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Mechanism of the inverse-electron demand Diels–Alder reaction of 2-aminopyrroles with 1,3,5-triazines: detection of an intermediate and effect of added base and acid

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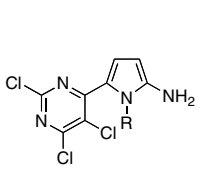
Abstract—In base, a 2-aminopyrrole reacted with a 1,3,5-triazine to give a zwitterion (Meisenheimer complex). Acid promoted its conversion to the pyrrolo[2,3-*d*]pyrimidine. A cascade mechanism with reversible steps is proposed to explain why both a base and an acid are needed for the cycloaddition to occur.

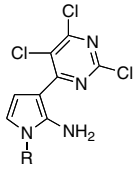
Substitution by addition–elimination was observed when 1-alkyl-2-aminopyrroles reacted with 2,4,5,6-tetrachloropyrimidine.[1] The structures of two of the isolated compounds are shown below. Spectral evidence could not be used to conclusively establish the structures of **1** and **2**. Compound **1** would be expected to undergo the inverse electron-demand Diels–Alder reaction (IEDDA) with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**3**) to give a pyrrolo[2,3-*d*]pyrimidine **8**.[2–4] But **2** would not be expected to react with **3** based on the expected steric interaction between the pyrrole substituent on C-3 and the 1,3,5-triazine ring. This difference in reactivity could then be used to distinguish between **1** and **2**. Reaction of **1a** (R = methyl) and **1b** (R = ethyl) and **3** did indeed give the expected pyrrolo[2,3-*d*]pyrimidines **8**—but not under neutral conditions. Only when a catalytic amount of base was present did the reaction take place with the resulting formation of an intermediate. This Letter examines the structure of the intermediate and how it is formed and converted to the final cycloaddition product **8**.

Scheme 1 summarizes the proposed mechanism for the formation of the pyrrolo[2,3-*d*]pyrimidines **8**. Evidence for this mechanism is given below.

No reaction was observed after 35 min when **1** and **3** (1.5 equiv) were combined in THF. Reaction only took



1 (R = CH_3)



2 (R = t-C_4H_9)

place after a catalytic amount (0.25 equiv) of triethylamine (TEA) was added to the reaction mixture. In the presence of a base, the starting 2-aminopyrrole **1** was not observable after 90 min. It became clear from the NMR spectra of the reaction mixture (THF-d_8) that an intermediate was present in the solution. Proton NMR indicated the presence of one pyrrole ring proton and an NH_3^+ group in the intermediate; the ^{19}F NMR showed the presence of two CF_3 groups in a ratio of 2:1. Based on this, the intermediate was identified as zwitterion **5** in the proposed mechanism (Scheme 1).[6] Intermediate **5** was stable in the presence of TEA. Addition of 5 equiv of trifluoroacetic acid (TFA) converted **5** to pyrrolo[2,3-*d*]pyrimidines **8**. Proton NMR spectra in Figure 1 (R = ethyl) illustrate the changes that occurred during the reaction. Products **8** were isolated by flash chromatography and their structures confirmed by spectral evidence and X-ray crystallography.[6,7] After five days, under the same reaction conditions, there was no evidence that **2** had reacted with **3**. This difference in reactivity supported the assigned structures.[1]

Theoretical studies have concluded that the IEDDA reaction of 2-aminopyrroles with 1,3,5-triazines follows

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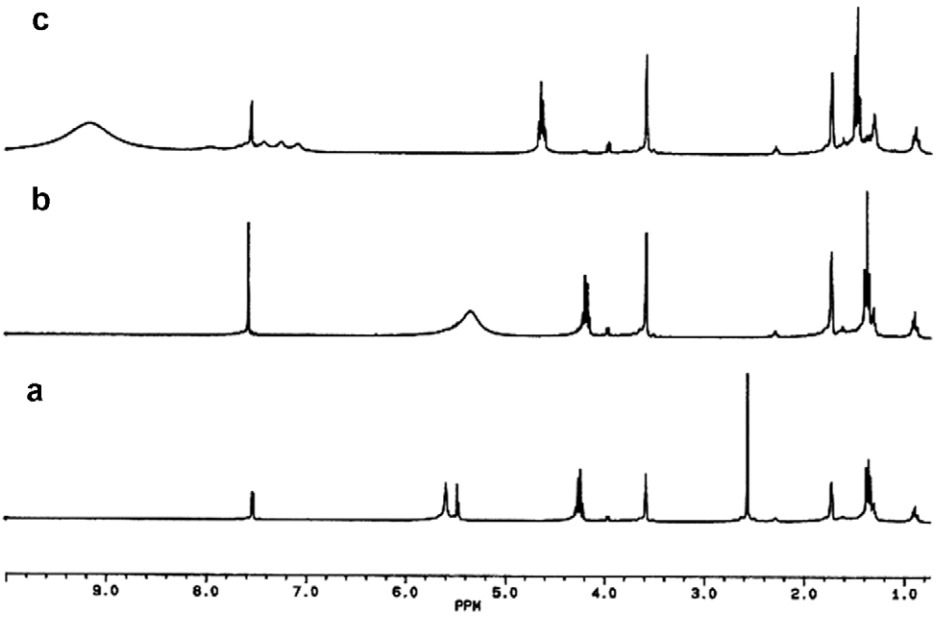
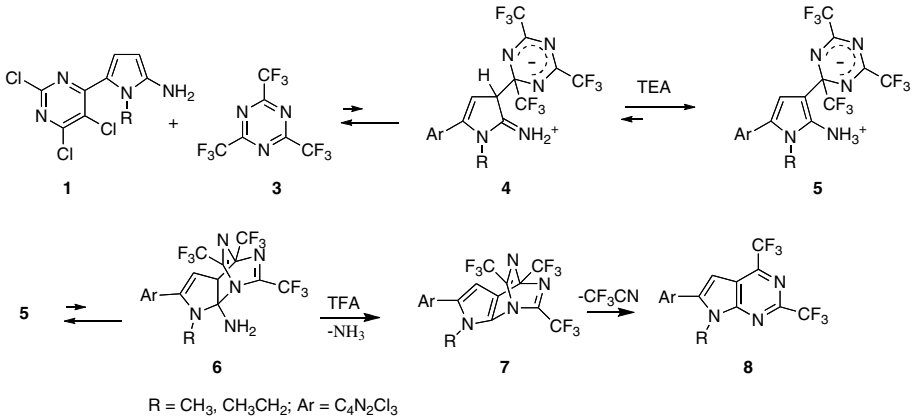


Figure 1. (a) Starting mixture of 2-aminopyrrole **1b** and 1,3,5-triazine **3** in THF-d_8 (peak at ca. δ 2.6 is water); (b) 90-min after the addition of 0.25 equiv of $(C_2D_5)_3N$; (c) 210 min after the addition of 5 equiv of TFA.

a cascade mechanism in which the cycloadduct first eliminates NH_3 to form pyrrole **7** followed by a retro Diels–Alder reaction to give the final product **8**.[5] None of the proposed intermediates (**5**–**7**) have been previously detected.[2,5] Initial nucleophilic addition of 2-aminopyrrole **1** to 1,3,5-triazine **3** gave zwitterion **4**.[2] Based on the catalytic effect of TEA, it is proposed that **4** was not stable with respect to the starting materials. Addition of TEA catalyzed the tautomerization of **4** to the more stable (aromatic) **5**. Analogous zwitterions have been detected[8] or isolated[9,10] in IEDDA reactions of 1,2,4-triazines[10] and 1,2,4,5-tetrazines.[8,9] They have also been reported to be in equilibrium with starting materials.[8–10]

An attempt was made to isolate zwitterion **5b** by flash chromatography. On silica gel zwitterion **5b** reverted to the starting materials and also gave the final product. This indicated that in solution, **5** may also be in equilibrium with the starting materials.[8–10] Addition of 5 equiv of TFA converted **5b** smoothly to pyrrolo[2,3-*d*]pyrimidine **8b** (Fig. 1). Acids have been reported to catalyze both the retro Diels–Alder reaction and the aromatization step, where the amino group is lost.[11]

No product was formed in the absence of added acid. This suggested that there also existed an equilibrium between zwitterion **5** and cycloadduct **6**. Addition of strong acid led to the rapid and irreversible elimination of ammonia; this was followed by a retro Diels–Alder reaction to give the final product. When TFA was added the ^{19}F NMR signals of the two non-equivalent CF_3 groups in **5** broadened. This was the most likely evidence for an equilibrium between **5** and **6**. Similar equilibria could not be ruled out in IEDDA reactions of 1,2,4-triazines[10] and 1,2,4,5-tetrazines.[9] Another possibility was that **5** was in equilibrium with a small amount of the protonated zwitterion.[8,10] The latter reaction would be a blind alley in that the protonated zwitterion would not be expected to go on to the final product.[8,10]



Scheme 1.

Any proposed mechanism, for the reaction under study, must include intermediates that can be affected by added base and acid in separate steps. The effects of added base and acid, on the progress of the reaction, can best be explained by a cascade mechanism in which there is a tautomeric equilibrium between zwitterions **4** and **5** and only the last two steps, loss of ammonia and retro Diels–Alder, are not reversible (Scheme 1). This is the first example in which such an intermediate has been detected in an IEDDA reaction of pyrroles[12] or 2-aminopyrroles.[2,3] Additionally, to our best knowledge, this appears to be the only example of an inverse electron demand Diels–Alder reaction in which both a base and an acid are needed for the reaction to proceed to the final product.

Studies are underway to determine the generality of the proposed mechanism in 2-aminopyrroles.

Acknowledgements

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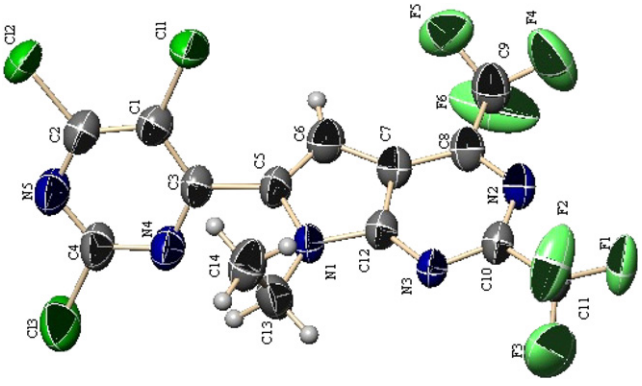
6. Compound **5a**: ^1H NMR δ_H (300 MHz, THF-d_8): 7.55 (s, 1H), 5.28 (br s), 3.63 (s, 3H); ^{19}F NMR δ_F (282 MHz, THF-d_8, CF_3COOH reference): −74.07 (s, 6F), −82.98 (s, 3F). Compound **5b**: ^1H NMR δ_H (300 MHz, THF-d_8): 7.61 (s, 1H), 5.40 (br s), 4.17 (q, 2H, $J = 7.0$ Hz), 1.37 (t, 3H, $J = 7.0$ Hz); ^{19}F NMR δ_F (282 MHz, THF-d_8, CF_3COOH reference): −74.14 (s, 6F), −83.18 (s, 3F). Compound **8a**: white crystalline solid ($EtOH/H_2O$) mp 161.5 °C; 74% yield (94% isolated yield); ^1H NMR δ_H (300 MHz, THF-d_8): 7.58 (q, 1H, $J = 1.7$ Hz), 4.094 (s, 3H); ^{19}F NMR δ_F (282 MHz, THF-d_8, CF_3COOH reference): −67.46 (d, 3F, $J = 1.7$ Hz), −69.40 (s, 3F); IR (polyethylene film): 2901, 2837, 1536, 1513, 1420, 1311, 1281, 1208, 1159, 977, 774 cm^{-1}. Compound **8b**: white crystalline solid ($EtOH/H_2O$) mp 123 °C; 67% yield (88% isolated yield; ^1H NMR δ_H (300 MHz, THF-d_8): 7.55 (q, 1H, $J = 1.7$ Hz), 4.63 (q, 2H, $J = 7.1$ Hz), 1.48 (t, 3H, $J = 7.1$ Hz); ^{19}F NMR δ_F (282 MHz, THF-d_8, CF_3COOH reference): −67.49 (d, 3F, $J = 1.7$ Hz), −69.40 (s, 3F); IR (polyethylene film): 2926, 2880, 1508, 1432, 1297, 1270, 1236, 1152, 990, 773 cm^{-1}.
7. Below is the ORTEP diagram for **8b**. X-ray crystallographic data: Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Nos. CCDC 621301 and 621302. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].



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