mL) was heated at reflux for 20 h. Evaporation of the solvent under reduced pressure gave a yellow oil which was triturated with isopropyl ether, and the precipitated white solid was recrystallized from methylene chloride/isopropyl ether to give 6-heptynoic acid hydrazide (**12**) (5.00 g, 35.67 mmol, 80% for the last step, 34% overall starting from 5-hexyn-1-ol) as shiny white plates: mp 56.0–58.0 °C; IR (KBr) 2100, 1625, 1530, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (br s, 1 H), 3.80 (br s, 2 H), 2.23–2.13 (m, 4 H), 1.96 (t, J = 2.6 Hz, 1 H), 1.80–1.55 (m, 4 H). Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 60.27; H, 8.42; N, 19.75.

5,6-Diphenyl-3-(5-hexynyl)-1,2,4-triazine (9g). A solution of 6-heptynoic acid hydrazide (**12**) (1.25 g, 8.93 mmol), benzil (1.89 g, 9.00 mmol), and ammonium acetate (11.4 g, 148 mmol, 16 equiv) in glacial acetic acid (20 mL) was heated at reflux for 5 h (116 °C). The resulting dark red solution was poured into water (100 mL), and the aqueous mixture was extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were extracted with water (150 mL) followed by a saturated solution of sodium bicarbonate (150 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield an amber oil (2.5 g). Chromatography of this oil using silica gel (60 g), eluting with 15% ether/petroleum ether, gave **9g** (1.45 g, 4.64 mmol, 52%) as a yellow solid, mp 72.0–74.0 °C; IR (KBr) 2110, 1600, 1500, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.26 (m, 10 H), 3.24 (t, J = 7.5 Hz, 2 H), 2.32–1.71 (m, 7 H), including 1.95 (t, J = 2.6 Hz, 1 H); LRMS m/z (relative intensity) 313 (M^+, 12), 178 (100). Anal. Calcd for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.36; H, 5.96; N, 13.32.

6-Phenyl-2,3-cyclopentenopyridine (5i) and 5-Phenyl-2,3-cyclopentenopyridine (5h). To a stirred solution of 5-hexynoic acid hydrazide (**11**) (0.75 g, 6.0 mmol) and phenylglyoxal (0.90 g, 6.0 mmol, 1.0 equiv) in glacial acetic acid (15 mL) was added ammonium acetate (7.5 g, 97 mmol, 16 equiv), and the resulting mixture was heated at reflux (ca. 118 °C) for 5 h. The dark orange-red solution was then poured into water (50 mL), and the mixture was extracted with methylene chloride (2 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed over a column of silica gel (ca. 30 g). Elution with a 25–33% ether/petroleum ether gradient gave 6-phenyl-2,3-cyclopentenopyridine (**5i**) (R_f = 0.40, methylene chloride) (0.20 g, 1.0 mmol, 17%) as a yellow solid: mp 82.0–83.0 °C (lit.[13] mp 79 °C or 80 °C); IR (KBr) 1580, 1565, 1440, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00–7.86 (m, 2 H), 7.60–7.25 (m, 5 H), 3.09 (t, J = 7.6 Hz, 2 H), 2.96 (t, J = 7.6 Hz, 2 H), 2.32–1.93 (m, 2 H); LRMS m/z (relative intensity) 195 (M^+, 100), 115 (14), 91 (14).

(13) Gill, N. S.; James, B. K.; Lions, F.; Potts, K. T. *J. Am. Chem. Soc.* **1952**, *74*, 4923.

Evaporation of a second fraction (R_f = 0.15, methylene chloride) gave 5-phenyl-2,3-cyclopentenopyridine (**5h**) (0.21 g, 1.1 mmol, 18%) as an orange solid: mp 92.0–93.0 °C; IR (KBr) 1620, 1595, 1460, 1445, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (br m, 1 H), 7.67–7.32 (m, 6 H), 3.14–2.90 (m, 4 H), 2.33–1.99 (m, 2 H); LRMS m/z (relative intensity) 195 (M^+, 100), 115 (4), 91 (3). Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 85.92; H, 6.91; N, 7.26.

5,6-Diphenyl-2,3-cyclopentenopyridine (5g). To a solution of **11** (0.85 g, 6.8 mmol) and benzil (1.42 g, 6.8 mmol) in glacial acetic acid (15 mL) was added ammonium acetate (8.5 g, 110 mmol, 16 equiv), and the resulting mixture was heated at reflux for 4 h. Cooling and scratching induced the separation of a pale orange precipitate. Water (50 mL) was added, and the separated solid was removed by suction filtration and washed well with water. Drying in vacuo gave a tan solid (1.50 g), which was recrystallized from isopropyl ether to yield **5g** (1.24 g, 4.6 mmol, 68%) as golden needles: mp 161.0–163.0 °C; IR (KBr) 1595, 1545, 1490, 1445, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 7.33–7.14 (m, 10 H), 3.21–2.94 (m, 4 H), 2.27–2.11 (m, 2 H); LRMS m/z (relative intensity) 271 (M^+, 55), 270 (100), 165 (6), 135 (7). Anal. Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.24; H, 6.53; N, 5.15.

2,3-Diphenyl-5,6,7,8-tetrahydroquinoline (10g). A solution of 5,6-diphenyl-3-(5-hexynyl)-1,2,4-triazine (**9g**) (0.75 g, 2.4 mmol) in bromobenzene (3 mL) was heated at reflux (156 °C) with exclusion of moisture for 20 h. The reaction mixture was chromatographed over a column of silica gel (20 g); elution with 15% ether/petroleum ether gave **10g** (0.62 g, 2.2 mmol, 91%) as a white solid: mp 109.0–111.0 °C; IR (KBr) 1600, 1590, 1575, 1540, 1490, 1445, 1415, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.28–7.15 (m, 10 H), 3.10–2.79 (m, 4 H), 2.00–1.84 (m, 4 H); LRMS m/z (relative intensity) 285 (M^+, 100), 256 (7), 123 (7). Anal. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.32; H, 6.81; N, 4.71.

Registry No. **1**, 130905-53-2; **2f**, 130905-54-3; **3a**, 106814-27-1; **3c**, 42809-56-3; **3d**, 106814-28-2; **3e**, 106814-29-3; **4a**, 83413-00-7; **4b**, 105783-78-6; **4f**, 106814-26-0; **5a**, 106814-31-7; **5b**, 106814-32-8; **5d**, 106814-34-0; **5e**, 106814-35-1; **5f**, 106814-33-9; **5g**, 126005-06-9; **5h**, 101161-85-7; **5i**, 56396-63-5; **6**, 74090-14-5; **8a**, 130905-55-4; **8d**, 91012-16-7; **8e**, 106814-30-6; **9d**, 106814-37-3; **9e**, 106814-36-2; **9g**, 130905-56-5; **10d**, 106814-39-5; **10e**, 106814-38-4; **10g**, 82132-58-9; **11**, 4230-19-7; **12**, 130905-57-6; $HC{:}C(CH{=}2)_3COOH$, 53293-00-8; $HC{:}C(CH_2)_3COOMe$, 77758-51-1; dimethyl malonate, 108-59-8; ethyl acetoacetate, 141-97-9; ethyl cyanoacetate, 105-56-6; malonitrile, 109-77-3; 4-iodo-1-butyne, 43001-25-8; 4-iodo-1-butene, 7766-51-0; 5-iodo-1-pentyne, 2468-55-5; 5-hexyn-1-ol, 928-90-5; 5-hexynyl methanesulfonate, 79496-61-0; 6-cyano-1-hexyne, 15295-69-9; 6-heptynoic acid, 30964-00-2; methyl 6-heptynoate, 56909-02-5; benzil, 134-81-6; phenylglyoxal, 1074-12-0.

Pteridines. 54. A Novel Synthetic Approach to C-6 Carbon Substituted Pterins via Intermolecular 1,3-Dipolar Cycloaddition Reactions[1]

Edward C. Taylor* and Partha S. Ray[†]

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received June 14, 1990

A number of 5-[(hydroxyimino)methyl]pyrazines and 6-[(hydroxyimino)methyl]pterins were converted to their respective nitrile oxides in the presence of dipolarophiles to give side-chain isoxazoles and isoxazolines as potential intermediates for the construction of multifunctional C-6 pterin substituents.

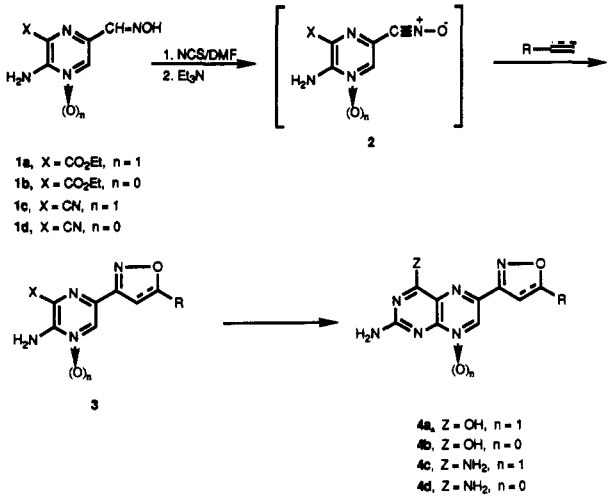
In earlier papers in this series we have described a variety of novel and unequivocal synthetic routes to 6-carbon-substituted pteridine derivatives, since most biologically significant pterins and chemotherapeutically useful pteridine derivatives are of this type (e.g., biopterin, folic acid, methotrexate, 10-deazafolic acid, the molybde-

[†] Present address: Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543.

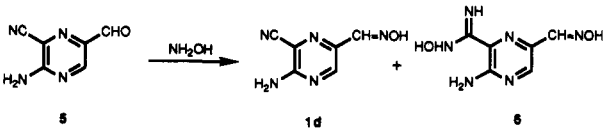
(1) (a) We are indebted to the Burroughs Wellcome Company, Research Triangle Park, NC, for its generous support of this work. (b) For the previous paper in this series: Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1988**, *53*, 35.

0022-3263/91/1956-1812$02.50/0

Scheme I



Scheme II



num cofactor, etc.).[2-7] In this paper we describe an alternate synthetic strategy, using 1,3-dipolar cycloaddition chemistry, which should permit the preparation of a variety of pterins carrying multifunctional carbon side chains at position 6.

The 1,3-dipolar cycloaddition between a nitrile oxide and an alkene or an alkyne provides a convenient route to isoxazolines and isoxazoles, respectively.[8] These heterocycles are themselves versatile intermediates in synthesis, since the labile N–O bond is readily cleaved to provide a variety of bifunctional open-chain derivatives.[8] Thus, we envisioned that reaction of a pyrazine nitrile oxide such as **2** (generated in situ from the corresponding 5-[(hydroxyimino)methyl]pyrazine **1b** or **1d** or the *N*-oxides **1a** or **1c**) (see Scheme I) with appropriate dipolarophiles could, in principle, provide the cycloadducts **3**. Annulation of the pyrimidine by reaction with guanidine should then give the pteridine derivatives **4**. Further manipulation of these derivatives including, inter alia, cleavage of the N–O heterocyclic bond should then lead to multifunctional carbon side chains at the 6-position of the pteridine or pterin.

Table I. Reaction of Pyrazine Nitrile Oxides 2a–c with 2,3-Dihydrofuran

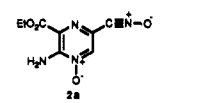
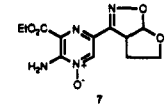
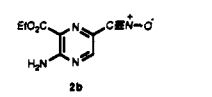
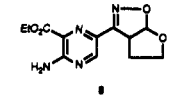
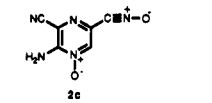
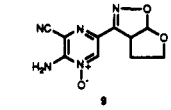
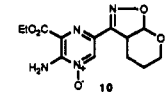
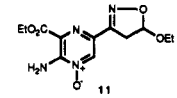
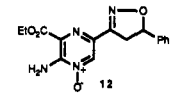
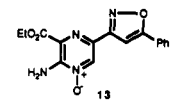
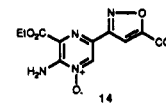
entry	nitrile oxide	cycloadduct	yield, %
1			60
2			55
3			10

Table II. Reaction of the Pyrazine Nitrile Oxide 2a with Dipolarophiles

entry	dipolarophile	cycloadduct	yield, %
1		**7**	60
2			55
3	H_2C=CHOEt		58
4	H_2C=CHPh		58
5	HC≡CPh		55
6	HC≡CCO_2CH_3		30

We have previously reported the synthesis of 2-amino-3-carbethoxy-5-[(hydroxyimino)methyl]pyrazine 1-oxide (**1a**)[9] and 2-amino-3-cyano-5-[(hydroxyimino)methyl]-pyrazine 1-oxide (**1c**),[3b] and we have now prepared the deoxygenated 5-[(hydroxyimino)methyl]pyrazine **1b** in 76% yield by treatment of **1a** with sodium dithionite in aqueous THF at reflux for 0.5 h. A similar deoxygenation of **1c** to **1d**, however, was unsuccessful. Since it is known that treatment of **1c** with phosphorus trichloride in THF results in dehydration of the (hydroxyimino)methyl group to a nitrile as well as deoxygenation of the *N*-oxide, giving 2-amino-3,5-dicyanopyrazine,[10] we sought an alternative approach to **1d**. 2-Amino-3-cyano-5-formylpyrazine (**5**) can be prepared from 2-amino-3-cyano-5-(chloromethyl)-pyrazine by the Kröhnke oxidation.[11] We hoped that reaction of the 5-formylpyrazine **5** with hydroxylamine would provide the desired oxime **1d**. In the event, however, reaction of **5** with 1 equiv of hydroxylamine, even at −5 °C, gave an inseparable mixture of the desired oxime **1d** together with the hydroxy amidine **6** (Scheme II), and we

(2) Taylor, E. C. In *Chemistry and Biology of Pteridines*; Iwai, K., Akino, M., Goto, M., Ywamani, Y., Eds.; International Academic Printing: Tokyo, 1970; p 79.

(3) (a) Taylor, E. C.; Perlman, K. L.; Sword, I. P.; Sequin-Frey, M.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6407. (b) Taylor, E. C.; Perlman, K. L.; Kim, Y.-H.; Sword, I. P.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6413.

(4) (a) Taylor, E. C. In *Chemistry and Biology of Pteridines*; Pfleiderer, W., Ed.; Walter de Gruyter: Berlin, 1975; p 543. (b) Taylor, E. C. In *Chemistry and Biology of Pteridines: Pteridines and Folic Acid Derivatives*; Blair, J. A., Ed., Walter de Gruyter: Berlin, 1983; p 23.

(5) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1987**, *52*, 3997.

(6) Taylor, E. C.; Ray, P. S. *Synth. Commun.* **1987**, *17*, 1865.

(7) Taylor, E. C.; Ray, P. S.; Darwish, I. S.; Johnson, J. L.; Rajagopalan, K. V. *J. Am. Chem. Soc.* **1989**, *111*, 7664.

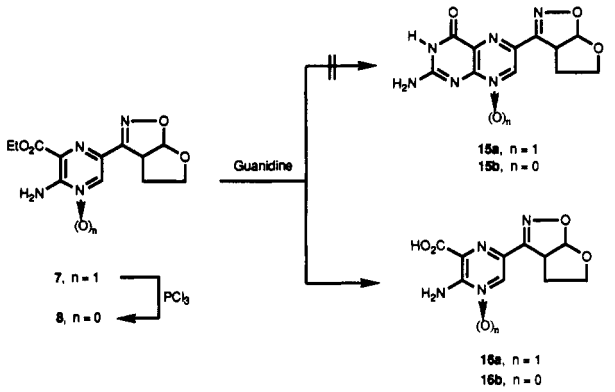
(8) (a) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 291. (b) Lang, S. A.; Lin, Y. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; 1984; Vol. 6, p 1. (c) Kozikowski, A. P., ref 8b, Vol. 1, p 453. (d) Grundmann, C.; Grunanger, P. *The Nitrile Oxides, Versatile Tools of Theoretical and Preparative Chemistry*: Springer-Verlag: Berlin, 1971. (e) Jager, V.; Grund, H.; Buss, V.; Schwab, W.; Muller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039. (f) Curran, D. P. In *Advances in Cycloaddition*: JAI Press: 1988; p 129. (g) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis.* VCH Publishers: 1988. (h) Kashima, C. *Heterocycles* **1979**, *12*, 1343.

(9) Taylor, E. C.; Lenard, K. *Justus Liebigs Ann. Chem.* **1969**, *726*, 100.

(10) Taylor, E. C.; Shepard, T. Unpublished results.

(11) Taylor, E. C.; Henrie, R. N., II; Portnoy, R. C. *J. Org. Chem.* **1978**, *43*, 736.

Scheme III



were unable to find conditions that gave the [(hydroxyimino)methyl]pyrazine **1d** as the sole product. Nevertheless, with the three 5-[(hydroxyimino)methyl]pyrazines **1a–c** in hand, we explored their conversion to the nitrile oxides **2a–c** respectively, and 1,3-dipolar cycloaddition reactions of the latter with 2,3-dihydrofuran as the dipolarophile.

Thus, reaction of the 5-[(hydroxyimino)methyl]pyrazines **1a–c** with *N*-chlorosuccinimide in DMF at 60 °C followed by cooling to 2 °C, sequential addition of an excess of 2,3-dihydrofuran (typically 5 equiv), and then slow, dropwise addition of triethylamine gave the corresponding cycloadducts **7**, **8**, and **9**, respectively.[12] These results are summarized in Table I. It is of interest to note that there is no significant difference in the isolated yields of **7** and **8** obtained from the nitrile oxide **2a** and its deoxygenated analogue **2b**, respectively, indicating that the pyrazine *N*-oxide functionality does not appear to have a detrimental effect on the cycloaddition reaction. More significantly, the reaction between the nitrile oxide **2c** and 2,3-dihydrofuran gave the cycloadduct **9** in only 10% yield (Table I, entry 3), together with formation of a complex mixture of side products that were not characterized. As a consequence, the reactions between the in situ generated nitrile oxide **2a** and a variety of additional dipolarophiles were examined. Our results are summarized in Table II. Electron-rich dipolarophiles such as enol ethers, styrene, and phenylacetylene all react with **2a** to give fair to good yields of the corresponding cycloadducts (Table II, entries 1–5). Reaction with methyl propiolate, however, was less successful and gave the cycloadduct **14** in only 30% yield. In none of these cycloaddition reactions were other chacterizable products isolated.

With these *o*-aminocarbethoxypyrazine cycloadducts in hand, we attempted to construct the pterin nucleus by the classical ring annulation reaction with guanidine. None of these attempts, however, was successful. For example, reaction of **7** with guanidine in a variety of solvents under anhydrous conditions gave the amino acid **16a** rather than the desired pterin **15**. Reaction temperatures above 65 °C brought about destruction of the molecule, and no characterizable product was isolated. A similar result was obtained upon reaction of guanidine with the deoxygenated analogue **8** (alternatively prepared in 90% yield from deoxygenation of **7** with phosphorus trichloride (Scheme III)). Analogous disappointing annulation results were obtained upon reaction of guanidine or 1,1-dimethylguanidine with the other pyrazine cycloadducts. Thus, an alternative approach to pterin cycloadducts (e.g., **15**) was sought.

(12) As expected, this cycloaddition reaction yielded cis-fused products, as indicated by the NMR spectra of compounds **7**, **8**, **9**, **10**, and **25a** (doublets between δ 6–6.4 with J = 6.0–6.2 Hz; see Experimental Section).

Scheme IV

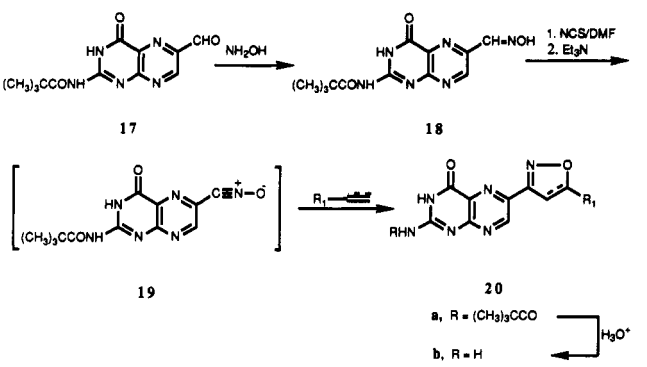
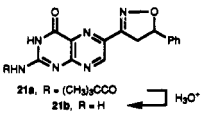
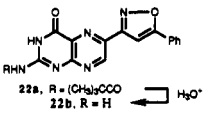
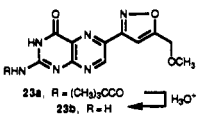
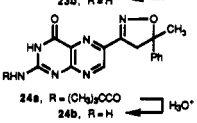
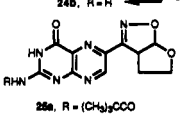
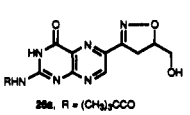


Table III. Reaction of 2-Pivaloylpterin Nitrile Oxide 19 with Dipolarophiles

entry	dipolarophile	cycloadduct	% yield, R = (CH3)3CCO	% yield, R = H
1	$H_2C{=}CHPh$	 21a, R = (CH3)3CCO; 21b, R = H	65	73
2	$HC{\equiv}CPh$	 22a, R = (CH3)3CCO; 22b, R = H	62	78
3	$H_2C{=}CHCH_2OCH_3$	 23a, R = (CH3)3CCO; 23b, R = H	62	80
4	$PhC(=CH_2)CH_3$	 24a, R = (CH3)3CCO; 24b, R = H	57	72
5		 25a, R = (CH3)3CCO	58	
6	$H_2C{=}CHCH_2OH$	 26a, R = (CH3)3CCO	46	

We have recently reported a highly efficient procedure for the synthesis of 2-pivaloyl-6-formylpterin (**17**) involving a palladium-catalyzed coupling of 2-pivaloyl-6-chloropterin with styrene, followed by ozonolysis of the resulting 6-stryryl derivative.[6] Reaction of **17** with hydroxylamine provided an easy access to the oxime **18** in high yield (Scheme IV). We have found that reaction of the oxime **18** with *N*-chlorosuccinimide in DMF followed by treatment with triethylamine (to give the intermediate nitrile oxide **19**) in the presence of an excess of a dipolarophile gave the corresponding cycloadducts **21–26a** in good yields (Table III).[12] Facile acid hydrolysis of the 2-pivaloyl grouping was demonstrated with **21–24a** to give **21–24b**, respectively (and in view of the ease of this deprotection, no attempt was made to deprotect **25a** or **26a**). Reductive N–O bond cleavage of the isoxazoline or isoxazole ring in these pterin cycloadducts should, in principle, provide derivatives with highly functionalized carbon chains at the 6-position. Such chemistry is currently under investigation.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. The ^1H NMR

data were recorded on a Bruker WP250 (250 MHz) or a General Electric QE300 (300 MHz) instrument and chemical shifts are reported in ppm relative to residual nondeuterated solvent. IR spectra were recorded on a Perkin-Elmer 1320 instrument and are reported in cm^{-1}. Mass spectral data were obtained by Dr. Dorothy Little on a Kratos MS50TC spectrometer. Elemental analyses were performed by the Burroughs Wellcome Company, Research Triangle Park, NC. Column chromatography was performed on Merck silica gel 60 (240–400 mesh). TLC analyses were routinely carried out on Bakerflex IB2-F plates utilizing UV visualization.

2-Amino-3-carbethoxy-5-[(hydroxyimino)methyl]pyrazine (1b). A mixture of 2-amino-3-carbethoxy-5-[(hydroxyimino)-methyl]pyrazine 1-oxide[9] (2.26 g, 0.01 mol), sodium dithionite (3.48 g, 0.02 mol), THF (120 mL), and water (60 mL) was heated under gentle reflux for 0.5 h. The THF was removed under reduced pressure and the resulting solid was suction-filtered, washed well with water, and air-dried. Recrystallization from absolute ethanol gave 1.60 g (76%) of a cream-colored microcrystalline powder, mp 218–219 °C: NMR (Me_2SO-d_6) δ 1.3 (t, 3 H, J = 7 Hz), 4.3 (q, 2 H, J = 7 Hz), 7.5 (br, 2 H), 8.0 (s, 1 H), 8.65 (s, 1 H), 11.4 (s, 1 H); IR (KBr) 3440, 3300, 1700, 1610 cm^{-1}. Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.76; N, 26.67. Found: C, 45.65; H, 4.83; N, 26.64.

General Procedure for the in Situ Generation of the Pyrazine Nitrile Oxides 2a–c and Subsequent Trapping with Dipolarophiles. To a solution or suspension of 2-amino-3-carbethoxy-5-[(hydroxyimino)methyl]pyrazine 1-oxide[9] *or* 2-amino-3-cyano-5-[(hydroxyimino)methyl]pyrazine 1-oxide[3b] *or* 2-amino-3-carbethoxy-5-[(hydroxyimino)methyl]pyrazine (5 mmol) in anhydrous DMF (15 mL) was added *N*-chlorosuccinimide (5 mmol). The mixture was stirred at 60 °C under nitrogen for 3 h. The mixture was cooled to 2 °C and the dipolarophile (25 mmol) was added. A mixture of triethylamine (5 mmol) in DMF (5 mL) was added dropwise over a 20-min period. The reaction mixture was allowed to warm to room temperature and was stirred for a further 2–3 h, the solvent was removed in vacuo, and the residue was worked up as described below.

Cycloadduct 7. The residue was triturated with ethyl acetate and the resulting solid was collected by vacuum filtration. Recrystallization from absolute ethanol gave 875 mg (60%) of yellow needles, mp 198–200 °C: NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz), 2.22–2.38 (m, 1 H), 2.45–2.53 (m, 1 H), 3.5–3.65 (m, 1 H), 4.1 (m, 1 H), 4.25 (m, 1 H), 4.48 (q, 2 H, J = 7.1 Hz), 6.32 (d, 1 H, J = 6.2 Hz), 7.6 (br, 2 H), 8.9 (s, 1 H); IR (KBr) 3440, 3320, 1690, 1610 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.76; N, 19.05. Found: C, 49.10; H, 5.01; N, 18.81.

Cycloadduct 8. The residue was triturated with ethyl acetate and the resulting solid was collected by vacuum filtration. Recrystallization from absolute ethanol gave 760 mg (55%) of yellow needles, mp 148–149 °C: NMR ($CDCl_3$) δ 1.45 (t, 3 H, J = 7.1 Hz), 2.25–2.40 (m, 1 H), 2.48–2.58 (m, 1 H), 3.56–3.68 (m, 1 H), 4.05–4.12 (m, 1 H), 4.28–4.35 (m, 1 H), 4.45 (q, 2 H, J = 7.1 Hz), 6.3 (d, 1 H, J = 6.2 Hz), 8.9 (s, 1 H); IR (KBr) 3440, 3300, 1700, 1615 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.04; N, 20.14. Found: C, 51.56; H, 5.11; N, 19.89.

Cycloadduct 9. The residue was triturated with ethyl acetate, the mixture was evaporated under reduced pressure, and the remaining oil was subjected to radial chromatography on silica gel, using a mixture of 1–5% methanol in chloroform as eluent. The fractions containing the product were combined and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to give 125 mg (10%) of yellow needles, mp 244–246 °C: NMR (Me_2SO-d_6) δ 2.0–2.35 (m, 2 H), 3.2–3.45 (m, 1 H), 3.85–4.28 (m, 1 H), 4.28–4.45 (m, 1 H), 6.25 (d, 1 H, J = 6.2 Hz), 8.3 (br, 2 H), 8.75 (s, 1 H); IR (KBr) 3400, 3290, 2240, 1630 cm^{-1}. Anal. Calcd for $C_{10}H_9N_5O_3$: C, 48.58; H, 3.64; N, 28.34. Found: C, 48.45; H, 3.70; N, 28.03.

Cycloadduct 10. The residue was triturated with ethyl acetate and the resulting solid was collected by vacuum filtration. Recrystallization from absolute ethanol gave 850 mg (55%) of yellow needles, mp 227–228 °C: NMR ($CDCl_3$) δ 1.45 (t with overlapping m, 4 H, J = 7.2 Hz), 1.75 (m, 1 H), 2.1 (m, 1 H), 2.45 (m, 1 H), 3.7 (m, 1 H), 3.8 (m, 2 H), 4.5 (q, 2 H, J = 7.2 Hz), 6.02 (d, 1 H, J = 6.2 Hz), 7.6 (br, 2 H), 8.9 (s, 1 H); IR (KBr) 3440, 3320, 1690, 1610 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.65; H, 5.15; N, 18.18. Found: C, 50.53; H, 5.25; N, 18.12.

Cycloadduct 11. The residue was triturated with ethanol and the resulting solid was collected by vacuum filtration. Recrystallization from absolute ethanol gave 858 mg (58%) of yellow needles, mp 183–184 °C: NMR ($CDCl_3$) δ 1.15–1.65 (2 overlapping t, 6 H, J = 7.1 Hz), 3.45 (d, 2 H, J = 5.6 Hz), 3.8 (q, 2 H, J = 7.1 Hz), 4.45 (q, 2 H, J = 7.1 Hz), 5.7 (t, 1 H, J = 5.6 Hz), 7.6 (br, 2 H), 8.9 (s, 1 H); IR (KBr) 3440, 3320, 1690, 1610 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.40; N, 18.91. Found: C, 48.45; H, 5.48; N, 18.57.

Cycloadduct 12. The residue was triturated with water and the resulting solid was collected by vacuum filtration. Recrystallization from absolute ethanol gave 950 mg (58%) of a yellow microcrystalline powder, mp 191–192 °C: NMR ($CDCl_3$) δ 1.42 (t, 3 H, J = 7.1 Hz), 3.5 (m, 1 H), 3.9 (m, 1 H), 4.45 (q, 2 H, J = 7.1 Hz), 5.8 (m, 1 H), 7.3–7.46 (m, 5 H), 7.46–7.7 (br, 2 H), 8.96 (s, 1 H); IR (KBr) 3430, 3300, 1695, 1610 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_4O_4 \cdot 0.3H_2O$: C, 57.58; H, 4.97; N, 16.80. Found: C, 57.32; H, 4.90; N, 17.10.

Cycloadduct 13. The residue was triturated with water and the resulting solid was collected by filtration at the pump and washed with cold ethanol. Recrystallization from ethyl acetate gave 896 mg (55%) of yellow needles, mp 205–206 °C: NMR ($CDCl_3$) δ 1.52 (t, 3 H, J = 7.1 Hz), 4.54 (q, 2 H, J = 7.1 Hz), 7.16 (s, 1 H), 7.45–7.67 (br and m, 5 H), 7.82–7.9 (m, 2 H), 9.0 (s, 1 H); IR (KBr) 3430, 3300, 1695, 1610 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_4O_4 \cdot 0.15H_2O$: C, 58.41; H, 4.38; N, 17.03. Found: C, 58.34; H, 4.36; N, 17.29.

Cycloadduct 14. The residue was triturated with ethyl acetate and the resulting mixture was evaporated under reduced pressure. The remaining oil was subjected to radial chromatography on silica plates, eluting with a mixture of 40% ethyl acetate in hexanes. The fractions containing the product (R_f = 0.5 in 5% methanol in methylene chloride on silica gel plates) were combined, the solvent was removed in vacuo, and the residual solid was recrystallized from methanol to give 460 mg (30%) of yellow needles, mp 201–202 °C: NMR ($CDCl_3$) δ 1.48 (t, 3 H, J = 7.1 Hz), 4.02 (s, 3 H), 4.05 (q, 2 H, J = 7.1 Hz), 7.58–7.85 (br and s, 3 H), 9.0 (s, 1 H); IR (KBr) 3430, 3310, 1735, 1695, 1615 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_4O_6$: C, 46.75; H, 3.89; N, 18.18. Found: C, 46.70; H, 3.94; N, 18.14.

Preparation of Cycloadduct 8 from Deoxygenation of 7. A suspension of the pyrazine *N*-oxide **7** (2.94 g, 0.01 mol) in dry THF (100 mL) was cooled to 0 °C. Phosphorus trichloride (3.5 mL, 0.04 mole) was added dropwise to the stirred mixture, which was allowed to warm to room temperature. Stirring was continued for a further hour, and the solvent and excess phosphorus trichloride were removed by evaporation under reduced pressure. The oily residue was added carefully to ice water, and the resulting solid was collected by vacuum filtration, washed well with water, and air-dried. Recrystallization from ethanol gave 2.5 g (90%) of yellow needles, which were identical in all respects with the product obtained from cycloaddition of the nitrile oxide **2b** with 2,3-dihydrofuran.

6-[(Hydroxyimino)methyl]-2-pivaloylpterin (18). A mixture of 6-formyl-2-pivaloylpterin[6] (3.8 g, 13.8 mmol), hydroxylamine hydrochloride (0.98 g, 14.1 mmol), pyridine (10 mL), and ethanol (100 mL) was stirred at room temperature for 18 h. The solvent was removed by evaporation under reduced pressure and the residue was suspended in water (200 mL) and stirred at room temperature for 2 h. The suspended solid was collected by vacuum filtration and dried in vacuo at 80 °C to give 3.6 g (90%) of a colorless solid, mp 210–215 °C dec: NMR ($CDCl_3$) δ 1.24 (s, 9 H), 8.21 (s, 1 H), 9.21 (s, 1 H), 11.58 (br, 1 H), 12.16 (s, 1 H), 12.50 (br, 1 H); IR (KBr) 3020–3680 (br), 1720 (shoulder), 1685, 1620 cm^{-1}; HRMS calcd for $C_{12}H_{14}N_6O_3$ m/z 290.1127, found m/z 290.1122. Anal. Calcd for $C_{12}H_{14}N_6O_3$: C, 49.66; H, 4.86; N, 28.95. Found: C, 49.55; H, 4.90; N, 28.88.

General Procedure for the Preparation of 2-Pivaloylpterin Cycloadducts 21–26a. *N*-Chlorosuccinimide (125 mg, 0.936 mmol) was added to a solution of 6-[(hydroxyimino)methyl]-2-pivaloylpterin (250 mg, 0.861 mmol) in anhydrous DMF (5 mL) heated at 60 °C under a dry nitrogen atmosphere. A precipitate formed after 5–10 min. The mixture was stirred at 60 °C for an additional 0.5 h and cooled to 2 °C, and the dipolarophile (4.305 mmol) was added to the mixture with a syringe. A mixture of

triethylamine (0.9 mmol) in DMF (1 mL) was added to the reaction mixture over a 0.5-h period by means of a syringe pump. The reaction mixture was stirred at 2 °C for a further 0.5 h and then at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate or methylene chloride (30 mL) and water (10 mL). The organic layer was separated, dried (anhydrous $MgSO_4$), and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue worked up as described below.

2-Pivaloylpterin Cycloadduct 21a. The residue was chromatographed on silica gel, eluting with a mixture of 1% methanol in chloroform. The fractions containing the pure product were combined and the solvent was removed in vacuo to give 220 mg (65%) of a colorless solid, mp 222-223 °C: NMR ($CDCl_3$) δ 1.37 (s, 9 H), 3.67 (m, 1 H), 4.03 (m, 1 H), 5.88 (m, 1 H), 7.39 (m, 5 H), 8.38 (br, 1 H), 9.59 (s, 1 H), 12.48 (br, 1 H); IR (KBr) 3300-3680 (br), 3020-3300 (br), 1725, 1685, 1620 cm^{-1}; $C_{20}H_{20}N_6O_3$ m/z 392.1596, found m/z 392.1589. Anal. Calcd for $C_{20}H_{20}N_6O_3$: C, 61.22; H, 5.14; N, 21.42. Found: C, 61.15; H, 5.14; N, 21.37.

2-Pivaloylpterin Cycloadduct 22a. The residue was recrystallized from ethanol to give 208 mg (62%) of a colorless microcrystalline solid, mp 278-280 °C: NMR ($CDCl_3$) δ 1.38 (s, 9 H), 7.44 (s, 1 H), 7.53 (m, 3 H), 7.89 (m, 2 H), 8.46 (br, 1 H), 9.67 (s, 1 H), 12.50 (br, 1 H); IR (KBr) 3340-3680 (br), 3020-3320 (br), 1720, 1685, 1620 cm^{-1}; HRMS calcd for $C_{20}H_{18}N_6O_3$ m/z 390.1440, found m/z 390.1445. Anal. Calcd for $C_{20}H_{18}N_6O_3 \cdot 0.75H_2O$: C, 59.42; H, 4.83; N, 20.80. Found: C, 59.52; H, 4.72; N, 20.83.

2-Pivaloylpterin Cycloadduct 23a. The residue was chromatographed on silica gel, using ethyl acetate as eluent, the fractions containing the product were combined (R_f = 0.4 in ethyl acetate on silica gel plates), and the solvent was removed under reduced pressure. Recrystallization of the residue from ethanol gave 190 mg (62%) of a cream-colored microcrystalline solid, mp 232-233 °C: NMR ($CDCl_3$) δ 1.38 (s, 9 H), 3.48 (s, 3 H), 4.65 (s, 2 H), 7.15 (s, 1 H), 8.80 (br, 1 H), 9.61 (s, 1 H), 12.50 (br, 1 H); IR (KBr) 3360-3620 (br), 3020-3360 (br), 1725, 1685, 1620 cm^{-1}; HRMS calcd for $C_{16}H_{18}N_6O_4$ m/z 358.1389, found m/z 358.1379. Anal. Calcd for $C_{16}H_{18}N_6O_4$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.66; H, 5.08; N, 23.43.

2-Pivaloylpterin Cycloadduct 24a. The residue was chromatographed on silica gel, eluting with ethyl acetate. The fractions containing the product were combined (R_f = 0.5 in ethyl acetate using silica gel plates) and the solvent was removed under reduced pressure. The residue was triturated with diethyl ether and the solid was collected by vacuum filtration to give 200 mg (57%) of colorless microcrystals, mp >200 °C (gradual dec): NMR ($CDCl_3$) δ 1.36 (s, 9 H), 1.83 (s, 3 H), 3.78 (m, 2 H), 7.27-7.49 (m, 5 H), 8.65 (br, 1 H), 9.54 (s, 1 H), 12.48 (br, 1 H); IR (KBr) 3340-3680 (br), 3020-3320 (br), 1725, 1685, 1620 cm^{-1}; HRMS calcd for $C_{21}H_{22}N_6O_3$ m/z 406.1753, found m/z 406.1743. Anal. Calcd for $C_{21}H_{22}N_6O_3$: C, 62.06; H, 5.46; N, 20.68. Found: C, 61.96; H, 5.42; N, 20.62.

2-Pivaloylpterin Cycloadduct 25a. The residue was chromatographed on silica gel, using a mixture of 2% methanol in chloroform as eluent. The fractions containing the pure product were combined and the solvent was removed under reduced pressure to give 180 mg (58%) of a colorless solid, mp 270-271 °C: NMR ($CDCl_3$) δ 1.38 (s, 9 H), 2.45 (m, 2 H), 3.62 (m, 1 H), 4.07 (m, 1 H), 4.42 (m, 1 H), 6.41 (d, 1 H, J = 6 Hz), 8.45 (br, 1 H), 9.53 (s, 1 H), 12.48 (br, 1 H); IR (KBr) 3300-3680 (br), 3020-3300 (br), 1725, 1685, 1620 cm^{-1}; HRMS calcd for $C_{16}H_{18}N_6O_4$ m/z 358.1389, found m/z 358.1373. Anal. Calcd for $C_{16}H_{18}N_6O_4 \cdot 0.25H_2O$: C, 52.97; H, 5.10; N, 23.17. Found: C, 52.99; H, 5.13; N, 23.15.

2-Pivaloylpterin Cycloadduct 26a. The residue was recrystallized from absolute ethanol to give 137 mg (46%) of a cream-colored microcrystalline solid, mp 233-234 °C: NMR ($CDCl_3$) δ 1.37 (s, 9 H), 3.61 (m, 2 H), 3.68 (m, 2 H), 3.88 (m, 1 H), 5.01 (m, 1 H), 8.40 (br, 1 H), 9.50 (s, 1 H), 12.50 (br, 1 H); IR (KBr) 3300-3680 (br), 3020-3300 (br), 1725, 1685, 1620 cm^{-1}; HRMS calcd for $C_{15}H_{18}N_6O_4$ m/z 346.1389, found m/z 346.1390. Anal. Calcd for $C_{15}H_{18}N_6O_4 \cdot 0.25H_2O$: C, 51.31; H, 5.27; N, 23.94. Found: C, 51.40; H, 5.29; N, 23.97.

General Procedure for the Preparation of the Pterin Cycloadducts 21-24b by Hydrolysis of the Corresponding 2-Pivaloylpterin Cycloadducts 21-24a. A mixture of the 2-pivaloylpterin cycloadduct (100 mg), dioxane (10 mL), and 1.0 N hydrochloric acid (0.2 mL) was heated at 70-80 °C until all the starting material had been consumed (1-2 h). The progress of the hydrolysis was monitored by TLC. The solvent was removed under reduced pressure and the residue was triturated with water. The solid was collected by vacuum filtration, washed well with water, and ethanol, and then with diethyl ether, and dried at 80 °C in vacuo.

Pterin cycloadduct 21b: 58 mg (73%) of a cream-colored microcrystalline powder was obtained, mp >300 °C: NMR (Me_2SO-d_6/2 drops of CF_3CO_2D) δ 3.43 (m, 1 H), 4.0 (m, 1 H), 5.85 (m, 1 H), 7.32-7.53 (m, 5 H), 9.27 (s, 1 H); HRMS calcd for $C_{15}H_{12}N_6O_2$ m/z 308.1021, found m/z 308.1046. Anal. Calcd for $C_{15}H_{12}N_6O_2 \cdot 1.375H_2O$: C, 54.04; H, 4.35; N, 25.22. Found: C, 54.08; H, 4.04; N, 25.19.

Pterin cycloadduct 22b: 68 mg (78%) of a cream-colored microcrystalline powder was obtained, mp >300 °C: NMR (Me_2SO-d_6/2 drops of CF_3CO_2D) δ 7.55 (m, 3 H), 7.61 (s, 1 H), 8.0 (m, 2 H), 9.29 (s, 1 H). Anal. Calcd for $C_{15}H_{10}N_6O_2 \cdot 1.375H_2O$: C, 54.37; H, 3.63; N, 25.37. Found: C, 54.25; H, 3.45; N, 23.25.

Pterin cycloadduct 23b: 61 mg (80%) of a cream-colored microcrystalline powder was obtained, mp >300 °C: NMR (Me_2SO-d_6/2 drops of CF_3CO_2D) δ 3.30 (s, 3 H), 4.58 (s, 2 H), 7.05 (s, 1 H), 9.31 (s, 1 H). Anal. Calcd for $C_{11}H_{10}N_6O_3 \cdot 0.25H_2O$: C, 47.36; H, 3.76; N, 30.14. Found: C, 47.48; H, 3.74; N, 29.90.

Pterin cycloadduct 24b: 57 mg (72%) of a cream-colored microcrystalline powder was obtained, mp >300 °C: NMR (Me_2SO-d_6/2 drops of CF_3CO_2D) δ 1.72 (s, 3 H), 3.6 (m, 2 H), 7.27-7.5 (m, 5 H), 9.19 (s, 1 H). Anal. Calcd for $C_{16}H_{14}N_6O_2 \cdot 2H_2O$: C, 53.63; H, 3.91; N, 23.46. Found: C, 53.93; H, 4.23; N, 23.55.

Acknowledgment. We are deeply indebted to Dr. Thomas Shepard, who first demonstrated the cycloaddition reaction between **2a** and 2,3-dihydrofuran to give the cycloadduct **7**.

Model Studies Directed toward the Molybdenum Cofactor: 2-Alkylidene- and 2-(Phenylimino)-1,3-dithioles from Acetylenes

Edward C. Taylor* and Reinhard Dötzer

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received July 23, 1990

The cycloaddition of activated alkynes, among them 6-alkynylpterins, with the tributylphosphine–carbon disulfide complex followed by a Wittig reaction of the resulting ylid with carbonyl compounds or nitrosobenzene affords novel 2-alkylidene- or 2-(phenylimino)-1,3-dithioles in moderate to very good yields. The pterin-substituted species are potential intermediates in the synthesis of the molybdenum cofactor.

The molybdenum cofactor (proposed structure **1** for the xanthine oxidase cofactor),[1] essential for the activity of several redox enzymes,[2] contains a molybdenum dithiolene ring which is, as well as the underlying enedithiol moiety,

0022-3263/91/1956-1816$02.50/0