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Benzimidazopurine nucleosides from *N*⁶-aryl adenosine derivatives by PhI(OAc)₂-mediated C–N bond formation, *no metal needed*

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Abstract

The reaction of a variety *N*⁶-aryl 2'-deoxyadenosine and adenosine derivatives with PhI(OAc)₂ in 1,1,1,3,3,3-hexafluoro-2-propanol provides facile access to benzimidazopurine nucleoside analogues by *metal-free* C–N bond formation with a purinyl nitrogen atom. These reactions likely proceed via radical-cation/radical processes as indicated by radical inhibition experiments.

Modified nucleosides are central in disease treatment, particularly as antiviral and anticancer agents.^{1–3} Thus, approaches to the facile modification of these exceptionally important biomolecules is of paramount importance, particularly in the context of emerging viral diseases as well as resistance to existing drugs.³ Modified nucleosides are also important biological probes, such as for fluorescence monitoring.⁴

Hypervalent iodine reagents have gained importance as reagents because they are easy to synthesize and handle, and cross-dehydrogenative coupling products can be obtained in the absence of any metal catalyst. Hence, they find novel applications in the synthesis of heterocyclic compounds.^{5–7} Of relevance to the present work are the approaches to synthesis of benzimidazoles and azabenzimidazoles using hypervalent iodine reagents. Examples include cyclizations of appropriate precursors with PhI/CH₃CO₃H,⁸ PhI(OAc)₂ or PhI(OTFA)₂,^{9–11} PhI(OAc)₂/*m*-CPBA/*p*-TsOH or Koser's reagent,¹² and rearrangements of *N*-benzyl-2-aminopyridines.¹³

Hypervalent iodine reagents have not seen significant use for modifying nucleosides, and this represents a new area for investigation. To our information, there is only a single report in the literature wherein 2',3',5'-tri-*O*-acetyl-protected *N*⁶-aryl adenosine derivatives were converted to benzimidazopurine nucleoside analogues via the reaction with PhI(OAc)₂/Cu(OTf)₂ in AcOH-Ac₂O, at 80 °C.¹⁴ Not only was a metal catalyst necessary for the conversion but also the applicability of this chemistry to the substantially more sensitive

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purine 2'-deoxyribonucleosides is presently unknown. Pertinent to the stability discussion of nucleosides, at 37 °C, the $t_{1/2}$ for the deglycosylation of 2'-deoxyadenosine was found to be 15 min in 0.1 M HCl.¹⁵ By contrast, the $t_{1/2}$ for deglycosylation of adenosine was 11 days under the same conditions.¹⁵

In order to evaluate the applicability of the previously reported conditions to the 2'-deoxyribosyl series, we conducted a preliminary experiment wherein *N*⁶-phenyl-3',5'-di-*O*-(*t*-butyldimethylsilyl)-2'-deoxyadenosine, **1** in Scheme 1, was exposed to PhI(OAc)₂/Cu(OTf)₂ in AcOH-Ac₂O, at 80 °C. Only *ca.* 11% of the product was isolated. By contrast, 88% yield of the corresponding product has been reported from *N*⁶-phenyladenosine 2',3',5'-tri-*O*-acetate.¹⁴ This clearly showed that a method is needed that goes beyond the relatively stable purine ribonucleoside substrates with stability-enhancing protecting groups.

This led us to consider other options for producing a C–N bond-forming reaction between the purinyl N1 atom and the aryl ring. A variety of solvents have been utilized in prior heterocyclic syntheses involving I(III) reagents, which include CH₂Cl₂, ClCH₂CH₂Cl (DCE), MeCN, and fluorinated solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and 2,2,2-trifluoroethanol (TFE). The last two solvents are notable not only for their pK_a values (HFIP = 9.3, TFE = 12.9)¹⁶ but also for their ability to sustain radical cations¹⁷ that can be formed in reactions with hypervalent iodine reagents. Thus, we conducted a screening of conditions for the conversion of **1** → **2** (see Scheme 1), and the data are shown in Table 1.

From Table 1, certain factors become evident. AcOH/Ac₂O is clearly detrimental and MeCN proved to be better, more so in the absence of Cu(OTf)₂. Reactions in PhMe, DCE, DMF, and 1,4-dioxane remained incomplete (*inc.*). Finally, in MeNO₂ a cleaner reaction was observed but good to excellent outcomes occurred in TFE and HFIP. In fact, a high 92% yield was observed at *room temperature* in a relatively fast reaction. Reducing the amount of PhI(OAc)₂ from 1.3 to 1.0 equiv. lowered the product yield. Having identified optimal conditions, a series of *N*⁶-aryl 2'-deoxyadenosine and adenosine derivatives were evaluated (please see the Supporting Information for approaches to precursors). Results of the cyclization reactions are shown in Figure 1.

From these reactions, several facts emerge. The conditions are readily applicable to the 2'-deoxyribose precursors. A lower yield was observed in the naphthyl case **7**. This reaction was conducted in MeCN because in HFIP, the substrate was decomposed. The product yield here was similar to that reported from 2',3',5'-tri-*O*-acetyl *N*⁶-(1-naphthyl)adenosine (40%).¹⁴ Thus, the 1-naphthyl moiety appears to be responsible for the two outcomes. However, in our case we also obtained a second, fairly unstable product. By carefully evaluating its spectroscopic data, we propose the iminoquinone structure **7'** (12% yield, overall yield of products was 50%), and not the peri-annulated perimidine that would result from the reaction of the purinyl N1 atom at the C8 position of the naphthalene. The rationale for the structural assignment to **7'** arises from (a) the J values of the two coupled doublets at δ = 7.05 and 6.70 ppm ($\approx$ 10.5 Hz) and (b) the appearance of a ¹³C resonance at δ = 185.1 ppm. These data appear typical of *N*-aryl-1,4-naphthoquinone monoimines.¹⁸ A potential mechanism for the formation of **7'** is described under the mechanistic analysis that follows.

As seen from products **5** and **8** as well as **13** and **14**, there was practically no difference in the reactivities of 2'-deoxyribosyl and ribosyl precursors. Protecting groups elicit no influence as seen from the yields of products **5** and **13** as well as **8** and **14**.

Notably, the yield of **14** is higher via this procedure in comparison to the literature¹⁴ (86% *versus* 62%). Similarly, the high 87% yield of product **12** can be contrasted to the 51% obtained from the corresponding 2',3',5'-tri-*O*-acetyl *N*⁶-(*o*-methylphenyl)adenosine.¹⁴ In addition to these observations, the reactions are generally insensitive to substituent effects because methoxy, halogen, acetyl, and nitrile are all well tolerated. We also evaluated reactions with the di-*O*-silyl *N*⁶-(*p*-nitrophenyl) and *N*⁶-(*o*-nitrophenyl) 2'-deoxyadenosine derivatives, anticipating a lack of reactivity due to the extreme electron deficiency. Consistent with this, no product formation was observed. It should be noted that the complete absence of reactivity in the presence of nitro groups has been recorded once in reactions mediated by an I(III) reagent,¹⁰ other benzimidazole syntheses generally do not report reactivity or lack thereof with this substituent. As seen in Fig. 2, the products exhibit interesting properties under UV light that appear to be modulated by the aryl ring substituents. Further studies along these lines are anticipated in future work.

Reactions mediated by $\text{PhI}(\text{OAc})_2$ and $\text{PhI}(\text{OTFA})_2$ can proceed via multiple pathways, namely, radical cations,¹⁹ nitrogen-centered radicals,²⁰ and nitrenium ions.²¹ Therefore, in order to gain mechanistic insight, we chose to perform radical inhibition experiments using 2,6-di-*t*-butyl-4-methylphenol (BHT) and 1,1-diphenylethene (DPE), both of which have seen prior use in the evaluation of potential radical pathways in I(III)-mediated reactions.^{10,22} Thus, two 2'-deoxyribosides and one riboside with varying electronics in the *N*⁶-aryl ring of the adenine moiety were selected. Reactions were conducted with 1.3 equiv. of $\text{PhI}(\text{OAc})_2$ in HFIP at room temperature, in the presence of 1 equiv. of BHT or DPE. The results are summarized in Table 2.

From these experiments it appears that radical species could be the reactive intermediates. As shown in Scheme 2, should the formation of radical cations (**I**) become feasible, as with an electron-rich aryl ring, the capture by the N1 atom could lead to species **II**. Alternatively, the reaction of $\text{PhI}(\text{OAc})_2$ at the exocyclic nitrogen atom can lead to **III** that can fragment via a radical pathway to **IV**. A reaction via the N1 atom (resonance form **IV'**) can also lead to **II**, ultimately resulting in product via the loss of a hydrogen radical. It should be noted that **PhI** was isolated from the two 0.9 mmol reactions reported in Figure 1.

The formation of byproduct **7'** can be rationalized on the basis of Scheme 2. Aryl amides and anilines are known to undergo oxidation with I(III) reagents,^{23,24} and the former undergo hydroxylation at the *para* position via an oxidative dearomatization.²³ In a similar manner, the *N*⁶-(1-naphthyl)-2'-deoxyadenosine precursor can undergo acetoxylation via a nitrenium ion formed from **III** (a radical process via **IV** is also plausible). Hydrolysis of the resulting acetate can occur in isolation procedures, as we have previously observed.²⁵ The resulting 4-hydroxy-1-naphthylamine derivative can then undergo rapid oxidation to iminoquinone **7'**, a structure which would also account for its instability. Support for this pathway can also be obtained in the aromatic acetoxylation observed in $\text{PhI}(\text{OAc})_2$ -mediated cyclizations of *N*-(biphenyl)pyridin-2-amines.¹⁰

In conclusion, we have demonstrated facile conversion of N^6 -aryl adenine nucleosides to benzimidazopurine nucleoside derivatives by simply utilizing $\text{PhI}(\text{OAc})_2$ in HFIP, at room temperature, with MeCN as a solvent of second choice. *No metal catalyst is necessary for this reaction.* Generally good reactions were observed and they are independent of the protecting groups used, show good functional group compatibility, and are not influenced by a substituent proximal to the reaction site. This chemistry, which is applicable to both 2'-deoxyribosides as well as ribosides, should be a significant contributor to nucleoside modification strategies, providing a rapid access to a variety of novel compounds with potentially diverse applications, from medicinal products to detection tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Reaction times and product yields from the cyclization reactions (the new bond formed is shown with a solid line). ^a Yield from a 0.9 mmol reaction.

Figure 2.
Fluorescence of the eleven compounds (1 mg mL^{-1} in CH_2Cl_2) under a 365 nm UV lamp.

Scheme 1.

Initial test of a C–N bond formation in comparison to a known result (the new bond formed is shown with a solid line).

Scheme 2.

Plausible mechanistic courses for the transformation *via* radical intermediates.

Table 1Optimization of conditions for the reaction of substrate **1** with $\text{PhI}(\text{OAc})_2$ ^a

Entry	Additive	Solvent, T °C	Time	Result
1 ^b	$\text{Cu}(\text{OTf})_2$ 5 mol %	AcOH, Ac_2O , 80 °C	2 h	11% ^c
2 ^d	$\text{Cu}(\text{OTf})_2$ 5 mol %	MeCN, 80 °C	2 h	39%
3	—	MeCN, 55 °C	4 h	61% ^e
4	—	PhMe, 55 °C	16 h	20% (inc) ^f
5	—	$\text{ClCH}_2\text{CH}_2\text{Cl}$, 55 °C	16 h	7% (inc)
6	—	DMF, 55 °C	16 h	13% (inc)
7	—	1,4-Dioxane, 55 °C	22 h	7% (inc)
8	—	MeNO_2 , 55 °C	4 h	46%
9	—	TFE, 55 °C	4 h	75%
10	—	HFIP, 55 °C	2.5 h	78%
11	—	HFIP, 25–30 °C	4 h	92%
12 ^g	—	HFIP, 25–30 °C	4 h	64%

^a Reactions were performed at 0.1 M concentration of **1** (0.05 mmol) with 1.3 equiv. of $\text{PhI}(\text{OAc})_2$, except where indicated, and yields are of chromatographically isolated product.

^b As published (ref 14), 1.5 equiv. of $\text{PhI}(\text{OAc})_2$ was used in 1 : 1 AcOH/ Ac_2O (0.34 mL).

^c Clean conversion was not observed.

^d Amount of $\text{PhI}(\text{OAc})_2$ used was 1.5 equiv.

^e Byproducts were formed and the reaction was not clean.

^f About 29% of **1** was recovered after 16 h, inc = incomplete.

^g Amount of $\text{PhI}(\text{OAc})_2$ used was 1.0 equiv.

Table 2Inhibition experiments with three substrates^a

Entry	R = X =	Inhibitor time	Result ^b
1	H	BHT	Trace of product, 81% SM recovered
	H	4 h	
2	H	DPE	Trace of product, 57% SM recovered
	H	4 h	
3	CN	BHT	88% SM recovered
	OTBDMS	4 h	
4	CN	DPE	89% SM recovered
	OTBDMS	4 h	
5	OMe	BHT	Trace of product, 76% SM recovered
	H	1 h	
6	OMe	DPE	Trace of product, 90% SM recovered
	H	1 h	

^aReactions were performed with 0.05 mmol of each substrate, 1.3 equiv. of PhI(OAc)₂, and 1.0 equiv. of the inhibitor.^bProduct, when detected, was identified by thin-layer chromatography, and starting material (SM) was recovered by chromatography.