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Tetrahedron Letters 49 (2008) 3273–3275
Tetrahedron Letters

# Synthesis of nucleoside derivatives via heterocyclocondensation reactions

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Received 14 February 2008; revised 6 March 2008; accepted 17 March 2008
Available online 19 March 2008

**Abstract**

A new synthesis of nucleoside analogues has been developed. The cyclocondensation of a glycosylated diazadiene or thiazadiene, with acyl chlorides or α-halogenoketones, respectively, resulted in good yields and excellent regioselectivities. We report an efficient method for the production of glucosyl pyrimidinones and glucosylamino thiazoles.


*Keywords:* Nucleosides; Cyclocondensations; Diazadienes; Thiazadienes; Glycosyl heterocycles; Glycosylamino heterocycles

There has been recent interest in the synthesis of *N*-glycosyl heterocycles as nucleoside analogues, which exhibit biological and pharmaceutical activities.[1,2] Several variations have been made on both the heterocyclic base and the sugar moiety in the search for effective and selective derivatives.[3,4] Classically, the strategy for the synthesis of nucleosides has been the condensation of glycosides with activated nucleobases.[5–7] More rarely, the heterocyclic moieties are built by the cycloaddition reactions. The Arévalo group has been largely involved in asymmetric [3+2] cycloadditions of 1,3-thiazolium-4-olates using carbohydrates as stereodifferentiating elements.[8,9] A modified Huisgen 1,3-dipolar cycloaddition reaction (click chemistry) of glycosyl azides with terminal acetylenes is an efficient method and has been notably developed by Houston[10–12] and Rutjes.[13] The cycloaddition reactions of 4-nitro and 5-nitro-1-vinylimidazoles have been investigated by Ramsden.[14] The cycloadducts obtained are potential intermediates for the synthesis of purine nucleoside analogues via reduction to the corresponding aminoimidazoles.

Surprisingly, only few [4+2] cycloaddition or cyclocondensation reactions have been described for the synthesis of nucleoside analogues by the construction of the heterocyclic moiety.[15–18] Recently, we described intermolecular [4+2] cyclizations between an azadienium iodide and glycosyl isothiocyanates affording *N*-glycosyl pyrimidines.[19] We now report an alternative approach to this class of nucleoside analogues, based on [4+2] cyclization reactions, in which the carbohydrate moiety is at first linked to the heterodiene rather than to the dienophile. Peracetylated 1-glucosyl-1,3-diazabuta-1,3-diene **1** was used as a model to prove the feasibility of the methodology. Previously, we described the reactivity of variously substituted 1,3-diazabutadienic chains towards dienophiles or electrophiles for the preparation of thioxopyrimidinones,[20,21] thiadiazine-1,1-dioxydes,[22] thiazolopyrimidines,[23] imidazobenzothiazoles[24] or pyrimidothiazines.[25] Here, we describe cyclocondensations between glucosyl diazadiene **1** and acyl chlorides in a basic medium to afford *N*-glucosyl pyrimidinones **2–5** (Scheme 1).

Glucosyl diazadiene **1** was obtained in six steps from peracetylated glucoside, via glucosyl isothiocyanate **6** (Scheme 2).[26] Glycosyl isothiocyanates have been widely

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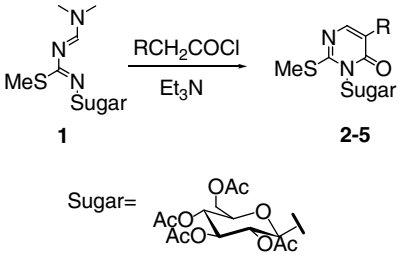
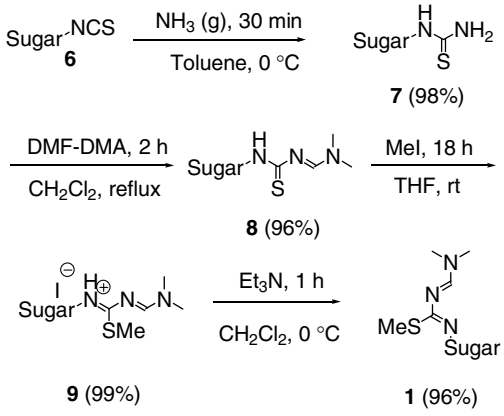
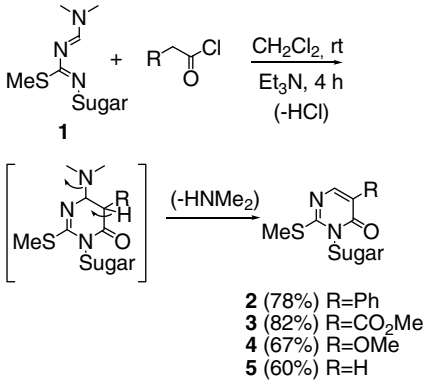
doi:10.1016/j.tetlet.2008.03.069




Scheme 1. General strategy for the synthesis of nucleosides.




Scheme 2. Synthesis of the key intermediate glucosyl diazadiene.




Scheme 3. Synthesis of glucosyl pyrimidinones.

used as important intermediates in synthetic approaches to nucleoside analogues.[27,28] The reaction of β-glucosyl isothiocyanate **6** with ammonia gas gave thiourea derivative **7** in 98% yield without deacetylation of the sugar moiety. The subsequent treatment using *N*,*N*-dimethylformamide dimethyl acetal afforded the desired thiazadiene **8** in good yield. The alkylation of compound **8** with methyliodide provided the corresponding *S*-methyl salt **9** containing the diazadiene chain. This iodide **9** was dehydrohalogenated using triethylamine giving rise to the key intermediate glucosyl diazadiene **1**. The structure of **1** was assigned by the full analysis of the $^{1}H$, $^{13}C$, HMBC and HMQC NMR spectra.[29]

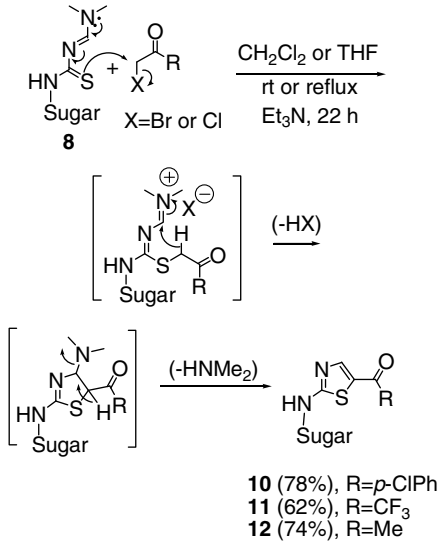
The treatment of β-glucosyl diazadiene **1** with acyl chlorides was then investigated. The reactions were performed at room temperature in dichloromethane with triethylamine. The cyclocondensations occurred, followed by the loss of dimethylamine, leading to β-glucosyl pyrimidin-4-ones **2–5** in good yields and excellent regioselectivities (Scheme 3). The $^{1}H$ NMR spectra of **2–4** showed a singlet (or a doublet for **5**) in position 6 due to the loss of dimethylamine, and thus excluded the regioisomeric pyrimidin-5-one structure. The retention of the anomeric configuration has been easily confirmed by measuring the anomeric coupling constant $J_{1,2}$. The $J_{1,2}$ value (~9.5 Hz) indicated glucoses **2–5** to be β.

Neither a first intermediate resulting from the acylation of the anomeric nitrogen atom, nor the cycloadduct before deamination, could be isolated. Therefore, it has not been possible to ascertain the reaction mechanism, which could possibly involve a [4+2] cycloaddition (with an in situ generated ketene from acyl chloride and triethylamine), or two ionic steps (acylation of the anomeric nitrogen atom, followed by the cyclization with the loss of hydrochloric acid).

To complete this study we investigated the reactivity of compound **8**,[30] containing a thiazadiene chain, towards α-halogenoketones to give glucosylamino thiazoles **10–12**. Very little work related with exocyclic amino nucleosides has been carried out despite such compounds showing interesting activities. For example, Clitocine, a natural ribofuranosylamino pyrimidine, is an inhibitor of adenosine kinase and exhibits insecticidal activity.[31,32] Synthetic exocyclic amino nucleosides like ribofuranosylamino pyrimido[5,4-*d*]pyrimidine show antitumour and antiviral properties.[33,34] Other glucosylamino pyrimidines,[35,36] triazines[37] and triazoles,[38] with various activities, have also been reported. Classically, these exocyclic amino nucleosides are prepared by the condensation reaction of glycosylamine derivatives with chloronucleobases (Kamikawa's procedure)[39] or by the coupling of silylated aminoheterocycles with peracetylated glycosides (Kini's synthesis).[40,41]

On the basis of the above literature, it is of interest to develop new methodologies for the synthesis of compounds containing a similar structural feature. Amino thiazoles **10–12** were thus synthesized from β-glucosyl thiazadiene **8**. The cyclocondensation reactions were performed between the thiazadiene chain and α-bromo- or chloro-ketones. The spontaneous deamination of the intermediate cycloadduct afforded β-aminosugars **10–12** in good yields (Scheme 4). The β anomeric configuration was fully preserved, and we observed only 1,2-*trans* glucosidic linkage. No intermediate could be isolated; however, the alkylation of the sulphur atom is thought to occur first, with triethylamine neutralizing the hydracid generated during the ring closure step.

In summary, we have shown that glucosyl heterodienes (diazadiene or thiazadiene) can be used as the building blocks for regioselective heterocyclocondensation reactions with acyl chlorides or α-halogenoketones to prepare nucleoside or aminonucleoside analogues (glucosyl or glucosylamino heterocycles). Further studies will aim to couple other dienophiles to variously glycosylated heterodiene skeletons.




Scheme 4. Synthesis of glucosylamino thiazoles.

## Acknowledgements

The French Ministry of Education and CNRS are gratefully acknowledged for financial support.

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29. *Spectroscopic data of compound* **1**: Mp: 109–110 °C. IR (KBr): 2963, 1751, 1730, 1635, 1588 $cm^{-1}$. $^1H$ NMR (DMSO) $\delta$ 1.86, 1.93, 1.98, 2.01 (4s, 12H, $CH_3$); 2.20 (s, 3H, $SCH_3$); 2.96, 3.06 (2s, 6H, $N(CH_3)_2$); 3.91–4.05 (m, 2H, $H_5$ and $H_{6a}$); 4.14 (dd, 1H, $J = 12.2$ Hz, $J = 5.1$ Hz, $H_{6b}$); 4.81 (t, 1H, $J = 9.4$ Hz, $H_2$); 4.91 (t, 1H, $J = 9.4$ Hz, $H_4$); 5.24 (t, 1H, $J = 9.4$ Hz, $H_3$); 5.40 (d, 1H, $J = 9.4$ Hz, $H_1$); 7.86 (s, 1H, $H_4$ diene). $^{13}C$ NMR (DMSO) $\delta$ 13.9, 20.3, 20.5, 34.1, 39.9, 62.3, 68.7, 72.0, 72.2, 72.8, 85.2, 154.9, 166.1, 168.8, 169.3, 169.6, 170.1. MS *m/z*: 476 (100, $[M+H]^+$). HRMS (ESI) *m/z* calcd for $C_{19}H_{30}N_3O_9S$ $[M+H]^+$ 476.1703, found 476.1705.
30. *Spectroscopic data of compound* **8**: Mp: 89–90 °C. IR (KBr): 3354, 2940, 1750, 1629, 1507, 1224 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 2.03, 2.05, 2.08 (3s, 12H, $CH_3$); 3.06, 3.17 (2s, 6H, $N(CH_3)_2$); 3.89 (ddd, 1H, $J = 9.7$ Hz, $J = 4.3$ Hz, $J = 2.1$ Hz, $H_5$); 4.12 (dd, 1H, $J = 12.4$ Hz, $J = 2.1$ Hz, $H_{6a}$); 4.33 (dd, 1H, $J = 12.4$ Hz, $J = 4.3$ Hz, $H_{6b}$); 5.08 (t, 1H, $J = 9.7$ Hz, $H_2$); 5.11 (t, 1H, $J = 9.7$ Hz, $H_4$); 5.38 (t, 1H, $J = 9.7$ Hz, $H_3$); 5.96 (t, 1H, $J = 9.7$ Hz, $H_1$); 7.08 (d, 1H, $J = 9.7$ Hz, N*H*); 8.81 (s, 1H, $H_4$ diene). $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.6, 20.7, 35.9, 41.5, 61.7, 68.3, 70.6, 73.0, 73.4, 82.5, 163.0, 169.6, 169.9, 170.7, 170.8, 196.6. MS *m/z*: 462 (100, $[M+H]^+$). HRMS (ESI) *m/z* calcd for $C_{18}H_{28}N_3O_9S$ $[M+H]^+$ 462.1546, found 462.1548.
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