar to that of 9-benzyl-protected hypoxanthines and adenines. Consequently, a comparison of the IR spectra of the polymer-bound compounds with their 9-benzyl protected analogues–which have been fully characterized earlier[2]–was used to ensure the correctness of the assigned structures. Although the formation of the daughter product logically supported the structural assignment to the polymer-bound substrates, the comparison of the IR spectra was found to be very useful.

The usual precautions were observed to ensure that the cyclic pathway involved only polymer-bound compounds. After each step in the reaction, the polymer beads were thoroughly washed and dried to a constant weight. It was also ensured that all unreacted monomeric substrates and reagents could be effectively removed by this operation.[8]

A suspension of Ⓟ-CH_2-6-chloropurine (DF 0.84; 2.45 mequiv/g) in 1 N HCl was refluxed for 18 h, cooled, filtered, washed with water, saturated sodium bicarbonate, water, methanol, and ether, and dried in vacuo to a constant weight at 60 °C to afford Ⓟ-CH_2-hypoxanthine (**1**) (DF 0.81; 2.4 mequiv/g).

Interestingly, in the hydrolysis of polymer-bound 6-chloropurine, when the washing of the product with sodium bicarbonate was dispensed with, the product obtained was Ⓟ-CH_2-6-hydroxypurine hydrochloride (**9**) (DF 0.48; 2.88 mequiv/g). The structural assignment for (**9**) was supported by, C, H, N analytical values, the presence of free chloride, and its transformation to polymer-bound 6-acetoxypurine (**10**) on treatment with acetic anhydride–pyridine (DF 0.5; 2.93 mequiv/g).

First Cycle. A suspension of polymer-bound hypoxanthine **1** was stirred for 2 h with 0.4 M methanolic potassium hydroxide and then admixed gradually with excess phenacyl bromide in absolute methanol. The resulting mixture was refluxed for 45 h, filtered, washed with ether, methanol, water, and acetone, and dried to constant weight in vacuo, leading to the phenacyl compound **2** (DF 0.99; 1.62 mequiv/g). A suspension of the phenacyl compound **2** in dry xylene was admixed with benzylamine and *p*-TsOH, refluxed for 35 h, cooled, and filtered. The residue was washed with ethyl acetate until the washings were colorless, and the filtrate thus obtained was evaporated in vacuo and chromatographed to yield the daughter product 1-benzyl-5-phenylimidazole (**5**) (30%), mp 110 °C, which was found to be identical in all respects with an authentic sample.[2] The residual beads, in turn, were further washed with water, methanol, and ether and dried to constant weight to give 1-polymer-bound 5-amino-4-(benzylcarbamoyl)imidazole (**3**) (DF 0.71; 1.3 mequiv/g). The 30% yield of the daughter product derived from the immobilized precursor **2** compares well with the 36% yield reported with the corresponding soluble analogue, namely 9-benzyl-1-phenacylhypoxanthine.[2] Compound **3** was treated with hot methanesulfonic acid for 30 h, cooled, neutralized with aqueous ammonia, filtered, washed repeatedly with cold water, methanol, and ether, and dried to constant weight to yield 1-polymer-bound 5-amino-imidazole-4-carboxamide (**4**) (DF 0.97; 1.6 mequiv/g). Compound **4** was treated with formamide at 190 °C for 1 h, cooled, filtered washed successively with hot water, methanol, and ether, and dried to constant weight to give **1** (DF 0.98; 1.85 mequiv/g), thus completing the first cycle.

Second Cycle. The polymer-bound **1**, prepared by recycling, was processed through a second iteration via procedures described earlier. Thus, reaction of **1** with phenacyl bromide yielded **2** (DF 0.81; 1.31 mequiv/g), which on treatment with benzylamine afforded in the second cycle 14% of the daughter product, 1-benzyl-5-phenylimidazole (**5**) and the polymer-bound 5-amino-4-(benzylcarbamoyl)imidazole (**3**) (DF 0.83; 1.2 mequiv/g). The daughter products obtained from the first and the second cycle were identical in all respects. The 14% yield achieved in the second cycle compares fairly well with the 30% from the first cycle. In the event if every step in the cycle was optimized, a polymer-bound template such as **1** could be effective in the regeneration of the daughter product through many cycles.[9] The overall transformations thus far described are presented in Scheme I.[10]

9-Benzyladenine has also been demonstrated to be effective in the production of daughter imidazole products although the pathways involved here are more complicated.[2] In endeavors directed at the demonstration of immobilized adenine as an entry point in the template cycle, Ⓟ-CH_2-adenine (**6**) was prepared. A suspension of

(4) In a functional group transformation C–X → C–Y, 100% yield would represent a degree of functionalization equal to one (DF 1). In solution chemistry, the weight of the pure product would directly give the actual yield. In reactions where the unit undergoing change is immobilized, the extent of change is commonly represented as DF, since this convention permits the use of parameters other than weight change to monitor the reaction (please see ref 3).

(5) Of the increase in weight "*A*", grams, $35.5A/48.5$ g or $10^3A/48.5$ mequiv would correspond to chlorine. Thus, "*B*" grams of the polymer product would have $10^3A/48.5B$ mequiv of Cl/g. The degree of functionalization (DF) would be $10^3A/48.5C$ where *C* is the millimoles of the polymer used initially.

(6) Beaman, A. G.; Robins, R. K. *J. Appl. Chem.* **1962**, *12*, 432.

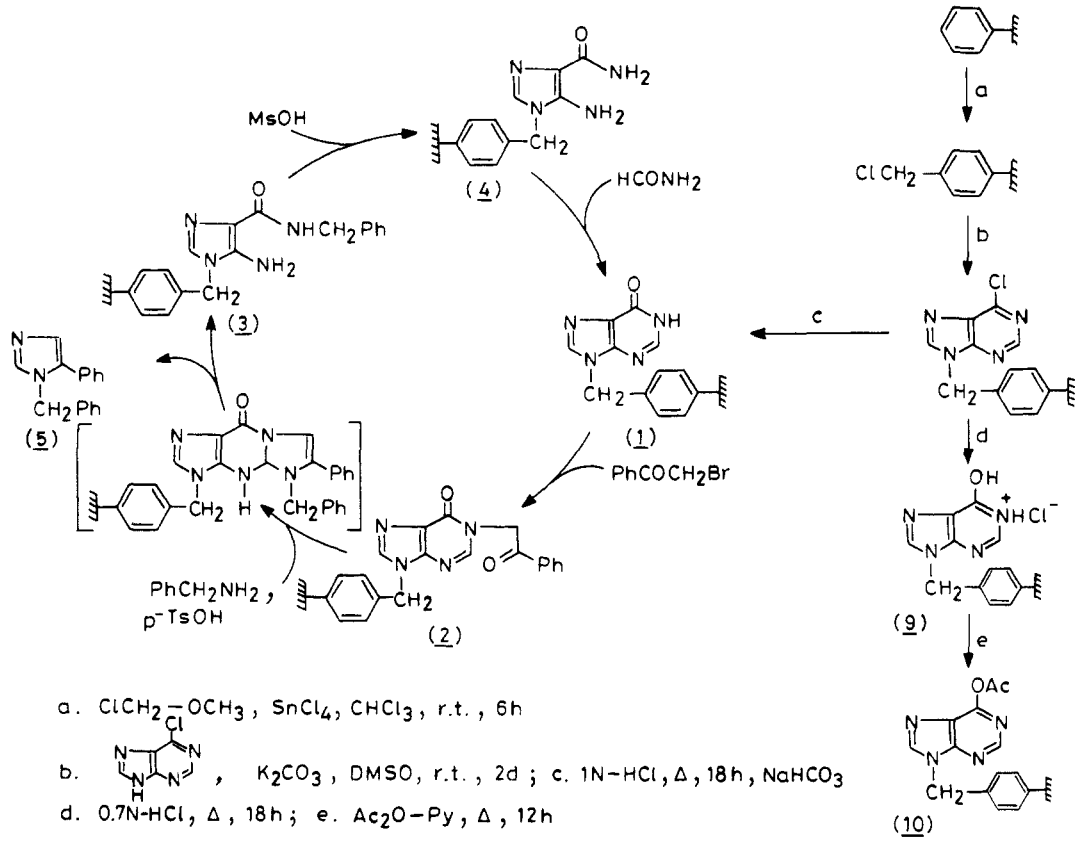
(7) If "*X*" is the percentage found value for nitrogen and "*A*" grams the weight of the polymer product, then actual millimoles of nitrogen present is $A(0.01X)/0.014$ or $A(0.01X)/0.014m$ mequiv of polymer-bound purines, where "*m*" is the number of nitrogen atoms present ($m = 4$ for hypoxanthine; $m = 5$ for adenine). The milliequivalents of the desired product/gram would be $0.01X/0.014m$ and the degree of functionalization computed to be $A(0.01X)/0.014mn$ where *n* is the milliequivalents of substrate present initially.

(8) The substrates as well as the reagents were thoroughly mixed with unchloromethylated macroporous polystyrene, filtered, and washed according to the appropriate protocol. In each case, the added compound was recovered.

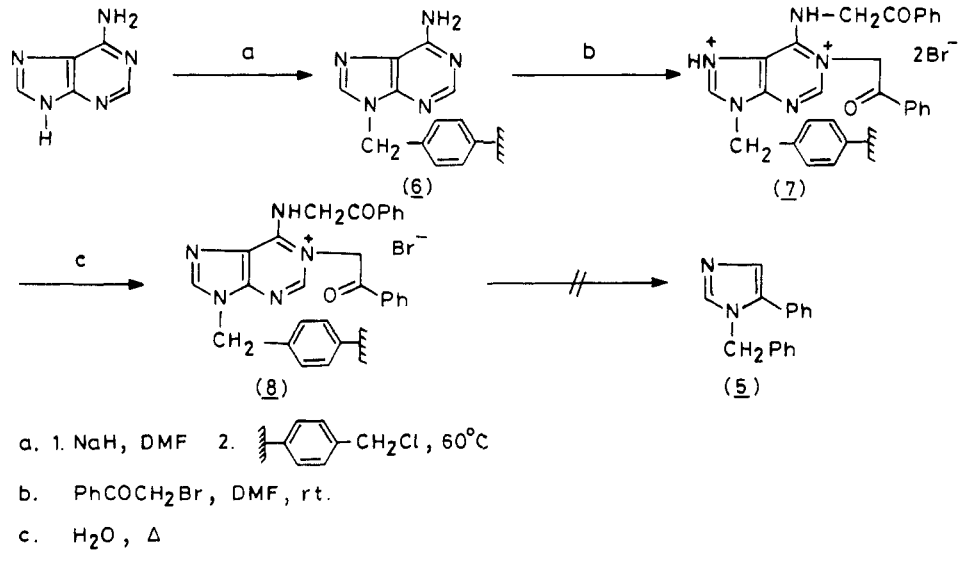
(9) The loss of yield in the second cycle principally arises due to contamination of the immobilized template in the step leading to **5** and **3** in the first cycle (Scheme I). The yields obtained in the 9-benzylhypoxanthine series (ref 2) generally match with the degree of functionalization (DF) of the corresponding steps in Scheme I, excepting for the above which afforded a 36% yield of the daughter product **5**–which agrees well with the 30% isolated in the first cycle–and a 33% yield of the modified parent. This low yield is not reflected in the immobilized cycle (DF 0.71). Considering the fact that in the 4-oxoquinazoline series (ref 2) the very same step yielded 69% of the daughter imidazole and 71% of the modified parent, it appears that the major diversion arises by the attack of benzylamine on the imidazolyl carbon 8 of the purine system.

(10) For a preliminary report dealing with some of this chemistry, see: Ranganathan, D.; Rathi, R. *Tetrahedron Lett.* **1986**, 2491.

Scheme I



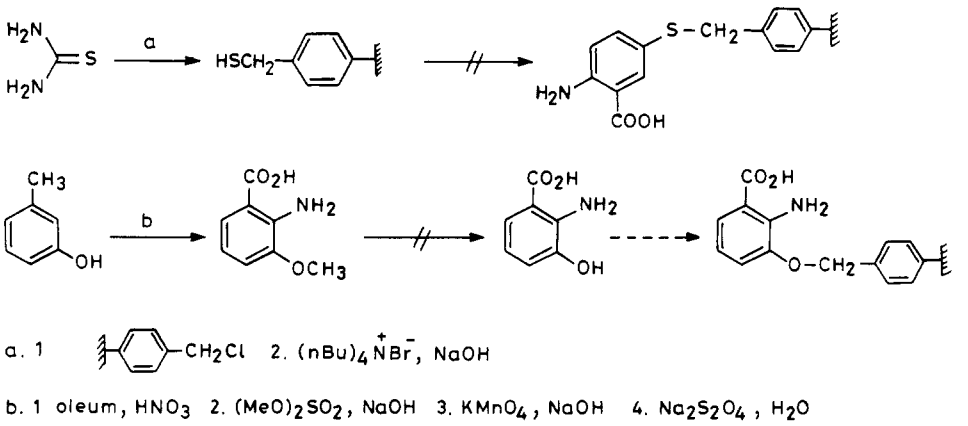
Scheme II



adenine and sodium hydride in dry DMF was left stirred for 2 h, admixed with Ⓟ-CH_2Cl, left stirred for 2 h at room temperature and then at 60 °C for 30 h, filtered, washed with dichloromethane, dioxane, distilled water, and methanol, and dried in vacuo at 60 °C to yield Ⓟ-CH_2-adenine (DF 0.27; 1.2 mequiv/g). In sharp contrast to **1**, the degree of functionalization in this case was very poor, and several attempts to improve this did not succeed. This was not altogether surprising since the best yield that has been reported in the reaction of sodioadenine with benzyl chloride was 30%.[11] The structural assignment for **6** was supported by IR comparison with 9-benzyladenine. Similar methods were followed in the characterization of further compounds in this series. Compound **6** was treated with excess phenacyl bromide in DMF for 2 days at room temperature, washed with methanol and ether, and dried to give product to which was assigned the bis-alkylated bis-salt structure (**7**) on the basis of earlier studies[2] (DF 0.74; 0.69 mequiv/g). The bis-salt **7** was treated with boiling water for a brief period, adjusted to pH 8 with aqueous ammonia, washed with water, methanol, and ether, and dried to afford the bis-alkylated mono-salt **8** (DF 0.85; 0.7 mequiv/g). Compound **8** was refluxed in xylene with benzylamine and *p*-TsOH for 30 h, cooled, filtered, and washed with ethyl acetate. The organic extracts were devoid of the expected daughter product, *N*-benzyl-5-

(11) Carraway, K. L.; Huang, P. C.; Scott, T. G. In *Synthetic Procedures in Nucleic Acid Chemistry*; Interscience: New York, 1968; Vol. I, p 3.

Scheme III



phenylimidazole (**5**) (TLC) (Scheme II). The failure of the polymer bound adenine to act as a template for daughter imidazole synthesis possibly arises from poor functionalization at each step.

To improve the efficiency of the immobilized template cycle, polymer-bound 4-oxoquinazoline was considered attractive, since this system has been demonstrated to be superior to purines, in the generation of daughter imidazoles.[2,9] Polymer-bound anthranilic acid was considered as a suitable precursor to the immobilized 4-oxoquinazoline.

A stirred suspension of chloromethylated polystyrene and thiourea in dry THF–EtOH (7:2) was refluxed for 2 days and washed with water, THF, and benzene; the resulting polymer-bound thiouronium chloride was suspended in benzene, treated with a solution of tetrabutylammonium bromide–sodium hydroxide, stirred at 80 °C under nitrogen for 2 days, filtered, washed with THF, water, THF, 6 N HCl, water, THF, acetone, methylene chloride, and methanol, and dried in vacuo to a constant weight to yield the desired polymer-bound CH_2SH unit.[12] Attempted linking of ⊕-CH_2SH with 5-iodoanthranilic acid[13] under various reaction conditions did not succeed.

The second route to polymer-bound anthranilic acid envisaged the linking of 3-hydroxyanthranilic acid[14] with chloromethylated polystyrene. *m*-Cresol was nitrated, the hydroxyl group was protected with dimethyl sulfate, the methyl group was oxidized, and the resulting 2-nitro-3-methoxybenzoic acid on reduction with sodium dithionate gave 2-amino-3-methoxybenzoic acid. Unfortunately, all attempts to cleanly deprotect this compound to the desired 3-hydroxyanthranilic acid did not succeed. These efforts are outlined in Scheme III.

Although polymer-bound templates are well known in Nature, such as those present in nucleic acids which have the ability to recognize on the basis of hydrogen bonding, in the present illustration involving **1**, the polymer-bound template actively participates in the making and breaking of covalent bonds, ultimately regenerating itself to start another cycle. A close analogy to this facet are immobilized enzymes which bring about the transformation of the substrate to product and at the same time make themselves available for another cycle after the product is released from the active site. In the context of increasing recognition of the utility of immobilized enzymes in the preparation of a variety of compounds, we believe that the methodology delineated in this work has potential for further exploitation.[15]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 580 spectrophotometr, and the ^1H NMR spectrum of the daughter product was obtained on FT R-600 spectrometer. Silica gel (Acme, 100–200 mesh) was used for column chromatography of the derived imidazole.

Chloromethylated Macroporous Polystyrene.[3] Macroporous polystyrene (Aldrich) (6 g, 9.6 mequiv/g) was suspended in a solution of chloromethyl methyl ether (12 mL, 0.158 mol) in dry chloroform (45 mL), left stirred for 2 h at room temperature, admixed with, in drops, $SnCl_4$ (2 mL) followed by an additional lot of chloromethyl methyl ether (6 mL, 0.079 mol). The reaction mixture was left stirred for additional 4 h, filtered, washed repeatedly with methanol, chloroform, dioxane–water (3:1), dioxane–3 N HCl (3:1), dioxane, dioxane–water (3:1), water, and methanol, and dried in vacuo at 60 °C to a constant weight to yield 7.835 g of product containing 4.82 mequiv Cl/g, DF 0.66; IR (KBr) 680 cm^{-1}.

9-Polymer-Bound 6-Chloropurine. With stirring and protection from moisture, freshly ignited K_2CO_3 (5 g, 0.036 mol) followed by ⊕-CH_2Cl (3 g, 14.46 mequiv Cl) was added to a solution of 6-chloropurine (5 g, 0.032 mol) in dry DMSO (90 mL). The reaction mixture was left stirred at room temperature for 2 days, filtered, washed successively with hot water, dioxane, acetone, and ether (each 3 × 20 mL), and dried in vacuo at 60 °C to constant weight to give 4.96 g of product containing 2.45 mequiv of ⊕-CH_2-6-chloropurine/g; DF 0.84 (based on nitrogen analysis). Anal. Found: N, 13.73. Calcd for $C_{14}H_{11}N_4Cl$: N, 20.70%. IR (KBr): 1590, 1565 cm^{-1}.

9-Polymer-Linked Hypoxanthine (1). A suspension of ⊕-CH_2-6-chloropurine (4.8 g; 11.76 mequiv of polymer-bound compound) in 1 N HCl (170 mL) was refluxed for 18 h, cooled, filtered, washed successively with distilled water, saturated bicarbonate, distilled water, MeOH, and ether (each 3 × 20 mL), and dried in vacuo to a constant weight at 60 °C to give 4.0 g of compound containing 2.4 mequiv of 1/g; DF 0.81. Anal. Found: N, 13.36. Calcd for $C_{14}H_{12}N_4O$: N, 22.22. IR (KBr): 1680, 1610, 1580 cm^{-1}.

First Cycle. 9-Polymer-Bound 1-Phenacylhypoxanthine (2). A mixture of ⊕-CH_2-hypoxanthine (3.795 g, 9.1 mequiv of **1**) and methanolic potassium hydroxide–prepared by dissolving KOH (1.68 g, 0.03 mol) in dry methanol (50 mL)–was left stirred at room temperature for 2 h, admixed with phenacyl bromide (8.955 g, 0.045 mol) in dry methanol (10 mL), refluxed for 45 h, cooled, filtered, washed with ether, methanol, distilled water, and acetone (each 3 × 20 mL), and dried in vacuo at 60 °C to a constant weight to give 5.546 g of polymer containing 1.62 mequiv of **2**/g; DF 0.99. Anal. Found: N, 9.14. Calcd for $C_{22}H_{18}N_4O_2$; N, 15.13. IR (KBr): 1690, 1595, 1570 cm^{-1}.

(12) Frechet, J. M.; de Smet, M. D.; Farrall, M. J. *Polymers* **1979**, *20*, 675.
(13) Wallingford, V. H.; Krueger, P. A. Organic Syntheses; Wiley: New York, 1943; Collect. *Vol.* II, p 349.
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(15) Zaborsky, O. R. *Immobilized Enzymes*; CRC Press: West Palm Beach, 1973. Suckling, C. J. *Chem. Soc. Rev.* **1977**, *7*, 215.

Reaction of 2 with Benzylamine: Isolation of the Derived Product 1-Benzyl-5-phenylimidazole (5) and the Modified Template 1-Polymer-Bound 5-Amino-4-(benzylcarbamoyl)-imidazole (3). A stirred mixture of anhydrous *p*-TsOH (7.22 g, 0.042 mol), dry xylene (80 mL), benzylamine (5.992 g, 0.056 mol), and 1-phenacyl-Ⓟ-CH_2-hypoxanthine (5.194 g, 8.41 mequiv of **2**) was refluxed for 35 h, cooled, filtered, and washed with ethyl acetate (3 × 20 mL), the combined filtrates were evaporated, and the residue was chromatographed on silica gel. Elution with PhH–EtOAc, 1:1, gave 0.590 g (2.5 mmol, 30%) of 1-benzyl-5-phenylimidazole (**5**), mp 110 °C (lit.[2] mp 111 °C). Anal. Found: C, 81.76; H, 5.44; N, 11.80. Calcd for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.96. NMR ($CDCl_3$): δ 5.1 (s, 2 H), 6.75–7.85 (m, 12 H). MS: m/z 234 (M^+).

The polymer-bound **3** was washed successively with distilled water, methanol, and ether (each 3 × 20 mL) and dried in vacuo at 60 °C to constant weight to give 4.5 g of polymer containing 1.3 mequiv of **3**/g; DF 0.71. Anal. Found: N, 7.43. Calcd for $C_{20}H_{20}N_4O$: N, 16.86. IR (KBr): 1685, 1610, 1570 cm^{-1}.

1-Polymer-Bound 5-Amino-4-carbamoylimidazole (4): A stirred suspension of 5-amino-4-benzylcarbamoyl-Ⓟ-CH_2-imidazole (8 g, 10.4 mequiv of **3**) in methanesulfonic acid (50 mL) was held at 125–30 °C for 30 h, cooled, admixed with water (50 mL), neutralized with aqueous ammonia, filtered, washed with cold water, methanol, and ether (each 3 × 20 mL), and dried in vacuo at 60 °C to a constant weight to give 6.34 g of polymer containing 1.6 mequiv of **4**/g; DF 0.97. Anal. Found: N, 8.95. Calcd for $C_{13}H_{14}N_4O$: N, 23.14. IR (KBr): 1690, 1600, 1580 cm^{-1}.

Reaction of 4 with Formamide: Regeneration of Template 1. A stirred suspension of 5-amino-4-carbamoyl-Ⓟ-CH_2-imidazole (3 g, 4.8 mequiv of **4**) in formamide (12 mL) was held at 190 °C for 1 h, cooled, admixed with water (50 mL), filtered, washed with water, methanol, and ether (each 3 × 20 mL), and dried in vacuo at 60 °C to constant weight to give 2.54 g of polymer containing 1.85 mequiv of **1**/g; DF 0.98. Anal. Found: N, 10.35. Calcd for $C_{14}H_{12}N_4O$: N, 22.22. IR (KBr): 1685, 1600, 1575 cm^{-1}.

Second Cycle. Reaction of Regenerated 1 with Phenacyl Bromide: Preparation of 2. A mixture of Ⓟ-CH_2-hypoxanthine (2.47 g, 4.57 mequiv of **1**) and methanolic potassium hydroxide–prepared by dissolving KOH (1 g, 0.0196 mol) in dry methanol (50 mL)–was left stirred at room temperature for 2 h, admixed with phenacyl bromide (5.85 g, 0.0294 mol) in dry methanol (10 mL), refluxed for 45 h, cooled, filtered, washed successively with ether, MeOH, distilled water, acetone, and methanol (each 2 × 20 mL), and dried in vacuo at 60 °C to a constant weight to give 2.8 g of polymer containing 1.31 mequiv of **2**/g; DF 0.81. Anal. Found: N, 7.36. Calcd for $C_{22}H_{18}N_4O_2$: N, 15.13. IR (KBr): 1685, 1595, 1570 cm^{-1}.

Reaction of 2 with Benzylamine: Isolation of Daughter Product 1-Benzyl-5-phenylimidazole (5) and Modified Template 3. A stirred mixture of anhydrous *p*-TsOH (3.76 g, 0.0219 mol), dry xylene (100 mL), benzylamine (3.12 g, 0.0292 mol), and 1-phenacyl-Ⓟ-CH_2-hypoxanthine (2.7 g, 3.54 mequiv of **2**) was refluxed for 30 h, cooled, filtered, and washed with ethyl acetate (2 × 20 mL); the combined filtrates were evaporated in vacuo; and the residue was chromatographed on silica gel. Elution with PhH–EtOAC, 1:1, gave 0.127 g (0.5 mmol, 14%) of 1-benzyl-5-phenylimidazole (**5**), mp 110 °C, identical with that obtained from the first cycle.

The polymer-bound **3** was washed successively with distilled water, methanol, and ether (each 2 × 20 mL) and dried in vacuo at 60 °C to a constant weight to give 2.45 g of polymer containing 1.2 mequiv of **3**/g; DF 0.83. Found: N, 6.87. Calcd for $C_{20}H_{20}N_4O$: N, 16.86. IR (KBr): 1675, 1605, 1565 cm^{-1}.

9-Polymer-Bound Adenine (6). A suspension of adenine (2.5 g, 0.0185 mol) and sodium hydride (1.4 g, 50% suspension in oil, 0.029 mol) in dry DMF (80 mL) was left stirred for 2 h and admixed with Ⓟ-CH_2Cl (3 g, 14.46 mequiv of Cl). The reaction mixture was left stirred for 2 h at room temperature and then at 60 °C for 30 h, filtered, washed with CH_2Cl_2, dioxane, distilled water, and methanol (each 2 × 30 mL), and dried in vacuo at 60 °C to a constant weight to yield 3.243 g of product containing 1.2 mequiv of Ⓟ-CH_2adenine/g; DF 0.27. Anal. Found: N, 8.48. Calcd for $C_{14}H_{13}N_5$: N, 27.88. IR (KBr): 1640 cm^{-1}.

Reaction of 6 with Phenacyl Bromide: Preparation of Bis-alkylated 9-Polymer-Bound Adenine Salt 7. A suspension of Ⓟ-CH_2-adenine (2.52 g, 3 mequiv of **6**) and phenacyl bromide (3 g, 0.015 mol) in dry DMF (50 mL) was left stirred for 2 days at room temperature, filtered, washed with methanol (3 × 20 mL), and ether (4 × 20 mL), and dried to constant weight in vacuo to yield 3.2 g of polymer containing 0.69 mequiv of **7**/g; DF 0.74. Anal. Found: N, 4.88. Calcd for $C_{30}H_{27}N_5O_2Br_2$: N, 10.78. IR (KBr): 3420, 3060, 1690, 1630, 1600 cm^{-1}.

Hydrolysis of 7. Preparation of the Polymer-Bound Bis-alkylated Monosalt (8). A hand-shaken suspension of the bis-salt **7** (3 g, 2.07 mequiv of **7**) in 50 mL of distilled water was immersed in a boiling water bath for 0.25 h, cooled, adjusted to pH ~8 with aqueous ammonia, filtered, washed successively with water, methanol, and ether (each 2 × 20 mL), and dried in vacuo at 90 °C to constant weight to yield 2.5 g of polymer containing 0.7 mequiv of **8**/g, DF 0.85. Anal. Found: N, 4.76. Calcd for $C_{30}H_{26}N_5O_2Br$: N, 12.32. IR (KBr): 3460, 3020, 1710, 1660, 1600 cm^{-1}.

The Reaction of 8 with Benzylamine: Attempted Preparation of the Daughter Product 1-Benzyl-5-phenylimidazole (5). A stirred mixture of anhydrous *p*-TsOH (1.72 g, 0.01 mol), dry xylene (40 mL), benzylamine (2.14 g, 0.02 mol), and the polymer-bound bis-alkylated adenine mono-salt (1.85 g, 1.3 mequiv of **8**) was refluxed for 30 h, cooled, and filtered; the residue was washed with ethyl acetate; and the combined filtrates were evaporated. TLC demonstrated the complete absence of the desired daughter product.

9-Polymer-Bound 6-Hydroxypurine Hydrochloride (9). A stirred suspension of Ⓟ-CH_2-6-chloropurine (1 g, 5.52 mequiv of polymer bound compound) in 0.7 N HCl (35 mL) was refluxed for 18 h, cooled, filtered, washed successively with distilled water, methanol, and ether (each 2 × 5 mL), and dried in vacuo at 100 °C to give 0.92 g of compound containing 2.88 mequiv of **9**/g; DF 0.48. Anal. Found: N, 16.30. Calcd for $C_{14}H_{13}N_4OCl$: N, 19.41.

Reaction of 9 with Acetic Anhydride–Pyridine: 9-Polymer-Bound 6-Acetoxypurine (10). A stirred suspension of Ⓟ-CH_2-6-hydroxypurine hydrochloride (2 g, 5.76 mequiv of **9**), Ac_2O (10 mL), and pyridine (10 mL) was refluxed for 12 h, cooled, filtered, washed with CH_2Cl_2 and ether (each 5 × 10 mL), and dried in vacuo to give 1.0 g of compound containing 2.93 mequiv/g of **10**; DF 0.5. Anal. Found: N, 16.64. Calcd for $C_{16}H_{14}N_4O_2$: N, 19.04. IR (KBr): 1700 cm^{-1}.

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Registry No. **5**, 53704-79-3; ATP, 56-65-5; $PhCOCH_2Br$, 70-11-1; $PhCH_2NH_2$, 100-46-9; polystyrene, 9003-53-6; 6-chloropurine, 87-42-3; adenine, 73-24-5.

Supplementary Material Available: IR spectra of compounds **1** → **4** of the first and the second cycle, as well as the IR and NMR spectra of the daughter product 1-benzyl-5-phenylimidazole (**5**) obtained from both cycles along with the spectra of the authentic sample (16 pages). Ordering information is given on any current masthead page.