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X-ray Crystallographic and ^{13}C NMR Investigations of the Effects of Electron-Withdrawing Groups on a Series of Pyrroles

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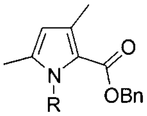
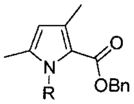
ABSTRACT



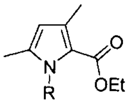
2 R = H
3 R = Boc
4 R = Ms
5 R = Tf

A series of pyrroles substituted with various electron-withdrawing groups (EWGs) on the N atom have been synthesized and full characterization including X-ray crystal structures obtained. Analysis of ^{13}C chemical shifts and X-ray crystal structures reveals that a trend between decreased aromaticity and the strength of the EWG exists. Experimental results regarding alternative mechanisms of nucleophilic substitution reactions can thus be rationalized.

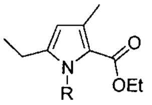
A recent report from the laboratory of Battersby[1] has shown that nucleophilic substitution of pyrroles of type **1**, which may proceed via both S_N2 and azafulvene mechanisms, can be controlled by use of electron-withdrawing groups (EWGs) on the nitrogen atom of the pyrrolic ring (Scheme 1). Battersby and co-workers deduced that *N*-Tf pyrroles would be most likely to effect nucleophilic substitution via the S_N2 pathway, since the strongly electron withdrawing Tf group suppresses azafulvene formation. Thus, a range of enantioenriched N-deactivated deuterated (hydroxymethyl)pyrroles were subjected to nucleophilic substitution reactions with (*S*)-(−)-camphanic acid under Mitsunobu conditions and the diastereomeric ratio of the products determined. Pyrroles with strongly EWGs (*N*-Tf) showed the highest diastereomeric ratio of products since the substitution reaction proceeded largely via the stereospecific S_N2 mechanism (path a). Pyrroles with only weakly EWGs (*N*-H, *N*-Ac, *N*-Boc, *N*-Ms) gave low diastereomeric ratios after exposure to Mitsunobu conditions, since the alternative nonstereoselective azafulvene mechanism (path b) was dominant.



2 R = H
3 R = Boc
4 R = Ms
5 R = Tf

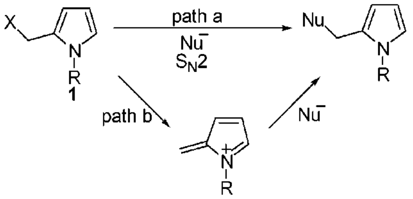


7 R = H
8 R = Boc
9 R = Ms



10 R = H
11 R = Boc
12 R = Ms

Scheme 1



Factors governing the nucleophilic substitution mechanism adopted by pyrroles of type **1** (path a or path b, Scheme 1) include the nature of the transition state, as alluded to by

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Battersby[1] and Abell,[2] the nature of the ground state, and the inherent activation energies of the competing mechanisms. We wished to investigate the nature of the ground state for model pyrroles **2**−**5** by X-ray crystallography and ^{13}C NMR spectroscopy and thus investigate the factors governing competing S_N2 and azafulvene mechanisms of nucleophilic substitution of pyrroles of type **1**. A number of X-ray structures of N-substituted pyrroles have been reported,[3−5] but a full crystallographic or ^{13}C spectroscopic investigation of pyrroles N-substituted by EWGs of varying strengths has not, to our knowledge, been published.

The four major full octet resonance forms **A**−**D** of pyrroles of type **2**−**5** are shown in Figure 1. The electron-withdrawing 2-ester moiety results in a contribution from a significant population of resonance form **B**. We reasoned that the introduction of an EWG on the N atom of the pyrrole would significantly change the contributions of the resonance forms, due to the decreased availability of the nitrogen lone pair. This should be evident by changes in bond lengths and ^{13}C chemical shifts as the resonance forms **B**, **C**, and **D** become less populated.

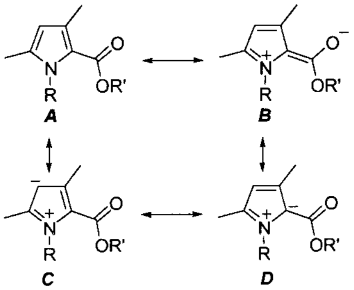
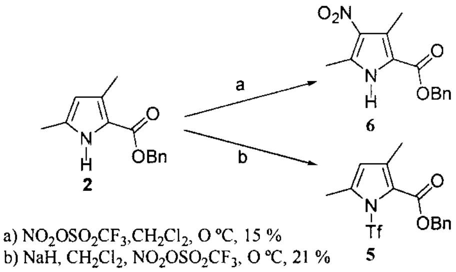


Figure 1. Major resonance forms **A**−**D**.

We report herein the synthesis and full characterization of pyrroles **3**−**5**, which are N-substituted derivatives of benzyl 3,5-dimethylpyrrole-2-carboxylate (**2**).[6] The X-ray crystal structures and ^{13}C NMR data for pyrroles **2**−**5** reveal some interesting effects on the aromaticity of the pyrrole ring due to the EWGs. Future predictions regarding the effects of EWGs on aromaticity can thus be drawn by analysis of ^{13}C chemical shifts of appropriate systems.

Preparation of **3** was achieved by treatment of **2** with di-*tert*-butyl dicarbonate and DMAP.[7] Treatment of **2** with sodium hydride and methanesulfonyl chloride[8] gave pyrrole **4**. The preparation of *N*-Tf pyrrole **5** proved more problematic. A variety of methods utilizing NaH, BuLi, Et_3N, Hünig's base, pyridine, DMAP, and imidazole and trifluoromethanesulfonic anhydride, trifluoromethanesulfonyl chloride, and trifluoromethanesulfonimide in a number of solvents under various conditions of temperature, order of addition, and length of reaction[9] all proved fruitless, and only starting material was recovered. Given this total lack of success, our efforts turned to the preparation of benzyl 3,5-dimethyl-1-nitropyrrole-2-carboxylate. We reasoned that *N*-nitro pyrroles would experience sufficient electron withdrawal[10] to produce noticeable changes in the structure of the pyrrolic ring. Consequently, we used nitronium trifluoromethanesulfonate ($NO_2OSO_2CF_3$)[11,12] as shown in Scheme 2a. However, our initial experiments in dry CH_2Cl_2 at 0 °C gave a 15% yield of benzyl 3,5-dimethyl-4-nitropyrrolecarboxylate (**6**) and 79% recovered starting material. The use of Hünig's base gave similar results as identified by TLC.

Scheme 2



a) $NO_2OSO_2CF_3$, CH_2Cl_2, 0 °C, 15 %
b) NaH, CH_2Cl_2, $NO_2OSO_2CF_3$, 0 °C, 21 %

Cognizant that the use of sodium hydride would give rise to a harder pyrrolyl anion, thus increasing the likelihood of N-substitution rather than 4-substitution, we repeated the experiment according to Scheme 2b. We were delighted to observe only a trace of benzyl 3,5-dimethyl-4-nitropyrrole-carboxylate (**6**) by TLC, along with larger quantities of a previously unobserved product. Workup and purification[13] yielded a colorless oil. ^{1}H NMR spectroscopy showed the absence of a broad singlet at ≈ 8.6 ppm, indicative of N-substitution. However, EI mass spectrometry gave a peak at M^+ 361 which does not correspond to benzyl 1-nitro-3,5-dimethylpyrrole-2-carboxylate, which would have M^+ 274. Serendipitously, M^+ 361 instead corresponds to the *N*-Tf pyrrole **5**, which was our original target. Studies using ^{19}F and ^{13}C NMR spectroscopy confirmed the identity of **5**.[13] Presumably, under the reaction conditions employed triflylation of **2** becomes favorable. It is unclear why triflylation

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of pyrrole **2** was initially so problematic, but similar difficulties have been reported previously.[8] We are currently investigating the scope of nitronium trifluoromethanesulfonate as a triflylating agent for pyrroles.

Single crystals of **2**, **3**, and **4** suitable for X-ray crystallographic study were grown by diffusion of hexane into a dichloromethane solution. Pyrrole **5** presented more problems, since the compound was found to have a melting point of −22 °C. Crystals of **5** could readily be grown from a pentane solution which had been prefrozen with liquid nitrogen and then left in a freezer at −25 °C for 4 days. However, the crystals were difficult to store since at −78 °C deposition of material onto the crystals was found to occur, while addition of more cold pentane merely served to dissolve the crystals. We were, however, able to mount a freshly grown crystal of **5** for X-ray diffraction at 173 K with the use of an acetone−dry ice bath and extremely expedient manipulation. Pyrrole **5** was not sensitive to moisture.

Each of the pyrrole rings was observed to crystallize in an essentially planar conformation. As expected, the phenyl ring of the benzyloxycarbonyl substituent is not planar to the pyrrole ring in any of the structures and instead makes angles of 18, 72, 74, and 128° to the pyrrole rings within **2**, **3**, **4**, and **5** respectively. Significant trends are observed by considering selected bond lengths of pyrroles **2**, **3**, **4**, and **5** as detailed in Table 1 (see Table 2 for atom labels). These trends largely map the electron-withdrawing ability of the N-substituents, *N*-H < *N*-Boc < *N*-Ms < *N*-Tf.[10] In particular, N(1)−C(5) increases from 1.351(3) Å in **2** to 1.428(3) Å in **5** through 1.393(2) Å for **3** and 1.407(3) Å for **4**. Similarly, C(4)−C(5) shows a decrease in length for **5** compared to that for **4**, **3**, and **2**. This can be rationalized by consideration of resonance forms **A**−**D** as shown in Figure 1. As the strength of the EWG increases, the availability of the nitrogen lone pair decreases and resonance forms **B**−**D** become less significant. Consequently, longer N(1)−C(5), N(1)−C(2), and C(3)−C(4) bonds and shorter C(4)−C(5) bonds result in **5** cf. **2**. In general, as the strength of the EWG increases, the bond lengths change to values closer to those found by microwave spectroscopy for pyrrole itself.[14] Table 1 also shows that the N(1)−S(18) bond is significantly shorter in **5** than in **4**. This is indicative of a stronger N−S bond for **5**, as a result of the superior electron-withdrawing ability of Tf over Ms.

Table 1. Selected Bond Lengths [Å] for Pyrroles **2**, **3**, **4**, and **5**

bond	**2**	**3**	**4**	**5**
N(1)−C(2)	1.384(3)	1.403(2)	1.420(3)	1.427(3)
N(1)−C(5)	1.351(3)	1.393(2)	1.407(3)	1.428(3)
C(2)−C(3)	1.391(3)	1.369(2)	1.375(3)	1.368(4)
C(2)−C(8)	1.436(3)	1.469(2)	1.463(3)	1.474(3)
C(3)−C(4)	1.409(3)	1.418(2)	1.415(4)	1.424(4)
C(3)−C(7)	1.497(3)	1.499(2)	1.502(4)	1.503(4)
C(4)−C(5)	1.380(3)	1.357(2)	1.353(4)	1.353(4)
C(5)−C(6)	1.491(3)	1.486(2)	1.495(4)	1.489(4)
O(9)−C(8)	1.221(2)	1.202(2)	1.216(3)	1.208(3)
O(10)−C(8)	1.344(2)	1.342(2)	1.337(3)	1.344(3)
S(18)−N(1)			1.687(2)	1.649(2)

The ^{13}C NMR spectra of pyrroles **2**−**5** reveal interesting information regarding the electron density distribution within the pyrrolyl rings. Assignments of chemical shifts for **3**, **4**, and **5** were completed by use of known additive substituent chemical shift and steric compression effects[15] for a range of substituted pyrroles and thiophenes.[16,17] Various ^{1}H and ^{13}C NMR experiments and assignment of ^{13}C chemical shifts of analogues **7**−**12** all proved useful. Previous reports from our laboratory[3] have shown that the presence of two electron-withdrawing substituents at both 2- and 5-positions does not result in an additive decrease in pyrrole ring aromaticity. Rather, a competition effect was observed with the most strongly EWG dominating.

Abraham et al. have reported that N-methylation of pyrrole results in a downfield shift of the α-carbon resonances by 3.8 ppm and the β-carbon resonances by 0.2 ppm.[15] Additionally, they reported that N-methylation of tetrasubstituted pyrroles shifts the α-carbon resonances downfield by 1.0−3.0 ppm and the β-carbon resonances between 1.0 ppm downfield and 0.5 ppm upfield. The effects of electron-withdrawing substituents on the ^{13}C chemical shifts of pyrroles have been previously discussed[3], but to our knowledge, the effects of N-substitution with an EWG have not been reported. Pyrrole **2** has been fully characterized and served as our reference point for assignments.[15]

The pyrrolic ring carbon atoms were of most interest to our study since it is these atoms that experience the most direct effects of *N*-EWG substitution, as appreciated by consideration of Figure 1. The C^4 chemical shifts were easily assigned by using an attached proton test experiment. The C^2 chemical shifts were assigned by comparison to literature assignments.[3,15] The assignment of C^3, C^5, and the quaternary benzyl chemical shifts was not initially evident. Thus, we prepared the ethyl ester analogues **7**,[6] **8**, and **9**, allowing us to then assign the quaternary benzyl chemical shifts of **3**, **4**, and **5** by analogy.

It has been reported[3] that replacement of a methyl substituent by an ethyl substituent results in a deshielding

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(13) To a solution of pyrrole **2** (100 mg, 0.44 mmol) in dry CH_2Cl_2 (2 mL) under a flow of N_2 was added NaH (14 mg, 0.57 mmol). The resulting mixture was stirred at room temperature under N_2 for 15 min before being cooled to 0 °C. To a suspension of finely ground ammonium nitrate (141 mg, 1.76 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added trifluoromethanesulfonic anhydride (149 μL, 0.88 mmol) dropwise. The resulting solution was stirred at 0 °C for 1 h before being added to the pyrrolyl solution prepared above. After stirring at 0 °C for 20 min, the solution was quenched by the addition of phosphate buffer pH 7 solution. The crude product was then extracted with CH_2Cl_2 (3 × 10 mL) and dried over $MgSO_4$ before the solvents were removed in vacuo. Purification by column chromatography on silica gel eluting with 97:3 hexanes:ethyl acetate gave benzyl 3,5-dimethyl-1-trifluoromethanesulfonylpyrrole-2-carboxylate **5** as a colorless oil (34 mg, 21%): mp −22 °C; δ_H (200 MHz; $CDCl_3$) 2.12 (3H, s), 2.39 (3H, s), 5.28 (2H, s), 5.99 (1H, s), 7.30−7.46 (5H, m); δ_F (188 MHz; $CDCl_3$) 3.90; *m/z* EI 361 (10%, M^+), 254 (20, $(M - OCH_2Ph)^+$), 227 (64, $(MH - CO_2CH_2Ph)^+$), 91 (100, $(CH_2Ph)^+$) (found: (M^+), 361.0591, $C_{15}H_{14}F_3NO_4S$ requires 361.0596).

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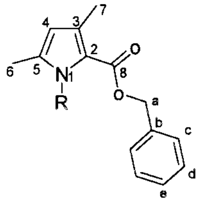
Table 2. ^{13}C Chemical Shifts for Pyrroles **2**−**5**[a]



pyrrole, R	C^2	C^3	C^4	C^5	C^6	C^7	C^8	a	b	c, d, e	others
2 H	117.47	129.64	111.56	133.32	13.13	13.03	161.78	65.55	136.71	127.98 128.05 128.58	
3 Boc	120.88	131.04	113.08	135.99	14.03	12.67	161.22	66.09	136.20	128.03 128.20 128.45	$\mathrm{C}(C\mathrm{H}_3)_3$ 27.55 $C(\mathrm{CH}_3)_3$ 84.32 $C\mathrm{O}_2{}^t\mathrm{Bu}$ 149.69
4 Ms	122.92	131.55	115.09	137.72	14.98	12.53	160.95	66.77	135.33	128.21 128.39 128.49	$\mathrm{SO}_2C\mathrm{H}_3$ 43.18
5 Tf	124.99	133.19	118.30	138.43	14.68	12.34	160.13	67.48	135.17	128.44 128.53 128.77	$C\mathrm{F}_3$ 119.40, q, *J* 323 Hz

[a] For consistency, we report our ^{13}C chemical shift values, although **2** has been fully assigned previously.[15]

of 6.0−7.0 ppm at the point of attachment and a shielding of ≈ 0.6 ppm at adjacent pyrrolic positions. Consequently, we prepared analogues **10**,[18] **11**, and **12**. Assignment of C^5 and C^3 for **11**, **12**, **8**, and **9** allowed assignment of C^3 and C^5 for **3**, **4**, and **5** by analogy (see Supporting Information). These assignments were consistent with literature reports as mentioned previously.

Table 2 shows complete ^{13}C chemical shift assignments for pyrroles **2**−**5**. As expected, a general deshielding effect is observed with shifts to lower field upon introduction of *N*-EWGs. Interestingly, the ester carbonyl signal is found to move upfield by 1.65 ppm upon N-triflylation of **2**. This observation monitors the return of the ester carbonyl signal to a normal value for esters,[19] thus indicating that electron density redistribution through resonance form **B** is not a significant contributor for **5**. The C^2 and C^4 pyrrolic atoms experience the greatest ^{13}C chemical shift differences between pyrroles **2** and **5**. Analysis of Figure 1 reveals that positions C^2 and C^4 exist as formal anions in resonance forms **C** and **D**. As the electron-withdrawing ability of the N-substituent increases, these resonance forms will be less likely to be populated (**A** will dominate) and an effective decrease in electron density at the C^2 and C^4 positions occurs.

With the introduction of EWGs onto the N atom, the aromaticity and electron density distribution within the pyrrole ring decreases as observed for this series of pyrroles. Although Abell et al.[4] have shown that *N*-Ts pyrroles comprise relatively long N(1)−C(2) and N(1)−C(5) bonds and relatively short C(2)−C(3) and C(4)−C(5) (cf. pyrrole itself) bonds indicative of decreased ring aromaticity, our X-ray crystallographic study of a series of N-substituted pyrroles shows the direct effects of EWGs within a series of pyrroles. It is of particular usefulness that the benzyl ester functionality was used as the 2-substituent in our study, since this allowed the effects of resonance form population to be assessed. Analysis of the fully assigned ^{13}C NMR spectra for pyrroles **2**−**5** has allowed us to conclude that the electron-withdrawing effects of N-substituents of pyrroles can be predicted on the basis of ^{13}C chemical shifts alone.

Our studies show that the structure of the pyrrole ground state changes as EWGs are introduced onto the N-substituent. Thus, *N*-Tf pyrroles experience decreased availability of the nitrogen lone pair. This effect on the ground state will be even more dramatic on an azafulvene-like intermediate with a resulting increase in activation energy. Consequently, *N*-Tf pyrroles are less likely to undergo nucleophilic substitution via the azafulvene mechanism, as experimentally determined by Battersby. Future work involving N-substitution of pyrroles with EWGs will benefit from this study, since ^{13}C NMR data will suffice when assessing the aromaticity and electron density distribution of pyrrole rings. Indeed, predictions regarding the effects of EWGs on the mechanism of pyrrole nucleophilic substitution reactions can be made using ^{13}C NMR data.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada.

Supporting Information Available: Full experimental data for compounds **3**, **4**, **6**, **8**, **9**, **11**, and **12**. Complete X-ray crystallographic data and ORTEP diagrams for pyrroles **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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