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β-Selective nucleoside analog synthesis from chlorofuranoses

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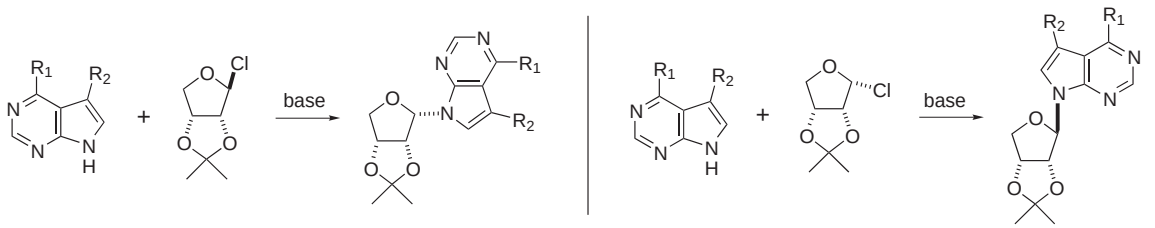
Abstract

A method to form glycosyl linkages between nitrogen-containing heterocycles and appropriately protected furanoses is described. The method is highly beta-selective, operationally simple, and utilizes readily available reagents making the process amenable to scaleup. Representative examples of coupling between chlorofuranoses and purines or pyrrolopyrimidines are described. © 2000 Published by Elsevier Science Ltd.

In the course of our research, we required a reliable method to form a glycosyl linkage between novel pyrrolopyrimidines and appropriately protected erythrose and deoxyribose sugars. A common method for glycosyl bond formation involves the use of Lewis acid promoted coupling, typically with the aid of an acyl-protected hydroxyl at C2 which provides neighboring-group participation to achieve beta selectivity. Unfortunately, pyrrolopyrimidines often fail to react in the desired fashion in such Lewis acid type reactions.[1] Previously published work on related systems has centered on the displacement of anomeric halides by the anion of the heterocycle. Typically, the anion is formed from NaH[2] or under phase-transfer conditions (KOH, TDA-1).[3] This method consists of direct displacement of an anomeric halide, with the hydroxyls at the 2 and 3 positions of the furanose typically protected as an acetonide. A key element of this method (Scheme 1) is that the anomeric configuration is inverted in the coupling; to obtain the desired beta configuration one must utilize the alpha-chlorofuranose.



Scheme 1.

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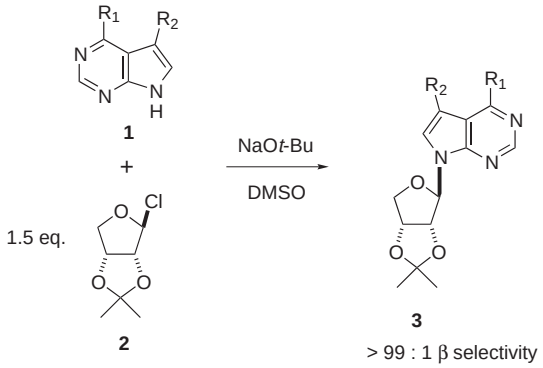
This anionic method was used successfully for the synthesis of the initial quantities of our desired product using 2,3-*O*-isopropylidene-α-D-erythrofuranosyl chloride. One concern was that the formation of the α-chloride required special conditions.[4] Of greater concern for our purposes was that the α-chloride was thermally unstable, readily isomerizing to the thermodynamically more stable β configuration over a short time frame (generally over a couple of hours at rt). The lack of robustness in this coupling prevented use of this method to generate large quantities of desired pharmaceutical compounds, and therefore we searched for an alternate method.

Previous work had examined the use of the configurationally stable β-chloride with limited success. Goto et. al. utilized the anionic method (NaH) with a pyrrolopyrimidine and the β-chloride derived from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose. By using halide additives,[5] a double displacement mechanism was accessed which increased the β:α ratio from 1:3 (without additive) to 2:1 by the addition of NaBr in DMF in the most selective example.[6] Although this method proves an important concept, we hoped to obtain a higher diastereoselectivity in our process.

Our research was aimed at solvating the chloride as a means of activation, in hopes of developing reaction conditions that would allow a reliable and selective condensation starting with β-chlorofuranoses.[7] In the course of these studies, we discovered a rather remarkable set of reaction conditions which significantly extends the anionic glycosylation methodology. The stable, crystalline β-chloride of 2,3-*O*-isopropylidene erythrose[8] (**2**) was coupled with a pyrrolopyrimidine of general structure **1** using DMSO as the solvent and NaOtBu[9] as the base (Scheme 2). Under these conditions the desired β-glycosylation product can be formed with exceptional β:α selectivity.



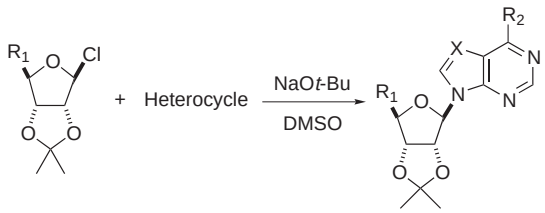
Scheme 2.

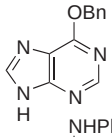
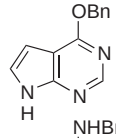
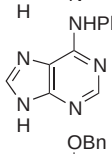
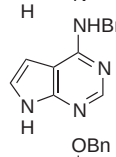
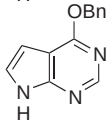
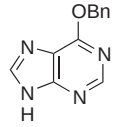
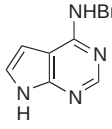
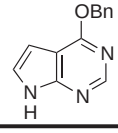
DMSO appears to be a key component that serves to efficiently solvate the anomeric chloride. We believe the reaction proceeds through an intermediate sulfoxonium species, which can rapidly isomerize through its α and β forms via solvent displacement.[10] Such a species would be an intermediate in a Kornblum-type oxidation, however lactone is not seen as a by-product as the use of *t*-butoxide as base shuts down this potential oxidation pathway.[11] An important aspect of the reaction is that the starting ratio of α and β chlorides does not affect the β-selectivity of the product.[12] The stereoselectivity of the product is thus controlled solely by the

stereochemistry of the 2,3-*O*-isopropylidene group. In the furanoses used in this study, the β-chlorofuranoses are the thermodynamically more favored, and thus much simpler to prepare. However, in systems which might form mixtures at the anomeric center, the crude sugars can be used without separation of isomers.

To exemplify the power of this methodology, we have carried out this reaction using different purines and pyrrolopyrimidines as shown in Table 1.[13] Note that the selectivities are highest with the erythrose substrates (entries **1**–**4**). The deoxyribose (entries **5**–**6**) and protected ribose substrates (entries **7**–**8**) also offer high levels of selectivity, suggesting the isopropylidene remains the overriding stereochemical determinant in these transformations.

Table 1



Entry	R_1	Heterocycle	yield β pdt	β : α ratio	Entry	R_1	Heterocycle	yield β pdt	β : α ratio
1	H		60 %	> 99 : 1	5	CH_3		84 %	55 : 1
2	H		39 %	> 99 : 1[a]	6	CH_3		63 %	35 : 1
3	H		65 %	> 99 : 1[a]	7	OCH_3		45 %	32 : 1
4	H		58 %	> 99 : 1[a]	8	OCH_3		71 %	32 : 1

[a] The α-isomer was completely undetectable for these examples.

From a practical standpoint, the reagents and substrates are readily available and the process is operationally simple.[14] The chlorosugars are formed from the lactols under standard conditions,[8] and any ratio of α and β chlorofuranose anomers can be used. Both pyrrolopyrimidines and purines have been examined as the heterocyclic partner as the limiting reagent. Due to side reactions that take place on the chlorofuranoses, this reagent is used in excess (typically 1.5–2 equiv.). One further caveat is that under the base promoted reaction conditions, glycosylation at nitrogens other than the desired N7 of the heterocycle can take place, reducing the yield of the desired isomer. In such cases, we have found that optimization of the base counterion and cosolvent[15] can influence such ratios, but were not optimized for the examples in Table 1. Further details on this reaction and its use as a scalable process will be reported in due course.

References

1. It is common for these structures to form orthoamides which do not rearrange. Such results were seen in our research when attempting to use sugars with acyl protecting groups at the 2-hydroxyl of erythrose derivatives and the desired pyrrolopyrimidine. Also see Seela, F.; Lüpke, U.; Hasselmann, D. *Chem. Ber*. **1980**, *113*, 2808–2813 and Ramasamy, K.; Robins, R. K.; Revankar, G. R. *J. Heterocycl. Chem*. **1987**, *24*, 863.
2. See for example: Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc*. **1984**, *106*, 6379–6382 and Ramasamy, K.; Imamura, N.; Robins, R. K.; Revankar, G. R. *Tetrahedron Lett*. **1987**, *28*, 5107–5110.
3. Rosemeyer, H.; Seela, F. *Helv. Chim. Acta* **1988**, *71*, 1573–1585.
4. Typically the α-chloroisomers are synthesized at low temperature using the method of Wilcox (CCl_4, HMPT): Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett* **1986**, *27*, 1011–1014.
5. The addition of Et_4NBr as an additive in the formation of α-pyranosides from the α-pyranosyl bromide was demonstrated previously: Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*. **1975**, *97*, 4056–4062. The work of Goto et. al. demonstrates that this method is not easily transferred to furanoses.
6. Kondo, T.; Okamoto, K.; Yamamoto, M.; Goto, T. *Tetrahedron* **1986**, *42*, 199–205.
7. There are examples of related reactions that achieve anomeric chloride solvation by means of metal complexation. Our aim was to develop chemistry that avoided the use of toxic or expensive metal additives (e.g. Hg, Ag, or Sn salts).
8. This material was synthesized from commercially available 2,3-*O*-isopropylidene-D-erythronolactone by a two step procedure (1. DIBAL-H, CH_2Cl_2, 0°C; 2. $SOCl_2$, pyr., CH_2Cl_2, 0°C) based on literature references: Cohen, N.; Banner, B.; Lopresti, R.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, E.; Liebman, A. *J. Am. Chem. Soc*. **1983**, *105*, 3661–3672; Lerner, L. *Carbohydr. Res*. **1969**, *9*, 1–4. The term 'stable' is in reference to the anomeric isomerization; for long-term storage the chlorofuranose should be stored under refrigeration.
9. Other bases that provide complete anion formation are successful, however NaOtBu and KOtBu have provided the cleanest reactions and highest yields. Amine bases are ineffective under these reaction conditions.
10. Another possibility is that the DMSO serves to solvate the chloride to form an ion pair/oxonium ion which is the reactive species. Circumstantial evidence favors the sulfoxonium intermediate, but our studies have been inconclusive. Further mechanistic details will be reported when results are available.
11. In identical test experiments, 2,3-*O*-isopropylidene-D-erythrose in DMSO was treated with SO_3·pyridine/DMSO using NaOtBu or NEt_3 as the base. No oxidation was observed in the NaOtBu reaction (over 1 h), while rapid oxidation to the lactone (within minutes) was seen with NEt_3.
12. A mixture of α and β chlorides was synthesized independently and used under identical reaction conditions. The results confirm that the anomeric configuration of the chlorosugar is inconsequential to the reaction selectivity.
13. For each example, α-isomers were synthesized independently, and ratios of the isomers in the crude reaction samples were determined by analytical HPLC. Stereochemistry was determined by ^1H NMR coupling constants, and confirmed using NOESY experiments with both α and β isomers. Yields refer to purified isolated products.
14. Typical procedure (entry 3, Table 1): to a solution of 4-benzyloxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.4168 g, 1.85 mmol) in DMSO (2.5 mL) at rt was added NaOtBu (0.3731 g, 3.882 mmol) followed by a solution of 2,3-*O*-isopropylidene-β-D-erythrofuranosyl chloride (0.6597 g, 3.69 mmol) in THF (1.8 mL). The solution immediately turned dark red. After 30 min, the reaction solution was added to MTBE (30 mL) and water (30 mL). The phases were separated and the organic layer concentrated and purified by SiO_2 chromatography (15% EtOAc/hexanes) to provide 0.4426 g (65%) of the β-coupled product as a white crystalline solid. HPLC analysis on the crude reaction mixture failed to detect any α-isomer, as compared to an authentic sample independently synthesized.
15. Cosolvents typically employed are THF, MTBE, EtOAc, or CH_3CN. The DMSO used in the reaction is usually 50% or greater of the total volume to provide an efficient and rapid reaction; however, lower ratios of DMSO have been tested successfully. Often the sugar is added in a cosolvent for ease of processing. Additionally, cosolvents offer solubility advantages for some substrates. Cosolvents do not have a significant affect on the anomeric selectivity.

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