Synthesis and Reactions of Allenic Sulfone-Modified Thymidine: The First Allenic Sulfone to Alkylate Deoxyadenosine

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Abstract: 3′-(*S*)-(allenic sulfonyl)-5′-benzoyl-3′-deoxythymidine has been synthesized from 1-(5-*O*-trityl-3-*O*-mesyl-2-deoxy-β-D-*threo*pentofuranosyl) thymine via 3′-(*S*)-(propargylthio)-5′-trityl-3′-deoxythymidine in six steps. 3′-(*S*)-(allenic sulfonyl)-3′-deoxythymidine reacts very efficiently with a wide array of nucleophiles. This is also the first report on the alkylation of adenine moiety by some allenic sulfone modified compounds.

Key words: reactive nucleosides, allenic sulfone, alkylating nucleoside

‘Reactive nucleosides’ constitute a rare and little studied group of organic molecules with the potential to act as biologically relevant alkylating agents.[2] Antitumor properties of 5-bis (2-chloroethyl) aminouracil or uramustine, a modified nucleobase belonging to this category were reported more than four decades back.[3] A series of *N*-glycosyl-halomethyl derivatives of 1,2,3-triazole, pyrazole, imidazole, and 1,2,4-triazole was studied for their antitumor properties. The design of these nucleosides as potential anticancer drugs is based on the use of the chemically alkylating benzylic halide type active moieties attached to the nucleobases.[4] Interestingly, there are very few reports on the introduction of a reactive functional group to the sugar component of nucleosides. 5′-[Bis(2-chloroethyl)amino]-5′-deoxyuridine or uridine mustard **1**, which was shown to be substantially less leukopenic than the equitherapeutic dose of uracil mustard, remains to be the only successful application of such a concept.[5] 3′-Deoxy-3′-thiocyanatothymidine (**2**) or 3′-deoxy-3′-isothiocyanatothymidine (**3**), where the choice of the groups at the 3′-position was based on their possible covalent binding to reverse transcriptase, were found to be ineffective against HIV.[6] Nucleoside based epoxides **4**, another class of reactive alkylating agents have also been studied for their biological properties (Figure 1).[7]

In an attempt to design new chemical entities for this understudied but conceptually attractive area of reactive nucleosides, we have been searching[8] for suitable functional groups capable of undergoing conjugate addition reactions and, at the same time, easily attachable to the sugar moiety of a nucleoside. It has been reported that acetylenic sulfone is a highly reactive group toward conjugate addition reactions although there are only a few reports on

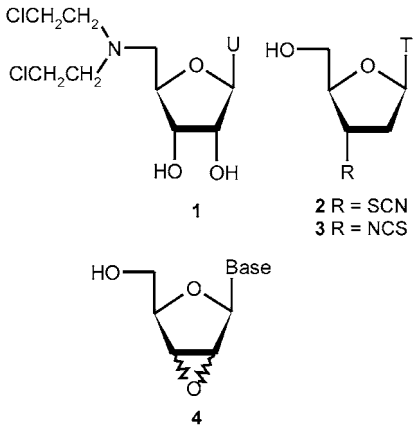

Figure 1

the biological properties of compounds functionalized with acetylenic and allenic sulfone groups.[9] Propargyl sulfone-modified steroids and triazoles were shown to inhibit glucose-6-phosphate dehydrogenase and human leukocyte elastase.[9] The usefulness of this functional group was further highlighted by the reports on the DNA-cleaving properties of cyclic bispropargylic sulfones as well as acyclic monopropargylic sulfones.[9,10] Since monopropargylic sulfones exhibited much higher potencies than the cyclic bispropargylic sulfones as DNA cleaving agents via alkylation mechanism,[10a] we envisaged that the incorporation of the allenic sulfone moiety in the sugar part of a nucleoside may generate alkylating agents with novel properties.

1-(5-*O*-Trityl-3-*O*-mesyl-2-deoxy-β-D-*threo*pentofuranosyl) thymine (**5**) was converted to 3′-(*S*)-(acetylthio)-3′-deoxythymidine (**6**) following a literature procedure.[11] Alkaline hydrolysis of **6** at low temperature furnished the free thiol derivative **7**. A dichloromethane solution of crude **7** was treated with propargyl bromide in the presence of DBU at room temperature for 15 hours to furnish after purification 3′-(*S*)-(propargylthio)-5′-*O*-trityl-3′-deoxythymidine (**8**) in 68% yield in two steps. Compound **8** could be easily deprotected at this stage to generate a propargylthio analogue of AZT, namely 3′-deoxy-3′-(*S*)-(propargylthio) thymidine (**9**).[12] Although it was possible to convert **9** to the corresponding unprotected allenic sulfone derivative, it was necessary to have a protecting group at the 5′-position for the purification of compounds obtained from addition reactions. Therefore, **9** was benzoylated using standard procedure to obtain the 5′-*O*-benzoyl derivative **10** in 88% yield. Oxidation of **10** with

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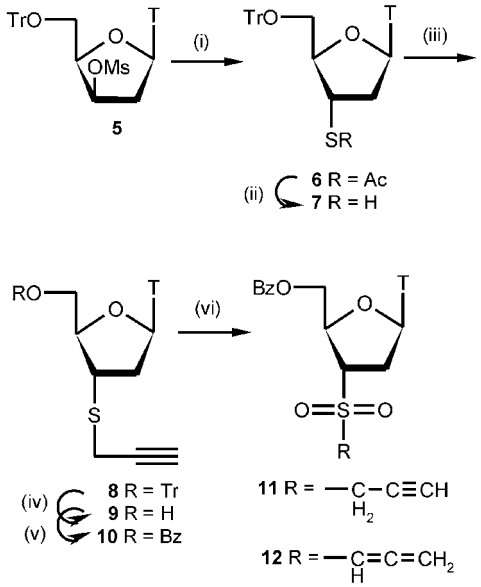
m-chloroperbenzoic acid afforded either **11** or **12** in 83% yield. However, structure **12** was attributed unambiguously to the product because of the presence of a triplet (=CH, δ = 6.26 ppm or 6.07 ppm) and peaks at δ = 211.8 ppm (=C=), 96.3 ppm (=CH) and 84.3 ppm (=CH_2) in the ^{1}H- and ^{13}C NMR spectra, respectively (Scheme 1).[13] It should be noted that propargyl sulfone easily undergoes isomerization to allenic sulfone and that allenic sulfone is more stable than its propargylic isomer by 8.2 kcal/mol,[9,14a] although it has been shown recently that in some cases propargylic sulfone is the more stable isomer.[14b]

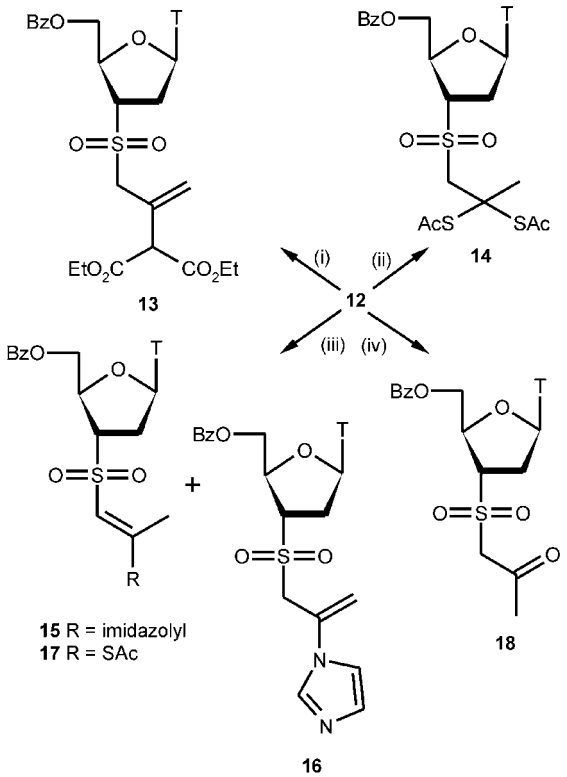


Scheme 1 *Reagents and conditions*: (i) CH_3COSK, DMF, 90 °C; (ii) 1 N KOH, EtOH–H_2O (1:1), 5–10 °C, 3 h; (iii) $CHCCH_2Br$, CH_2Cl_2, DBU, r.t., 15 h (**6** → **7** → **8** 68%); (iv) 80% aq HOAc, 90 °C, 1.5 h, 81%; (v) BzCl, pyridine, 0 °C to r.t., 3 h, 88%; (vi) *m*-CPBA, CH_2Cl_2, r.t., 1 h, 83%.

In order to establish the reaction pattern of the newly synthesized allenic sulfone-modified nucleoside, **12** was reacted with different nucleophiles. Thus, **12** on reaction with seven equivalents of the sodium salt of diethyl malonate in THF at room temperature for 2.5 hours afforded **13** in 82% yield where one equivalent of carbon nucleophile formed the adduct as expected. On the other hand, reaction of **12** at room temperature for 15 hours with two equivalents of the sulfur nucleophile generated by a strong organic base DBU from thioacetic acid in dichloromethane produced **14** in 44% yield. In this case, however, two equivalents of the sulfur nucleophile reacted with the allenic sulfone system. It is likely that the reaction proceeded through an intermediate like **17**, which underwent further addition of the thioacetate nucleophile to produce **14**. To the best of our knowledge, this is one of the rare examples of the double addition of a nucleophile to an allenic sulfone system.[15] Reactions of two equivalents of imidazole with **12** in CH_2Cl_2 at room temperature produced a mixture of **15** and **16** within 2 hours in 35% and 33% yields, respectively (Scheme 2).[16]

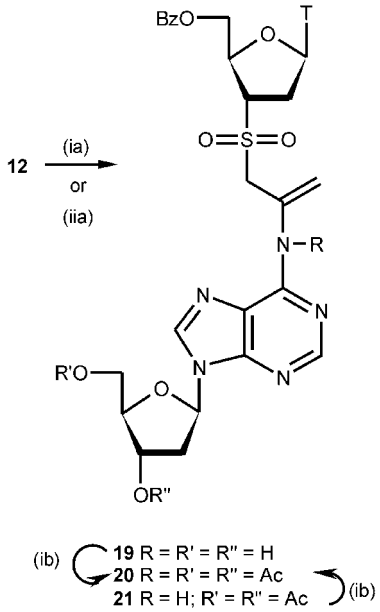
Interestingly, reactions of **12** with amines produced completely different results. Compound **12** on treatment with four equivalents of a strong base and an efficient nucleophile, piperidine in CH_2Cl_2 at room temperature for 5 hours did not produce any addition product. Instead a keto derivative **18** was isolated in 70% yield. On the other hand, a weak base and a lethargic nucleophile, 3-fluoroaniline after 24 hours at room temperature also produced the same keto compound **18** in 68% yield. Since there were several reports on the isolation of stable enamines from various allenic sulfones,[9,14b] it was surprising that the enamines, which were expected from **12**, were so highly unstable that they underwent instantaneous hydrolysis to produce **18** (Scheme 2).

Taking into consideration, the pattern of reactions of amines of two extreme pK_a values with **12** mentioned above, **12** was not expected to react with nucleobases to form any stable compounds. Moreover, reactions of 4-(naphthalene-1-sulfonyl)-buta-2,3-dien-1-ol with adenine and guanine reportedly produced labile adducts which hydrolyzed to the expected 2-keto derivative.[10a] However, when slightly more than one equivalent of 2′-deoxyadenosine was reacted with **12** in dioxane for 2 days, a stable dimeric product **19** was formed and the product was isolated as the triacetate derivative **20** in 46% overall yield.[17] In order to establish the structure of the product **20** unambiguously, 1.5 equivalents of 3′,5′-di-*O*-acetyl-2′-deoxy-



Scheme 2 *Reagents and conditions*: (i) $CH_2(CO_2Et)_2$, NaH, THF, r.t., 2.5 h, 82%; (ii) CH_3COSH, CH_2Cl_2, DBU, r.t., 15 h, 44%; (iii) imidazole, CH_2Cl_2, r.t., 2 h, **15** 35%, **16** 33%; (iv) piperidine, CH_2Cl_2, r.t., 5 h, 70% or 3-fluoroaniline, CH_2Cl_2, r.t., 24 h, 68%.

adenosine was reacted with **12** in CH_2Cl_2 at room temperature for 28 hours to obtain **21** in 68% yield. In this case also the product was stable enough to withstand all purification conditions. After full characterization, **21** [HRMS (FAB^+): *m/z* calcd for $C_{34}H_{38}N_7O_{12}S$ $[M+H]^+$: 768.2299; found: 768.2314] was acetylated with Ac_2O in pyridine at room temperature for 15 hours to furnish **20** in 88% yield (Scheme 3).[17]



Scheme 3 *Reagents and conditions*: (i) a. 2′-deoxyadenosine, dioxane, r.t., 2 d; b. Ac_2O, pyridine, r.t., 15 h (**12** → **19** → **20** 46%); (ii) a. 2′-deoxy-3′,5′-di-*O*-acetyladenosine, CH_2Cl_2, r.t., 28 h, 68%; b. [see (i), b.], 88%.

In conclusion, we have reported the first synthesis of an allenic sulfone-modified reactive nucleoside. The reaction pattern of **12** with various nucleophiles is dependent on the properties of the nucleophiles used. It should be noted that all allenic sulfones reported so far reacted exclusively with guanine residues of DNA[10] and the product of the reactions between propargyl sulfone-modified naphthalene and adenine was not stable enough for isolation.[10a] We have established for the first time that it is indeed possible to isolate a stable product from the reaction between at least one allenic sulfone carrying organic molecule **12** and the adenine residue of deoxyadenosine. Using different nucleoside and carbohydrate derived propargylic sulfones, the impact of the sugar moiety of the nucleoside on the properties of allenic sulfone group as an alkylating agent is currently under investigation.

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(12) **Compound 9**: ^1H NMR (360 MHz, $CDCl_3 + D_2O$): δ = 7.55 (s, 1 H, H-6), 6.13 (dd, *J* = 4.7, 7.0 Hz, 1 H, H-1′), 4.06–3.96 (m, 2 H), 3.87 (dd, *J* = 2.6, 11.9 Hz, 1 H), 3.73 (q, 1 H, *J* = 7.9 Hz), 3.36 (m, 2 H, SCH_2), 2.65 (m, 1 H), 2.51 (m, 1 H), 2.32 (t, *J* = 2.6 Hz, 1 H, acetylenic), 1.91 (s, 3 H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 164.2, 150.5, 136.6, 110.7, 85.5 (C-1′), 85.5 (acetylene), 79.6 (C-4′), 72.0 (acetylene), 61.3 (C-5′), 40.9 (C-3′), 39.6 (C-2′), 19.4 (SCH_2), 12.4 (CH_3). HRMS (FAB^+): *m/z* calcd for $C_{13}H_{17}N_2O_4S$ $[M + H]^+$: 297.0909; found: 297.0911.

(13) **Compound 12**: mp 86–87 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.67 (s, 1 H, NH), 8.01–7.41 (m, 5 H, phenyl), 7.15 (s, 1 H, H-6), 6.26 (t, *J* = 6.2 Hz, 1 H, allene CH), 6.07 (t, *J* = 6.5 Hz, 1 H, H-1′), 5.59 (m, 2 H, =CH_2), 4.79 (m, 2 H, H-4′, H-5′a), 4.56 (dd, *J* = 4.1, 12.2 Hz, 1 H, H-5′b), 4.07 (m, 1 H, H-3′), 2.97 (m, 1 H, H-2′a), 2.52 (m, 1 H, H-2′b), 1.64 (s, 3 H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 211.8 (=C=), 165.9 (ester CO), 163.8 (C-4), 150.1 (C-2), 135.4 (C-6), 133.6, 129.5, 129.1, 128.6 (phenyl), 111.3 (C-5), 96.3 (HC=), 86.5 (C-1′), 84.3 (=CH_2), 77.0 (C-4′), 64.7 (C-5′), 63.7 (C-3′), 33.4 (C-2′), 12.1 (CH_3). HRMS (FAB$^+$): *m/z* calcd for $C_{20}H_{21}N_2O_7S$ [M + H]$^+$: 433.1061; found: 433.1061.

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(15) Methoxide ion adds to $MeCCSO_2Ph$ to produce $MeC(OMe)_2CH_2SO_2Ph$, see ref.[8]

(16) **Compound 15**: mp 169–170 °C. ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.38 (s, 1 H), 8.30–7.08 (m, 10 H), 6.22 (t, *J* = 6.5 Hz, 1 H), 4.73–4.37 (m, 4 H), 2.83 (m, 1 H), 2.69 (s, 3 H), 2.64 (m, 1 H), 1.56 (s, 3 H). ^{13}C NMR (90 MHz, DMSO-d_6): δ = 165.4 (benzoyl CO), 163.5, 150.3, 148.5, 136.5, 135.5, 133.6, 130.5, 129.3, 129.1, 128.8, 117.4, 111.7, 110.0, 84.3, 75.3, 65.1 (C-5′), 63.4, 31.4 (C-2′), 15.4, 11.8. HRMS (FAB$^+$): *m/z* calcd for $C_{23}H_{25}N_4O_7S$ [M + H]$^+$: 501.1444; found: 501.1449. **Compound 16**: mp 103–104 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 10.57 (br s, 1 H), 7.95–7.02 (m, 9 H), 5.98 (t, *J* = 6.4 Hz, 1 H), 5.52 (s, 1 H), 5.37 (s, 1 H), 4.82 (m, 1 H), 4.69 (d, *J* = 12.2 Hz, 1 H), 4.58 (d, *J* = 14.7 Hz, 1 H), 4.50 (dd, *J* = 4.2, 12.2 Hz, 1 H), 4.33 (d, *J* = 14.7 Hz, 1 H), 3.86 (m, 1 H), 2.96 (m, 1 H), 2.33 (m, 1 H), 1.58 (s, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 165.9, 164.1, 150.5, 136.1, 135.4, 133.6, 130.4, 130.0, 129.5, 129.0, 128.6, 118.0, 114.1 (=CH_2), 111.2, 86.5, 75.8, 64.9 (C-5′), 60.8, 56.8 (SO_2CH_2), 33.5 (C-2′), 12.1. HRMS (FAB$^+$): *m/z* calcd for $C_{23}H_{25}N_4O_7S$ [M + H]$^+$: 501.1444; found: 501.1431.

(17) **Compound 20**: A solution of **12** (0.140 g, 0.32 mmol) and 2′-deoxyadenosine (0.095 g, 0.36 mmol) in dioxane (15 mL) was stirred at r.t. for 2 d. Solvent was evaporated to dryness and the residue was purified over silica gel to give **19**. Ac_2O (0.6 mL, 6.40 mmol) was added to a solution of **19** in pyridine (15 mL) and the mixture was stirred at r.t. After 15 h the reaction mixture was worked-up in the usual way and the product was purified over silica gel to give **20** (0.120 g, 46%); mp 137–138 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.52 (s, 1 H), 7.97–7.07 (m, 8 H), 6.27 (dd, *J* = 6.1, 8.0 Hz, 1 H), 5.93 (t, *J* = 6.8 Hz, 1 H), 5.83 (s, 1 H), 5.66 (s, 1 H), 5.33 (m, 1 H), 4.79–4.12 (m, 9 H), 2.88–2.73 (m, 2 H), 2.58 (m, 2 H), 2.27 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.61 (s, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 184.0, 170.4, 170.2, 165.9, 163.6, 149.9, 147.4, 144.2, 143.2, 138.0, 136.0, 134.5, 133.5, 129.6, 129.1, 128.6, 124.7 (=CH_2), 121.2, 111.2, 87.1, 84.4, 82.7, 76.1, 74.3, 64.8 (CH_2), 63.6 (C-5′, CH_2), 61.3, 55.1 (CH_2), 37.8 (CH_2), 33.6 (CH_2), 26.5, 20.8, 20.7 (2 peaks), 12.1. HRMS (FAB$^+$): *m/z* calcd for $C_{36}H_{40}N_7O_{13}S$ [M + H]$^+$: 810.2405; found: 810.2410.