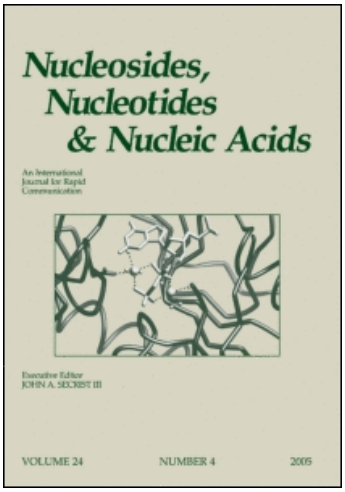

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Dalibor Odadzic[a]; Joachim W. Engels[a]
[a] Institute for Organic Chemistry and Chemical Biology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

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DIFFERENT STRATEGIES FOR THE SYNTHESIS OF 2′-*O*-AMINOETHYL ADENOSINE BUILDING BLOCKS

Dalibor Odadzic and Joachim W. Engels □ *Institute for Organic Chemistry and Chemical Biology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany*

□ *The chemical modification of the 2′-O-position of nucleosides proved to be of great importance for the RNA stability. Greater stability of RNA duplexes allows a longer half life in the cell and, therefore, a better effect of RNA Interference. Here we investigated the synthesis of 2′-O-aminoethyl adenosine as a cationic modified building block.*

Keywords 2′-*O*- position; RNA stability; building blocks

INTRODUCTION

The availability of chemically modified nucleosides has shown to be of great importance for antisense and RNA Interference mediated gene silencing applications.[1] A large number of oligonucleotides derivates that have a 2′-*O*-tethered modification have been reported.[2] As the result of the high nuclease resistance and affinity for complementary oligonucleotides of 2′-*O*-aminopropyl[3] and 2′-*O*-guanidinoethyl,[4] we decided to synthesize 2′-*O*-aminoethyl modified adenosine with cationic modification and to analyze their stabilizing effect in the duplex. The rationale for the synthesis of 2′-*O*-cationic modified nucleosides is, on one hand, a higher nuclease resistance and, on the other hand, a potentially better cellular uptake.

Here, we report different strategies for the synthesis of the 2′-*O*-aminoethyl adenosine. The main problem regarding adenosine is the N^6 exocylic amino group, so we chose different protecting group strategies to get the desired product in good yield and in few steps. Scheme 1 shows the 2′-*O*-aminoethyl adenosine building block **A1**.

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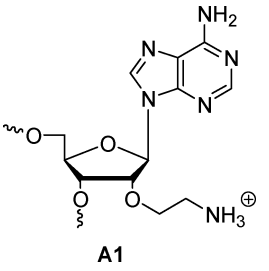
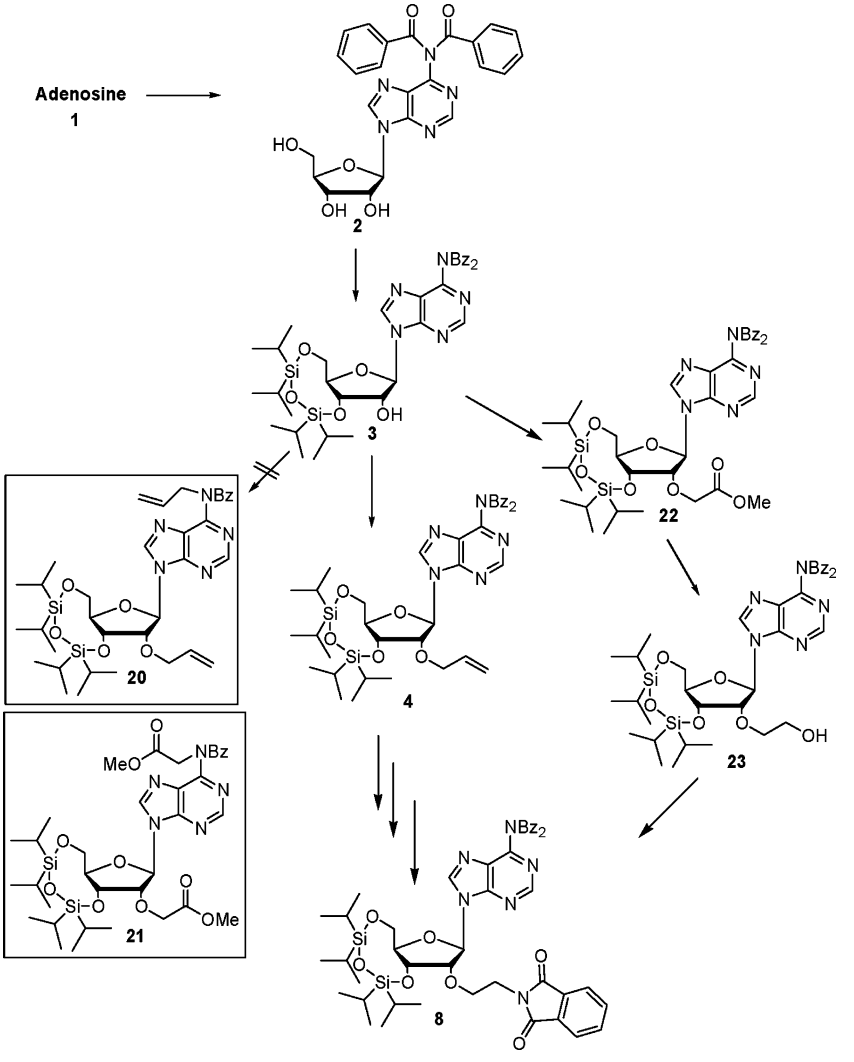
Address correspondence to Joachim W. Engels, Institute for Organic Chemistry and Chemical Biology, Johann Wolfgang Goethe University, Max-von-Laue-Str. 7, 60438 Frankfurt am Main, Germany. E-mail: joachim.engels@chemie.uni-frankfurt.de



SCHEME 1 2′-*O*-aminoethyl adenosine building block.



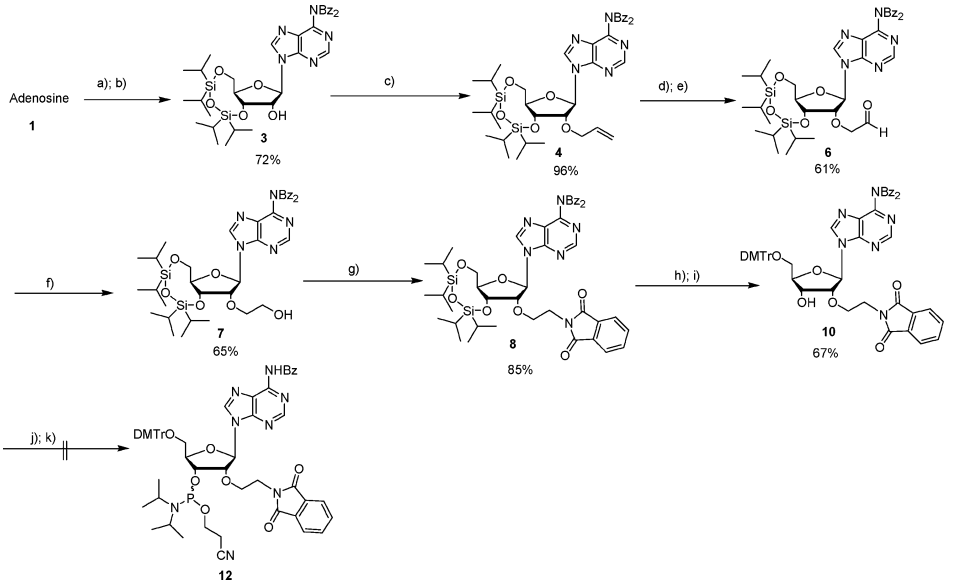
SCHEME 2 Advantage of dibenzoyl-strategy.

RESULTS AND DISCUSSION

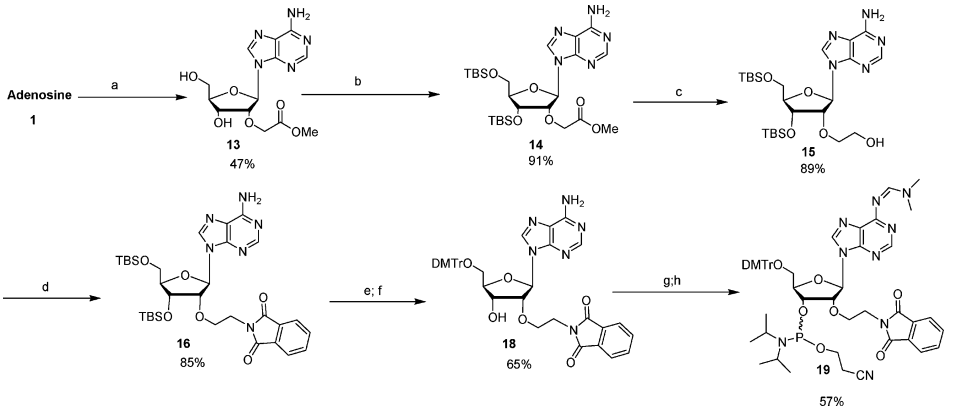
For the synthesis of **A1** we tried different strategies. Scheme 2 (see below) highlights the advantage of the dibenzoyl-strategy over the monobenzoyl strategy.[5]

Without two benzoyl groups at N^6, we always got two products during the allylation with a high amount of 2′-*O*-N^6-di-allyl-adenosine (**20**) as side product. The alkylation with bromo-acetate was unsuccessful with the monobenzoylated compound. Here we got the 2′-*O*-N^6-di-methoxycarbonyl- adenosine (**21**) as main product. The synthesis of **A1** with the dibenzoylstrategy[6] is shown in Scheme 3.

The problem of using the dibenzoylstrategy was the deprotection of only one benzoyl group on N^6. During the reaction we could indentify on TLC the deprotection of both benzoyl groups. We could not synthesize the compound **12** by using the dibenzoylstrategy. Nevertheless, we point out here some steps in this strategy. The first step is a transient protection method[7] with good yield of 80%. The next steps are the Pd catalysed allylation[8] with a yield of 96% and the introduction of the phthalimide group via Mitsunobu conditions[9] in 85%.



SCHEME 3 Dibenzoyl-strategy. TMS-Cl; pyridine; RT; 3 hours; Bz-Cl; RT; 8 hours **b** TIPDS-Cl; pyridine; RT; 24 hours **c** Allyl-Ethyl-Carbonate; $Pd_2(dpa)_2$; dppb; 70°C; 1 hour **d** OsO_4; NMO; dioxane; RT; 15 hours **e** $NaIO_4$; CH_2Cl_2; RT; 4 hours **f** $NaCNBH_3$; PPTS; RT; 4.5 hours **g** Phthalimide; PPh_3; DEAD; THF; RT; 2 hours **h** TBAF/THF; THF; RT; 1 hour **i** DMTr-Cl; NEt_3; pyridine; RT; 24 hours **j** 30% NH_4OH; pyridine; RT 0.5 hour **k** 1-Methylimidazole; sym. Collidine; CEP-Cl; acetonitrile; 0°C.



SCHEME 4 Methoxycarbonyl-strategy. **a** $BrCH_2COOMe$; NaH; RT; 8 hours **b** TBDMS-Cl; Imidazole; pyridine; RT; 24 hours **c** $LiAlH_4$; ether; 0°C; 0.5 hours **d** Phthalimide; PPh_3; DEAD; THF; RT; 1 hour **e** TBAF/THF; THF; RT; 16 hours **f** DMTr-Cl; NEt_3; pyridine; RT; 24 hours **g** DMF-dimethyl acetal; DMF; 60°C; 1 hour **h** 1-Methylimidazole; sym. Collidine; CEP-Cl; acetonitrile; 0°C.

Finally, we tried the synthesis of **A1** without protection of the N^6 amino group. The synthesis of the building block **A1** with the methoxycarbonyl strategy is shown in Scheme 4.

With this strategy we could synthesize the 2′-*O*-aminoethyl adenosine building block in good yield. The first step of this strategy is the direct alkylation of unprotected adenosine with NaH and bromo acetate with a yield of 47%.[10] Thus, we found an efficient method for the synthesis of 2′-*O*-aminoethyl modified adenosine building block in 8 steps and an overall yield of 12%.

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