Non-Dipolar Behavior of Mesoionic Heterocycles: Synthesis and Tautomerism of 2-Alkylthioisomünchnones

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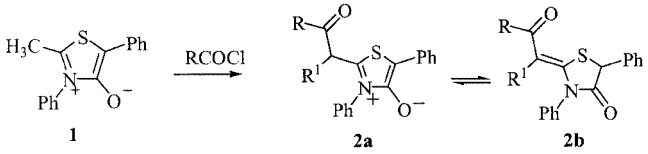
This paper describes a general preparation of a series of 1,3-thiazolium-4-olates, each bearing an alkyl group at C-2, through reactions between *N*-arylthiocarboxamides and α-haloacyl halides. Unlike the 2-aryl-substituted derivatives, such alkylated mesoionic compounds exist in equilibria with their non-dipolar tautomers, the corresponding 2-alkylidene-1,3-thiazolidin-4-ones. The unambiguous characterization of such tautomers and their relative stabilities have now been assessed by spectroscopic and computational studies. The presence of *o*,*o*′-disubstituted aryl groups at N-3 of the heterocyclic ring slows down free rotation around the N–Ar bond, thus opening access to a promising class of non-biaryl atropisomers. Finally, treatment of *N*-arylthioformamides with α-haloacyl halides gives rise to *N*-acylthioformamides instead of the corresponding mesoionic species.

Introduction

The inherent importance of mesoionic compounds, five-membered aromatic heterocycles that cannot be represented by Lewis structures not involving charge separation,[1] derives from their behavior as masked dipoles, and they are therefore amenable and versatile substrates for [3+2] cycloadditions.[2] A well-established family of such heterocycles, anhydro-4-hydroxy-1,3-thiazolium hydroxides (colloquially referred to as thioisomünchnones), containing thiocarbonyl ylide dipole components, have proven to be extremely useful synthons in our hands for almost two decades. Serendipity played its role when it was observed that the presence of an amino substituent at C-2 drove their subsequent scission routes.[3−6] Thus, by starting from 2-aminothioisomünchnones, 2,3-dihydrothiophenes,[3] 1,2,3-triazin-4-ones,[4] β-lactams,[5,6] and thiiranes[5,6] could be obtained, whereas the classical 2-aryl-substituted thioisomünchnones gave bicyclic compounds,[7] 2-pyridones,[7,8] thiophenes,[8] and *N*-acyl enamines,[9] respectively, with the same range of dipolarophiles.

Recently, it was also shown that 3,5-diphenyl-2-methylthioisomünchnone, in addition to its dipolar character, also behaved as a mild nucleophile towards reactive electrophiles, thereby affording a novel carbon−carbon bond-forming reaction.[10] While aliphatic acid chlorides yielded α-aryl-substituted ketones (Scheme 1: compound **2**; R = alkyl, R^1 = H), the aromatic counterparts gave α-aryl-substituted β-diketones (**2**; R = aryl, R^1 = COR).



Scheme 1

These results provide the first evidence of differential reactivity of the tautomeric species of a mesoionic heterocycle. It is fair to say that the equilibrium between a 2-methylthioisomünchnone derivative and its tautomer, the 2-methylenethiazolidin-4-one, had been detected previously by Baudy et al. through IR and NMR monitoring.[11] Moreover, valence tautomers in mesoionic chemistry have long been sought. In the early 1970s, it was suggested that münchnones (anhydro-5-hydroxy-1,3-oxazolium hydroxides) react with imines to yield β-lactams via the corresponding ketene tautomers.[12] Ketenes have never been detected, however, and formation of β-lactams can now be interpreted as a classical [3+2] cycloaddition.[5] Likewise, isomünchnones (anhydro-4-hydroxy-1,3-oxazolium hydroxides) were thought to exist in equilibria with their tautomeric oxazol-4(5*H*)-ones, which would react with acetylenes. The resulting cycloadducts would then undergo retro-Diels−Alder reactions with loss of isocyanic acid to give furans.[13] An alternative Diels−Alder reaction via an enol tautomer was equally suggested.[14]

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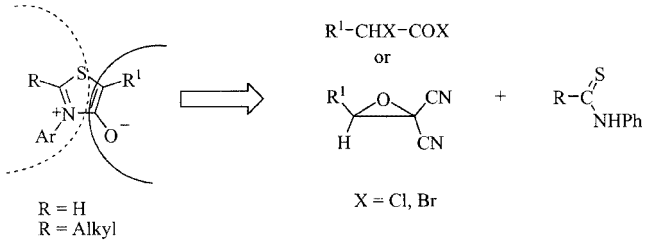
In this paper we introduce a systematic route to 2-alkylthioisomünchnones. Their tautomeric equilibria have also been explored by spectroscopic and computational (DFT) methods. In addition, several aryl substituents have been incorporated onto the heterocyclic nitrogen atom. This structural feature increases the steric barrier to rotation and can be utilized to generate a novel class of non-biaryl atropisomers with axial asymmetry. Finally, the reactions between *N*-arylthioformamides and 2-chloro-2-phenylacetyl chloride have also been explored in an attempt to obtain unsubstituted thioisomünchnones. An unexpected route to unsymmetrical *N*-acylthioformamides was found nevertheless.

Results and Discussion

Retrosynthetic Analysis and Preparation

Baudy and co-workers were able to prepare a few 2-methylthioisomünchnones through the reactions between thioamides and *gem*-dicyano epoxides.[11,15] Unfortunately, the latter substances are not readily available, and we therefore chose the condensation of thioamides with the commercially available α-haloacyl halides, a strategy that has proven to be a convenient route for the construction of 2-aryl-[16] and 2-(dialkylamino)thioisomünchnones.[3−6] A facile retrosynthetic analysis shows that the sulfur and nitrogen atoms, as well as the substituent at C-2 of the thioisomünchnone, are provided by the starting thioamide, whereas the α-haloacyl halide or dicyano epoxide serve as synthons for the rest of the heterocycle (Scheme 2).



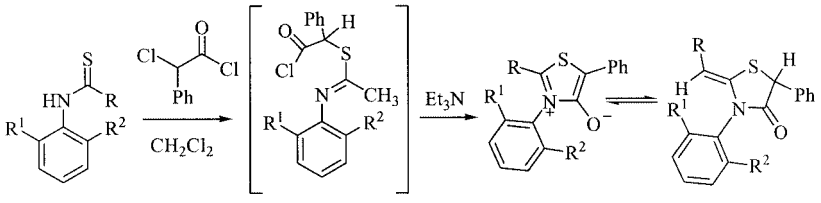
Scheme 2

Accordingly, compounds **8**−**12** were easily prepared by treatment of thioamides **3**−**7** with 2-chloro-2-phenylacetyl chloride in CH_2Cl_2/Et_3N. Under such conditions, both the alkylation and the subsequent cyclodehydration occur in a one-pot procedure (Scheme 3). With the sole exception of the commercially available thioacetanilide (**3**), thioamides were obtained from the corresponding amides by ultrasound-induced O/S exchange with P_4S_{10} in THF solution.[17] Similarly, the amides and formamides employed as raw materials in this study could easily be generated by acylation of amines with acetic anhydride or formic acid at reflux.[18]

Tautomeric and Rotational Equilibria

Despite the inherent instability of most thioisomünchnones in solution, they can be isolated by precipitation or crystallization at room temperature after conventional workup. Compounds **8**−**12** show NMR signals attributable to both tautomers. Fortunately, careful recrystallization or crystallization at lower temperatures allowed us to obtain samples of the pure tautomers **8b**, **10b**, **11b**, and **12b**, thereby facilitating their spectroscopic characterization.

In $CDCl_3$ solution, such thiazolidinones slowly equilibrate with their tautomeric thioisomünchnones. Moreover, all attempts to purify the mesoionic structures by chromatographic methods were unsuccessful, and tautomeric mixtures were invariably obtained. Table 1 shows a series of distinctive proton resonances for both sets of tautomers. In the thiazolidinones the heterocyclic proton at C-5 appears as singlet at δ = 5.28−5.19 ppm. The methylidene derivatives **8b**, **11b**, and **12b** show olefinic protons as doublets with coupling ($J \approx 3$ Hz) consistent with their geminal dispositions. The upfield resonances have been attributed to protons in *cis* dispositions relative to the sulfur atom.[19] In the ethylidene and 2-propylidene derivatives (**9b** and **10b**, respectively) these protons appear as singlets at δ = 4.65 ppm. The (*Z*) geometries around the double bonds have also been tentatively assigned on the basis of previous results with **2b** (R = CH_3, R^1 = H), for which the crystallographic structure is known.[10] In stark contrast, no proton is directly linked to the mesoionic structures, although the alkyl fragments at C-2 have a diagnostic value, appearing



3–7 8a–12a 8b–12b

	3	4	5	6	7	8a	8b	9a	9b	10a	10b	11a	11b	12a	12b
R	Me	Et	Prop	Me	Me	Me	H	Et	Me	Prop	Et	Me	H	Me	H
R^1	H	H	H	Me	Me	H	H	H	H	H	H	Me	Me	Me	Me
R^2	H	H	H	Me	Et	H	H	H	H	H	H	Me	Me	Et	Et

Scheme 3

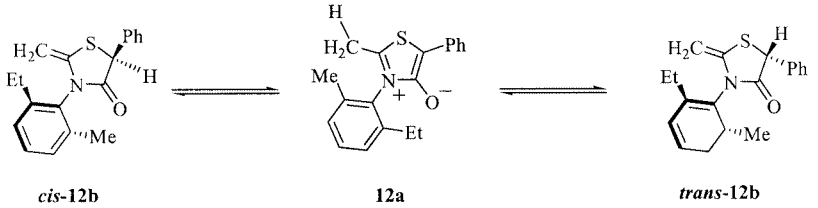
Table 1. Characteristic proton chemical shifts of mesoionic (**8a**−**12a**) and thiazolidinone (**8b**−**12b**) structures

	Mesoionics (**a**)				Thiazolidinones (**b**)		
Compd.	C-2−CH_x	R^1, R^2	**b/a** ratio	Compd.	C-2=CH_x	C-5−H	R^1, R^2
8a	2.46, s, 3 H		3.8:1.0	**8b**	4.39, d, J = 3.1 Hz, 1 H 4.27, d, J = 3.1 Hz, 1 H	5.22, s, 1 H	
9a	3.07, q, 2 H		2.3:1.0	**9b**	4.67, q, J = 6.8 Hz, 1 H	5.20, s, 1 H	
10a	0.98, t, 2 H		1.0:1.0	**10b**	4.64, t, J = 7.27 Hz, 1 H	5.19, s, 1 H	
11a	2.34, s, 3 H	2.10, s, 6 H	4.3:1.0	**11b**	4.32, d, J = 2.8 Hz, 1 H 4.05, d, J = 2.8 Hz, 1 H	5.26, s, 1 H	2.18, s, 3 H 2.12, s, 3 H
12a	2.36, s, 3 H	2.08, s, 3 H 2.53−2.40, q, 2 H 1.25−1.16, t, 3 H		*cis*-**12b**	4.33, d, J = 2.9 Hz, 1 H 4.04, d, J = 2.9 Hz, 1 H	5.28, s, 1 H	2.11, s, 3 H 2.50, dq, 2 H 1.21, t, 3 H
				trans-**12b**	4.32, d, J = 2.9 Hz, 1 H 4.04, d, J = 2.9 Hz, 1 H	5.26, s, 1 H	2.17, s, 3 H 2.44, q, 2 H 1.07, t, 3 H

as singlets at δ ≈ 2.4 ppm in **8a**, **11a**, and **12a**. In **9a** and **10a** those alkyl groups exhibit the expected coupling patterns at δ ≈ 3.1 ppm.

In compounds **11** and **12**, the *ortho* substituents on the phenyl ring also cause hindrance to rotation around the *N*−Ar bond. The presence of a stereogenic center at C-5 makes the *ortho*-methyl groups of **11b** diastereotopic, and so they resonate at clearly differentiated chemical shifts (δ = 2.18 and 2.12 ppm). Furthermore, compound **12b** exhibits an element of axial chirality, due to the existence of chemically different *ortho* substituents (Me, Et). In fact, the tautomeric equilibrium in **12** appears to be particularly complex. A freshly prepared solution of **12** contains a *cis*/*trans* mixture (with respect to the relative disposition of the ethyl group and the phenyl substituent at C-5) of the tautomer **12b** in an approximate ratio of 3:1 (in ^{1}H NMR integration; see Table 1 data), and evolves into a tautomeric mixture containing **12a** (**12b**/**12a** ≈ 4.3:1). At equilibrium, **12b** consists of a 1:1 *cis*/*trans* mixture. We have tentatively assigned a *cis* disposition to the most populated diastereomer, in which the signal for $ArCH_2CH_3$ is most deshielded. Unfortunately, no suitable crystals of **12b** could be obtained for single-crystal diffraction analysis. Remarkably, this *cis*/*trans* equilibration proceeds very slowly (several days by NMR monitoring) and only occurs when the concentration of the mesoionic structure **12a** is close to its equilibrium value. This fact suggests that protonation of **12a** at C-5 on its upper or lower faces takes place more rapidly than rotation around the N−Ar bond of the thiazolidinone component (Scheme 4). This slow interconversion might be exploitable for the preparation of a novel class of molecular switches,[20] which will be studied in future work.

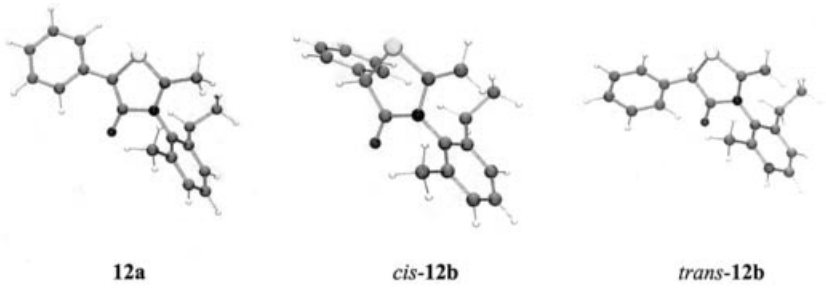
Tautomeric equilibria also manifest themselves in ^{13}C NMR measurements (Table 2). The C-5 and C-4 atoms of the thiazolidinone ring resonate at δ ≈ 51 and 171 ppm, respectively. The latter is more shielded in mesoionic structures (δ ≈ 160 ppm). Moreover, C-4 may not be observable in mesoionics under these experimental conditions. The exocyclic carbon at C-2 exhibits resonances typical of olefinic carbon atoms in thiazolidinones and also those character-



Scheme 4

Table 2. ^{13}C NMR chemical shifts of mesoionic (**8a**−**12a**) and thiazolidinone (**8b**−**12b**) tautomers

	Mesoionics (**a**)			Thiazolidinones (**b**)		
Compd.	C-2−*C*H_x	C-4	Compd.	C-2=*C*H_x	C-4	C-5
8a	17.5	159.9	**8b**	86.1	171.5	51.4
9a	45.6		**9b**	96.9	171.3	51.0
10a			**10b**	104.4	171.4	51.0
11a	16.8	158.9	**11b**	85.1	170.7	51.5
12a	ca. 17	ca. 160	**12b** (*cis*/*trans*)	85.4	171.0, 170.9	51.4



Scheme 5. Computationally generated (B3LYP/6-31G* level) tautomeric and rotameric structures for compound **12**

istic of alkyl groups in mesoionic rings. Undergoing *cis*/*trans* isomerism, compound **12b** also exhibits two close resonances for the C-4 atom (δ = 171.0 and 170.9 ppm).

Lastly, computational results (at PM3 and B3LYP/6-31G* levels of theory)[21] shed light on the tautomeric structures. Scheme 5 depicts the situation for compound **12**, although similar behavior, excluding rotational isomerism, is also observed for **8**−**11**. The *N*-aryl moiety is invariably orthogonal to the heterocyclic ring. The phenyl group at C-5 adopts a coplanar arrangement in mesoionics **8a**−**12a**.

In full agreement with the experimentally obtained results, the tautomeric structures show small energy differences, thiazolidinones being slightly favored by only 0.01 kcal/mol. A similarly small difference was also observed for the *cis* and *trans* rotamers of **12b**, the former moreover being more stable at both levels, thus accounting for the previous assignment.

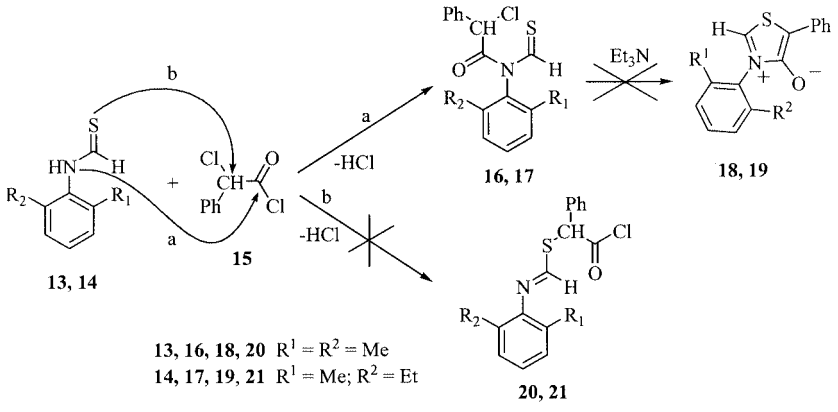
In a final stage, the preparation of derivatives unsubstituted at C-2 was also envisaged. However, thioformamides **13** and **14** did not afford the corresponding mesoionics **18** and **19** upon treatment with 2-chloro-2-phenylacetyl chloride, either in the presence or in the absence of Et_3N. Instead, the *N*-acylthioformamides **16** and **17** could be isolated (Scheme 6). All attempts to promote the cyclization of **16** and **17**, even under Ohta's conditions with α-halo acids,[22] were unsuccessful and resulted in complex, yellowish mixtures. This negative result paradoxically has one striking aspect, as *N*-acylthioformamide structures have never been isolated in the course of these preparative reactions. Despite the pronounced nucleophilicity of the sulfur atom, the formation of *N*-acylated compounds such as **16** or **17** has now been observed. Nevertheless, *S*-alkylated intermediates (such as the alternative structures **20** or **21**) have sometimes been isolated by treatment of thioamides with α-haloacyl halides.[16a]

Table 3. Energy and energy differences for the reaction of **13** and **15** at the B3LYP/6-31G* level

Compd.	**13** + **15**	**16** + HCl	**18** + 2 HCl	**20** + HCl
E [kcal/mol]	−1321920.9	−1321914.9	−1321905.3	−1321911.1
Δ*E* [kcal/mol]		6.0	15.6	9.8

Table 3 summarizes the energy profile of the reactions outlined in Scheme 6 for compound **13**. At the B3LYP/6-31G* level the three reactions are clearly endothermic, although the formation of **16** (6.0 kcal/mol) is more favorable than those leading to **18** (15.6 kcal/mol) or **20** (9.8 kcal/mol).

The structures of **16** and **17** are consistent with the observation of characteristic carbon resonances at δ = 194.1 (C=S), 167.4 (C=O), and 59.9 (CHCl) ppm. The thioformyl and α-carbonyl protons appear as singlets at δ = 10.86 and 5.18 ppm, respectively. The molecular peak [M^+] for **16** and [M^+ + 1] for **16** and **17** could also be detected by mass spectrometry techniques. As would be expected, the exist-

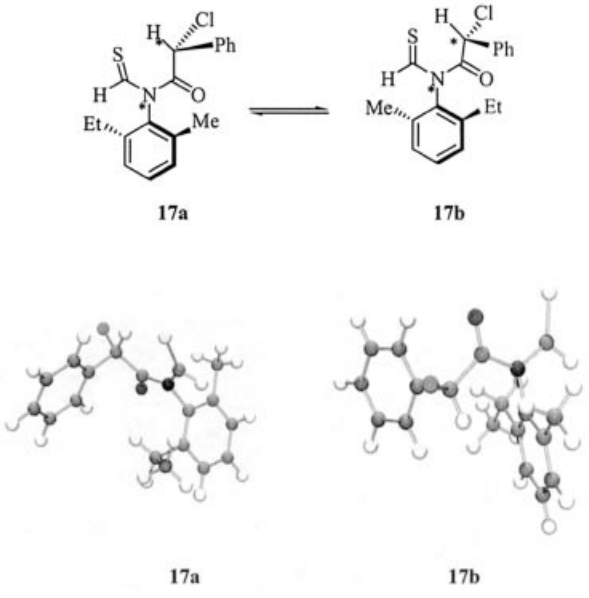


Scheme 6

ence of a stereogenic center and the restricted rotation around the *N*−Ar bond give two signals for the diastereotopic *ortho*-methyl groups of compound **16** in both the ^{1}H and the ^{13}C NMR spectra. The situation is more complicated for **17**, as the chiral axis and the stereogenic center cause the existence of a diastereomeric pair, and so two signal sets can be observed in its NMR spectra (**17a**/**17b** = 4.7:1.0). The anisotropic effect is especially noticeable for the CH_3−CH_2−Ar protons, which resonate at δ = 1.26 and 0.79 ppm, respectively.

In order to assign structures for compounds **17a** and **17b**, we performed a preliminary conformational analysis, at the PM3 level, by rotating the *N*−Ar bond. The most stable rotamers obtained by this procedure were further optimized at this level by rotations around the CO−CHCl bond and, finally, such minima were fully optimized without any constraints at the B3LYP/6-31G* level of theory.

Structure **17a** (Scheme 7) was found to be more stable by ca. 3 kcal/mol. The downfield resonance at δ = 1.26 ppm for the CH_3−CH_2−Ar moiety of **17a** could now be attributed to the deshielding effect caused by the carbonyl group of the amide function.[18]



Scheme 7. Structures and optimized geometries for **17a** and **17b** at the PM3//B3LYP-6-31G*

Conclusion

To sum up, we have developed a general strategy for the preparation of 2-alkylthioisomünchnones, which exist as tautomeric mixtures in equilibrium. Some derivatives also exhibit atropisomeric behavior that has been studied by spectroscopic and theoretical methods. Further synthetic studies aimed at selectively trapping the thiazolidinone tautomers, as well as the preparation of stable atropisomers, are under way.

Experimental Section

General Remarks: Melting points (m.p.) were determined with a capillary apparatus and are uncorrected. TLC was conducted on 0.25 mm silica gel plates (Merck F254), whereas flash chromatography was employed for preparative separations. IR spectra (KBr pellets) were recorded with a Midac FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ solution) were recorded at 400 MHz and 100 MHz, respectively, with a Bruker AM 400 spectrometer; the chemical shifts are given in ppm relative to TMS as internal standard and coupling constants in Hz. Elemental analyses were performed with a Leco CHNS 932 instrument. Mass spectra were recorded at the Universidad de Córdoba, Spain. Computational calculations were performed at the PM3 and B3LYP/6-31G* levels of theory with the Gaussian 98 package.[21]

General Procedure for the Synthesis of 2-Alkyl-3-aryl-5-phenyl-1,3-thiazolium-4-olates 8a−12a and 2-Alkylidene-3-aryl-5-phenyl-1,3-thiazolidin-4-ones 8b−12b: A solution of 2-chloro-2-phenylacetyl chloride (6.61 mmol) in CH_2Cl_2 (5 mL) and then a solution of Et_3N (13.2 mmol) in CH_2Cl_2 (5 mL) were added dropwise and successively to a magnetically stirred solution of thioamide **3**−**7** (6.61 mmol) in CH_2Cl_2 (20 mL). After 15 min at room temperature, the reaction mixture was washed repeatedly with brine, dried with anhydrous $MgSO_4$, and concentrated to a quarter of its initial volume.

2-Methyl-3,5-diphenyl-1,3-thiazolium-4-olate (8a) and 2-Methylidene-3,5-diphenyl-1,3-thiazolidin-4-one (8b): Application of the above procedure to thioamide **3** gave a solution, which was kept at −20 °C, yielding yellow crystals of **8** (4.6 mmol, 70%); m.p. 180 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 1705, 1628 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.3 Hz, 1 H, ArH, **8a**), 7.53−7.09 (m, ArH, 9 H of **8a** and 10 H of **8b**), 5.22 (s, 1 H, 5-H, **8b**), 4.39 (d, *J* = 3.1 Hz, 1 H, C-2=CH^aH^b, **8b**), 4.27 (d, *J* = 3.1 Hz, 1 H, C-2=CH^aH^b, **8b**), 2.46 (s, 3 H, CH_3, **8a**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (C-4, **8b**), 159.9 (C-4, **8a**), 149.8, 141.4, 137.3, 135.8, 135.3, 133.4, 129.8, 129.8, 129.7, 129.0, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.8, 127.0, 124.6, 123.6 (ArC, ArN, **8a**, **8b**), 86.1 (C-2=CH$_2$, **8b**), 51.4 (C-5, **8b**), 17.5 (CH_3, **8a**) ppm. $C_{16}H_{13}NOS$ (267.07): calcd. C 71.88, H 4.90, N 5.24, S 11.99; found C 72.21, H 5.44, N 5.09, S 11.75.

2-Ethyl-3,5-diphenyl-1,3-thiazolium-4-olate (9a) and 2-Ethylidene-3,5-diphenyl-1,3-thiazolidin-4-one (9b): Starting from **4**, the final solution was concentrated to dryness and the resulting residue was crystallized from diethyl ether (4.9 mmol, 75%); m.p. 131.2 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 1702, 1646 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.25 (m, 10 H, ArH, **9a**, **9b**), 5.20 (s, 1 H, C-5−H, **9b**), 4.67 (q, *J* = 6.9 Hz, 1 H, C-2=CH, **9b**), 3.07 (q, *J* = 7.3 Hz, 2 H, CH_3CH_2, **9a**), 1.65 (d, *J* = 6.8 Hz, 3 H, CH_3CH, **9b**), 1.38 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2, **9a**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (C-4, **9b**), 137.7, 135.8, 135.2, 129.6, 128.9, 128.8, 128.3, 128.0 (ArC, ArN, **9a**, **9b**), 96.9 (C-2=CH, **9b**), 51.0 (C-5, **9b**), 45.6 (CH_3CH_2, **9a**), 12.6 (CH_3, **9b**), 9.9 (CH_3CH_2, **9a**) ppm. $C_{17}H_{15}NOS$ (281.09): calcd. C 72.57, H 5.37, N 4.98, S 11.40; found C 72.40, H 5.34, N 4.92, S 11.9.

3,5-Diphenyl-2-propyl-1,3-thiazolium-4-olate (10a) and 3,5-Diphenyl-2-propylidene-1,3-thiazolidin-4-one (10b): Starting from **5**, the final solution was concentrated and the resulting residue was crystallized from diethyl ether to give yellow crystals of **10b** (4.6 mmol, 70%); m.p. 107.7 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1701, 1664, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.25 (m, 10 H, ArH), 5.19 (s, 1 H, C-5−H), 4.64 (t, *J* = 7.3 Hz, 1 H, C-2=CH),

2.05 (m, 2 H, $J_{CH3-CH2}$ = 7.5, J_{CH2-CH} = 14.9 Hz, CH_3CH_2), 0.97 (t, J = 7.4 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (C-4), 137.7, 135.9, 134.2, 129.6, 128.9, 128.8, 128.3, 128.1 (ArC, ArN, C2), 104.4 (C-2=*C*H), 51.0 (C-5), 21.2 (CH_2CH_3), 14.1 (CH_2CH_3) ppm. $C_{18}H_{17}NOS$ (295.10): calcd. C 73.19, H 5.80, N 4.74, S 10.86; found C 72.70, H 5.94, N 4.72, S 10.97. A solution of **10b** in $CDCl_3$, if left at room temp. for several days, evolved into a mixture of **10a** and **10b** (1:1 ratio). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.25 (m, 10 H, ArH, **10a**), 2.60 (t, J = 7.38 Hz, 2 H, $CH_3CH_2CH_2$, **10a**), 1.70 (m, 2 H, $J_{CH3-CH2}$ = 7.4, $J_{CH2-CH2}$ = 7.5 Hz, $CH_3CH_2CH_2$, **10a**), 0.97 (t, J = 7.5 Hz, 3 H, $CH_3CH_2CH_2$, **10a**) ppm.

3-(2,6-Dimethylphenyl)-2-methyl-5-phenyl-1,3-thiazolium-4-olate (11a) and 3-(2,6-Dimethylphenyl)-2-methylidene-5-phenyl-1,3-thiazolidin-4-one (11b): Application of the general procedure to thioamide **6** gave a solution. This was concentrated, and the residue was crystallized from diethyl ether (3.8 mmol, 58%); m.p. 122 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 1697, 1646, 1596 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.6 Hz, 1 H, ArH, **11a**), 7.53−7.11 (m, ArH, 9 H of **11a** and 10 H of **11b**), 5.26 (s, 1 H, CH, **11b**), 4.32 (d, J = 2.8 Hz, 1 H, C-2=CH_2, **11b**), 4.05 (d, J = 2.8 Hz, 1 H, C-2=CH_2, **11b**), 2.34 (s, 1 H, CH_3, **11a**), 2.18, 2.12 (s, 6 H, ArCH_3, **11b**), 2.10 (s, 6 H, ArCH_3, **11a**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (C-4, **11b**), 158.9 (C-4, **11a**), 139.0, 137.1, 136.6, 136.4, 135.1, 133.8, 133.0, 129.9, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 124.5, 123.4, 85.1 (C-2=*C*H$_2$, **11b**), 51.5 (C-5, **11b**), 17.6, 17.4 (CH_3Ar, **11a**, **11b**), 16.8 (C-2−CH_3, **11a**) ppm. $C_{18}H_{17}NOS$ (295.10): calcd. C 73.19, H 5.80, N 4.74, S 10.86; found C 72.66, H 6.07, N 4.549, S 11.11. HRMS (CI$^+$): calcd. for $C_{18}H_{17}NOS$ 295.10308; found 295.102895; Δ = 0.6 ppm. HRMS (FAB$^+$): calcd. for $C_{18}H_{17}NOSH^+$ 296.11091; found 296.111390; Δ = −1.6 ppm. The above mixture of tautomers **11a** and **11b** was dissolved in CH_2Cl_2, diluted with diethyl ether until precipitation, and kept at −20 °C. Tautomer **11b** crystallized on standing. IR (KBr): $\tilde{\nu}_{max}$ = 1695, 1595 cm^{-1}.

3-(2-Ethyl-6-methylphenyl)-2-methyl-5-phenyl-1,3-thiazolium-4-olate (12a) and 3-(2-Ethyl-6-methylphenyl)-2-methylidene-5-phenyl-1,3-thiazolidin-4-one (12b): Diethyl ether was added to the CH_2Cl_2 solution resulting from thioamide **7** to give crystals of **12a** and **12b** (4.0 mmol, 60%); m.p. 107.1 °C (dec.). IR ($CDCl_3$, solution): $\tilde{\nu}_{max}$ = 1710, 1629 cm^{-1}. Alternatively, diethyl ether was added to the CH_2Cl_2 solution resulting from thioamide **7** until incipient precipitation and the mixture was kept at −20 °C, yellow crystals of **12b** (*cis*/*trans*) thus being obtained (1.3 mmol, 20%). IR (KBr): $\tilde{\nu}_{max}$ = 1697, 1601 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (*cis*-**12b**): δ = 7.53−7.12 (m, 10 H, ArH, *cis*-**12b**, *trans*-**12b**), 5.28 (s, 1 H, CH, *cis*-**12b**), 5.26 (s, 1 H, CH, *trans*-**12b**), 4.33 (d, J = 2.9 Hz, 1 H, C-2=CH^aH^b, *cis*-**12b**), 4.32 (d, J = 2.8 Hz, 1 H, C-2=CH^aH^b, *trans*-**12b**), 4.04 (d, J = 2.9 Hz, 1 H, C-2=CH^aH^b, *cis*-**12b**, *trans*-**12b**), 2.50 (dq, 2 H, J = 7.4 Hz, ArCH_2CH$_3$, *cis*-**12b**), 2.44 (q, J = 7.4 Hz, 2 H, ArCH_2CH$_3$, *trans*-**12b**), 2.17 (s, 3 H, ArCH_3, *trans*-**12b**), 2.11 (s, 3 H, ArCH_3, *cis*-**12b**), 1.21 (t, J = 7.5 Hz, 3 H, $ArCH_2CH_3$, *cis*-**12b**), 1.07 (t, J = 7.5 Hz, 3 H, $ArCH_2CH_3$, *trans*-**12b**) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) (**12a**): δ = 7.53−7.12 (m, 9 H, ArH), 7.91 (d, J = 7.0 Hz, 1 H, ArH), 2.53−2.40 (q, J = 7.52 Hz, 2 H, ArCH_2CH$_3$), 2.36 (s, 3 H, C-2−CH_3), 2.08 (s, 3 H, ArCH_3), 1.25−1.16 (t, J = 7.6 Hz, 3 H, $ArCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.9 (C-4, **12a**, **12b**), 159.2 (C-4, **12a**), 142.3, 139.6, 139.6, 137.2, 136.6, 132.4, 130.1, 129.5, 128.9, 128.6, 128.5, 128.4, 128.3, 127.0, 123.4 (ArC, ArN, C-2, **12a**, **12b**), 85.4 (C-2=*C*H$_2$, **12b**), 51.5 (C-5, **12b**), 24.1, 24.0, 23.8 (ArCH_2CH$_3$, **12a**, **12b**), 17.6, 17.5, 17.4, 17.0 (C-2−CH_3, **12a**, ArCH_3, **12a**, *cis*-**12b**, *trans*-**12b**), 14.4, 14.2, 13.8 ($ArCH_2CH_3$, **12a**, *cis*-**12b**, *trans*-**12b**) ppm. $C_{19}H_{19}NOS$ (309.12): calcd. C 73.75, H 6.19, N 4.53, S 10.36; found C 73.62, H 6.30, N 4.23, S 10.52.

General Procedure for the Preparation of *N*-Thioformyl-*N*-acetanilides 16−17: A solution of 2-chloro-2-phenylacetyl chloride (6.61 mmol) in CH_2Cl_2 (5 mL) was added dropwise, with magnetic stirring, to a solution of thioformamide **13** or **14** (6.61 mmol) in CH_2Cl_2 (20 mL), followed after 25 min by a second solution of Et_3N (13.2 mmol) in CH_2Cl_2 (5 mL). The organic layer was washed repeatedly with brine, dried ($MgSO_4$), and concentrated to a quarter of its initial volume.

***N*-[Chloro(phenyl)acetyl]-*N*-thioformyl-2,6-dimethylaniline (16):** Starting from **13**, the CH_2Cl_2 solution was diluted with diethyl ether and petroleum ether until incipient precipitation. The resulting suspension was kept at −20 °C, and crystallized on standing (3.3 mmol, 50%); m.p. 143 °C. IR (KBr): $\tilde{\nu}_{max.}$ = 1724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.86 (s, 1 H, CSH), 7.37−7.02 (m, 10 H, ArH), 5.19 (s, 1 H, CH), 2.23 (s, 3 H, ArCH_3), 1.34 (s, 3 H, ArCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.1 (CS), 167.4 (CO), 137.4, 135.8, 134.4, 133.5, 130.3, 130.0, 129.3, 129.0, 128.7 (ArC, ArN), 57.9 (CH), 17.9 16.9 (ArCH_3) ppm. $C_{17}H_{16}NOSCl$ (317.06): calcd. C 64.24, H 5.07, N 4.41, S 10.09; found C 63.78, H 5.06, N 4.04, S 11.04. HRMS (IQ$^+$): calcd. for $C_{17}H_{16}ClNOS$ 317.06411; found 317.06660; Δ = 4.6 ppm. HRMS (BAR$^+$): calcd. for $C_{17}H_{16}ClNOS$ + H$^+$ 317.07194; found 318.071839; Δ = 0.3 ppm.

***N*-[Chloro(phenyl)acetyl]-2-ethyl-6-methyl-*N*-thioformylaniline (17):** Starting from **14**, the CH_2Cl_2 solution was diluted with diethyl ether and petroleum ether until incipient precipitation. The resulting suspension was kept at −20 °C, and an orange solid crystallized (2.4 mmol, 36%); m.p. 140.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2945, 1785 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.89 (s, 1 H, CSH, **17b**), 10.88 (s, 1 H, CSH, **17a**), 7.42−7.02 (m, 10 H, ArH, **17a**, **17b**), 5.20 (s, 1 H, CH, **17a**), 5.16 (s, 1 H, CH, **17b**), 2.60−2.46 (m, J = 7.7 Hz, 2 H, $ArCH_3CH_2$, **17a**, **17b**), 2.24 (s, 3 H, ArCH_3, **17a**), 2.16 (s, 3 H, ArCH_3, **17b**), 1.26 (t, J = 7.4 Hz, 3 H, ArCH_3CH_2, **17a**), 0.79 (t, J = 7.4 Hz, 3 H, ArCH_3CH_2, **17b**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5 (CSH, **17a**, **17b**), 167.5 (CO, **17a**, **17b**), 142.1, 141.1, 137.2, 133.8, 133.4, 130.4, 130.0, 129.1, 129.0, 128.7, 127.0, 126.6 (ArC, ArN, **17a**, **17b**), 58.0 (CH, **17a**), 57.6 (CH, **17b**), 23.7 (ArCH_2CH_3, **17a**), 22.6 (ArCH_2CH_3, **17b**), 17.9 ($ArCH_2CH_3$, **17b**), 16.9 ($ArCH_2CH_3$, **17a**), 13.9 (ArCH_3, **17a**), 12.9 (ArCH_3, **17b**) ppm. $C_{18}H_{18}NOSCl$ (331.08): calcd. C 65.15, H 5.47, N 4.22, S 9.66; found C 64.80, H 5.57, N 4.61, S 9.42. HRMS (BAR$^+$): calcd. for $C_{18}H_{18}ClNOS$ + H$^+$ 332.08759; found 332.090286; Δ = −8.1 ppm.

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