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Registry No. PAA, 9003-01-4; PMAA, 25087-26-7; methyl viologen, 1910-42-5; malonic acid, 141-82-2; succinic acid, 110-15-6; glutaric acid, 110-94-1.

Diels–Alder Reactions of Aza Dienes: A Facile Approach to the Synthesis of Pyridine- and Pyridazine-Substituted Pyrimidine Nucleosides

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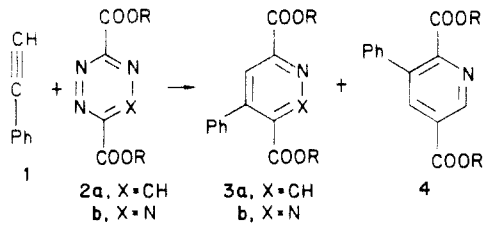
Recently, we initiated studies on the mechanism of the redox chemistry of the enzyme thymidylate synthetase. For this purpose we have needed derivatives of the substrate that would act as probes for studying two-electron transfer via a nicotinamide derivative and one-electron transfer via a metal chelated to a pyridazine dicarboxylate derivative. Therefore, methods have been explored for the synthesis of 5-pyridine- and 5-pyridazine-2′-deoxyuridines. Previous studies on the synthesis of 5-arylpyrimidine nucleosides have shown that both photochemical[1] and palladium(0)-catalyzed coupling reactions[1a,2] are possible routes to a variety of substituted phenyl derivatives. However, preliminary studies on the synthesis of heteroaromatic derivatives of pyrimidine nucleosides were not promising using these methods.

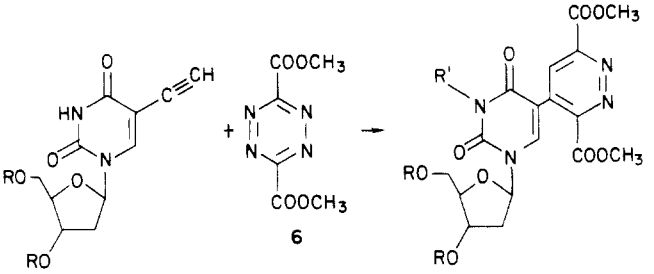
Diels–Alder reactions of both triazines and tetrazines have been found to be versatile routes for the preparation of a variety of heterocyclic systems.[3] The general reaction of alkyne 1 with electron-deficient 1,2,4-triazines (**2a**) or 1,2,4,5-tetrazines (**2b**) via a [4 + 2] cycloaddition reaction results, after nitrogen elimination, in the formation of the



corresponding pyridine **3a** or pyridazine **3b**. In the former, addition proceeds exclusively across carbons 3 and 6 of the tetrazine. However, phenylacetylene addition to the triazine **2a** was not regioselective, yielding both the 4-phenyl and the 3-phenyl derivatives **3a** and **4**.[4]

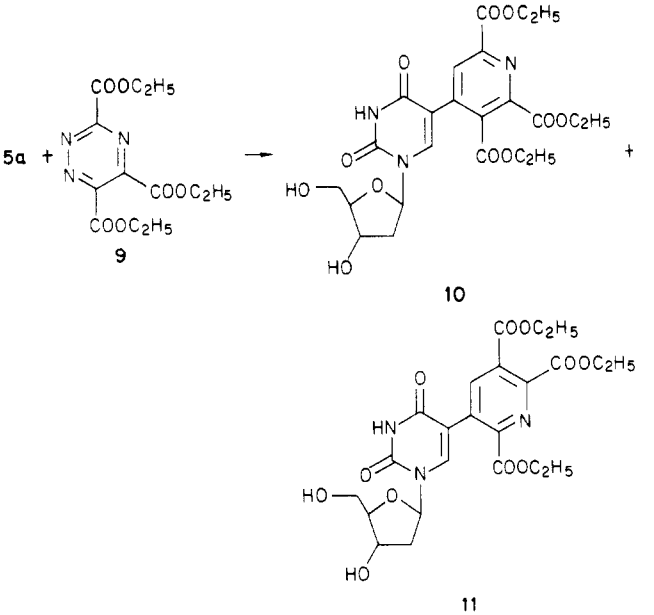
We have investigated methods for synthesizing the target compounds using the inverse electron-demand Diels–Alder reaction between alkyne-substituted deoxynucleoside and heterocyclic aza dienes. The former serves as the electron-rich dienophile, and the carboxylate-substituted tetrazine or triazine serves as the electron-deficient diene. This cycloaddition reaction offers a new method for introducing a nitrogen heterocycle onto a nucleoside that has not been previously explored and has not been reported by other routes.

The reaction of 5-ethynyl-2′-deoxyuridine[5] (**5a**) or the di-*O*-acetyl derivative **5b** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[6] (**6**) at 60 °C in dioxane leads to the 5-substituted pyrimidine deoxynucleosides **7a** or **7b** in 70% yield. The course of the reaction can be visually monitored because the initial red color of the reaction changes to yellow as the tetrazine derivative is consumed.



It has been reported that dicarboxylate-substituted pyridazines participate in Diels–Alder reactions at 100 °C with electron-rich dienophiles.[7] For this reason further elaboration of compound **7b** via a second Diels–Alder reaction with 1,1-dimethoxyethylene to synthesize a 5-substituted phenyl nucleoside was attempted. However, even at 165 °C the cycloaddition reaction did not occur. The only product that was isolated from the reaction was the 3-*N*-methyl nucleoside **8**. Since nucleosides, as a rule, are not stable to Lewis acids these catalysts were not studied in this reaction.

The reaction of **5a** with triethyl 1,2,4-triazine-3,5,6-carboxylate[8] (**9**) provided a 30% yield of the 5-pyridine-substituted deoxynucleosides **10** and **11**. It has been re-



(1) (a) Bigge, C. F.; Mertes, M. P. *J. Org. Chem.* **1981**, *41*, 1994–1997. (b) Al-Razzak, L.; Hassan, M. E.; Mertes, M. P. *Nucleosides Nucleotides* **1983**, *2*, 243–248.
(2) Chang, G.; Mertes, M. P. *Tetrahedron Lett.* **1984**, *25*, 2431–2434.
(3) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939.
(4) (a) Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171–5174. (b) Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2901–2904. (c) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435–1446.
(5) Robbins, M. J.; Barr, P. J. *J. Org. Chem.* **1982**, *48*, 1854–1862.
(6) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377–5379.
(7) Neunhoeffer, J.; Wernber, G. *Liebigs Ann. Chem.* **1973**, 437–442, 1955–1962.
(8) (a) Ratz, R.; Schroeder, J. *J. Org. Chem.* **1958**, *23*, 1931. (b) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth.*, submitted for publication.

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ported that more vigorous conditions are required for cycloaddition reactions employing triazines compared to the more electron-deficient tetrazines.[9] This was also observed in the preparation of **10** and **11** where the reaction required heating to 155 °C for 19 h. The addition occurs across carbons 3 and 6 of the triazine **9** to give an equal mixture of the regioisomers **10** and **11**. The structures were evident in the ^1H and ^{13}C NMR where the pyridine proton chemical shifts for the two isomers were observed; the isomer distribution was determined by ^1H NMR and high performance LC.

Experimental Section

Reagent-grade *p*-dioxane was purified by passage through an alumina column. HPLC analyses were carried out on a Waters Model 6000A instrument using a Whatman ODS 5 column. NMR spectra were obtained on a Varian Model FT-80 A or a Varian XL 300 spectrometer. Chemical shifts are reported in parts per million relative to internal tetramethysilane. Chemical ionization mass spectra (CIMS) were recorded on a Varian CH-5 spectrometer. Microanalyses were performed on a Hewlett-Packard model 185 CHN analyzer.

5-Ethynyl-2′-deoxyuridines **5a** and **5b** were prepared by reported procedures[5] as were dimethyl 1,2,4,5-tetrazine-3-6-dicarboxylate[6] (**6**) and triethyl 1,2,4-triazine-3,5,6-tricarboxylate[8] (**9**).

5-(3,6-Dicarbomethoxypyridazin-4-yl)-2′-deoxyuridine (7a). 5-Ethynyl-2′-deoxyuridine (**5a**; 140 mg, 0.56 mmol) and 150 mg of dimethyl 1,2,4,5-tetrazinedicarboxylate (**6**; 0.76 mmol) were dissolved in 3 mL of dioxane. The reaction mixture was flushed with argon and sealed in a 10-mL Teflon-capped vial. The vial was heated at 60 °C for 19 h. Removal of the solvent in vacuo and chromatography (silica gel, 10% $C_2H_5OH/CHCl_3$ eluant) afforded 165 mg (71%) of pure product (**7a**): UV (MeOH) λ_{max} 295 nm; ^1H NMR (acetone-d_6) δ 8.65 (s, 1 H, H_5 pyridazine), 8.21 (s, 1 H, H_6), 6.25 (t, 1 H, $H_{1'}$), 3.88 and 4.00 (s, 3 H, CO_2Me) [plus sugar proton multiplets]; ^{13}C NMR (CD_3OD) 166.5 (CO_2Me), 163.2 (C_4), 154.9 (C_6 pyridazine), 153.6 (C_3 pyridazine), 151.6 (C_2), 143 (C_6), 135.4 (C_4 pyridazine), 130.2 (C_5 pyridazine), 110.7 (C_5), 89.4 ($C_{1'}$), 87.5 ($C_{4'}$), 71.6 ($C_{3'}$), 62.3 ($C_{5'}$), 53.8 (CO_2Me), 42.1 ($C_{2'}$) ppm; CIMS, *m/e* 423 (M + 1).

3′,5′-Di-*O*-acetyl 5-(3,6-Dicarbomethoxypyridazin-4-yl)-2′-deoxyuridine (7b). Compound **7b** was prepared by the same procedure as compound **7a** with the exception that it was purified on silica gel with 5% $C_2H_5OH/CHCl_3$: UV (H_2O) λ_{max} 295 nm (ϵ 10000), (0.1 M HCl) λ_{max} 293 nm (ϵ 10400), (0.1 M NaOH) λ_{max} 293 nm (ϵ 8200); ^1H NMR ($CDCl_3$) δ 8.2 (s, 1 H, H_5 pyridazine), 8.0 (s, 1 H, H_6), 4.2 and 4.1 (s, 3 H each, CO_2Me), 2.2 and 2.1 (s, 3 H each, OAc) [plus sugar multiplets]; ^{13}C NMR ($CDCl_3$) 170.3 (OAc), 165.1 and 163.7 (CO_2Me), 160.7 (C_4), 153.3 and 152 (C_3 and C_6, pyridazine), 149.4 (C_2), 139.2 (C_6), 132.4 (C_4, pyridazine), 128.4 (C_5, pyridazine), 110.3 (C_5), 86.2 ($C_{1'}$), 83 ($C_{4'}$), 74 ($C_{3'}$), 63.5 ($C_{5'}$), 53.6 (CO_2Me), 38 ($C_{2'}$), 20.8 (CH_3) ppm; CIMS, *m/e* 507 (M + 1). Anal. Calcd for $C_{21}H_{22}N_4O_{10}\cdot 1.5\ H_2O$ (M_r 517.44): C, 48.74; H, 4.87; N, 10.83. Found: C, 49.01; H, 5.00; N, 10.58.

3′,5′-Di-*O*-acetyl 3-*N*-Methyl-5-(3,6-dicarbomethoxypyridazin-4-yl)-2′-deoxyuridine (8). The pyridazine derivative **7b** (90 mg, 0.18 mmol) was dissolved in 3.0 mL of dioxane in a 10-mL teflon-capped vial. The vial was flushed with argon, and 120 μL (~1.5 mmol) of 1,1-dimethoxyethylene was added to the reaction via a syringe. The reaction was stirred and heated to 165 °C for 9 h. Purification by silica gel chromatography (5% $C_2H_5OH/CHCl_3$) afforded 55 mg (59%) of compound **8** as the major product: UV (CH_3OH) λ_{max} 296 nm; ^1H NMR ($CDCl_3$) δ [identical spectrum with that of **7b** with the addition of] 3.5 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) 170.2 (OAc), 165.1 and 163.6 (CO_2Me), 160.3 (C_4), 153.4 and 151.9 (C_6 and C_3 pyridazine), 149.8 (C_2), 137 (C_6), 132.9 (C_4 pyridazine), 128.2 (C_5 pyridazine), 109.3 (C_5), 86.8 ($C_{1'}$), 82.9 ($C_{4'}$), 73.8 ($C_{3'}$), 63.3 ($C_{5'}$), 53.4 (CO_2Me), 38.1 ($C_{2'}$), 28.1 (NCH_3), 20.7 (Me) ppm; CIMS, *m/e* 521 (M + 1).

5-(2,5,6-Tricarbethoxypyridin-4-yl)-2′-deoxyuridine (10) and 5-(2,5,6-Tricarbethoxypyridin-3-yl)-2′-deoxyuridine (11). Compound **5a** (50 mg, 0.2 mmol) and 52 mg of triethyl 1,2,4-triazine-3,5,6-carboxylate (**9**; 0.2 mmol) were dissolved in 3 mL of dioxane in a 10-mL Teflon-capped vial. The reaction mixture was flushed with argon, sealed, and heated with stirring at 155 °C for 19 h. Purification by chromatography (silica gel, 10% $C_2H_5OH/CHCl_3$ as eluant) afforded 28 mg (32%) of an equal mixture of regioisomers **10** and **11** as determined by HPLC and ^{1}NMR: UV (H_2O) λ_{max} 275 nm (ϵ 10300); ^1H NMR (methanol-d_4) δ 8.16 and 8.25 (s, 1 H, C6), 8.31 and 8.34 (s, 1 H, H5 and H4 pyridine), 6.25 (t, 1 H, $H_{1'}$) [plus sugar proton multiplets and three carboethoxy groups]; ^{13}C NMR (CD_3OD) 167.2, 167.1, 166.9, 166.6, 165.6, 165.1 (CO_2Et), 163.4, 164 (C_4), 152.1, 151.8, 151.7, 151.3 (C_2 and C_6 4-pyridine, C_2 and C_6 3-pyridine), 151, 150 (C_2), 144.7 (C_4 4-pyridine), 142.3, 142.1 (C_6), 141.1 (C_4 3-pyridine), 132, 131.7 (C_3 4-pyridine and C_5 3-pyridine), 129.2 (C_5 4-pyridine), 129.2 (C_3 3-pyridine), 113.1, 112.3 (C_5), 89.3 ($C_{1'}$), 87.3 ($C_{4'}$), 72 ($C_{3'}$), 63.6 ($C_{5'}$), 62–63.7 (6-CO_2Et), 42 ($C_{2'}$), 14 (6-CO_2Et) ppm; CIMS, *m/e* 522 (M + 1). Anal. Calcd for $C_{23}H_{27}N_3O_{11}\cdot H_2O$ (M_r 539.49): C, 51.20; H, 5.41; N, 7.79. Found: C, 50.75; H, 5.38; N, 7.61.

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Registry No. **5a**, 61135-33-9; **5b**, 100021-00-9; **6**, 2166-14-5; **7a**, 100020-99-3; **7b**, 100021-01-0; **8**, 100021-02-1; **9**, 74476-38-3; **10**, 100021-03-2; **11**, 100021-04-3.

(9) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621–623.

Acylation of Organolithium Reagents by Esters in the Presence of Chlorotrimethylsilane

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The preparation of carbonyl compounds through the acylation of organometallic reagents is often complicated by the formation of alcohols that result from the premature collapse of the initially formed adduct **1** (Scheme I).[1,2] Recently a number of clever methods for the acylation of Grignard reagents have appeared that center on the use of carboxyl derivatives designed to give intermediate adducts that are more resistant to premature release of the carbonyl compound.[3] Successful acylations of alkyllithium reagents, however, usually require additions to either carboxylate salts[4] or to amides that give stabilized intermediates.[3a,5] Esters of normal reactivity usually give tertiary alcohols.[2]

In light of the fact that alkyllithium reagents are known to react relatively slowly with some chlorosilanes,[6] we have

(1) Mathieu, J.; Weill-Raynal, J. "Formation of C-C Bonds"; Georg Thieme: Stuttgart, 1979; Vol. III, p 346.
(2) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974; p 138.
(3) See, among others: (a) Nahn, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Meyers, A. I.; Comins, D. L. *Ibid.* **1978**, 5179. (c) Mukaiyama, T.; Araki, M.; Takai, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763. (d) Kende, A. S.; Scholz, D.; Schneider, J. *Synth. Commun.* **1978**, 59. (e) Fujisawa, T.; Iida, S.; Uehara, H.; Sato, T. *Chem. Lett.* **1983**, 1267.
(4) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.
(5) (a) Evans, E. A. *J. Chem. Soc.* **1956**, 4691. (b) Olah, G. A.; Arvanghi, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 878. (c) Amaratunga, W.; Frechet, J. M. J. *Tetrahedron Lett.* **1983**, *24*, 1143.
(6) Bey, A. E.; Weyenberg, D. R. *J. Org. Chem.* **1966**, *31*, 2036. (b) Seyferth, D.; Vick, S. C. *J. Organomet. Chem.* **1977**, *144*, 1. (c) Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534. (d) Seyferth, D.; Simon, R. M.; Sepelak, D. J.; Klein, H. A. *Ibid.* **1983**, *105*, 4634.

0022-3263/86/1951-0951$01.50/0