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On the reactivity of 2-alkyl-1,3-thiazolium-4-olates toward electrophiles

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Dedicated to the memory of Professor Marcial Moreno-Mañas

Abstract—On the basis of our synthetic methodologies employing mesoionic synthons, the nucleophilic character of 2-alkyl-1,3-thiazolium-4-olates (2-alkylthioisomünchnones) has been envisaged and developed, at the expenses of their common role as masked 1,3-dipoles. Reactions with aliphatic acid chlorides lead to monoketones derived from thiazolidin-4-ones, whose structure can be rationalized in terms of orbital interactions by computational studies. Aromatic acid chlorides invariably produce 1,3-dicarbonyl compounds, yet maintaining the mesoionic core. Unlike [3+2]-cycloadditions reported previously for thioisomünchnones with isocyanates and isothiocyanates, these heterocumulenes react with 2-alkylthioisomünchnones affording conjugated amides or thioamides.

1. Introduction

The mesoionic heterocycles have become useful and versatile synthons en route to varied and functionalized heterocyclic systems or advanced materials with extended conjugation.[1,2] The reactivity stems from their masked 1,3-dipolar character, thus interacting with a wide range of dipolarophiles in cycloaddition reactions. In some cases, such as in our previously reported selective reactions with 1,3-thiazolium-4-olates (thioisomünchnones), the mesoionic ring triggers a sequential process in which the initial cycloadduct is not stable enough and undergoes further ring opening leading to novel heterocyclic or acyclic structure. The protocol can be tailored by a careful choice of the substitution pattern on the mesoionic ring.[1]

In general, the presence of aromatic groups largely stabilizes the mesoionic system and has a profound effect on the dipolar character. An acyl group at a vicinal position to the exocyclic heteroatom markedly decreases the ability of these dipolar species as cycloadditive partners. Conversely, an electron-releasing substituent at C-2 not only enhances rates, but it is also responsible for the subsequent cycloadduct evolution.[1,3] It is therefore surprising that the scarce number of monocyclic mesoionics alkylated at C-2. The first derivative of a 2-methylthioisomünchnone was reported by Robert et al. in 1978 proving spectroscopically that this substance coexists in solution with its non-mesoionic tautomer of 2-methylenethiazolidine-4-one.[4]

Recently, we envisaged the possibility of generating other alkylated derivatives of thioisomünchnones at C-2 and set out to prepare them. Their tautomeric equilibria were equally elucidated by spectroscopy and computation.[5] The present study is aimed at exploring the reactivity of 2-alkylthioisomünchnones against a range of electrophiles that include acid chlorides, isocyanates, and isothiocyanates and demonstrating the methodology can be an efficient diversity oriented functionalization in organic synthesis.

2. Results and discussion

In a logical fashion theory should be preceding experiments. Our preliminary calculation of the charge distribution, at the B3LYP/6-31G(d) level of theory, of 2-methyl-1,3-thiazolium-4-olate (**1**) and its tautomer 2-methylenethiazolidine-4-one (**2**) (Scheme 1) reveals the nucleophilic character of the exocyclic carbon at C-2 of both heterocycles. The nucleophilicity manifests itself regardless of the computational methodology employed to estimate the charges (Table 1):[6] Mulliken population analysis (MPA), natural population analysis (NPA), electrostatic potential-derived charges using

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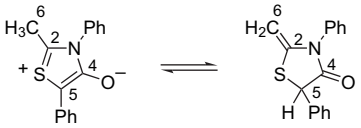
the CHelpG scheme of Breneman (CHelpG), or electrostatic potential-derived charges using the Merz–Kollman–Singh algorithm (MKS).



1 **2**

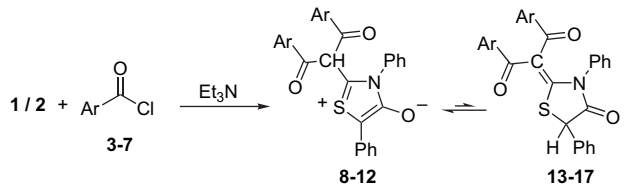
Scheme 1.

Table 1. Charge distribution at the B3LYP/6-31G(d) level on the carbon atoms of compounds **1** and **2**

Heterocycle	Position	MPA	NPA	CHelpG	MKS
1	2	0.13	0.05	0.22	0.28
	4	0.60	0.59	0.52	0.49
	5	−0.37	−0.38	−0.31	−0.32
	6	−0.51	−0.72	−0.15	−0.42
2	2	0.17	0.01	0.24	0.13
	4	0.61	0.71	0.48	0.46
	5	−0.49	−0.47	0.16	−0.17
	6	−0.43	−0.52	−0.47	−0.54

2.1. Reactions with acid chlorides

The simultaneous behavior of the exocyclic double bond of compound **2** as both enamine and vinyl thioether unravels its reactivity toward electrophiles. Thus, when the tautomeric system **1/2** reacts with the aromatic acid chlorides (**3–7**) in CH_2Cl_2 at ambient temperature and in the presence of Et_3N, the resulting 2-heteroaryl-1,3-diketones were obtained as mixtures of tautomers **8–12** and **13–17** (Scheme 2). The process does not stop at monosubstitution, but adds a second molecule of acid chloride, regardless of the amounts of acid chloride and Et_3N employed. The best yields (42–78%) were obtained by using 1 equiv of **1/2** and 2 equiv of both acid chloride and Et_3N. Larger excesses did not improve the above yields to a significant extent. The tautomeric equilibrium is entirely shifted to the mesoionic form in the case of compounds **8**, **9**, and **12**; however, aryl groups with an electron-withdrawing substituent at *para* position still favor the mesoionic structures (**10** and **11**) over the thiazolidinones (**15** and **16**) in a 2.5:1 ratio.



3-7 **8-12** **13-17**

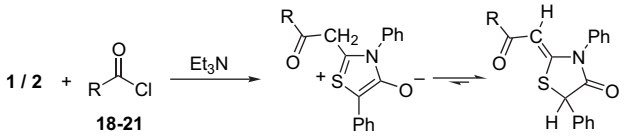
3, 8, 13 Ar = Ph
4, 9, 14 Ar = 4-$MeOC_6H_4$
5, 10, 15 Ar = 4-$NO_2C_6H_4$
6, 11, 16 Ar = 4-ClC_6H_4
7, 12, 17 Ar = 2-FC_6H_4

Scheme 2.

The above procedure represents a novel entry to α,β-unsaturated 2-heteroaryl ketones, which could also be applied to the functionalization of 2-alkyl imidazolidines.[7] In this context, the selective synthesis of α,β-unsaturated ketones remains an interesting challenge in view of their synthetic utility,[8] and some syntheses have been recently reported.[9] Furthermore, the formation of such 2-heteroaryl-1,3-diketones occurs under mild conditions and constitutes an alternative to the use of enolates. In fact, it is known that vinyl or aryl halide does not react with enolates unless strong electron-withdrawing groups are present at *ortho* or *para* position, or under drastic conditions leading to benzynes as intermediates.[10]

1,3-Diketones **8–12** exhibit a singlet at 6.20 ppm attributed to the only non-aromatic proton. For compounds **10** and **11** an additional singlet at 5.30 ppm (H-5 of tautomers **15** and **16**) can also be observed. Striking differences also emerge from their ^{13}C NMR spectra: the exocyclic carbon linked to C-2 lies in the range 88.2–93.2 ppm for **8–12**, whereas that carbon resonates at 144.6 and 141.4 ppm for **15** and **16**, respectively.

When the tautomeric system **1/2** was exposed to aliphatic acid chlorides (**18–21**, 2 equiv) and Et_3N (2 equiv), compounds **26–29** were obtained (Scheme 3) with satisfactory yields (51–70%). Unlike the aryl derivatives, this transformation stops invariably at a monosubstitution stage. The use of acid chloride excess, higher temperatures, or prolonged reaction times did not afford the corresponding 1,3-dicarbonyl compounds at all. Moreover, when **26** was treated with benzoyl chloride (as well as with acetyl chloride), the starting material was recovered unaffected.



18-21 **22-25** **26-29**

18, 22, 26 R = Me
19, 23, 27 R = Et
20, 24, 28 R = Pr
21, 25, 29 R = CH_2OCH_3

Scheme 3.

Only one signal set was observed for **26–29** in their proton NMR spectra. The H-5 proton invariably resonates at 5.10 ppm whereas the olefinic proton lies in the range 5.60–5.90 ppm, substantially more deshielded than those of the methylene group in **2** (4.27 and 4.39 ppm). The ^{13}C resonances for C-4 and C-5 at 173.3 and 50.1 ppm, respectively, also support the tautomeric structure of thiazolidine-4-one of compounds **26–29**. As noted in our preliminary communication,[11] both the *Z* configuration of the exocyclic double bond and the *s-Z* conformational arrangement of the enone moiety were established by X-ray diffraction analysis. Further semiempirical (at the PM3 level) and DFT calculations reveal the greater stability of the non-mesoionic tautomers **26–29** (Table 2).

Although acylation of the exocyclic carbon appears to occur with a complete stereoselection leading to *Z*-configured products, we were also intrigued by the fact that the *Z*- and

Table 2. Energy differences (kcal/mol) between mesoionic (**22–25**) and non-mesoionic tautomers (**26–29**)

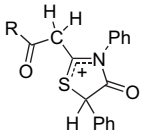
Tautomeric systems	ΔE (PM3)	ΔE (B3LYP/6-31G(d))
22/26	14.58	18.88
23/27	14.83	18.54
24/28	14.14	18.44
25/29	14.83	19.79

Table 3. Energy differences (kcal/mol) between *E*- and *Z*-diastereomer of **26–29**

Compound	ΔE_{E-Z} (PM3)
26	1.18
27	0.94
28	1.05
29	0.60

E-diastereomer of **26–29** are separated by small energy differences as evidenced by a rapid computational screening at the PM3 level (Table 3).

We then sought a stereoelectronic effect forcing the intermediate **30** to adopt a conformation capable of minimizing the steric repulsion between the N–Ph group and the substituent at C-2. The latter would be favored by a non-bonding intramolecular interaction S···O arising from the overlapping of $n_{(C=O)}$ and $\sigma^*_{(C=S)}$ orbitals.[12]



30

Structures **26–29** were first optimized at B3LYP/6-31G(d) level. When energies were plotted against the dihedral angle O=C–C=C, two minima having *Z,s-Z* and *Z,s-E* conformations could be detected (Fig. 1), which display a coplanar arrangement between the carbonyl group and the double bond. The former (*Z,s-Z*) is stabilized by 6.1 kcal/mol with respect to the *Z,s-E* conformer. Furthermore, the non-bonded S···O length is 2.684 Å, in close agreement with crystallographic data (2.699 Å).

2.2. Reactions with heterocumulenes

Pioneering work by Potts et al. in the 1970s showed that 1,3-thiazolium-4-olates may react either with isocyanates or with isothiocyanates affording stable cycloadducts.[13] Hamaguchi and Nagai noted that for thioisomünchnones lacking substituents at C-5 the resulting cycloadducts further evolved to the starting heterocycle after undergoing acylation at C-5.[14] A polycyclic 2-aminothioisomünchnone followed a different pathway nevertheless, leading to six-membered betaines after sulfur extrusion.[15]

When mesoionic compound **1** as well as **31–34** were treated with an equimolar amount of chlorosulfonylisocyanate (**39**) or chlorocarbonylisocyanate (**40**) in CH_2Cl_2 at room temperature for 1–4 h, the resulting conjugated amides **41–45** could be isolated (Scheme 4). It is worth pointing out the absence of chlorosulfonyl or chlorocarbonyl functionalities in products; such labile groups were most likely removed during work-up protocols, which involve chromatographic purification. Moreover, an excess of isocyanate does not add another carboxamido group.

Heterocycles **41–45** do not show the NMR pattern found for the mesoionic tautomers, whilst a series of resonances are consistent with a thiazolidinone moiety: two singlets in the range 4.88–5.54 ppm characteristic of the H-5 proton and the olefinic one (when R^1=H) along with a typical tertiary carbon (C-5) at approximately 50 ppm.

Remarkably, other less reactive isocyanates (**46–48**) and isothiocyanates (**49** and **50**) led likewise to 2-carbamoyl (or 2-thiocarbamoyl)methylenethiazolidin-4-ones (**51–55**) as the sole tautomers, although reactions were only practical in refluxing toluene (Scheme 5). These findings evidence again that an alkyl group at C-2 of 1,3-thiazolium-4-olates has a substantial chemoselective effect enhancing the nucleophilicity of these heterocycles at the expenses of their cycloadditive ability.

The overall process involving 2-alkylthioisomünchnones and iso(thio)cyanates can easily be interpreted as depicted in Scheme 6, i.e., nucleophilic addition of the exocyclic double bond to the heterocumulene carbon giving rise to a dipolar intermediate (**52**) followed by a fast proton exchange that produces the conjugated (thio)amide.

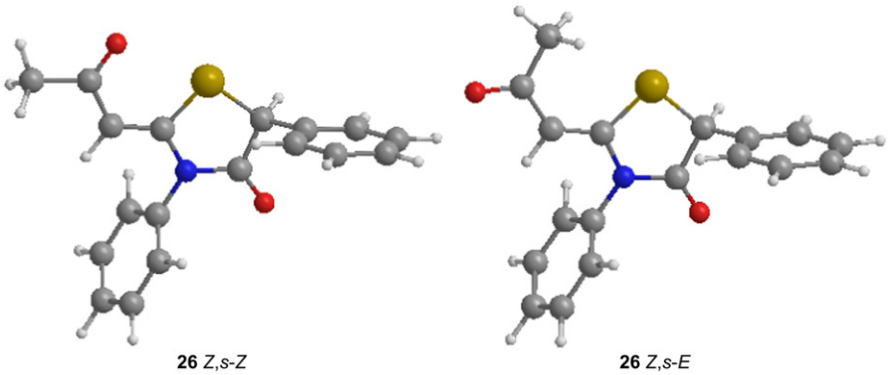
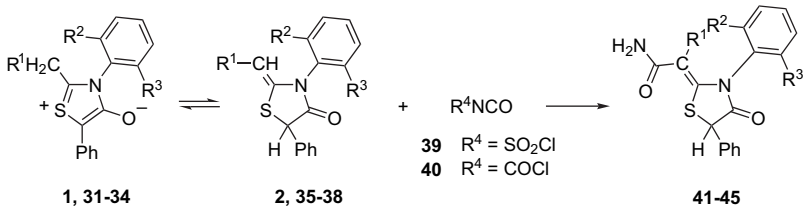
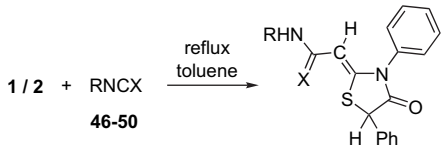


Figure 1. Conformational arrangements (*Z,s-Z* and *Z,s-E*) for compound **26**, whose energies have been refined at the B3LYP/6-31G(d) level.



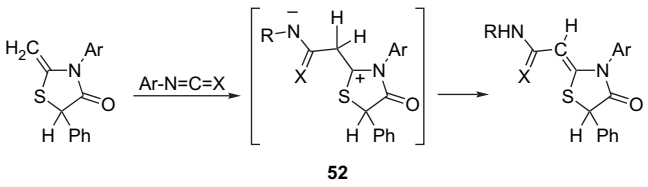
1, 2, 41 $R^1 = R^2 = R^3 = H$
31, 35, 42 $R^1 = H$, $R^2 = R^3 = Me$
32, 36, 43 $R^1 = H$, $R^2 = Me$, $R^3 = Et$
33, 37, 44 $R^1 = Me$, $R^2 = R^3 = H$
34, 38, 45 $R^1 = Et$, $R^2 = R^3 = H$

Scheme 4.



46, 51 R = Ph, X = O
47, 52 R = 2-$NO_2C_6H_4$, X = O
48, 53 R = 4-$NO_2C_6H_4$, X = O
49, 54 R = COOEt, X = S
50, 55 R = 4-$NO_2C_6H_4$, X = S

Scheme 5.



Scheme 6.

Since the amide functionality represents a ubiquitous motif in syntheses oriented to drug discovery,[16] the aforementioned strategy allows for a facile construction of amides and thioamides conjugated with ketene *N*,*S*-ketals, whose synthetic utility will further be pursued in our laboratories.

In conclusion, we have reported the distinctive behavior of 2-alkylthioisomünchnones toward a series of common and reactive electrophiles producing a major functionalization of the parent heterocycle with extended conjugation. These reactions also unmask the nucleophilic character of mesoionics, rather than their usual 1,3-dipolar behavior, which can now be harnessed in a practical way.

3. Experimental

3.1. General methods

Melting points were determined on Gallenkamp and/or Electrothermal apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on precoated Merck 60 GF_{254} silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. Flash chromatography was conducted on Merck 60 silica gel (230–400 mesh). IR spectra were recorded in the range 4000–600 cm^{-1} on a FT-IR MIDAC spectrophotometer. NMR spectra were recorded on Bruker spectrometers operating at 400 MHz for ^1H nuclei or 100 MHz for ^{13}C resonances, in $CDCl_3$ or DMSO-d_6 solutions. Tetramethylsilane (TMS) was used as the internal standard (δ=0.00 ppm). Combustion microanalyses were performed at the University of Extremadura and high-resolution mass spectra at the University of Santiago de Compostela (*Servicio de Espectrometría de Masas*). Geometry optimizations of reactants and transition structures were carried out at the PM3[17] and density functional theory (DFT) levels, the latter using the B3LYP[18] functional and the 6-31G(d)[19] basis set. All calculations were performed using the Gaussian03 package.[20]

3.2. General procedure for the preparation of 1,3-dicarbonyl compounds (8–12/13–17)

To a stirred solution of **1** (50 mg, 0.187 mmol) in CH_2Cl_2 (5.0 mL) were added the corresponding aroyl chloride (0.374 mmol) and Et_3N (52.2 μL, 0.374 mmol). After 48 h at room temperature, analytical TLC (ethyl acetate/hexane 1:2) revealed the disappearance of **1**; the organic phase was then washed with brine (3× 40.0 mL), dried ($MgSO_4$), and evaporated until crystallization was started. Then it was kept into the refrigerator favoring crystals to be formed. They were filtered and washed with diethyl ether to give the title compounds.

3.2.1. 2-Dibenzoylmethyl-3,5-diphenyl-1,3-thiazolium-4-olate (8). Following the above general procedure, the title compound was obtained in 38% yield (yellow crystals). Mp: 204 °C; IR (cm^{-1}): 1759, 1629, 1562; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.26 (m, 18H, Ar-H), 6.21 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.88 (C2), 163.04 (C4), 159.86 (CO), 139.32, 135.14, 134.56, 134.45, 130.53, 130.17, 130.02, 129.74, 129.01, 128.72, 128.23, 128.14, 127.71, 126.93, 126.77, 126.65 (Ar-C), 108.39 (C5), 88.45 (CH) ppm. Anal. Calcd for $C_{30}H_{21}NO_3S$: C, 75.77; H, 4.45; N, 2.95; S, 6.74. Found: C, 75.64; H, 4.51; N, 2.80; S, 6.50.

3.2.2. 2-(Di-4-methoxybenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (9). Following the above general procedure, the title compound was obtained in 73% yield (yellow crystals). Mp: 197 °C (dec); IR (KBr) ν_{max} 1749,

1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–6.84 (m, 18H, Ar-H), 6.15 (s, 1H, CH), 3.83, 3.80 (s, 3H, CH_3O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.03 (C2), 164.56 (C4), 162.59, 161.52 (CO), 159.41, 135.23, 134.23, 132.43, 132.11, 129.96, 129.89, 128.89, 128.71, 128.26, 127.47, 126.48, 118.83, 114.00, 113.28 (Ar-C), 107.85 (C5), 87.95 (CH), 55.49, 55.21 (CH_3O) ppm. Anal. Calcd for $C_{32}H_{25}NO_5S$: C, 71.76; H, 4.70; N, 2.62; S, 5.99. Found: C, 71.98; H, 4.79; N, 2.54; S, 5.83.

3.2.3. 2-(Di-4-nitrobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (10) and 2-(di-4-nitrobenzoyl)methylene-3,5-diphenyl-1,3-thiazolidine-4-one (15). Following the above general procedure, the title tautomers were obtained in 78% yield (red crystals). Mp: 197 °C; IR (KBr) ν_{max} 1772, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25, 8.20, 8.00, 7.90 (d, 8H, Ar-H), 7.54–7.36 (m, 10H, Ar-H), 6.20 (s, 1H, CH, **10**), 5.30 (s, 1H, C5H, **15**) ppm, ratio **10/15**=2:1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.05 (C2), 161.41 (C4), 160.92, 159.89 (CO), 148.79, 134.66, 133.84, 131.29, 130.68, 130.38, 129.26, 128.96, 128.44, 128.03, 127.83, 126.87, 123.96, 123.53 (Ar-C), 144.58 (C2=*C*), 88.89 (CH) ppm. Anal. Calcd for $C_{30}H_{19}N_3O_7S$: C, 63.71; H, 3.39; N, 7.43; S, 5.67. Found: C, 63.92; H, 3.60; N, 7.23; S, 5.66.

3.2.4. 2-(Di-4-chlorobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (11) and 2-(di-4-chlorobenzoyl)-methylene-3,5-diphenyl-1,3-thiazolidine-4-one (16). Following the above general procedure, the title tautomers were obtained in 72% yield (yellow crystals). Mp: 235 °C (dec); IR (KBr) ν_{max} 1757, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07, 7.77, 7.71 (d, 8H, Ar-H), 7.52–7.26 (m, 10H, Ar-H), 6.14 (s, 1H, CH, **11**), 5.29 (s, 1H, C5H, **16**) ppm, ratio **11/16**=2.5:1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.40 (C2), 162.23 (C4), 161.26, 160.11 (CO), 141.39, 137.60, 136.54, 134.96, 134.17, 131.84, 131.47, 130.23, 130.11, 129.47, 129.34, 129.23, 129.08, 128.33, 128.14, 127.93, 126.99, 126.65, 125.04 (Ar-C), 141.39 (C2=*C*), 108.84 (C5), 88.16 (CH) ppm. Anal. Calcd for $C_{30}H_{19}Cl_2NO_3S$: C, 66.18; H, 3.52; N, 2.57; S, 5.89. Found: C, 66.26; H, 3.52; N, 2.31; S, 5.80.

3.2.5. 2-(Di-2-fluorobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (12). The residue obtained after evaporation was purified by flash chromatography (ethyl acetate/hexane, gradient from 1:3 to 1:1), the title compound was obtained as yellow crystals in 49% yield. Mp: 185 °C (ethyl acetate); IR (KBr) ν_{max} 1766, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–6.96 (m, 18H, Ar-H), 6.27 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.65 (C2), 163.41 (C4), 161.75, 160.78 (CO), 160.41, 159.75, 159.26, 136.33, 136.24, 134.93, 134.08, 132.20, 131.72, 131.63, 130.67, 130.06, 129.93, 129.54, 129.02, 128.17, 127.87, 127.62, 127.50, 126.80, 124.27, 127.09, 117.37, 117.16, 116.04, 115.79, 115.37 (Ar-C), 108.90 (C5), 93.19 (CH) ppm. Anal. Calcd for $C_{30}H_{19}F_2NO_3S$: C, 70.44; H, 3.74; N, 2.74; S, 6.27. Found: C, 70.61; H, 3.76; N, 2.58; S, 5.98.

3.3. General procedure for the synthesis of α,β-unsaturated ketones (26–29)

To a stirred solution of **1** (50 mg, 0.187 mmol) in CH_2Cl_2 (5.0 mL) were added the corresponding acid chloride (0.374 mmol) and Et_3N (52.2 μL, 0.374 mmol). After 48 h at room temperature, the solvent was evaporated and the residue was purified by preparative thin-layer or flash chromatography afforded the title compounds.

3.3.1. (*Z*)-2-Acetylmethylene-3,5-diphenyl-1,3-thiazolidin-4-one (26). Following the above general procedure and purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:3) compound **26** was obtained, which was further crystallized from ethyl acetate (52%). Mp: 156 °C (ethyl acetate); IR (KBr) ν_{max} 1720, 1647, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.25 (m, 10H, Ar-H), 5.60 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.11 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.14 (*C*OCH_3), 173.30 (C4), 158.04 (C2), 135.57, 130.13, 129.77, 129.11, 128.65, 128.29, 127.93 (Ar-C), 100.88 (=CH), 50.03 (C5), 30.14 (CO*C*H_3) ppm. Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53; S, 10.36. Found: C, 70.09; H, 5.17; N, 4.38; S, 10.51.

3.3.2. (*Z*)-3,5-Diphenyl-2-propanoylmethylene-1,3-thiazolidin-4-one (27). Following the above procedure and purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:2) compound **27** was obtained, which was further crystallized from ethyl acetate (46%). Mp: 219 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3048, 1714, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.34 (m, 10H, Ar-H), 5.65 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.36 (CH_2CH_3), 1.05 (CH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.57 (CO), 173.30 (C4), 157.63 (C2), 135.66, 135.17, 130.13, 129.75, 129.11, 128.65, 128.32, 127.96 (Ar-C), 100.21 (=CH), 50.09 (C5), 36.12 (CO*C*H_2CH_3), 8.47 ($COCH_2CH_3$) ppm. Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; S, 9.91. Found: C, 70.45; H, 5.37; N, 3.98; S, 9.81.

3.3.3. (*Z*)-2-Butanoylmethylene-3,5-diphenyl-1,3-thiazolidin-4-one (28). Purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:1) yielded **28**, which was further crystallized from ethyl acetate (70%). Mp: 153 °C (ethyl acetate); IR (KBr) ν_{max} 1738, 1718, 1649, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.25 (m, 10H, Ar-H), 5.64 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.32 (t, 2H, $CH_3CH_2CH_2$–), 1.59 (m, 2H, $CH_3CH_2CH_2$–), 0.88 (t, 3H, $CH_3CH_2CH_2$–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.11 (CO), 173.33 (C4), 157.68 (C2), 135.66, 135.18, 130.14, 129.75, 129.11, 128.65, 128.32, 127.96 (Ar-C), 100.56 (=CH), 50.10 (C5), 45.03 (CO*C*H_2–CH_2–CH_3), 18.03 ($COCH_2$–*C*H_2–CH_3), 13.83 ($COCH_2$–CH_2–*C*H_3) ppm. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15; S, 9.50. Found: C, 70.97; H, 5.71; N, 4.26; S, 9.38.

3.3.4. (*Z*)-3,5-Diphenyl-2-methoxyacetylmethylene-1,3-thiazolidin-4-one (29). Purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:3) yielded **29**, which was further crystallized from ethyl acetate (65%). Mp: 147 °C (ethyl acetate); IR (KBr) ν_{max} 1717, 1638, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.26 (m, 10H, Ar-H), 5.92 (s, 1H, =CH), 5.12 (s, 1H, H-5), 3.93 (s, 2H, CH_3OCH_2–), 3.32 (s, 3H, CH_3OCH_2–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.53 (CO), 173.32 (C4), 159.92 (C2), 135.38, 134.93, 130.17, 129.86, 129.17, 128.74, 128.32, 127.86 (Ar-C), 96.71

(=CH), 50.16 (C5) ppm. Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found: C, 67.34; H, 5.12; N, 3.90; S, 9.52.

3.4. Synthesis of carbamoylalkylidene-1,3-thiazolidine-4-ones (41–45)

To a stirred solution of **1** or **31–34** (1.0 mmol) in CH_2Cl_2 (5.0 mL/g) was added chlorosulfonylisocyanate or chlorocarbonylisocyanate (1.2 mmol). After 4 h at room temperature, the solvent was evaporated and the residue was subjected to chromatographic purification.

3.4.1. (*Z*)-2-Carbamoylmethylene-3,5-diphenyl-1,3-thiazolidine-4-one (41). This compound was obtained from **1** following the above procedure, purification by flash chromatography (ethyl acetate/hexane, gradient from 1:5 to 1:1), and further crystallization from ethyl acetate in 58% yield. Mp: 243 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3472, 3344, 1726, 1659 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.61–7.33 (m, 10H, Ar-H), 7.24 (bs, 1H, NH), 6.73 (br s, 1H, NH), 5.38 (s, 1H, =CH), 5.17 (s, 1H, H-5); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.07 (C4), 168.15 ($CONH_2$), 152.75 (C2), 138.00, 136.01, 130.21, 129.59, 129.09, 128.76, 128.71, 128.29 (Ar-C), 95.01 (=CH), 49.24 (C5). Anal. Calcd for $C_{17}H_{14}N_2O_2S\cdot 1/2H_2O$: C, 63.93; H, 4.73; N, 8.77; S, 10.04. Found: C, 64.24; H, 4.64; N, 8.54; S, 10.18.

Compound **41** could also be obtained from **1** and chlorocarbonylisocyanate after chromatographic purification (ethyl acetate/hexane 1:3), and further crystallization from ethyl acetate in 65% yield.

3.4.2. (*Z*)-2-Carbamoylmethylene-3-(2,6-dimethyl)-phenyl-5-phenyl-1,3-thiazolidine-4-one (42). The solution obtained by applying the general procedure to **31** and chlorosulfonylisocyanate was evaporated, and the resulting white crystals were filtered and washed with cold CH_2Cl_2. The title compound isolated in 45% yield was pure enough and had mp: 166 °C (dec); IR (KBr) ν_{max} 3070, 1625, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.45–7.28 (m, 10H, Ar-H), 7.56 (s, 1H, NH), 7.18 (s, 1H, NH), 5.54 (s, 1H, =CH), 5.02 (s, 1H, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.45 (C4), 168.11 ($CONH_2$), 150.07 (C2), 137.45, 136.18, 135.93, 135.75, 133.42, 130.23, 129.72, 129.17, 128.87, 127.99, 127.84, 126.20 (Ar-C), 94.86 (=CH), 48.89 (C5), 17.17, 17.02 (CH_3-Ar) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.24; H, 5.64; N, 8.50; S, 9.38.

3.4.3. (*Z*)-2-Carbamoylmethylene-3-(2-ethyl-6-methyl)-phenyl-5-phenyl-1,3-thiazolidine-4-one (43). The solution obtained by applying the general procedure to **32** and chlorosulfonylisocyanate was evaporated and the residue purified by preparative thin-layer chromatography (ethyl acetate/hexane 1:1). White crystals of **43** (42% yield) were obtained from ethyl acetate. Mp: 183 °C (dec); IR (KBr) ν_{max} 3450, 1735, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.15 (m, 10H, Ar-H), 6.36 (br s, 1H, NH), 5.55 (bs, 1H, NH), 5.12 (s, 1H, H-5), 4.88 (s, 1H, =CH), 2.48 (m, 2H, CH_3CH_2-Ar), 2.10 (s, 3H, CH_3-Ar), 1.05 (t, 3H, CH_3CH_2-Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.56 (C4), 167.25 ($CONH_2$), 150.2 (C2), 135.45, 134.86, 132.64, 131.58, 130.48, 130.12, 128.95, 127.48, 127.05, 125.23 (Ar-C), 94.80 (=CH), 50.15 (C5), 28.9 (CH_3CH_2-Ar), 19.9 (CH_3-Ar), 13.25 (CH_3CH_2-Ar) ppm. Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.10; H, 5.68; N, 8.04; S, 9.28.

3.4.4. (*Z*)-2-(1-Carbamoyl)ethylidene-3,5-diphenyl-1,3-thiazolidine-4-one (44). The solution obtained by applying the general procedure to **33** and chlorosulfonylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:4). The title compound was obtained in crystalline form (60% yield) from ethyl acetate. Mp: 189 °C (dec); IR (KBr) ν_{max} 3148, 1715, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, 1H, NH), 8.38 (d, 1H, NH), 7.67–7.38 (m, 10H, Ar-H), 5.29 (s, 1H, H-5), 2.15 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.30 (C4), 172.18 ($CONH_2$), 149.52 (C2), 137.08, 134.63, 132.63, 129.36, 128.36, 126.86, 126.68, 124.01 (Ar-C), 89.58 (=C), 51.12 (C5), 11.48 (CH_3) ppm. Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.68; H, 4.56; N, 8.84; S, 10.12.

3.4.5. (*Z*)-2-(1-Carbamoyl)propylidene-3,5-diphenyl-1,3-thiazolidine-4-one (45). The solution obtained by applying the general procedure to **34** and chlorosulfonylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:4). Crystals of **45** were isolated from ethyl acetate in 58% yield. Mp: 176 °C (dec); IR (KBr) ν_{max} 3210, 1735, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, 1H, NH), 8.27 (d, 1H, NH), 7.67–7.30 (m, 10H, Ar-H), 5.29 (s, 1H, H-5), 2.65 (q, 2H, CH_2CH_3), 1.19 (t, 3H, CH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.63 (C4), 170.89 ($CONH_2$), 150.85 (C2), 138.25, 137.61, 133.18, 132.47, 129.73, 127.45, 127.08, 124.49, 124.23 (Ar-C), 90.05 (=C), 51.28 (C-5), 14.67 (CH_3CH_2), 11.40 (CH_3CH_2) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.25; H, 5.51; N, 8.34; S, 9.61.

3.5. Synthesis of 2-(*N*-arylcarbamoyl)alkylidene-1,3-thiazolidine-4-ones (51–55)

To a stirred solution of **1** (1.11 mmol) in toluene (5.0 mL) was added the corresponding arylisocyanate (2.2 mmol) and the reaction mixture was refluxed until TLC analysis (ethyl acetate/hexane 1:2) revealed the disappearance of **1** (48–72 h).

3.5.1. (*Z*)-3,5-Diphenyl-2-(*N*-phenylcarbamoyl)methylene-1,3-thiazolidine-4-one (51). The solution obtained by applying the general procedure to **1** and phenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). The title compound was isolated as white crystals from ethyl acetate in 45% yield. Mp: 174 °C (ethyl acetate); IR (KBr) ν_{max} 3205, 1720, 1632, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.55 (s, 1H, NH), 7.57–6.94 (m, 15H, Ar-H), 5.14 (s, 1H, =CH), 4.73 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.41 (C4), 169.81 (CONH), 159.81, 152.15, 138.02, 137.90, 135.26, 134.47, 129.71, 129.41, 129.20, 129.10, 128.86, 128.41, 128.23, 127.38, 123.80, 120.10, 116.67 (Ar-C), 94.80 (=CH), 50.34 (C5). Anal. Calcd for $C_{23}H_{18}N_2O_2S$:

C, 71.48; H, 4.69; N, 7.25; S, 8.30. Found: C, 71.25; H, 4.62; N, 7.34; S, 8.35. HRMS-FAB$^+$, found: 409.0981 ($C_{23}H_{18}N_2O_2S$+Na requires 409.0987), Δ=−0.44 ppm.

3.5.2. (*Z*)-3,5-Diphenyl-2-[*N*-(2-nitrophenyl)carbamoyl]-methylene-1,3-thiazolidine-4-one (52). The solution obtained by applying the general procedure to **1** and *o*-nitrophenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). Compound **52** was isolated as yellowish crystals from ethyl acetate in 58% yield. Mp: 212 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3338, 1720, 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H, NH), 8.85 (d, 1H, Ar-H), 8.16 (dd, 1H, Ar-H), 7.63–7.09 (m, 7H, Ar-H), 5.32 (s, 1H, =CH), 5.16 (s, 1H, H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.81 (C4), 165.38 (CONH), 158.13 (C2), 135.87, 134.90, 130.35, 130.04, 129.10, 128.71, 128.23, 127.95, 125.68, 122.71, 122.01 (Ar-C), 94.92 (=CH), 50.22 (C5). Anal. Calcd for $C_{23}H_{17}N_3O_4S$: C, 64.03; H, 3.97; N, 9.74; S, 7.43. Found: C, 63.89; H, 3.65; N, 10.09; S, 7.33. HRMS-CI$^+$, found: 454.0826 ($C_{23}H_{17}N_3O_4S$+Na requires 454.0832), Δ=1.39 ppm.

3.5.3. (*Z*)-3,5-Diphenyl-2-[*N*-(4-nitrophenyl)carbamoyl]-methylene-1,3-thiazolidine-4-one (53). The solution obtained by applying the general procedure to **1** and *p*-nitrophenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). Yellow crystals of **53** (from ethyl acetate) were collected in 55% yield. Mp: 234 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3337, 1726, 1597, 1554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H, NH), 8.85 (d, 1H, Ar-H), 8.16 (dd, 1H, Ar-H), 7.63–7.09 (m, 7H, Ar-H), 5.35 (s, 1H, =CH), 5.15 (s, 1H, H5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.951 (C4), 168.45 (CONH), 158.02 (C2), 134.57, 133.59, 132.84, 131.08, 130.10, 129.51, 128.89, 127.39, 125.18, 123.91, 123.05 (Ar-C), 95.63 (=CH), 51.85 (C5). Anal. Calcd for $C_{23}H_{17}N_3O_4S$: C, 64.03; H, 3.97; N, 9.74; S, 7.43. Found: C, 64.25; H, 3.75; N, 9.45; S, 7.22.

3.6. Synthesis of 2-(*N*-thiocarbamoyl)alkylidene-1,3-thiazolidine-4-ones (54 and 55)

To a stirred solution of **1** (1.86 mmol) in toluene (8.0 mL) was added the corresponding isothiocyanate (2.2 mmol) and the reaction mixture was refluxed for approximately 36 h (TLC monitoring, ethyl acetate/hexane 1:2, revealed the disappearance of **1**).

3.6.1. (*Z*)-2-(*N*-Ethoxycarbonylthiocarbamoyl)methylene-1,3-thiazolidine-4-one (54). The solution obtained by applying the above procedure to **1** and ethoxycarbonyl isothiocyanate was subsequently cooled at 0 °C. Yellow crystals of the title compound were collected and washed with Et_2O (65% yield). Mp: 223 °C (dec); IR (KBr) ν_{max} 3184, 1739, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, NH), 7.58–7.24 (m, 10H, Ar-H), 7.55 (s, 1H, =CH), 5.10 (s, 1H, H-5), 4.06 (q, 2H, CH_3CH_2O), 1.19 (t, 3H, CH_3CH_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.25 (CSNH), 173.38 (CONH), 165.77 (C4), 149.73, 130.20, 130.01, 129.23, 128.74, 128.41, 127.86 (C-Ar), 104.45 (=CH), 62.12 (CH_3CH_2O), 51.40 (C5), 14.13 (CH_3CH_2O) ppm. Anal. Calcd for $C_{20}H_{18}N_2O_3S_2$: C, 60.28; H, 4.55; N, 7.03; S, 16.09. Found: C, 60.56; H, 4.75; N, 7.27; S, 15.93. HRMS-CI$^+$, found: 398.076984 ($C_{20}H_{18}N_2O_3S_2$ requires 398.07588), Δ=−2.8 ppm.

3.6.2. (*Z*)-2-[*N*-(4-Nitrophenyl)thiocarbamoyl]methylene-1,3-thiazolidine-4-one (55). The solution obtained by applying the general procedure to **1** and *p*-nitrophenyl isothiocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane, gradient from 1:5 to 1:1). Yellow crystals of **55** in 55% yield were obtained in ethyl acetate cooled at −15 °C. Mp: 261 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3316, 2360, 1723 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H, NH), 8.20–7.36 (m, 14H, Ar-H), 6.17 (s, 1H, =CH), 5.44 (s, 1H, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.13 (CSNH), 166.47 (C4), 159.98, 145.73, 143.06, 136.93, 135.81, 130.32, 130.20, 129.72, 129.02, 128.87, 128.23, 124.32, 121.59 (Ar-C), 105.67 (=CH), 50.07 (C5) ppm. Anal. Calcd for $C_{23}H_{17}N_3O_3S_2$: C, 61.73; H, 3.83; N, 9.39; S, 14.33. Found: C, 61.44; H, 3.88; N, 9.29; S, 14.51. HRMS-CI$^+$, found: 447.071481 ($C_{23}H_{17}N_3O_3S_2$ requires 447.07113), Δ=−0.8 ppm.

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