Synthesis of Unsymmetrical Pyrazines by Reaction of an Oxadiazinone with Enamines[1]

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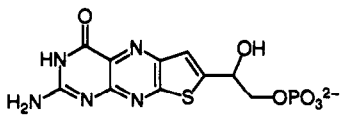
Heterocycle 1 (form B)[2] is an in vitro degradation product of the highly labile molybdenum cofactor,[3] present in all molybdenum-containing enzymes except nitrogenase. The structural assignment of form B rests on chemical, mass spectral, and NMR data comparison with known pterins but has not been confirmed unambiguously by total synthesis.[4] In this paper, we report the development of a convenient synthetic method for the construction of unsymmetrical pyrazines such as that found in form B.



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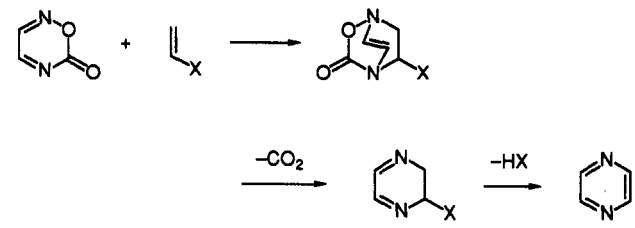
As pericyclic reactions often occur under mild conditions, we were attracted to the possibility of pyrazine formation by a hetero Diels–Alder reaction with a 1,4-diazabutadiene as the 4π electron component. Although a few such reactions are known,[5] none of them were suitable for our purpose. Instead, we decided to develop the process outlined in Scheme I. Here, an oxadiazinone adds regioselectively to an alkene activated by the group X. Loss of carbon dioxide regeneratesd a 1,4-diaza diene, which aromatizes by loss of HX. Overall, this chemistry has analogies in the Diels–Alder reactions of pyrones.[6]

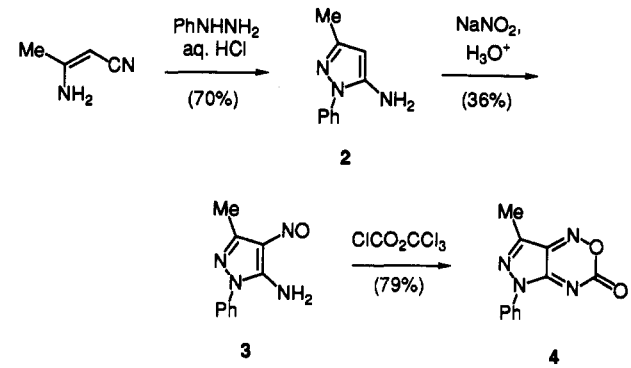
There is some precedent for Scheme I in the reaction of oxadiazinones with carbanions derived from 1,3-diactivated carbonyl compounds reported by Guarneri and co-workers.[7] On the basis of the isolation of an intermediate in one case, the authors proposed a polar, stepwise condensation. We resynthesized Guarneri's oxadiazinone 4 according to a minor modification of literature methods[8] (Scheme II) to see if similar condensations could be carried out with a ketone enolate or enamine.

It was gratifying to find that oxadiazinone 4 reacts with the pyrrolidine enamine of cyclohexanone to give the desired product (eq 1). At room temperature, the reaction

Scheme I



Scheme II



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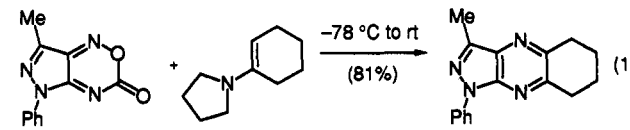
3 4

occurs instantaneously with visible gas evolution. As the byproduct pyrrolidone can itself react with the oxadiazinone, better yields are obtained by mixing the reactants at −78 °C (at which temperature no reaction occurs) followed by warming to room temperature. This reaction may proceed in a stepwise manner, but the absence of a detectable intermediate cannot rule out a concerted, asynchronous mechanism. The reaction rate appears fast by Diels–Alder standards, but the novelty of the diene prevents meaningful comparison with other systems.



(1)

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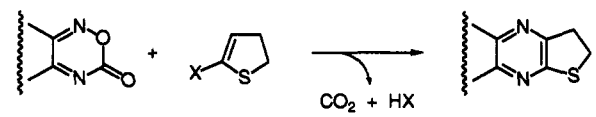
The reactivity of the enamine was crucial in this reaction. Less reactive substitutes such as enol ethers gave no reaction under a variety of thermal or Lewis acid-catalyzed conditions, and the use of a lithium or potassium ketone enolate led to decomposition products. We next tried unsymmetrical enamines to ensure that the reaction was regiospecific. The pyrrolidine enamines of propionaldehyde and 2-methylcyclohexanone both gave single products (Scheme III). The structures of the products could not be assigned unambiguously by NMR, but the structures indicated would be predicted by either a stepwise or concerted process. Further evidence for the suggested structures comes from the X-ray crystal structure of a related compound (vide infra).

The eventual application of this method for the synthesis of form B (1) would involve an analogous cycloaddition of a vinyl sulfide, where X could be an anionic or neutral leaving group:



Neither the enolate nor the thioenol ether of γ-thiobu-

(1) Taken in part from the Ph.D. thesis of A. Ganesan, University of California, Berkeley, 1992.
(2) Johnson, J. L.; Hainline, B. E.; Rajagopalan, K. V.; Arison, B. H. *J. Biol. Chem.* **1984**, *259*, 5414.
(3) For a recent review, see: Rajagopalan, K. V.; Johnson, J. L. *J. Biol. Chem.* **1992**, *267*, 10199.
(4) For recent syntheses of other degradation products of the cofactor, see: (a) Taylor, E. C.; Reiter, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 285. (b) Taylor, E. C.; Ray, P. S.; Darwish, I. S.; Johnson, J. L.; Rajagopalan, K. V. *J. Am. Chem.* **1989**, *111*, 7664.
(5) (a) Taylor, E. C.; French, L. G. *J. Org. Chem.* **1989**, *54*, 1245. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.
(6) For a recent review, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.
(7) Giori, P.; Veronese, A. C.; Poli, T.; Vicentini, C. B.; Manfrini, M.; Guarneri, M. *J. Heterocycl. Chem.* **1986**, *23*, 585. (b) Giori, P.; Poli, T.; Veronese, A. C.; Vicentini, C. B.; Manfrini, M.; Guarneri, M. *J. Heterocycl. Chem.* **1986**, *23*, 1661.
(8) See ref 7a as well as: (a) Mohr, E. *J. Prakt. Chem.* **1909**, *79*, 1. (b) Lahoti, R. J. *Ind. J. Chem. B* **1981**, *20*, 490. (c) Grundberg, I. I.; Klyuchko, G. V. *J. Gen. Chem. (USSR)* **1962**, *32*, 1876.

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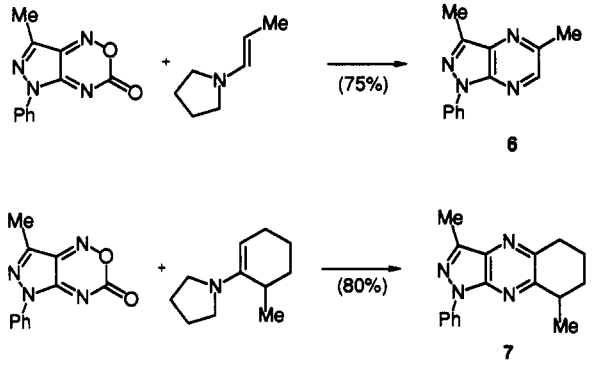
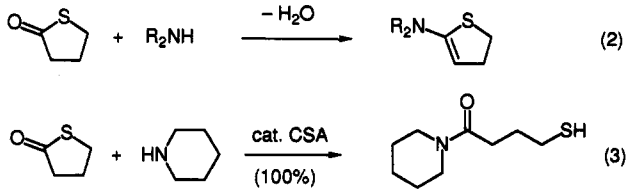
Scheme III

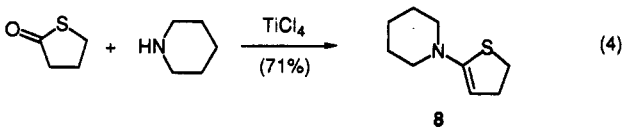


tyrolactone yielded the desired condensation product with oxadiazinone 4. On the basis of the earlier successes with enamines, the logical choice was the S,N-ketene acetal of γ-thiobutyrolactone which, in principle, could be obtained by the reaction in eq 2. In practice, however, no reaction



was observed between γ-thiobutyrolactone and a secondary amine with either phosphorus pentoxide or anhydrous magnesium sulfate as dehydrating agents, while the use of camphorsulfonic acid promoted amide formation (eq 3).

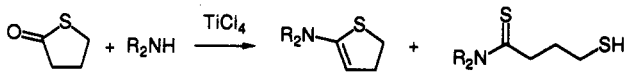
We next employed titanium tetrachloride, known to be a useful reagent in the synthesis of enamines from sterically hindered ketones,[9] a reaction with some similarity to eq 2. In this case, treatment of γ-thiobutyrolactone and piperidine with $TiCl_4$ resulted in a clean (by TLC analysis) and rapid reaction. Kugelrohr distillation of the reaction mixture enabled isolation of the air- and moisture-sensitive *S,N*-ketene acetal 8 in good yield (eq 4). Compound 8



appears to be the first example of a cyclic *S,N*-ketene acetal which is unstabilized by an electron-withdrawing group at the β-position.[10]

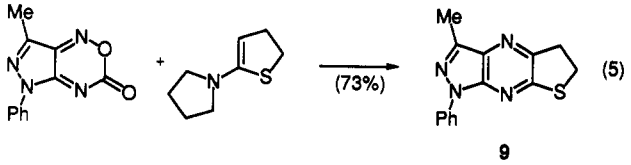
The choice of piperidine in the $TiCl_4$ reaction was purely arbitrary, but a fortuitous one. Three other secondary amines that were investigated (pyrrolidine, diethylamine, and morpholine) gave mixtures of the *S,N*-ketene acetal and the ring-opened amide. The ratios of the two products (Table I) do not correlate well with simple physical properties of these amines. Furthermore, the method does not seem to be applicable to preparation of *N,O*-ketene acetals: reaction of γ-butyrolactone and piperidine produced the ring-opened amide, presumably due to the stronger Ti–O bond strength relative to Ti–S.

Table I. Results of $TiCl_4$-Mediated Reaction between γ-Thiobutyrolactone and Secondary Amines



R_2NH	relative ratio of products	
piperidine	>95	<5
pyrrolidine	0	100
diethylamine	70	30
morpholine	25	75

With *S,N*-ketene acetal 8 in hand, its reaction with oxadiazinone 4 was attempted under identical reaction conditions to the anamine reactions. As hoped for, the pyrazine annulation product was isolated in good yield (eq 5). The structure of adduct 11 was determined by



X-ray crystallographic analysis, which confirmed that the reaction had occurred in a regiospecific manner.[11] This result suggests that form B can be synthesized in this manner, using an appropriate pyrimidinooxadiazinone. Results along these lines will be reported in due course.

Experimental Section

General. The following reaction solvents were distilled immediately prior to use: tetrahydrofuran (THF) from potassium; benzene and dichloromethane (CH_2Cl_2) from CaH_2. Piperidine, pyrrolidine, diethylamine, and morpholine were distilled from CaH_2 and refrigerated over 3-Å molecular sieves. All reactions were conducted at ambient room temperature (rt), unless otherwise stated. Reactions involving air- or moisture-sensitive components were conducted under a N_2 atmosphere in oven-dried glassware. Reactions and chromatography fractions were analyzed using Analtech μm silica gel GF plates and visualized by UV or staining by phosphomolybdic acid (PMA) or *p*-anisaldehyde. IR spectra were recorded as thin films, and NMR spectra were obtained in $CDCl_3$ solvent. NMR *J* values are given in hertz.

5-Amino-3-methyl-1-phenylpyrazole (2). A solution of β-aminocrotonitrile (3.48 g, 42.4 mmol in 40 mL of 1 N HCl) and phenylhydrazine (4 mL, 40.7 mmol, 0.95 molar equiv) was refluxed for 4 h. The resulting reddish liquid was cooled to rt and basified to alkaline pH with aqueous NaOH. The precipitate was collected and recrystallized from hot ethanol to provide 5.13 g (70%) of the pyrazole as a colorless solid, mp 111–112 °C (lit.[7b] mp 116 °C). ^1H NMR (250 MHz): δ 2.23 (s, 3), 3.78 (s, 2), 5.44 (s, 1), 7.31–7.734 (m, 1), 7.45 (t, 2, *J* = 7.1), 7.54 (d, 2, *J* = 8.6).

5-Amino-3-methyl-4-nitroso-1-phenylpyrazole (3). A solution of pyrazole 2 (1.59 g, 9.2 mmol in 10 mL of ethanol) was treated dropwise with a solution of $NaNO_2$ (0.71 g, 10.1 mmol in 2 mL of water), followed by addition of 4 mL of 2 N HCl. The reaction mixture, which turned from yellow to red, was stirred overnight. Upon neutralization with saturated aqueous $NaHCO_3$, an orange solid precipitated. The precipitate was washed with ether to yield 0.67 g (36%) of the nitroso compound as a reddish-orange solid, mp 190–193 °C dec (Lit.[7a] mp 190–197 °C dec). ^1H NMR (400 MHz): δ 2.82 (s, 3), 6.91 (s, 2), 7.43–7.56 (m, 5). ^{13}C

(9) (a) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (b) Nilsson, Å; Carlson, R. *Acta Chem. Scand. B* **1984**, *38*, 523 and references cited therein.

(10) For a recent review on *S,N*-ketene acetals, see: Schaumann, E. In *Methoden der Organischen Chemie (Houben-Weyl)*; Klamann, D., Ed.; Georg Thieme: Stuttgart, 1985; Vol. E 11, Part 1, pp 325–341.

(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

NMR (100-MHz): δ 11.57, 123.57, 128.87, 130.08, 134.55, 135.59, 151.08, 152.51.

5-Phenyl-7-methylpyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5*H*)-one (4). A solution of nitroso amine **3** (0.67 g, 3.3 mmol in 25 mL of THF) and trichloromethyl chloroformate (0.44 mL, 3.6 mmol, 1.1 molar equiv) was stirred overnight. Removal of the solvent followed by recrystallization from chloroform–petroleum ether gave 0.595 g (79%) of the oxadiazinone as a reddish-orange solid, mp 155–156 °C (lit.[5a] mp 161 °C). ^{1}H NMR (250 MHz): δ 2.61 (s, 3), 7.34–7.37 (m, 1), 7.49 (t, 2, *J* = 7.8), 8.05 (d, 2, *J* = 8.9).

General Procedure for Enamine–Oxadiazinone Reactions. A solution of the oxadiazinone **4** (ca. 0.02 m) in dry CH_2Cl_2 or THF was cooled to −78 °C under a nitrogen atmosphere. The enamine (1.5–2.0 molar equiv, dissolved in an appropriate solvent) was then added in a single portion and the reaction mixture warmed to rt over 1 h. The product was isolated by concentration of the reaction mixture followed by chromatography on silica, eluting with 5:1 hexanes–ether.

5,6,7,8-Tetrahydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (5). Reaction of oxadiazinone **4** (50 mg, 0.22 mmol in 1 mL of CH_2Cl_2) with 1-pyrrolidinocyclohexene (50 mg, 0.33 mmol, 1.5 molar equiv in 0.8 mL of CH_2Cl_2) in the foregoing manner afforded 47 mg (81%) of the product as a white solid, mp 69–70 °C. An experiment on a similar scale using the morpholine enamine of cyclohexanone resulted in a yield of 67%. IR: 1600, 1510 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.98 (t, 4, *J* = 3.4), 2.69 (s, 3), 3.10–3.12 (m, 4), 7.25 (t, 1, *J* = 7.4), 7.48 (t, 2, *J* = 8.0), 8.25 (d, 2, *J* = 7.7). ^{13}C NMR (125 MHz): δ 11.36, 22.64, 22.88, 32.57, 32.28, 119.75, 125.28, 128.98, 132.53, 139.36, 142.56, 142.63, 148.89, 152.31. Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.71; H, 6.10; N, 21.19. Found: C, 72.84; H, 6.36; N, 21.18.

3,5-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyrazine (6). Reaction of oxadiazinone **4** (61 mg, 0.27 mmol in 1 mL of THF) with 1-pyrrolidinopropene (65 mg, 0.54 mmol, 2 molar equiv in 0.5 mL of THF) in the foregoing manner provided 45 mg (75%) of the product as a pale yellow solid, mp 85–86 °C. IR: 1600, 1510 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.73 (s, 3), 2.74 (s, 3), 7.29 (t, 1, *J* = 7.4), 7.51 (t, 2, *J* = 8.0), 8.21 (d, 2, *J* = 7.7), 8.41 (s, 1). ^{13}C NMR (125 MHz): δ 11.30, 21.67, 120.14, 125.76, 128.27, 128.48, 128.54, 129.14, 142.83, 149.98, 149.25. Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.63; H, 5.39; N, 24.97. Found: C, 69.59; H, 5.75; N, 24.69.

5,6,7,8-Tetrahydro-3,8-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (7). Reaction of oxadiazinone **4** (82 mg, 0.36 mmol in 1 mL of THF) with 1-pyrrolidino-6-methylcyclohexene (90 mg, 0.54 mmol, 1.5 molar equiv in 0.5 mL of THF) in the foregoing manner provided 80 mg (80%) of the product as a pale yellow solid, mp 80–81 °C. IR: 1600, 1510 cm^{-1}. ^{1}H NMR (250 MHz): δ 1.51 (d, 3, *J* = 7.0), 1.65–2.18 (m, 4), 2.71 (s, 3), 3.10–3.19 (m, 3), 7.25 (t, 1, *J* = 7.4), 7.50 (t, 2, *J* = 8.0), 8.32 (d, 2, *J* = 7.6). ^{13}C NMR (100 MHz): δ 11.42, 20.80, 20.88, 31.16, 33. 36.88, 119.55, 125.18, 129.01, 132.39, 139.56, 142.58, 142.8 48.74, 156.16. Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.36; H, 6.52 20.12. Found: C, 73.03; H, 6.77; N, 19.89.

4-Thiobutanoic Acid, Piperidinoamide. A solution of γ-thiobutyrolactone (0.44 mL, 5 mmol in 30 mL of benzene), piperidine (0.5 mL, 5 mmol), and camphorsulfonic acid (230 mg, 1 mmol, 0.2 molar equiv) was refluxed for 8 h with a Dean–Stark apparatus. The raction mixture was filtered, concentrated, and distilled in a Kugelrohr apparatus (oven temperature 120 °C, pressure = 1 Torr) to yield 0.94 g (100%) of the amide as a colorless liquid. IR: 3460, 1720, 1630 cm^{-1}. ^{1}H NMR (250 MHz, mixture of rotamers): δ 1.34 (t, 1, *J* = 8.0), 1.52–1.64 (m, 4), 1.94 (quintet, 2, *J* = 7.1), 2.27 (quintet, 2, *J* = 7.1), 2.45 (t, 2, *J* = 7.4), 2.51 (t, 2, *J* = 8.1), 2.62 (q, 2, *J* = 4.9), 3.40 (t, 4, *J* = 6.4), 3.54 (t, 2, *J* = 5.4). ^{13}C NMR (100 MHz): δ 23.85, 24.00, 25.07, 25.23, 28.90, 30.86, 33.14, 40.72, 42.08, 46.04, 169.73.

2-Piperidino-4,5-dihydrothiophene (8). A solution of γ-thiobutyrolactone (0.87 mL, 10 mmol in 10 mL of benzene) and piperidine (3.4 mL, 35 mmol, 3.5 molar equiv) was cooled to 0 °C, followed by the dropwise addition of titanium tetrachloride (5 mL of a 1 M solution in toluene, 5 mmol, 0.5 molar equiv). The reaction mixture was warmed to rt and stirred for 30 min. Filtration and concentration resulted in a viscous reddish oil which upon Kugelrohr distillation (1 Torr, oven temperature 105 °C) gave 120 g (71%) of the ketene acetal as a colorless liquid. IR: 1640, 1600 cm^{-1}. ^{1}H NMR (250 MHz, in C_6D_6): δ 1.22–1.40 (m, 6), 2.51 (dt, 2, *J* = 2.6, 7.8), 2.85–2.93 (m, 6), 4.28 (t, 1, *J* = 2.6). ^{13}C NMR (50 MHz, in C_6D_6): δ 24.62, 25.80, 32.17, 34.22, 52.00, 91.57, 153.39.

5,6-Dihydro-3-methyl-1-phenyl-1*H*-thieno[2,3-*b*]pyrazolo-[3,4-*e*]pyrazine (9). A solution of oxadiazinone **4** (50 mg, 0.22 mmol in 1 mL of CH_2Cl_2) was cooled to −78 °C under nitrogen, followed by the addition of **8** (60 mg, 0.33 mmol, 1.5 molar equiv in 1 mL of CH_2Cl_2). The reaction mixture was warmed to rt over 2 h, concentrated, and chromatographed on 10 g of silica, eluting with 4:1 hexanes–ether, to afford 43.0 mg (73%) of the product as a white solid, mp 150–151 °C. IR: 1600, 1510 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.65 (s, 3), 3.50 (t, 2, *J* = 6.5), 3.57 (t, 2, *J* = 6.5), 7.28 (t, 1, *J* = 7.4), 7.49 (t, 2, *J* = 7.9), 8.17 (d, 2, *J* = 7.8). ^{13}C NMR (125 MHz): δ 11.23, 28.91, 33.11, 120.36, 125.83, 129.09, 130.09, 139.02, 142.88, 143.28, 152.13, 161.59. Anal. Calcd for $C_{14}H_{12}N_4S$: C, 62.59; H, 4.51; N, 20.88. Found: C, 62.40; H, 4.53; N, 20.46.

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Supplementary Material Available: Spectral data (^{1}H and ^{13}C NMR) for all new compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.