Nucleoside Synthesis

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An Efficient Approach to the Synthesis of Nucleosides: Gold(I)-Catalyzed N-Glycosylation of Pyrimidines and Purines with Glycosyl *ortho*-Alkynyl Benzoates**

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The synthesis of nucleosides has continuously been a topical subject in efforts to develop new therapeutic agents (e.g., antitumor and antiviral drugs),[1] to manipulate genetic processes (e.g., antisense oligonucleotides and RNA interference),[2] and to expand the genetic code and understand the scope and limits of Watson–Crick base pairing.[3] However, the key technique for such syntheses, namely, the N-glycosidic coupling of sugars and nitrogen heterocycles, is rather conventional. A Vorbrüggen-type reaction[4] involving the coupling of sugar acetates with trimethylsilylated nucleobases under the action of strong Lewis acids (mostly stoichiometric amounts of trimethylsilyl triflate and $SnCl_4$) is still the predominant method.[5] The coupling yields are not always high. In particular, when purines are used, low coupling yields (or even failure of the reaction to occur) and moderate N9/N7 regioselectivity have been encountered.[6,7] Protecting groups and temporary substituents have thus been introduced onto purines to enhance their reactivity and hinder the reaction of nonglycosylated nitrogen atoms.[8] However, the choice of protecting groups is limited by the harsh conditions required for Vorbrüggen-type reactions. Variation of the anomeric leaving group of the glycosyl donors could enable N-glycosylation under milder conditions. However, only limited success has been reported for nucleoside synthesis with privileged O-glycosylation donors, including glycosyl chlorides/bromides,[5,9] trichloroacetimidates,[10] phosphites,[11] sulfoxides,[12] thioglycosides,[13] *n*-pentenyl glycosides,[14] and sugar 1,2-anhydrides.[15] One rationale is that nucleobases are poorly nucleophilic (and often poorly soluble) and thus compete unfavorably for glycosidation with other nucleophilic species that occur in a glycosylation system, such as those derived from the leaving groups and promoters.

These considerations led us to try glycosyl *N*-phenyltrifluoroacetimidate (PTFAI) donors[16] for nucleoside synthesis, since these donors have been shown to be advantageous for the N-glycosylation of amides owing to the poor competitiveness of the *N*-phenyltrifluoroacetamide leaving entity.[17] PTFAI donors could be coupled smoothly with silylated pyrimidines;[18] however, they underwent decomposition when much more poorly nucleophilic purine derivatives were used as acceptors. In such circumstances, the stability of the donors is not only beneficial to handling but is also demanding for an effective glycosidic coupling to proceed (prior to decomposition). It is probably for this reason that sugar acetates are still the prevailing donors for nucleoside synthesis (i.e., the Vorbrüggen-type reaction). Our recently introduced glycosyl *ortho*-alkynyl benzoates are as stable as sugar acetates, yet can be activated for glycosidation under mild conditions by catalysis with a gold(I) complex (e.g., commercially available and shelf-stable $[Ph_3PAuNTf_2]$; Tf = trifluoromethanesulfonyl).[19] Furthermore, the leaving entity (an isocoumarin) and the promoter introduce no competitive nucleophilic species.[20] Thus, we aimed to tackle the problem of purine glycosylation with this new glycosylation protocol.

We first examined the N-glycosylation of pyrimidine nucleobases with glycosyl *ortho*-hexynylbenzoates **1** (Schemes 1 and 2). Thus, uridine (**2a**) was silylated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) in acetonitrile and then subjected to coupling with the perbenzoyl ribofuranosyl *ortho*-hexynylbenzoate **1a** in the presence of $[Ph_3PAuNTf_2]$ (0.1 equiv) at room temperature. The reaction was slow and required 3 days to reach completion. Nevertheless, it provided the desired nucleoside **3** cleanly (85%). The coordination of acetonitrile to the gold(I) catalyst accounts for the slow reaction rate.[19b] With nitromethane as the solvent, the equivalent reaction was complete within 24 hours. Other solvents often used for O-glycosylation, such as dichloromethane, 1,2-dichloroethane, and toluene, are poor solvents for the bases and therefore led to failure of the coupling reaction.

Without optimizing the present N-glycosylation conditions, we examined the coupling of the three pyrimidine nucleobases, that is, uridine (**2a**), thymine (**2b**), and *N*4-benzoylcytosine (**2c**), with peracyl furanosyl and pyranosyl *ortho*-hexynylbenzoates **1a**, **1b**, and **1d–g**. The coupling reactions with furanosyl donors **1a** and **1b** provided the desired nucleosides **3–8** in excellent yields (85–96%). With the peracetyl galactopyranosyl and rhamnopyranosyl donors

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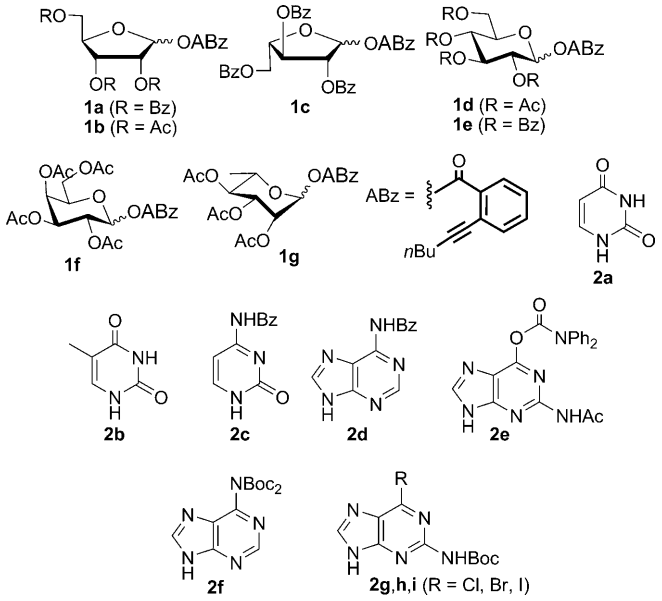
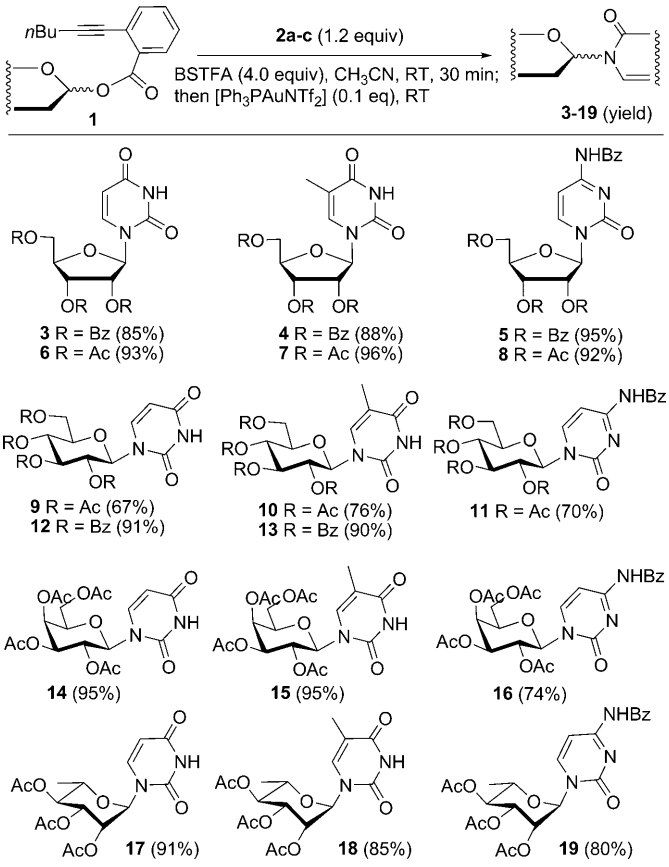


Scheme 1. Coupling partners for N-glycosylation. Bz = benzoyl.

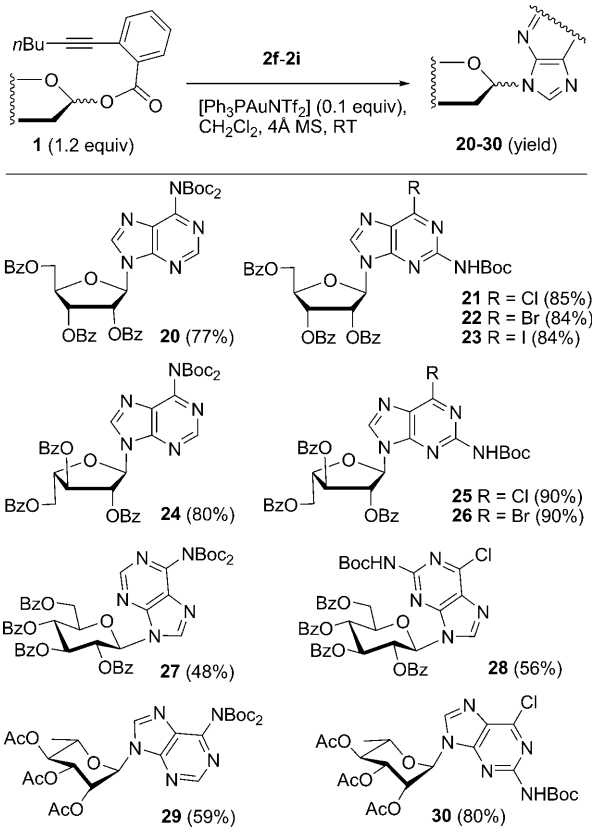


Scheme 2. N-glycosylation of pyrimidines **2a–c** with glycosyl *ortho*-hexynylbenzoates.

1f and **1g**, the coupling yields were still satisfactory; the reactions led to the nucleoside products **14–19** in 74–95% yield. Only when the peracetyl glucopyranosyl *ortho*-hexynylbenzoate **1d** was used as the donor did the coupling yields become lower, with nucleosides **9–11**[21] formed in 67–76% yield. Nevertheless, upon replacement of the peracetyl donor **1d** with its perbenzoyl counterpart **1e**, the coupling yields increased significantly, with nucleosides **12** and **13** formed in about 90% yield. Moreover, we later found that the addition of HOTf (0.1 equiv) to the reaction mixture could greatly increase the reaction rate. Thus, the coupling of **1a** with pyrimidine nucleobases **2a–c** was complete within 3–6 hours to provide nucleosides **3–5** in 92–98% yield (HOTf itself could not promote these glycosylation reactions). The coupling of uridine (**2a**) with the ribofuranosyl *ortho*-hexynylbenzoate **1a** was readily scaled up to a gram scale, which enabled us to quickly assemble the nucleoside lipid derivative JBIR-68. This compound was recently identified from *Actinobacteria* as a potent anti-influenza agent.[22,23]

We then explored the real challenge of purine N-glycosylation. However, under similar conditions to those used for the above pyrimidine N-glycosylation, the coupling of ribofuranosyl *ortho*-hexynylbenzoate **1a** or **1b** with routinely protected purine nucleobases, that is, *N*6-benzoyladenine (**2d**) and *N*2-acetyl-6-*O*-(diphenylcarbamoyl)guanine (**2e**; Scheme 1),[8e,f,24] led to either low yields of the coupling products (about 28% yield for the coupling with **2d**) or marginal N9/N7 regioselectivity (1.3:1 for the coupling with **2e** in a total yield of about 70%). Fortunately, the mild glycosylation conditions with *ortho*-alkynyl benzoates as donors would be compatible with a large variety of protecting groups on purines, including protecting groups that would not survive under conventional N-glycosylation conditions. Our immediate choice was to use the *tert*-butoxycarbonyl (Boc) group, one of the most frequently used N-protecting groups, to protect the exocyclic amino group of purines. In fact, *N*6-bis(*tert*-butoxycarbonyl)adenine (**2f**) and *N*2-*tert*-butoxycarbonyl-2-amino-6-chloropurine (**2g**) have already been conveniently prepared and effectively used in Mitsunobu-type N-alkylation reactions (with high N9/N7 regioselectivity).[25,26] The good solubility of purine derivatives **2f** and **2g** enabled their glycosylation to be carried out in dichloromethane and without the need for prior silylation. The coupling of **2f** with **1a** in the presence of $[Ph_3PAuNTf_2]$ (0.1 equiv) in dichloromethane proceeded smoothly at room temperature to give the N9 nucleoside **20** in good yield (77%) within 12 hours (Scheme 3). Only a trace amount of the mono-Boc-protected product was isolated as a side product,[23] and the corresponding N7 nucleoside was not detected at all.

Glycosylation of the *N*2-Boc-2-amino-6-halopurines **2g–i** with **1a** led to the corresponding N9 nucleosides **21–23** in better yields (ca. 85%). The perbenzoyl arabinofuranosyl donor **1c**[21] performed better than the ribofuranosyl counterpart **1a** in coupling with purines **2f–h**: the N9 nucleoside products **24–26** were obtained in 80–90% yield. The perbenzoyl glucopyranosyl and peracetyl rhamnopyranosyl *ortho*-hexynylbenzoates **1e** and **1g** also underwent coupling with Boc-protected purines **2f** and **2g**, although the desired coupling products **27–30** were formed in lower yields (48–80%) than those observed with furanose donors. Nevertheless, the reactions were still clean; remaining starting materials mainly accounted for the lower yields, and no N7-nucleoside products were detected. The *N*-Boc groups on the resulting nucleosides **20–30** were removed selectively in



Scheme 3. N-glycosylation of Boc-protected purines **2f–i** with glycosyl *ortho*-hexynylbenzoates. MS = molecular sieves.

greater than 90% yield under the effect of $BuOH/H_2O$[27] or $CF_3COOH/ClCH_2CH_2Cl$;[28] the acyl groups on the sugar units were not affected.[23] The 6-halopurine nucleosides synthesized are useful precursors to the corresponding guanine nucleosides or their 6-substituted derivatives.[26,29]

In conclusion, readily accessible and shelf-stable glycosyl *ortho*-hexynylbenzoates have been shown to be superior donors for the N-glycosylation of nucleobases under the catalysis of $[Ph_3PAuNTf_2]$. The success of this highly efficient and regioselective N9-glycosylation of purines can be attributed to the mild glycosylation conditions that enable Boc-protected purine derivatives to be used as coupling partners for the first time. Further improvement of the coupling efficiency through careful tuning of the reaction parameters for individual coupling partners and the application of this efficient method to nucleoside synthesis are anticipated.

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