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The bromination of purines with a charge transfer complex between bromine and lutidine

Wolfgang K.-D. Brill* and Claudia Riva-Toniolo

Combinatorial Chemistry Unit, Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basle, Switzerland

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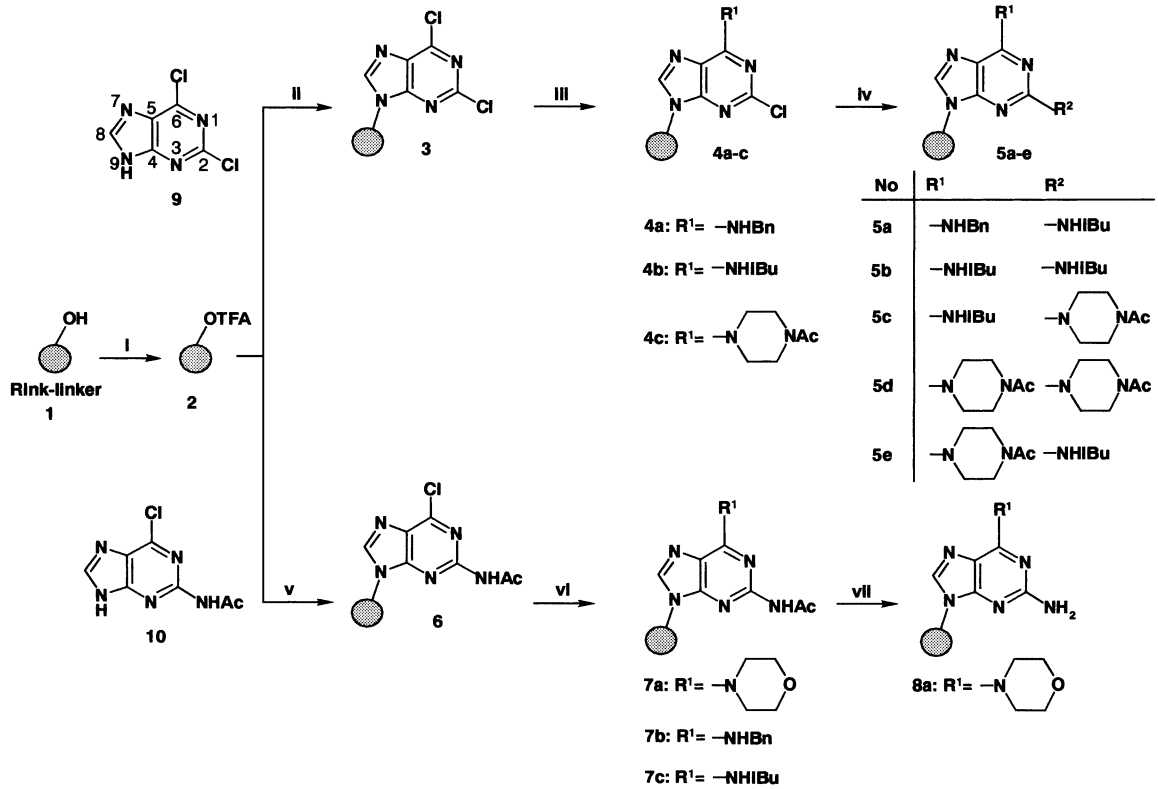
Abstract—Diaminopurines, immobilized on a polymeric support are treated with a charge transfer complex of bromine and lutidine to afford 8-brominated derivatives. An ionic complex of bromine and lutidine did not oxidize the purines. 2,6-Dialkylaminopurines could also be oxidized on the α-carbon of their 2-alkylamino group.

Purine libraries, either synthesized in solution or on solid supports, have received great attention due to their potential to target nucleotide-binding proteins, which play a significant role in many biological processes.[1] While the aforementioned libraries focus on substituting purine on its 2, 6 and 9 positions, most methods to obtain 8-substituted purines have been performed with adenosine[2] or guanosine,[3] but not with 2,6-diamino-



Scheme 1. (i) TFAA/lutidine, rt; (ii) dichloropurine (**9**), NMP, rt; (iii) amine, cat. TFA, 55°C, 90 h; (iv) amine, NMP, 125°C; (v) 6-chloro-3-acetylaminopurine (**10**), NMP, rt; (vi) amine, (vii) cat. TFA, 55°C, 3 days; KOH, DMSO.

* Corresponding author. Present address: Discovery Research Oncology, Pharmacia Corp., Viale Pasteur 10, I-20014 Nerviano, Italy. E-mail: wolfgang.brill@am.pnu.com

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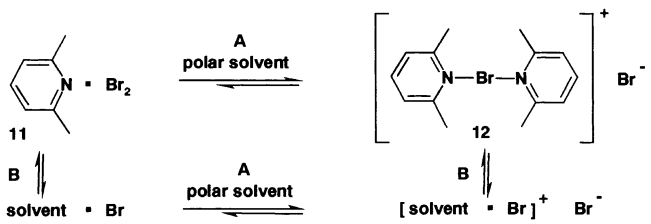

Scheme 2. (A) Slow disproportionation of the lutidine bromine complexes in polar solvents: **11** converts into **12** in 5 h in $DMFD_7$. (B) Rapid exchange of bromine solvating lutidine or other solvent molecules. Mixtures of **11** and **12** in $DMFD_7$ depict average NMR spectra.

purines. Here, we report a scope and limitations study of the bromination of various 2,6-disubstituted purines their 8 position.

The synthesis of 2,6-disubstituted purines begins with immobilizing 2,6-dichloropurine (**9**) or 6-chloro-purin-2-yl-amine (**10**)[4] on 'Rink'-acid resin (**1**)[5] after activating the linker as its trifluoroacetate (**2**).[6] The immobilized 2-acetylamino-6-chloropurine (**6**) is then treated with amines such as morpholin to afford **7a**–**c**. Deacetylation of **7a** with KOH/DMSO gave **8a**.[7] The other 2,6-diaminopurines are synthesized in a stepwise fashion. The substitution at C6 was catalyzed by TFA, substitution at C2 was done at elevated temperatures (Scheme 1).[1]

Bromination on C8 was performed with complex **11**[8,9] (Scheme 2), which gives cleaner conversions than Br_2 in mixtures of aq. buffer and an organic co-solvent.[10] It brominates the C8 of diaminopurines efficiently in NMP, but does even better in benzene, without loss of purine bound to 'Rink'-resin by its N9 position. NMR studies revealed a rapid interchange with polar solvents (DMF) or other lutidine molecules. Compound **11** also disproportionates in the presence of 2,6-lutidine in polar solvents to afford **12**,[11,12] which cannot brominate purines. This conversion proceeds in the presence of one equivalent of 2,6-lutidine in heptadeutero-DMF within 5 hours at 25°C (Scheme 2).

The oxidizing power of **11** was mediated by the solvent (Scheme 3). In NMP the polystyrene-support itself was not modified in benzene, it was brominated on its benzylic positions. The latter resin could be debrominated quantitaively via KOtBu-mediated elimination. In NMP, where **11** disproportionates to **12**, fresh reagent has to be added in several portions to complete the reaction[13] and the brominations of purines bearing electron withdrawing substituents (**6**, **7a**) are unsuccessful or sluggish. In benzene,[14] where **11** is not deactivated, even purines **7b** and **7c** are brominated in high yields to afford **13i** and **13j**, respectively. The bromination with **11** is incompatible with aliphatic amines in NMP and benzene. Aromatic residues less or equally activated than toluene and amide functions remain unchanged. In benzene 2,6-dialkylaminopurines are oxidized selectively in benzene on their substituent at C2.[15] Neither 'Rink'-linker nor polystyrene mediates this oxidation, as indicated by a model reaction in solution phase (Table 1 entry 14). We believe that this process begins by a transfer of a Br_2-molecule from 2,6-lutidine to N1 (Scheme 4). The resulting complex (**16**) may undergo a series of double bond migrations followed by an HBr-elimination to give a purine–C2–alkylimine **18**. The latter my either hydrolyze 2-amino-purine **21** or be oxidized by **11** to afford an imidoyl bromide **19**,[16] which my then become hydrolyzed to the amide.[17]

The purinyl-piperazine **5d** affords **13g** probably via bromination and hydrolysis of a C2-bound 1,4-diazacyclohexene intermediate.

We demonstrated the bromination of purines on a solid support using a charge-transfer complex of bromine with lutidine. The solvent has a profound influence on the oxidation reaction of 2,6-diaminopurines. The methods outlined here may be applied in derivatizations of purines on solid supports.

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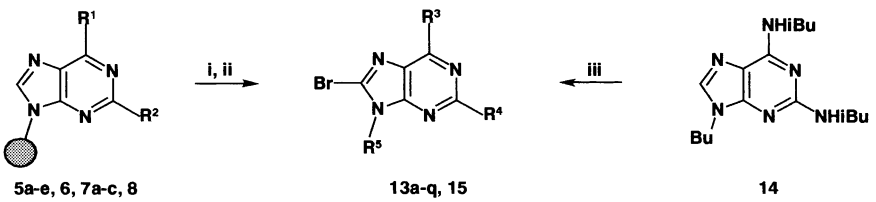
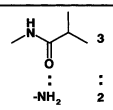
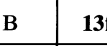
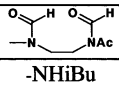
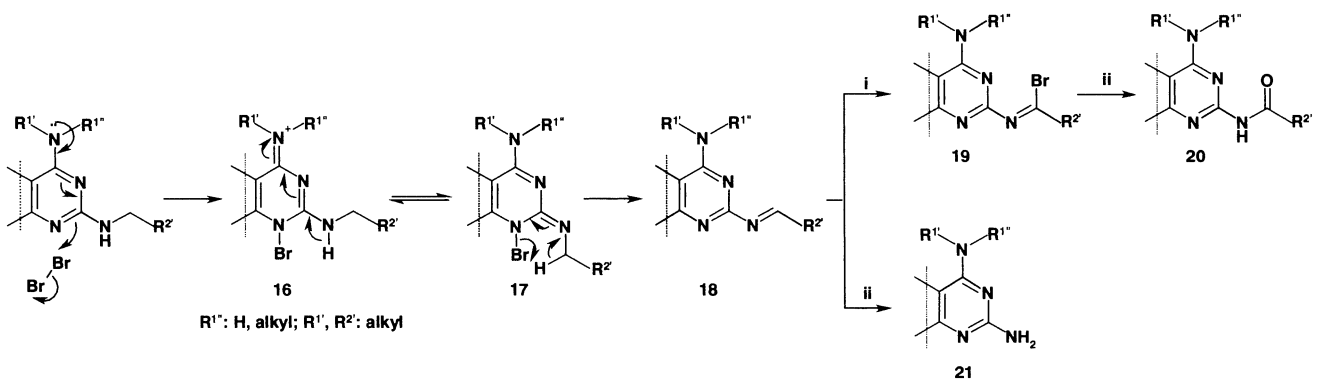


Scheme 3. (i) Bromination according to Table 1; (ii) 5×20% TFA in $ClCH_2CHCl$.

Table 1.

Entry	Starting material	Method	Product No	R^3	R^4	R^5	HPLC-purity	Isolated yield[1]
1	**5a**	A	**13a** / **13b**	-NHBn / -NHBn		H	quant. (2 prod.)	n.d.
2	**5b**	B	**13c**	-NHiBu	-NHiBu	H	quant.	61.7
3	**5b**	A	**13d**	- " -		H	95.4	75
4	**5c**	B	**13e**	- " -		H	quant.	78.3
5	**5d**	B	**13f**		- " -	H	quant.	76.3
6	**5d**	A	**13g**	- " -		H	quant.	n.d.
7	**5e**	C	**13h**	- " -	-NHiBu	H	40.6	n.d.
8	**5e**	B	**13h**	- " -	- " -	H	quant.	78
9	**6**	B	-	-	-	-	no reaction	
10	**7a**	B	-	-	-	-	- " -	
11	**7b**	A	**13i**	-NHBn	-NHAc	H	78[2]	79
12	**7c**	A	**13j**	-NHiBu	- " -	H	76[2]	86
13	**8**	B	**13k**		$-NH_2$	H	quant.	97.5
14	**14**	D	**15**	-NHiBu		-Bu	n.d.	79

[1]The products contain 1 equiv. of TFA; conditions; [2]the rest is starting material. (A) 0.1 M **11**, 0.1 M 2,6-lutidine, benzene, 48 h; (B) 0.1 M **11**, 0.1 M 2,6-lutidine, NMP, Ref. 13; (C) 0.1 M Br_2, 1 M NaOAc in dioxane/H_2O 4/1 (v/v); (D) 0.1 M **11**, 5.67 equiv. 0.1 M 2,6-luitidine, 5.67 equiv. benzene, 48 h.



Scheme 4. Proposed mechanism for the oxidative C2-modification of diaminopurines with complex **11**: (i) **11**, benzene; (ii) hydrolysis.

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9. Complex **11**: To lutidine (28.45 mL) at 0°C was added bromine (1.54 mL, 29.96 mmol) over a period of 40 min upon stirring. A yellow precipitate was formed. The reaction was stirred for another two hours. The precipitate was filtered off through a glass frit and washed briefly with *n*-pentane. To remove included bromine, the product was dissolved in minimal amounts of dichloroethane (5 mL) and precipitated into *n*-pentane (250 mL). The orange product was dried for one hour at rt at 0.9 mbar and kept at 4°C in the dark. Yield: 5.54 g (69.28%); ^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H), 6.95 (d, 2H), 2.55 (s, 6H); elemental analysis (C_7H_9 Br_2N): calcd: 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%.
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11. Compound **12** probably has a structure like the 'Lemieux complex' between bromine and collidine: Lemieux, R. U.; Morgan, A. R. *Can. J. Chem*. **1965**, *43*, 2190–2198.
12. Complex **12**: **11** was taken up in dichloromethane (5 mL) and precipitated into diethyl ether (250 mL). The yellow product was dried for one hour at rt at 0.9 mbar and kept at 4°C in the dark. Yield 43%; ^{1}H NMR ($CDCl_3$) δ 8.12 ppm (1H, t), 7.46 ppm (2H, d) 2.95 ppm (6H, s); elemental analysis ($C_{14}H_{18}$ Br_2N_2): calcd C, 44.95%; H, 4.85%; Br, 42.72%; N, 7.49%. Found: C, 42.70%; H, 4.91%; Br, 45.37%; N, 7.1%.
13. Table 1, entry 2: **8-Bromo-N^2,N^6-diisobutyl-purine-2,6-diamine (13c)**: A 1.5 mL of solution of **11** (266.97 mg, 1 mmol) and 2,6-lutidine (10.14 mg, 0.947 mmol) in NMP (10 mL) was added to a resin bearing **5c** (30 mg, 0.5 mmol/g, 15 μmol). The slurry was shaken at rt for five hours. The reagent solution was then drained. This process was repeated twice and the resin was washed with 5×1 M aq. TEA/DMA 1/4 (v/v) and 5×DMA. Alternating washes followed with 5×MeOH and CH_2Cl_2 and 5×CH_2Cl_2 and *n*-pentane. The product was liberated by treating the resin with TFA/$ClCH_2CH_2Cl$ (6×1 min). The solvents were removed in vacuo to afford the product. ^{1}H NMR (DMSO-D_6) δ 3.42 (m, 2H, CH_2(iBu)), 3.12 (m, 2H, CH_2(iBu)), 1.9 (m, 2H, CH(iBu)), 0.95 (double d, 6H, Me(iBu)); ^{13}C NMR (DNSO-D_6) δ (38, 39, CH_2(iBu)), 27 (CH(iBu)), 21 (Me(iBu)); HPLC-purity at 254 nm: 89.9%; UV (gradient): 219 nm (min); 240 nm (max); 249 nm (shoulder); 270 nm (min) 294 nm (max); MS: 343.
14. Table 1, entry 12: ***N*-(8-Bromo-6-isobutylamino-purin-2-yl)-acetamide (13j)**: 1.5 mL of a solution of **11** (266.97 mg, 1 mmol) and 2,6-lutidine (10.14 mg, 0.947 mmol) in dry benzene (10 mL) was added to resin bearing **5c** (30 mg, 0.5 mmol/g, 15 μmol). The slurry was shaken at rt for 24 hours and worked up as **13c**.^{1}H NMR ($DMSOD_6$) δ 3.25 (m, 2H, CH_2(iBu)), 1.21 (s, 3H, acetyl), 1.95 (m, 1H, CH(iBu)), 0.9 (d, 6H, Me(iBu)); ^{13}C NMR (HSQC) (DMSO-D_6) δ 48 CH_2(iBu), 29 (CH(iBu)), 26 (Me-acetyl), 20.5 (Me(iBu)); UV (gradient): 223 nm (min), 243 nm (max), 258 nm (min), 279 nm (max) (The UV spectrum is identical to that of **13i**); MS: 327.13 $(M+H)^+$; impurity: 249.17 $(M+H)^+$:**7c**.
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