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Solid-phase synthesis of 2,6,8-trisubstituted purines

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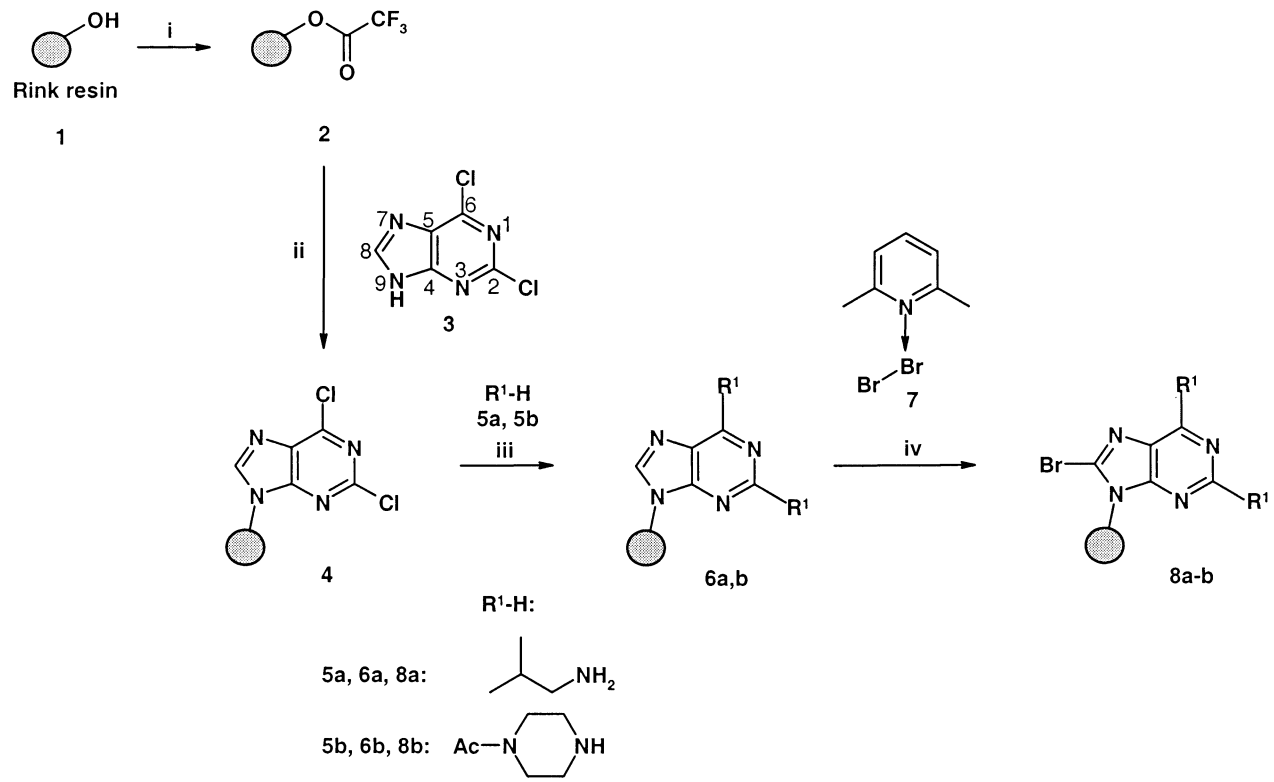
Abstract—2,6,8-Trisubstituted purines were synthesized from 2,6-dichloropurine bound to polystyrene-based Rink resin at the N(9) position. Selective successive displacements of the chlorine atoms in the 2- and 6-positions followed. Bromination of C(8) and Stille coupling concluded the synthesis. © 2001 Published by Elsevier Science Ltd.

Purine libraries, either synthesized in solution or on solid supports, have received great attention due to their potential as target nucleotide-binding proteins,[1] which play a significant role in many biological processes.[2]

Most aforementioned libraries have focused on substituting purine at its 2-, 6- and 9-positions. Here, we report a solid-phase synthesis of 2,6,8-trisubstituted purines,[3] which includes bromination of the purine at C(8), followed by a Pd-mediated coupling reaction.



Scheme 1. All the above reactions were performed in a glass-frit reactor (Ref. 10b). (i) TFAA, 2,6-lutidine; (ii) **3**, NMP, 2,6-lutidine (Ref. 5); (iii) **5a**,**b** (2 M, 26.67 equiv.), 125°C, NMP, 90 h; (iv) **7** (5×) NMP, 3 h, rt (Ref. 8).

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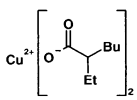
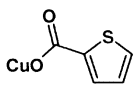
The synthesis of 2,6,8-trisubstituted purines commences with the immobilization of 2,6-dichloropurine (**3**) on Rink acid resin (**1**)[4] after activating the linker as its trifluoroacetate (**2**).[5] The displacement of the chlorine atoms follows smoothly with amines **5a**,**b** at 125°C to yield **6a**,**b**.

Displacement of H(8) by bromine is carried out using a bromine lutidine complex[6,7] (**7**) in NMP. The bromination tolerates alkyl, benzyl, amide and ether groups. Electron-rich aromatics, such as anilines, are brominated; aliphatic amines are decomposed to give complex mixtures. Freshly prepared solutions of **7** must be added to the resins in five portions successively to afford complete bromination[8] (Scheme 1).

During the displacement of the 8-bromo function by aryl, alkenyl or alkynyl residues (Table 1), the key side reaction is the dehalogenation of the purine, probably due to solvolysis of a Pd–purine intermediate. We attempted Suzuki coupling conditions, shown to be successful with other substrates,[9,10] between **8a**,**b** and 4-trifluoromethyl benzene boronic acid, 4-acetylbenzene boronic acid and 3-ethoxybenzene boronic acid (**9a**). In all these cases a sluggish reaction or complete dehalogenation of the aryl halide was observed (entries 1 and 2). Our previously used Stille-coupling condition also failed (entry 3).[9,11] Attempted Stille couplings using CuO as co-catalyst[12] resulted in no conversion, probably due to a lack of interaction between the insoluble CuO and the polymer-bound arylhalide. The use of more soluble copper(II) salts (entries 5 and 6) results in substantial dehalogenations. In turn, Cu_2O, together with various Pd sources, leads to high coupling efficiencies with little or no dehalogenations. Cu_2O is clearly superior over CuI and Cu(I) thiophene carboxylate in promoting coupling reactions (entries 7 and 8). The Pd sources, $Pd(OAc)_2$ and $Pd(PhCN)_2Cl_2$, used in conjunction with 1,3-bis(diphenylphosphino)propane, gave similar results for most substrates (Scheme 2). These catalysts where slightly better than $Pd(MeCN)_2Cl_2$ and $Pd_2(dba)_3$. With the $Pd(OAc)_2$–Cu_2O coupling method[13] in hand, aromatic acetylenic and vinylic functionalities can be introduced at C(8) of various diaminopurines. Purines with primary alkylamino substituents in their 2- and 6-positions (**8a**) give better coupling results than those bearing secondary amino functions (**8b**,**c**). Vinyl and alkynyl stannanes give better results than some aromatic functions, especially pyridyl.

Table 1. Pd-mediated couplings in the 8-position of purines

Entry	Starting material	R^3-E	Solvent	Cu cat.	Pd cat.	Co-ligand	Coupling product[a]	Product yield[a] (%)	Dehalog.[a] (%)
1[b]	**8a**	**9a**	Dioxane	–	$Pd(OAc)_2$	–	**10a**	21	<5[c]
2[d]	**8a**	**9a**	NMP	–	Pd_2dba_3	P(*tert*-Bu)$_3$	**10a**	–	>98
3[e]	**8a**	**9b**	Dioxane	–	Pd_2dba_3	$As(Ph)_3$	**10b**	–	>5[c]
4	**8a**	**9b**	NMP	CuO	Pd_2dba_3	dppp[f]	**10b**	n.r.[c]	n.r.[c]
5	**8a**	**9b**	NMP	$Cu(OAc)_2$	Pd_2dba_3	dppp	**10b**	–	91.6
6	**8a**	**9b**	NMP		Pd_2dba_3	dppp	**10b**	51.5	48.5
7	**8a**	**9b**	NMP	CuI	Pd_2dba_3	dppp	**10b**	20	–
8	**8a**	**9b**	NMP		Pd_2dba_3	dppp	**10b**	35.7	64.1
9	**8a**	**9b**	NMP	Cu_2O	–	–	**10b**	n.r.[c]	n.r.[c]
10	**8a**	**9b**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**10b**	>98	–
11	**8a**	**9c**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**10c**	>92[g]	–
12	**8a**	**9d**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**10d**	90	10
13	**8a**	**9e**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**10e**	94.6	>5
14	**8a**	**9f**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**10f**	67.6	30
15	**8b**	**9f**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**11a**	78.2	15.7
16	**8b**	**9f**	NMP	Cu_2O	$Pd(PhCN)_2Cl_2$	dppp	**11a**	65.2	14.7[c]
17	**8b**	**9g**	NMP	Cu_2O	$Pd(OAc)_2$	dppp	**11b**	70.4	5[c]

[a] No product was lost due to premature cleavage from the resin. The purities are given by HPLC analysis at 215 nm. Compounds with purities >98% appeared as one compound by NMR and MS.

[b] Suzuki coupling (Refs. 10a,b).

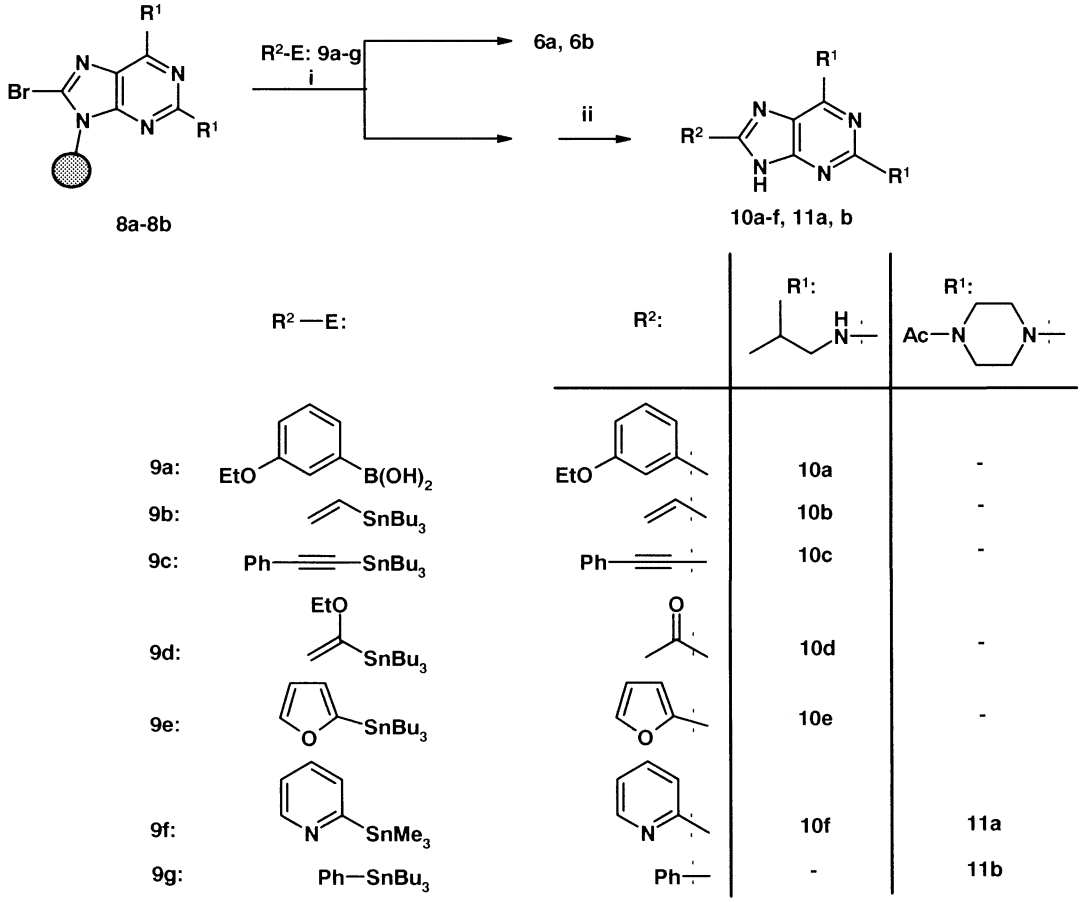
[c] n.r., no reaction; starting material was recovered.

[d] Resin bearing **8a** (30.0 mg, 0.015 mmol), **9a** (32.1 mg, 12.87 equiv.), Cs_2CO_3 (30.0 mg, 6.13 equiv.), P(*t*-Bu)$_3$ (10.0 mg, 3.2 equiv.), Pd_2dba_3 (3.1 mg 0.23 equiv.), NMP (1 mL), 24 h, 100°C.

[e] Stille coupling (Refs. 10a and 11).

[f] 1,3-Bis(diphenylphosphino)propane.

[g] Traces of hydrolysis of acetylenic group.



Scheme 2. (i) Pd-mediated coupling (see Table 1); (ii) 20% TFA/$ClCH_2CH_2Cl$ (7×).

In conclusion, we succeeded in performing Pd-mediated coupling reactions on the highly oxidized 8-bromo-2,6-diaminopurine on a polymeric support. These reaction conditions have been implemented in ongoing combinatorial chemistry projects.

Acknowledgements

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7. *Bromine lutidine complex* **7**: To lutidine (28.45 mL) at 0°C was added bromine (1.54 mL, 29.96 mmol) over a period of 40 min with stirring. A yellow precipitate formed. The reaction was stirred for a further 2 h. The precipitate was filtered through a glass frit and washed briefly with *n*-pentane. To remove the included bromine, the product was dissolved in minimal amounts of dichloroethane (5.00 mL) and precipitated in *n*-pentane (250.00 mL). Note that all the solvents should not contain stabilizers, which may inhibit the radical bromination of purines. The orange product was dried for 1 h at rt/0.9 mbar and was kept in the dark at 4°C. Yield: 5.54 g (69.28%); ^{1}H NMR ($CDCl_3$): δ 7.48 (t, 1H), 6.95 (d, 2H), 2.55 (s, 6H). Anal. calcd for $C_7H_9Br_2N$: C, 31.49; H, 3.40; Br, 59.86; N, 5.25. Found: C, 31.02; H, 3.25; Br, 60.2; N, 5.25%.
8. *General procedure to form 2,6-diamino-8-bromopurines*: The brominating agent was prepared as follows: To 2,6-lutidine (0.11 mL, 10.1 mg, 0.947 mmol) and NMP (10.00 mL) was added **7** (266.9 mg, 1 mmol). To resin bearing a 2,6-diaminopurine (30.0 mg, 0.5 mmol/g, 0.015 mmol) was added the brominating agent (1.50 mL). The slurry of resin and brominating agent was shaken at rt for 5 h and the reagent solution was then drained. This process was repeated four more times. The resin was washed with DMA (10×), DCM then MeOH (5×), DCM (5×) and *n*-pentane (5×).
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13. *General procedure for performing Stille coupling on diaminopurines*: Typical coupling reactions were performed in a Flexchem-block™ (Robbins Scientific Corporation, 814 San Aleso Ave., Sunnyvale, CA 94086-1411, USA). The NMP was distilled over CaH_2 under Ar at 20 torr. Resins bearing **8a** or **8b** (60 mg, 0.030 mmol) and Cu_2O (36.0 mg, 0.25 mmol, 8.3 equiv.) were also placed in the reaction block as solids. The block was then sealed and flooded with Ar. Through the septa in the block was added 0.5 mL of a stock solution containing $Pd(OAc)_2$ (1.38 mg, 0.006125 mmol, 0.2 equiv.) and 1,3-bis-(diphenylphosphino)propane (dppp) (5.15 mg, 0.01249 mmol, 0.41 equiv.) in NMP. Subsequently, 0.25 mmol (8.3 equiv.) of the appropriate stannane was added as a 0.25 M solution in NMP. The reaction block was kept at 100°C for 20 h. The reaction wells were then washed ten times with 0.5 mL of the following solvents: (1) aq. 0.25 M TEAA in DMA/H_2O 4:1 (v/v); (2) acetonitrile/HOAc/DMA 2:1:2 (v/v) (this solubilized the excess Cu_2O, which may clot frits); (3) 5% sodium *N*,*N*-diethyldithiocarbonate in DMA. The washing was concluded as described in Ref. 8. The resin was dried and the reaction was repeated as before. After the 'double coupling,' the products were liberated from the resin using 30 s treatments with 20% TFA in $ClCH_2CH_2Cl$ (7×, 0.2 mL each). The crude reaction mixtures were evaporated to dryness in vacuo and subjected to HPLC–MS, UV and NMR.
For example: Compound **10c**: ^{1}H NMR (DMSO-d_6): δ 7.62 (m, 2H, Ph), 7.49 (m, 3H, Ph), 3.27 (m, 2H, CH_2), 3.1 (m, 2H, CH_2), 1.88 (m, 2H, CH), 0.9 (broad s, 12H, Me); MS: 363.3 (M+H); crude isolated yield: 14.0 mg, 97% as TFA salt.