Synthesis of a Novel *N*-Hydroxypyrrole via Lithium Perchlorate Accelerated Diels–Alder Methodology

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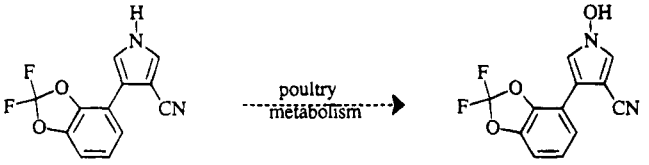
As part of a poultry metabolism study involving pyrrole fungicide **1** (CGA-173506), our animal metabolism group postulated *N*-hydroxypyrrole **2** as a fecal metabolite based on mass spectral data. In order to verify this structural assignment, we devised a synthesis of this suspected metabolite. In this note, we would like to report the synthesis of the novel *N*-hydroxypyrrole **2**,



1 **2**

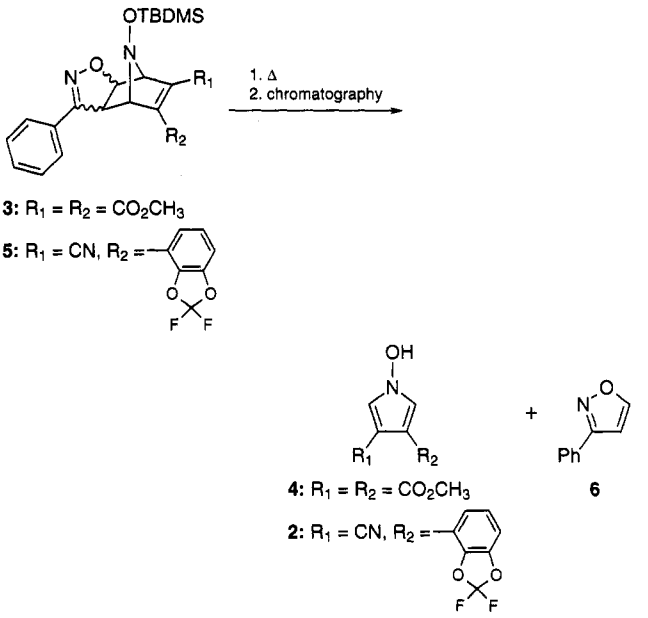
utilizing a lithium perchlorate mediated Diels-Alder reaction as the key step.

There are relatively few methods in the literature for the synthesis of 3,4-substituted *N*-hydroxypyrroles, and one method that seemed particularly adaptable to our target **2** was a route devised by Keana et al.[1] in the synthesis of dimethyl 1-hydroxy-3,4-pyrroledicarboxylate **4** (Scheme 1). In this synthesis, Keana relied upon a retro-Diels–Alder reaction of the *N*-siloxyazanorbornadiene **3** to provide the desired pyrrole **4** along with 3-phenylisoxazole **6**.

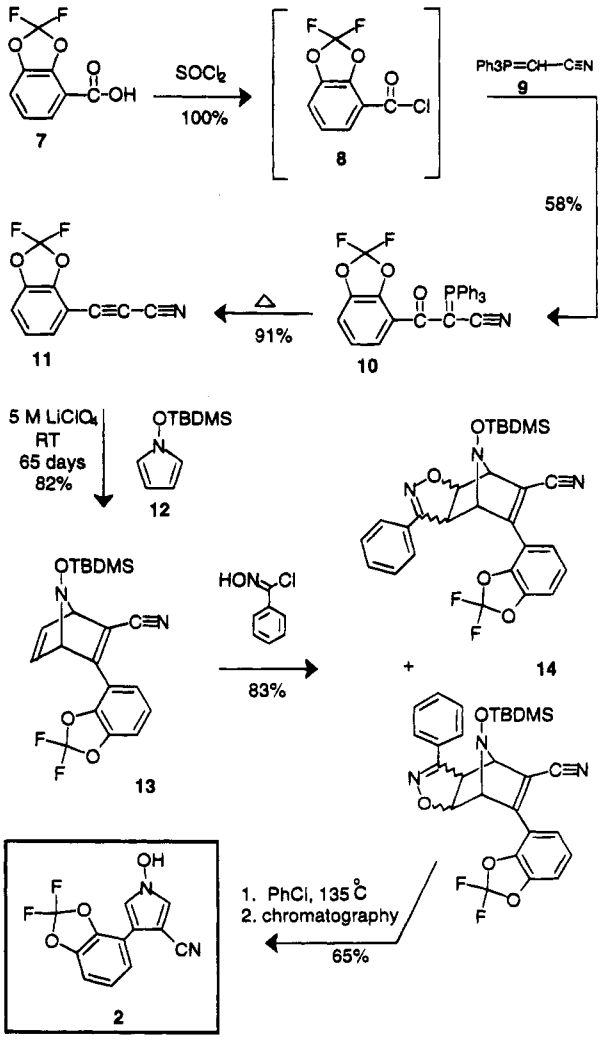
An analogous route to our target **2** would require synthesis of the *N*-siloxyazanorbornadiene **5**. This was achieved as illustrated in Scheme 2. Treatment of the benzoic acid **7**[2] with thionyl chloride afforded the acid chloride **8**[3] which was not isolated but reacted immediately with the phosphorane **9**[4] to afford adduct **10** in 58% yield. Pyrolysis of **10** at 300 °C/10 mm Hg gave a 91% yield of the Wittig elimination product **11**.

In direct analogy to Keana's synthesis, we planned to react the propynenitrile **11** with the N-siloxypyrrole **12**[5] in a Diels-Alder fashion to provide the N- siloxyazanorbornadiene **13**. As illustrated in Table 1, entry 3, initial attempts at this reaction under sealed tube conditions at 90 °C afforded only modest yields (50% based on recovered starting materials) of the desired adduct. Longer reaction times and higher temperatures lead to deprotection of the siloxypyrrole **12** and/or complete degradation of **11** and **12**. Attempted reaction of the deprotected hydroxypyrrole with the dienophile **11** in a separate experiment failed to provide the desired product

Scheme 1



Scheme 2



2 and the starting materials were recovered unchanged. Varying the stoichiometry of the reactions also failed to improve the yields. The use of several solvents under sealed tube reaction conditions was also investigated

(1) Keana, J. F. W.; Heo, G. S.; Mann, J. S.; Van Nice, F. L.; Lex, L.; Prabhu, V. S.; Ferguson, G. *J. Org. Chem.* **1988**, *53*, 2268.
(2) Ackermann, P.; Kaenel, H. R.; Schaub, B. Eur. Patent Appl. EP 333,685, 1989; *Chem. Abstr.* **1990**, *112*, 158228.
(3) Knueppel, P. C.; Marhold, A.; Hausner, T. P.; Santel, H. J.; Luerssen, K.; Schmidt, R. R.; Dehne, H. W. Eur. Patent Appl. EP 490,-220, 1992; *Chem. Abstr.* **1992**, *117*, 843.
(4) Schiemenz, G. P.; Engelhard, H. *Chem. Ber.* **1961**, *94*, 578.
(5) For a review of catalyzed Diels–Alder reactions, see Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

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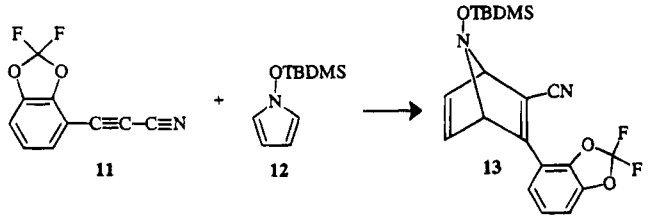
Table 1. Diels–Alder Reaction of Nitrile 11 and Pyrrole 12



11 12 13

entry	ratio 11:12	conditions	temp (°C)	solvent	catalyst	time (h)	yield 13[a]
1	1:1	c	25	N/A	N/A	1.5	NR[e]
2	1:1	c	75	N/A	N/A	24	NR[e]
3	1:1	b	90	N/A	N/A	1.5	25[a,e]
4	1:1	b and c	120	N/A	N/A	1.5	0%
5	1:1	b	100	benzene	N/A	1.0	0%
6	1:1	b	200	benzene	N/A	1.0	6%
7	1:1	b	100	THF	N/A	1.0	6%
8	1:1	b	60	Et_2O	N/A	1.0	<4%
9	1:1	b	0	CH_2Cl_2	$AlCl_{3(5\ equiv)}$	0.3	0%
10	1:2	b	90	N/A	N/A	1.0	10%
11	1:2	b	00	Et_2O	N/A	1.0	<6%
12	1:2	b	100	THF	N/A	1.0	<6%
13	1:2	b	100	benzene	N/A	1.0	<4%
14	1:1.5	c	60	Et_2O	$LiClO_4$	24	68%[f]
15	1:1.5	c	60	Et_2O	$LiClO_4$	48	62%[f]
16	1:2	c	60	Et_2O	$LiClO_4$	24	55%[f]
17	1:3	c	60	Et_2O	$LiClO_4$	24	49%[f]
18	1:2	c	25	Et_2O	$LiClO_4$	1560	83%[e,f]

[a] 50% based on recovered starting materials. [b] Sealed tube. [c] In a capped vial. [d] Determined by HPLC analysis. [e] Isolated. [f] Deprotection of pyrrole occurred. [g] Complete decomposition of starting materials occurred; NR indicates no reaction with recovery of starting compounds.

(entries 5–13). None of these afforded more than negligible amounts of the desired Diels–Alder adduct.

Having exhausted the more conventional options, we turned to Lewis acid catalyzed approaches to the Diels–Alder reaction.[6] The use of lithium perchlorate (5.0 M in diethyl ether)[7] improved our yields of desired product **13** significantly (Table 1, entries 14–18). Using these conditions over a period of 65 days, we found reaction of the protected pyrrole **12** with the propynenitrile **11** produced an 82% yield (isolated) of the desired siloxyazanobornadiene **13**. The use of other Lewis acids such as aluminum chloride, titanium tetrachloride, and boron trifluoride etherate under a variety of conditions failed to afford the desired product and led to complete decomposition of the starting materials.

With the requisite azanorbornadiene **13** in hand, we continued with the synthesis as outlined in Scheme 2. As in Keana's synthesis, direct thermolysis of **13** failed to produce the desired product **2** and resulted in decomposition of the starting material. Reaction of **13** with benzohydroxamoyl chloride provided the endo and exo cycloadducts **14** in an 83% isolated yield. The lability of these compounds precluded their chromatographic separation and the mixture was carried forward to the next step. Pyrolysis of **14** in chlorobenzene followed by reverse phase chromatography to remove the phenylisoxazole afforded the desired *N*-hydroxypyrrole **2** (65% yield) and an unidentified byproduct (1.3%) which co-eluted with **2**. Separation of this impurity by flash chromatography followed by an analysis of its ^1H NMR spectrum surprisingly revealed this impurity as the pyrrole **1** (CGA-173506).

This structure of **1** was easily confirmed by comparison of its spectral and chromatographic data to those of our known standard. This material was either generated from a reductive cleavage during the final pyrolysis reaction or was the result of incomplete pyrrole oxidation during the synthesis of **12**. None of the analytical data, however, supports the latter explanation.

In conclusion, the synthesis of the novel *N*-hydroxypyrrole **2** was completed in seven steps in an overall yield of 23% from known starting materials. Use of the lithium perchlorate mediated Diels–Alder reaction at room temperature provided the azanorbornadiene **13**, a crucial intermediate, in excellent yield.

Experimental Section

General Procedure. Melting points are uncorrected. TLC analysis was performed on silica gel 60 plates and visualized by UV 254, iodine vapors, or charring after spraying with 5% phosphomolybdic acid in ethanol. All reagents and solvents were used as received from commercial sources unless otherwise noted. Flash chromatography was performed with Baker 40 μm flash chromatography packing (7024-01) and reverse phase chromatography was performed on YMC gel (ODS, 120A); ratio gel:substrate was 70:1. NMR spectra were recorded in the solvents indicated on a FTNMR instrument at 400.13 (^1H) and 100.61 (^{13}C) MHz. Infrared spectra were recorded on a FTIR. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Gas chromatographic analyses were conducted under the conditions indicated. High performance liquid chromatography was performed using a Spherisorb ODS2 column with a mobile phase of 85:15 = acetonitrile:20 mM H_3PO_4 at a flowrate of 1 mL/min and detector wavelength of 220 nm. All moisture sensitive reactions were performed under inert atmosphere conditions using oven-dried glassware.

2,2-Difluoro-β-oxo-α-(triphenylphosphoranylidene)-1,3-benzodioxole-4-propanenitrile (10). To a turbid solution of the phosphorane **9** in benzene, freshly distilled from sodium and benzophenone ketyl (17 mL), was added dropwise a solution of **8** (327 mg) in benzene (1.0 mL). After stirring overnight at room temperature, the resulting suspension was filtered and the salt washed with benzene. Concentration of the filtrate afforded a brown oil (553 mg) which was purified by flash chromatography in 1:1 ethyl acetate:hexane to afford **10** as a colorless solid (417 mg, 58%): mp 170 °C; ^1H NMR ($CDCl_3$) δ 6.67 (m, 9H), 6.56–6.52 (m, 6H), 6.48 (quint, 1H), 6.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 185.3, 133.8, 133.6, 133.39, 133.36, 129.4, 129.2, 123.4 (t, J = 257.1), 123.1, 122.9, 122.0, 120.8, 110.9; IR (KBr pellet, in cm^{-1}) 3073, 2182, 1339, 1562, 1451, 1244, 1074. Anal. Calcd for $C_{28}H_{18}F_2NO_3P$: C, 69.28: H, 3.74: N, 2.89. Found: C, 69.17; H, 3.90; N,2.87.

2,2-Difluoro-1,3-benzodioxole-4-propynenitrile (11). Phosphorane **10** (8.3 g, 17.1 mmol) was distilled through a short-path condenser (10 mmHg, 300–325 °C) into a dry ice/acetone cooled receiver. The distillation apparatus was occasionally heated with a heat gun to prevent clogging of the condenser. Nitrile **11** was obtained as a white, crystalline solid (3.0 g, 85%): mp 60–61 °C; ^1H NMR ($CDCl_3$) δ 6.26 (dd, J = 9.1, 1.2, 1H), 6.21 (dd, J = 8.1, 1.2, 1H), 6.11 (t, J = 8.1, 1H); ^{13}C NMR ($CDCl_3$) δ 146.2, 143.8, 131.1 (t, J = 260), 127.9, 124.0, 113.0, 104.6, 100.6, 74.6, 67.9; IR (KBr pellet, in cm^{-1}) 3449, 2272, 1645, 1489, 1454, 1279, 1179, 1117, 783, 721. Anal. Calcd for $C_{10}H_3F_2NO_2$: C, 57.98: H, 1.46: N, 6.76. Found: C, 58.03; H, 1.63; N,6.59.

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-azabicyclo[1.1.1]-hepta-2,5-diene-2-carbonitrile (13). Method A. Siloxypyrrole **12** (95.0 mg, 0.48 mmol) and the nitrile **11** (50.0 mg, 0.24 mmol) were combined in a conical vial equipped with a magnetic stir bar. To this mixture was added a solution of 5.0 M $LiClO_4$ in Et_2O (0.48 mL, 2.4 mmol). The vial was capped and stirred for 65 days at room temperature. The resulting dark brown residue

(6) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

(7) Two methods were used to prepare adduct **13**. The 65 day room temperature reaction (Method A) was not optimized for larger scales and in the interest of time, alternative Method B was used to generate gram quantities of this product.

was diluted with Et_2O (5 mL) and washed with water (3 × 1 mL) and brine (1 × 1 mL) and dried over anhydrous $MgSO_4$. Filtration and concentration of the filtrate afforded a brown oil which was flash chromatographed in 2:3 = dichloromethane: hexane to afford the product **13** as a colorless solid (79.3 mg, 82%): mp 87−88 °C; ^1H NMR ($CDCl_3$) δ 6.63 (dd, J = 8.0, 1.2, 1H), 6.17 (t, J = 8.0, 1H), 6.11 (dd, J = 6.9,1.3, 1H); 6.92 (dd, J = 5.9, 2.4, 1H), 6.88 (dd, J = 5.9, 3.1, 1H), 4.96 (m, 1H), 4.58 (m, 1H), 0.85 (s, 9 H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.6, 144.0, 140.4, 139.6, 133.3, 131.2 (t, J = 257), 124.2, 122.4, 116.78, 116.77, 116.3, 111.0, 78.6, 78.5, 25.9, 17.6, −5.5; IR (KBr pellet, in cm^{-1}) 3418, 2931, 2858, 2229, 1504, 1458, 1271, 1234, 1134, 1033, 765; Anal. Calcd for $C_{20}H_{22}F_2N_2O_3Si$: C, 59.39: H, 5.48: N, 6.93. Found: C, 59.04; H, 5.51; N, 6.78.

Method B. Siloxypyrrole **12** (6.4 g, 32.7 mmol) and the nitrile **11** (4.5 g, 21.82 mmol) were combined with a 5.0 M solution of $LiClO_4$ in Et_2O (33.0 mL, 165 mmol). The flask was capped with a rubber septum and placed in a 60 °C oil bath for 48 h. HPLC analysis of an aliquot after this period gave the following results: desired product **13**, T_r = 6.76 min, 63%; siloxy pyrrole **12**, T_r = 5.21 min, 8.9%; nitrile **11**, T_r = 3.95 min, 3.9%, deprotected pyrrole, T_r = 2.96 min, 11.0%. The reaction was worked up as in Method A. Flash chromatography afforded **13** as a colorless solid (5.43 g, 62%), a 1:1 mixture of **11:12** = (190 mg), and deprotected pyrrole (250 mg). The spectral data for **13** are given above.

5-(2,2-Difluoro-1,3-benzodioxol-4-yl)-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3a,4,6,7a-tetrahydro-3-phenyl-4,6-imino-1,2-benzisoxazole-6-carbonitrile Isomer Mixture (14). A solution of benzhydroximic chloride (0.81 g, 5.2 mmol) in Et_2O (90 mL) was cooled to 0 °C and to it was added a solution of **13** (2.0 g, 4.9 mmol) in Et_2O (135 mL). Triethylamine (0.90 mL, 6.5 mmol) was added dropwise over 10 min to the stirring solution, and the reaction was stirred for an additional 1 h at 0 °C. Water (80 mL) was added to the reaction and the aqueous phase removed and extracted with Et_2O (1 × 80 mL). The combined ethereal layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation to afford **14** as a solid (2.14 g, 83%): mp 50−55 °C; The ^1H NMR and ^{13}C NMR spectra for this mixture were too complex for interpretation due to the number of isomers present. Attempts to separate this mixture by column or thin layer chromatography caused decomposition of the compounds. IR (KBr pellet, in cm^{-1}) 3063, 2957, 2931, 2887, 2858, 2214, 1739, 1454, 1251, 1180, 1107, 846, 783. Anal. Calcd for $C_{27}H_{27}F_2N_3O_4Si$: C, 61.93: H, 5.20: N, 8.03. Found: C, 62.21; H,5.25; N,8.13.

4-(2,2-Difluoro-1,3-benzodioxol-4-yl)-1-hydroxy-1*H*-pyrrole-3-carbonitrile (2). Carbonitrile mixture **14** was dissolved in chlorobenzene (25 mL) in a flask equipped with a reflux condenser and nitrogen inlet. This solution was heated to 135 °C for 20 min, and the chlorobenzene was then removed by rotary evaporation. The resulting residue was purified by reverse phase column chromatography using a mobile phase of 3:2 methanol:water. Deprotection of the hydroxyl functionality occurred during chromatography and **2** was obtained as a white solid (865 mg, 70%) which contained an impurity by normal phase TLC (5:95 EtOAc:CH_2Cl_2, R_f **2** = 0.25, R_f impurity = 0.48) and HPLC analysis (Spherisorb ODS2, 1:1 acetonitrile:water, 1 mL/min, 220 nm, T_r (**2**) = 6.48 min, 98.6%; T_r (impurity) = 8.30 min), 1.3%. Flash chromatography of this mixture afforded the impurity also as a solid which was identified from its ^1H NMR spectrum and HPLC against a known standard as the pyrrole **1**. The desired product **2** was isolated a white solid (803 mg, 65%); mp = 171−172 °C; ^1H NMR (CD_3CN) δ 9.43 (bs, 1H), 6.56 (dd, J = 8.1, 1.1, 1H), 6.51 (d, J = 2.5, 1H), 6.26 (d, J = 2.5, 1H), 6.21 (t, J = 8.0, 1H), 6.1 (dd, J = 8.0, 1.2, 1H); ^{13}C NMR (CD_3CN) δ 144.6, 140.6, 132.3 (t, J = 252.9), 127.0, 125.4, 119.6, 117.3, 117.0, 116.4, 115.5, 109.2, 86.91; IR (KBr pellet, in cm^{-1}) 3149, 3061, 2957, 2874, 2235, 1547, 1456, 1261, 1147, 752; Anal. Calcd for $C_{12}H_6F_2N_2O_3$: C, 54.56: H, 2.29: N, 10.60. Found: C, 54.25; H, 2.35; N, 10.43.

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