Reaction of *N*-Amino-4,6-dimethylpyrimidinium Mesitylene Sulfonate with Nucleophiles (1,2). A ^{15}N-Study

Henk C. van der Plas*, Sylwester Baloniak and Hugo Jongejan

Department of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

Received July 15, 1982

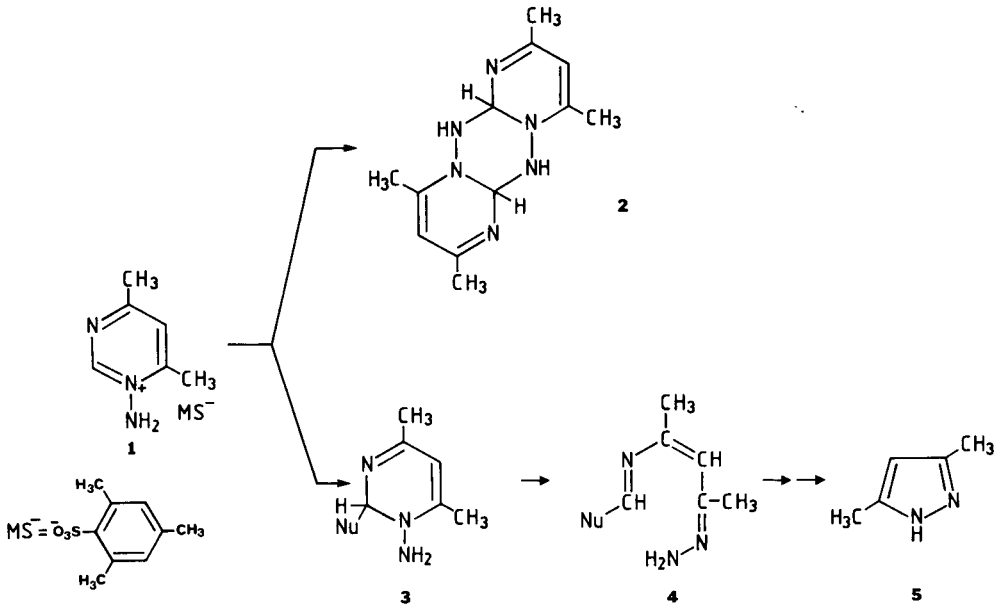
Reaction of *N*-amino-4,6-dimethylpyrimidinium mesitylene sulfonate with liquid ammonia, with an aqueous solution of sodium hydroxide or with hydrazine leads to 3,5-dimethylpyrazole. Reaction of this salt with ^{15}*N*-labelled hydrazine gave incorporation of nitrogen-15 in 3,5-dimethylpyrazole and in recovered starting material. Evidence has been presented that the initial step in the ring contraction with hydrazine is the addition of the nucleophile to C−2 and C−6. It is suggested that in the presence of a base the reactive species is probably 4,6-dimethylpyrimidinio amide.

J. Heterocyclic Chem., **20**, 415 (1983).

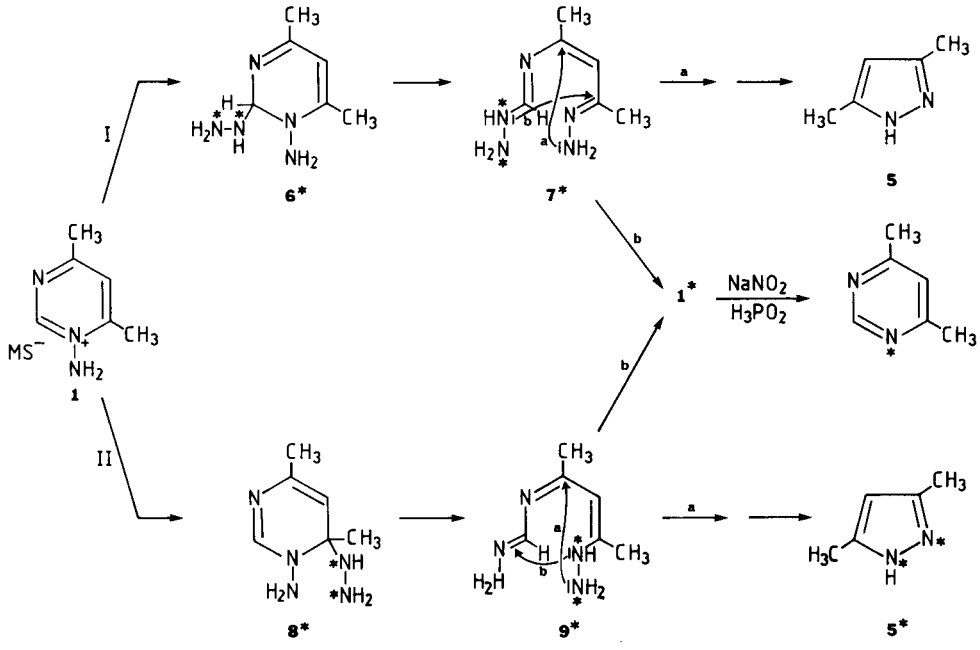
N-Amino-4,6-dimethylpyrimidinium mesitylene sulfonate (**1**) has been reported (3) to give with liquid ammonia dimer **2** and 3,5-dimethylpyrazole (**5**). The ring contraction was supposed to occur *via* the intermediacy of 1,2-diamino-1,2-dihydro-4,6-dimethylpyrimidine (**3**, Nu = NH_2) and *N*-(3-hydrazono-1,3-dimethylpropenyl)formamidine (**4**, Nu = NH_2) (Scheme 1). No nmr evidence for the intermediacy of **3** and **4** was found.

This mechanistic picture shows that ammonia serves as a nucleophile to form the dihydro compound **3**, but that it is not actually involved in the cyclisation step. It implies that **5** would also be formed if **1** was treated with a hydroxide solution. This has indeed been found. When reacting **1** with an aqueous solution of sodium hydroxide at room temperature at various *p*H's we observed that in the *p*H-range 7.8−10 compound **5** was obtained in a yield of about 90%. At a somewhat lower *p*H the yields were drastically lowered (*p*H = 7.5, yield 56%; *p*H = 7.3, yield 41%; *p*H = 6, yield 0%). From these results it is evident that also in the reaction of **1** with sodium hydroxide the nucleophilic hydroxide ion serves as reagent to form the intermediate (**3**, Nu = OH), but does not play a role in the cyclisation of **4** (Nu = OH) to **5**.

Compound **5** was also obtained in high yield (80%) when **1** was reacted with a solution of anhydrous hydrazine in THF at room temperature for three hours. However, in contrast to the reaction with liquid ammonia or sodium hydroxide, with hydrazine not one, but two mechanistic pathways can explain the formation of **5**: route I (see Scheme 2), describing a series of reaction steps, which start by addition of the hydrazine at C−2 (in analogy to the pathway given in Scheme 1, Nu = $NHNH_2$) and route II in which the initial addition of hydrazine occurs at C−6. As one can see route II differs from route I in



Scheme 1



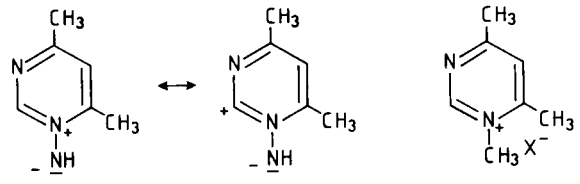
Scheme 2

respect to the role of hydrazine. Besides serving as reagent to form the dihydro compound, it is also involved in the cyclisation step.

In order to differentiate between both routes I and II we investigated the ring contraction of **1** into **5** with ^{15}N-double labelled hydrazine (% ^{15}N = 10.4%) [prepared from 1 equvalent of ^{15}N-labelled hydrazine sulfate and 1 equivalent of barium hydroxide]. When **1** was reacted with a slight excess (1.2 equivalent) of ^{15}N-labelled hydrazine at room temperature at *p*H = 8 for three hours, the 3,5-dimethylpyrazole was found to contain 4.0% of ^{15}N-labelling, allowing the conclusion that about 38% of 3,5-dimethylpyrazole was formed by route II and the remaining 62% by the competitive route I.

However, a more detailed investigation of the ring contraction indicates that the conclusion just presented above, needs to be modified, for if the reaction of **1** with the ^{15}N-double labelled hydrazine (% ^{15}N = 10.4) was carried out for ten minutes instead of three hours and starting material was recovered, we found that in the recovered material (**1***) a considerable excess of nitrogen-15 was present: removing the *N*-amino group from **1*** by diazotization with sodium nitrite and hypofosforic acid gave 4,6-dimethylpyrimidine with 5% of nitrogen-15. The incorporation of nitrogen-15 in the pyrimidine ring can only be explained by ring closure of the open-chain species **7*** and/or **9*** (Scheme 2).

This finding leads to the important consequence that **5*** needs not necessarily be formed by route II in Scheme 2, as suggested above, but can also occur by reaction of **1*** with unlabelled hydrazine, following route I in Scheme 2. Although the complexity of the reaction does not allow firm conclusion on the contribution of each of the pathways I and II to the formation of **5** (**5***), the results seem to indicate that hydrazine, in contrast to liquid ammonia or an aqueous base solution, can give addition at C−2 and C−6 in **1**. Further investigations have shown that if a greater excess of ^{15}N-double labelled hydrazine (10.4% ^{15}N) was used, the incorporation of nitrogen-15 in 3,5-dimethylpyrazole was considerably increased. With 5 equivalents of ^{15}N-labelled hydrazine 8.0% of ^{15}N was present in **5** (**5***), with 10 equivalents, 8.7% of ^{15}N was incorporated. This result is understood by assuming that with the excess of ^{15}N-labelled hydrazine the unlabelled hydrazine moiety in **7*** or **9*** is exchanged for the labelled hydrazino group, although it cannot by excluded that with a greater excess of hydrazine a di-adduct was formed which after ring opening and ring closure would lead to **5** (**5***) with a higher incorporation of nitrogen-15. The interesting question arises why with sodium hydroxide the addition takes place exclusively at C−2, while with hydrazine the addition probably takes place at C−2 and C−6. We suggest that in the presence of the hydroxide the active species was not **1** but its *N*-ylid **10a** ↔ **10b**, formed by deprotonation of the *N*-amino group. In this 4,6-dimethylpyrimidinio amide (**10**) position 2 is probably more electron-deficient than position **6** (4). Evidence for that supposition can be taken from formation of dimer **2** when **1** was reacted with liquid ammonia (Scheme 1), by a 1,3-dipolar cyclization of the *N*-ylid **10b** (3,4).



10a **10b** **11**

Scheme 3

We postulate that in the presence of hydrazine ($pH = 8$) compound **1** is not fully deprotonated and that at $pH = 8$ we deal with a mixture of **1** and its conjugated base **10** as actual substrates. Compound **1** can be expected to have similar reactivity as 1-methylpyrimidinium salt **11**. Since **11** shows an exclusive addition with hydrazine to C−6 we postulate that in the reaction of **1** with hydrazine the addition at C−2 occurs in **10** and the addition at C−6 in **1**.

EXPERIMENTAL

O-Mesitylene sulfonylhydroxylamine (MSH) and 1-amino-4,6-dimethylpyrimidinium mesitylene sulfonate were prepared as described in the literature (6,7). To keep the *p*H constant during the reactions we used a combination of a Radiometer ABU 80 Autoburette, a TTT Titrator and a PHM 64 Research *p*H-meter.

1. Reactions of 1-Amino-4,6-dimethylpyrimidinium Mesitylene Sulfonate (**1**).

a. With Double Labelled Hydrazine into ^{15}N-Labelled 4,6-Dimethylpyrimidine.

An amount of 0.09 g (6.9×10^{-4} moles) of hydrazine sulfate containing 10.4% of double labelled nitrogen-15, and 0.22 g (6.9×10^{-4} moles) of barium hydroxide octahydrate were mixed in 60 ml of water. The barium sulfate was filtered off and to the resulting solution 0.15 g (4.8×10^{-4} moles) of **1** was added. The reaction mixture was kept with stirring at *p*H = 8 for 10 minutes, then the mixture was brought to *p*H = 6 and the solution was evaporated to dryness *in vacuo* (bath temperature 35°). The residue was extracted with dichloromethane, the combined extracts dried over magnesium sulfate and distilled off. The residue (containing 0.15 g of **1**) was dissolved in 3 ml of water and 2 ml of hypophosphoric acid. To this solution, with stirring and at a temperature below 15°, 30 mg of sodium nitrite was added in small protions, after which the reaction mixture was stirred for half an hour. The mixture was then basified and extracted with ether. The ether was dried over magnesium sulfate and distilled off. The mass spectrum of the residue showed a (M + 1) peak of 5.0% (duplo 4.9%) of 4,6-dimethylpyrimidine (8). The ^1H nmr data: δ 8.82 ppm (s, H−2), 6.95 (s, H−5), 2.45 (s, 2 × CH_3).

b. With Double Labelled Hydrazine into ^{15}N-Labelled 3,5-Dimethylpyrazole.

Hydrazine sulfate [0.09 g (6.9×10^{-4} moles)] containing 12.1% of double labelled nitrogen-15 and 0.22 g (6.9×10^{-4} moles) of barium hydroxide octahydrate were mixed in 60 ml of water. Barium sulfate was filtered off and to the resulting solution 0.15 g (4.8×10^{-4} moles) of **1** was added. The reaction mixture was kept at *p*H = 8 for several hours with stirring, after which the solution was brought to *p*H = 6. After extraction with chloroform and drying the extracts over sodium sulfate the solvent was distilled off. The residue was crystallized from petroleum ether (40/60) yielding 0.05 g of 3,5-dimethylpyrazole, mp 106−108° (9); ^1H-nmr: δ 8.30 ppm (broad s, NH), 5.77 (s, 4−H), 2.21 (s, 2 × CH_3).

c. With Anhydrous Hydrazine and Tetrahydrofuran.

Compound **1** [0.15 g (4.8×10^{-4} moles)] was dissolved in 10 ml of dry tetrahydrofuran. A solution of 0.024 g (7.5×10^{-4} moles) of anhydrous hydrazine (10) in 5 ml of dry tetrahydrofuran was added dropwise to the stirred reaction mixture. After continuous stirring for 3 hours at room temperature the solvent was distilled off and the residue extracted with ether. The combined ether extracts were dried over sodium sulfate. After distilling off the solvent 80% of 3,5-dimethylpyrazole was obtained.

d. With Base.

Compound **1** [0.15 g (4.8×10^{-4} moles)] was dissolved in about 10 ml of water and reacted at room temperature, keeping the *p*H constant at the various desired values for 21 hours. The reaction was then stopped by acidifying the solution to *p*H = 6. The reaction mixture was extracted with chloroform, the combined extracts were dried over sodium sulfate and distilled off, yielding 3,5-dimethylpyrazole.

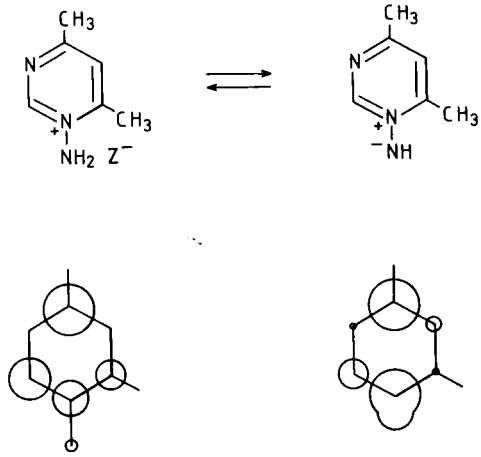
REFERENCES AND NOTES

(1) Part **92** on Pyrimidines. See for part **91**, V. N. Charushin and H. C. van der Plas, *J. Org. Chem.*, submitted.

(2) Part **28** on Ring Transformations of Heterocycles with Nucleophiles. See for part **27**, reference 1.

(3) F. Roeterdink and H. C. van der Plas, *Rec. Trav. Chim.*, **95**, 282 (1976).

(4) Tentative SCP-PPP calculations on the reactivity of *N*-amino- and *N*-methylpyrimidinium salts with ammonia using frontier molecular orbital theory, have been carried out. The parameters of the frontier orbital density of nucleophilic attack support the fact that the imino form **10a** is the reactive species and that C−2 in **10a** is much more favored for nucleophilic attack than C−6. Moreover these calculations indicate that the *N*-methyl (**11**) and *N*-amino-4,6-dimethylpyrimidinium salts (**1**) have a similar reactivity-pattern (R. J. Platenkamp, E. A. Oostveen, F. Roeterdink and H. C. van der Plas, unpublished results).



Scheme 4

(5) H. C. van der Plas and H. Jongejan, *Rec. Trav. Chim.*, **87**, 1065 (1968).

(6) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita and M. Ikeda, *Tetrahedron Letters*, 4133 (1972).

(7) K. Kasuga, M. Hirobe and T. Okamoto, *Chem. Pharm. Bull.*, **22**, 1814 (1974).

(8) H. Bredereck, R. Gomper and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

(9) A. I. Vogel "Textbook of Practical Organic Chemistry", Third Ed, 842, London, 1957.

(10) G. Braunitzer, *Chem. Ber.*, **88**, 2025 (1955).