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SYNTHESIS OF NEW MANNICH BASES DERIVED FROM 5-PHENYL-1,3,4-OXADIAZOLE-2-THIONE AND INVESTIGATION OF THE CONFORMATIONAL ISOMERS OF DIMETHYL 5-(5-PHENYL-2-THIOXO-1,3,4-OXADIAZOLE-3-METHYLAMINO)ISOPHTHALATE

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A series of new *N*-aminomethylation compounds has been obtained from 5-phenyl-1,3,4-oxadiazole-2-thione through reaction with formaldehyde and less common aliphatic and aromatic amines. The conformational isomers of 5-(5-phenyl-2-thioxo-1,3,4-oxadiazole-3-methylamino)isophthalate have been investigated using the STO-2G basis set. Four minimum energy structures have been found on the electronic potential energy surface. The relative stability of conformational isomers and the barrier height for conformational interconversion are presented.

INTRODUCTION

Oxadiazole derivatives have been the subject of numerous reports highlighting their chemistry and use in the recent past. Oxadiazole ring has been shown to impart anti-inflammatory properties in compounds designed as orally-active non-ulcerogenic agents[1] or in products formulated as analogs of fenamates for the inhibition of cyclooxygenase and 5-lipooxygenase.[2] Pharmacological screening of several 2-(acetylamino)-5-alkyl-1,3,4-oxadiazoles revealed their spasmolytic and potent hypotensive action.[3] 2,5-Disubstituted 1,3,4-oxadiazole derivatives were shown to be promising hypoglycemic agents able to reduce the level of blood glucose when administered at an oral dose of 100mg/kg.[4] A structure–activity relationship study towards the inhibition of monoamine oxidase A involved a series of tricyclics bearing oxadiazole moieties,[5] whereas oxadiazolones or oxadiazolethiones were found to be potent, reversible competitive inhibitors of monoamine oxidase B in mitochondria.[6] Recently, the design, synthesis and evaluation of Phe-Gly mimetics as replacements in dermorphin also comprised the use of a 1,3,4-oxadiazole ring system among the building blocks used in the preparation of pseudopeptides.[7]

The three-component condensation of a compound containing an acidic hydrogen atom with an aldehyde and an amine, currently known as Mannich reaction, has proved its significance in the preparation of natural and synthetic molecules with noteworthy biological activity. With respect to the Mannich reaction, oxadiazolethiones belong to the class of five-membered aromatic *N*-heterocycles substrates having the N-H reactive center involved in tautomeric equilibria with the thiocarbonyl group.[8,9] The early reports[10,11] on the Mannich reaction involving oxadiazolethiones have established that these compounds rather undergo *N*-aminomethylation than *S*-aminomethylation. Later papers either broadened

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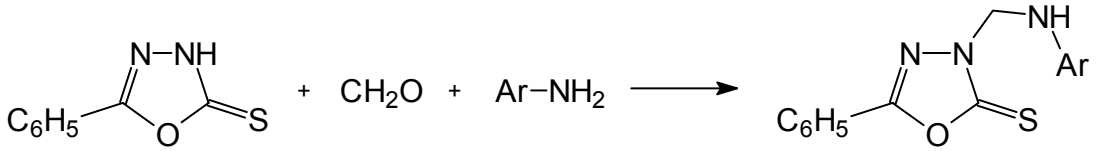
the scope of Mannich reaction of oxadiazolethiones by varying the substituent at position 2,[12-14] or associated the synthesis with the investigation of their biological activity.[15-18] However, in most cases, only common amines have been used in aminomethylations. The present paper investigates the aminomethylation of 5-phenyl-1,3,4-oxadiazole-2-thione with less common amines. Some of these amines, such as polychlorinated anilines, have been selected due to the potentially useful biological properties they can impart on the resulting Mannich bases.[19,20] Several heterocyclic amines have also been included as amine reagents in this study with the view to cast a light to their behaviour in the aminomethylation of this substrate.

The efforts made to better understand scope and limitations of the Mannich reaction have not been limited only to synthetic experiments. Attempts to enhance the comprehension of this important reaction led to theoretical studies,[21] the use of semiempirical computation,[22] the analysis of the influence of intramolecular hydrogen in phenolic Mannich based on their conformation[23] or on their spectroscopic properties.[24] Besides its synthetic part, the present paper aims at contributing to the pool of the published reports on computational studies of aminomethylation products by presenting the conformational isomers of a newly synthesized Mannich base derived from 5-phenyl-1,3,4-oxadiazole-2-thione.

RESULTS AND DISCUSSION

The aminomethylation of 5-phenyl-1,3,4-oxadiazole-2-thione **1** was performed by gradually adding a slightly larger amount of formaldehyde in the ethanolic solution of equimolar amounts of substrate and the required amine at room temperature. By employing aromatic and heteroaromatic primary amines, a series of seven new secondary mono-Mannich bases was readily available through this procedure (Scheme 1).

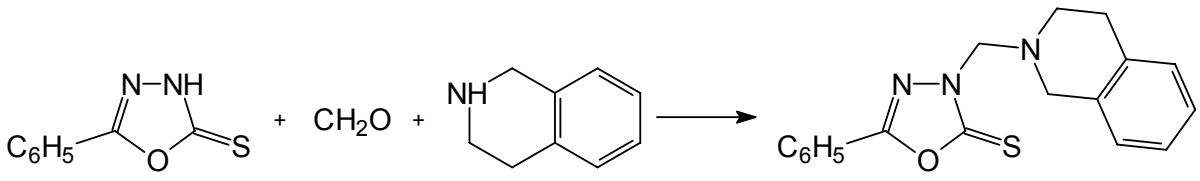


1 **2a-g**

Ar = 3,5-bis(methoxycarbonyl)phenyl (**2a**), 4-acetylphenyl (**2b**), 2,4,5-trichlorophenyl (**2c**), 3,4-dichlorophenyl (**2d**), 4-pyridyl (**2e**), 3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl (**2f**), 3-ethoxycarbonyl-4,5-trimethylenethiophen-2-yl (**2g**)

Scheme 1 – Synthesis of secondary Mannich bases **2a-g** from 5-phenyl-1,3,4- oxadiazole-2-thione **1** and primary aromatic or heteroaromatic amines.

Starting from 1,2,3,4-tetrahydroisoquinoline as amine component, a tertiary mono-Mannich base **2h** was prepared (Scheme 2).



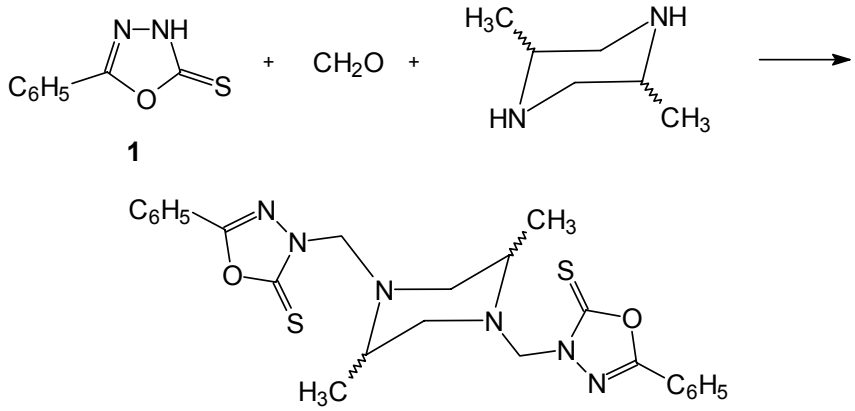
1 **2h**

Scheme 2 – Preparation of the tertiary Mannich base **2h** derived from 5-phenyl-1,3,4-oxadiazole-2-thione **1** and 1,2,3,4-tetrahydroisoquinoline.

A bis-Mannich base **2i** was also prepared starting from the above-mentioned oxadiazolethione by using a bifunctional amine such as *cis,trans*-2,5-dimethylpiperazine (Scheme 3).

In most cases, the reaction proceeded smoothly and the aminomethylation product began to separate soon after the addition of formaldehyde had been completed, and almost quantitative yields of crude reaction products could be attained after two hours. However, compound **2e** derived from 4-aminopyridine separated only after the reaction mixture had been kept at room temperature for 96

hours, and a much lower yield has been recorded for this Mannich base compared to the aminomethylation products **2a-d** derived from arylamines. This atypical behaviour is not surprising if one takes into account the poor nucleophilic character of 4-aminopyridine. On the other hand, strong nucleophilic heterocyclic amines such as 2-aminothiophenes reacted in a manner similar to arylamines to give the Mannich bases **2f** and **2g** in good yields.



1

2i

Scheme 3 – *cis, trans*-2,5-Dimethylpiperazine as the amine component in the synthesis of the bis-Mannich base **2i** from 5-phenyl-1,3,4-oxadiazole-2-thione **1**.

The new Mannich bases **2** have been subjected to elemental analysis, and they have all shown satisfactory results (within ±0.4% of the calculated values). Four aminomethylation compounds, namely **2a**, **2b**, **2f** and **2g**, have been investigated using IR spectroscopy. Besides the thione group absorption around 1200 cm^{-1} that all these compounds share, there have been identified other two absorption bands related to the secondary amino group and to a specific organic function (carbonyl and ester) introduced in the molecules of the Mannich bases with the amine component. The ^{1}H-NMR spectra recorded for the aminomethylation products **2** revealed the expected number of hydrogen nuclei. A common feature in all spectra is the signal at approximately 5.6 ppm attributed to protons in the methylene group bridging the oxadiazole and the amine moieties in the structure of Mannich bases **2**. The signals for the protons in the phenyl substituent of the oxadiazole ring (around 7.5 and 7.9 ppm), along with the peaks for protons in the amine moiety inserted *via* aminomethylation could be found in each case.

To the best of our knowledge, there are only a few articles concerning the structures of oxadiazolethiones,[25-27] but there are no articles on the structural analysis of their aminomethylated derivatives. On the other hand, since a significant number of reports ascribe interesting biological activities to 1,3,4-oxadiazole-2-thiones and their Mannich bases, any information about their three-dimensional structures may be of great interest for rational drug design. Therefore, the present work also aims to presenting computational data on the conformational isomers of a selected aminomethylated oxadiazolthione.

An extensive search for stationary points on the potential energy surface (PES) for the Mannich base **2a** was carried out using the GAMESS computational program.[28] The selected Mannich base is depicted in Fig. 1 together with the numbering scheme adopted. For this compound two dihedral angle ϕ (N4–N3–C6–N7) and ψ (N3–C6–N7–C1") were varied from –180° to 180° with a step of 20°. At each of 18 × 18 = 324 grid points geometry optimisations were performed via AM1 calculations, in which the torsions ϕ and ψ were kept constant, while all other structural parameters were relaxed without any constrains. All minimum energy structures were fully optimised with the RHF/STO-2G basis set without imposing any symmetry constraints using Quadratic Approximation method and the default GAMESS convergence criteria. Harmonic frequency calculations were also performed in order to characterize the located critical points on the PES (all frequencies positive for minimum energy structures and one imaginary frequency for transition state structures) and to evaluate the zero-point vibrational energies (ZPVE) and thermodynamic functions.

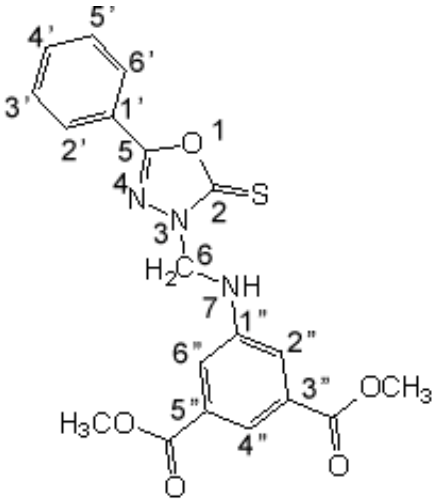


Fig. 1 – Structure of the selected Mannich base **2a**.

The conformational energy surface with respect to the two dihedral angles ϕ (N4–N3–C6–N7) and ψ (N3–C6–N7–C1") calculated at the AM1 level of theory is shown in Fig. 2. Four minimum energy structures have been found from the PES. The conformations of stable conformers of Mannich base **2a** are presented in Fig. 3.

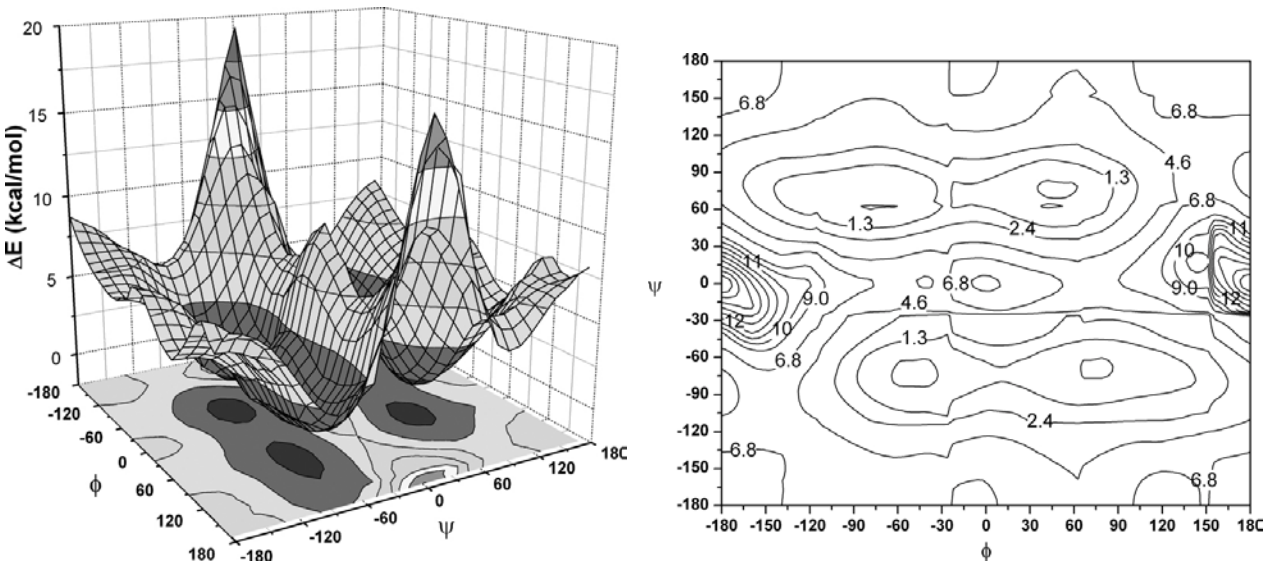


Fig. 2 – The conformational energy surface (kcal/mol) of Mannich base **2a** as function of ϕ (N4–N3–C6–N7) and ψ (N3–C6–N7–C1") calculated at the AM1 level of theory: a) two-dimensional PES; b) contour plot.

The values of the calculated bond lengths provide some information about the electron delocalization in the oxadiazolethione ring. The bond lengths between O1–C5, C2–N3 and N4–C5 are comparable to the reported values for partially double bond lengths in other organic compounds; the O–C distance in Mannich base **2a** is similar to O–C bond lengths in carboxylic acids, whereas the values of 1.389 Å and 1.32 Å for the N–C bonds in the aminomethylated oxadiazolethione **2a** are close to the value of 1.352 Å reported for the N–C bond in pyridine.[29] The usual thiol–thione tautomerism in substrate **1** is no longer possible for Mannich base **2a**, but the available π electrons are still shared within the oxadiazole ring, thus rendering it aromatic.

The calculated torsion angles show that the unsubstituted phenyl ring is coplanar with the oxadiazole ring. As for the aminomethyl group, this moiety is out of the oxadiazole plane, with the substituted phenyl ring being almost perpendicular on the heterocyclic five-membered ring system.

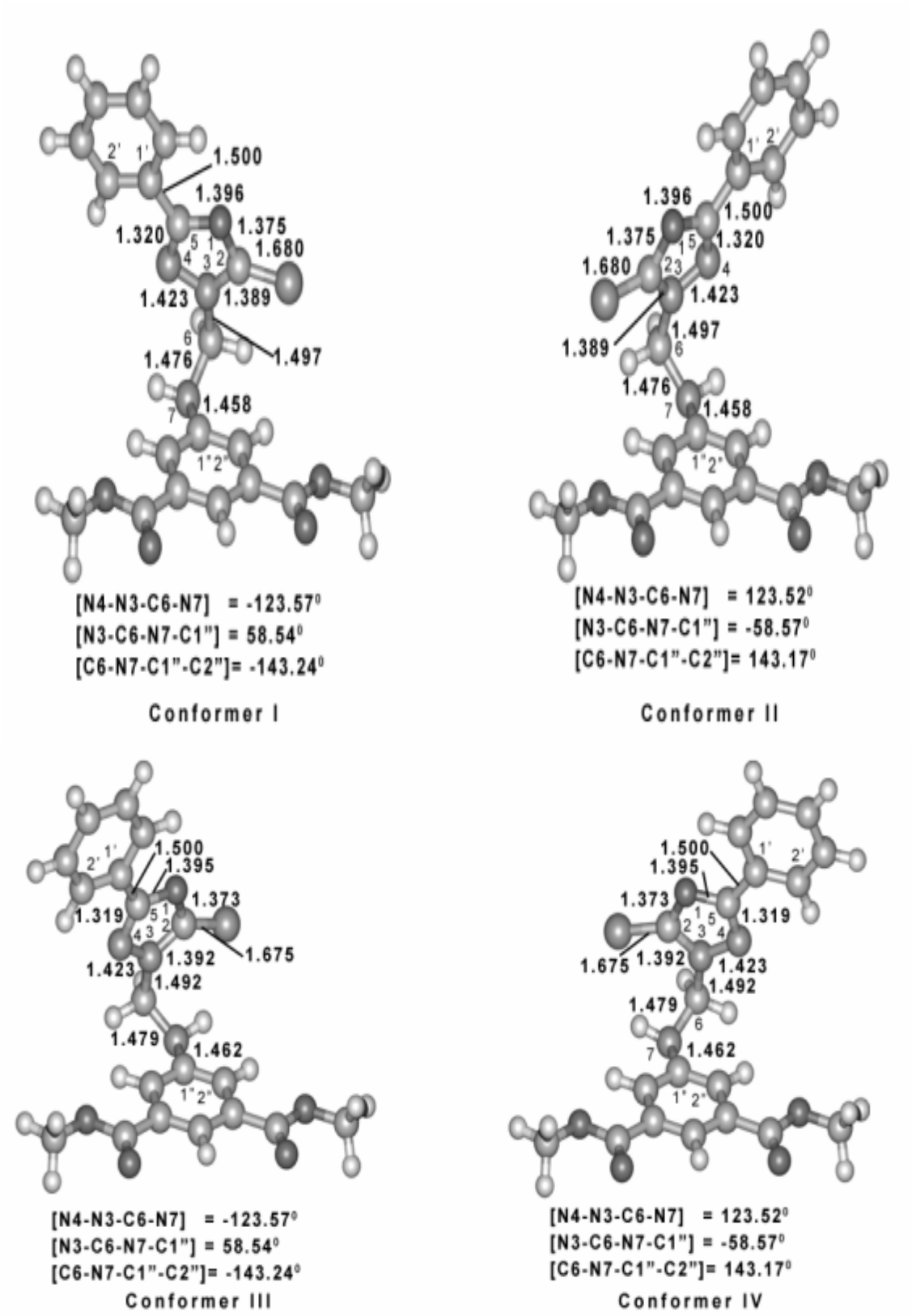


Fig. 3 – Optimized molecular structures at STO-2G level for Mannich base **2a** derived from 5-phenyl-1,3,4-oxadiazole-2-thione (bond length in Å, dihedral angles in degree).

The total electronic energy for four stable conformers is listed in Table 1. The most stable isomers correspond to a *cisoid* arrangement of the C2=S and N7–H bonds (conformers **I** and **II**). This preferred *cisoid* arrangement can be explained by the energy barrier values for the interconversion of conformers. For these conformers, the calculated distance between S and H7 atoms is about 2.614 Å.

Table 1

Calculated dihedral angles (in degrees), total energy (in hartree), relative energies (kcal/mol), and percentage of each conformer located on PES for Mannich base **2a**. Dihedral angles: of ϕ = N4–N3–C6–N7 and ψ = N3–C6–N7–C1" (Fig. 1); ΔE_0 is the total energy difference with zero point energy correction at 0 K; ΔG_{Tot} is the total Gibbs free energy difference at 298 K and 1 atm; the thermodynamic functions were evaluated using *ab initio* HF scaled (0.89) harmonic frequencies

Conformer	ϕ	ψ	Total energy	ΔE	ΔE_0	ΔG_{Tot}	P %
I	-123.57	58.54	-1596.60560	0.00	0.00	0.00	37.94
II	123.52	-58.57	-1596.60560	0.00	0.00	0.00	38.12
III	-61.95	-60.13	-1596.60637	1.21	1.14	0.75	10.68
IV	61.13	59.74	-1596.60366	1.21	1.13	0.62	13.27

The transition state structures for the isomerization of **I** into **IV** and **II** into **III** *via* rotation around the N3–C6 bond have also been explored. The located transition state structures have a dihedral angle ϕ close to 10°, which means that the C6–N7 bond is almost in the plane of the oxadiazole ring, whereas the value for the dihedral angle ψ of approximately 65° places the substituted phenyl ring above the oxadiazole ring (Table 2). For both transition structures, the transition state vector clearly indicates a displacement corresponding to a rotation around the N3–C6 bond. The rotational barriers for the interconversion of **I** into **IV** and **II** into **III** are small enough to allow a free rotation at room temperature. The first-order transition state structure which connects conformers **II** and **IV** on the two-dimensional PES is characterized by values of the dihedral angles ϕ and ψ different than the values of the same angles calculated for the transition states connecting either conformers **I** and **IV** or conformers **II** and **III**, and the barrier height for conversion of **II** into **IV** is higher, making this transition less probable. Attempts to locate a transition state structure of conversion **I** into **III** were not successful.

Table 2

Internal conversions of Mannich base **2a** conformers. For each **A** ↔ **TS** ↔ **B** the changes in ϕ and ψ (°) and energies (kcal/mol) with E_{AB} barrier height for conversion A into B and E_{BA} barrier height for conversion B into A are listed

	ϕ (N4–N3–C6–N7)	ψ (N3–C6–N7–C1")	E_{AB}	E_{BA}
I ↔ TS ↔ IV	-123.57 ↔ -9.79 ↔ 61.13	58.54 ↔ 64.27 ↔ 59.74	3.3600	2.1478
II ↔ TS ↔ III	123.52 ↔ 9.69 ↔ -61.95	-58.57 ↔ -64.29 ↔ -60.13	3.3615	2.1520
II ↔ TS ↔ IV	123.52 ↔ 94.29 ↔ 61.13	-58.57 ↔ 17.75 ↔ 59.74	8.2160	7.0039

EXPERIMENTAL PART

Elemental analysis was performed on a Carlo Erba-1106 analyzer. Melting points were taken on a Boëtius melting point microscope and are uncorrected. IR spectra were recorded on a SPECORD M80 spectrometer in KBr pellets. ^{1}H NMR analysis was conducted on a Brucker Avance instrument at 300 MHz. The signals owing to residual protons in the deuterated solvents were used as internal standards for the NMR spectra.

5-Phenyl-1,3,4-oxadiazole-2-thione **1** required as a substrate in the Mannich reaction was prepared through a two-step sequence comprising the transformation of methyl benzoate in benzhydrazide, followed by ring closure with CS_2 in the presence of KOH.[30] Ethyl 2-amino-4,5-trimethylenethiophene-3-carboxylate and ethyl 2-amino-4,5-tetramethylenethiophene-3-carboxylate have been synthesized according to an improved procedure[31] of the Gewald synthesis.[32] All other amine reagents involved in the Mannich condensation were commercially available products.

General procedure for the synthesis of Mannich bases **2**

5-Phenyl-1,3,4-oxadiazole-2-thione **1** (534 mg, 3 mmoles) and either (hetero)aromatic amine (3 mmoles), 1,2,3,4-tetrahydroisoquinoline (400 mg, 0.375 mL, 3 mmoles) or *cis, trans*-2,5-dimethylpiperazine 171 mg, 1.5 mmoles) were dissolved in ethanol (7 mL). Formaldehyde (37% soln. in water, 1 mL) has been added dropwise with good stirring to the warm solution. The solid that separated was filtered after 2 hrs (or 96 hrs in the case of **2e**) and recrystallized from the appropriate solvent to give the pure Mannich bases **2**.

Dimethyl 5-(((5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)amino)isophthalate **2a**. White crystals (814 mg, 68%), mp 189–190 °C (ethyl acetate). IR (KBr, cm^{-1}): ν 1150, 1725, 3400. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 6H, -

$COOCH_3$); 5.44 (bs, 1H, >NH); 5.60 (s, 2H, >N-CH_2-); 7.43–7.57 (m, 3H, aromatic protons in the benzene ring); 7.82 (d, 2H, $J_{1,3}$ = 0.9 Hz); 7.89 (d, 2H, $J_{1,2}$ = 7.8 Hz); 8.13 (s, 1H). Anal. calc. for $C_{19}H_{17}N_3O_5S$ (399): C, 57.14; H, 4.26; N, 10.52. Found: C, 57.33; H, 4.37; N, 10.28.

1-(4-(((5-Phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)amino)phenyl)ethanone **2b**. White crystals (702 mg, 72%), mp 187–188 °C (dec.) (ethyl acetate). IR (KBr, cm^{-1}): ν 1190, 1670, 3325. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, -$COCH_3$); 5.55 (bs, 1H, >NH); 5.58 (s, 2H, >N-CH_2-); 6.96 (d, $J_{1,2}$ = 8.7 Hz); 7.44–7.59 (m, 3H; 7.85–7.95 (m, 4H). Anal. calc. for $C_{17}H_{15}N_3O_2S$ (325): C, 62.76; H, 4.61; N, 12.92. Found: C, 62.58; H, 4.78; N, 13.11.

5-Phenyl-3-(((2,4,5-trichlorophenyl)amino)methyl)-1,3,4-oxadiazole-2(3H)-thione **2c**. White crystals (823 mg, 71%), mp 201–202 °C (ethyl acetate). ^{1}H-NMR (300 MHz, d_6-DMSO): δ 5.55 (s, 2H, >N-CH_2-); 6.75 (s, 1H); 7.39 (s, 1H); 7.48–7.59 (m, 3H); 7.91 (d, 2H, $J_{1,2}$ = 7.5 Hz). Anal. calc. for $C_{15}H_{10}Cl_3N_3OS$ (386.5): C, 46.57; H, 2.58; N, 10.86. Found: C, 46.73; H, 2.69; N, 11.04.

5-Phenyl-3-(((3,4-dichlorophenyl)amino)methyl)-1,3,4-oxadiazole-2(3H)-thione **2d**. White crystals (686 mg, 65%), mp 194–195 °C (dec.) (ethyl acetate). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.20 (bs, 1H, >NH); 5.50 (s, 2H, >N-CH_2-); 6.78 (dd, $J_{1,2}$ = 8.7 Hz, $J_{1,3}$ = 2.7 Hz); 7.07 (d, 1H, $J_{1,3}$ = 2.7 Hz); 7.26 (d, 1H, $J_{1,2}$ = 8.7 Hz); 7.46–7.61 (m, 3H); 7.87–7.96 (m, 2H). Anal. calc. for $C_{15}H_{11}Cl_2N_3OS$ (352): C, 51.13; H, 3.12; N, 11.93. Found: C, 51.29; H, 3.24; N, 12.06.

5-Phenyl-3-(((pyrid-4-yl)amino)methyl)-1,3,4-oxadiazole-2(3H)-thione **2e**. White crystals (102 mg, 12%), mp 175–177 °C (ethanol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.57 (s, 2H, > N-CH_2-); 6.86 (d, 2H, $J_{1,2}$ = 5.4 Hz); 7.47–7.60 (m, 3H); 7.93 (d, 2H, $J_{1,2}$ = 7 Hz); 8.35 (d, 2H, $J_{1,2}$ = 5.3 Hz). Anal. calc. for $C_{14}H_{12}N_4OS$ (284): C, 59.15; H, 4.22; N, 19.71. Found: C, 59.44; H, 4.03; N, 19.42.

Ethyl-2-(((5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **2f**. White crystals (560 mg, 45%), mp 143–144 °C (ethyl acetate). IR (KBr, cm^{-1}): ν 1220, 1670, 3360. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.35 (t, 3H, J = 7 Hz, -$CH_2C\underline{H}_3$); 1.76 (bs, 4H, -CH_2CH_2-); 2.09 and 2.16 (bs, 2H, -CH_2-); 4.28 (q, 2H, J = 7 Hz, -$C\underline{H}_2CH_3$); 5.53 (d, 2H, J = 7.4 Hz, >N-CH_2-); 7.47–7.59 (m, 3H); 7.95 (dd, 2H, $J_{1,2}$ = 7.8 Hz, $J_{1,3}$ = 1.1 Hz); 8.69 (t, 1H, J = 7.4 Hz, >NH). Anal. calc. for $C_{20}H_{21}N_3O_3S_2$ (415): C, 57.83; H, 5.06; N, 10.12. Found: C, 57.71; H, 4.97; N, 10.29.

Ethyl-2-(((5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)amino)-5,6- dihydrocyclopenta[b]thiophene-3-carboxylate **2g**. White crystals (698 mg, 58%), mp 164–165 °C (ethyl acetate). IR (KBr, cm^{-1}): ν 1210, 1670, 3340. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, -$CH_2C\underline{H}_3$); 2.24–2.36 (m, 2H, -$CH_2C\underline{H}_2CH_2$-); 2.71–2.87 (m, 4H, -$C\underline{H}_2CH_2C\underline{H}_2$-); 4.26 (q, 2H, J = 7.2 Hz, -$C\underline{H}_2CH_3$); 5.53 (d, J = 6.9 Hz, >N-CH_2-); 7.44–7.58 (m, 3H); 7.80–7.96 (m, 2H); 8.41 (t, 1H, J = 7.5 Hz, >NH). Anal. calc. for $C_{19}H_{19}N_3O_3S_2$ (401): C, 56.85; H, 4.73; N, 10.47. Found: C, 56.69; H, 4.61; N, 10.61.

5-Phenyl-3-((1,2,3,4-tetrahydroisoquinolin-2-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione **2h**. White crystals (688 mg, 71%), mp 134–135 °C (ethanol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.95 and 3.20 (t, 2H, J = 5.9 Hz, -CH_2-); 4.08 (s, 2H, -CH_2-); 5.29 (s, 2H, >N-CH_2-); 7.06–7.15 (m, 4H); 7.48-7.60 (m, 3H); 7.96 (dd, 2H, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 1.2 Hz). Anal. calc. for $C_{18}H_{17}N_3OS$ (323): C, 66.87; H, 5.26; N, 13.00. Found: C, 66.68; H, 5.33; N, 13.14.

3-((cis,trans-2,5-Dimethyl-4-((5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)-1-piperazinyl)methyl)-5-phenyl-1,3,4-oxadiazole-2(3H)thione **2i**. White crystals (445 mg, 60%), mp 206–207 °C (ethanol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.32 and 1.34 (s, 3H, -CH_3); 2.46 (t, 2H, J = 10.8 Hz,); 2.85–2.98 (m, 2H,); 3.16 (dd, J = 11.7 Hz and 2.7 Hz); 5.16 (dd, 4H, J = 30 Hz and 13.8 Hz); 7.46–7.61 (m, 6H); 7.88–7.98 (m, 2H). Anal. calc. for $C_{24}H_{26}N_6O_2S_2$ (494): C, 58.29; H, 5.26; N, 17.00. Found: C, 58.41; H, 5.17; N, 16.91.

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