Intramolecular Diels–Alder Chemistry of Pyrroles

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The 1-pyrrolyl fumarate (**5**), prepared by condensation of 1-hydroxypyrrole (**1a**) with *trans*-3-(methoxycarbonyl)-acryloyl chloride (**4**), undergoes a facile intramolecular Diels–Alder reaction to give the product (**6**), the first intramolecular cycloaddition of a pyrrole.

The partial aromatic character of pyrrole[1] limits its reactivity as a diene in the Diels–Alder reaction. While simple derivatives (substituted on nitrogen with acyl, aryl, and sulphonyl electron-withdrawing groups) have been condensed with highly reactive acetylenedicarboxylates, the yields are modest.[2] Such pyrroles also add labile allenedicarboxylates,[3] tosylacetylene,[4] and benzynes.[5] Rate and yield enhancements have been obtained with dimethyl acetylenedicarboxylate using Lewis acid catalysis[6] and high pressure techniques.[7] Recently, Kreher and Pawelczyk[8] have reported that 1-oxypyrroles (**1a,b**) condense with *N*-phenylmaleimide (**2**) at room temperature in yields of 55—75% (**3a,b**). We now report the first investigation of the intramolecular Diels–Alder chemistry of pyrroles.

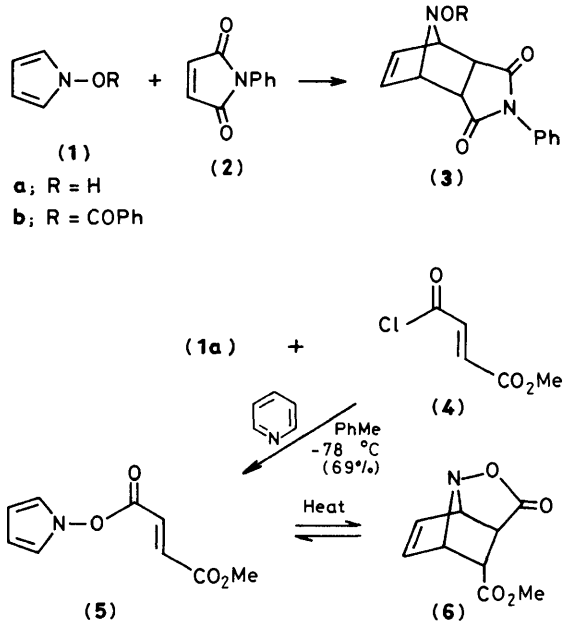


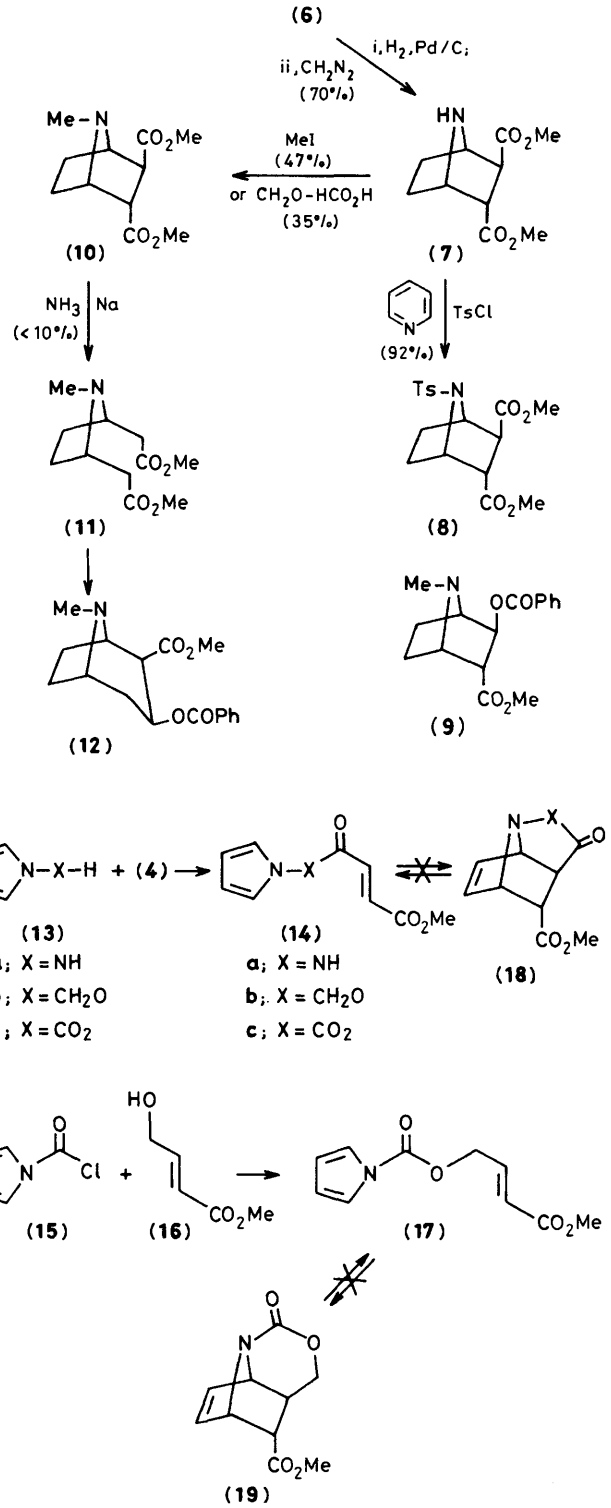
Table 1. Solution equilibrium of (**5**) : (**6**) with temperature.[a]

T/°C	(**5**) : (**6**)	*t*[b]
110	2.5 : 1	20 min
80	1.1 : 1	14 h
70	1 : 1.1	3 days
40	1 : 3	>2 weeks

[a] Equilibrium was determined by careful integration of the appropriate methyl singlets at δ 3.85 for (**5**) and δ 3.68 for (**6**) in the 60 MHz ^{1}H n.m.r. spectra. The equilibrium ratios at 80 and 110 °C were determined starting with either of the pure compounds. Extrapolation of the data to 25 °C gives the following approximate data: K = 5, ΔG_{298} = −1 kcal mol^{-1}, ΔH_{298} = −7 kcal mol^{-1} (1 kcal = 4.18 kJ), and ΔS_{298} = −79.5 J mol^{-1} deg.$^{-1}$ (−19 eu). [b] t = Approximate time to equilibrate.

Prior coupling of a diene and an olefin often effects an entropic enhancement in Diels–Alder reactivity.[9] By joining the pyrrole nucleus to fumarate and crotonate-type dienophiles (*via* potentially cleavable linkages from nitrogen) we sought such effects in this system.

Freshly prepared 1-hydroxypyrrole (**1a**)[8] was acylated with *trans*-3-(methoxycarbonyl)acryloyl chloride (**4**)[10] in toluene and pyridine at −78 °C to give methyl 1-pyrrolyl fumarate (**5**) in 69% yield (m.p. 79—80 °C). When (**5**) was heated for 20 minutes as a dilute (0.05 M) solution in refluxing toluene, it cleanly underwent intramolecular Diels–Alder cyclization to give a 2.5 : 1 equilibrium mixture of (**5**) : (**6**).[11] Lower temperatures shifted the ratio towards the adduct while retarding the cyclization rate (Table 1). Gradual lowering of the temperature of a toluene solution of (**5**) from 110 to 38 °C over a three-week period gave (**6**) in 68% yield [m.p. 109—111 °C; ^{1}H n.m.r. δ 6.08—6.38 (2H, m), 4.53—4.60 (2H, m), 3.68 (3H, s), 3.23—3.28 (2H, m); i.r. ($CHCl_3$), C=O, 1740, 1808 cm^{-1}] with 21% of (**5**) recovered by flash column chromatography (86% based on unrecovered starting material). Hydrogenolysis of (**6**) in methanol with 5% Pd/C followed by treatment with ethereal diazomethane gave dimethyl 2-*endo*-3-*exo*-7-azabicyclo[2.2.1]heptanedicarboxylate (**7**) as a distillable oil (b.p. 45 °C, 0.4 mmHg) in 70% yield. Treatment of (**7**) with toluene-*p*-sulphonyl chloride (TsCl) in dry pyridine gave



the sulphonamide (**8**) in 92% yield (m.p. 98—99 °C, lit.[12] 98—100 °C), a compound prepared during a synthesis of *pseudo*-4-norcocaine (**9**).

N-Methylation of (**7**) with methyl iodide or by the Eschweiler–Clark reaction gave (**10**) in 35—47% yield (oil, b.p. 42 °C, 0.4 mmHg). Unfortunately, attempted reductive cleavage of the 2,3-diester bond under the conditions of Gassman and Creary[13] gave only trace amounts of the pyrrolidine (**11**),[14] a known[15] intermediate for (±)-cocaine

(**12**). Thus, this is not an acceptable route to cocaine at present.

The ready cyclization of (**5**) suggested the possibility that other derivatives might work as well. 1-Aminopyrrole (**13a**)[16] and 1-(hydroxymethyl)pyrrole (**13b**)[17] were acylated with (**4**) in dry diethyl ether and pyridine at −78 °C to give the amide (**14a**) [60%, m.p. 146—147 °C, i.r. (KBr) 1650, 1705 cm^{-1}] and ester (**14b**) [67%, m.p. 64—66.5 °C, i.r. ($CDCl_3$) 1715 cm^{-1}]. Similar condensation of (**4**) with pyrrole-1-carboxylic acid (**13c**)[18] with triethylamine in toluene at 0 °C gave the anhydride (**14c**) [90%, oil, i.r. (neat) 1730, 1810 cm^{-1}]. The acid chloride (**15**), prepared *in situ* from (**13c**) using the Ghosez reagent,[19] was esterified with methyl *trans*-4-hydroxycrotonate (**16**)[20] to give (**17**) in 29% yield [oil, i.r. (neat) 1715 cm^{-1}].

To our dismay, (**14a—c**) and (**17**) were found to be unchanged on extended heating as dilute solutions over a range of temperatures from 35 to 210 °C, giving none of the expected adducts (**18a—c**) or (**19**). At higher temperatures, only decomposition of starting material was observed. Lewis acid catalysis with diethylaluminum chloride in hexane and ethereal boron trifluoride also failed.

We have shown that the notable Diels–Alder reactivity of 1-oxypyrroles reported in intermolecular examples is also noted in the intramolecular version. The origin of this effect is still unclear.[21]

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