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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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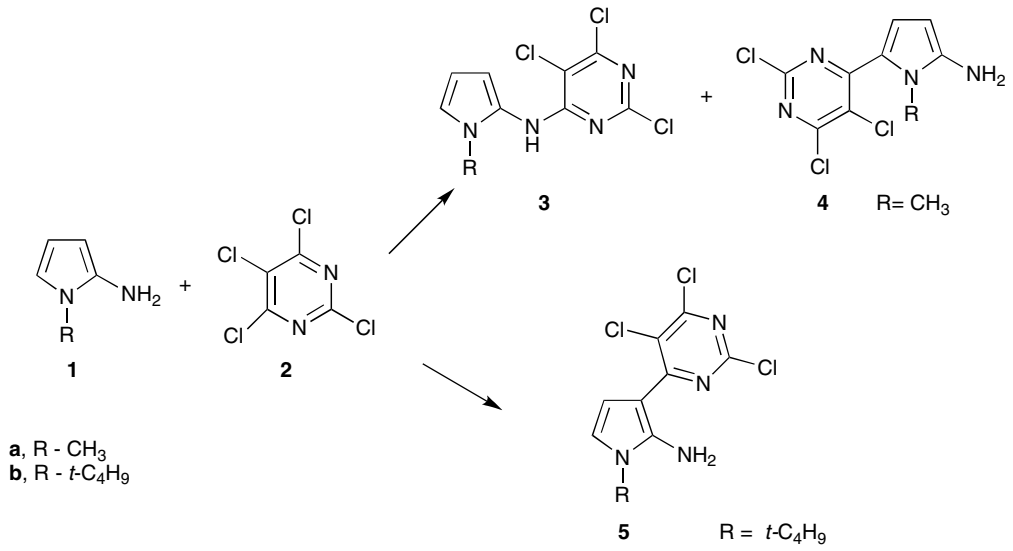
2-Aminopyrroles **1** were generated in situ by adding triethylamine (TEA) to a solution of the tetraphenylborate salt of the 2-aminopyrrole in THF and then adding 2,4,5,6-tetrachloropyrimidine (**2**).[6] Products were isolated by flash chromatography and identified by their spectral properties.[7] 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]

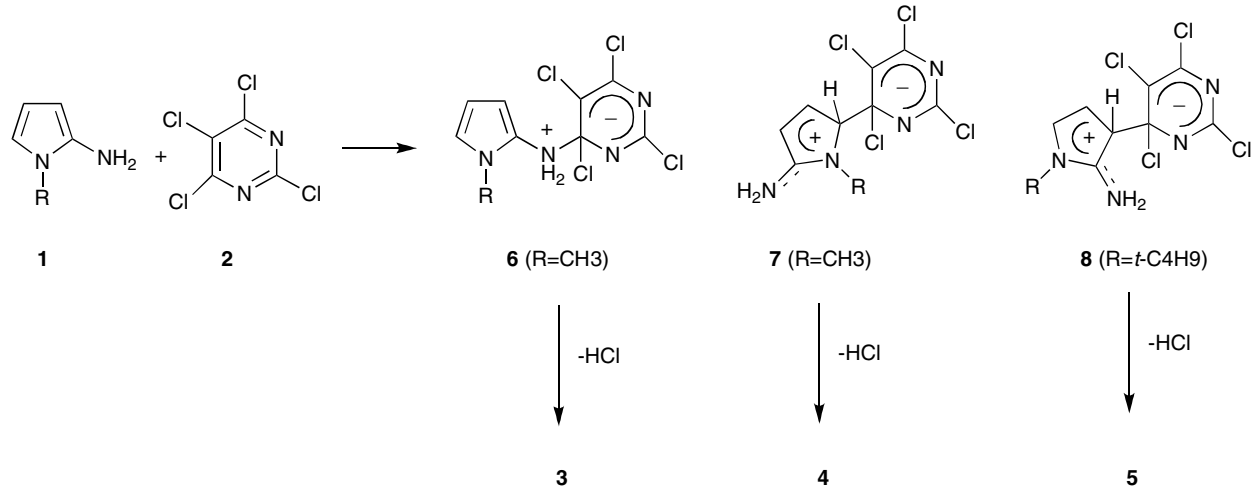
[a] Triethylamine.
[b] Isolated product.
[c] Yield based on 40% recovered **2**.
[d] Yield based on 26% recovered **2**.

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.