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Thiazolidin-4-one formation. Mechanistic and synthetic aspects of the reaction of imines and mercaptoacetic acid under microwave and conventional heating

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Microwave irradiation of a mixture of benzylidene-anilines and mercaptoacetic acid in benzene gives 1,3-thiazolidin-4-ones in very high yield (65–90%), whereas the same reaction performed through using the conventional method, at reflux temperature, requires a much longer time and gives a much lower yield (25–69%). This difference seems to be due to some intermediates and by-products formed during the conventional reaction. On the basis of ^{1}H NMR studies, two different mechanisms, acting in benzene and in DMF, respectively, have been hypothesized for the thiazolidin-4-one system formation.

Introduction

The thiazolidinones and correlated motifs have high biological relevance since they are present in both natural products and pharmaceutical compounds. In our ongoing research to synthesize new biologically active thiazolidinone derivatives, we have described a series of 2-(substituted phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones active as H_1-histamine antagonists,[1–5] obtained from the reaction between benzylidene-amines and mercaptoacetic acid. To improve the thiazolidin-4-one system formation in this very general reaction, the microwave-assisted method was used.

Microwave irradiation is an alternative heating method based on the ability of some compounds to transform electromagnetic energy into heat. This method, which increases chemical reaction rates[6] and forms cleaner products, can be successfully applied in pharmaceutical chemistry.

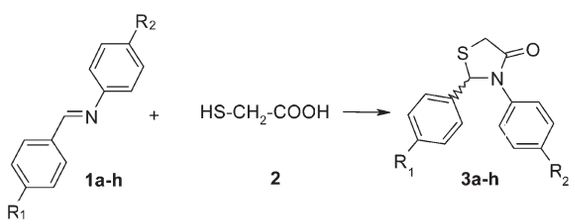
In this paper, we have compared the results of reaction between benzylidene-anilines and mercaptoacetic acid performed by the microwave-assisted method with the results of the same reaction obtained from the conventional procedure. To elucidate the experimental results, both synthetic routes have been investigated by ^{1}H NMR studies.

Results and discussion

Synthesis of the substituted thiazolidin-4-ones **3a**–**h** (Scheme 1) was performed in parallel using a microwave oven (ETHOS 1600, Milestone), specially designed for organic synthesis, and conventional procedure. The same concentration of product and volume of solvent were used in both procedures.

All the reactions were performed in closed vessels and the microwave program was composed of appropriate ramping and holding steps. Identification of the optimum profile power/time and temperature for the experiments is reported in Table 1.

Table 1 shows the yields of thiazolidin-4-ones **3a**–**h** arising from the reaction between mercaptoacetic acid and suitable benzylidene-anilines (**1a**–**h**)[7] in benzene, after 2 h at reflux temperature, and those obtained by microwave irradiation at 30 °C after 10 min. The data indicate that higher yields of **3a**–**h** were obtained (65–90%) under microwave irradiation than with the conventional method



	R_1	R_2		R_1	R_2
a	H	H	**e**	Cl	H
b	Me	Me	**f**	H	Cl
c	Me	H	**g**	NO_2	H
d	H	Me	**h**	H	NO_2

Scheme 1 Reaction between benzyliden-anilines **1a**–**h** and mercaptoacetic acid **2** to form 1,3-thiazolidin-4-ones **3a**–**h**.

at reflux temperature over a longer time frame (25–69%). To directly compare reaction results, the same solvent (benzene) used in the conventional method was used in the microwave-assisted method. Benzene is an apolar, aprotic solvent, not miscible with the water produced during the reaction and is characterized by low permittivity. Those latter two characteristics work in favor of the conventional reaction allowing the water removal from the reaction mixture and limit the microwave absorption only to the reacting species. In fact, the results reported in Table 1 seem to suggest that, under microwave irradiation at low temperature (30 °C), the yield increase could be related to the polarity induced in the benzylidene–anilines **1a**–**h** by decreasing polar substituents NO_2 > Cl > Me > H. Accordingly, **1h** and **1g**, both containing the highly polar nitro group, gave the best results.

In order to clarify the formation mechanism of the thiazolidin-4-ones, **3b** was synthesized by carrying out the reaction between **2** and the (4-methyl-phenyl)-(4-methylbenzylidene)-amine (**1b**) in C_6D_6, inside the NMR probe of a Bruker 500 MHz at 30 °C. The benzylidene-aniline **1b** was selected for the NMR investigation because it has well distinguishable resonance signals.

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Table 1 Yields of the thiazolidinones **3a**–**h** by conventional and microwave irradiation method in benzene

			Conventional method	Microwave[a]
			Reaction time = 2 h	Reaction time = 10 min
			Yield (%)	Yield (%)
3	R_1	R_2	reflux temperature	30 °C
a	H	H	60	80
b	Me	Me	69	90
c	Me	H	40	70
d	H	Me	50	85
e	Cl	H	38	70
f	H	Cl	35	70
g	NO_2	H	28	70
h	H	NO_2	25	65

[a] The experimental conditions (reagent concentrations, solvent volume) are similar to the conventional ones. The best power and time were 100 W and 10 min, respectively. The reactions were performed in triplicate.

Two parallel reactions between **1b** and **2** were monitored and compared by recording the ^{1}H NMR spectrum every five minutes after mixing. The first reaction, after microwave irradiation (100 W), showed proton signals arising from both the starting materials and the thiazolidin-4-one **3b**. No by-product or intermediate was detectable. The second reaction, heated with the conventional procedure, showed not only the starting materials and a small amount of **3b**, but also other signals suggesting the presence of different additional species. All those additional species were probably responsible for a slower reaction time and a lower yield. Specifically, the increasing signals of two new species **4b** and **5b** were detected. After 15 min, the ratio **4b**/**5b** became constant. After one hour, both **4b** and **5b** decreased and the main product present in the solution was the thiazolidin-4-one **3b**.

To demonstrate that the signals arising from the transient species **4b** and **5b** could not be attributed to **3b**, an authentic **3b** sample was added to the NMR sample. Since mercaptoacetic acid is present in the reaction mixture. To check the **3b** stability in acidic medium, a sample was monitored in DCl for 30′ at room temperature and no chemical decomposition was observed.

Table 2 reports the chemical shifts of the protons attributed to the species **1b** and **3**–**5b**.

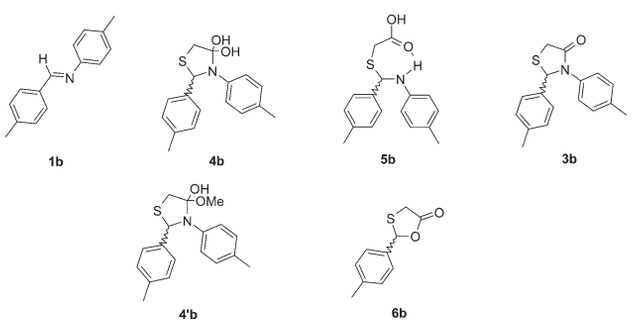
The structure of 2,3-di-*p*-tolyl–thiazolidine-4,4-diol was assigned to the transient species **4b** on the basis of ^{1}H NMR resonances. The C2–H signal appears as a doublet at 5.77 δ long-range coupled (1H, d; J = 1.5 Hz) with the higher field proton of the C5 geminal system at 3.32 δ (1H, d; J = 15.4 Hz) and 3.14 δ (1H, dd; J = 15.4, 1.5 Hz) in accordance with the cyclic structure **4b** reported in Scheme 2. This long range coupling is in contrast with that of the C2–H proton of **3b**, which is coupled with the more deshielded proton of the C5 geminal system, suggesting a more twisted ring geometry[8] for **4b**. On the basis of this evidence, it seems reasonable to attribute the structure of a cyclic *gem*-diol to the transient species **4b**, in which the two long-range coupled protons participate in a W-arrangement.

The structure of (*p*-tolyl-*p*-tolylamino–methylsulfanyl)–acetic acid was assigned to the transient species **5b** on the basis of ^{1}H NMR resonance. This intermediate species, previously hypothesized but not rigorously confirmed,[9–11] shows the aromatic protons lying at a lower field than the corresponding protons of **3b**, a broad singlet at 5.29 δ (1H), a sharp singlet (2H) at 3.52 δ and two singlets (3H) at 2.42 and 2.33 δ (Table 2).

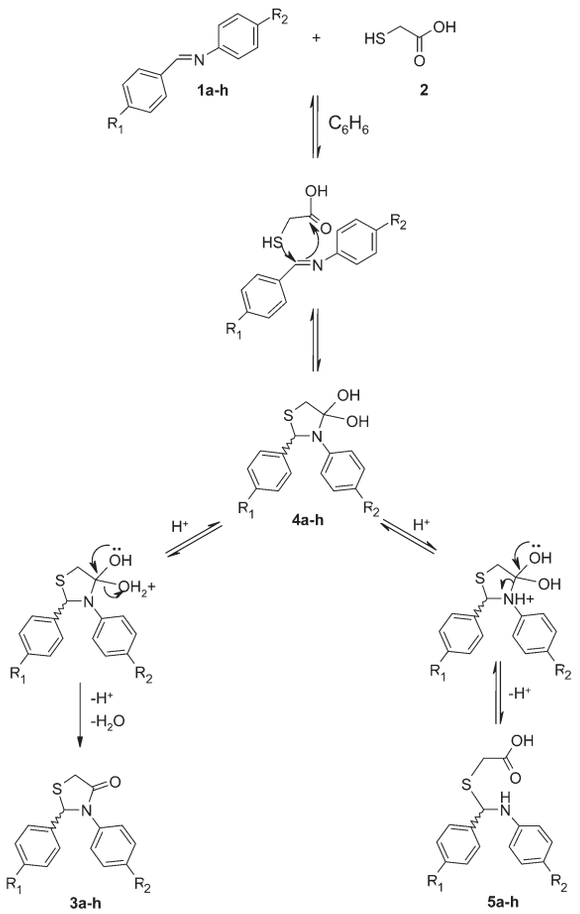
Calculation of NMR shieldings by quantum mechanical methods is becoming an important support to validate the process of the resonance assignments of experimental spectra. Particularly, the reliability of results can contribute to determinate the structure of transient species developing in a reaction performed in a NMR spectrometer probe. We have used a computational protocol, previously validated,[12,13] in which geometries optimized at the PBE0/6–31G(d) level[14,15] are used for single point computations of NMR absolute shieldings by the GIAO[16] approach using the same PBE0 density functional and the 6–311+G(d,p) basis set. In the next step, hydrogen chemical shifts (ppm) of thiazolidinone **3a** and of the transient species **4a** and **5a** are obtained summing the experimental chemical shift of this proton to each difference from the lower field methylene proton of **3a**. All the computations have been performed using the Gaussian03 package.[17] Table 3 reports the comparison of calculated and experimental values.

Fig. 1 shows the low energy conformation of **4b**, **5b** and **3b** obtained by quantum mechanical calculations. Full geometry optimizations at the PBE0/6–31G(d) level starting from these structures account for the more twisted conformation of **4b**

Table 2 Chemical shifts (δ) and *J* (in Hz) of the protons attributed to **1b**, **3**–**5b**, oxathiolane **6b** and 4-ethoxy-2,3-di-*p*-tolyl-thiazolidin-4-ol (**4′b**)



Comp	Aromatic	CH	CH_2	Me	Et
1b	7.78 (d), 7.26 (d), 7.18 (d), 7.13 (d)	8.42 (s)		2.41 (s), 2.37 (s)	
4b	7.37 (d), 7.24 (d), 6.95 (d), 6.62 (d)	5.77 (d; J = 1.5)	3.32 (1H, d; *J* = 15.4), 3.14 (1H, d; *J* = 15.4, 1.5)	2.39 (s), 2.35 (s)	
5b	7.35 (d), 7.32 (d), 7.15 (d), 7.09 (d)	5.29	3.52 (s)	2.42 (s), 2.33 (s)	
3b	7.18 (d), 7.08 (d), 7.06 (d), 7.02 (d)	6.01 (d; J = 1.7)	3.98 (1H, dd; *J* = 15.7, 1.7), 3.87 (1H, d; J = 15.7)	2.26 (s), 2.22 (s)	
6b	7.25 8 (d), 7.05 (d)	5.20	3.32 (1H, d; *J* = 15.2), 3.06 (1H, d; J = 15.2)	2.23 (s)	
4′b	7.39 (d), 7.14 (d), 6.96 (d), 6.62 (d)	5.76 (d; J = 1.0)	3.26 (1H, d; *J* = 15.4), 3.09 (1H, dd; *J* = 15.4, 1.0)	2.33 (s), 2.22 (s)	4.11 (q), 1 .21 (t)



Scheme 2 Hypothesized formation mechanism of the thiazolidin-4-ones **3a**–**h** in benzene.

compared to **3b** and for the presence of a hydrogen bond between NH hydrogen and the carbonyl oxygen of the carboxylic group in **5b** (Table 4). This latter intramolecular interaction contributes to stabilizing **5b**.

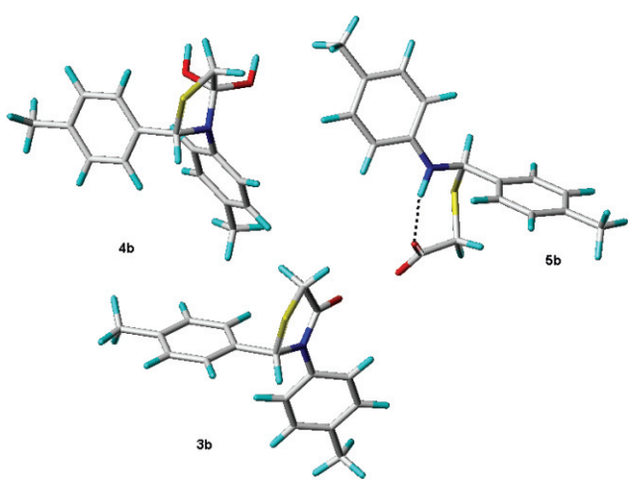


Fig. 1 Low energy conformations of **3**–**5b** obtained by *ab initio* calculations.

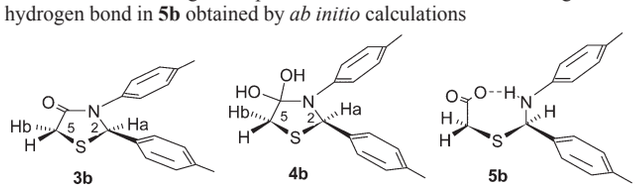
Rapid addition of **2** to the reaction mixture containing **1b** and/or a higher reaction temperature (60 °C) furnished another compound named **6b**, which was identified as 2-*p*-tolyl-1,3-oxathiolan-5-one[18] by comparison with an authentic sample prepared in our laboratory (Table 2). The presence of **6b** in the reaction mixture suggests that the imine **1b** is unstable under the reaction conditions and that oxathiolane formation is a highly favored reaction and decreases the thiazolidinone yield.

All the reactions yielding thiazolidin-4-ones **3a**–**h** were monitored by ^{1}H NMR investigation according to the above

Table 3 Comparison of calculated (PBE0/6–311+G(d,p)) and experimental ^{1}H chemical shifts (ppm) of thiazolidinone **3a** and transient species **4a** and **5a**

	CH		CH_2			
	Calculated	Experimental	Calculated		Experimental	
3a	6.48	6.04	4.15	3.81	3.95	3.81
4a	6.36	5.80	4.15	3.62	4.02	3.78
5a	5.91	5.31	3.53	3.58	3.52	

Table 4 Dihedral angles of species **3b** and **4b** and distance and angle of the hydrogen bond in **5b** obtained by *ab initio* calculations



Dihedral angles	**4b**	**3b**
Ha–C_2–C_5–H_5	−30.4°	2.5°
C_4–N–C_2–S	46.7°	−27.3°
5b		
Hydrogen bond distance H···O	16.57 nm	
Hydrogen bond angle ∠O···H–N	165.8°	

Table 5 Ratios of thiazolidinones **3a**–**h** and transient species **4a**–**h**, **5a**–**h** in the NMR samples in benzene after 15 min of reaction at 30 °C, calculated by integration (%)

	R_1	R_2	4	5	3
a	H	H	36	21	43
b	Me	Me	35	22	43
c	Me	H	28	14	58
d	H	Me	30	15	55
e	Cl	H	50	9	41
f	H	Cl	46	15	39
g	NO_2	H	52	8	40
h	H	NO_2	48	14	38

described procedure. The first products observed in the NMR sample were **4a**–**h**. Table 5 reports the ratios between the compounds **3a**–**h**, **4a**–**h** and **5a**–**h** present in the reaction mixtures after fifteen minutes from the mixing of the starting materials **2** and **1a**–**h**. Generally, the species **4a**–**h** and **3a**–**h** are present in solution in similar amounts, whereas the species **5a**–**h** are present in smaller amounts. The concentration of **4a**–**h** is greater when the substituent is an electron-withdrawing group and the concentration of **3a**–**h** is greater when the substituent is an electron donating group. Species **5a**–**h** follow the same trend observed for species **3a**–**h**. This suggests that the ratio **4**/**5** could be determined by their reciprocal stability or by their formation rate.

On this basis, the thiazolidinone formation mechanism was hypothesized as a concerted soft–soft reaction[19] between **2** and **1a**–**h** directly yielding the *gem*-diols **4a**–**h**. As illustrated in Scheme 2, protonation of the heterocyclic nitrogen or of the hydroxyl group could give rise to **5a**–**h** and **3a**–**h**, respectively. Since benzene does not solvate protons,[20] the proton activity is free. While the thiazolidine ring opening and **5a**–**h** formation are reversible processes, thiazolidinones **3a**–**h** are formed in an irreversible dehydration step which constitutes the driving force of this reaction. A weak influence of the substituents was observed, which confirms the hypothesis of a concerted reaction.

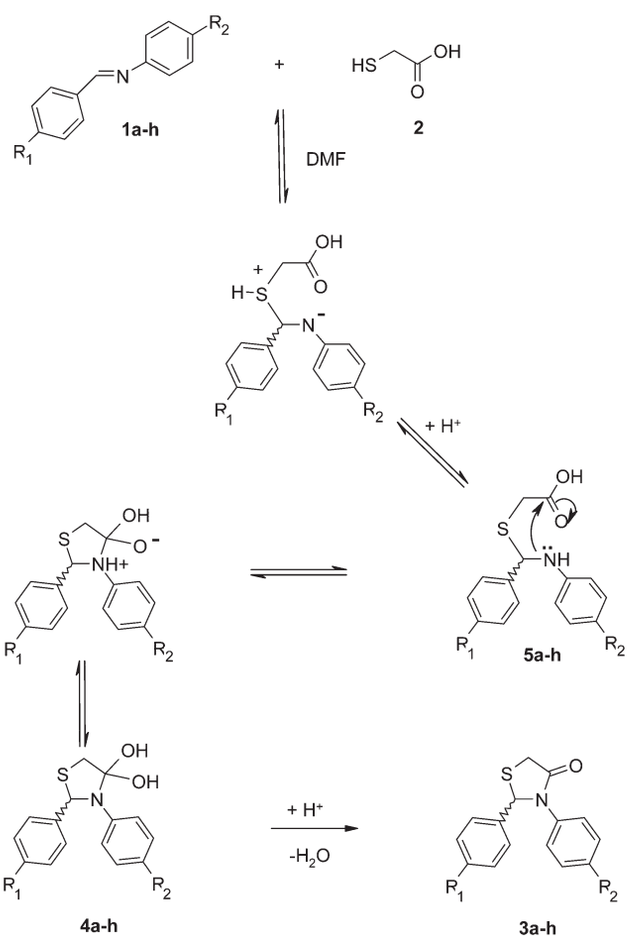
To further investigate this formation mechanism, the reaction between **1b** and **2** was carried out in DMF-d_7, a dipolar aprotic solvent, in the NMR probe, using the microwave and conventional methods described above. The yields in DMF at 100 °C from the conventional method and from the microwave heating were 30% and 80%, respectively. Table 6 reports the ratios between the species

Table 6 Ratios of thiazolidinone **3b** and transient species **4b**, **5b** in the NMR samples in C_6D_6 and DMFd-$_7$ after 15 min of reaction at 30 °C, calculated by integration (%)

4b		**5b**		**3b**	
C_6D_6	DMF-d_7	C_6D_6	DMF-d_7	C_6D_6	DMF-d_7
35	72	22	18	43	10

3b–**5b** present in the corresponding reactions performed at 30 °C, both in C_6D_6 and DMF-d_7. While **4b** was the first observed product in C_6D_6, **5b** was the first one in DMF-d_7. After 15 min, the formation of **3b** was about 35% in C_6D_6, whereas in DMF-d_7 **4b** was the main product (72%) and **3b** represents only 10%. Therefore, the reaction trend in DMF reverses the results observed in benzene.

Since **5b** is the first product to be formed in DMF, the possible cause could be that the thiol group attacks the imine bond and the proton shifts from the sulfur to the negatively-charged nitrogen (Scheme 3). In these conditions, the *gem*-diol **4b** is formed by intramolecular nucleophilic attack of the **5b** aminic nitrogen to the carbonyl carbon. Finally, dehydration gives rise to **3b**.



Scheme 3 Hypothesized formation mechanism of the thiazolidin-4-ones **3a**–**h** in DMF.

The data reported in Tables 5 and 6 seem to validate that **3b** is formed through the two above mentioned different mechanisms depending on the nature of the solvent. In accordance with the mechanism proposed in Scheme 3, the low yield of **3b** in DMF could be due to the low acidity of the medium. DMF is a dipolar, aprotic basic solvent capable of capturing protons and opposing the dehydration step. Microwave irradiation by-passes this problem by promoting dehydration and proves to be a very useful synthetic tool. The role played by DMF in preventing dehydration is also supported by the results observed in the reaction between **1b** and the mercaptoacetic ethyl ester **2′**, where the corresponding **5b** and **3b** are obtained only by acid addition. In fact, the reaction between **1b** and the mercaptoacetic acid ethyl ester (**2′**) performed in C_6D_6 inside the NMR probe, shows proton signals arising from the 4-ethoxy-2,3-di-*p*-tolyl-thiazolidin-4-ol intermediate (**4′b** in Table 2). The H2 signal appears as a doublet at 5.76 δ (1H, d; J = 1.0 Hz) coupled with the proton at higher field of the C5 geminal system at 3.26 δ (1H, d; J = 15.4 Hz) and 3.09 δ (1H, dd; J = 15.4, 1.0 Hz) and the ethoxy group at 4.11 δ (2H, q) and 1.21 δ (3H, t). Whenever **2′** is added to the NMR sample in small amounts, an equilibrium between the reagents and **4′b** is detectable. In fact, the addition of **2′** is followed by the decreasing signals of **1b** and by a constant ratio of **4′b**/**2′** while **1b** is present in the reaction mixture. According to this evidence, no thiazolidinone formation is observed on addition of **2′** to **1b** or to other imines in C_6D_6, probably because of the medium proton deficiency. In fact, the 4-ethoxy-2,3-di-*p*-tolyl-thiazolidin-4-ol (**4′b**) cannot evolve to thiazolidin-4-one by ethanol elimination. On the contrary, **4′b** gives the thiazolidin-4-one **3b** by addition of trifluoracetic acid.

In conclusion, using benzene as the solvent, the microwave-assisted reaction between benzyilidene-anilines and mercaptoacetic acid is a more efficient and faster method to produce thiazolidin-4-ones than the conventional one. The reaction studied by ^{1}H NMR has shown that thiazolidin-4-ones are directly formed from the starting materials under microwave irradiation. Under conventional irradiation, two intermediate species in equilibrium, the *gem*-diols **4a**–**h** and the sulfanylic acetic acids **5a**–**h**, have been detected. The nature of the solvent determines the formation mechanism of either **4a**–**h** or **5a**–**h** species. In benzene, **4a**–**h** are the first products formed trough a concerted soft-soft mechanism, while in DMF, **5a**–**h** are the first reaction products arising from negatively charged intermediates. In both microwave assisted and conventional procedures, dehydration is the crucial irreversible step of the overall process and represents the driving force of thiazolidinone formation. Microwave irradiation highly favoring the dehydration is seen to be a successful, efficient, alternative synthetic tool.

Experimental

General

Melting points were determined by a Kofler apparatus and are uncorrected. The elemental analysis (C, H and N) of reported compounds agrees with the calculated values and was within ±0.4% of theoretical values. The IR spectra were taken on a Perkin-Elmer 1760-X IFT spectrophotometer in potassium bromide and the amide carbonyl group ranges at 1690–1710^{-1}. The NMR spectra were recorded in benzene-d_6 on a Fourier-transform Bruker spectrometer AMX 500 equipped with a Bruker X-32 computer, using the UXNMR software package and are reported as δ. TMS was used as an internal standard. To enhance the results nitrogen was bubbled through the sample to remove the oxygen. Electron impact (EI, 70 eV) mass spectra were obtained on a VG ZAB 2F spectrometer. The purity of the compounds was checked by ascending TLC on Merck's precoated silica-gel plates (0.25 mm).

General procedure for the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (3a–h) and 2-phenyl-3-[2-(*N*,*N*-dimethylamino)ethyl]-1,3-thiazolidin-4-one (3i)

An equimolar mixture (0.01 mol) of aldehyde and appropriate amine (0.01 mol) in dry benzene (50 ml) was refluxed until no more water was collected in a Dean–Stark water separator. Mercaptoacetic acid (0.01 mol) was added, dropwise, to this crude mixture, and the reaction was carried out at reflux temperature until stoichiometric water was collected. The mixtures, cooled and evaporated *in vacuo*, afforded the crude compounds which were purified by TLC (Silica gel, Merck 0.5 mm; eluent: chloroform.

2,3-diphenyl-1,3-thiazolidin-4-one (3a)

White solid; mp 131–2 °C (Found: 70.50; H, 5.11; N, 5.50. Calc for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%); δ_H (C_6D_6) 7.25 (4H, d + t,

J 7.6), 7.22 (4H, d + t J 7.5), 7.20 (1H, t, J 7.6), 7.10 (1H, t, J 7.5), 6.04 (1H, d, J 1.6), 3.95 (1H, dd, J 15.7, 1.6), 3.81 (1H, d, 15.7); *m*/*z* (EI) 259 (M + 4), 257 (M + 2), 255 (M+).

2,3-di-*p*-tolyl-1,3-thiazolidin-4-one (3b)

White solid; mp 119–20 °C (Found: C, 72.15; H, 6.00; N, 4.93. Calc. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94%); δ_H (C_6D_6) 7.18 (2H, d, J 7.6), 7.08 (2H, d, J 7.5), 7.06 (2H, d, J 7.6), 7.02 (2H, d, J 7.5), 6.01 (1H, d, J 1.7), 3.98 (1H, dd, J 15.7, 1.7), 3.87 (1H, d, J 15.7), 2.26 (3H, s), 2.22 (3H, s); *m*/*z* (EI) 287 (M + 4), 285 (M + 2), 283 (M+).

2-*p*-tolyl-3-phenyl-1,3-thiazolidin-4-one (3c)

White solid; mp 106–7 °C (Found: C, 71.38; H, 5.60; N, 5.19. Calc. for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20%); δ_H (C_6D_6) 7.31 (1H, t, J 7.5), 7.27 (2H, d, J 7.5), 7.19 (4H, d + t, J 7.6), 7.10 (2H, d, J 7.5), 6.07 (1H, d, J 1.5), 3.99 (1H, dd, J 15.8, 1.5), 3.87 (1H, d, 15.8), 2.28 (3H, s); *m*/*z* (EI) 273 (M + 4), 271 (M + 2), 269 (M+).

2-phenyl-3-*p*-tolyl-1,3-thiazolidin-4-one (3d)

White solid; mp 115–7 °C (Found: C, 71.30; H, 5.59; N, 5.20. Calc. for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20%); δ_H (C_6D_6) 7.30 (1H, t, J 7.4), 7.29 (2H, d, J 7.4), 7.27 (2H, t, J 7.4), 7.14 (2H, d, J 8.4), 7.12 (2H, d, J 8.4), 6.06 (1H, d, J 1.5), 4.03 (1H, dd, J 15.8, 1.5), 3.90 (1H, d, 15.8), 2.21 (3H, s); *m*/*z* (EI) 273 (M + 4), 271 (M + 2), 269 (M+).

2-*p*-chlorophenyl-3-phenyl-1,3-thiazolidin-4-one (3e)

White solid; mp 129–30 °C (Found: C, 62.20; H, 4.18; N, 4.84. Calc. for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17; N, 4.83%); δ_H (C_6D_6) 7.30 (1H, t, J 7.5), 7.29 (4H, d + t, J 7.6), 7.25 (2H, d, J 7.5), 7.14 (2H, d, J 7.5), 6.10 (1H, d, J 1.6), 4.01 (1H, dd, J 15.8, 1.6), 3.89 (1H, d, 15.8); *m*/*z* (EI) 293 (M + 4), 291 (M + 2), 290 (M + 1), 289 (M+).

2-phenyl-3-*p*-chlorophenyl-1,3-thiazolidin-4-one (3f)

White solid; mp 110–1 °C (Found: C, 62.23; H, 4.16; N, 4.84. Calc. for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17; N, 4.83%); δ_H (C_6D_6) 7.22 (5H, m), 7.20 (2H, d, J 7.6), 7.07 (2H, d, J 7.6), 6.03 (1H, d, J 1.6), 3.94 (1H, dd, J 15.8, 1.6), 3.84 (1H, d, 15.8); *m*/*z* (EI) 293 (M + 4), 291 (M + 2), 290 (M + 1), 289 (M+).

2-*p*-nitrophenyl-3-phenyl-1,3-thiazolidin-4-one (3g)

White solid; mp 133–4 °C (Found: C, 59.98; H, 4.05; N, 9.32. Calc. for $C_{15}H_{12}N_2O3S$: C, 59.99; H, 4.03; N, 9.33%); δ_H (C_6D_6) 8.14 (2H, d, J 7.1), 7.47 (2H, d, J 7.1), 7.30 (2H, t, J 7.5), 7.19 (3H, d + t, J 7.5), 6.20 (1H, d, J 1.6), 4.01 (1H, dd, J 15.8, 1.6), 3.90 (1H, d, 15.8); *m*/*z* (EI) 304 (M + 4), 302 (M + 2), 300 (M+).

2-phenyl-3-*p*-nitrophenyl-1,3-thiazolidin-4-one (3h)

White solid; mp 102–3 °C (Found: C, 59.97; H, 4.05; N, 9.32. Calc. for $C_{15}H_{12}N_2O3S$: C, 59.99; H, 4.03; N, 9.33%); δ_H (C_6D_6) 7.99 (2H, t, J 7.5), 7.28 (2H, t, J 7.6), 7.26 (2H, d, J 7.5), 7.21 (1H, t, J 7.5), 6.56 (2H, d, J 7.5), 6.18 (1H, d, J 1.6), 3.94 (1H, dd, J 15.8, 1.6), 3.83 (1H, d, 15.8); *m*/*z* (EI) 293 (M + 4), 291 (M + 2), 290 (M + 1), 289 (M+).

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References

1 M. V. Diurno, G. Greco, O. Mazzoni, E. Novellino, A. Calignano, G. La Rana, A. Barbieri and A. Bolognese, *Med. Chem. Res.*, 1994, **4**, 578.
2 A. Bolognese, M. V. Diurno, G. Greco, P. Grieco, O. Mazzoni, E. Novellino, E. Perissutti and C. Silipo, *J. Recept. Res.*, 1995, **15**, 631.
3 M. V. Diurno, O. Mazzoni, G. Correale, I. Gomez Monterrey, A. Calignano, G. La Rana and A. Bolognese, *Farmaco*, 1999, **54**, 579.
4 M. V. Diurno, O. Mazzoni, E. Piscopo, A. Calignano, F. Giordano and A. Bolognese, *J. Med. Chem.*, 1992, **32**, 2910.
5 A. Bolognese, M. V. Diurno, O. Mazzoni, G. Correale, I. Gomez Monterrey and V. Barone, *J. Mol. Graph. Model.*, 1999, **54**, 579.
6 (*a*) S. Caddick, *Tetrahedron*, 1995, **51**, 10403; (*b*) S. A. Galema, *Chem. Soc. Rev.*, 1997, **26**, 233; (*c*) R. S. Varma, *Green Chem.*, 1999, **1**, 43; (*d*) A. Loupy and L. Perreux, *Tetrahedron*, 2001, **57**, 9199; (*e*) P. Lidström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 25; (*f*) M. Larhed and A. Hallberg, *DDT*, 2001, **6**, 406; (*g*) A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, 2002.
7 (*a*) M. V. Diurno, O. Mazzoni, E. Piscopo and A. Bolognese, *Farmaco*, 1992, **47**, 239; (*b*) A. Bolognese, M. V. Diurno, O. Mazzoni and F. Giordano, *Tetrahedron*, 1991, **47**, 7417.
8 Y. Allingham, R. C. Cookson and T. A. Crabb, *Tetrahedron*, 1968, **24**, 1989.
9 J. Tierney, *J. Heterocyclic Chem.*, 1989, **26**, 997.
10 A. R. Surrey, *J. Am. Chem. Soc.*, 1947, **69**, 2911.
11 G. W. Stacy and R. Morath, *J. Am. Chem. Soc.*, 1952, **74**, 3885.
12 V. Barone, O. Crescenzi and R. Improta, *Quant. Struct. Act. Relat.*, 2002, **21**, 105.
13 E. Langella, E. Rege, R. Improta, O. Crescenzi and V. Barone, *J. Comput. Chem.*, 2002, **23**, 650.
14 C. Adamo and V. Barone, *J. Chem. Phys.*, 1999, **110**, 6158.
15 J. B. Collins, P. R. Schleyer, J. S. Binkley and J. A. Pople, *J. Chem. Phys.*, 1976, **64**, 5142.
16 J. R. Cheeseman, G. W. Trucks, T. A. Keith and M. J. Frisch, *J. Chem. Phys.*, 1998, **104**, 5497.
17 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03*, Gaussian, Inc., Pittsburgh, 2003.
18 S. Higashiya, S. Narizuka, A. Konno, T. Maeda, K. Momota and T. Fuchigami, *J. Org. Chem.*, 1999, **64**, 133.
19 (*a*) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Chichester, U.K., 1976; (*b*) R. Breslow, *Organic Reaction Mechanisms*, W. A. Benjamin, Inc, New York, 1965.
20 (*a*) C. Reichardt, *Solvents and Solvent Effect in Organic Chemistry*, VCH Publishers, Weinheim, 2nd edn., 1988; (*b*) A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.