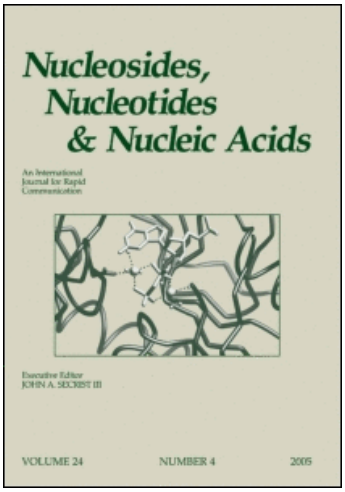

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SYNTHESIS STUDY OF 2′-O-(2-METHOXYETHYL)-PURINE DERIVATIVES

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□ *Alkylation of adenosine and 2-aminoadenosine was studied in dimethylsulfoxide with application of 1-methanesulfonyloxy-2-methoxyethane as an alkylating agent and t-BuOK, KOH and NaH as bases under mild heating. Using new reaction conditions, the improved synthesis of 2′-O-MOE-purine derivatives is described.*

Keywords Nucleosides; purine; methanesulfonyloxy-2-methoxyethane; 2′-O-MOE derivatives

INTRODUCTION

Among different 2′-O-alkyl nucleosides, 2′-O-(2-methoxyethyl) (2′-O-MOE) ribonucleosides are of special interest because antisense oligonucleotides containing them possess improved hybridization properties, favorable nuclease resistance and, therefore, belong to a promising class of potential chemotheraupetic agents. A number of synthetic routes to 2′-O-MOE-nucleosides have been investigated,[1–3] but the development of approaches which are best suited for preparing 2′-O-MOE-purine ribonucleosides is of importance. Previously, we have reported the synthesis of 2′-O-(2-methoxyethyl) purine derivatives by selective 2′-O-alkylation of adenosine and 2-aminoadenosine in moderate yields, using readily accessible 1-methanesulfonyloxy-2-methoxyethane (MOE-OMs) as alkylating agent and NaH in *N,N*-dimethylformamide followed by column chromatography on silica gel as a method for effective separation of alkylation products.[4] This article presents the synthetic study of direct 2′-O-alkylation of purine ribonucleosides by MOE-OMs in dimethylsulfoxide in presence of different bases.

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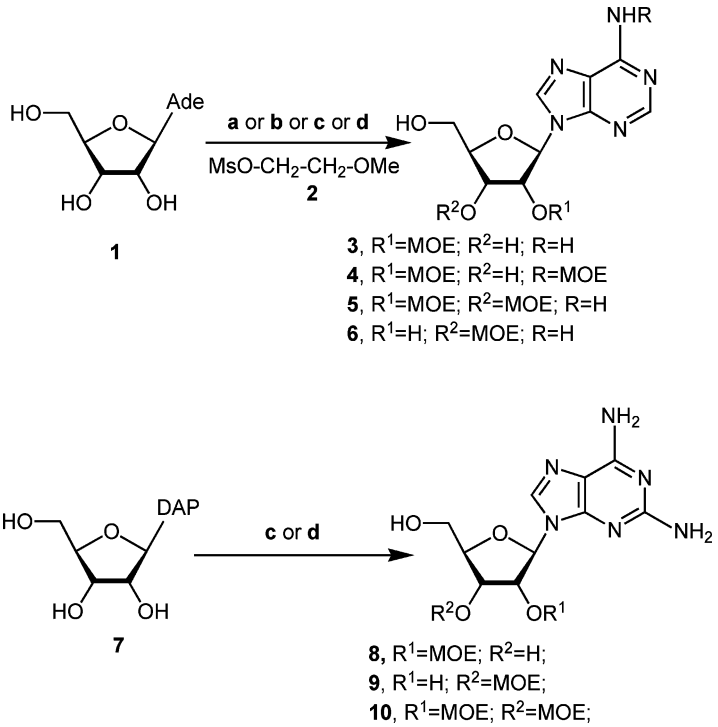
RESULTS AND DISCUSSION

The use of KOH/DMSO and MOE-Br or Cl was described for the efficient preparation of 2-O-MOE derivatives of D-ribose and 2-aminoadenosine.[5–6] MOE-OMs as a moderate electrophile displays lower reactivity in comparison with MOE-Br.[4] Taking into account this fact, selective 2′-O-alkylation of adenosine (**1**) by mesylate **2** was studied in dimethylsulfoxide in the presence of a strong base such as potassium tert-butoxide under mild heating (Scheme 1a). As a result of rapid alkylation of **1**, 2′-O-MOE-adenosine (**3**), N^6, 2′-di-O- MOE-derivative **4**, 2′,3′-di-O-MOE-derivative (**5**), 3′-O-MOE-derivative (**6**) were isolated by column chromatography on silica gel in 35, 30, 1, and 9% yields, respectively. From the previous study of 2′-O-alkylation of



SCHEME 1 Reagents and conditions: (a) **1**/ DMSO, t-BuOK (1.3 equiv.), rt, 7 minutes, mesylate **2** (2.1 equiv.), 48–49°C, 15 minutes, **2** (1.6 equiv.), 48–49°C, 35 minutes, SiO_2 column chromatography (**3**, 35%; **4**, 30%; **5**, 1%; **6**, 9%); (b) **1**/ DMSO, LiBr (3 equiv.), t-BuOK (1.5 equiv.), 8 minutes, mesylate **2** (2×2.3 equiv.), 50–52°C, 180 minutes, SiO_2 column chromatography (**3**, 38%; **4**, 3%; **5**, 10%; **6**, 10%); (c) **1**/ DMSO, LiBr (3 equiv.), KOH (Σ2.6 equiv.), mesylate **2** (Σ3.6 equiv.), 50–52°C, 18 hours, SiO_2 column chromatography (**3**, 33%); (d) [i] **1**/ DMF /LiBr (2 equiv.), NaH (1.2 equiv.), removal of solvent in vacuo; DMSO, mesylate **2** (1.7 equiv.), 50–52°C, 180 minutes; [ii] KOH (Σ1.7 equiv.), mesylate **2** (Σ2.2 equiv.), 18 hours, (**3**, 47%; **5**, 21%; **6**, 9%); (d) [i] **7**/ DMF, LiBr (2 equiv.)/DMF, NaH (1.3 equiv.), removal of solvent in vacuo; DMSO, mesylate **2** (1.7 equiv.), 50–52°C, 180 minutes; [ii] KOH (1.34 equiv.), mesylate **2** (1.27 equiv.), 18 hours, (**8**, 47%; **9**, 5%; **10**, 25%).

adenosine and 2-aminoadenosine by MOE-OMs in DMF under heating (70–72°C), it was noted that the simpler reaction mixture (TLC) was observed with the formation of O-alkylated derivatives **1** and **7** in the presence of anhydrous lithium bromide. The interesting influence of LiBr on selective alkylation of carbohydrates by alkyl bromides has been reported earlier.[7] Therefore, the alkylation of **1** in the presence of LiBr/t-BuOK was investigated under conditions (b) presented on Scheme 1. The derivatives of adenosine **3**, **4**, **5**, **6** were isolated by chromatography on silica gel in 38, 3, 10, and 10% yields, respectively, after alkylation. Comparing results of alkylation of **1** under conditions (a) and (b) it may be concluded that alkylation of adenosine in DMSO in the presence of LiBr resulted in reducing yield of undesirable 2′-O-MOE derivative **4** alkylated at the amino group of the heterocyclic base and increasing yield of 2′-O-MOE (**3**), 2′, 3′-di-O-MOE derivative (**5**), but reaction time rised in this case. Starting from this observation, alkylation of adenosine (**1**) by MOE-OMs in the presence of KOH and LiBr (Scheme 1c) was studied. It proceeded practically with the formation of derivatives **5**, **6**, and 2′-O-MOE derivative **3**, isolated in 33% yield after chromatography and crystallization. 2-Aminoadenosine is alkylated under above described conditions (c) to afford a similar distribution of alkylation products. The best results of selective alkylation of adenosine and 2-aminoadenosine were those utilizing sodium hydride in tandem with potassium hydroxide as bases (Scheme 1d). Thus, consecutive treatment of 2′-O-Na salts of purine ribonucleosides, generated from **1** or **7** in DMF in the presence of NaH/LiBr, by MOE-OMs in DMSO under mild heating followed by additional alkylation of unreacted starting nucleosides in the presence of KOH gave rise to 2′-O-MOE derivatives **3** and **8** in 47% yields after chromatography and crystallization.

It should be noted from the data above that alkylation of adenosine and 2-aminoadenosine by MOE-OMs in DMSO resulted in a more efficient preparation of 2′-O-MOE purine derivatives than the one in DMF. [4] An interesting effect of lithium salt on the alkylation in DMSO was noticed. Making use of sodium hydride and potassium hydroxide, sequentially, as bases for direct alkylation of **1** and **7** by mesylate **2** in DMSO permits us to prepare pure 2′-O-MOE-purine derivatives in high yields. But such an approach has the essential limitation that is due to the application of column chromatography for the isolation of target compounds.

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