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Two simple protocols for the preparation of diallylaminoethyl-substituted nucleic bases: a comparison

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Abstract—The syntheses of pyrimidine and purine nucleic bases substituted with diallylaminoethyl groups are reported following two different protocols. A comparison is made between the yield, expense, and difficulty of each route.

The importance of synthetic methods for the preparation of synthetic oligodeoxynucleotides (ODNs) has increased remarkably during the last decade,[1–3] because of their potential use in therapeutic applications, such as antisense and antigene, and diagnostic applications, such as biosensors and microarrays.[4] One critical requirement for synthetic ODNs is their stability in biological environments, and hence, reasonable half-life in vivo.[5] Exo- and endonucleases cleave the phosphodiester backbone in RNA and DNA; as a result, carbocyclic ODN analogs should be less susceptible to enzymatic fission than the furanosyl heterocycles.[2,6] One possible approach to synthetic neutral ODNs is the copolymerization of non-conjugated dienes containing nucleic bases with sulfur dioxide. Non-conjugated dienes such as diethyl diallylmalonate have been copolymerized with sulfur dioxide to form polysulfones.[7–9] We have also demonstrated in an earlier publication[10] that 1,6-heptadienes with nucleic bases attached directly to C-4 can be copolymerized with sulfur dioxide to form carbocyclic polynucleotides with sulfone groups replacing the phosphodiester backbone and cyclopentane rings substituting the furanose ring of nucleic acids. In addition, polysulfones have been formed via the copolymerization of several N-substituted diallylamines with sulfur dioxide.[11–13] Sulfones are neutral, achiral, and isoelectronic analogues of phosphodiesters and are stable to both chemical and biochemical degradations.[14] We report herein, the preparation of a new series of nucleoside analogs bearing a diallylaminoethyl group as potential precursors to carbocyclic polynucleotide analogs.

Two protocols (Scheme 1) have been investigated for the preparation of 1-(2-diallylaminoethyl)pyrimidine nucleic bases starting with uracil and thymine. In the first protocol, uracil and thymine were reacted with ethylene carbonate in dry dimethylformamide and catalytic amounts of sodium hydroxide following reported procedures[15–18] to from 1-(2-hydroxyethyl)uracil (**2a**) and 1-(2-hydroxyethyl)thymine (**2b**) in 30% and 33% yields respectively. The yields of these reactions were low due to the formation of the 1,3-bis(2-hydroxyethyl) and 3-(2-hydroxyethyl) derivatives, which were isolated from the desired compounds via lengthy and time consuming ion-exchange column chromatography.[19] Compounds **2a** and **2b** were reacted with thionyl chloride to afford 1-(2-chloroethyl)uracil (**3a**) and 1-(2-chloroethyl)thymine (**3b**) in 91% and 72% yields.[20] Finally, nucleophilic displacement of the chloro substituent with diallylamine resulted in the formation of 1-(2-diallylaminoethyl)uracil (**4a**) and 1-(diallylaminoethyl)thymine (**4b**) in 62% and 49% yields. The overall isolated yields of compounds **4a** and **4b** from uracil and thymine were 14% and 12%, respectively.[28]

An alternative route for the synthesis of compounds **4a** and **4b** has been investigated utilizing the Mitsunobu reaction (Scheme 1).[21] The N^3-protected uracil and thymine intermediates **5a** and **5b** were prepared from uracil (**1a**) and thymine (**1b**).[22,23] Uracil and thymine were allowed to react with benzoyl chloride to form the N^1,N^3-dibenzoyl derivatives that were subsequently hydrolyzed with aqueous potassium carbonate to yield

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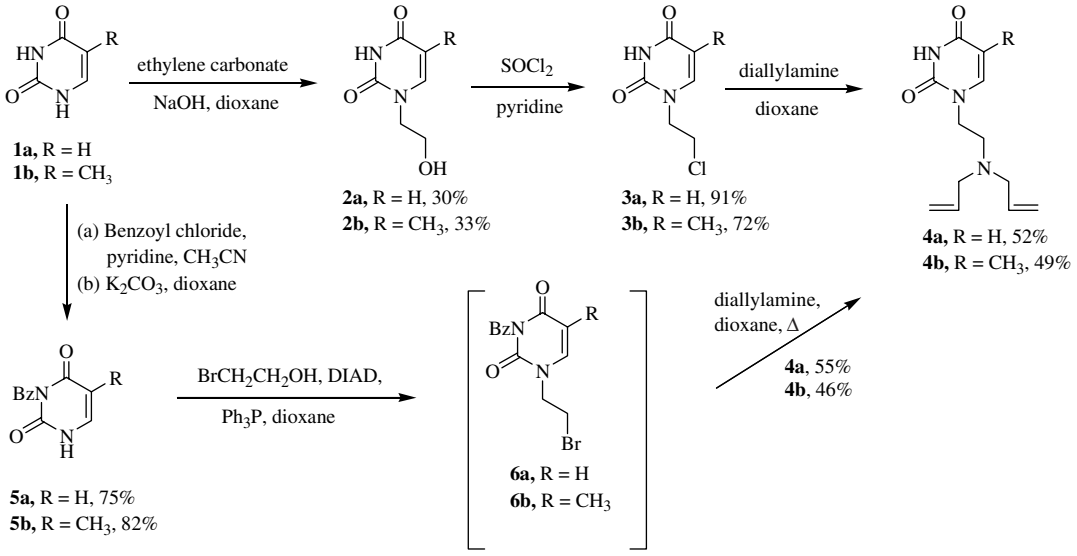
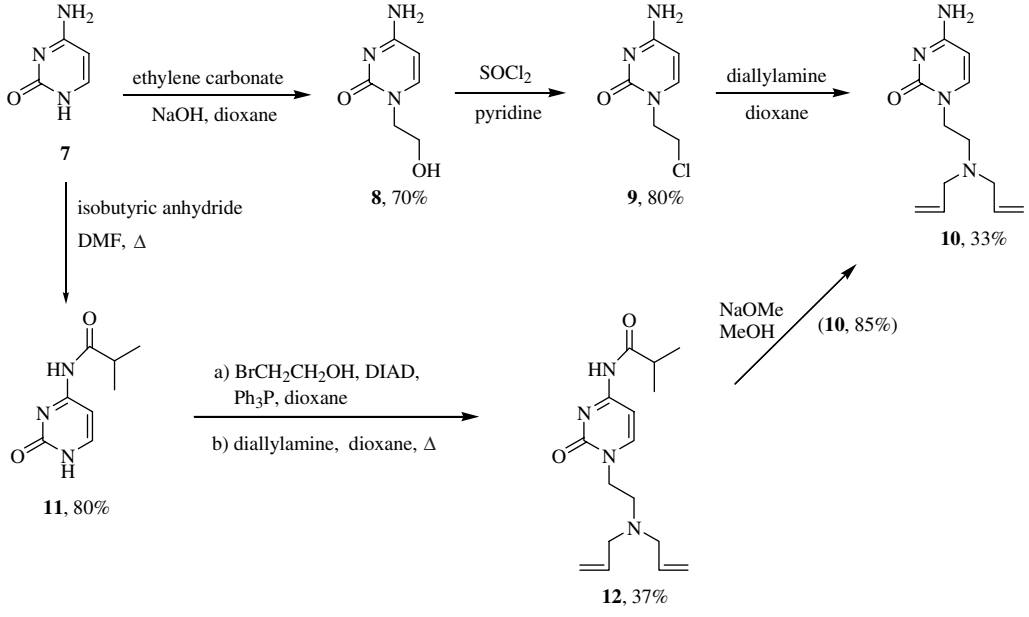


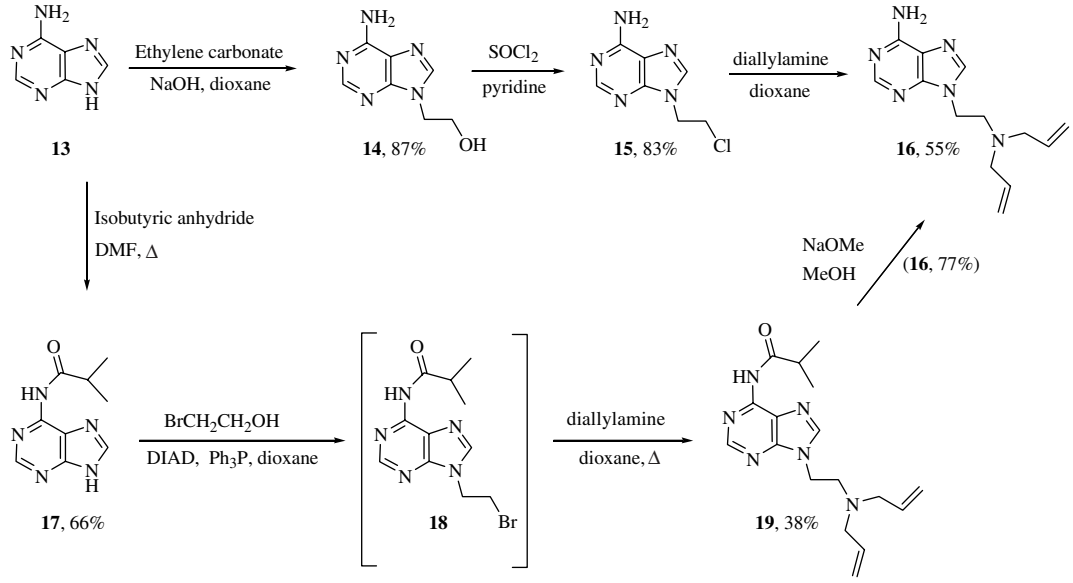
Scheme 1.

the N^3-benzoyluracil and N^3-benzoylthymine in 75% and 82% yields, respectively. The Mitsunobu reaction was employed to synthesize intermediates **6a** and **6b** by coupling **5a** and **5b** to 2-bromoethanol with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in dry dioxane.[24] The crude intermediates **6a** and **6b** were refluxed with diallylamine in dry dioxane to yield **4a** and **4b** in 55% and 46% yields, respectively (Scheme 1). Hence, the overall yields of **4a** and **4b** from uracil and thymine were 41% and 38%, respectively. In comparison, the first route was relatively more economical than the Mitsunobu route, which utilized the relatively expensive DIAD reagent; however, the overall yields of the Mitsunobu route were threefold for **4a** and **4b**. Moreover, the first route engaged the use of an ion-exchange chromatography, which necessitated the elution of the desired products with large amounts of aqueous solutions and resulted in prolonged work-up periods for both compounds.

We have applied these simple protocols to the synthesis of the cytosine derivative as well (Scheme 2). In the first protocol, cytosine was reacted with ethylene carbonate to give 1-(2-hydroxyethyl)cytosine (**8**) in 70% yield.[25] Compound **8** was then reacted with thionyl chloride to give 1-(2-chloroethyl)cytosine (**9**) in 80% yield.[26] Reacting compound **9** with diallylamine resulted in the formation of 1-(2-diallylaminoethyl)cytosine (**10**) in 33% yield. The overall yield of compound **10** from cytosine was 18%.[28] We have also prepared compound **10** following the second protocol. First, N^6-isobutyrylaminocytosine (**11**) was prepared from cytosine (**7**) via refluxing with



Scheme 2.



Scheme 3.

isobutyric anhydride followed by selective hydrolysis following a reported procedure.[22] Afterwards, the Mitsunobu reaction was utilized to couple intermediate **11** to 2-bromoethanol with triphenylphosphine and DIAD in dry dioxane followed by nucleophilic substitution with diallylamine to yield 1-(2-diallylaminoethyl)isobutyrylamidocytosine (**12**) in 37% yield.

Compound **12** was hydrolyzed in a methanolic solution of sodium methoxide to yield **10** in 85% yield (Scheme 2). Hence, the overall yield of **10** in the second protocol was 25% starting from cytosine. Both synthetic routes were simple and convenient to perform and resulted in comparable isolated yields; however, the first synthetic protocol is more economical especially for large-scale production of this compound.

In addition to the pyrimidine analogs, we have also prepared 9-(2-diallylaminoethyl)adenine **16** following both protocols (Scheme 3). In the first route, adenine was refluxed with ethylene carbonate to yield 9-(2-hydroxyethyl)adenine **14** in 87% yield. Intermediate **14** was then chlorinated utilizing thionyl chloride in dry dioxane to afford the chloro derivative **15** in 83% yield. Compound **15** was reacted with diallylamine to give 9-(2-diallylaminoethyl)adenine in 55% yield (overall yield of **16** from adenine was 40%).[28] Alternatively, adenine was protected following reported procedures by reaction with isobutyric anhydride followed by selective hydrolysis to afford 6-isobutyryl adenine **17** in 66% yield.[27] Compound **17** was coupled with bromoethanol via the Mitsunobu reaction to form the bromoethyl derivative **18**, which was not isolated. Compound **18** was refluxed with diallylamine in dry dioxane to yield 6-isobutyryl-9-(2-bromoethyl)adenine **19** in 38% yield. Hydrolysis of the isobutyryl group with sodium methoxide gave the 9-(2-diallylaminoethyl)adenine **16** in 77% yield (19% overall yield from adenine). As a result, the overall yield of **16** was more than twofold from the first procedure in comparison to the Mitsunobu route.

In summary, we have synthesized three pyrimidine and one purine nucleic bases with 2-diallylaminoethyl groups attached following two different procedures. The first procedure involved the reaction of the nucleic bases with ethylene carbonate followed by chlorination and nucleophilic displacement with diallylamine whereas the second procedure employed protection of the heterocyclic ring, Mitsunobu reaction and nucleophilic displacement with diallylamine followed by deprotection of the heterocyclic ring. The overall yields of the uracil and thymine derivatives were more than tripled in the second procedure, which rendered it more appropriate for these compounds. In comparison, the cytosine derivative was formed in comparable yields following both protocols. In contrast, the adenine derivative was obtained in higher yields following the first protocol due to eliminating the ion-exchange chromatography step.

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28. Compounds **2a**, **2b**, **3a**, **3b**, **5a**, **5b**, **8**, **9**, **11**, **14**, **15** and **17** were characterized through comparison with the literature data. Selected data for **4a**: mp 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (t, $J = 5.8$ Hz, 2H), 3.03 (d, $J = 6.4$ Hz, 4H), 3.71 (t, $J = 5.8$ Hz, 2H), 5.08 (m, 4H), 5.69 (d, $J = 7.8$ Hz, 1H), 5.66 (m, 2H), 7.19 (d, $J = 7.8$ Hz, 1H), 10.33 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.6 (t), 51.1 (t), 57.2 (t), 100.9 (d), 146.0 (d), 151.1 (s), 164.6 (s); FTIR (KBr disk, cm^{-1}) 3154, 3024, 2805, 1694, 1648, 1467, 1419, 1363, 1242, 920; HRMS (EI) calcd for $C_{12}H_{17}N_3O_2$ (M^+), 235.13208, found 235.13160.
Selected data for **4b**: mp 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.71 (t, $J = 5.9$ Hz, 2H), 3.12 (d, $J = 6.2$ Hz, 4H), 3.76 (t, $J = 5.9$ Hz, 2H), 5.12 (m, 4H), 5.75 (m, 2H), 7.08 (s, 1H), 10.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (q), 46.6 (t), 51.4 (t), 57.2 (t), 109.4 (d), 135.0 (d), 117.9 (t), 141.8 (d), 151.1 (s), 164.8 (s); FTIR (KBr disk, cm^{-1}) 3163, 3072, 3024, 2811, 1700, 1653, 1484.8, 1423, 915; HRMS (EI) calcd for $C_{13}H_{19}N_3O_2$ (M^+), 249.14773, found 249.14791.
Selected data for **10**: mp 103–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, $J = 7.1$ Hz, 1H), 5.74 (d, $J = 7.4$ Hz, 1H), 3.70 (t, $J = 5.6$ Hz, 2H), 2.65 (t, $J = 5.6$ Hz, 2H), 3.02 (d, $J = 6.0$ Hz, 2H), 5.60 (m, 1H), 5.06 (m, 2H), 6.06 (br s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (s), 165.2 (s), 93.3 (d), 146.9 (d), 51.6 (t), 48.1 (t), 57.2 (t), 135.1 (d), 117.8 (t); FTIR (KBr disk, cm^{-1}) 3352, 3139, 3005, 2976, 2924, 2799, 1656, 1614, 1523, 1485.9, 1456, 1383, 1268.8, 916, 808, 788, 677.8, 619; HRMS (EI) calcd for $C_{12}H_{18}N_4O$ (M^+), 234.14806, found 234.14771.
Selected data for **12**: mp >157 °C (decomposition); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.8$ Hz, 6H), 2.60 (h, $J = 6.8$ Hz, 1H), 7.34 (d, $J = 7.0$ Hz, 1H), 7.62 (d, $J = 7.1$ Hz, 1H), 3.90 (d, $J = 5.1$ Hz, 1H), 3.90 (d, $J = 5.7$ Hz, 1H), 2.78 (d, $J = 5.2$ Hz,1H), 2.78 (d, $J = 5.6$ Hz, 1H), 3.09 (d, $J = 6.1$ Hz, 4H), 5.67 (m, 2H), 5.14 (m, 4H), 8.30 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1 (q), 36.40 (d), 177.4 (s), 156.0 (s), 162.4 (s), 95.50 (d), 150.0 (d), 51.10 (t), 48.80 (t), 57.10 (t), 134.8 (d), 118.0 (t); FTIR (KBr disk, cm^{-1}) 3181, 3076, 2976, 2931, 2815, 1712, 1654, 1555, 1491, 1467, 1426, 1361, 1311, 1210, 919; HRMS (ESI) calcd for $C_{16}H_{24}N_4O_{26}$ $(M+1)^+$, 305.197203, found 305.1959.
Selected data for **16**: mp 142–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 8.35 (s, 1H), 4.23 (d, $J = 5.8$ Hz, 1H), 4.23 (d, $J = 6.0$ Hz, 1H), 2.85 (t, $J = 5.9$ Hz, 2H), 3.10 (d, $J = 6.4$ Hz, 4H), 5.95 (br s, NH_2), 5.08 (m, 4H), 3.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.4 (t), 134.4 (d), 57.1 (t), 41.9 (t), 52.0 (t), 141.3 (d), 119.3 (s), 155.5 (s), 152.5 (d), 149.9 (s); FTIR (KBr disk, cm^{-1}) 3290, 3119, 2979, 2801.48, 2679, 1670, 1644, 1602, 1574, 1514, 1478, 1414, 1352, 1322, 1205, 909; HRMS (EI) calcd for $C_{13}H_{18}N_6$ (M^+), 258.15929, found 258.15860.
Selected data for **19**: mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, $J = 6.8$ Hz, 6H), 3.20 (m, $J = 6.80$ Hz, 1H), 8.20 (s, 1H), 8.70 (s, 1H), 4.30 (d, $J = 5.5$ Hz, 1H), 4.30 (d, $J = 6.0$ Hz, 1H), 2.80 (d, $J = 5.7$ Hz, 1H), 2.80 (d, $J = 5.8$ Hz, 1H), 3.10 (d, $J = 6.3$ Hz, 4H), 5.60 (m, 2H), 5.10 (d, 4H), 10.00 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.8 (t), 56.9 (t), 134.7 (d), 42.1 (t), 51.8 (t), 151.6 (s), 143.7 (d), 121.9 (s), 149.3 (s), 152.0 (d), 176.6 (s), 35.5 (d), 19.1 (q); FTIR (KBr disk, cm^{-1}) 3544, 3304, 3172, 3090, 3034, 2970, 2925, 2806, 1709, 1675, 1611, 1579, 1542, 1489, 1458, 1436, 1401, 1349, 1316, 1275, 1216, 921; HRMS (ESI) calcd for $C_{17}H_{25}N_6O$ $(M+1)^+$, 329.208436, found 329.2091.