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Reactivity of 6-Aminopyrimidin-4-(3H)-ones Towards Dimethyl Acetylenedicarboxylate (DMAD). Tandem Diels-Alder/Retro Diels-Alder (DA/RDA) Reaction in the Synthesis of 2-Aminopyridines.[1]

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Abstract: The reactions of 6-aminopyrimidin-4-(3H)-one derivatives, 1a-d, with DMAD, 2, are discussed in this paper. 2-aminopyridines, 3, and 6-amino-5-vinylpyrimidin-4-(3H)-ones, 4 and 5, have been obtained as main products, which can be explained on the basis of DA/RDA reactions, or Michael Addition on pyrimidine derivatives.

INTRODUCTION

Recently, there has been a growing interest in Diels-Alder reactions of heterocyclic azadienes with appropriately substituted alkenes or alkynes. Concerning pyrimidines, both inter and intramolecular hetero Diels-Alder (HDA) reactions involving such heterocyclic derivatives in the role of azadienes have been reported, most of the reports discuss inverse electron demand HDA reactions,[2] while only few examples of normal demand HDA reactions performed on electron rich pyrimidines have been reported to date.[3] Probably, this reflects the difficulties associated with the overcoming the intrinsic π-electron defficient character in the pyrimidine ring system.

Our previous experience of the reactivity of 6-aminopyrimidine derivatives as electron sources towards different electrophylic species,[4] led us to regard them as good candidates for achieving results in the poorly explored field of pyrimidine azadienes in normal HDA reactions. Thus, herein we present a study on the reactivity of several 6-aminopyrimidin-4-(3H)-ones towards the electron-defficient acetylene derivative DMAD, whose behaviour as dienophile in normal DA reactions is well known. A discussion on the synthetic applicability of these reactions is also included.

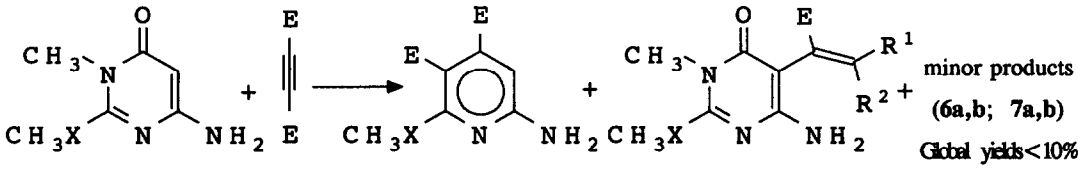
Furthermore, 2-aminopyridine derivatives obtained in these reactions constitute an important class of nitrogen heterocycles used in the agrochemical and pharmaceutical industries,[5] being also appropriately functionalized for obtaining other types of pyridine-fused heterocyclic systems, with potential biological interest.[6]

RESULTS AND DISCUSSION

The pyrimidines used as starting material were 6-aminopyrimidin-4-(3H)-ones **1a-d** (see Scheme 1 and 3). The C(2) atom bears an electron releasing substituent, CH_3O (**1a,c**) or CH_3S (**1b,d**), which together with the amino group at C(6) contribute to the increase of the electron-richness of the π-system in the heterocyclic nucleus. Aprotic solvents, namely acetonitrile and toluene, were selected as reaction media in order to reduce the obtention of undesired Michael adducts (by the addition of the C(5) atom or the 6-NH_2 group to DMAD). These compounds, in our experience[7], are always the main products in similar reactions performed in protic solvents.

As a general rule, reactions of **1a-d** towards DMAD reveal a marked difference of reactivity between compounds which have a methyl substituent at N(3), **1a,b**, and those bearing hydrogen, **1c,d**. Thus, by tlc monitoring, clean reactions were observed for **1a,b**, whereas **1c,d** afforded very complex reaction mixtures, from which the isolation of the main reaction products was hardly accomplished.

Firstly, the discussion will be centered on the reaction of the N(3)-methyl **1a,b** with DMAD, **2**, because they offer the cleanest and most valuable results. The main products obtained in these reactions were the pyridine derivatives **3**, together with 5-(dicarbomethoxy vinyl)pyrimidines **4a,b** and **5a,b** (see scheme 1 and table 1).



1a,b **2** **3a,b** **4a,b**: R^1=E; R^2=H

5a,b: R^1=H; R^2=E

E: COOMe

Scheme 1

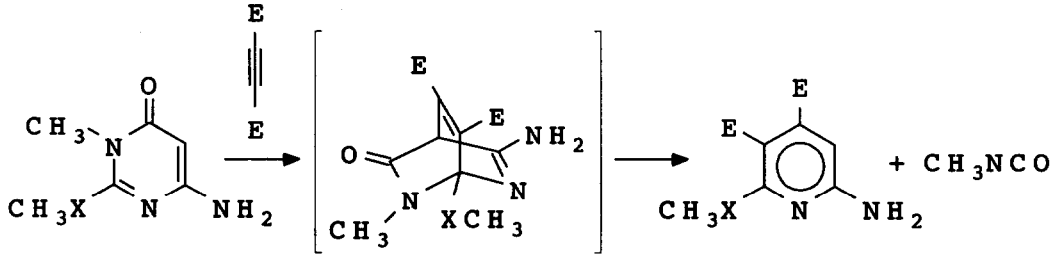
All of these compounds were fully characterized by spectroscopic methods and microanalysis. In addition, the structures of **3a** and **3b** were unambiguously confirmed by single crystal X-Ray diffraction analysis.[8]

As shown in scheme 1, the compound **4** and **5** are configurational isomers. The assignment of the Z or E configuration for their vinyl moieties was firstly made on the basis of the pmr shift observed for the vinyl and 6-amino protons,[9] and unambiguously determined by single crystal X-Ray diffraction analysis of compound **5a**.[10]

Table 1: Data for the reactions of **1a** and **1b** with DMAD **2**.

Starting compds.	X	Time	Reac. solv.	Yields (%)				
							Minor products	
				3	**4**	**5**	**6**	**7**
1a	**O**	**4 h**	acetonitrile	79	5	11	1.6	
1a	**O**	**3 h**	toluene	29	4.6	24	2.3	8.7
1b	**S**	**21 h**	acetonitrile	64	8.6	14.5	1.3	
1b	**S**	**19 h**	toluene	33	9.2	32	6	4

The formation of **3** is explained through a tandem DA/RDA reaction: normal DA reaction between the acetylene compound **2** and the 2-azadiene moiety at the pyrimidine ring (that is located between C(2)-C(5) atoms) to form a cycloadduct intermediate **a**, which undergoes a RDA reaction, with extrusion of methyl isocyanate fragment, resulting the aromatized pyridine **3**, as depicted in scheme 2.



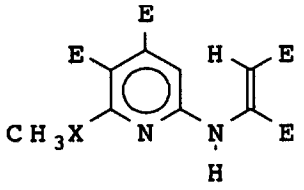
1 **a** **3**

Scheme 2

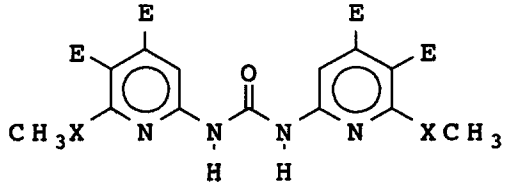
Furthermore, compounds **4** and **5** (Z and E isomers) arise from a Michael-type addition of the highly nucleophylic C(5) atom at the pyrimidine ring to DMAD, being in competition with the DA/RDA reaction.

As shown in table 1, the ratio **3/4+5**, i.e. cycloadditon towards Michael addition was clearly more favourable to cycloaddition in acetonitrile than in toluene. This effect can not be attributed to a solvent polarity change, an increase of which, from toluene to acetonitrile, should relatively favour the reaction having a more polar transition state, say Michael addition in the present case. Furthermore, studies on solvent effects on DA reactions indicate that changes in reaction rate cannot be ascribed to the polarity of the solvent but to molecular aggregation.[11]

Minor products **6** and **7** were isolated in these reactions and their structures were fully characterized by spectroscopic methods and microanalysis (see figure 1). They come from further reactions of the pyridine derivatives **3**, through their 2-amino group. Compounds **6** arise from a Michael addition of this 2-amino group to DMAD[12], while formation of compounds **7** involves two molecules of **3**, and can be explained by addition of one molecule of **3** to methyl isocyanate (produced in the RDA reactions) to give a N-methyl-N'-pyridylurea intermediate, followed by nucleophylic displacement of N-methylamine from this intermediate by another molecule of **3**.



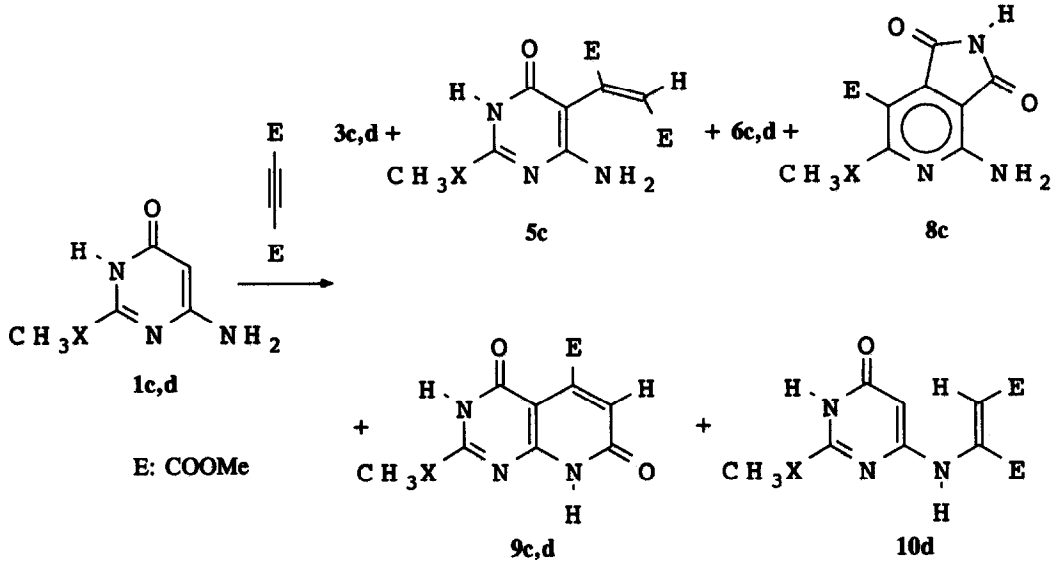
6	X
a	O
b	S



7	X
a	O
b	S

Figure 1

With reference to the reactions of **1c,d** with DMAD **2**, very complex reaction mixtures were observed[13] under similar conditions to those described for **1a,b**. In these mixtures several compounds could be isolated after careful column chromatography, but with poor global yields (see scheme 3 and table 2).

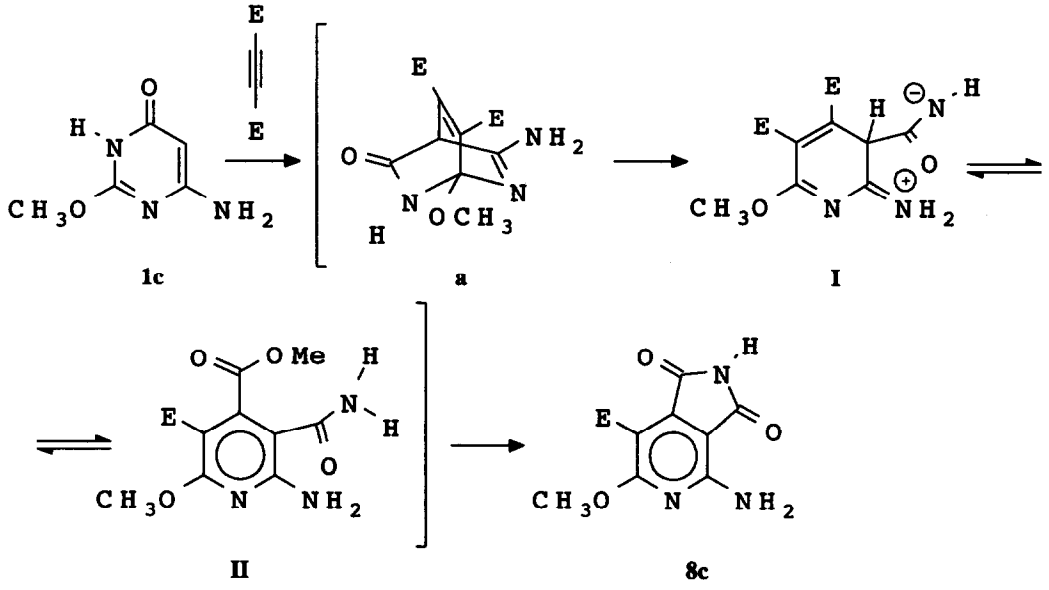


Scheme 3

Table 2: Data for the reactions of **1c** and **1d** with DMAD, **2**.

Starting compds.	X	Time	Reaction solvent	Yields (%) 3	5	6	8	9	10
1c	**O**	**23 h**	acetonitrile	13	10	2.3	18	-	
1c	**O**	**72 h**	toluene	-[13]	-[14]	-[13]		1.2	
1d	**S**	**20 h**	acetonitrile	25	-[14]	3		1	1.6
1d	**S**	**96 h**	toluene	-[13]	-[14]	-[13]		2.2	

As observed in scheme 3 and table 2, these reactions go on a reaction pattern basically similar to those described above, that is, a competition between Michael addition and DA processes. Thus, compounds **3**, and **6** (the same compounds as shown in scheme 1) indicate a tandem DA/RDA with extrusion of isocyanic acid in the present cases. Also, compound **8c** can be explained through a DA reaction, followed in this case by ring cleavage, aromatization of the resulting pyridine ring and further intramolecular cyclization, as depicted in scheme 4.



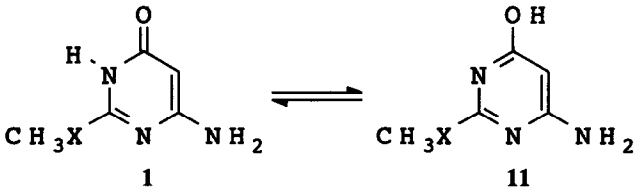
Scheme 4

On the other hand, compounds **5c**, and **9c,d** result from Michael addition, followed by intramolecular cyclization in the case of compound **9c,d**.

However, an additional feature of the pyrimidines carrying a hydrogen at N(3), **1c,d**, with reference to those carrying a methyl group, **1a,b**, can be observed. This is, the higher reactivity of 6-amino group of the former, reflected in the appearance of compounds **9c,d** and **10c,d**, which were not observed in the reactions of **1a,b**.

The marked relative reactivity differences of pyrimidines **1a,b** and **1c,d** towards DA reactions, associated with the presence of N(3)-methyl group or N(3)-H, can be tentatively explained in terms of FMO theory. If a normal electron demand HDA reaction is assumed, then the reaction should be controlled by $HOMO_{diene}$-$LUMO_{dienophile}$ interaction. Therefore, N(3)-methyl group enhances the reactivity of **1a,b** with reference to **1c,d** by $HOMO_{diene}$ energy level increase. This is due to two effects:

- The possibility of lactam-lactim tautomerism in **1c,d** (what produces a $HOMO_{diene}$ decrease by electronic delocalization of C(2)-C(5) azadiene moiety) is avoided in **1a,b** (see Scheme 5).



1 11

Scheme 5

- Methyl group is a better electron-donor than hydrogen.

As a support for this explanation, the reaction of 6-amino-4-methoxy-2-methylthiopyrimidine **11** (an isomer of **1b** with a fixed lactim form) with DMAD in refluxing acetonitrile was performed. Under these conditions, DMAD was quickly consumed by polimerization (reaction darkens) while only little starting pyrimidine reacted, and a very complex reaction mixture was obtained, no observing by tlc HDA products (this should be **3b**, as when starting from **1b**).

Further, the lactam-lactim tautomerism explains the higher nucleophylicity showed by the 6-amino group in **1c,d**: in the case of **1a,b** the presence of N(3)-methyl group only allows the lactam form, where the unshared electron pair of the nitrogen atom at C(6) is highly required by the push-pull character of the ß-amino-α,ß-unsaturated-amide system located between N(3)-C(6) atoms (see scheme 5), while the fully aromatized lactim form, allowed for **1c,d**, loses the push-pull character and enables a higher nucleophylicity of the 6-amino group.

In conclusion, the better behaviour of the N(3)-methyl derivatives, **1a,b**, for DA reactions, led us to regard them as *synthetic equivalent* of electron rich 2-aza-1,3-butadienes (usually unstable compounds[15]) for practical synthetic purposes, where introduction of different alkyl groups at N(3) position of pyrimidine derivatives could model their physical properties (say, solubility) and improve the handle, and ever their reactivity for DA reaction.

On the other hand, modifying of the 6-amino group, i.e. introduction of a glycosyl moiety at 6-amino, should not vary the behaviour above, yielding a new type of pyridine nucleosides[1], with a potential biological interest.

EXPERIMENTAL SECTION

Melting Points were determinated in a Melting Points Apparatus Gallenkamp and are uncorrected. Proton nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded in a Perkin-Elmer R-600 and Bruker AM-300 Spectrometer from "Servicios Técnicos de la Universidad de Granada" (STUGRA), using tetramethylsilane as internal standard; the following abreviations are used to describe signal multiplicity: s= singlet; bs=broad singlet. Carbon-13 Nuclear Resonance (^{13}C-NMR) spectra were recorded in a Bruker AM-300 Spectrometer from STUGRA. Ultraviolet and Visible (UV) spectra were recorded in a GBC UV/VIS 911 spectrophotometer. Infrared spectra were recorded in a Beckman 4250 spectrophotometer (potassium bromide pellets). The analysis C, H and N were performed in a Perkin-Elmer 240 C from STUGRA. Flash column chromatography was performed in an Eyela equipment EF10 on Merck Silica Gel 60 (0.040-0.063 mm) using the solvent system indicated in each case. Reaction progress and products purity were monitorized by thin layer chromatography (tlc) on Merck Silica Gel $60GF_{254}$ (0.2 mm) aluminium precoated sheets with fluorescent indicator, the spots were visualized by ultraviolet irradiatiion and by spraying with 4% sulphuric acid/methanol solution and subsequent heating. DMAD (99%) was purchased from Aldrich, and directly used without further purification.

General procedure for reactions of 6-aminopyrimidin-4-(3H)-ones, 1, with DMAD, 2.

Compounds **1** and **2** (molar ratio 1:2), were added to the appropriate apolar solvent (dry acetonitrile or dry toluene) (4 ml/mmol **1**), and the mixture was stirred under reflux until the starting compound **1** was not detected in tlc (methylene chloride/methanol 9:1). Reaction products were purified as indicated in each case.

Reaction of 6-amino-2-methoxy-3-methylpyrimidin-4-(3H)-one **1a** with DMAD **2** in acetonitrile

1,55 g (0.01 mol) of **1a** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of acetonitrile and refluxed for 4 h. The resulting solution was evaporated *in vacuo* to give 3.74 g of an oily residue. 2.50 g of which were applied on flash chromatography column (5x16 cm, 100g of Silica gel) and eluted with methylene chloride-ethyl ether (4:1). A main fraction was obtained, which after solvent elimination and crystallization from methylene chloride gave 1,27 g (79 %) of 2-amino-4,5-dicarbomethoxy-6-methoxy pyridine **3a**, mp: 106-108 °C; tlc: Rf=0.43 (methylene chloride-ethyl ether 4:1); UV ($5.83 \cdot 10^{-5}$ M, methylene chloride) $\lambda_{max}(\epsilon)$nm : 330 (sh), 316 (6390), 250 (8610); IR υ_{max} (cm^{-1}): 3460, s; 3360, s; 3000, w; 2940, w; 1710, w; 1680, s; 1620, s; 1595, s; 1560, s; 1450, s; 1360, s; 1190, w; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 3.7-3.85 (3s, 9H, two $COOCH_3$ and OCH_3), 6.4 (s, 1H, C(3)-H), 6.9 (s, 2H, NH_2, exchangeable with deuterium oxide); ^{1}H-MNR (deuteriochloroform, 300 MHz) δ (ppm): 3.83 (s, 3H), 3.85 (s, 3H) (two $COOCH_3$), 3.91 (s, 3H, OCH_3), 4.95-4.65 (bs, 2H, NH_2, exchangeable with deuterium oxide) 6.35 (s, 1H, C(3)-H); ^{13}C-MNR

(deuteriochloroform): 52.4, 52.8 (two $COO\underline{C}H_3$), 54.2 ($O\underline{C}H_3$), 99.0 (C-3), 104.1 (C-5), 142.5 (C-4), 158.3, 161.5 (C-2, C-6), 166.4, 166.9 (two $\underline{C}OCH_3$); Ms m/z (abundance %); 240(M^+, 29), 209(100), 181(18), 150(14), 123(9), 92(17), 78(6), 59(19); Anal. calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.00; N, 11.66; Found: C, 49.60; H, 4.99; N, 11.67.

Three minor fractions (called as A, B, C) were also separated, which after solvent elimination gave the following compounds:

Fraction A gave 4,5-dicarbomethoxy-6-methoxy-2(1,2-E-dicarbomethoxy ethenyl)amino pyridine **6a**, 0.04 g (1.6%), crystallized from ethanol, mp: 80-82 °C; tlc: Rf=0.64 (methylene chloride-ethyl ether 4:1), UV ($4.712 \cdot 10^{-5}$ M, water) $\lambda_{max}(\epsilon)$nm : 351 (2150), 294 (1050), 239 (sh); IR υ_{max} (cm^{-1}): 3260, w; 3000, w; 2960, w; 1720, s; 1685, s; 1630, s; 1600, s; 1575, s; 1500, w; 1460, s; 1435, s; 1360, s; 1340, s; 800, s; ^{1}H-MNR (deuteriochloroform) δ (ppm): 4-3.8 (2s, 15H, four $COOCH_3$ and OCH_3), 5.7 (s, 1H, C=C-H), 7.0 (s, 1H, C(3)-H), 10.3 (s, 1H, NH, exchangeable with deuterium oxide); ^{13}C-MNR (deuteriochloroform): 51.35, 52.26, 52.61, 52.95,(four $COO\underline{C}H_3$), 53.99 ($O\underline{C}H_3$), 101.64 (C=$\underline{C}$-H), 102.77 (C-3), 107.34 (C-5), 141.27, 143.16 (C-4, $\underline{C}$=C-H), 152.51, 159.50 (C-2, C-6), 164.63, 164.76, 165.14, 166.45,(four $\underline{C}$=O). MS m/z (abundance %); 382(M^+, 6), 351(7.6), 323(92), 291(100), 245(10), 240(0.3), 92 (8), 77 (5), 59(43); Anal. calcd. for $C_{16}H_{18}N_2O_9$: C, 50.26; H, 4.71; N, 7.33; Found: C, 49.90; H, 4.84; N, 7.31.

Fraction B gave 6-amino-2-methoxy-3-methyl-5(1,2-Z-dicarbomethoxy ethenyl)pyrimidin-4-(3H)-one **4a**, 0.10 g (5%), crystallized from methylene chloride, mp: 150 °C; tlc: Rf=0.17 (methylene chloride-ethyl ether 4:1); UV ($5.05 \cdot 10^{-5}$ M, methylene chloride) $\lambda_{max}(\epsilon)$nm : 334 (5810), 267 (sh), 231 (10940); IR υ_{max} (cm^{-1}): 3510, w; 3310, w; 2960, w; 1710, s; 1670-1600, s, broad; 1435, w; 1385, w; 1330, w; 1230, w; ^{1}H-MNR (dimethyl sulfoxide-d_6) δ (ppm): 3.2 (s, 3H, N_3-CH_3), 3.6 (s, 6H, two $COOCH_3$), 3.9 (s, 3H, OCH_3), 6.1 (s, 1H, =C-H), 6.9 (s, 2H, NH_2, exchangeable with deuterium oxide); Ms m/z (abundance %): 297 (M^+, 4), 239(12), 238(100), 206(22), 149(5), 59(13)

Fraction C gave 6-amino-2-methoxy-3-methyl-5(1,2-E-dicarbomethoxy ethenyl)pyrimidin-4-(3H)-one **5a**, 0.22 g (11%), crystallized from methanol, mp: 178-180 °C; tlc: Rf = 0.15 (methylene chloride-ethyl ether 4:1); UV ($5.05 \cdot 10^{-5}$ M, methylene chloride) $\lambda_{max}(\epsilon)$nm : 355 (2050), 266 (7800), 231 (9940); IR υ_{max} (cm^{-1}): 3450, s; 3330, s; 3000, w; 2950, w; 1710, s; 1660-1610, s, broad; 1440, w; 1390, w; 1250, s; ^{1}H-MNR (dimethyl sulfoxide-d_6) δ (ppm): 3.20 (s, 3H, N_3-CH_3), 3.60, 3.65 (2s, 6H, two $COOCH_3$), 4.0 (s, 3H, OCH_3), 6.30 (s, 2H, NH_2, exchangeable with deuterium oxide), 6.75 (s, 1H, =C-H); ^{1}H-MNR (deuteriochloroform) δ (ppm): 3.30 (s, 3H, N_3-CH_3), 3.80, 3.70 (2s, 6H, two $COOCH_3$), 3.90(s, 3H, OCH_3), 4.55 (s, 2H, NH_2, exchangeable with deuterium oxide), 6.95 (s, 1H, =C-H); Ms m/z (abundance %): 297 (M^+, 4), 239(12), 238(100), 206(22), 149(4), 59(14). Anal. calcd. for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.09; N, 14.13; Found: C, 48.33; H, 5.63; N, 13.97.

Reaction of 6-amino-2-methoxy-3-methylpyrimidin-4-(3H)-one **1a** with DMAD **2** in toluene

1,55 g (0.01 mol) of **1a** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of toluene and refluxed for 3 h. After cooling at room temperature a yellow solid precipitated which was collected by filtration, washed with cold toluene and dried at room temperature to give 0.87 g of a mixture of two compounds. This solid was

treated with a hot mixture of methylene chloride/ethanol (9:1) to give a solution, which after solvent elimination afforded 0.60 g (20%) of **5a**, while the remaining solid residue consisted in a chromatographycally pure compound, identified as N-N'-di[2(4,5-dicarbomethoxy-6-methoxy)pyridinil]urea **7a** , 0.22 g (8.7 %), mp: 266 °C (dc); tlc: Rf=0.57 (methylene chloride-ethyl ether-ethanol 3.8:0.9:0.1); UV ($4.738 \cdot 10^{-5}$ M, methanol) $\lambda_{max}(\epsilon)$nm: 330.3 (22440), 256 (22490), 204.8 (26740); IR υ_{max} (cm^{-1}): 3220, w; 3000, w; 2960, w; 1720, s; 1700, s; 1560, s; 1440, s; 1390, s; 1300, w; 1250, s; 1240, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ(ppm): 3.9-3.8 (3s, 18H, four $COOCH_3$, two OCH_3), 7.8 (s, 2H, two C_3-H), 10.7 (s, 2H, NH-CO-NH, exchangeable with deuterium oxide); ^{13}C-NMR (dimethyl sulfoxide-d_6): 52.33, 53.03 (four $COO\underline{C}H_3$), 54.26 (two $O\underline{C}H_3$), 102.76 (two C-3), 109.55 (two C-5), 140.85 (two C-4), 150.7 (NH-$\underline{C}$O-NH), 151.27, 159.28 (2 C-2, 2 C-6), 164.5, 164.99 (four $\underline{C}OCH_3$); MS m/z; 506.5 (M^+, 0.4), 267(5), 240(17), 235(16), 209(100), 181 (3), 59 (4); Anal. calcd. for $C_{21}H_{22}N_4O_{11}$: C, 49.80; H, 4.38; N, 11.06; Found: C, 49.63; H, 4.35; N, 11.15.

The mother liquors were evaporated *in vacuo* to dryness to give 2.60 g of an oily residue, 0.60 g of which were applied on a flash chromatography column (2x15 cm, 20g of silica gel). Elution with methylene chloride-ethyl ether (4:1) afforded by order of elution two pure fractions containing the compounds **6a** (0.02 g, 2.3 %), and **3a** (0.16 g, 29 %), respectively; together with another fraction containing a mixture of **4b** and **5b**, (0.06 g, 8.7 %) in a ratio **4a**:**5a** of 1:0.9 (determined by ^{1}H-NMR measurement).

Reaction of 6-amino-2-methylthio-3-methyl pyrimidin-4-(3H)-one **1b** with DMAD **2** in acetonitrile

0.66 g (3.85 mmol) of **1b** and 0.94 ml of **2** (7.64 mmol) were added to 16 ml of acetonitrile and refluxed for 21 h. After cooling at room temperature a yellow solid precipitated which was filtered, washed with cold acetonitrile, recrystallized from methanol and identificated as 6-amino-2-methylthio-3-methyl-5(1,2-E-dicarbomethoxy ethenyl)pyrimidin-4-(3H)-one **5b**, 0.13 g (10.8%), mp: 210-2 °C; tlc: Rf=0.15 (methylene chloride-ethyl ether 4:1), UV ($4.79 \cdot 10^{-5}$ M, methylene chloride) $\lambda_{max}(\epsilon)$nm : 353 (2630), 283 (6410), 230 (14880); IR υ_{max} (cm^{-1}): 3460, s; 3340, s; 3000, w; 2950, w; 1710, s; 1660-1590, s, broad; 1440, s; 1380, s; 1250, s; 1130, w; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 2.4 (SCH_3), 3.15 (s, 3H, N(3)-CH_3), 3.5, 3.55 (2s, 6H, two $COOCH_3$), 6.25 (s, 2H, NH_2, exchangeable with deuterium oxide), 6.60 (s, 1H, =C-H); ^{1}H-NMR (deuteriochloroform) δ (ppm): 2.50 (SCH_3), 3.40 (s, 3H, N_3-CH_3), 3.80-3.70 (2s, 6H, two $COOCH_3$), 4.55 (s, 2H, NH_2, exchangeable with deuterium oxide), 7.00 (s, 1H, =C-H); ^{13}C-NMR (deuteriochloroform): 15.02 ($S\underline{C}H_3$), 30.03 (N(3)-CH_3), 51.94, 52.87 (two $COO\underline{C}H_3$), 91.104 (C-5), 130.11 (C=$\underline{C}$-H), 139.06 ($\underline{C}$=C-H), 156.39, 159.83, 162.98 (C-2, C-4, C-6), 164.89, 166.37 (two $\underline{C}OCH_3$); Ms m/z(abundance %); 313 (M^+, 4), 256(6), 255(13), 254(100), 222(10), 206(3), 83(4). Anal. calcd. for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.82; N, 13.41; Found: C, 46.29; H, 4.86; N, 13.87.

The mother liquors were evaporated *in vacuo* to dryness to give 1.51 g of an oily residue, which were applied on flash chromatography column (5x16 cm, 100g of Silica gel) and eluted with methylene chloride-ethyl ether-ethanol mixtures (5:0:0 to 4:1:0.1). A main fraction was obtained, which after solvent elimination and crystallization from methylene chloride gave 0.63g (64 %) of 2-amino-4,5-dicarbomethoxy-6-methylthio pyridine **3b**, mp: 100 °C; tlc: Rf=0.44 (methylene chloride-ethyl ether 4:1); UV ($5.073 \cdot 10^{-5}$, methylene chloride) $\lambda_{max}(\epsilon)$nm: 326.8 (5960), 282.8 (9080), 241.3 (13060); IR υ_{max} (cm^{-1}): 3470, s; 3360, s; 3000, w;

2950, w; 1720, s; 1680, s; 1625, s; 1595, s; 1530, s; 1440, s; 1400, s; 1200, w; 710, w; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 2.35 (s, 3H, SCH_3), 3.8 (s, 3H), 3.7 (s, 3H) (two $COOCH_3$), 6.3 (s, 1H, C(3)-H), 7.0 (s, 2H, NH_2, exchangeable with deuterium oxide); ^{13}C-NMR (deuteriochloroform): 13.99 ($S\underline{C}H_3$), 52.66, 52.80 (two $COO\underline{C}H_3$), 102.02 (C-3), 112.92 (C-5), 142.75 (C-4), 158.44, 161.73 (C-2, C-6), 166.40, 167.40 (two $\underline{C}OCH_3$); MS m/z (abundance %); 256(M^+, 55), 224(100), 197(19), 166(48), 138(94), 91(67), 78(18), 59(54); Anal. calcd. for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93; Found: C, 46.98; H, 4.81; N, 10.65.

Three minor fractions (called as A, B, C) were also separated, which after solvent elimination gave the following compounds:

Fraction A gave 4,5-dicarbomethoxy-6-methylthio-2(1,2-E-dicarbomethoxy ethenyl)amino pyridine **6b**, 0.02 g (1.3 %), solid foam; tlc: Rf = 0.6 (methylene chloride-ethyl ether 4:1); IR υ_{max} (cm^{-1}): 3280, w; 3000, w; 2960, w, 2860, w; 1725, s; 1685, s; 1650-1620, s, broad; 1590, s; 1560, s; 1440, s; 1350, s; 1330, s; 790, s; ^{1}H-NMR (deuteriochloroform) δ (ppm): 2.5 (3H, s, SCH_3), 4-3.8 (2s, 12H, four $COOCH_3$), 5.7 (s, 1H, C=C-H), 6.9 (s, 1H, C(3)-H), 10.2 (s, 1H, NH, exchangeable with deuterium oxide); ^{13}C-NMR (deuteriochloroform): 13.90 ($S\underline{C}H_3$), 51.805, 52.805, 53.134 (four $COO\underline{C}H_3$), 100.18 (C=$\underline{C}$-H), 106.39 (C-3), 119.08 (C-5), 140.91, 145.08 (C-4, $\underline{C}$=C-H), 152.81, 160.07 (C-2, C-6), 164.80, 165.69, 1665.45, 169.13, (4 $\underline{C}$=O). MS m/z (abundance %); 398(M^+, 8), 367(7), 339(97), 307(100), 275(6), 240(2), 59(43); Anal. calcd. for $C_{16}H_{18}N_2O_8S$ $1/2H_2O$: C, 47.17; H, 4.70; N, 6.87; Found: C, 46.89; H, 4.36; N, 6.92.

Fraction B gave 6-amino-2-methyltio-3-methyl-5(1,2-Z-dicarbomethoxy ethenyl)pyrimidin-4-(3H)-one **4b**, 0.08 g (6.6%), crystallized from methylene chloride, mp: 162-4 °C; tlc: Rf=0.22 (methylene chloride-ethyl ether 4:1); UV ($4.79 \cdot 10^{-5}$ M, methylene chloride) $\lambda_{max}(\epsilon)$nm : 343 (5305), 276 (sh), 235 (11530); IR υ_{max} (cm^{-1}): 3420, s; 3320, s; 2950, w; 1710, s; 1660-1590, s, broad; 1440, s; 1380, w; 1350, s; 1225, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 2.5 (s, 3H, SCH_3), 3.3 (s, 3H, N_3-CH_3), 3.65 (s, 6H, two $COOCH_3$), 6.15 (s, 1H, =C-H), 7.0 (s, 2H, NH_2 ,exchangeable with deuterium oxide); ^{1}H-NMR (deuteriochloroform) δ (ppm): 2.60 (SCH_3), 3.50 (s, 3H, N_3-CH_3), 3.97-3.85 (2s, 6H, two $COOCH_3$), 5.40 (s broad, 2H, NH_2, exchangeable with deuterium oxide), 5.60 (s, 1H, =C-H); ^{13}C-NMR (deuteriochloroform): 14.89 ($S\underline{C}H_3$), 30.18 (N(3)-CH_3), 51.93, 52.83 (two $COO\underline{C}H_3$), 91.85 (C-5), 121.99 (C=$\underline{C}$-H), 141.99 ($\underline{C}$=C-H), 158.25, 160.50, 163.36 (C-2, C-4, C-6), 165.94, 168.97 (two $\underline{C}OCH_3$); MS m/z (abund. %); 313 (M^+,5), 256(6), 255(13), 254(100), 222(8), 206(2), 83(5). Anal. calcd. for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.82; N, 13.41; Found: C, 45.90; H, 4.74; N, 13.12.

Fraction C contained a mixture of **4b** and **5b** (0.07 g, 5.8%) in ratio **4b**:**5b** of 1:1.8 (determined by ^{1}H-NMR measurement).

Reaction of 6-amino-2-methylthio-3-methyl pyrimidin-4-(3H)-one **1b** with DMAD **2** in toluene

1.72 g (0.01 mol) of **1b** and 2.46 ml of **2** (7.64 mmol) were added to 40 ml of toluene and refluxed for 19 h. After cooling at room temperature a yellow solid precipitated which was collected by filtration, washed with cold toluene and dried at room temperature to give **5b**, 0.76 g (24 %).

The mother liquors were evaporated *in vacuo* to dryness to give 3.67 g of an oily residue, 1.02 g of which were applied on a flash chromatography column (5x16 cm, 110g of silica gel). Elution with methylene

chloride-ethyl ether mixtures (5:0 to 4:1) afforded by order of elution four pure fractions containing the compounds **6b** (0.02 g, 1.8 %), **3b** (0.11 g, 15.5 %), **4b** (0.08 g, 9.2%) and **5b** (0.07, 8%), respectively; together with 0.30 g of another fraction containing a mixture of several compounds, which were treated with hot ethanol to give 0.03 g (4 %) of a remaining solid residue , consisted in a chromatographycally pure compound, identified as N-N'-di[2(4,5-dicarbomethoxy-6-methyltio)pyridinil] urea **7b** (see below for analytical data), while solution after solvent elimination afforded 0.27 g, 0.17 g of which were applied on flash chromatography column (2x15 cm, 20g of Silica gel) and eluted with methylene chloride-ethyl ether (95.5:4.5) to give after solvent elimination **6b**, 0.03 g (4.3 %) and **3b**, 0.08 g (17.8%).

Analitical data for **7b** were: mp: 210-2 °C; tlc: Rf=0.41 (methylene chloride-ethyl ether 4:1). IR υ_{max} (cm^{-1}): 3220, w; 3000, w; 2960, w; 1720, s; 1690, s; 1560, s; 1440, s; 1380, s; 1300, s; 1260-1240, s, broad; 1195, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ(ppm): 2.6 (s, 6H, two SCH_3), 4.0 (2s, 12H, four $COOCH_3$,), 8.1 (s, 2H, two C_3-H), 10.5 (s, 2H, NH-CO-NH, exchangeable with deuterium oxide); MS m/z; 538.5 (M^+, 0.4), 282(29), 256(35), 250(100), 225(73), 197 (10.4), 78 (8), 59(21.5); Anal. calcd. for $C_{21}H_{22}N_4O_9S_2$: C, 46.88; H, 4.11; N, 10.40; Found: C, 46.84; H, 4.01; N, 10.38.

Reaction of 6-amino-2-methoxy pyrimidin-4-(3H)-one **1c** with DMAD **2** in acetonitrile

1,41 g (0.01 mol) of **1c** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of acetonitrile and refluxed for 23 h. During the reaction a yellow solid precipitated which was collected by filtration, washed with cold acetonitrile, recrystallized from N-N-dimethylformamide and identificated as 7-amino-4-carbomethoxy-5-methoxy pyrrolo[3,4-c]pyridin-1,3-dione **8c**, 0.45 g (18%), mp: 230-232 °C (d). UV ($4.78\cdot10^{-5}$ M, water) $\lambda_{max}(\epsilon)$nm : 422.6 (5680), 306 (sh), 262.2 (12660), 224.5 (11950), 202.9 (18540), 192.3 (17450). IR υ_{max} (cm^{-1}): 3450 w; 3340 w; 2800-2220 t, broad; 1680 t; 1630 t; 1540, t, broad; 1470-1450, t, broad; 1360 t; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 3.8 (s, 3H, OCH_3), 3.9 (3H, s, $COOCH_3$), 7.6-6.4 (s, broad, 4H, N_2-H, C_4-NH_2, exchangeable with deuterium oxide); ^{13}C-NMR (dimethyl sulfoxide-d_6): 50.0 ($COO\underline{C}H_3$), 54 ($O\underline{C}H_3$), 96.7, 100.1 (C-3, C-5), 140.8 (C-4), 163.2, 164.3, 165.1, 166.5 (C-2, C-6, $\underline{C}$=O). Ms m/z (Abundance %); 251(M^+, 44), 220(57), 206(100), 192(23), 188(25), 163(63), 162(11), 135(33), 92(23), 78(16), 59(11), 43(14). Anal. calcd. for $C_{10}H_9N_3O_5\cdot1/2\ H_2O$: C, 46.15; H, 3.85; N, 16.15; Found: C, 45.80; H, 3.45; N, 16.36;

Examination by tlc of the mother liquors indicated very complex mixture, which were evaporated *in vacuo* to dryness, and the oily residue obtained was applied on column chromatography (6x60 cm). Elution with methylene chloride-ethyl ether-ethanol mixtures (4:1:0 to 4:4:2) afforded by order of elution three fractions, which after fractional crystallization from ethanol yielded, respectively, the compounds **6a** (0.09 g, 2.4 %), **3a** (0.31 g, 13 %) and another identified as 6-amino-2-methoxy-5(1,2-E-dicarbomethoxy ethenyl)pyrimidin-4-(3H)-one **5c**, 0.28 g (10 %), mp: 176-8 °C (d); tlc: Rf=0.13 (methylene chloride-ethyl ether-ethanol 3.8:0.9:0.1) UV ($5\cdot10^{-5}$ M, methyl alcohol) $\lambda_{max}(\epsilon)$nm : 353 (1400), 331 (2200), 319 (2400), 265 (11900), 224 (12300); IR υ_{max} (cm^{-1}): 3320, w; 3210, w; 2940, w; 2840, w; 1710, s, 1640, s; 1600, s; 1565, s; 1515, s; 1435, s; 1360, s; 1265, s; 1225, w; 1015, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 3.65, 3.70 (2s, 6H, two $COOCH_3$), 3.90 (s, 3H, OCH_3), 6.30 (s, 2H, NH_2, exchangeable with deuterium oxide),

6.70 (s, 1H, =C-H), 11.6 (s broad, 1H, N(3)H, exchangeable with deuterium oxide); Anal. calcd. for $C_{11}H_{13}N_3O_6$: C, 46.65; H, 4.63; N, 14.83; Found: C, 46.32; H, 4.90; N, 14.41.

Reaction of 6-amino-2-methoxy pyrimidin-4-(3H)-one **1c** with DMAD **2** in toluene

1,41 g (0.01 mol) of **1c** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of toluene and refluxed for 72 h, observing by tlc a very complex mixture.[13] After cooling at room temperature a yellow solid precipitated which was collected by filtration, washed with cold toluene and dried at room temperature to give 0.112 g of a mixture of two compounds. This solid was treated with hot methanol to give a remaining solid consisted in a chromatographycally pure compound, identificated as 5-carbomethoxy-2-methoxy-pyrido[2,3-d]pyrimidin-4,7-(3H, 8H)-dione **9c**, 0.03 g (1 %), mp: 250-2 °C. UV ($4.98 \cdot 10^{-5}$ M, methanol) $\lambda_{max}(\epsilon)$nm : 352 (1940), 318 (10380), 280 (2900), 273 (sh), 222 (12670); IR υ_{max} (cm^{-1}): 3030, w; 2950, w; 1750, s; 1670, s; 1640, s; 1610, s; 1520, s; 1260, w; 1210, s; 1030, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 3.80 (s, 3H, $COOCH_3$), 4.00 (s, 3H, OCH_3), 6.20 (s, 1H, C(5)=C(6)H), 12.5 (s broad, 2H, N(3)H, N(8)H, exchangeables with deuterium oxide); Anal. calcd. for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.61; N, 16.73; Found: C, 47.73; H, 3.63; N, 16.96.

Reaction of 6-amino-2-methylthio pyrimidin-4-(3H)-one **1d** with DMAD **2** in acetonitrile

1,57 g (0.01 mol) of **1d** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of acetonitrile and refluxed for 20 h. Examination by tlc of the mother liquors indicated very complex mixture[13], which were evaporated *in vacuo* to dryness give 3.74 g of an oily residue, 1.52 g of which were applied on flash chromatography column (5x16 cm, 110g of silica gel). Elution with methylene chloride-ethyl ether-methanol mixtures (10:0:0 to 8:2:0 and 9:0:1) afforded by order of elution two pure fractions containing the compounds **6b** (0.05 g, 3 %) and **3b** (0.26 g, 25%); together with 0.68 g of another fraction mixture of several compounds, from which two compounds were separated by fractional crystallization from methanol, and identificated in order of crystallization as 5-carbomethoxy-2-methylthio pyrido[2,3-d]pyrimidin-4,7-(3H,8H)-dione **9d**, 0.01 g (1%); mp: 292-4 °C (d); tlc: Rf= 0.44 (methylene chloride-methanol 9:1); UV ($4.64 \cdot 10^{-5}$ M, methanol) $\lambda_{max}(\epsilon)$nm : 329 (26300), 292 (16500), 245 (21500), 224 (31700); IR υ_{max} (cm^{-1}): 3040, w; 2920, w; 1750, s, 1680-1640, s, broad; 1595, s; 1500, s; 1440, w; 1360, w; 1250, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 2.50 (s, 3H, SCH_3), 3.70 (s, 3H, $COOCH_3$), 6.20 (s, 1H, C(5)=C(6)H), 12.5 (bs, 2H, N(3)H, N(8)H, exchangeables with deuterium oxide); Anal. calcd. for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; N, 15.72; Found: C, 44.88; H, 3.36; N, 16.03; and 2-methylthio-6[(1,2-(E)-dicarbomethoxyethenyl)amino]pyrimidin-4-(3H)-one **10d**, 0.02 g (1.6%); mp: 222 °C (d); tlc: Rf= 0.56 (methylene chloride-methanol 9:1); UV ($4.91 \cdot 10^{-5}$ M, methanol) $\lambda_{max}(\epsilon)$nm : 320 (20100), 284 (19400), 243 (11600), 224 (12500); IR υ_{max} (cm^{-1}): 3250, w; 3000, w; 2940, w; 1740, s; 1680, s; 1650, s; 1610, s; 1430, s; 1370, w; 1280, s; 1210, s; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ (ppm): 2.40 (s, 3H, SCH_3), 3.70 (s, 6H, two $COOCH_3$), 5.50 (s, 1H, C(5)H), 5.80 (s, 1H, C=C-H); 9.80 (s, 1H, C(6)-NH, exchangeable with deuterium oxide); Anal. calcd. for $C_{11}H_{13}N_3O_5S$: C, 44.14; H, 4.38; N, 14.04; Found: C, 44.17; H, 4.24; N, 14.10;

Reaction of 6-amino-2-methyltio pyrimidin-4-(3H)-one **1d** with DMAD **2** in toluene

1,57 g (0.01 mol) of **1d** and 2.46 ml of **2** (0.02 mol) were added to 40 ml of toluene and refluxed for 96 h, observing a very complex mixture by tlc.[13] After cooling at room temperature a brown solid precipitated which was collected by filtration, washed with cold toluene and dried at room temperature to give 0.29 g of a mixture of two compounds. From which 0.06 g (2.2 %) of **9d** were separated by recrystallization from ethanol-acetone (50:50 v:v).

4,5-dicarbomethoxy-6-methoxy-2(1,2-E-dicarbomethoxy ethenyl)amino pyridine **6a**

To a solution of 0.24 g (1 mmol) of **3a** in 7 ml of absolute ethanol 0.25 ml (2 mmol) of DMAD **2** were added, and the solution was stirred at room temperature for 24 days, and then evaporated *in vacuo* to dryness to give an oily residue, which was purified by flash column chromatography (2x15 cm, 20g of Silica gel). Elution with methylene chloride-ethyl ether (97:3) gave a homogeneous residue, which was crystallized from ethanol to yield **6a**, 0.3 g (80%).

4,5-dicarbomethoxy-6-methyltio-2(1,2-E-dicarbomethoxy ethenyl)amino pyridine **6b**

To a solution of 0.115 g (0.45 mmol) of **3b** in 3 ml of absolute ethanol 0.1 ml (0.9 mmol) of DMAD **2** were added, and the solution was stirred at room temperature for 19 days, and then evaporated *in vacuo* to dryness to give an oily residue, which was purified by flash column chromatography (2x15 cm, 20g of Silica gel). Elution with methylene chloride-ethyl ether (98:2) gave a homogeneous residue as solid foam, yielding **6b**, 0.11 g (62%).

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12. This fact was proved by obtention of compounds **6** starting from **3** and **2** in a medium that helps the Michael addition, like ethanol.
13. Compounds **3a** and **3b** were detected by tlc as majority products in their respective reactions, also little amounts of **6a** and **6b** were observed.
14. Compounds **5c** and **5d** must form in their respective reactions although were not isolated, due to these compounds are intermediate compounds in the formation of **9c** and **9d**.
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