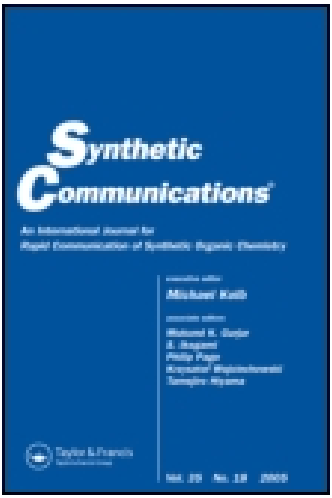

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Synthesis of New Sulfur Heterocycles

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SYNTHESIS OF NEW SULFUR HETEROCYCLES

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abstract *: Dithiepine, dithiocine, thiolactones were synthetized by thermolysis of Meldrum's acid derivatives.*

In a previous paper, we described a new synthetic route to medium and large size ring enaminolactones by cyclisation of aminomethyleneketene intermediates bearing a hydroxy group in the ω-position (X = NR, Z = O), via an intramolecular nucleophilic addition.[1] We will show that this cyclisation is not affected by the nature of the heteroatoms and most particularly by that of the nucleophilic group (Scheme 1).

We report here the synthesis of seven to eight membered thiolactones : 2,3-dihydro-5H-1,4-dithiepin-5-one and 7,8-dihydro-2H, 6H-1,5-dithiocin-2-one, a new class of sulfur compounds of which first derivatives [2] have recently been described. Here we also report an unexpected transposition of thioarylmethyleneketene **3f** into benzothiazol.

Thus we studied the thermal reactivity of alkylthiomethyleneketenes with several chains (n : 0, 1) and bearing a hydroxy or a mercapto group (Z = S, O) in the ω-position. We also studied the thermal behaviour of two (aromatic and an aliphatic) ω-mercaptoaminomethyleneketenes (X = NH, Z = S). The

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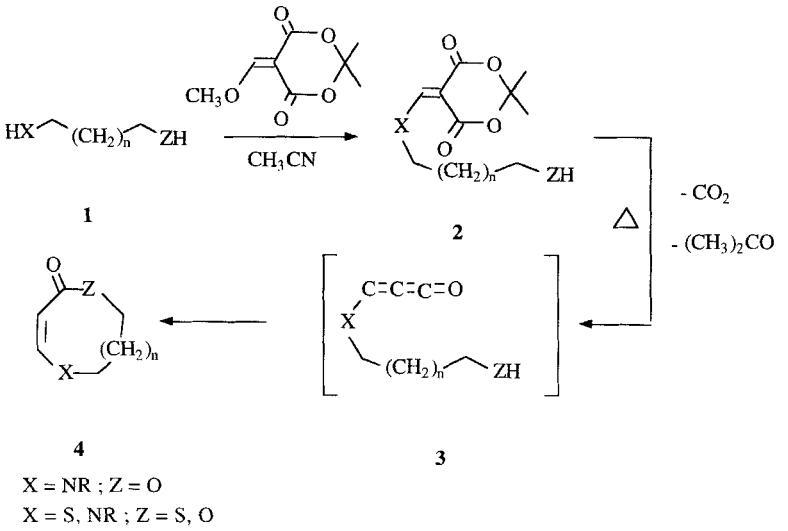
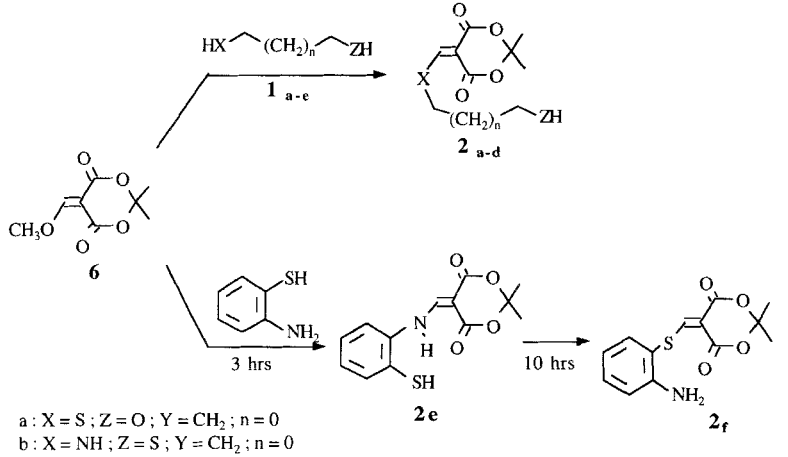


Scheme 1



Scheme 2

thioalkylmethyleneketenes $\mathbf{3_{a,c,d}}$ (X = S, Z = S, O) were generated by thermolysis of Meldrum's acid derivatives $\mathbf{2_{a,c,d}}$ (Scheme 1).

Meldrum's acid derivatives **2** were obtained by treatment of thioalcohol, dithiols or ω-mercaptoamino compounds with 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione **6** (Scheme 2). [3] Starting materials are commercialy available thiols : 2-mercapto ethanol $\mathbf{1_a}$, 2-mercapto ethaneamine $\mathbf{1_b}$, ethan-1,2-dithiol $\mathbf{1_c}$, propan-1,3-dithiol $\mathbf{1_d}$, and 2-aminothiophenol $\mathbf{1_e}$.According to a typical procedure, the addition of one equivalent of 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione **6** to one equivalent of thiol $\mathbf{1_{a-e}}$ in acetonitrile leads to Meldrum's acid derivatives $\mathbf{2_{a-e}}$. (Scheme 2)

Derivatives $\mathbf{2_{a-d,f}}$ were isolated and purified by chromatography on silica gel with yields ranging between 54-71%. (Table 1)

Table 1 Isolated yields of Meldrum's acid derivatives $\mathbf{2_{a-d,f}}$.

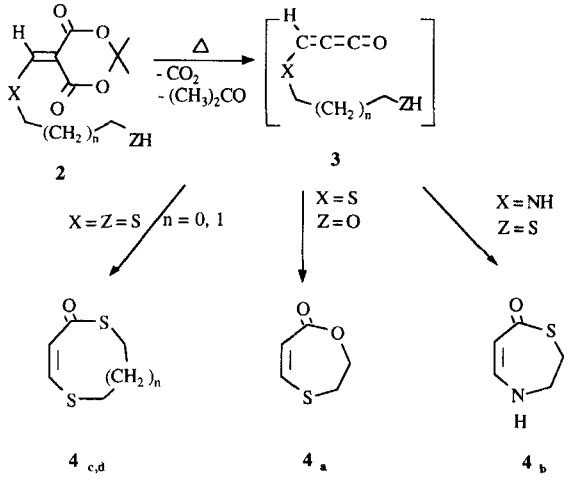
compounds **2**	X	Z	n	Yield %
$\mathbf{2_a}$	S	O	0	54
$\mathbf{2_b}$	NH	S	0	61
$\mathbf{2_c}$	S	S	0	61
$\mathbf{2_d}$	S	S	1	69
$\mathbf{2_f}$	S	NH	-	71

The cyclisation was achieved by thermolysis in flow conditions.[4] Decomposition of the derivatives $\mathbf{2_{a-d}}$ with temperature from 420 to 500°C gave the expected medium sized sulfur heterocycles $\mathbf{4_{a-d}}$ as the only product. Medium sized ring heterocycles $\mathbf{4_{a-d}}$ were isolated by chromatography on silica gel with the yields indicated in Table 2.

Table 2 Yields of isolated compounds **4**.

Compound **4**	X	Z	n	Yield %
$\mathbf{4_a}$	S	O	0	74
$\mathbf{4_b}$	NH	S	0	64
$\mathbf{4_c}$	S	S	0	66
$\mathbf{4_d}$	S	S	1	37

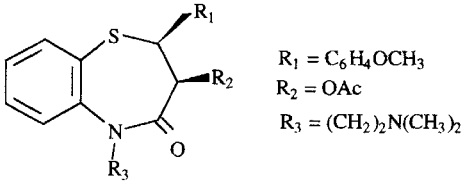
The thermal behaviour must involve an intramolecular nucleophilic addition of the terminal group (ZH) to the central double bond of the methyleneketene, leading to thiolactones $\mathbf{4_{a-d}}$ (Scheme 3).



2 3 $4_{c,d}$ 4_a 4_b

Scheme 3

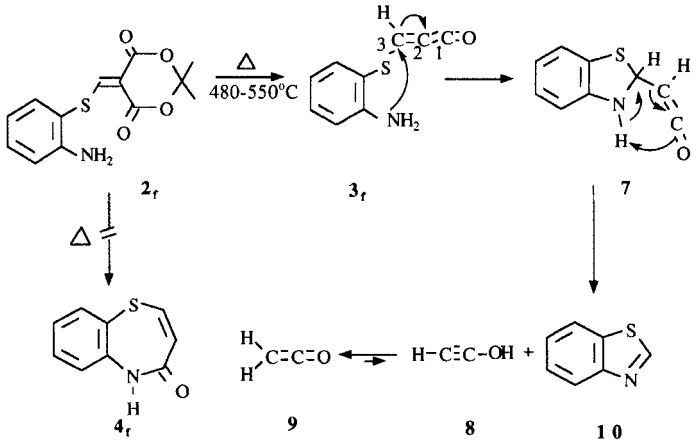
In order to obtain a diltiazem analog,[5] Meldrum's acid derivative $\mathbf{2_f}$ was prepared from 2-aminothiophenol $\mathbf{1_e}$ and enol ether **6**. After three hours, only Meldrum's acid derivative $\mathbf{2_e}$ was formed, but this kinetic product was slowly transformed into the thermodynamic derivative $\mathbf{2_f}$, the only product observed after ten hours at room temperature. The thermolysis achieved at 550°C did not lead to



Diltiazem

the expected lactam $\mathbf{4_f}$, but exclusively to benzothiazol (77%). The mechanism could assume a nucleophilic attack of the amino group on the C_3 carbon of the methyleneketene $\mathbf{3_f}$; the thermal instable intermediate **7** could eliminate ketene **9** giving benzothiazol **10** (Scheme 4).

Flash vacuum thermolysis experiments at 950°C (P = 10^{-4} torr) allowed ketene **9** to be trapped (identified by IR spectroscopy at -80°C ; ν = 2125 cm^{-1}),[6] and probably arising from the very unstable ethynol intermediate **8**. Ethynol



Scheme 4

formation was already observed by flash vacuum thermolysis of Diels-Alder bis adducts. [7]

In conclusion, various sulfur heterocycles **4** including thiolactones, dithiocine, dithiepine, were easily prepared in relatively good yields by thermolysis of Meldrum's acid derivatives. Thermal rearrangement of 2-aminoarylthiomethyleneketene leads to benzothiazol and the ketene **9** formed from the unstable ethynol **8**.

Experimental

methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione **6**

Meldrum's acid (10 g, 70.10^{-3} mol) and methylorthoformiate (40 ml, 365.10^{-3} mol) were introduced in a two necked flask equiped with a reflux condenser. The solution is refluxed for 3 hrs and the solvent was rotavapory evaporated. Recristallisation in tetrahydrofuran, petroleum ether : (1 : 5), gave 11 g (59.10^{-3} mol : 85%) as a yellow solid, mp = 120°C.

NMR ^{1}H ($CDCl_3$) δ = 1,73 (s, 6H); 4,28 (s, 3H); 8,15 (s, 1H)

NMR ^{13}C ($CDCl_3$) δ = 27,4 (1C); 66,5 (1C); 97 (1C); 104,9 (1C); 158,8 (1C); 163,3 (1C); 172,5 (1C)

MS (m/z) = 186 (0,9); 172 (8); 157 (13); 144 (5); 115 (24); 103 (6); 97 (10); 69 (28); 59 (100)

IR (KBr) ν = 3020; 2950; 1750; 1715; 1590; 1410; 1380; 1285; 1200; 1140.

5-(2'-hydroxyethylthiomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **2a**

According to a typical procedure **2 a** was obtained from 1g (128.10^{-4} mol) of 2-hydroxyethanthiol **1a** and 2,38 g (1eq) of enol ether **6** . The collected solid was washed with petroleum ether and acetone : (1 : 2) to give 1,61 g (69.10^{-4} mol ; 54%) as a white solid, mp = 55°C.

NMR ^{1}H ($CDCl_3$) δ = 1,7 (s, 6H); 3,15 (t, 2H, J = 7,1); 3,9 (t, 2H); 4,05 (sl, 1H); 9,1 (s, 1H)

NMR ^{13}C ($CDCl_3$) δ = 26,5 (2C); 39,4 (1C); 60,4 (1C); 104,3 (1C); 107,6 (1C); 160,0 (1C); 160,3 (1C); 171,8 (1C)

MS (m/z) = 234 (0,1); 233 (0,1); 232 (0,8); 214 (1,3); 175 (7,2); 174 (11); 157 (1,3); 156 (4,8); 146 (1,5); 144 (7,1); 61 (7,7); 60 (7,7); 58 (18,6); 55 (2,4); 54 (1,7); 53 (35,9); 48 (6,1); 47 (10,9); 46 (7,6); 45 (32,4); 44 (19,8); 43 (100); 42 (10,6); 41 (7,1)

IR (KBr) ν = 3600-3100; 2975; 2950; 1722; 1703; 1531; 1382; 1374; 1347; 1282; 1223; 1205; 1053, 1005; 941; 921; 893; 872; 790; 705.

5-(2'-mercaptoethylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **2b**

This was obtained from 1 g (13.10^{-3} mol) of 2-mercaptoethanamine and 2,4 g (1eq) of enol ether **6** according the same procedure as for **2a**. Purification by chromatography on silica gel with dichloromethane, aceton : (1 : 8) gave 1,83 g (79.10^{-4} mol ; 61%) as a white solid, mp = 158°C.

NMR ^{1}H ($CDCl_3$) δ = 1,42 (t, 1H, J = 8,7); 1,65 (s, 6H); 2,74 (m, 2H); 3,6 (qd, 2H, J = 6,4); 8,11 (d, 1H, J = 12); 9,6 (sl, 1H)

NMR ^{13}C ($CDCl_3$) δ = 24,1 (1C); 26,4 (2C); 52,4 (1C); 83, 8 (1C); 13,9 (1C); 159,7 (1C); 163,2 (1C); 164,6 (1C)

MS (m/z) = 231 (24,7); 174 (20,9); 173 (82,1); 145 (17,4); 129 (16,7); 126 (27,3); 114 (6,8); 101 (8,4); 100 (7,2); 88 (10,6); 87 (41,5); 82 (18,1); 70 (30,9); 61 (16,1); 60 (72,8); 59 (47,2); 58 (57,4); 45 (14,1); 44 (13,2); 43 (100)

IR (KBr) ν = 3272; 3032; 2994; 2960; 1728; 1664; 1632; 1456; 1378; 1338; 1302; 1284; 1262; 1222; 1202; 1006; 926; 818; 776; 736; 668.

5-(2'-mercaptoethylthiomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **2c**

This was obtained from 1 g (106.10^{-4} mol) of 1,2-ethandithiol and 1,98 g (1eq) of enol ether **6** by the same procedure as for **2a**. The collected product was washed with chloroform to give 1,61 g (648.10^{-5} mol ; 61%) as a yellow solid, mp = 224°C.

NMR ^{1}H (DMSO) δ = 1,65 (s, 6H); 3,15 (m, 2H); 3,4 (m, 2H); 3,7 (sl, 1H), 9,3 (s, 1H)
MS (m/z) = 250 (0,2); 249 (0,2); 248 (1,4); 191 (2,8); 190 (8,2); 164 (8,7); 163 (5,3); 162 (69,7); 134 (12,2); 120 (2,8); 119 (2,4); 118 (33,4); 107 (2,5); 106 (1,6); 105 (19); 94 (14,1); 61 (35,9); 60 (35,2); 59 (43,3); 58 (50,8); 57 (22,7); 53 (20,5); 47 (55,4); 46 (20,8); 44 (23,2); 43 (100); 42 (16,5); 41 (16,2)
IR (KBr) ν =3600-3200; 3000; 2980; 2934; 2852; 1785; 1747; 1701; 1571; 1388; 1330; 1302; 1294; 1210; 1082; 1058; 1018; 995; 895; 870.

5-(3'-mercaptopropylthiomethylene)-2,2-dimethyl- 1,3-dioxane-4,6-dione **2_d**
It was obtained by the same procedure as for **2_a** from 1 g (925.10^{-5} mol) of propan-1,3-dithiol and 1,72 g (1eq) of enol ether **6**. Purification by chromatography with chloroform, aceton : (1 : 1) yielded to 1,67 g (638.10^{-5} mol ; 69%) as a yellow oil.
NMR ^{1}H ($CDCl_3$) δ = 1,27 (t , 1H, J = 8,1); 1,65 (s, 6H); 1,75 (m, 2H); 2,6 (ml, 2H); 3,12 (t, 2H, J = 7,1); 8,9 (s,1H)
Two rotamers were observed in NMR ^{13}C.
NMR ^{13}C (CDCl3) δ = 21,8-21,9 (1C); 26,6-26,7 (1C); 32,7 (1C); 35,9-36,1 (1C); 104,2-104,4 (1C); 108,0-108,6 (1C); 159,6 (1C); 100,1(1C); 168,7-169,9 (1C)
MS (m/z) = 262 (not observed); 206 (0,3); 205 (0,5); 204 (2,15); 178 (2,5); 119 (7,5); 108 (1,1); 107 (0,8); 106 (4,7); 87 (1,8); 86 (2,6); 75 (1,5); 74 (5,2); 73 (2,5); 43 (100)
IR (NaCl) ν = 3010; 2955; 1718; 1698; 1522; 1394; 1346; 1286; 1198; 1036; 1006; 926; 868; 794; 706.

5-(2'-mercaptoanilinomethylene)-2,2-dimethyl- 1,3-dioxane-4,6-dione **2_e**
2_e was obtained from 1 g (8.10^{-3} mol) of 2-aminothiophénol **1_e**, and 1,48 g (1eq) of enol ether **6**. The mixture is stirred for three hours at room temperature in acetonitrile. The solvent was evaporated to give 2,16 g (77.10^{-4} mol ; 97%) of a yellow oil. Derivative **2_e** was slowly transformed in **2_f**.
NMR ^{1}H ($CDCl_3$) δ = 1,68 (s, 6H); 3,3 (sl, 1H); 7,09 (m, 1H); 7,28 (d, 2H, J = 4); 7,48 (d, 1H, J = 8); 8,5-8,61 (2s, 1H); 11,62-11,68 (2s)
NMR ^{13}C ($CDCl_3$) δ = 27,2 (2C); 88,3 (1C); 105,2 (1C); 116,8 (1C); 119,8 (1C); 126,8 (1C); 129,5 (1C); 135,4 (1C); 138,7 (1C); 152 (1C); 163,5 (1C); 165,3 (1C)

MS (m/z) = 280 (1, 3); 279 (5,7); 247 (29,3); 221 (50,5); 189 (28,1); 144 (43,1); 136 (68,6); 135 (100); 117 (32,6); 43 (47,9)
IR (NaCl) ν = 3400-3100; 3176; 2998; 1728; 1684; 1608; 1582; 1508; 1494; 1438; 1390; 1380; 1372; 1324; 1304; 1274; 1226; 1198; 928; 908; 856; 786; 748.

5-(2'-aminophenylthiomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **2_f**

2_f was obtained from 1 g of 2-aminothiophenol **1_e** (8. 10^{-3} mol) and 1,48 g (1eq) of enol ether **6** according to the same procedure employed for **2_a**. The mixture was stirred at room temperature for 10 hrs. Purification by chromatography on silica gel with chloroform, cyclohexan, aceton : (1 : 1: 1), yielded to 1,58 g (56. 10^{-4} mol ; 71%) as a orange solid, mp = 125-130°C. **2_f** could also be obtained from **2_e** by filtration on silica gel with chloroform, cyclohexan, acéton : (1 :1 : 1) with the same yield. Derivative **2_f** could also be obtained by thermolysis of **2_e**.at 250°C **:** thermolysis of 200 mg (71.10^{-5} mol) of **2_e** yielded after purification by chromatography on silica gel with chloroform, cyclohexan, aceton : (1 : 1 : 1), to 126 mg (45.10^{-5} mol ; 63%) of **2_f** .
NMR ^{1}H ($CDCl_3$) δ = 1,7 (s, 6H); 3,66 (s, 2H); 7,48 (m, 2H); 7,95 (d, 1H, J = 8); 8,15 (d, 1H); 9,1 (s, 1H)
NMR ^{13}C ($CDCl_3$) δ = 27,6 (2C); 106,3 (1C); 118,5 (1C); 121,9 (1C); 123,6 (1C); 125,6 (1C); 126,2 (1C); 133,7 (1C); 154 (1C); 163,1 (1C)
MS (m/z) = 280 (0,2); 279 (0,5); 256 (0,3); 247 (1,7); 189 (1,2); 144 (1,5); 136 (11,1); 135 (100); 108 (9,9); 58 (3,1); 43 (12,8)
IR (NaCl) ν = 3600-3100; 3068; 3002; 2930; 1726; 1684; 1606; 1582; 1470; 1426; 1388; 1378; 1354; 1322; 1302; 1280; 1266; 1224; 1204; 1196; 1084; 1014; 978; 956; 932; 756; 730; 692.

2,3-dihydro-7H-1,4-oxathiepin-7-one **4_a** [8]

Thermolysis of 200 mg (86.10^{-5} mol) of **2_a** at 420°C gave after purification by chromatography on silica gel with chloroform, aceton : (1 : 3), 83 mg (63.10^{-5} mol ; 74%) of **4_a** as a yellow oil.
NMR ^{1}H ($CDCl_3$) δ = 3,2 (t, 2H, J = 4,4); 4,7 (t, 2H); 5,2 (d, 1H, J =8,5), 6,58 (d, 1H)
NMR ^{13}C ($CDCl_3$) δ = 28,3 (1C); 74,4 (1C); 107,3 (1C); 151,6 (1C); 192,9 (1C)
MS (m/z) = 132 (0,1); 131 (0,2); 130 (0,3); 102 (0,1); 61 (12,5); 60 (55,5); 59

(55,6); 58 (14,1); 57 (8,1); 51 (8,8); 49 (22,9); 47 (17,3); 46 (16,4); 45 (100); 43 (22,3); 42 (24,1); 41 (14,1)

IR (NaCl) ν = 2955; 1730; 1615; 1458; 1412; 1317; 1265; 1223; 1082; 1023; 905; 800.

2,3-dihydro-7H-1,4-thiazepin-7-one $\mathbf{4_b}$

Thermolysis of 200 mg (86.10^{-5} mol) of $\mathbf{2_b}$ at 500°C yielded after purification by chromatography on silica gel with aceton, methanol : (3 : 1) to 71 mg (52.10^{-5} mol ; 64%) as a yellow oil.

NMR ^{1}H ($CDCl_3$) δ = 3,12 (t, 2H, J = 4,3); 3,84 (ml, 2H); 4,9 (d, 1H, J = 10,1); 5,95 (sl, 1H); 6,46 (dd, 1H, J = 10,1 and 9)

NMR ^{13}C ($CDCl_3$) δ = 29,5 (1C); 50,3 (1C); 99,6 (1C); 143,5 (1C); 194,4 (1C)

MS (m/z) = 131 (5,2); 130 (6,3); 129 (81,1); 101 (100); 82 (20,1); 70 (28,2); 68 (16,7); 60 (15,2); 59 (8,5); 56 (8,9); 54 (22,6); 45 (9,3); 42 (15,9); 41 (9,7)

IR (NaCl) ν = 3300-3200; 3074; 2964; 1714; 1620; 1574; 1538; 1532; 1520; 1504; 1454; 1338; 1262; 1226; 1094; 1030; 910; 800;.

2,3-dihydro-5H-1,4-dithiepin-5-one $\mathbf{4_c}$

Thermolysis of 200 mg (8.10^{-4} mol) of $\mathbf{2_c}$ at 420°C gave after purification by chromatography on silica gel with dichloromethane, petroleum ether : (95 : 5) ,78 mg (53.10^{-5} mol ; 66%) as a orange oil. .

NMR ^{1}H ($CDCl_3$) δ = 3,4 (m, 4H); 6,26 (d, 1H, J = 12,3); 6,88 (d, 1H)

NMR ^{13}C ($CDCl_3$) δ = 29,4 (1C); 34,8 (1C); 127,9 (1C); 134,2 (1C); 196 (1C)

MS (m/z) = 148 (1,4); 147 (1,9); 146 (14,3); 90 (18,3); 64 (13,1); 60 (15,9); 59 (30,4); 58 (100); 57 (57,3); 53 (14,9); 47 (8,3); 46 (37,2); 45 (82,7)

IR (NaCl) ν = 3002; 2962; 2922; 1720; 1634; 1564; 1414; 1364; 1280; 1266; 1186; 1102; 1050; 928; 882; 766; 694.

7,8-dihydro-2H,6H-1,5-dithiocin-2-one $\mathbf{4_d}$

Thermolysis of 250 mg (95.10^{-5} mol) of $\mathbf{2_d}$ at 430°C yielded after purification by chromatography on silica gel with dichloromethane, petroleum ether : (9 : 1) to 57 mg (35.10^{-5} mol ; 37%) of $\mathbf{4_d}$ as a yellow oil.

NMR ^{1}H ($CDCl_3$) δ = 2,1 (qt, 2H, J = 5,5); 3,2 (m, 2H); 3,45 (m, 2H); 5,87 (d, 1H, J = 12,7); 6,45 (d, 1H)

NMR ^{13}**C** ($CDCl_3$) δ = 26,4 (1C); 29,2 (1C); 31,7 (1C); 120,2 (1C); 134,1 (1C); 196 (1C)

MS (m/z) = 162 (9,5); 161 (9,8); 160 (87,9); 134 (9,4); 133 (9,2); 132 (100); 119 (7,6); 118 (15,9); 108 (8,8); 107 (6,2); 106 (96,4); 88 (6,3); 87 (30,1); 86 (95,3); 75 (11,4); 74 (70,6); 60 (13); 59 (39,8); 58 (92,8)

IR (NaCl) ν = 2964; 1730; 1622; 1418; 1260; 1074; 1023; 800; 700

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