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Effect of the leaving group on the reaction of 2-aminopyrroles with electron deficient heteroaromatic azadienes: substitution by addition–elimination versus cycloaddition

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Abstract—When a good leaving group is present in the heteroaromatic azadiene, reaction with 2-aminopyrroles occurs by substitution by addition–elimination instead of cycloaddition. This novel reaction is sensitive to steric effects and takes place in 2-amino-1-methylpyrrole at C-5 and the exo amino group but at C-3 in 2-amino-1-*t*-butylpyrrole.

Only a few examples of inverse-electron demand Diels–Alder (IEDDA) reactions of pyrroles have appeared.[1] Recently, it has been shown that 2-aminopyrroles undergo the IEDDA reaction with 1,3,5-triazines to give pyrrolo[2,3-*d*]pyrimidines.[2,3] IEDDA reactions are governed by the LUMO of the electron deficient azadiene.[4] Based on work[3] on the reaction of simple 2-aminopyrroles[5] with symmetrical 1,3,5-triazines, electron deficient azadienes whose LUMO energies are more negative or comparable to that of the 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (−1.477 eV) would be expected to give cycloaddition products. Reaction of 2,4,5,6-tetrachloropyrimidine with 2-aminopyrroles was studied as a possible route to azaindoles. Its LUMO value (see below) is −1.333 eV and based on this it could be expected that this azadiene would also react with 2-aminopyrroles. Reaction did occur but no evidence for the formation of any cycloaddition product was found. Instead substitution by addition–elimination occurred at both the exo amino group and C-5 or at C-3, depending on the size of the 1-alkyl substituent. This communication reports on the mechanism of this novel 2-aminopyrrole reaction.

Keywords: 2-Aminopyrroles; Substitution; Addition–elimination; Ambident behaviour; Zwitterions; Meisenheimer complex; Leaving group; Steric effects.
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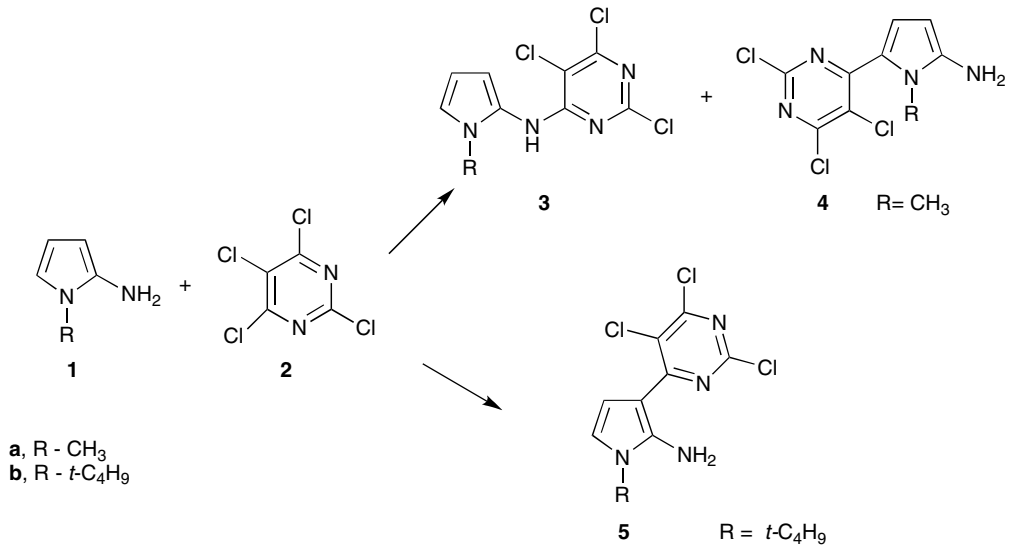
2-Aminopyrroles **1** were generated in situ by adding triethylamine (TEA) to a solution of the tetraphenylborate salt of the 2-aminopyrrole in THF and then adding 2,4,5,6-tetrachloropyrimidine (**2**).[6] Products were isolated by flash chromatography and identified by their spectral properties.[7] Each of the reaction products (**3**–**5**) had an amino group and three chlorine atoms.[7] Scheme 1 illustrates the products obtained and Table 1 summarizes the reaction conditions and yields. No evidence for cycloaddition or other products was found by TLC.

Nucleophilic attack by ammonia and aliphatic and aromatic amines has been reported to occur almost exclusively at C-4(6) of 2,4,5,6-tetrachloropyrimidine (**2**).[9] Structures proposed for 2-aminopyrroles **3**–**5** reflected these results. The ^{1}H NMR spectrum of **3** showed the presence of three-pyrrole ring protons.[7] This compound was therefore assigned the structure indicated in Scheme 1.[8]

The ^{1}H NMR spectra of **4** and **5** each contained a pair of doublets and it seemed unlikely, given the differences in chemical shift, that **4** and **5** were homologs.[7] ^{1}H NMR spectral data could not be used to definitively determine the pattern of substitution in **4** and **5**.[10] Compound **4** reacted with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (IEDDA) in 300 min to give a pyrrolo[2,3-*d*]pyrimidine.[2,3] In contrast after five days, under the same reaction conditions, there was no evidence that **5** had reacted



Scheme 1.

Table 1. Yields and reaction times for addition–elimination reactions

R	Product(s)	**1**/**2**/TEA[a]	Reaction time (h)	Yield[b] (%)
Me	**3**	1.9:1:1.1	20	44
	4			10
Me	**3**	1.1:1:3.1	3	52
	4			15
t-Butyl	**5**	1.9:1:1.1	20	27
t-Butyl	**5**	1.5:1:1	23	75[c]
t-Butyl	**5**	1.1:1:2.1	25	67[d]

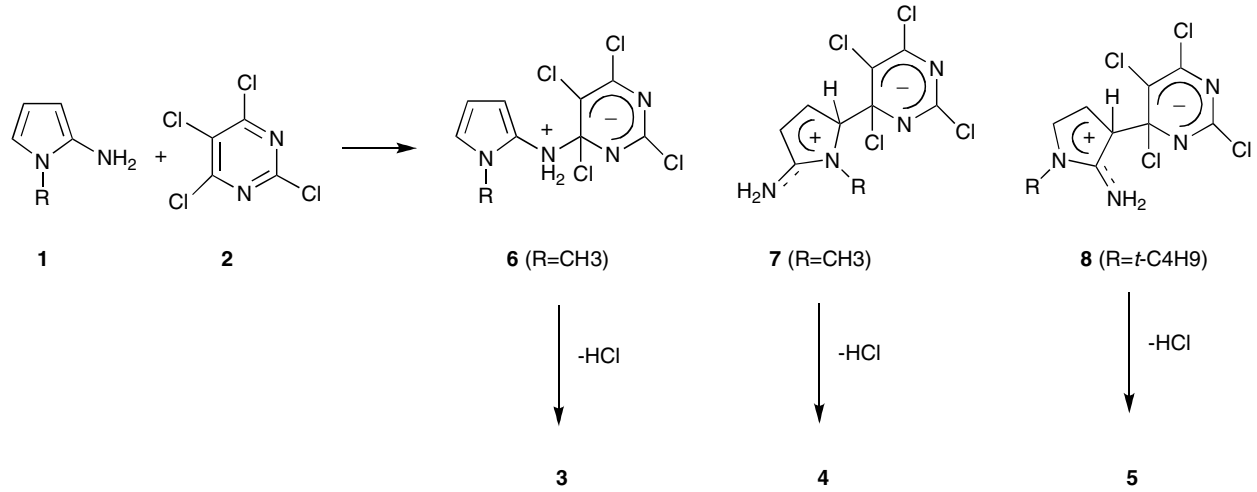
[a] Triethylamine.
[b] Isolated product.
[c] Yield based on 40% recovered **2**.
[d] Yield based on 26% recovered **2**.

with this 1,3,5-triazine. This difference in reactivity was used to distinguish between **4** and **5**.[11]

Stepwise reaction of a pyrrole with a neutral electrophile gives a zwitterion (Meisenheimer complex). Zwitterions, analogous to **6**–**8** (Scheme 2), have been proposed as the initially formed intermediates in the normal Diels–Alder,[12,13] inverse-electron demand Diels–Alder[14] and Michael addition[12,13] reactions of pyrroles. The difference between these cases where addition took place, and this work (addition–elimination), was the presence of a good leaving group (chloride) in the zwitterion. Loss of chloride to give an addition–elimination product was faster than cyclization of the zwitterion.

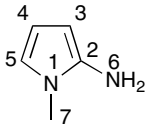
A zwitterion intermediate analogous to **6** has been observed by ^{1}H and ^{19}F NMR in the IEDDA reaction of 2-amino-5-substituted pyrroles with a 1,3,5-triazine.[11] Interestingly this zwitterion does not contain a good leaving group and the expected cycloaddition product was formed.[2,3] Substitution by addition–elimination competed with cycloaddition in the reactions of pyrrole and 1-methylpyrrole with 4,5-dicyanopyridiazine.[15] In these examples the expected zwitterion intermediate also had a good leaving group—cyanide ion.

Reaction of 2-amino-1-*t*-butylpyrrole (**1b**) with **2** occurred exclusively at C-3 to give **5**. Electrophilic sub-



Scheme 2.

Table 2. HOMO and LUMO energies, charge distributions and coefficients for 2-aminopyrroles



	e/au	**1a**		e/au	**1b**	
		HOMO	LUMO		HOMO	LUMO
E/eV:		−7.99	1.29		−7.96	1.36
N-1	−0.1453	−0.075390	−0.406416	−0.1289	−0.072338	−0.408374
C-2	−0.0037	−0.501123	0.570941	−0.0062	−0.515103	0.568207
C-3	−0.2389	−0.420141	−0.308394	−0.2411	−0.406978	−0.317184
C-4	−0.1764	0.297924	−0.249957	−0.1834	0.310311	−0.229477
C-5	−0.1459	0.543809	0.506341	−0.1449	0.546671	0.497878
N-6	−0.2823	0.349849	−0.095750	−0.2839	0.309007	0.076818
C-7	−0.0707	−0.007001	−0.082816	0.0921	0.010530	−0.092915
	$\mu = 2.29$ D $\Delta H_f = 44.933$ kcal mol^{-1}			$\mu = 2.30$ D $\Delta H_f = 36.299$ kcal mol^{-1}		

stitution in pyrroles is very sensitive to the steric bulk of the substituents on the pyrrole nitrogen.[16] Recently the phosphorylation of 1-*t*-butylpyrrole was reported to have occurred exclusively at C-3.[17] It has been reported that in 2-aminofurans substitution by addition–elimination took place at C-5 with 2-aminofuran; but when C-5 was substituted, reaction took place at C-3.[18] Results with 2-amino-1-*t*-butylpyrrole (**1b**) were therefore attributed to a steric effect.[16–18]

Table 2 shows the HOMO/LUMO energies, coefficients and charge distributions calculated for 2-amino-1-methylpyrrole (**1a**) and 2-amino-1-*t*-butylpyrrole (**1b**).[19] As expected the HOMO/LUMO values and the properties at C-3, C-5 and N-6 of the two 2-aminopyrroles are essentially the same. Values calculated for 2,4,5,6-tetrachloropyrimidine (**2**) are: HOMO (−10.318 eV) and LUMO (−1.333 eV). Based on these results 2,4,5,6-tetrachloropyrimidine (**2**) can be classified as a soft electrophile and the 2-aminopyrroles as intermediate between hard and soft nucleophiles. Similar combinations of electrophiles and amines (nucleophiles) have been reported to react preferentially at carbon—as observed in this work (Table 1).[20]

Reaction at C-3 would be predicted (Table 2) to be likely in both 2-aminopyrroles **1a** and **1b**. No C-3 substituted product was observed in the reaction of 2-amino-1-methylpyrrole (**1a**) with **2**. This suggested the possibility that the formation of **5** (with $R = Me$) was not kinetically controlled. Equilibrium between the reactants and zwitterion **8** (with $R = Me$) could explain why no C-3 substitution was observed with **1a**. Zwitterion **8** (with $R = Me$) formed, but loss of chloride ion was slower than its reversion to reactants and subsequent formation of **3** and **4** from their respective zwitterions. The possibility that the formation of all of products (**3**–**5**) was not kinetically controlled cannot be explicitly eliminated. Reversible formation of the initial zwitterion intermediate has been proposed in the IEDDA reaction of 2-amino-5-substituted pyrroles.[11] Similarly the reversible formation of zwitterion intermediates has been reported in the IEDDA reactions of 1,2,4-triazines[21] and 1,2,4,5-tetrazines.[22] It should also be noted that the reversible formation of a Meisenheimer complex (zwitterion) has been observed in aromatic nucleophilic substitution reactions where the nucleophile is an amine.[23]

Reactions described in this communication can be considered to be, with respect to 2,4,5,6-tetrachloropyrimidine, an S_NAR process with an ambident nucleophile (2-aminopyrrole). Ambident behaviour has been reported for 2-aminofurans[18] and 5-aminoimidazoles.[20] The results reported in this communication, are to our best knowledge, novel in the chemistry of 2-aminopyrroles; there are no other reported examples of a 2-aminopyrrole reacting as an enamine or dienamine—undergoing substitution by *competitive* addition–elimination reactions.[24,25] It has been reported that simple 2-aminopyrroles reacted with dimethyl acetylenedicarboxylate (DMAD) to give Michael addition products at C-5.[26] DMAD reacted with a 2-amino-3-cyano-3,4-dimethylpyrrole at the exo amino group and at C-5.[27] The latter reaction gave a non-pyrrolic addition product.

When 2,4,5,6-tetrachloropyrimidine (**2**) is used as the electron deficient heteroaromatic azadiene substitution by addition–elimination takes place not because it is a super electrophile, but because it contains a good leaving group. Substitution by addition–elimination would be expected to be a competitive process in non-concerted IEDDA reactions when the electron deficient azadiene bears a potential leaving group.[15]

Acknowledgements

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