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On the Mechanism of Condensation between 5-Amino-4, 6-dichloro-2-methylpyrimidine and 1-Acetyl-2-imidazolin-2-one

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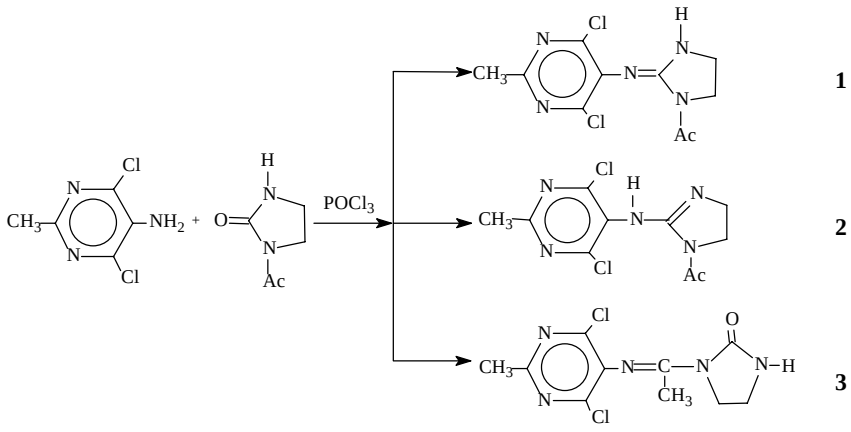
Abstract: The condensation reaction between 5-amino-4, 6-dichloro-2-methylpyrimidine and 1-acetyl-2-imidazolin-2-one using $POCl_3$ as solvent gave 4, 6-dichloro-2-methyl-5-(1-acetyl-tetrahydro-imidazo-2-ylidene)-aminopyrimidine predominantly and 4, 6-dichloro-2-methyl-5-{1-[1-(2-oxo-tetrahydro-imidazolyl)]-acetyene}-aminopyrimidine as by-product. No 4, 6-dichloro-2-methyl-5-(1-acetyl-2-imidazolin-2-yl)-aminopyrimidine was found. The result indicated an esterifi- cation-addition-elimination mechanism.

Keywords: Moxonidine, X-ray single crystal diffraction, GHMBC.

The condensation reaction of 5-amino-4, 6-dichloro-2-methylpyrimidine and 1-acetyl-2-imidazolin-2-one is a key step to prepare Moxonidine hydrochloride. It had been reported[1] that **2** was the main product in this reaction, but **1** and **3** could be possible obtained according to the formation mechanism of Schiff base[2] (**Scheme 1**). It was difficult to differentiate **1** and **2** by routine 1D ^1H or ^{13}CNMR. However, with the aids of 2DNMR(GHMBC) and X-ray diffraction spectrum, the real structure of the main product was confirmed to be **1**.

Scheme 1



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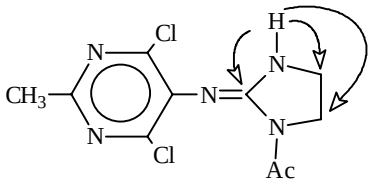
In our experiment, only two products of this reaction had been obtained and separated by PTLC and repeated recrystallization in the yield of 46% and about 1% respectively. Indeed the main product had the same melting point as the reported compound **2**[1], but according to its GHMBC spectrum (**Figure 1**) the structure of the main product was **1**.

Figure 1 The H-C correlations indicated in GHMBC



The GHMBC spectrum shows two crosspeaks between the NH proton and the two $-CH_2-$ C-atoms, *i.e.* the NH proton couples with the two methylene carbon atoms. This indicates that the NH is adjacent to the $-CH_2-$. Likewise, no crosspeak is observed between the NH proton and the aromatic carbons. Such crosspeaks should definitely have been observed if the NH proton was adjacent to the aromatic ring. The more direct and confirmative evidence is the X-ray diffraction spectrum of that compound (**Figure 2**), which indicated without doubt its real structure to be as illustrated as **1**. In the same way, the molecular perspective of compound **3** (mp 228°C) was also obtained (**Figure 3**)[4].

Figure 2 Molecular perspective for compound **1**

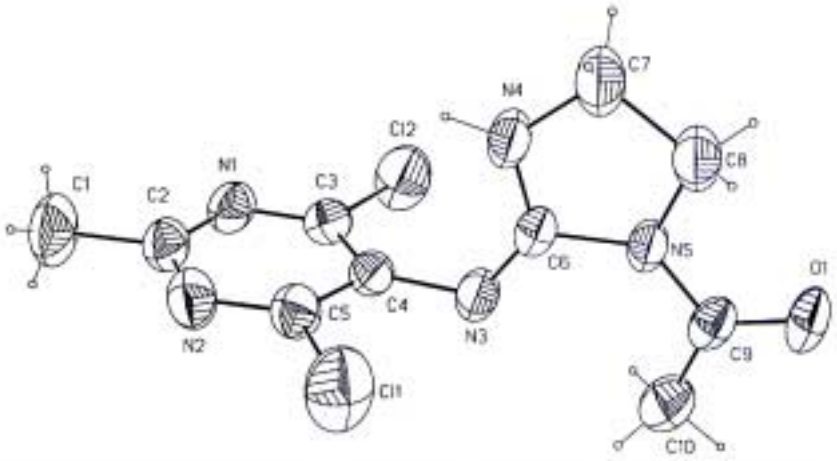
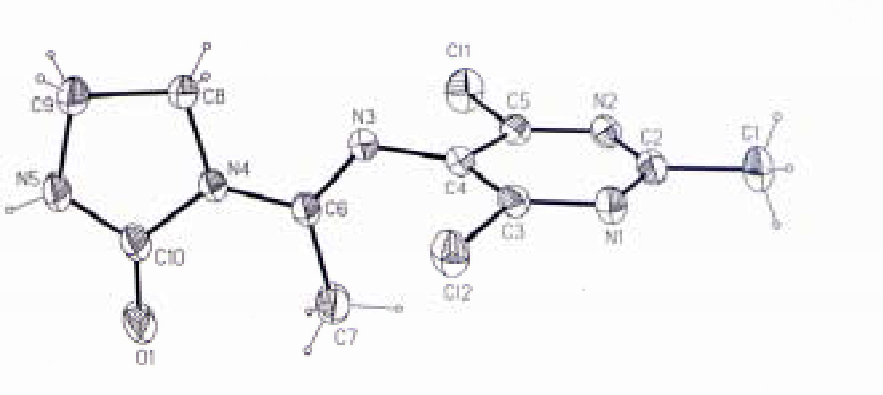
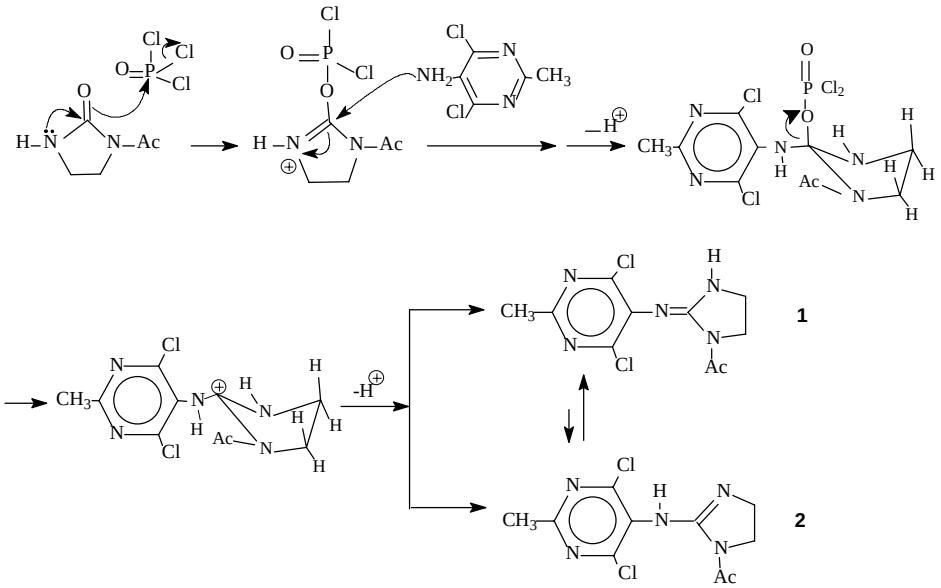


Figure 3 Molecular perspective for compound **3**



The mechanism for this reaction might be somewhat different to the classical Schiff base formation process[2], because in this experiment $POCl_3$ was used as solvent. In addition, the carbonyl group was affected greatly by the unshared pair of electrons on the adjacent nitrogen, so it was difficult for the initial addition between the amine group and the carbonyl group. According to the mechanism of Bischler-Napieralski synthesis[3], it was speculated that this reaction could be an esterification-addition-elimination mechanism showed in **Scheme 2**.

Scheme 2



In the first step, the carbonyl group was esterificated by $POCl_3$and then was attacked by the amine group to give the additive intermediate. If the carbonyl group was attacked prior to the esterification, then **3** would be the main product because the

carbonyl group of the acetyl was affected only by one nitrogen. It was more active than the carbonyl group of the imidazolin. However, in the esterification process, due to the neighboring group participation of the unshared pair of electrons on the two adjacent nitrogens, the carbonyl group of the imidazolin was more active, and therefore it was the main reaction position and would give **1** or **2** predominantly. The reason why compound **2** was not obtained was still unclear. The possible explanation we suggest is that the nitrogen hydrogen bond in the imidazolin ring is not coplanar with the unoccupied *p* orbital of the carbocation due to the rigid structure of the imidazol ring, and thus the proton on the imidazole ring leaves more difficultly than the proton outside the ring, or compound **2** is less stable than **1** in dynamics.

References and Notes

1. S. Wolfgang, F. Wolfgang, C. Erich, A. Ben, [P], GE: 2847537, **1980-05-19** (CA **1980**, 93: 239453g).
2. A. Wingrove, R. L. Caret, *Organic Chemistry*, 2nd ed., NewYork, N.Y., **1981**, pp.1121-1122.
3. R. O. C. Norman, *Principles of Organic Chemistry*, 2nd ed., London, **1978**, p.683-684.
4. Crystallographic parameters have been deposited in the editorial office of CCL.

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