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An improved procedure for the preparation of 8-substituted guanines†

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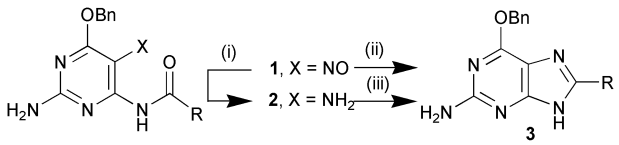
The preparation of 8-substituted guanines using a new phosphorus(III)-mediated cyclisation of 4-acylamino-5-nitrosopyrimidines as the key step is described.

The synthesis of purines and purine nucleosides continue to attract medicinal interest[1] due to their antimicrobial properties[2] and their interaction with adenosine receptors.[3] The double condensation of 4,5-diaminopyrimidines with one-carbon electrophiles (Traube synthesis) and related methods[4] remain by far the most important routes for the construction of purines, although closure of the imidazole ring to give C(8)-substituted derivatives is generally more difficult than in the case of C(8)-unsubstituted purines. In recent years, however, the direct transformation of 4-amino- or 4-acylamino-5-nitrosopyrimidines into purines by thermally driven processes[5] or reductions,[6] without isolation of the 5-amino derivatives have been reported. Such nitroso compounds also react with Mannich bases,[7] Vilsmeier-Haak reagents[8] and 1,1-dimethylhydrazones,[9] to form fused imidazole rings. We wish to report an improved procedure for the reductive cyclisation of 4-acylamino-5-nitrosopyrimidines to give 8-substituted guanines.

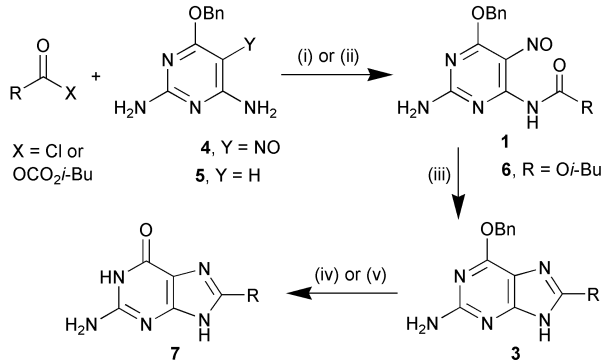


Scheme 1 [5a] *Reagents and conditions*: i. Raney Ni, H_2, EtOH; ii. Raney Ni, H_2, EtOH, AcOH; iii. AcOH, EtOH, reflux.

In the context of ongoing research we prepared C(8)-substituted guanine derivatives using the methodology described by Pfleiderer[5a] (Scheme 1). This entailed the preparation of **4** in two steps[10] from commercially available 6-chloro-2,4-diaminopyrimidine followed by regioselective acylation with either an acid anhydride or acyl chloride to give **1** (57–67%) and then reduction to the triamine **2** (51–68%) or direct reduction to purine **3** using a catalytic amount of Raney nickel and hydrogen in the presence of acetic acid.[5a] In our hands, imidazole ring-closure to give the protected guanine **3** could be effected by heat or treatment with $SOCl_2$ but in only 65% or 48% yield, respectively.[11]

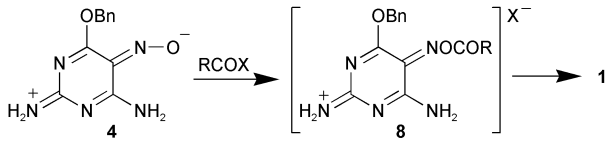
In an effort to improve the efficiency of this synthesis, we reasoned that treatment of the *o*-nitrosoamide **1** with a phosphorus(III) reagent might accomplish the direct transformation of **1** into the desired guanine derivative **3**. Upon testing this hypothesis on a number of substrates we found that the conversion of **1** into **3** using two molar equivalents of triphenylphosphine does indeed occur in high yield (Table 1).

Two procedures for the N^4-acylation of **4** were investigated. The first involved treatment with a mixed anhydride, prepared *in situ* from the corresponding carboxylic acid, *iso*-butyl-chloroformate and *N*-methylmorpholine. This procedure did not prove satisfactory. Yields were variable and poor for sterically hindered acids and, in addition, we observed a significant amount of carbamate co-product **6** in some cases. However, reaction of **4** with an acyl chloride in THF in the presence of K_2CO_3 or triethylamine gave consistently higher yields of amide **1** than the mixed anhydride method.



Scheme 2 *Reagents and conditions*: i. X=OCO*i*-Bu, CH_2Cl_2 solution of mixed anhydride at 0° treated with pyridine solution of **4**; ii: X = Cl, THF solution of **4** at rt treated with 1.1 eq. acyl chloride and K_2CO_3 or Et_3N; iii: 2.2 eq. Ph_3P, *o*-xylene, reflux; iv: 10 mol% $Pd(OAc)_2$, 6 bar H_2, MeOH, rt; v: 10% Pd/C, HCO_2H, MeOH, reflux.

When acylation of the corresponding non-nitrosated pyrimidine **5** was attempted, the above methods gave little (using acyl chloride) or no (mixed anhydride) products. Clearly, the neighbouring nitrosyl group of **4** participates in the amide-forming reaction. It is plausible that the nitroso group first undergoes *O*-acylation and that migration of the acyl moiety to the adjacent amino group follows (Scheme 3). Indeed, there is precedent for this type of reaction in uracil systems: in the case of 4-amino-2,6-dioxo-5-nitrosopyrimidines it has been shown that both the nitroso and amine functions are efficiently acylated by a variety of acyl chlorides and that both of these acyl groups can be transferred to nucleophiles.[12]



Scheme 3 Acylation of the 4-amino group may proceed *via* the 5-acyloxyimino intermediate **8**.

Phosphorus(III)-mediated reductive cyclisation of amides **1** proceeded most conveniently in xylene at reflux.‡ Reactions also worked well in toluene but gave slightly lower yields. In many cases, the product precipitated from solution upon cooling and could be isolated in analytically pure form by filtration.§ Otherwise, products were separated from the phosphine oxide, the only other product observed, by column chromatography of the reaction mixture. In cases where removal of triphenyl- or tributylphosphine oxide proved problematic, 1 molar equivalent of 1,2-bis(triphenylphosphino)ethane (DPPE) was the reagent of choice due to the quantitative precipitation of its bis-oxide from the reaction medium. The yields of purine derivatives **3** are generally good to excellent and compare well with those already reported for alternative methods for this transformation.

† Electronic supplementary information (ESI) available: characterisation of new compounds. See http://www.rsc.org/suppdata/cc/b3/b302529b/

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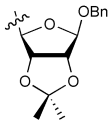
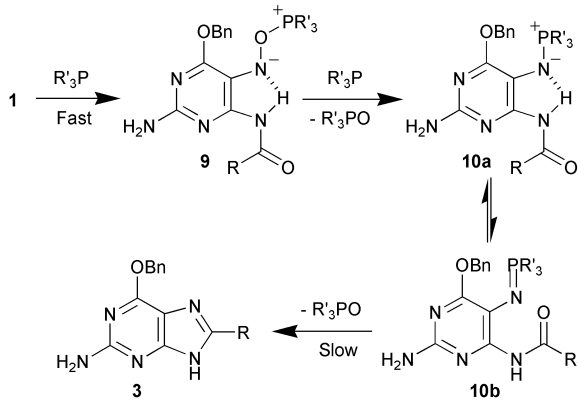
Table 1 Preparation of 8-substituted guanines from **4** according to Scheme 2.

Entry	R	X	Yield of **1**	Cyclisation conditions[a]	Yield of **3**	Debenzylation conditions[b]	Yield of **7**
a	Me	OCO*i*–Bu	71	A	82	D	95[c]
		Cl	73				
b	*i*-Pr	OCO*i*–Bu	34	A	95	D	95 [c]
		Cl	68				
c	*t*–Bu	OCO*i*–Bu	35	A	58	D	95 [c]
		Cl	73				
d	Ph	OCO*i*–Bu	59	A	90	D	95 [c]
		Cl	49				
e	Ph_2CH	OCO*i*–Bu	41	A	40	D	70 [c]
		Cl	57				
f	$C_{17}H_{35}$	OCO*i*–Bu	71	A	86	E	96
		Cl	75				
g	2-Furyl	OCO*i*–Bu	68	A	94	E	94
		Cl	79				
h	2-Styryl	OCO*i*–Bu	71	A	86	E	91[d]
		Cl	87				
i	3-Pyridyl	OCO*i*–Bu	20	B	92	E	85
		Cl	90				
j		OCO*i*–Bu	60	B	75	E	83
		Cl	61	C	80		

[a] **A**: 2.2 eq. PPh_3, *o*-xylene, reflux, 24 h; **B**: 2.2 eq. Bu_3P, *o*-xylene, reflux, 24 h. **C**: DPPE, toluene, reflux. [b] **D**: $Pd(OAc)_2$, HCO_2H, 12 h; **E**: H_2, Pd/C, MeOH, 12 h. [c] Isolated as the formate salt. [d] Double bond was also reduced to give 8-phenethylguanine.

Aliphatic, aromatic and heteroaromatic substituents are all tolerated and the availability of the 8-*tert*-butyl and benzhydryl derivatives, albeit in lower yields, is notable. Reductive cleavage of the O^6-benzyl group[13] yielded the desired 8-substituted guanines **7** in high yield.



Scheme 4 Possible mechanism of phosphorus(III)-mediated reductive cyclisation.

Although mechanistic studies of the cyclisation step have not been carried out, a plausible pathway is shown in Scheme 4. Nucleophilic addition of a trialkylphosphine to the nitroso group of **1** is expected to lead to a zwitterion **9** which is then converted into the iminophosphorane **10** by a second equivalent of phosphine, either by substitution or elimination–addition. This should be followed by an "aza-Wittig" process leading to the guanine **3**. This transformation is analogous to the synthesis of indoles from *o*-acylaminobenzyltriphenylphosphonium salts reported by Le Corré *et al*.[14]

In conclusion, this method can be used to prepare a variety of novel 8-substituted guanines from the readily available nitrosopyrimidine **4** in good to excellent overall yields. The key phosphorus-mediated cyclisation step is a simple and efficient alternative to existing methodology which typically yields less than 50% of the desired product. We are currently applying this method to other substrates.

Notes and references

‡ On addition of two molar equivalents of triphenylphosphine to a solution of the amide **1** in *o*-xylene at 23 °C, a colour change from blue to green then yellow was observed over 10–20 min. At this point TLC showed that the substrate had been completely consumed and converted into a more polar compound and that all the phosphine had also disappeared. Upon heating at reflux for up to 24 h, this intermediate was slowly converted into the purine **3**.

§ All new compounds were characterised by their ^1H and ^{13}C NMR, IR and mass spectra and elemental analysis.†

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