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C-GLYCOSYLATION OF SUBSTITUTED HETEROCYCLES UNDER FRIEDEL-CRAFTS CONDITIONS (I): A TWO-STEP SYNTHESIS OF THE THIENO[3,4-d]PYRIMIDINE C-NUCLEOSIDE ANALOG OF INOSINE.[1]

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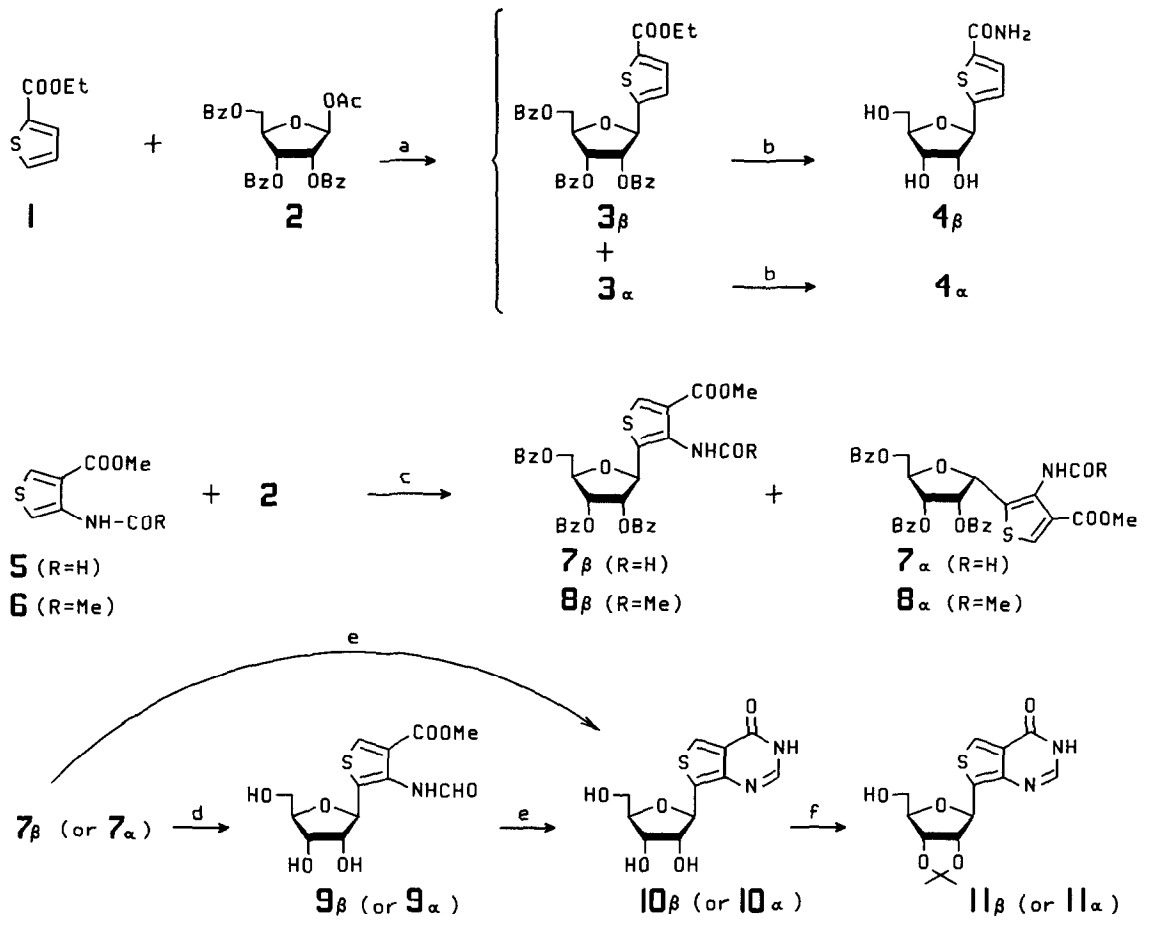
Abstract: Direct stannic chloride catalyzed C-glycosylation of N-formyl-4-amino-3-carboalkoxy thiophenes with 1-O-acetyl-tri-O-benzoyl-β-D-ribofuranose, followed by annelation of a fused pyrimidone ring upon treatment with ammonia, constitutes a short approach to the synthesis of a new C-nucleoside inosine analog.

Several "purine-like" C-nucleoside analogs of inosine and adenosine prepared in our laboratory have been found to possess important antiprotozoal as well as other biological activities.[2-7] These analogs incorporate structural modifications of the original purine system in which the fused imidazole ring has been replaced by a variety of π-excessive[8-11] and π-deficient[12] fused systems. All of these analogs were obtained by the stepwise elaboration of the desired heterocycle from simple acyclic C-glycosyl derivatives. While this general approach has been by far the most fruitful strategy developed to date for the synthesis of a wide range of C-nucleosides,[13-14] the development of new and shorter procedures still remains a high priority. Of particular interest to us, because of its shortness, was the direct Friedel-Crafts type of glycosylation of preformed heterocycles. C-Glycosylation of furan[15-16] and thiophene[16-17], and certain mono-alkyl derivatives[16b], with appropriately substituted glycosyl halides, esters or imidates to give the corresponding 2-furyl and 2-thienyl derivatives has already been reported. To our knowledge, however, the glycosylation of more highly functionalized heterocycles to give directly a close structural C-nucleoside analog or some intermediate suitable for direct conversion to such congeners has not yet been reported.

In a preliminary evaluation of this strategy, we found that ethyl-2-thiophenecarboxylate **1**[18] (Figure 1) in large excess (8.5 eq.) reacted with 1-O-acetyl-tri-O-benzoyl-β-D-ribofuranose **2** (1.0 eq.) in the presence of $SnCl_4$ (4.3 eq.) to give a mixture of 5-glycosylated 2-carboalkoxythiophene α,β isomers **3** (35% yield, β/α = 1.5).[19] These were separated by flash chromatography and further converted to amides **4α** and **4β**.[20] The anomeric configurations of the latter were assigned on the basis of the ^{1}H-NMR spectra of their isopropylidene derivatives.[21] Encouraged by these results, methyl-4-formamido-3-thiophene carboxylate **5** was next selected as an ideal system for our purpose, since both formamido and carboxyl functions combine in directing electrophilic substitution to C-5. It was also expected that the formyl group would protect the amino function as well as serve as carbon C-2 in the final skeleton of the thieno[3,4-d]pyrimidine system. Indeed, reaction of **5**[22] (2 eq.) with **2** (1 eq.) at reflux in 1,2-dichloroethane for 4 hr in the presence of $SnCl_4$ (2 eq.) afforded **7α** and **7β** in 43% overall yield (β/α ≈ 2.4), after standard workup and chromatographic separation of the products on silica gel. Unreacted base **5** was recovered almost quantitatively. Significant amounts of benzoic acid were also collected, formed via partial decomposition of benzoylated

FIGURE 1



a) $SnCl_4$, 60-70°C, 3.5 hrs. b) Liq. NH_3 + EtOH (1:1), 65°C. c) $SnCl_4$ (2 equiv)/CH_2ClCH_2Cl, reflux, 4hrs.
d) Satd. NH_3/MeOH, 100°C, 2hrs. e) Same as d), but 6hrs. f) Acetone, DMP, p-TSA, 0.5 hrs (for 10β). acetone, p-TSA, O.N. (for 10α).

sugars. Under similar conditions, utilization of acetamido derivative **6** (4.0 eq.) instead of **5** afforded somewhat better yields of glycosylated products **8α** and **8β** (60% overall yields after 3 hrs). Unfortunately, attempted deacetylation of the amino function (a necessary step prior to annelation of the pyrimidine ring) was found to be unsuccessful. Under all conditions tried (sat. NH_3/MeOH, 3 days, 110°C or NaOMe/MeOH, reflux, 2 days), only debenzoylation of the ribosyl moiety was observed.

Prolonged treatment of ribosylated thiophenes **7β** or **7α** with sat. NH_3/MeOH at 100°C for 6 hrs afforded directly the desired inosine analogues **10β** or the corresponding α-isomer **10α**, respectively, each in ~30% yield. Shorter treatment of **7β** (or **7α**) with NH_3 (1-2 hrs) at 100°C afforded only the corresponding debenzoylated derivatives **9β** (or **9α**) in ~50% yield.

An analytical sample of **10β** was obtained after recrystallization from MeOH: mp 197-198°C; ^{1}H-NMR (300 MHz; D_2O) δ 3.80 (dd, 1H, H-5'A, $J_{5'a,5'b}$ = 12.5 Hz), 3.88 (dd, 1H, H-5'a), 4.18 (m, 1H, H-4', $J_{4',5'a}$ = 4.6 Hz, $J_{4',5'b}$ = 3.4 Hz), 4.28 (dd, 1H, H-3', $J_{3',4'}$ = 3.7 Hz), 4.36 (dd, 1H, H-2', $J_{2',3'}$ = 5.3 Hz), 5.47 (d, 1H, H-1', $J_{1',2'}$ = 7 Hz), 7.85 (s, 1H, H-2), 8.36 (s, 1H, H-7). A pure sample of **10α** was obtained as a foam after preparative TLC using CH_2Cl_2:MeOH (8:2) as developing agent. ^{1}H-NMR (90 MHz; D_2O) δ 5.74 (d, 1H, H-1', $J_{1',2'}$ = 2.7 Hz), 7.77 (s, 1H, H-2), 8.34 (s, 1H, H-7).

The anomeric configurations assigned to **10α** and **10β** and their respective isopropylidene derivatives **11α** and **11β** on the basis of ^{1}H-NMR measurements[21,23a] were further supported by studies of their ^{13}C-NMR spectra.[23b] Thus, the finding that C-1' in **11α** (δ 77.69) resonates upfield of C-1' in **11β** (δ 81.48) is in accord with previous observations of anomeric chemical shifts in ribofuranosyl N-nucleosides[21f] as well as C-ribofuranosyl compounds.[21b,g,h] In addition, the chemical shift patterns of the three isopropylidene carbons in **11α** and **11β**, measured in deuterioacetone, are very close to the ranges reported by the groups of Moffatt[21b] and Secrist[21c] for a number of isopropylidenated α and β C-ribosyl compounds in deuteriochloroform.

Although the overall yields of **10β** are rather modest, the shortness of this procedure and the potential for further improvements makes this approach a useful addition to existing methodologies for the synthesis of related C-nucleosides. The antiprotozoal activities of **10β** will be communicated elsewhere.

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19) The ratio of isomers was found to be highly dependent on the reaction conditions, with higher temperatures and longer reaction times favoring the formation of the β anomer. Minor amounts of the corresponding 4-glycosylated isomers were also found.

20) Satisfactory analytical and spectroscopic data were obtained for all new compounds.

21) A number of NMR criteria were used to determine the anomeric configuration of these C-nucleosides. The relative chemical shifts of the anomeric proton, the multiplicities of the H-4' signals, and the Δδ values of the isopropylidene groups were all consistent with the empirical rules derived from studies with both C- and N- nucleosides. a) De Bernardo, S., Weigele, M. J. Org. Chem., 1977, 42, 109. b) Ohrui, H., Jones, G. H., Moffatt, J. G., Maddox, M. L., Cristensen, A. T., Byram, S. K. J. Am. Chem. Soc., 1975, 97, 4602. c) Cousineau, T. J., Secrist, J. A., III. J. Org. Chem., 1979, 44, 4351. d) Rayner, B., Tapiero, C., Imbach, J. -L. Carbohydr. Res., 1976, 47, 195. e) MacCoss, M., Robins, M. J., Rayner, B., Imbach, J. -L. Carbohydr. Res., 1977, 59, 575. f) Sugiyama, H., Yamaoka, N., Shimuzu, B., Ishido, Y., Sato, S. Bull. Chem. Soc. Japan, 1974, 47, 1815. g) Ferris, J. P., Badesha, S. S., Ren, W-Y., Huang, H. C., Sorcek, R. J. J. Chem. Soc. Chem. Commun, 1981, 110.

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23) a) ^{1}H-NMR (90 MHz, CD_3COCD_3), **11β**: δ 1.33 (s, 3H, CH_3), 1.57(s, 3H, CH_3), 3.72 (pseudo d, 2H, H-5'), 3.84 (br. m, 1H, OH, ex. in D_2O), 4.20 (m, 1H, H-4'), 4.89 (m, 2H, H-2'and H-3'), 5.43 (d, 1H, H-1', $J_{1',2'}$ = 4.7 Hz), 7.86 (s, 1H, H-2), 8.34 (s, 1H, H-5). **11α**: δ 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.74 (pseudo d, 2H, H-5'), 4.14 (pseudo t, 1H, H-4'), 4.88 (dd, 1H, H-2', $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 6.0 Hz), 5.00 (dd,1H, H-3, $J_{3',4'}$ = <1 Hz), 6.49 (d, 1H, H-1'), 7.82 (s, 1H, H-2), 8.35 (s, 1H, H-5).
b) ^{13}C-NMR (22.52 MHz, CD_3COCD_3, ribosyl and vinyl assignments of both anomers confirmed by selective decoupling experiments). **11β**: δ 25.73 (CH_3), 28.00 (CH_3), 63.38 (C-5'), 81.48 (C-1'), 83.37 (C-3'), 86.03 (C-4'), 87.43 (C-2'), 114.69 (Ip. quat), 126.50 (C-5), 144.30 (C-2). **11α**: δ 24.97 (CH_3), 26.71 (CH_3), 63.00 (C-5'), 77.69 (C-1'), 82.78 (C-2'), 84.30 (C-3'), 85.49 (C-4'), 113.01 (Ip. quat), 127.63 (C-5), 143.83 (C-2).

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