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THE ACTION OF MALEIC ANHYDRIDE TOWARD 4-METHYLPYRIMIDINE

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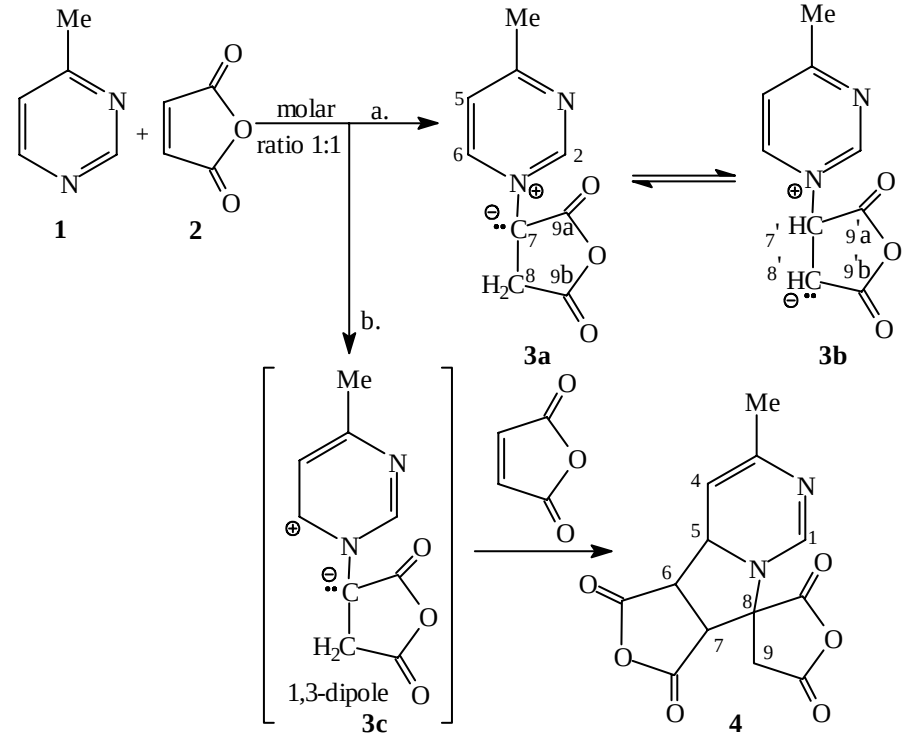
Abstract-A method for obtaining a new class of pyrimidinium ylides (type **3**) is presented. Their structures have been proved both by chemical and spectral methods (including two-dimensional experiments: 2D-COSY, 2D-HETCOR and 2D-HETCOR long range). The ability of the ylide to react with activated alkynes and alkenes has been studied. The ylide (**3)** could act as an initiator in anionic polymerisation leading to oligomers.

Few studies have been performed of reactions of *N*-heterocycles with unsaturated anhydrides in order to obtain *N*-ylides.[1-8] Moreover, these studies have been focused particularly on the reactions between *N*-heterocycles and unsaturated anhydrides in a molar ratio 1:2 leading to spiro compounds or bis-anhydride adducts. Less is known about the reactions[2,3,5] using a molar ratio of 1:1 and the results are rather irrelevant.[8] As for pyrimidine, this type of reactions has not been studied at all.

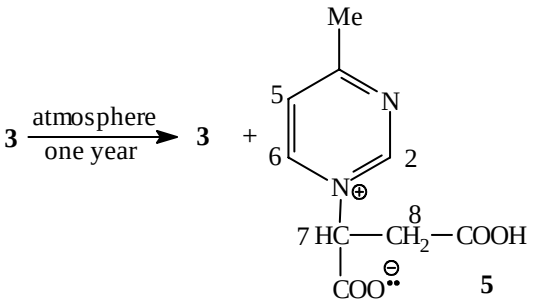
Taking into account the points above and the possible practical uses of the newly obtained compounds as well (biological,[9] semiconductors[10] etc.), we have conducted a detailed study of the reaction between 4-methylpyrimidine and maleic anhydride.

First we considered the reaction between 4-methylpyrimidine and maleic anhydride in a molar ratio of 1:1, in order to prepare the new ylide (**3)**. It was possible to obtain **3** only in the solid-phase by grinding the two reactants in an agate mortar (pathway a). Despite literature data[2,3,5,6] according to which such ylides can be prepared in solution, our attempts in this respect failed. Although we employed a wide range of solvents with different polarities and boiling points (benzene, xylene, chloroform, acetone, acetonitrile, acetic acid), the reaction did not take place leading to recovery of starting materials or complex mixtures of products, which lacked the ylide structure.

The yield of the ylide (**3)** was low (25-30%) and so we re-examined the brownish residue subsequent to the recrystallization of **3**. Unexpectedly, after purifying the residue, we isolated the spiro compound (**4)**.



Perhaps part of the ylide (**3)** reacts *in situ*, most probably *via* a [3+2] dipolar cycloaddition, with the anhydride leading to the spiro compound (**4**) (pathway b). Ylide (**3)** has two tautomeric forms (**3a**) and (**3b**). Analysis of its ^{1}H-NMR spectra immediately after preparation shows the formation of the two tautomers in a molar ratio of 7:1 (**3a**/**3b**). A thorough tautomeric study extended over a period of one year showed that the tautomeric equilibrium does not vary significantly with time, and the ylide (**3**) was kept under anhydrous conditions in vacuum. In an atmospheric environment, the ylide (**3**) was partially hydrolysed, with the formation of a mixture of the ylide and the acid (**5**)**.**



The structure of ylide (**3)** was proved by spectral analysis and chemical proves [elemental analysis (C, H, N) and reactions]. As far as the spectral analysis is concerned, the following experiments have been conducted: IR, ^{1}H NMR, ^{13}C NMR, MS and two-dimensional experiments 2D-COSY, 2D-HETCOR, 2D-HETCOR long range. They all confirm the suggested
structure.

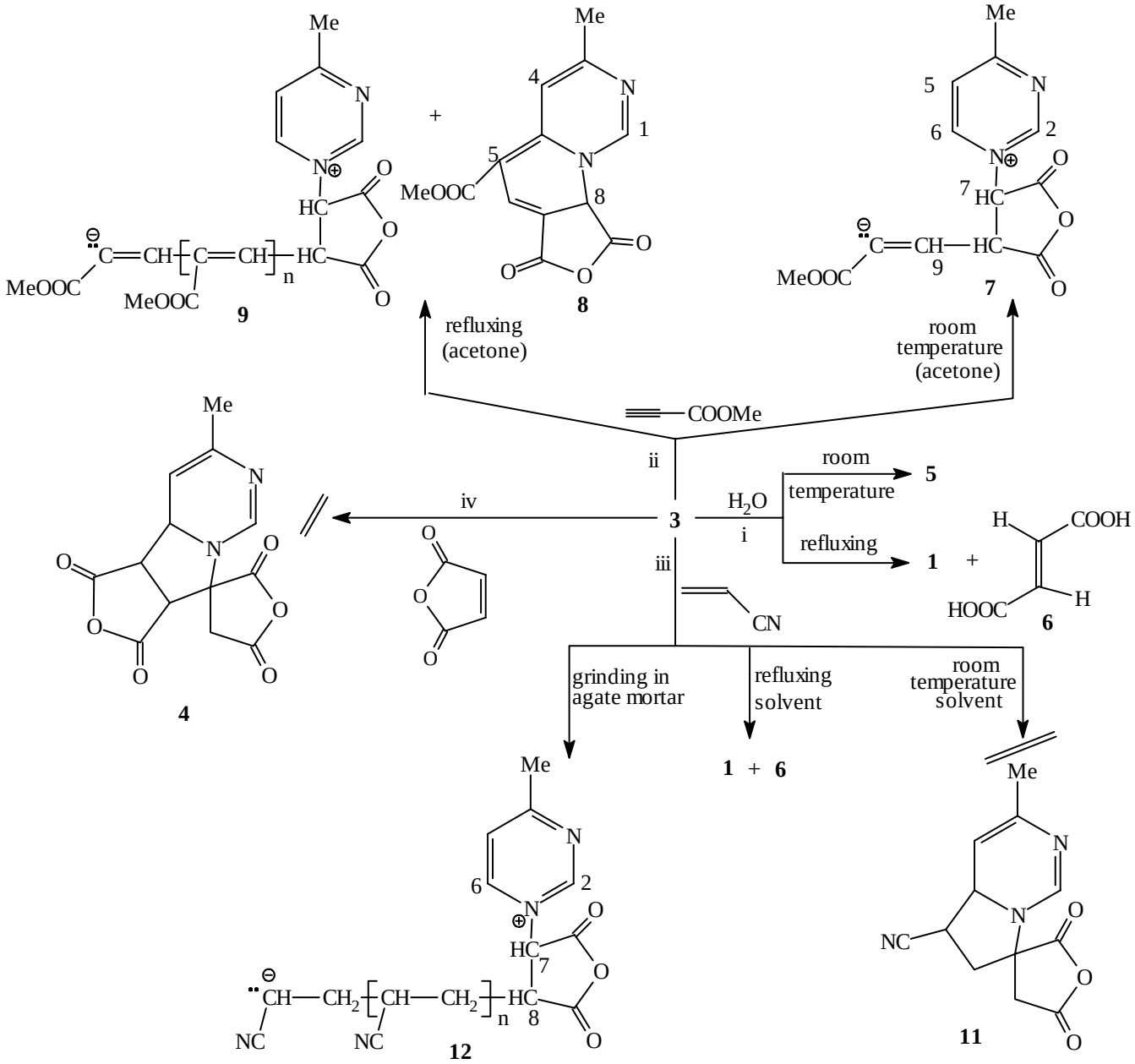
The chemical proves include:

1. Hydrolysis (pathway i). The course of the reaction depends on the reaction conditions: acid (**5**) is the result of hydrolysis at room temperature, while refluxing the ylide in water leads to the basic heterocycle (**1)** and fumaric acid.

2. Reaction with activated alkynes (pathway ii). The reaction with methyl propiolate gives different products according to the reaction conditions:

The dipole (**7)** forms, when reaction is running in anhydrous acetone at room temperature;

With refluxing in anhydrous acetone, the outcome of the reaction is a mixture of the cycloadduct (**8**)



(20% yield) and the oligomeric compound of type (**9**) (80% yield). Compounds (**8**) and (**9**) have been separated by flash chromatography.

3. Reaction with activated alkenes (pathway iii). No matter which conditions were employed, reaction with compounds such as acrylonitrile did not lead to the anticipated cycloadducts of type (**11**).

In acetone or acetonitrile at room temperature, the starting materials were isolated. Under reflux, the reaction products are the heterocycle (**1**) and fumaric acid (**6**).

When the reaction takes place by grinding in an agate mortar, the oligomer (**12**) were obtained with a polymerisation degree n = 7 (from NMR and MS).

The formation of products such as (**12**) and (**9**) has led us to the conclusion that ylide (**3**) may act as an initiator in anionic polymerisation. Indeed, attempts to polymerise acrylonitrile using ylide (**3)** as initiator

have resulted in the anticipated compounds of type (**12**). Further detailed studies in this respect remain to be done.

4. The reaction of ylide (**3**) with maleic anhydride (pathway iv). This reaction has been developed in order to prove both the structure of ylide (**3**) and the spiro compound (**4**). Ylide (**3**) does not react with maleic anhydride to form the spiro compound (**4**) no matter which conditions were employed (pathway iv), either the starting materials or the constituents of the ylide (**3**) (the heterocycle (**1**) and fumaric acid) or the acid (**5**) were isolated.

We notice that ylide (**3**) give [3+2] cycloaddition reactions with activated alkynes but not with alkenes, including anhydrides. This behaviour could be explained by the difference of reactivity of alkynes and alkenes and by the low reactivity of the ylide (**3**).

We have obtained the spiro compound (**4**) in an other way. We considered the reaction between 4-methylpyrimidine and maleic anhydride in a molar ratio 1:2. Our first attempts to carry out the reaction in solid phase (grinding in mortar) as well as under the conditions suggested by the other authors[1,4,8] failed. The reaction either does not take place in solid phase or gives complex mixtures of unidentified products. In order to get **4**, we have refluxed a mixture of 4-methylpyrimidine and maleic anhydride in a molar ratio 1:2, for 20 h in xylene. The literature[2,3,4] data show that a bis-anhydride adduct could also formed. We do not exclude the formation of a such compound, but we were not able to isolate it.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were run on a Bruker Avance 400 DRX spectrometer at 400 MHz in $CDCl_3$, acetone-d_6 or DMSO-d_6. The mass spectra are by electron impact. The IR spectra are in KBr. Relevant data:

Ylide (**3**). 4-methylpyrimidine (940 mg, 10 mmol) and maleic anhydride (980 mg, 10 mmol) were grinding in an agate mortar for 1 h, intermittently. The mixture was left over night in a vacuum oven and then was recrystallized from 1,2-dichoroethane. White crystals. Yield 25-30%, mp= 89-90^{0}C. ^{1}H NMR δ : 9.03 (s, H_2), 8.65-8.63 (d, H_6, J= 6.0), 7.42-7.40 (d, H_5, J= 6.0), 6.60-6.58 (d, $H_{7'}$, J= 6.0), 6.27 (s, CH_2 (H_8)), 5.80-5.78 (d, $H_{8'}$, J= 6.0), 2.40 (s, CH_3). ^{13}C NMR δ : 167.22 (C=O, C_{9a}, C_{9b}, $C_{9'a}$), 166.47 (C=O, $C_{9'b}$), 158.57 (C_2), 157.10 (C_6), 134.47 ($C_{7'}$), 130.65 (C_8, C_7, C_4), 121.76 (C_5), 24.08 (C, CH_3). MS m/z: M^+-missing, 123(8), 97(7), 95(100), 79(6), 59(5), 52(3). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.19; N, 14.58. Found : C, 56.18; H, 4.10; N, 14.45. IR ν : 1740, 1650, 1295, 1205, 1100, 1040.

Compound (**4**). A mixture of 4-methylpyrimidine and maleic anhydride in a molar ratio 1:2, has been refluxed for 20 h in xylene (20 mL). The clear solution was precipitated with ethyl ester and then was recrystallized from acetone. Reddish crystals. Yield 50%, mp= 238-239^{0}C. ^{1}H NMR δ : 9.05 (s, H_1), 7.80-7.60 (d, H_4, J= 6.0), 6.25-6.00 (t, H_5, J= 6.0), 4.30-4.15 (d, H_7, J= 8.0), 4.15-3.90 (m, H_6), 3.45 (s, $H_9(CH_2)$), 2.50 (s, CH_3). MS m/z: M^+-missing, 262(1), 260(0.5), 168(4.1), 167(50.9), 150(10), 149(100), 121(2.5), 120(2.5), 105(4), 104(5.8), 59 (2). IR ν : 1760, 1750, 1660, 1650, 1300, 1110.

Compound (**5**). Ylide (**3**)(384 mg, 2 mmol) was solved in 10 mL of distilled water and left several days to evaporation at rt. Yellow-white crystals. Yield 99%, mp= 131-134^{0}C. ^{1}H NMR δ : 10.40 (H from COOH, disappear at deuteration), 9.20 (s, H_2), 8.80-8.60 (d, H_6, J= 6.0), 7.60-7.40 (d, H_5, J= 6.0), 6.80-6.50 (t, $1H_7$, J= 10.0), 6.50-6.00 (d, $2H_8$, J= 10.0), 2.40 (s, CH_3). IR ν : 1710, 1660, 1440, 3150.

Compound (**7**). Ylide (**3**) (384 mg, 2 mmol) was solved in 5 mL of acetone and then methyl propiolate (168 mg, 2 mmol) was added. The mixture was stirred overnight at rt, precipitated with ethyl ester and then was recrystallized from ethyl acetate. Reddish crystals. Yield 75%, mp= 89-90^{0}C. ^{1}H NMR δ : 9.05 (s, H_2), 8.60-8.55 (d, H_6, J= 6.0), 7.40-7.35 (d, H_5, J= 6.0), 6.50-6.20 (m, 3H: H_7, H_8, H_9), 4.85 (s, $COOCH_3$), 2.50 (s, CH_3). IR ν : 1745, 1730, 1650, 1290, 1240, 1110, 1040.

Compound (**8**). Ylide (**3**)(384 mg, 2 mmol) was solved in 5 mL of acetone and then methyl propiolate (168 mg, 2 mmol) was added. The mixture has been refluxed for 2 h in acetone, precipitated with ethyl ester and then **8** separated by flash chromatography (silica, dichloromethane-methanol 99:1). Recrystallized from ethanol. Cream crystals. Yield 20%, mp= 136-137^{0}C. ^{1}H NMR δ : 7.80 (s, H_1), 6.80 (s, H_4), 6.40-6.20 (m, 2H: H_8, H_6), 3.75 (s, $COOCH_3$), 3.50 (s, CH_3). MS m/z: 274(0.4, M^+), 259(16), 241(11), 228(1), 129(100), 111(7), 104(5.8), 58 (6). IR ν : 1755, 1730, 1650, 1290, 1240, 1110, 1040.

Compound (**12**). Ylide (**3**)(384 mg, 2 mmol) and acrylonitrile(53 mg, 10 mmoles) were grinding in an agate mortar for 1 hour, intermittently. The mixture was left over night in a vacuum oven. White compound (unrecrystallized). Yield 95%, mp= 80-83^{0}C. ^{1}H NMR δ : 9.00 (s, H_2), 7.95-7.90 (d, H_6, J= 6.0), 7.40-7.35 (d, H_5, J= 6.0), 6.40-6.20 (m, 2H: H_7, H_8), 3.25 (m, CH from acrylonitrile), 2.50 (s, CH_3), 2.30-2.00 (m, CH_2 from acrylonitrile). MS m/z: M^+(616)-missing, 602(0.1), 535(0.8), 505(0.2), 504(1), 503(6), 502(26.7), 323(0.9), 322(11.6), 321(76,7), 307(0.4), 306(7.2), 305(21.6), 267(0.2), 266(0.5), 265(5.7), 264(47.8), 182(8.2), 181(100). IR ν : 2245, 1750, 1640, 1300, 1205, 1100.

REFERENCES

1. R. C. Cookson and N. S. Isaacs, *Tetrahedron*, 1963, **19**, 1237.
2. I. Zugravescu, M. Pertovanu, A. Caraculacu, and A. Sauciuc, *Rev. Roum. Chim.*, 1967, **12**, 109.

3. M. Caprosu, M. Pertovanu, and I. Zugravescu, *Rev. Roum. Chim.*, 1970, **15**, 619.
4. L. Zirngibl, G. Kunz, and E. Pretsch, *Tetrahedron Lett.*, 1971, 4189.
5. R. Huisgen, *Proc. Chem. Soc.*, 1961, 357; R. Huisgen, R. Grachey, and H. Gotthardt, *Chem. Ber.*, 1968, **101**, 829.
6. E. Rucinschi, I. Gabe, A. Caraculacu, and I. Zugravescu, *Rev. Roum. Chim.*, 1968, **13**, 637.
7. S. Soto and M. Ohata, *Bull. Chem. Soc. Japan*, 1969, 2054.
8. M. B. Hocking, *J. Heterocycl. Chem.*, 1977, **14**, 829.
9. I. Mangalagiu, M. Ungureanu, G. Mangalagiu, G. Grosu, and M. Petrovanu, *Ann. Pharmacceutiques Francaise*, 1998, **56**, 181.
10. I. Mangalagiu, C. Baban, D. Mardare, and G. I. Rusu, *Appl. Surface Science*, 1997**, 108**, 205.

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