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A REGIOSPECIFIC SYNTHESIS OF UNSATURATED NUCLEOSIDES, CARBOHYDRATES AND OTHER OLEFINS

Tai-Shun Lin,* Jing-Hua Yang, Mao-Chin Liu, and Ju-Liang Zhu

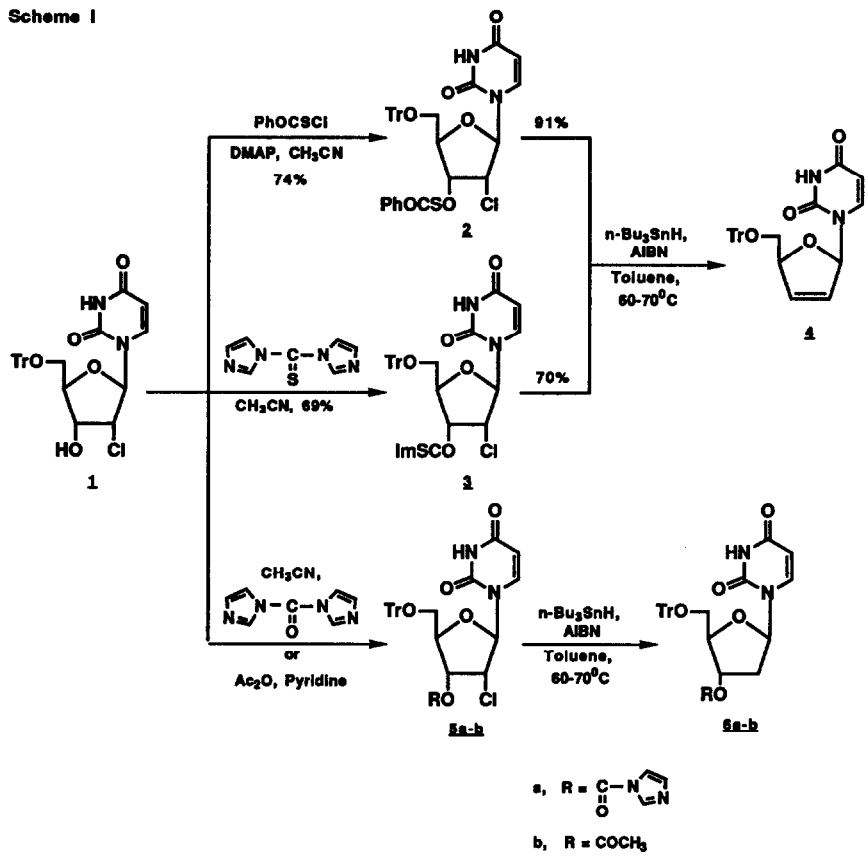
Department of Pharmacology and Comprehensive Cancer Center,
Yale University School of Medicine, New Haven, CT 06510.

Summary: Vicinal disubstituted nucleosides, carbohydrates and cyclohexane derivatives with a pair of radical leaving groups, such as chloro, bromo, phenoxythiocarbonyloxy, and imidazolylthiocarbonyloxy groups, have been successfully converted to the corresponding olefins in high yields (60-90%) without observed side products, by reaction with tri-n-butyltin hydride and azobisisobutyronitrile in an appropriate solvent.

2′,3′-Dideoxy and 2′,3′-unsaturated nucleoside analogues such as 2′,3′-dideoxycytidine (d2C), 2′,3′-didehydro-2′,3′-dideoxycytidine (d4C) and 2′,3′-didehydro-3′-deoxythymidine (d4T) are potent anti-HIV agents[1-6]. Thus, it is desirable to develop an efficient and regiospecific synthesis for the preparation of 2′,3′-unsaturated nucleosides. Tri-n-butyltin hydride is a useful reagent for reduction of organic compounds such as halides, aldehydes, ketones, S-methyl xanthates, and thionocarbonates[7]. Robins et al[8] developed a general procedure, using this reagent, for the deoxygenation of secondary hydroxyl group in nucleosides. Ribonucleosides, for example, could be converted to 2′-deoxynucleosides. Strunk et al[9] also reported that reduction of 2′,3′-dibromobutane and 2′,3′-dichlorobutane with tri-n-butyltin hydride under ultraviolet irradiation gave corresponding butene and butane, respectively. Barrett et al[10] described the conversions of carbohydrate vicinal diols to olefinic compounds by reaction of the derived bisxanthates with tri-n-butyltin hydride. David et al[11] also described the conversion of 1-(5-O-benzoyl-2,3-dichloro-2,3-dideoxy-β-D-ribofuranosyl)uracil to the corresponding 2′,3′-unsaturated nucleoside by reduction with tri-n-butyltin hydride and azobisisobutyronitrile (AIBN).

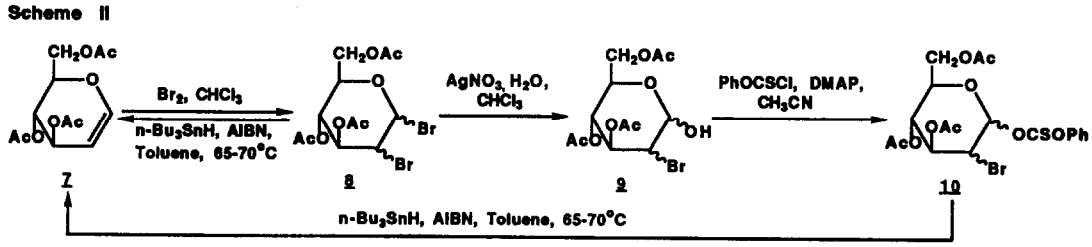
Based on these findings, we extended this reaction to the synthesis of 2′,3′-unsaturated nucleoside analogues from mixed 2′,3′-disubstituted nucleosides. This methodology was also used for the synthesis of unsaturated carbohydrates and cyclohexene derivatives. For instance, treatment[8] of 2′-chloro-2′-deoxy-5′-O-trityluridine[12] (**1**) with phenyl chlorothionocarbonate and 4-dimethylaminopyridine in acetonitrile under nitrogen at room temperature yielded the 2′-chloro-3′-O-phenoxythiocarbonyl derivative **2**[13] (74%) which has two different vicinal groups at the 2′- and 3′- positions. Reduction[8] of **2** (0.6g, 0.94mmol) with tri-n-butyltin hydride (0.55mL, 2.00mmol) and azobisisobutyronitrile (AIBN, 0.5g, 3.00mmol) in dry toluene at 60-70°C for 4h produced the 2′, 3′-unsaturated nucleoside **4**[14] in 91% yield. Compound **4** was also obtained in 80% yield by conversion of **1** to the corresponding 3′-O-imidazolylthiocarbonyl derivative **3**[15] (69%), followed by reduction of **3** with tri-n-butyltin hydride and AIBN in dry toluene. Treatment of **1** with 1, 1′-carbonyldiimidazole in acetonitrile, and acetic anhydride in pyridine gave the corresponding 3′-O-imidazolycarbonyl and 3′-O-acetyl nucleosides **5a** (84%) and **5b** (89%), respectively[16]. However, reduction of compounds **5a-b** with tri-n-butyltin hydride and AIBN only yielded the 2′-deoxynucleosides **6a-b**[17] in 97% and 96% yields, respectively (Scheme I).

Scheme I



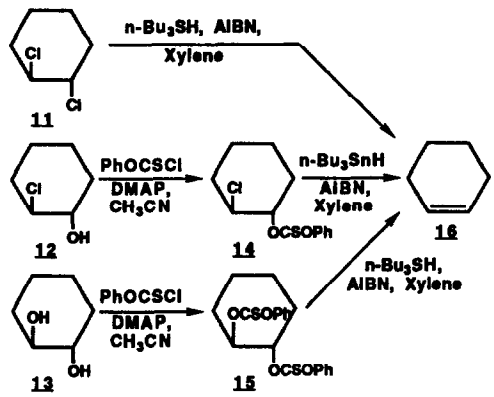
We also extended this reaction to disubstituted carbohydrates and cyclohexane derivatives. The dibromo compound (**8**)[18] was produced by bromination of triacetylglucal (**7**) and the 1-O-phenoxythiocarbonyl-2-bromo derivative **10**[19] was prepared by a two-step synthesis from **8**. Treatment of compounds **8** and **10** with tri-n-butyltin hydride and AIBN in dry toluene gave triacetylglucal (**7**) in 92% and 83% yields, respectively (Scheme II).

Scheme II



Treatment of *trans*-1,2-dichlorocyclohexane (**11**)[20], *trans*-1-chloro-2-phenoxythiocarbonyloxycyclohexane (**14**)[21] and *trans*-1,2-diphenoxythiocarbonyloxycyclohexane (**15**)[22], respectively, with tri-n-butyltin hydride and AIBN in xylene at 110-120°C yielded cyclohexene[23] (**16**) in 60-82% yield (Scheme III).

Scheme III



A free radical chain mechanism is proposed for the olefin formation reaction as described by Barrett et al[10].

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12. Compound **1** was prepared in 84% yield by treatment of 2,2′-anhydrouridine (2.26g, 10.0mmol) with trityl chloride (3.34g, 12.0mmol) in dry pyridine (80mL) at 120°C for 3.5h.
13. **2**: White foam: UV (CH_3OH) λ_{max} 257nm (ε 10702), λ_{min} 244nm (shoulder); MS, m/z 641(M^+ + 1); ^{1}HNMR (DMSO-d_6): δ 3.76 (br, 2H, 5′-H), 4.25 (m, 1H, 4′-H), 5.04 (t, 1H, 2′-H), 5.23 (m, 1H, 3′-H), 5.57 (d, 1H, 5-H), 5.99 (d, 1H, 1′-H), 7.26-7.37 (M, 20H, ArH), 7.70 (d, 1H, 6-H), 11.52 (br, 1H, 3-NH, D_2O) exchangeable). Anal. calcd. for $C_{35}H_{29}N_2O_6ClS$: C, 65.57; H, 4.85; N, 4.37. Found: C, 65.46; H, 4.85; N, 4.55.

14. **4**: mp 192-194°C (lit. mp 195-197°C, Horwitz, J.P., Chua, J., DaRooge, M.A., Noel, M., Klundt, I.L., *J. Org. Chem.* **1966**, *31*, 205). ^{1}HNMR (DMSO-d_6): δ 3.12 (m, 1H, 5′-H_A), 3.28 (m, 1H, 5′-H_B), 4.91 (m, 2H, 4′-H and 5-H), 5.99 (t, 1H, 3′-H), 6.52 (t, 1H, 2′-H), 6.80 (d, 1H, 1′-H), 7.25-7.34 (m, 15H, ArH), 7.52 (d, 1H, 6-H), 11.33 (s, 1H, 3-NH, D_2O, exchangeable).
15. Compound **3** was prepared by treatment of compound **1** with 1,1-thiocarbonyldiimidazole in CH_3CN under N_2 at room temperature for 20h (69%): mp 136-137°C; UV (CH_3OH) λ_{max} 261nm (ε 11302), λ_{min} 244nm; ^{1}HNMR (DMSO-d_6): δ 3.42 (m, 2H, 5′-H), 5.31 (d, 1H, 5-H), 5.94 (d, 1H, imidazolyl-4-H), 5.96 (d, 1H, 1′-H), 7.27-7.38 (m, 17H, ArH and imidazolyl-2-H), 7.74 (d, 1H, 6-H), 11.44 (br, 1H, 3-NH). Anal. calcd. for $C_{32}H_{27}O_5N_4ClS\ H_2O$: C, 60.70; H, 4.61; N, 8.85. Found: C, 60.74; H, 4.67; N, 8.47.
16. **5a**: mp 181-183°C (from benzene); ^{1}HNMR ($CDCl_3$): δ 3.35 (m, 2H, 5′-H), 4.28 (m, 1H, 4′-H), 4.58 (t, 1H, 2′-H), 5.20 (m, 1H, 3′-H), 5.35 (d, 1H, 5-H), 6.13 (d, 1H, 1′-H), 7.15-7.38 (m, 18H, ArH and imidazolyl-H), 7.68 (d, 1H, 6-H). Anal calcd. for $C_{32}H_{27}N_4O_6Cl$: C, 64.16; H, 4.54; N, 9.35. Found: C, 64.37; H, 4.82; N, 9.07. **5b**: foam, ^{1}HNMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3CO), 3.51 (m, 2H, 5′-H), 4.20 (m, 1H, 4′-H), 4.55 (t, 1H, 2′-H), 5.28 (m, 1H, 3′-H), 5.35 (d, 1H, 5-H), 6.15 (d, 1H, 1′-H), 7.15-7.35 (m, 15H, ArH), 7.68 (d, 1H, 6-H) 9.40 (br, 1H, 3-NH, D_2O exchangeable). Anal. calcd. for $C_{30}H_{27}N_2O_6Cl$: C, 65.87; H, 4.98; N, 5.12. Found: C, 66.25; H, 5.32; N, 5.00.
17. **6a**: mp 148-150°C (from ether); ^{1}HNMR (DMSO-d_6): δ 2.40 (m, 2H, 2′-H), 3.30 (m, 2H, 5′-H), 4.10 (m, 1H, 4′-H), 5.16 (m, 1H, 3′-H), 5.59 (d, 1H, 5-H), 6.11 (t, 1H, 1′-H), 7.26-7.37 (m, 18H, ArH and imidazolyl-H), 7.61 (d, 1H, 6-H), 11.38 (br, 1H, 3-NH, D_2O exchangeable). Anal. calcd. for $C_{32}H_{28}N_4O_6$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.38; H, 5.03; N, 9.86. **6b**: mp 205-207°C; ^{1}1HNMR (DMSO-d_6): δ 2.00 (s, 3H, CH_3CO), 2.35 (m, 2H, 2′-H), 3.30 (m, 2H, 5′-H), 4.05 (m, 1H, 4′-H), 5.20 (m, 1H, 3′-H), 5.40 (d, 1H, 5-H), 6.13 (t, 1H, 1′-H), 7.15-7.36 (m, 15H, ArH), 7.55 (d, 1H, 6-H). Anal. calcd. for $C_{30}H_{28}N_2O_6$: C, 70.29; H, 5.51; N, 5.47. Found: C, 70.01; H, 5.48; N, 5.41.
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19. Compound **10** was synthesized by treatment of compound **9** with phenyl chlorothionocabonate and 4-dimethyl-aminopyridine in acetonitrile at 0°C for 4h and obtained as a syrup (70%). ^{1}HNMR ($CDCl_3$): δ 2.07 and 2.10 (two s, 9H, CH_3CO), 3.65-3.90 (m, 1H, 5-H), 4.20 (m, 2H, CH_2), 4.65-4.80 (m, 1H, 2-H), 5.07-5.28 (m, 1H, 4-H), 5.47-5.55 (m, 1H, 3-H), 6.65-6.70 (m, 1H, 1-H), 7.05-7.40 (m, 5H, ArH).
20. Compounds **11, 12**, and **13** were purchased from Aldrich Chemical Company.
21. Compound **14** was prepared by treatment of (+) 2-chlorocyclohexanol with equimolar phenyl chlorothio-nocarbonate and 4-dimethylaminopyridine in acetonitrile at room temperature for 20h and purified by column chromatography to afford an oil (45%). ^{1}HNMR (DMSO-d_6): δ 4.02-4.21 (m, 1H, CHCl), 5.22-5.42 (m, 1H, CHOCSO-), 7.10-7.45 (m, 5H, ArH). Anal. calcd. for $C_{13}H_{15}O_2SCl$: C, 57.66; H, 5.15. Found: C, 57.96; H, 5.26.
22. **15**: foam, ^{1}HNMR ($CDCl_3$): δ 5.25-5.38 (m, 2H, 1,2-CHOCSO-), 7.05-7.41 (m, 10H, ArH). Anal. calcd. for $C_{20}H_{20}O_2S_2$: C, 53.13; H, 6.37, Found: C, 53.41; H, 6.16.
23. Compound **16** was identical in physical and spectroscopic properties with an authentic sample (Aldrich).

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