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Electrochemical synthesis of azanucleoside derivatives using a lithium perchlorate–nitromethane system†

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We have developed a highly efficient synthetic method for azanucleosides using a lithium perchlorate–nitromethane reaction medium, allowing direct and exclusive installation of various nucleophiles, including protected nucleobases into prolinol derivatives at the preferred 5-position.

Nucleoside analogues have played a crucial role in the treatment of viral infections and cancer.[1] A variety of nucleoside analogues have been developed with the aim of improving their therapeutic effects and reducing toxicity. Exploration of new active analogues has primarily been focused on modification of the sugar moiety.[2] Specifically, the design of furanose rings through the introduction of various heteroatoms has been one of the most useful approaches in the search for new nucleoside analogues with beneficial biological activity. Azanucleosides, in which the furanose oxygen atom is replaced by a nitrogen atom, have attracted considerable attention due to the possibility of their further modification through the nitrogen atom and structural similarity to the furanose ring system.[2a,b,e] Romeo and co-workers recently reported the biological evaluation of the 3′-deoxy-4′-azaribonucleosides as novel nucleoside templates.[3] The synthesized compounds were shown to be HCV inhibitors in a cell-based replicon assay in nanomolar order with no or low toxicity.

Given their attractive features, many efforts have been made to develop efficient methods for the synthesis of azanucleoside derivatives.[2a] A commonly used synthetic strategy relies on *N*-glycosyl bond formation through an iminium ion intermediate. This process involves the incorporation of leaving groups, such as alkoxy, acetoxy or halogen groups, into pyrrolidinyl precursors, in order to generate key reactive intermediates. However, access to such precursors requires a multi-step synthetic sequence, cumbersome operations and harsh reaction conditions associated with protection–deprotection and oxidation–reduction steps.

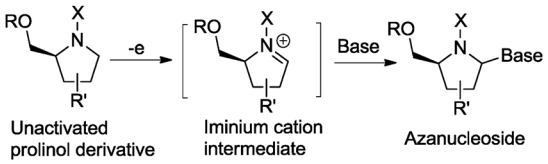

Fig. 1 Schematic view of an electrochemically direct transformation reaction of non-activated prolinol derivatives for the synthesis of azanucleosides.

Indeed, this process often removes the opportunity of providing diverse azanucleosides based on further modification of the nitrogen atom. Therefore, a remaining challenge in the synthesis of azanucleosides is the reliance on the preparation of precursors bearing leaving groups.

To address this challenge, we reasoned that direct selective attachment of a nucleobase to a prolinol moiety at the N-α position would preclude the need for activation through the introduction of leaving groups and its related redundant synthetic efforts. We proposed that an electro-organic method might provide such an approach to overcome the challenge of direct introduction of a nucleobase into an unactivated pyrrolidine moiety (Fig. 1).[4] An electrochemical method provides a clean, versatile and powerful synthetic tool for organic synthesis, such as direct C–H activation.[4g–j] Specifically, we took advantage of the $LiClO_4$–CH_3NO_2 reaction system, which provides a mild and efficient method for accessing key intermediates by electrochemical oxidation.[5] This reaction system can accumulate desired intermediates, anodically derived from *N*-protected pyrrolidine derivatives such as *N*-acetyl- or methoxycarbonyl proline methyl ester, by means of the media effect of the highly concentrated $LiClO_4$–CH_3NO_2 solution, enabling coupling with a variety of nucleophiles in one-pot reactions.

In this communication, we report a mild, operationally simple and straightforward strategy for coupling an unactivated prolinol derivative with a nucleobase through anodic oxidation using a $LiClO_4$–CH_3NO_2 solution system, and demonstrate the utility of this transformation by addition of various nucleophiles to readily available prolinol derivatives in a regioselective manner.

Substituents on the pyrrolidine ring moiety, particularly a hydroxymethyl group at the 2-position, can serve important

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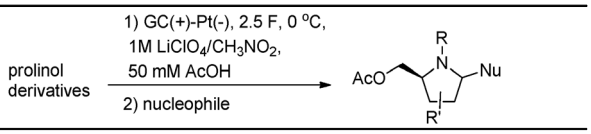
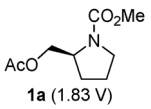
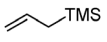
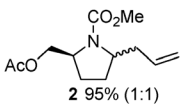
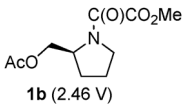
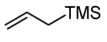
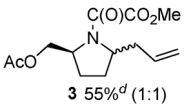
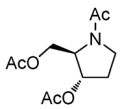
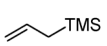
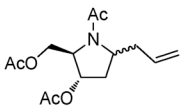
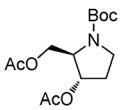
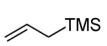
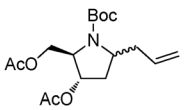
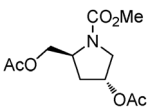
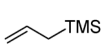
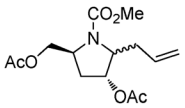
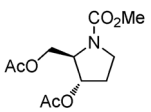
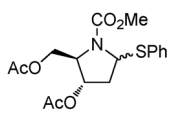
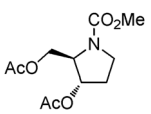
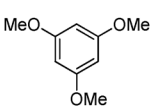
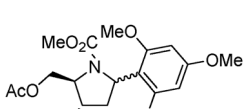
functions in biological activity or in the incorporation of a nucleoside analogue into a DNA/RNA sequence through chemical ligation (for example, the phosphoramidite method[6]). Moreover, it has been shown that substituents around the pyrrolidine ring, including *N*-protective groups, have a major effect on the regioselectivity of methoxylation by anodic oxidation. For example, when *N*-Boc-*trans*-4-hydroxy-proline methyl ester was used, regioselectivity was low and significant amounts of the over-oxidized compounds were produced.[4d,e] The use of RuO_2–xH_2O/$NaIO_4$ as an oxidation reagent often results in the same difficulty as the electrochemical method.[2c] It was unclear whether the $LiClO_4$–CH_3NO_2 system could generate and accumulate the desired intermediate, derived from the prolinol moiety, to react with various nucleophiles at the favoured 5-position, although it was expected that the potential over-oxidation reaction would be suppressed. Initially, we prepared several *N*-protected prolinol derivatives. All reactions were carried out in 1 M $LiClO_4$–CH_3NO_2 in the presence of 50 mM AcOH using an undivided cell, a glassy carbon anode and a platinum cathode. The results are summarized in Table 1. Electrolysis conducted under a constant current (0.5 mA cm^{-2}, 2.5 F mol^{-1}) at 0 °C followed by addition of allyltrimethylsilane (3 equiv.) as a nucleophile successfully gave the coupled products in high yields. Furthermore, compounds **1a–e** were exclusively allylated at the 5-position (the 1′-position in the nucleoside analogue). The accumulation system contributed significantly to this regioselectivity. Although the anodic methoxylation reaction can preferentially provide the 5-methoxylated product, further anodic oxidation reaction results in a loss of the regioselectivity due to the existence of nearly equal oxidation potential between the starting substrate and the product. This system suppresses further oxidation of the products because the intermediates possess higher oxidation potentials than the substrate. This also implies that no significant racemization took place during each step (electrolysis, accumulation and coupling), as no diastereomers, other than the α,β-anomeric isomers, were observed.

When thiophenol and 1,3,5-trimethoxy-benzene were used as nucleophiles, the desired reactions took place smoothly to provide the corresponding products **7** and **8** in a yield of 71% and 84%, respectively. Cleavage of the acid-labile C–S bond did not occur under this electrolytic condition. In this reaction, the

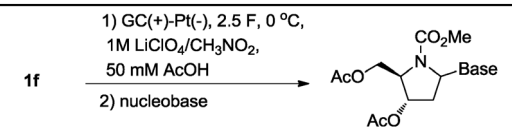
Table 1 Anodic coupling reaction of prolinol derivatives with nucleophiles in LPC–NM solution[a]

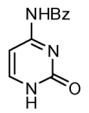
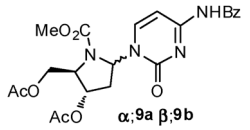
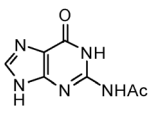
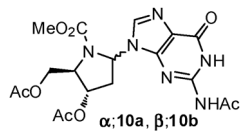
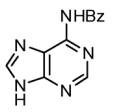
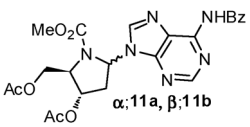
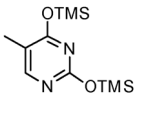
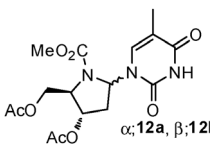


Entry	Substrate (E_{ox} *vs.* Ag/AgCl)[b]	Nucleophile	Product yield[c] (α : β)
1	 **1a** (1.83 V)		 **2** 95% (1:1)
2	 **1b** (2.46 V)		 **3** 55%[d] (1:1)
3	 **1c** (1.82 V)		 **4** 71% (1:1)
4	 **1d** (1.86 V)		 **5** 69% (1:1)
5	 **1e** (1.72 V)		 **6** 74% (3:7)
6	 **1f** (182 V)		 **7** 71% (1:1)
7	 **1f** (1.82 V)		 **8** 84% (3:7)

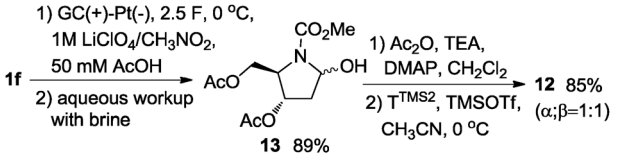
[a] All reactions were performed using an undivided cell. [b] The oxidation potential was determined using cyclic voltammetry. [c] Isolated yield. [d] The reaction completes upon passing 10 F mol^{-1} of electricity.

Table 2 Anodic coupling reaction of compound **1f** with nucleobases[a]



Entry	Nucleobase	Product	Yield[b]
1		 α;**9a** β;**9b**	52% (α : β = 1 : 1)
2		 α;**10a**, β;**10b**	44% (α : β = 3 : 2)
3		 α;**11a**, β;**11b**	54% (α : β = 1 : 1)
4		 α;**12a**, β;**12b**	ND[c,d]

[a] All reactions were performed using an undivided cell. [b] Isolated yield. [c] Not detected. [d] Electrochemical reaction was also tested in the absence of $T(TMS)_2$ to afford the hydroxylated product **13** in almost the same yield (refer to Scheme 1).



Scheme 1 Introduction of thymine into hydroxylated compound **13**.

undivided cell plays an important role in the suppression of the unfavourable C–S bond cleavage.

Encouraged by these results, we then examined the coupling reaction of prolinol **1f** with four protected nucleobases, *N*-benzoyl adenine (A^{bz}), *N*-benzoyl guanine (G^{bz}), *N*-acetyl cytosine (C^{ac}) and 2,4-bis(trimethylsilyl)thymine (T^{TMS2}), under similar conditions. The result is summarized in Table 2. The relative configurational assignments for **9–11** were determined using ^{1}H NMR and NOE experiments (see ESI†). The reaction of **1f** with A^{bz}, G^{bz}, C^{ac} afforded the desired products in good yields. In such reactions, if proline activated at the 5-position is used, reduction of the ester group (2-position) to an alcohol group is required in the later synthetic steps for the synthesis of azanucleosides. These processes often lead to some difficulties associated with isolation or decomposition of synthetic intermediates. However, this electrolytic transformation did not require such a process. The use of T^{TMS2} gave hydroxylated compound **13**, which was obtained from aqueous workup, instead of the thymine coupling product (Table 2, entry 4, and Scheme 1). The resulting product **13** was acetylated using anhydrous acetic acid, triethylamine (TEA) and 2,2-dimethylaminopyridine (DMAP) in CH_2Cl_2 to provide the compound **13**, which was then treated with TMSOTf to afford thymine-type azanucleosides.

In conclusion, we have developed a highly efficient synthetic method for azanucleosides, which allows the installation of various nucleophiles, including protected nucleobases, into prolinol derivatives directly and exclusively at the 5-position. The $LiClO_4$–CH_3NO_2 system anodically converted prolinol derivatives into the corresponding iminium cation intermediates, which were stabilized and efficiently trapped by various nucleophiles. The applicability and limitations of this system are currently under investigation.

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