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Generation and Trapping of 5,6-Dimethylenepyrimidin-4-ones in Diels-Alder and Michael Additions

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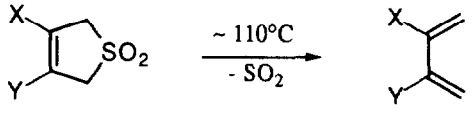
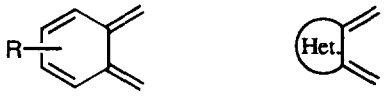
Abstract: Pyrimidone fused sulfones **5-7** were obtained from the reaction of amidines with 3-methoxycarbonyl-4-oxotetrahydrothiophene followed by N-methylation and oxidation with mCPBA. On heating in solution at 150°C, extrusion of SO_2 occured to give the highly reactive 5,6-dimethylenepyrimidin-4-ones which were intercepted *in situ* in Diels-Alder reactions to give the adducts **24-28** and in conjugate addition reactions with thiol nucleophiles to give the thioethers **29** and **30**.

1. INTRODUCTION

Extrusion of sulfur dioxide from 3-sulfolenes **1** is a versatile route to 1,3-dienes **2**.[1] Similarly, extrusion of sulfur dioxide from benzo- or heteroaromatic-fused 3-sulfolenes gives the corresponding *o*-quinodimethanes **3** and **4** [2,3] which are now well established as useful intermediates in organic synthesis.



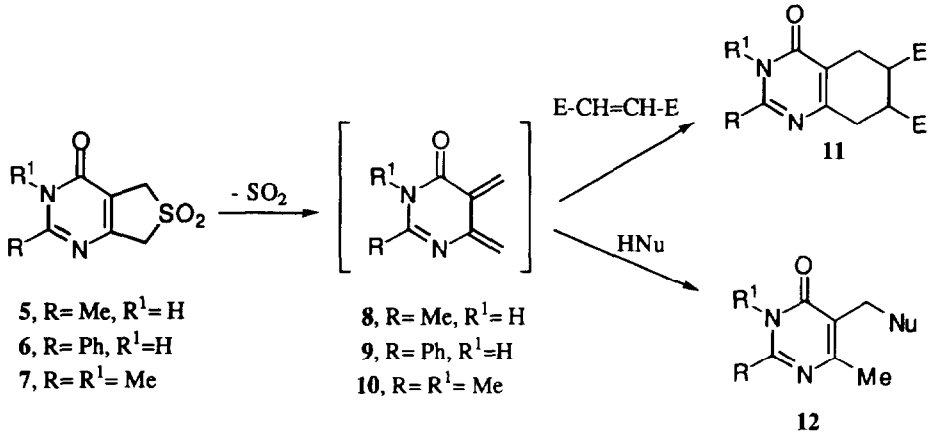
1 **2**



3 **4**

Recently we have described [4] the generation of 2-methyl-5,6-dimethylenepyrimidin-4-one **8** by thermal extrusion of sulfur dioxide from the pyrimidone-fused 3-sulfolene **5**. This novel and highly reactive diene, which is formally a pyrimidone *o*-quinodimethane, was trapped, *in situ*, with dienophiles. This exploratory

work has now been extended to the synthesis of 2-phenyl- and N-alkylpyrimidone-fused 3-sulfolenes to show the general applicability of this type of compound to the generation of the pyrimidone *o*-quinodimethanes.



5, R= Me, R^1= H
6, R= Ph, R^1=H
7, R= R^1= Me

8, R= Me, R^1= H
9, R= Ph, R^1=H
10, R= R^1= Me

Scheme 1

We now present full details of the thermal extrusion of sulfur dioxide from pyrimidones **5-7** in the presence of dienophiles to give the corresponding 5,6,7,8-tetrahydroquinazolin-4-ones **11** (Scheme 1). On the other hand, when the extrusion is conducted in the presence of nucleophiles pyrimidones of type **12** are obtained by addition of the nucleophiles to the α,β-unsaturated carbonyl system.

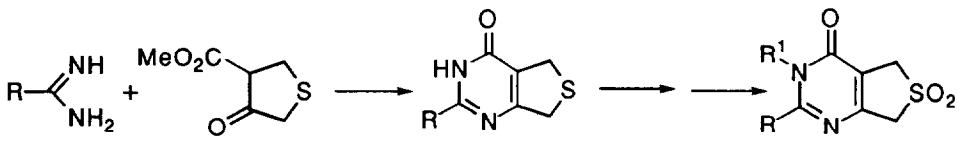
5,6,7,8-Tetrahydroquinazolines are known to possess important biological activities and some compounds of this type have been patented for their pharmacological activity.[5] New routes to this class of compounds are, thus, very important. Our approach to the synthesis of these compounds, based on the generation and trapping of pyrimidone *o*-quinodimethanes with dienophiles, is versatile and of general applicability.

2. RESULTS AND DISCUSSION

2.1 Synthesis of pyrimidone-fused 3-sulfolenes

The pyrimidones **16** and **17** were prepared from the reaction of the readily available keto-ester **15** [6] with amidines, by the general procedure for the synthesis of this type of compounds.[7] Thus reaction of keto-ester **15** with acetamidine or benzamidine liberated from the corresponding hydrochlorides gave the dihydrothienopyrimidones **16** and **17** respectively in good yields. Oxidation at sulfur and N-substitution gave the pyrimidone-fused 3-sulfolenes **5-7** (Scheme 2).

The synthesis of pyrimidones **16** and **17** involves the neutralization of the amidine hydrochlorides with sodium ethoxide in anhydrous ethanol and in these conditions the pyrimidone is obtained in good yield. However, in the case of pyrimidone **16** attempts to use sodium acetate instead of sodium ethoxide as base gave



13, R= Me
14, R= Ph

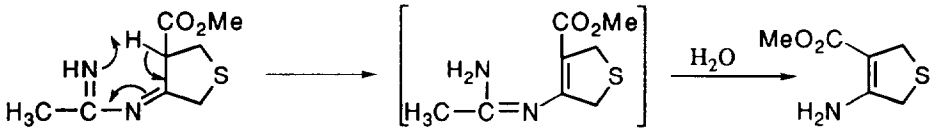
15

16, R= Me
17, R= Ph

5, R= Me, R^1= H
6, R= Ph, R^1=H
7, R= R^1= Me

Scheme 2

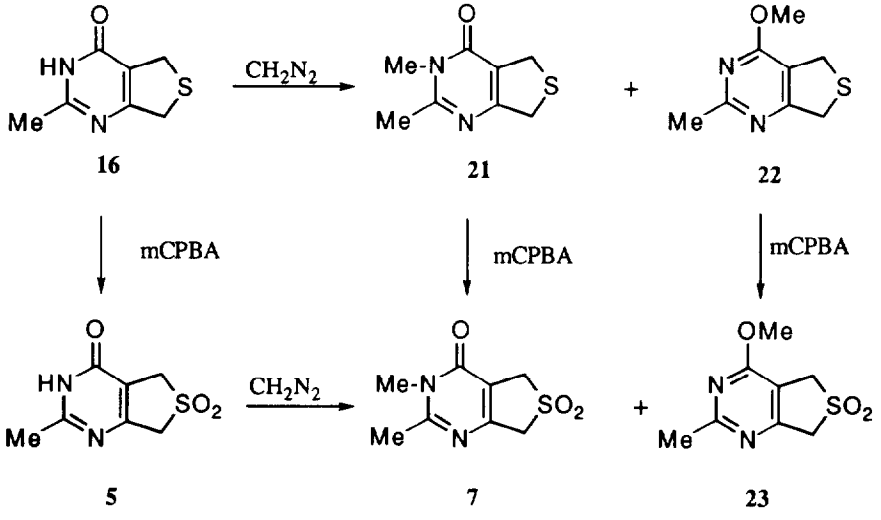
the amino-ester **20** as the only isolated product (52% yield); presumably this is formed by hydrolysis of the intermediate **19**.



18 **19** **20**

Scheme 3

Sulfones **5** and **6** were obtained by oxidation of the pyrimidones **16** and **17** with two equivalents of mCPBA in 94% and 90% yields respectively. Methylation of pyrimidone sulfone **5** with diazomethane gave a mixture of two compounds in an overall yield of 72% which were separated by column chromatography and



16 **21** **22**

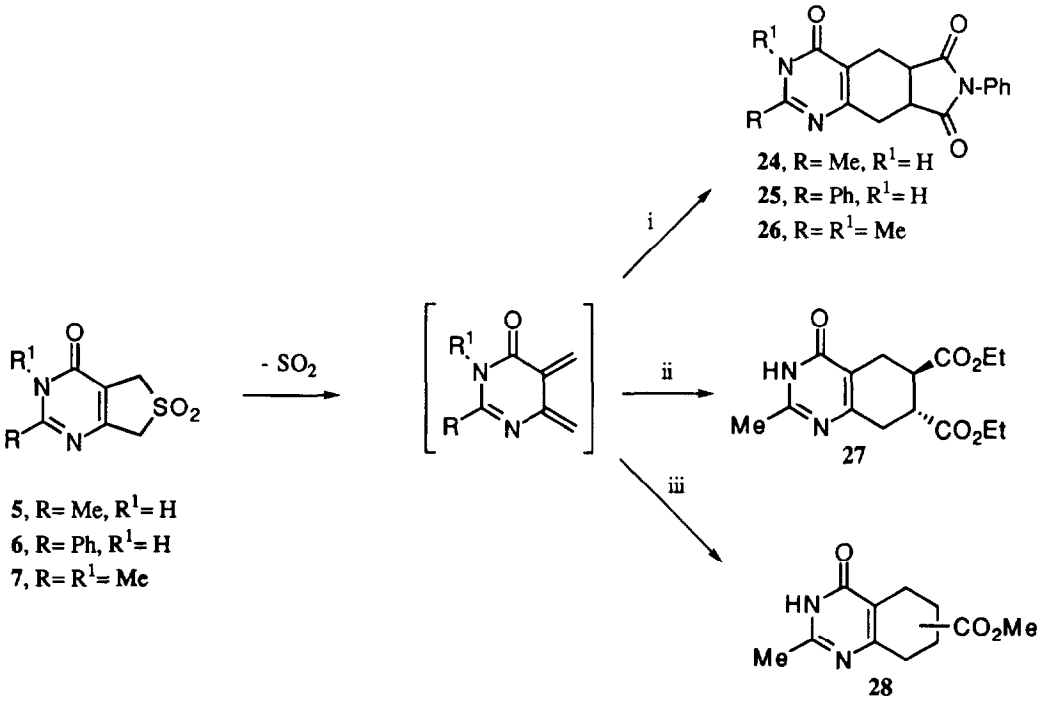
5 **7** **23**

Scheme 4

were identified as the 3-methylpyrimidone **7** (the compound with lower R_f; 47%) and the 4-methoxypyrimidine **23** (higher R_f; 25%). These two isomers were easily identified by their ^1H NMR spectra where the signals due to the NCH_3 and OCH_3 groups appear at δ 3.57 and 4.03 ppm respectively. The ^{13}C NMR spectra of these two compounds are, however, more informative because the difference between the signals corresponding to the NCH_3 and OCH_3 groups is more evident: δ 31.5 and 53.5 ppm, respectively. A better route to the same sulfones involves reversal of the sequence of oxidation and methylation of the sulfide **16**. Thus, methylation of the sulfide **16** with diazomethane gave, once again, the NCH_3 and OCH_3 products **21** and **22** in a ratio of approximately 2:1, respectively, in an overall yield of 96%. These two compounds were separated by column chromatography and were oxidized, in good yields, to the sulfones **7** and **23**,[8] respectively. The two alternative routes for the synthesis of these sulfones, starting from pyrimidone **16** (scheme 4), gave similar overall yields but the route involving methylation-separation-oxidation is more convenient than the oxidation-methylation-separation route because of the low solubility of the sulfones in the usual organic solvents.

A much more regioselective methylation of pyrimidone **16** was achieved with methyl iodide and potassium carbonate in refluxing acetone, but the yield was lower (74%). By this method, the N-methylpyrimidone **21** was obtained in 70% yield and the 4-methoxypyrimidine **22** in a 4% yield.

2.2 Thermal extrusion of sulfur dioxide from pyrimidone-fused 3-sulfolenes



5, R= Me, R^1= H
6, R= Ph, R^1= H
7, R= R^1= Me

24, R= Me, R^1= H
25, R= Ph, R^1= H
26, R= R^1= Me

27

28

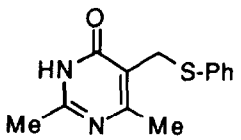
i) N-phenylmaleimide; ii) diethyl fumarate; iii) methyl acrylate

Scheme 5

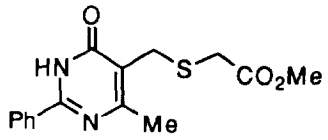
When heated in solution at ca. 150°C, the pyrimidones **5-7** lose sulfur dioxide to give the dienes **8-10**. If the extrusion is carried out in the presence of dienophiles, the corresponding Diels-Alder adducts of these dienes are obtained in moderate to good yields (scheme 5).

Heating a solution of sulfone **5** and N-phenylmaleimide (two equivalents) in 1,2,4-trichlorobenzene at 200°C for 3h yielded the adduct **24** in 95% yield. The adducts **25** and **26** were obtained by the same procedure, but in refluxing 1,2-dichlorobenzene. Extrusion of SO_2 from pyrimidone **5** in the presence of diethyl fumarate yielded the 5,6,7,8-tetrahydroquinazoline **27** in 53%. The reaction of the same sulfone with methyl acrylate was conducted in a sealed tube because of the volatility of this dienophile. This yielded an inseparable mixture of the two possible regioisomeric adducts **28** in 49% overall yield. The ^1H NMR spectrum of the adducts **28** shows only one set of signals but in the ^{13}C NMR spectrum signals due to the individual isomers were largely resolved and indicated a ratio of approximately 3:1. However, unambiguous assignment of the two regioisomers was not possible.

No adducts were obtained when the diene **8** was generated in the presence of dimethyl acetylenedicarboxylate or vinyl acetate. These results are consistent with those obtained by Kaneko et al. with a similar diene.[9]

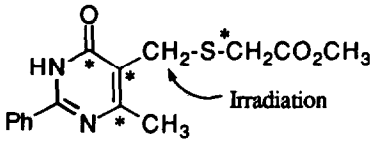


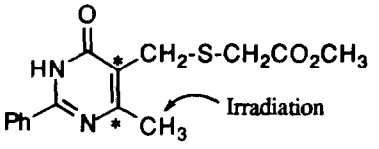
29



30

The 5,6-dimethylenepyrimidin-4-ones have the unusual feature of one of the C-C double bonds being conjugated with a carbonyl group. Such structure may allow this type of compounds to react with nucleophiles in a Michael addition type reaction. To explore this possibility, the sulfone **5** and thiophenol were heated together in a sealed tube at 200°C and as expected an adduct was obtained (61% yield). This was shown by ^1H and ^{13}C NMR spectroscopy to be a single compound, presumably with structure **29**, as a result of the nucleophilic attack of the thiophenol to the most reactive double bond. A similar reaction ocurred when the sulfone **6** was heated under reflux in 1,2-dichlorobenzene in the presence of methyl thioglycolate. The adduct **30** was obtained in 78% yield and its structure was confirmed by NMR spectroscopy. For an unambiguous assignment of the structure of compound **30**, two Selective INEPT experiments[10-12] were carried out: selective irradiation of the $\underline{CH_2}SCH_2CO_2Me$ protons revealed coupling to C4, C5, C6 and $S\underline{C}H_2CO_2Me$; selective irradiation of the 6-CH_3 protons gave coupling only to C5 and C6.[13] These results confirm the regiochemistry of the addition of nucleophiles to the 5,6-dimethylenepyrimidin-4-ones.





* indicates observed coupling

Attempted thermolysis of sulfone **7** in the presence of amines (benzylamine or diethylamine) resulted only in decomposition products.

3. EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer 1600 Series FTIR spectrometer. The NMR spectra were recorded on a Bruker AMX 300 and on a Bruker ACE 200 spectrometers. Deuteriochloroform was used as solvent (except when indicated) and TMS as internal reference. Coupling constants are in Hz. Mass spectra were recorded under electron impact (EI) at 70 eV on a VG Micromass 7070E and on a VG AutoSpec-Q instrument. Microanalysis were performed in the microanalytical laboratory at Liverpool University.

3.1 Synthesis of pyrimidones

3-Methoxycarbonyl-4-oxo-tetrahydrothiophene, **15**

This compound was prepared in two steps, in an overall yield of 73%, from methyl thioglycolate and methyl acrylate according to a variation of the method of Woodward and Heastman.[6] After purification by column chromatography (silica), using petroleum ether: dichloromethane (9:1) as eluent, the keto-ester was crystallized from cyclohexane/petroleum ether (1:1). M.p. 36-38°C (lit.[6] 37.8°C). **^{1}H NMR**: 3.75-3.84 (m, 7H), 10.95 (s, OH, enolic form).

2-Methyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one, **16**

This compound was prepared by the general method for the synthesis of pyrimidones described by McCasland and Bryce.[7]

To a solution of sodium ethoxide (43 mmol) in dried ethanol (200 ml) was added acetamidine hydrochloride (4.07 g; 43 mmol). The suspension was stirred for one hour at room temperature and the NaCl formed was removed by filtration. The keto-ester **15** (6.60 g; 41 mmol) was added to the filtered solution and the mixture was stirred overnight at room temperature and then heated under reflux for 4 h. On cooling white crystals were formed. These were filtered off, washed with cold ethanol and petroleum ether and dried (5.20 g). Evaporation of the crystallization solvent and recrystallization of the residue from acetone yielded more pyrimidone (1.30 g). The total yield of **16** was 96%. M.p. 273-275 °C (dec.); **IR** ν_{max} (Nujol) 1652, 1148, 912, 765 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + DMSO-d_6): 2.36 (s, 3H, CH_3), 3.99-4.02 (m, 2H, CH_2), 4.08-4.10 (m, 2H, CH_2), 12.53 (s largo, 1H, NH); **^{13}C NMR** ($CDCl_3$ + DMSO-d_6): 20.6 (CH_3), 32.4 (C-5), 39.0 (C-7), 119.5 (C-4a), 158.5 (C-2), 160.5 (C-7a), 164.7 (C-4); **MS** m/z (rel. int.): 168 ($M^{+\cdot}$, 100), 124 (24), 99 (10), 84 (8), 69 (9).

Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found : C, 49.94; H, 4.80; N, 16.72%.

2-Phenyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one, **17**

This compound was prepared by the same method as 2-methylpyrimidone **16**, but using benzamidine hydrochloride instead of acetamidine hydrochloride. The pyrimidone was obtained in 65% yield. M.p. 275-277°C.; **IR** ν_{max} (KBr) 2360, 1654, 1540, 1508, 699 cm^{-1}; **^{1}H NMR** (DMSO-d_6): 3.99-4.02 (m, 2H, CH_2), 4.17-4.20 (m, 2H, CH_2), 7.40-7.55 (m, 3H, Ar-H), 8.04-8.09 (m, 2H, Ar-H); **^{13}C NMR** (DMSO-d_6): 32.6

(C-5), 38.9 (C-7), 120.4 (C-4a), 127.8 (C-2'+C-6'), 128.9 (C-3'+C-5'), 131.8 (C-4'), 132.0 (C-1'), 157.1 (C-2), 160.8 (C-7a), 165.1 (C-4)
MS m/z (rel. int.): 230 ($M^{+\cdot}$, 100), 229 (68), 186 (17), 104 (14), 93 (5), 77 (14).
Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.52; H, 4.35; N, 12.13%.

4-Amino-3-methoxycarbonyl-2,5-dihydrothiophene, **20**

A suspension of the keto-ester **15** (4.36 g; 27 mmol), acetamidine hydrochloride (2.65 g; 28 mmol) and sodium acetate (2.46 g; 30 mmol) in methanol (80 ml) was refluxed for 3 h. After cooling at room temperature, the mixture was added to cold water and extracted with dichloromethane (3 x 25 ml). Part of the solvent was evaporated and the residue was purified by column chromatography (silica). The unchanged keto-ester was eluted with petroleum ether: ethyl acetate (2:1) and then the amino-ester **20** was eluted with petroleum ether: ethyl acetate (1:1). The amino-ester (2.23 g; 52%) was crystallized from dichloromethane/hexane. M.p. 128-129°C.; **IR** ν_{max} (Nujol) 3441, 3323, 1667 cm^{-1}; **^{1}H NMR**: 3.71 (s, 3H, CO_2CH_3), 3.77-3.86 (m, 4H, 2 x CH_2), 5.90 (broad s, 2H, NH_2); **^{13}C NMR**: 34.5, 38.2 (2 x $\underline{C}H_2$), 50.6 ($CO_2\underline{C}H_3$), 94.6 (C-4), 158.3 (C-3), 167.4 ($\underline{C}O_2Me$); **MS** m/z (rel. int.): 159 ($M^{+\cdot}$, 100), 144 (37), 128 (37), 127 (55), 126 (67), 100 (75), 99 (77), 80 (15), 72 (18), 67 (32), 54 (29), 45 (27).
Anal. Calcd for $C_6H_9NO_2S$: C, 45.27; H, 5.70; N, 8.80. Found: C, 45.21; H, 5.67; N, 8.72%.

3.2 Alkylation of the pyrimidones 16 and 5

3.2.1- Reaction of pyrimidone **16** with diazomethane

Diazomethane (generated by alkaline decomposition of N-methyl-N-nitroso-4-methylphenylsulfonamide (2.5 equiv.)) was added to a suspension of pyrimidone **16** (1.0 g; 5.9 mmol) in ethyl acetate (25 ml). The mixture was stirred for 20 h at room temperature. A TLC of the reaction mixture show that all the pyrimidone was methylated and that two new compounds were formed in a proportion of approximately 2:1. The excess of diazomethane was removed with a current of nitrogen, the solvent was evaporated and the residue was dissolved in dichloromethane. The two products of the reaction were separated by column chromatography (silica) using dichloromethane as eluant. The compound with higher R_f (0.37 g; 34%) was identified as 4-methoxypyrimidine **22** while the compound with lower R_f (0.67 g; 62%) was identified as N-methylpyrimidone **21**.

3.2.2- Reaction of pyrimidone **16** with methyl iodide

To a solution of the pyrimidone **16** (1.68 g; 10 mmol) in acetone (250 ml) was added potassium carbonate (2.76 g; 20 mmol) and methyl iodide (3.1 ml; 50 mmol). The mixture was stirred for 14 h at room temperature. The reaction mixture was warmed at 50°C for 15 minutes, then it was cooled and filtered. The acetone was evaporated and the residue was purified by column chromatography (silica) using dichloromethane: ethyl acetate (8:2) as eluant. A first fraction corresponding to the 4-methoxypyrimidine **22** (67 mg; 4%) was eluted, and then a second fraction corresponding to the N-methylpyrimidone **21** (1.28 g; 70%) was obtained.

2,3-Dimethyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one, **21**

This compound was crystallized from dichloromethane/petroleum ether. The crystals melt at 127-129°C. **IR** ν_{max} (KBr) 2360, 1654, 1540, 1430, 764 cm^{-1}; **^{1}H NMR**: 2.56 (s, 3H, 2-CH_3), 3.55 (s, 3H, N-CH_3),

4.07-4.11 (m, 2H, CH_2), 4.13-4.15 (m, 2H, CH_2); **^{13}C NMR**: 23.3 (2-CH_3), 30.9 (N-CH_3), 33.6 (C-5), 39.5 (C-7), 120.1 (C-4a), 159.0 (C-2), 160.2 (C-7a), 162.9 (C-4); **MS** m/z (rel. int.): 182 ($M^{+\cdot}$, 100), 167 (10), 124 (35), 84 (11), 56 (53).
Anal. Calcd for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37. Found : C, 52.66; H, 5.52; N, 15.44%.

4-Methoxy-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine, **22**

This compound was crystallized from dichloromethane/petroleum ether. The crystals melt at 75-76°C. **IR** ν_{max} (KBr) 1578, 1466, 1412, 1368, 1088, 766 cm^{-1}; **^{1}H NMR**: 2.60 (s, 3H, 2-CH_3), 4.00 (s, 3H, OCH_3), 4.06-4.07 (m, 2H, CH_2), 4.19-4.21 (m, 2H, CH_2); **^{13}C NMR**: 25.2 (2-CH_3), 31.7 (C-5), 38.5 (C-7), 53.5 (OCH_3), 113.7 (C-4a), 165.8 (C-7a), 167.2 (C-2), 169.7 (C-4); **MS** m/z (rel. int.): 182 ($M^{+\cdot}$, 100), 167 (50), 164 (27), 151 (13), 124 (77), 110 (16), 83 (28), 56 (30).
Anal. Calcd for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53; N, 15.37. Found : C, 52.66; H, 5.50; N, 15.44%.

3.2.3- Reaction of pyrimidone **5** with diazomethane

The experimental procedure for methylation of pyrimidone **5** with diazomethane is similar to that used for the methylation of the pyrimidone **16** with the same reagent. Methylation of 0.15 g (0.75 mmol) of pyrimidone yielded 0.75 g (47%) of N-methylpyrimidone **7** and 40 mg (25%) of 4-methoxypyrimidine **23**.

2,3-Dimethyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one 6,6-dioxide, **7**

Obtained by methylation of pyrimidone **5** with diazomethane or by oxidation of the sulfide **21** with a solution of the mCPBA (2.2 equiv.) in dichloromethane.To a solution of the sulfide **21** (0.68 g; 3.73 mmol) in dichloromethane (30 ml), at room temperature, was added a solution of the mCPBA (1.67 g; 8.2 mmol; 2.2 equiv.) in dichloromethane (40 ml). The mixture was stirred at the same temperature for 18 h. The excess of mCPBA was reduced with a few drops of a sodium thiosulfate solution and*m*-chlorobenzoic acid was removed by extraction of the residue with a saturated solution of $NaHCO_3$ (2 x 20 ml). The product was purified by column chromatography (silica) using a mixture of chloroform: acetone (90:10) as eluant. The sulfone (0.76; 95%) was crystallized from acetone/petroleum ether, yielding white crystals. M.p. 228-229°C; **IR** ν_{max} (KBr) 2954, 2915, 2360, 1670, 1540, 1313, 1117, 767 cm^{-1}; **^{1}H NMR**: 2.58 (s, 3H, 2-CH_3), 3.57 (s, 3H, N-CH_3), 4.27 (s, 2H, CH_2), 4.28 (s, 2H, CH_2); **^{13}C NMR**: 23.6 (2-CH_3), 31.5 (N-CH_3), 55.0 (C-5), 58.9 (C-7), 114.8 (C-4a), 154.6 (C-2), 158.5 (C-7a), 161.2 (C-4); **MS** m/z (rel. int.): 214 ($M^{+\cdot}$, 11), 150 (100), 135 (12), 109 (22), 80 (12), 56 (45).
Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.73; H, 4.68; N, 13.17%.

4-Methoxy-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **23**

Obtained as a minor product of the methylation of pyrimidone **5** with diazomethane or by oxidation of the sulfide **22** with a solution of the mCPBA (2.2 equiv.) in dichloromethane. The pyrimidine was crystallized from dichloromethane/petroleum ether. M.p. 119-121°C; **IR** ν_{max} (KBr) 2968, 1570, 1475, 1311, 1253, 1133, 1079, 758 cm^{-1}; **^{1}H NMR**: 2.63 (s, 3H, 2-CH_3), 4.03 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 4.35 (s, 2H, CH_2); **^{13}C NMR**: 25.9 (2-CH_3), 53.5 (OCH_3), 54.4 (C-5), 57.9 (C-7), 108.6 (C-4a), 159.7 (C-7a), 165.3 (C-2), 169.0 (C-4); **MS** m/z (rel. int.): 214 ($M^{+\cdot}$, 5), 150 (100), 120 (9), 94 (8), 79 (13), 66 (15).
Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.87; H, 4.70; N, 13.04%.

3.3 Oxidation of the dihydrothienopyrimidin-4-ones

2-Methyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one 6,6-dioxide, **5**

To a solution of the sulfide **16** (0.51 g; 3.0 mmol) in methanol (20 ml), cooled in a ice bath, was added a solution of the mCPBA (1.2 g; 6.2 mmol; 2.1 equiv.) in dichloromethane (20 ml). The mixture was stirred at room temperature for 18 h. The excess of mCPBA was reduced with a few drops of a sodium thiosulfate solution. The *m*-chlorobenzoic acid was removed by extraction of the residue with hot toluene (2 x 20 ml). The compound insoluble in toluene (0.56 g; 94%) was identified as sulfone **5** and is pure enough for the following reactions. A small portion of the sulfone was purified by column chromatography (silica), using a mixture of chloroform: acetone (75:25) as eluant. It was crystallized from acetone/petroleum ether. The same sulfone was obtained, in a yield of 60%, by oxidation of the sulfide **16** with Oxone ($2KHSO_5.KHSO_4.K_2SO_4$). M.p. 234-236°C (dec.); **IR** ν_{max} (KBr) 2360, 1654, 1559, 1320, 1125 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + DMSO-d_6): 2.41 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 12.91 (s broad, 1H, NH); **^{13}C NMR** ($CDCl_3$ + DMSO-d_6): 21.5 (CH_3), 54.3 (C-5), 58.8 (C-7), 115.0 (C-4a), 156.7 (C-2), 159.3 (C-7a), 160.9 (C-4); **MS (CI)** m/z (rel. int.): 201 ($(M+H)^+$, 28), 167 (15), 137 (100), 123 (26), 104 (38), 88 (27), 74 (84), 70 (32); **MS** m/z (rel. int.): 200 ($M^{+\cdot}$, 4), 136 (100), 108 (5), 94 (5), 67 (14).
Anal. Calcd for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99. Found: C, 41.94; H, 4.01; N, 14.05%.

2-Phenyl-3*H*-5,7-dihydrothieno[3,4-d]pyrimidin-4-one 6,6-dioxide, **6**

A solution of mCPBA (1.13 g; 5.54 mmol; 2.2 equiv.) in dichloromethane (50 ml) was added to the sulfide **17** (0.58 g; 2.5 mmol), dissolved in a mixture of methanol (20 ml) and dichloromethane (50 ml). The mixture was stirred at room temperature for 18 h. The excess of mCPBA was reduced with a few drops of a sodium thiosulfate solution, the dichloromethane was evaporated and the mixture was dissolved in a saturated aqueous solution of $NaHCO_3$ (120 ml). The sulfone was precipitated by careful acidification of the aqueous solution with concentrated acetic acid. The sulfone was filtered and dried (0.59 g; 90%) and is pure enough for the following reactions. M.p. 240-244°C.; **IR** ν_{max} (KBr) 1654, 1311, 1131, 703 cm^{-1}; **^{1}H NMR** (DMSO-d_6): 4.30 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 7.47-7.58 (m, 3H, Ar-H), 8.08-8.11 (m, 2H, Ar-H); **MS** m/z (rel. int.): 262 ($M^{+\cdot}$, 4), 228 (23), 198 (100), 156 (18), 139 (17), 125 (17), 104 (35), 95 (16), 77 (23), 66 (11).

3.4 Generation and trapping of 2-methyl- and 2-phenyl-5,6-dimethylenepyrimidin-4-one

General procedure:

a) Reflux in 1,2,4-trichlorobenzene

The sulfone and the dienophile (2 or 3 equiv.), in 1,2-dichlorobenzene (or 1,2,4-trichlorobenzene) (5 ml/mmol of sulfone) were refluxed, under nitrogen atmosphere, for 3 h. After cooling, the mixture was applied to the top of a column of silica and the dichlorobenzene was eluted with petroleum ether: dichloromethane (2:1). The adduct was then eluted with the appropriate eluant. Alternatively, the adduct was precipitated by addition of petroleum ether to the cooled reaction mixture, filtered off and purified by column chromatography.

b) Sealed tube

The sulfone and the dienophile (10 equiv.) in toluene (5 ml/mmol of sulfone) in a sealed tube were heated at 190-220°C for 3 h. After cooling, the mixture was applied on the top of a column of silica and the adduct was eluted with the appropriate eluant.

2-Methyl-7-phenyl-3*H*-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-4,6,8-trione, **24**

Obtained in 95% yield by reaction of the sulfone **5** with N-phenylmaleimide, in trichlorobenzene. M.p. > 320°C. **IR** ν_{max} (Nujol) 1712, 1644, 1603, 1211, 1186 cm^{-1}; **^{1}H NMR** (DMSO-d_6): 2.24 (s, 3H, CH_3), 2.49-3.54 (m, 6H, CH_2 and CH), 7.06-7.10 (m, 2H, Ar-H), 7.38-7.48 (m, 3H, Ar-H); **MS** m/z (rel. int.): 309 ($M^{+\cdot}$,100), 161 (75), 136 (13), 118 (12), 93 (8), 71 (15).
Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.92; H, 4.90; N, 13.51%.

2,7-Diphenyl-3*H*-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-4,6,8-trione, **25**

Obtained in 91% yield by reaction of the sulfone **6** with N-phenylmaleimide, in dichlorobenzene. M.p. 314-316°C; **^{1}H NMR** ($CDCl_3$ + DMSO-d_6): 2.84-3.60 (m, 6H, CH_2 and CH), 7.16-7.20 (m, 2H, Ar-H), 7.33-7.55 (m, 6H, Ar-H), 8.12-8.15 (m, 2H, Ar-H), 12.65 (s, 1H, NH); **^{13}C NMR**: 20.8 (C-5), 31.2 (C-9), 38.9, 39.4 (C-5a/C-8a), 117.5 (C-4a), 126.3, 127.7, 128.5, 128.7, 128.9, 131.6, 131.8, 132.1 (2 x C_6H_5), 155.4, 160.6, 162.0 (C-2, C-4, C-9a), 177.8 (C-6 + C-8); **MS** m/z (rel. int.): 371 ($M^{+\cdot}$,7), 223 (6), 97 (6), 84 (78), 72 (12), 66 (100).

2,3-Dimethyl-7-phenyl-3*H*-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-4,6,7-trione, **26**

Obtained by reaction of the sulfone **7** (0.24 g; 1.12 mmol) with N-phenylmaleimide (0.39 g; 2.24 mmol; 2 equiv.) in refluxing 1,2-dichlorobenzene (6 ml) for 3h, under nitrogen atmosphere. The adduct was precipitated with petroleum ether, filtered off and purified by column chromatography (silica). The N-phenylmaleimide was eluted with dichloromethane and the adduct was eluted with chloroform: acetone (75:25). The adduct **26** (0.35 g; 97%) was crystallized from toluene. M.p. 232-234°C; **IR** ν_{max} (Nujol) 1704, 1660, 1520, 1181, 820 cm^{-1}; **^{1}H NMR**: 2.50 (s, 3H, 2-CH_3), 2.81-3.50 (m, 6H, CH_2 and CH), 3.52 (s, 3H, N-CH_3), 7.20-7.23 (m, 2H, Ar-H), 7.35-7.45 (m, 3H, Ar-H); **^{13}C NMR**: 21.4 (C-5), 23.3 (2-CH_3), 30.6 (C-9), 31.4 (N-CH_3), 38.9, 39.3 (C-5a/C-8a), 116.3 (C-4a), 126.1 (C-2' and C-6'), 128.5 (C-4'), 129.0 (C-3' and C-5'), 131.7 (C-1'), 157.7, 157.9 (C-2/C-9a), 160.9 (C-4), 177.6, 177.7 (C-6/C-8); **MS** m/z (rel. int.): 323 ($M^{+\cdot}$,100), 175 (80), 118 (19), 91 (11), 83 (12), 77 (14), 56 (36).
Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.66; H, 5.30; N, 12.93%.

trans-6,7-bis(Ethoxycarbonyl)-2-methyl-3*H*-5,6,7,8-tetrahydroquinazolin-4-one, **27**

Obtained by reaction of the sulfone **5** with diethyl fumarate, in trichlorobenzene, with a yield of 53%. The adduct was crystallized from chloroform/hexane. M.p. 175-177°C; **IR** ν_{max} (Nujol) 1729, 1648, 1148 cm^{-1}; **^{1}H NMR**: 1.21-1.30 (overlapping t, 6H, 2 x $CH_2\underline{CH_3}$), 2.43 (s, 3H, CH_3), 2.50-3.08 (m, 6H, CH_2 and CH), 4.10-4.23 (overlapping q, 4H, 2 x $\underline{CH_2}CH_3$), 11.0 (broad s, 1H, NH); **MS** m/z (rel. int.): 308 ($M^{+\cdot}$, 34), 263 (28), 235 (100), 207 (7), 189 (6), 161 (75), 118 (38), 92 (4), 77 (8).
Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.05. Found: C, 58.46; H, 6.55; N, 9.05%.

6-Methoxycarbonyl-2-methyl-3*H*-5,6,7,8-tetrahydroquinazolin-4-one and 7-Methoxycarbonyl-2-methyl-3*H*-

5,6,7,8-tetrahydroquinazolin-4-one, **28**

Obtained in 49% yield by reaction of sulfone **5** with methyl acrylate, in sealed tube. The adduct was crystallized from chloroform/hexane. M.p. 180-185°C; **IR** ν_{max} (Nujol) 1732, 1652, 1613, 940 cm^{-1}; **^{1}H NMR**: 1.74-2.94 (m, 7H, CH and CH_2), 2.44 (s, 3H, CH_3), 3.73 (s, 3H, CO_2CH_3), 12.74 (broad s, 1H, NH); **MS** m/z (rel. int.): 222 ($M^{+\cdot}$, 40), 163 (100), 161 (54), 118 (13), 77 (12), 52 (10), 42 (44). **Anal.** Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.44; H, 6.37; N, 12.58%.

2,6-Dimethyl-5-phenylthiomethyl-3*H*-pyrimidin-4-one, **29**

Obtained by reaction of the sulfone **5** with thiophenol, in sealed tube, with a yield of 61%. The adduct was crystallized from acetone/hexane. M.p. 167-168°C; **IR** ν_{max} (Nujol) 1652, 1607, 1319, 1215, 1155, 944, 773 cm^{-1}; **^{1}H NMR**: 2.19 (s, 3H, 6-CH_3), 2.44 (s, 3H, 2-CH_3), 4.06 (s, 2H, $\underline{CH_2}$SPh), 7.26-7.34 (m, 3H, Ar-H), 7.44-7.48 (m, 2H, Ar-H), 13.09 (br. s, 1H, NH); **^{13}C NMR**: 21.52, 21.54 (2-CH_3/6-CH_3), 30.0 (CH_2SPh), 117.7 (C-5), 126.9 (C-4'), 128.9 (C-2'+ C-6'), 131.3 (C-3'+C-5'), 136.0 (C-1'), 156.5 (C-2), 163.6 (C-6), 164.5 (C-4); **MS** m/z (rel. int.): 246 ($M^{+\cdot}$, 18), 137 (100), 109 (18), 96 (11), 53 (14), 42 (59); **Anal.**: Found (%) : C, 63.45; H, 5.71; N, 11.40; Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37

5-(Methoxycarbonyl)methylthiomethyl-6-methyl-2-phenyl-3*H*-pyrimidin-4-one, **30**

A mixture of pyrimidone 6 (0.21 g; 0.8 mmol), methyl thioglycolate (1.5 ml) and 1,2-dichlorobenzene was refluxed for 2 h, under nitrogen atmosphere. After cooling, the mixture was applied on the top of a column of silica and the dichlorobenzene was eluted with petroleum ether: dichloromethane (2:1). The adduct was then eluted with chloroform. After evaporation of the eluant, the adduct was crystallized from chloroform/hexane to yield yellow crystals (0.19 g ; 78 %). M.p. 140-142°C; **IR** ν_{max} (KBr) 2948, 2360, 1718, 1653, 1540, 1289, 1146, 705 cm^{-1}; **^{1}H NMR**: 2.52 (s, 3H, 6-CH_3), 3.36 (s, 2H, S$\underline{CH_2}CO_2$Me), 3.70 (s, 2H, CO_2CH_3), 3.90 (s, 2H, $\underline{CH_2}SCH_2CO_2$Me), 7.53-7.58 (m, 3H, Ar-H), 8.23-8.26 (m, 2H, Ar-H), 13.25 (br. s, 1H, NH); **^{13}C NMR**: 22.0 (6-CH_3), 27.3 ($\underline{C}H_2SCH_2CO_2$Me), 33.9 (S$\underline{C}H_2CO_2$Me), 52.4 ($CO_2\underline{C}H_3$), 119.1 (C-5), 127.7 (C-2'+C-6'), 129.0 (C-3'+C-5'), 131.8/ 131.9 (C-1'/ C-4'), 154.3 (C-2), 163.7 (C-6), 164.7 (C-4), 171.0 ($\underline{C}O_2$Me); **MS** m/z (rel. int.): 304 ($M^{+\cdot}$, 20), 231 (32), 200 (53), 199 (100), 104 (30), 77 (11).

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