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Synthesis of the Marine Alkaloid Leucettamine B

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Abstract: The marine natural product leucettamine B **2** has been prepared in good yield *via* two different routes, starting with glycine or with 3-methyl thiohydantoin, involving simple aldol condensation, and finally transamination of the thiohydantoin derivative.

Keywords: leucettamine B, oxazolone, glycocyamidine, thiohydantoines, aldol condensation, transamination.

Introduction

Marine natural products, in particular those derived from sponges, have proved to be a rich source of novel compounds with various types of biological activity [1]. In particular, several 2-aminoimidazoles: oroidin [2], tauroacidin [3], naamidine [4], axinellamine [5], have been isolated recently from various marine sponges.

Three other members of this class were isolated in 1993 from the sponge *Leucetta microraphis* Haeckel (alcarea class) of the Argulpelu Reef in Palau [6], *viz.* leucettamine A **1**, leucettamine B **2**, and leucettamidine **3** (Figure 1). They belong to the leukotriene B_4 receptor antagonist family (LBR), and have been shown to possess an important role as mediators of inflammation [7].

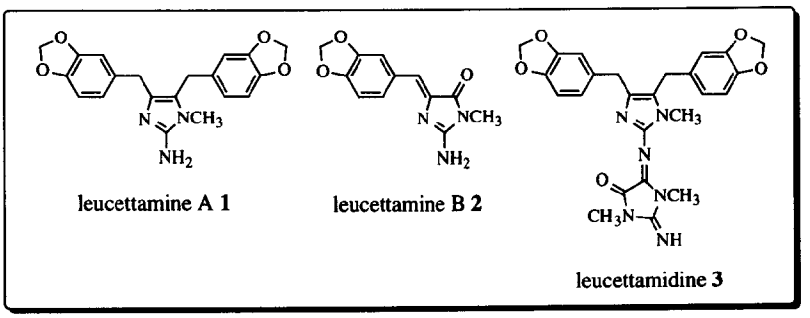

Figure 1

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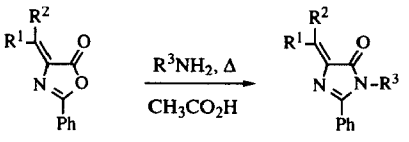
To date, the synthesis of leucettamine A **1** has been described only by Boehm et al. [8], whose strategy was based on the formation of 2-aminoketones [8], which can serve as precursors to 2-aminoimidazole by reaction with cyanamide. Carver attempted in vain the synthesis of **1** *via* metal-halogen exchange on *N*-protected 4,5-diiodoimidazoles with EtMgBr [9].

Currently, we are developing general synthetic approaches to these alkaloids and in this paper we will describe two procedures for the total synthesis of leucettamine B **2** [10]. Up to now, only one synthesis has been available using a four step route involving the highly toxic reagents, ethyl azidoacetate and methyl isocyanate [11].

Results and Discussion

Oxazolone route

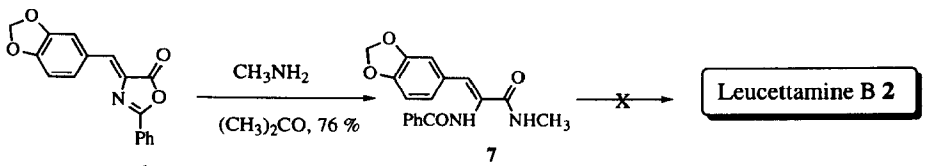
Interest in the chemistry of unsaturated azlactones continues unabated because of their usefulness as intermediates in the synthesis of diverse heterocyclic compounds [12, 13]. The cleavage of the 1,5-bond of 2-oxazolin-5-ones by suitable amines is known in the literature [13, 14] and its application is important in the synthesis of products such as dehydropeptides and *N*-substituted amides. These reactions afford alkenamides which can be cyclized to 1,2-disubstituted-4-arylmethylene-2-imidazolin-5-ones, depending upon the substituents present and the reaction conditions [15] (Scheme 1).



4 **5**

Scheme 1

The aminolysis of 2-phenyl-4(*Z*)-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6** with methylamine in acetone gave the corresponding (*Z*)-2-benzamido-3-(3,4-methylenedioxyphenyl)methylene-2-propenamide **7** quantitatively [16]. Treatment of **7** with BrCN failed to produce the expected leucettamine B, which could be explained in terms of too deactivated amide functions (Scheme 2).



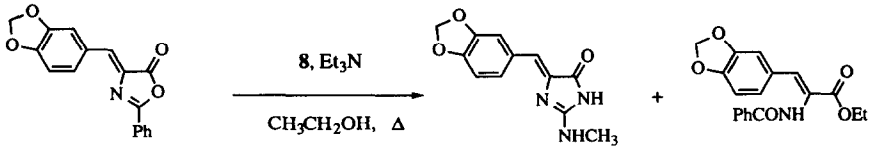
6 **7**

Scheme 2

Recently, the synthesis of 2-aminoimidazolin-5-ones was described, starting with the corresponding oxazolin-5-one, reacting with *S*-benzyl isothiouronium bromide (Figure 2) in ethanolic solution in the presence of triethylamine [17].

Figure 2

Application of these conditions to 2-phenyl-4(*Z*)-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6** with the *S*-ethyl-*N*-methyl isothiouronium bromide **8** [18, 19] and *S*-ethyl isothiouronium salt **9** [20] led to the 2-iminoimidazolidin-5-one (**10**, **12** and **13**) and the ethyl (*Z*)-3-(3,4-methylenedioxyphenyl)methylene-2-benzoylaminoacrylate **11** respectively (Scheme 3).

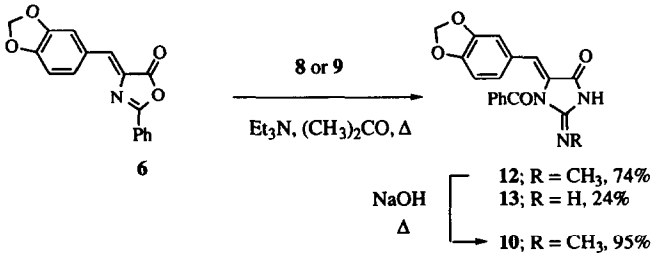


6 **10**, 62% **11**, 33%

Scheme 3

The formation of **10**, **12** and **13** can be rationalised by an initial 1,5-bond cleavage of **6**, followed by cyclisation based on the counter attack principle. The formation of **11** is the result of partial alcoholysis of the unsaturated oxazolones. The *N*-debenzoylation is due to the presence of ethoxide ions in the mixture.

Hence with acetone as solvent, only the *N*-benzoyl-*N*-methyl compound **12** was obtained with the *S*-ethyl-*N*-methyl isothiouronium bromide **8**, which could be easily deprotected under basic conditions to **10** in 70% yield (Scheme 4).



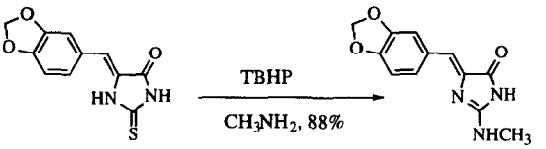
6

Scheme 4

In the case of *S*-ethyl isothiouronium bromide **9**, a mixture of different products was obtained, from which the *N*-benzoyl-2-iminoimidazolidin-5-one **13** was isolated in only 24% yield.

The spectral data of **10** were similar to those of leucettamine B **2**. The ^1H NMR spectrum was slightly different from that of the natural product **2** [21], with two NH signals at δ 10.8 and 7.26 (exchangeable with D_2O). For **2** we observed only one signal for two exchangeable protons at δ 7.54. Also the leucettamine **2** moved a bit faster in tlc (R_f 0.15, with the eluant 4% CH_3OH in CH_2Cl_2) than the isomer **10** (R_f 0.07 in the same solvant).

To confirm the structure of the isomer **10**, the thiohydantoin **14** was reacted with methylamine using a modified oxidative procedure. Thus the thiono function was converted with *tert*-butylhydroperoxide (TBHP), into the corresponding sulfinic acid, which was converted to the desired product with methylamine (Scheme 5). This protocol was introduced by Lindel [22] and has been used for the synthesis of the marine natural product dispacamide.



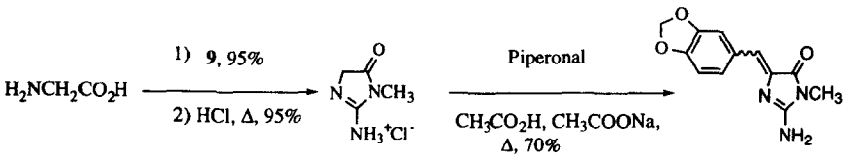
14 **10**

Scheme 5

Glycocyamidine route

Natural products in which glycocyamidine comprise the parent structural unit are relatively rare. To date creatinine [23] has commanded the most attention due to its abundance in animals and plants and its great biological importance [24]. Recently, scattered reports describing the occurence of glycocyamidine metabolites from marine origin have appeared [25].

Our second approach involved condensation of aromatic aldehydes with 3-methyl-glycocyamidines [26]. The 3-methyl-glycocyamidine **15** [27] was obtained in the first step by reaction of glycine and the *N*-methyl-*S*-ethyl isothiouronium bromide **9** [19, 28, 29], and subsequent treatment under acidic conditions led to the salt **15** in 95% yield [30] (Scheme 6).



15 **2**

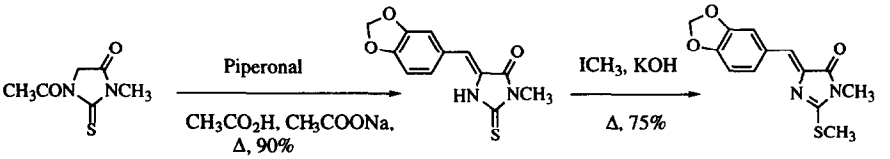
Scheme 6

Like the hydantoins, the glycocyamidines may be condensed with aromatic aldehydes to yield 5-arylidene derivatives. Piperonal reacted with **15** under basic conditions and gave a mixture of (*Z*/*E*) leucettamine B **2** in a ratio of 9.5/0.5.

Thiohydantoin route

Several reactions for the transformation of 2-thiohydantoin into glycocyamidines are known [31, 32]. The latter transformation may be achieved either directly by desulfurizing the 2-thiohydantoins in the presence of amines or indirectly by the ammonolysis of the *S*-alkyl derivatives of the 2-thiohydantoins. The second procedure is in general more convenient.

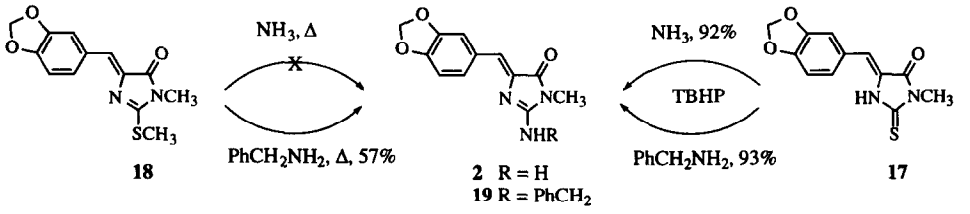
The readily available 1-acetyl-3-methyl-2-thiohydantoin **16** [33, 34] was condensed with piperonal in acetic acid, which gave stereochemically pure (*Z*)-4-(3,4-methylenedioxyphenyl)methylene-2-thiohydantoin **17** (90 % yield) (Scheme 7).



16 **17** **18**

Scheme 7

Subsequently, regioselective *S*-methylation yielded the imidazolone **18**. However, as displacement of the SCH_3 group with amines gave unsatisfactory results under non-extreme conditions (Scheme 8), a modified procedure with *tert*-butylhydroperoxide (TBHP), already used for the synthesis of **11** was employed. This afforded leucettamine B **2** in 92% yield and *N*-benzyl leucettamine B **19** in 93% yield (Scheme 8).



18 **2** R = H, **19** R = $PhCH_2$ **17**

Scheme 8

Conclusion

In conclusion, the marine natural product leucettamine B **2** has been synthesized *via* two different pathways, starting from glycine in three steps with 63% yield overall, and from the thiohydantoin in two steps with 83% yield overall. A key step was the transamination with aqueous ammonia on the sulfinic acid function. In the case of the oxazolone route, it was possible to obtain a regioisomer of the natural product.

Experimental Section

Melting points were determined with a Büchi melting point B-545 apparatus and were uncorrected. Microanalyses were carried out by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Mass spectra were performed on a Micromass Platform II spectrometer and Finigan MATSSQ710, both with a direct inlet, at 70 eV. IR Spectra were recorded on a Perkin-Elmer 1600 FT-IR. NMR Spectra were determined on a Bruker DPX 300 (300 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield from Me_4Si; J values are given in Hz. All solvents were purified by distillation or were HPLC grade. Silica Gel Merck 60 (70-230 mesh) was used for flash column chromatography.

Leucettamine B **2**.

Method A: Piperonal (200 mg, 1.34 mmol) was added to a mixture of glycocyamidine hydrochloride **15** (200 mg, 1.34 mmol) in acetic acid (1.3 ml) and sodium acetate (329 mg, 4.01 mmol). Whereupon the mixture was heated at reflux during 2 h. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography with 4% CH_3OH/CH_2Cl_2 to give a colorless powder (229 mg, 70%). The (*Z*/*E*)-leucettamne B was obtained in a ratio of 9.5/0.5.

Method B: TBHP (70%, 317 µl, 2.3 mmol) was added to a solution of **17** (200 mg, 0.76 mmol) in methanol (20 ml) and aqueous ammonia (25 %, 4 ml). The solution was stirred for 72 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography as described above, to give pure (*Z*)-leucettamine B **2** (172 mg, 92 %).

(*Z*)-Leucettamine B **2**. mp 243.3 °C (Lit. [11] 253-255 °C); *m/z* 246 (9), 245 ($M^{+\cdot}$, 53), 161 (23), 160 (8), 103 (10), 76 (14), 57 (100); IR (KBr) ν_{max} 3377, 3018, 1694, 1677, 1628, 1566, 1483, 1444, 1338, 1258, 1154, 1036 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.12 (3H, s), 6.08 (2H, s), 6.42 (1H, s), 6.96 (1H, d, J = 8.0), 7.47 (1H, d, J = 8.0), 7.54 (2H, s), 8.00 (1H, s); ^{13}C NMR δ 25.5, 101.0. 108.2, 109.5, 112.4, 125.0, 130.3, 139.3, 146.6, 147.2, 159.3, 169.6; Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.80; H, 4.61; N, 16.99.

(*E*)-Leucettamine B **2**. ^1H NMR (DMSO-d_6) δ 3.03 (3H, s), 6.02 (2H, s), 6.53 (1H, s), 6.87 (1H, d, J = 8.0), 7.33 (1H, d, J = 8.0), 7.6-7.1 (2H, s), 8.13 (1H, s).

2-Phenyl-4(*Z*)-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6**. Hippuric acid (2.4 g, 13.4 mmol) was added to a mixture of piperonal (2 g, 13.3 mmol) in acetic anhydride (4.2 ml) and sodium

acetate (1.2 g, 14.6 mmol). The mixture became homogeneous at 60°C with occasional stirring, and was refluxed 1 h more, when the precipitate began to appear. After standing overnight at 0°C, some ice was added and the precipitate was filtered and dried, to give yellow crystals **6** (1.6 g, 42%); mp 194.6 °C; IR (KBr) ν_{max} 1779, 1763, 1645, 1485, 1449, 1265, 1167, 1034, 928 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.93 (2H, s), 6.77 (1H, d, J = 8.0), 7.02 (1H, s), 7.41 (4H, m), 7.95 (1H, s), 8.04 (2H, d, J = 7.0); ^{13}C NMR δ 101.9, 108.9, 111.4, 126.1, 128.5 (2C), 128.6, 129.1 (2C), 129.5, 131.7, 131.8, 133.2, 148.6, 150.7, 163.0, 167.8.

(*Z*)-2-benzamido-3-(3,4-methylenedioxyphenyl)methylene-2-propenamide **7**. Methylamine (40%, 86 µl, 0.4 mmol) was added to a stirred solution of 2-phenyl-4(*Z*)-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6** (107 mg, 0.36 mmol) in acetone (0.5 ml). The temperature of the reaction increased rapidly and a white precipitate appeared which was isolated after 30 min (68 mg), and the filtrate was concentrated and purified on a column (CH_2Cl_2/CH_3OH 96/4). The total amount of compound **7** was 90 mg (76%); mp 198.2 °C; IR (KBr) ν_{max} 3214, 1645, 1626, 1504, 1482, 1445, 1344, 1255, 1036, 927 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.67 (3H, d, J = 4.5, became (s) when exchanged with D_2O), 5.99 (2H, s), 6.91 (1H, d, J = 8.0), 7.15 (1H, d, J = 1.2), 7.23 (1H, s), 7.56 (3H, m), 7.70 (1H, dd, J = 8.1 and 1.2), 8.03 (3H, m, became (2H, d, J = 7.7) when exchanged with D_2O), 9.82 (1H, s, exchangeable with D_2O); ^{13}C NMR δ 26.3, 101.3, 108.3, 108.4, 124.9, 127.5, 127.9 (2C), 128.2, 128.3 (2C), 129.2, 131.6, 133.7, 147.3, 147.6, 165.4, 165.7.

Addition of *S*-ethyl-*N*-methyl isothiouronium bromide **8** and *S*-ethyl isothiouronium bromide **9** to 2-phenyl-4(*Z*)-4-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6**

2-*N*-Methylamino-5-(3,4-methylenedioxyphenyl)methylene-3,5-dihydroimidazolo-4-one **10**.

Method A: Triethylamine (1.02 mmol, 143 µl) was added to a stirred suspension of 2-phenyl-4(*Z*)-(3,4-methylenedioxyphenyl)methylene-4*H*-oxazolon-5-one **6** (100 mg, 0.34 mmol) in acetone (1.5 ml), and *S*-ethyl-*N*-methyl isothiouronium bromide **8** (0.34 mmol). The mixture was warmed at reflux during 3 h, the solvent was removed under vacuum, and the residue was purified on a column. Light yellow crystals (62 %, CH_2Cl_2/CH_3OH 96/4); mp 256.4°C; *m/z* 246 (12), 245 ($M^{+\cdot}$, 79), 161 (82), 160 (16), 103 (19), 76 (18), 57 (100); IR (KBr) ν_{max} 3440, 3073, 1667, 1635, 1503, 1123, 619 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.92 (3H, s), 6.00 (2H, s), 6.24 (1H, s), 6.87 (1H, d, J = 8.0), 7.26 (1H, s), 7.32 (1H, d, J = 8.0), 7.93 (1H, m), 10.8 (1H, s); ^{13}C NMR δ 27.4, 100.5, 107.8, 108.9, 110.4, 124.2, 130.1, 142.8, 146.2 (2C), 149.2, 165.9; Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13; Found: C, 58.73; H, 4.53; N, 17.25.

Method B: Debenzoylation of **12**.

The mixture of **12** (15 mg) in a solution of NaOH (20%, 1.5 ml) was refluxed gently during 2.5 h. The solution was acidified slowly with HCl (4%), and the precipitate of **10** was collected and dried (10 mg, 95%).

Method C: Transamination of **14**.

TBHP (70%, 0.33 ml) was added to a solution of **14** (200 mg, 0.81 mmol) in methanol (21 ml) and methylamine (40%, 16.1 mmol, 1.38 ml). The solution was stirred at room temperature for 24 h, and the solvent was evaporated and the residue was purified by chromatography to give **10** (173 mg, 88%).

Ethyl 2-amino-3-(3,4-methylenedioxyphenyl)methylenacrylate **11**.

Method A: (Ethanol, and *S*-ethyl-*N*-methyl isothiouronium bromide **8**). Colorless powder (33 %, CH_2Cl_2/CH_3OH 96/4); mp 129.8 °C; IR (KBr) ν_{max} 3288, 2981, 1714, 1651, 1504, 1480, 1447, 1260, 1235, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.1), 4.21 (2H, q, J = 7.1), 5.85 (2H, s), 6.63 (1H, d, J = 8.0), 6.91 (1H, d, J = 8.0), 6.94 (1H, s), 7.30 (1H, s), 7.34 (2H, d, J = 7.1), 7.41 (1H, t, J = 7.0), 7.76 (2H, d, J = 7.3), 7.82 (1H, s); ^{13}C NMR δ 14.4, 61.8, 101.5, 108.4, 109.1, 122.5, 125.9, 127.6 (2C), 128.2, 128.9 (2C), 132.1, 132.3, 133.9, 148.0, 148.8, 165.7, 165.9.

2-Methylamine-5-(3,4-methylenedioxyphenyl)methylene-3,5-dihydroimidazolo-4-one **12**.

Method A: (Acetone, and *S*-ethyl-*N*-methyl isothiouronium bromide **8**). Colorless crystals (74 %, CH_2Cl_2/CH_3OH 98/2); mp 258.3°C; IR (KBr) ν_{max} 3345, 3030, 1719, 1670, 1597, 1487, 1405, 1314, 1226, 1185, 758, 664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (3H, s), 5.82 (2H, s), 6.13 (1H, s), 6.36 (1H, d, J = 8.0), 6.45 (1H, d, J = 8.0), 6.75 (1H, s), 7.06 (2H, m), 7.25 (3H, m), 7.91 (1H, s); ^{13}C NMR δ 30.0, 101.4, 108.5 (2C), 119.3, 123. 1, 127.8, 128.0 (2C), 128.6 (2C), 130.2, 132.5, 133.2, 147.7, 147.9, 165.5, 169.6, 175.3

2-*N*-Methylamino-1-*N*-benzoylamino-5-(3,4-methylenedioxyphenyl)methylene-3,5-dihydro imidazolo-4-one **13**.

Method A: (Acetone, and *S*-ethyl isothiouronium bromide **9**). Light colorless laque (24%, CH_2Cl_2/CH_3OH 96/4); ^1H NMR ($CDCl_3$) δ 5.84 (2H, s), 6.15 (1H, d, J = 1.2), 6.39 (1H, dd, J = 8.0 and 1.1), 6.47 (1H, d, J = 8.0), 6.77 (1H, s), 7.08 (2H, m), 7.27 (4H, d, J = 7.5), 7.61 (1H, s). ^{13}C NMR δ 101.4, 108.5 (2C), 119.5, 123. 2, 127.6, 128.1 (2C), 128.7 (2C), 129.6, 132.3, 133.4, 147.8, 148.1, 165.9, 169.0, 174.8.

3-Methylglycocyamidine **15** [35]. A solution of *S*-ethyl isothiourea (28.9 g, 0.16 mol) in water (20 ml) was added slowly to a stirred solution of glycine (11.4 g, 0.15 mol) in NaOH 4 M (37.7 ml), cooled in a ice bath. The solution was stirred slowly overnight. The amino acid was collected (18.6 g, 95%); IR (KBr) ν_{max} 3600-2537 (l), 3418, 3232, 3032, 1691, 1635, 1406, 1370 cm^{-1}.

The amino acid (2 g, 15.3 mmol) in HCl (18%, 45 ml) was heated at reflux (140°C) during 18 h. The water was evaporated and the compound was redissolved in hot ethanol and precipitated with ether. White powder (2.17 g, 95 %). mp 294.0°C dec.; *m/z* 113 (93), 85 (53), 84 (46), 57 (100), 56 (73), 55 (59), 54 (23), 42 (23); IR (KBr) ν_{max} 3650-2262, 3059, 1782, 1682, 1556, 1407, 1314, 1267, 1117, 1026, 966, 714, 608 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.06 (3H, s), 4.11 (2H, s), 8.87 (2H, s). ^{13}C NMR δ 26.0, 48.1, 159.0, 172.3.

1-Acetyl-3-methyl-2-thiohydantoin **16** was synthesized according to a literature procedure [33] in 50% yield. mp 147.9 °C (Lit. [32] 142-143 °C); *m/z* 172 ($M^{+\cdot}$, <1), 137 (23), 130 (100), 125 (23), 115 (23), 102 (33), 74 (27), 73 (48), 72 (31), 71 (26); IR (KBr) ν_{max} 2934, 1759, 1691, 1421, 1392, 1339, 1274, 1227, 1123, 963 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.73 (3H, s), 3.15 (3H, s), 4.45 (2H, s); ^{13}C NMR δ 27.2, 28.2, 50.9, 169.4, 169.5, 182.2.

3-Methyl-5-(3,4-methylenedioxyphenyl)methylene-4-(5*H*)-2-thiohydantoin **17**. Piperonal (870 mg, 5.8 mmol) was added to a solution of **16** (1 g, 5.8 mmol) in acetic acid (2.2 ml) with sodium acetate (477 mg, 5.8 mmol). The mixture was heated at reflux during 1 h. The precipitate was collected, washed with water and dried. The product **17** was obtained as yellow crystals (1.37 g, 90%). mp 245.1°C (Lit. [33] > 260 °C); *m/z* 263 (15), 262 ($M^{+\cdot}$, 100), 261 (14), 173 (21), 161 (91), 87 (22), 76 (42), 74 (35); IR (KBr) ν_{max} 3241, 1718, 1652, 1612, 1471, 1438, 1354, 1248, 1027 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.19 (3H, s), 6.11 (2H, s), 6.57 (1H, s), 6.98 (1H, d, J = 9.7), 7.29 (1H, dd, J = 9.8 and 1.8), 7.47 (1H, d, J = 1.9), 12.29 (1H, s); ^{13}C NMR δ 27.5, 101.9, 109.0, 109.6, 113.6, 124.9, 126.8, 148.2, 148.8, 164.4, 178.8; Anal. Calcd for $C_{12}H_{10}N_2O_3S_1$: C, 54.95; H, 3.84; N, 10.68; S, 12.22 Found: C, 54.86; H, 3.91; N, 10.60; S, 12.31.

1-Methyl-2-methylthio-4-(3,4-methylenedioxyphenyl)methylene-5-(4*H*)-imidazolone **18**. The compound **17** (500 mg, 1.9 mmol) and methyl iodide (187 µl, 3 mmol) was added to a solution of KOH (0.17 g, 3 mmol) in ethanol abs (4.6 ml). The mixture was heated at reflux for 2 h. The precipitate was collected and gave **18** as yellow crystals (393 mg, 75%). mp 195.2 °C; *m/z* 276 (51), 186 (20), 88 (100); IR (KBr) ν_{max} 1697, 1630, 1593, 1498, 1440, 1373, 1334, 1264, 1154, 1033, 931, 898, 827 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.63 (3H, s), 3.00 (3H, s), 6.01 (2H, s), 6.75 (1H, s), 6.92 (1H, d, J = 8.2), 7.50 (1H, d, J = 8.2), 7.95 (1H, s); ^{13}C NMR δ 12.5, 26.4, 101.6, 108.6, 109.9, 122.3, 127.9, 128.6, 136.7, 147.5, 148.8, 164.8, 168.8; Anal. Calcd for $C_{13}H_{12}N_2O_3S_1$: C, 56.51; H, 4.38; N, 10.14; S, 11.60 Found: C, 56.34; H, 4.45; N, 10.11; S, 11.75.

1-Methyl-2-benzylamino-4-(3,4-methylenedioxyphenyl)methylene-5-(4*H*)-imidazolone **19**.

Method A: Benzylamine (0.54 mmol, 59 µl) was added to the mixture of **18** (100 mg, 0.36 mmol) in acetonitrile (3 ml). The mixture was heated at reflux during 24 h. The solvent was evaporated and the residue was purified on a column (CH_2Cl_2/MeOH 98/2), to give **19** as yellow crystals (69 mg, 57 %).

Method B: TBHP (70%, 317 µl, 2.3 mmol) was added to a solution of **17** (200 mg, 0.76 mmol) in methanol (20 ml) and benzylamine (1.66 ml, 15.2 mmol). The solution was stirred for 48 h at room temperature. The solvent was concentrated and the residue was purified on a column (CH_2Cl_2/MeOH 98/2) to give **19** (237 mg, 93 %), yellow powder; mp 206.7 °C; IR (KBr) ν_{max} 3336, 2924, 1697, 1654, 1578, 1439, 1375, 1263, 1153, 1033, 930 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.08 (3H, s), 4.62 (2H, d, J = 5.7), 6.02 (2H, s), 6.38 (1H, s), 6.90 (1H, d, J = 8.0), 7.95-7.26 (6H, m), 7.95 (1H, s), 8.25 (1H, t, J = 5.5); ^{13}C NMR δ 25.5, 44.5, 101.0. 108.3, 109.5, 113.1, 125.3, 127.1, 127.7, 128.3, 130.3, 138.7, 139.0, 146.7, 147.2, 158.2, 169.6.

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