

Efficient One-Pot Synthesis of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylates and Single-Crystal X-Ray Structure of Methyl 2-(Diisopropylamino)-4-phenylthiazole-5-carboxylate

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The reaction between secondary amines, benzoyl isothiocyanate, and dialkyl acetylenedicarboxylates (=dialkyl but-2-ynedioates) in the presence of silica gel (SiO₂) led to alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates in fairly high yields. The structures of the products were confirmed by their IR, ¹H- and ¹³C-NMR, and mass spectra, and by a single-crystal X-ray structure determination.

Introduction. – The thiazoles and their derivatives have attracted the attention of chemists for many years [1][2]. Thiazole derivatives occur widely in a range of natural products. For example, the thiazolium ring present in vitamin B₁ serves as an electron sink, and its coenzyme form is important for the decarboxylation of α -keto acids [3]. Thiazoles and their derivatives are known to exhibit pharmacological activity. Among them, antimicrobial, antihistaminic, antiparasitic, antihelminthic, antipyretic, and antiviral activities were found [4–9]. Aryl-substituted thiazoles are also important organic functional materials such as fluorescent dyes and liquid crystals. Thiazole orange is used as a fluorescent intercalator for determining DNA binding affinity and sequence selectivity of small molecules [10]. Due to their broad utility in the pharmaceutical industry [11–17], the development of novel methods for the synthesis of thiazol-2-amines would provide additional lead molecules for drug discovery. Thiazoles have traditionally been synthesized by the *Hantzsch* synthesis [18][19], but its multi-step character and need to isolate the intermediate such as bromo ketones possessing lacrimatory properties are some of its disadvantages. Recently, powerful methods involving Pd mediated coupling processes have emerged [20–24]; the disadvantages of the methods are the use of toxic and hazardous Pd compounds. Herein, we report a hitherto unknown, one-pot, three-component reaction, which, starting from readily available benzoyl isothiocyanate (**1**), secondary amines **2**, and acetylenedicarboxylates **4**, afforded the alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates **8a–8l**, wherein the catalytic role of SiO₂ powder in the conversion of *S*-vinylated *N*-benzoylisothioureia derivatives **5** to **8a–8l** under solvent-free thermal conditions in fairly high yields was a crucial factor.

Results and Discussion. – Our new synthetic method that led to the title compounds is shown in the *Scheme*. The reaction of *N*-benzoylthiourea derivatives **3**, which were derived from the addition of secondary amines **2** to benzoyl isothiocyanate (**1**), with acetylenedicarboxylates (= but-2-ynedioates) **4** proceeded in CH_2Cl_2 at room temperature to give compound **5**. SiO_2 Powder was found to catalyze the conversion of **5** to the alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates **8** under solvent-free conditions at 90° in fairly good yields without the formation of by-products (*Table 1*).

Scheme. Proposed Mechanism for the Formation of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylate Derivatives

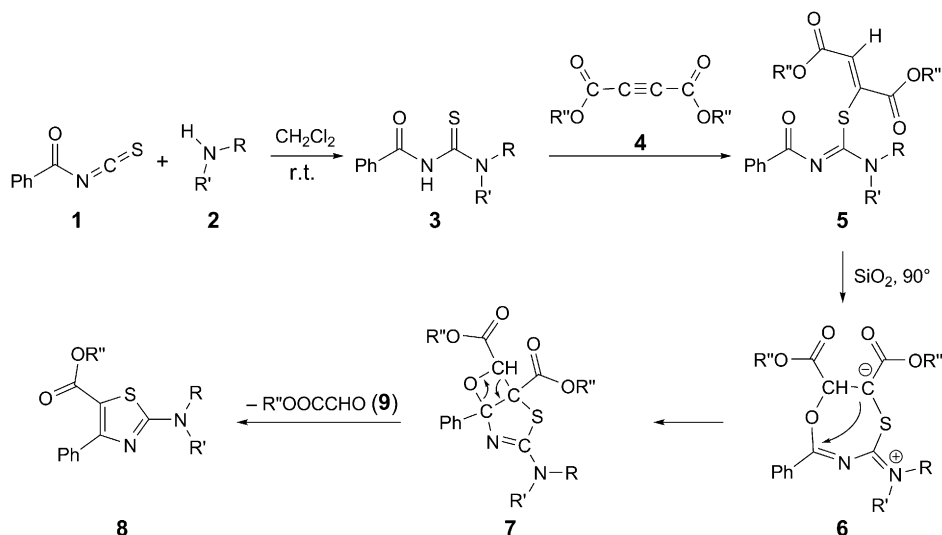


Table 1. *Synthesis of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylates 8 (see Scheme)*

8	R	R'	R''	Yield [%] ^{a)}
a	Et	Et	Me	86
b	Et	Et	Et	85
c	i-Pr	i-Pr	Me	85
d	i-Pr	i-Pr	Et	83
e		(CH ₂) ₅	Me	81
f		(CH ₂) ₅	Et	79
g		(CH ₂) ₂ O(CH ₂) ₂	Me	84
h		(CH ₂) ₂ O(CH ₂) ₂	Et	80
i	Bn	Me	Me	80
j	Bn	Me	Et	77
k	Bn	Bn	Me	78
l	Bn	Bn	Et	75

^{a)} Yield of isolated products.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (*Scheme*).

Presumably, the initial event is the reaction of the secondary amine **2** and benzoyl isothiocyanate (**1**) which leads to a thiourea derivative **3**. After addition of **3** to the acetylenedicarboxylate **4**, the benzoyl O-atom of intermediate **5** attacks the vinyl moiety to give **6**, which undergoes intramolecular nucleophilic attack to produce fused bicyclic compound **7**, which eliminates **9** to give **8**.

To confirm our proposed mechanism, the four intermediates **3a**, **3g**, **3i**, and **3k** were isolated and characterized (Table 2). The latter were then treated with compound **4** to give intermediates **5a**, **5g**, **5i**, and **5k** which were also isolated and characterized (Table 3). The spectroscopic data confirmed the molecular structures of **3a**, **3g**, **3i**, **3k**, **5a**, **5g**, **5i**, and **5k**, and TLC monitoring indicated that **5a**, **5g**, **5i**, and **5k** were converted to the corresponding final products **8a**, **8g**, **8i**, and **8k** in the presence of SiO₂ at 90° after 1 h. In this last step, we also used MgO, ZnO, or CuO, MnO₂, Al₂(SO₄)₃, Al₂O₃, Cu(NO₃)₂, Na₂CO₃, NaHCO₃, NaHSO₄, FeSO₄, Mn(NO₃)₂, or Cu(NO₃)₂ powder instead of SiO₂ but no corresponding product **8** was observed.

Table 2. Synthesis of Some Intermediates **3** by the Two-Component Reaction of **1** and **2** (see Scheme)

3	R	R'	Yield [%] ^{a)}	3	R	R'	Yield [%] ^{a)}
a	Et	Et	97	i	Bn	Me	94
g		(CH ₂) ₂ O(CH ₂) ₂	96	k	Bn	Bn	94

^{a)} Yield of isolated products.

Table 3. Synthesis of Some Intermediates **5** from Two-Component Reaction of Isolated Intermediates **3** and **4** (see Scheme)

5	R	R'	R''	5	R	R'	R''
a	Et	Et	Me	i	Bn	Me	Me
g		(CH ₂) ₂ O(CH ₂) ₂	Me	k	Bn	Bn	Me

The structures of products **8** were confirmed by their IR and ¹H- and ¹³C-NMR spectra, and by a single-crystal X-ray structure determination of **8c**. The mass spectra of these compounds displayed molecular-ion peaks at the appropriate *m/z* values. The ¹H-NMR spectrum (CDCl₃) of **8c** consisted of a *d* for the two Me₂CH groups (δ (H) 1.42, ³*J*(H,H) = 6.9 Hz), a *s* for the MeO group (δ (H) 3.74), a *m* for the two Me₂CH groups (δ (H) 3.92–3.96), and two *m* for the aromatic H-atoms (δ (H) 7.39–7.42 and 7.81–7.84). The ¹H-decoupled ¹³C-NMR spectrum of **8c** showed 11 distinct resonances; a partial assignment of these resonances is given in the *Exper. Part*. The ¹H- and ¹³C-NMR spectra of compounds **8a**–**8l** were similar to those of **8c**, except for the resonances of the R, R', R'' groups which exhibited characteristic signals with appropriate chemical shifts.

In the X-ray crystal structure of compound **8c** (Fig. 1., and Table 4), the COOMe group is planar and is almost coplanar with the plane of the thiazole ring. As seen from the value of the torsion angle S(1)–C(3)–C(4)–O(2) (Table 5), the molecule has the C=O,S *anti*-periplanar conformation. Similarly, the exocyclic N(2)-atom and C(12) and C(15) attached to it, which form a roughly planar moiety, are coplanar with the thiazole ring, due to the conjugation of the N-atom lone pair with the thiazole system, resulting

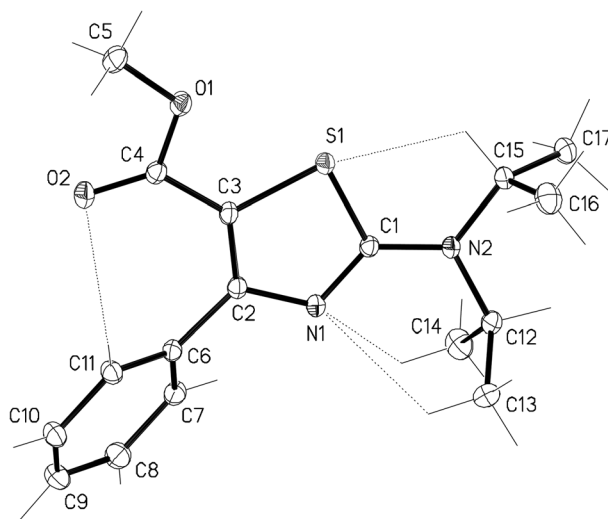


Fig. 1. X-Ray crystal structure of compound **8c**, showing intramolecular C–H···O/N/S H-bonds forming *S*(7), *S*(6), and *S*(5) motifs, respectively (dotted lines). Arbitrary atom numbering; 50% probability ellipsoids.

Table 4. Crystallographic Data of Compound **8c**

Crystallized from	hexane	Scan type	ω and φ
Empirical formula	$C_{17}H_{22}N_2O_2S$	θ Range [°]	4.24–35.00
M_r	318.43	Index range	$-10 \leq h \leq 11$
Crystal color, habit	colorless, block		$-22 \leq k \leq 22$
Crystal dimensions [mm]	$0.55 \times 0.47 \times 0.41$		$-27 \leq l \leq 26$
Radiation type, λ [Å]	MoK α , 0.71073	Measured reflections	26825
Temperature [K]	100(2)	Independent reflections	7301
Crystal system	monoclinic	Reflections with $I > 2\sigma(I)$	6143
Space group	$P2_1/c$	R_{int}	0.023
Z	4	Refinement on	F^2
Unit cell parameters:		Data, restraints, parameters	7301, 0, 287
a [Å]	7.239(3)	$R (F_o^2 > 2\sigma(F_o^2))$	$R_1 = 0.033^a$
b [Å]	13.813(5)		$wR_2 = 0.098^a$
c [Å]	16.780(6)	R (all data)	$R_1 = 0.040$
β [°]	97.31(3)		$wR_2 = 0.100$
V [Å ³]	1664.2(11)	Goodness-of-fit = S	1.07
D_x (calc.) [g cm ⁻³]	1.271	Weighting parameter a/b	0.0692/0.0428
μ [mm ⁻¹]	0.203	$\Delta\rho$ (max; min) [e Å ⁻³]	0.66; -0.29
$F(000)$ [e]	680		

^a) $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR_2 = \sqrt{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]}$. Weighting scheme: $w = 1 / [\sigma(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2) / 3$.

in formal N-sp² hybridization (see also the N(2)–C(1) bond length in Table 5). The N(2)-atom deviates little (0.086 Å) from the plane defined by C(1), C(12), and C(15), and this plane is inclined only slightly (at 5.4(1)°) to the thiazole-ring plane. In contrast,

Table 5. Selected Interatomic Distances, Bond Angles, and Torsion Angles of **8c**

Bond lengths [Å]			
S(1)–C(1)	1.7553(8)	N(2)–C(1)	1.3466(10)
S(1)–C(3)	1.7454(9)	N(2)–C(12)	1.4867(10)
N(1)–C(1)	1.3293(9)	N(2)–C(15)	1.4779(10)
N(1)–C(2)	1.3721(10)	C(2)–C(3)	1.3842(10)
Bond angles [°]			
C(1)–S(1)–C(3)	89.14(4)	C(15)–N(2)–C(12)	118.46(6)
C(1)–N(1)–C(2)	111.31(6)	O(1)–C(4)–C(3)	109.64(6)
C(1)–N(2)–C(15)	119.35(6)	O(2)–C(4)–C(3)	127.54(7)
C(1)–N(2)–C(12)	121.11(6)		
Torsion angles [°]			
C(2)–N(1)–C(1)–N(2)	179.87(6)	C(1)–N(2)–C(12)–C(14)	66.76(9)
C(12)–N(2)–C(1)–N(1)	–10.00(10)	C(15)–N(2)–C(12)–C(14)	–125.18(7)
C(15)–N(2)–C(1)–N(1)	–177.96(6)	C(1)–N(2)–C(12)–C(13)	–61.14(9)
C(12)–N(2)–C(1)–S(1)	169.65(5)	C(15)–N(2)–C(12)–C(13)	106.92(8)
C(15)–N(2)–C(1)–S(1)	1.69(9)	C(1)–N(2)–C(15)–C(16)	95.43(8)
C(5)–O(1)–C(4)–C(3)	–177.69(6)	C(12)–N(2)–C(15)–C(16)	–72.85(8)
S(1)–C(3)–C(4)–O(2)	173.95(6)	C(1)–N(2)–C(15)–C(17)	–137.81(7)
N(1)–C(2)–C(6)–C(11)	138.98(7)	C(12)–N(2)–C(15)–C(17)	53.92(8)

the benzene-ring plane is inclined to a much larger extent (at an angle of 38.9(1)°) to the thiazole-ring plane. The orientation of the isopropyl groups (towards the N(1)- and away from the S(1)-atom) is accompanied by the intramolecular C–H···N/S contacts, as shown in *Fig. 1*.

The crystal structure of **8c** is stabilized by weak C–H···S and C–H··· π interactions involving the benzene ring (*Fig. 2* and *Table 6*). The adjacent molecules located down

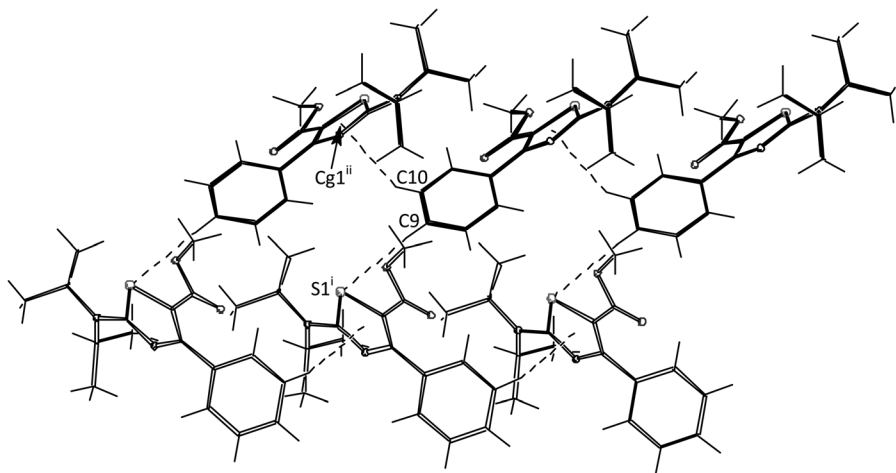


Fig. 2. Arrangement of the molecules within the layers parallel to the (001) plane in the crystal of **8c**. Intermolecular C–H···S and C–H··· π contacts are shown with dashed lines. Intramolecular interactions are omitted for clarity. Symmetry codes are given in *Table 6*.

Table 6. Geometry of Proposed C–H $\cdots\pi$ Close Contacts for **8c**

D–H $\cdots$ A ^{a)}	D–H [Å]	H $\cdots$ A [Å]	D $\cdots$ A [Å]	D–H $\cdots$ A [°]
C(9)–H(9) $\cdots$ S(1) ⁱ	0.98(2)	2.90(2)	3.869(2)	170(1)
C(11)–H(11) $\cdots$ O(2)	0.97(2)	2.48(2)	2.949(2)	110(1)
C(13)–H(13C) $\cdots$ N(1)	0.99(2)	2.58(2)	3.134(2)	115(1)
C(14)–H(14A) $\cdots$ N(1)	0.98(2)	2.52(2)	3.067(2)	115(1)
C(15)–H(15) $\cdots$ S(1)	1.00(2)	2.39(2)	2.984(2)	118(1)
C(10)–H(10) $\cdots$ Cg(1) ⁱⁱ	0.99(2)	2.91(2)	3.614(2)	129(1)

^{a)} Symmetry codes: *i*: $-x, y - 1/2, -z + 1/2$; *ii*: $x - 1, y, z$; Cg(1) is the centroid of the thiazole ring S(1)–C(1)–N(1)–C(2)–C(3).

the *a*-axis are joined with each other via C(10)–H(10) $\cdots\pi$ [Cg(1)]ⁱⁱ contacts. At the same time, the benzene moiety forms a C(9)–H(9) $\cdots$ S(1)ⁱ contact with the neighboring, 2₁-screw-axis-related molecule, giving rise to layers parallel to the (001) plane, as shown in Fig. 2.

Conclusions. – In summary, the reported method offers a mild, simple and efficient route for the preparation of alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates. The easy workup, high yield, and fairly mild reaction conditions, make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

Experimental Part

General. Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography (FC): preparation of columns with Merck silica gel (SiO₂) powder. M.p.: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu-IR-460 spectrometer; $\tilde{\nu}$ in cm^{–1}. ¹H- and ¹³C-NMR Spectra: Bruker-DRX-300-Avance spectrometer; at 300.13 (¹H) and 75.467 MHz (¹³C); in CDCl₃; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. MS: Finnigan-MAT-8430 mass spectrometer; ionization potential 20 eV. Elemental analyses: Heraeus-CHN-O-Rapid analyzer.

X-Ray Crystal-Structure Determination of 8c (Table 4 and Fig. 1)¹⁾. Single crystals of **8c** were prepared in hexane at 40° during two weeks by using the branch-tube method. The white crystals were filtered off, washed with cold hexane, and dried at r.t. (m.p. 105.4°). The crystallographic measurement was performed on a κ -geometry Xcalibur-PX automated four-circle diffractometer with graphite-monochromatized MoK α radiation (λ 0.71073 Å). The data for the crystal were collected at 100(2) K by using an Oxford-Cryosystems cooler. Data collection, cell refinement, and data reduction and analysis were carried out with the Xcalibur-PX software (Oxford Diffraction Ltd.): CrysAlis CCD and CrysAlis RED, resp. [25]. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods with the SHELXS-97 program [26] and refined by a full-matrix least-squares technique by using SHELXL-97 [26] with anisotropic thermal parameters for all non-H-atoms. All H-atoms were found in difference Fourier maps and were refined isotropically. All figures were made with the XP program [27]. A summary of the conditions for the data collection and the structure-refinement parameters are given in Table 4.

¹⁾ CCDC-812743 contains the supplementary crystallographic data for **8c**. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk>.

Compounds 3a, 3g, 3i, and 3k: General Procedure. To a magnetically stirred soln. of benzoyl isothiocyanate (**1**; 0.163 g, 1 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise a soln. of secondary amine **2** (1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. The mixture was stirred for 15 min at r.t. The solvent evaporated and the viscous residue purified by FC (SiO_2 , petroleum ether/AcOEt 10:1): product **3**.

N'-Benzoyl-*N,N*-diethylthiourea (= *N*-[*(Diethylamino)thioxomethyl*]benzamide; **3a**): Yield 230 mg (97%). White crystals. M.p. 96.8–97.6°. IR (KBr): 3209, 3031, 2971, 2930, 1681, 1227. $^1\text{H-NMR}$: 1.33 (br. s, 2 Me); 3.62 (br. s, 2 CH_2); 4.02 (br. s, NH); 7.45–7.50 (*m*, 2 arom. H); 7.55–7.60 (*m*, 1 arom. H); 7.84–7.86 (*m*, 2 arom. H). $^{13}\text{C-NMR}$: 11.51, 13.25 (2 Me); 47.69, 47.78 (2 CH_2); 127.84, 128.82, 132.866 (5 arom. C); 132.75 (C); 164.05 (C=S); 179.61 (C=O).

N'-(Morpholinocarbonothioyl)benzamide (= [*(Morpholin-4-yl)thioxomethyl*]benzamide; **3g**): Yield 241 mg (96%). White crystals. M.p. 129.1–129.8°. IR (KBr): 3243, 3035, 2969, 2923, 1666, 1524, 1268, 1241, 1223, 1114. $^1\text{H-NMR}$: 3.68–3.98 (*m*, 4 CH_2); 4.23 (br. s, NH); 7.47–7.52 (*m*, 2 arom. H); 7.58–7.63 (*m*, 1 arom. H); 7.83–7.86 (*m*, 2 arom. H). $^{13}\text{C-NMR}$: 43.28 ($(\text{CH}_2)_2\text{N}$); 63.79 ($(\text{CH}_2)_2\text{O}$); 127.79, 128.97, 133.18 (5 arom. C); 132.31 (C); 163.23 (C=S); 179.24 (C=O).

N'-Benzoyl-*N*-benzyl-*N*-methylthiourea (= *N*-[*Methyl(phenylmethyl)amino*]thioxomethyl]benzamide; **3i**): Yield 268 mg (94%). White crystals. M.p. 126.7–127.4°. IR (KBr): 3182, 3062, 3028, 2915, 1688, 1543, 1256, 1215, 1183. $^1\text{H-NMR}$: 3.18 (s, Me); 4.81 (br. s, NH); 5.30 (s, CH_2); 7.33–7.60 (*m*, 8 arom. H); 7.87 (br. s, 2 arom. H). $^{13}\text{C-NMR}$: 40.35 (Me); 59.63 (CH_2); 127.91, 128.82, 128.91, 133.10 (10 arom. C); 130.27, 132.51 (2 C); 163.53 (C=S); 181.52 (C=O).

N'-Benzoyl-*N,N*-dibenzylthiourea (= *N*-[*Bis(phenylmethyl)amino*]thioxomethyl]benzamide; **3k**): Yield 341 mg (94%). White crystals. M.p. 142.0–142.9°. IR (KBr): 3329, 3085, 3059, 2952, 2919, 1689, 1515, 1266, 1277, 1192. $^1\text{H-NMR}$: 4.54 (br. s, NH); 4.75 (br. s, 2 CH_2); 7.35–7.50 (*m*, 9 arom. H); 7.57–7.61 (*m*, 3 arom. H); 7.82–7.84 (*m*, 3 arom. H). $^{13}\text{C-NMR}$: 55.82, 56.46 (2 CH_2); 127.77, 127.95, 128.88, 133.08 (15 arom. C); 132.51, 134.72, 135.38 (3 C); 164.24 (C=S); 182.20 (C=O).

Compounds 5a, 5g, 5i, and 5k: General Procedure. To a magnetically stirred soln. of thiourea derivative **3** (1 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise a soln. of dimethyl but-2-enedioate **4** (0.142 g, 1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. The mixture was stirred for 1 h at r.t. The solvent was evaporated and the viscous residue purified by FC (SiO_2 , petroleum ether/AcOEt 10:2): product **5**.

Dimethyl (2*Z*)-2-[[*(Benzoylimino)diethylamino*]methyl]thio]but-2-enedioate (**5a**): Viscous oil. IR (KBr): 3059, 2876, 2949, 1727, 1628, 1546, 1314, 1249, 1203. $^1\text{H-NMR}$: 1.26–1.35 (*m*, 2 MeCH_2); 3.58, 3.79 (2 s, 2 MeO); 3.68–3.79 (*m*, 2 MeCH_2); 6.77 (s, 1 olef. H); 7.36–7.44 (*m*, 2 arom. H); 7.73–7.74 (*m*, 1 arom. H); 7.96–7.98 (*m*, 2 arom. H). $^{13}\text{C-NMR}$: 12.45, 13.22 (2 MeCH_2 , Et_2N); 45.61, 45.77 (2 MeCH_2); 52.23, 53.23 (2 MeO); 127.51 (olef. =CH); 127.67, 129.304, 131.41 (5 arom. C); 136.79, 139.74, 159.66 (3 C); 163.89, 164.59 (2 C=O, ester); 172.01 (C=O, ketone).

Dimethyl (2*Z*)-2-[[*(Benzoylimino)(morpholin-4-yl)methyl*]thio]but-2-enedioate (**5g**): Viscous oil. IR (KBr): 3059, 2654, 2856, 1726, 1545, 1253, 1203. $^1\text{H-NMR}$: 3.64, 3.79 (2 s, 2 MeO); 3.74–3.84 (*m*, 4 CH_2); 6.78 (s, 1 olef. H); 7.35–7.40 (*m*, 2 arom. H); 7.45–7.50 (*m*, 2 arom. H); 7.95–7.98 (*m*, 1 arom. H). $^{13}\text{C-NMR}$: 48.89 ($(\text{CH}_2)_2\text{N}$); 52.30, 53.40 (2 MeO); 66.36 ($(\text{CH}_2)_2\text{O}$); 127.88, 129.43, 131.99 (5 arom. C); 127.98 (olef. =CH); 135.91, 140.56, 158.51 (3 C); 163.80, 164.64 (2 C=O, ester); 173.72 (C=O, ketone).

Dimethyl (2*Z*)-2-[[*(Benzoylimino)[methyl(phenylmethyl)amino]*methyl]thio]but-2-enedioate (**5i**): Viscous oil. IR (KBr): 3060, 3029, 2950, 2855, 1728, 1612, 1548, 1328, 1250, 1200. $^1\text{H-NMR}$: 3.20 (s, MeN); 3.62, 3.80 (2 s, 2 MeO); 4.91 (s, CH_2); 6.82 (s, 1 olef. H); 7.36–7.45 (*m*, 8 arom. H); 7.96–7.99 (*m*, 2 arom. H). $^{13}\text{C-NMR}$: 38.22 (MeN); 52.26, 53.37 (2 MeO); 56.33 (CH_2); 127.78, 128.86, 129.44, 129.85, 131.61 (10 arom. C); 127.93 (olef. =CH); 135.56, 136.44, 139.88, 161.23 (4 C); 163.96, 164.57 (2 C=O, ester); 172.48 (C=O, ketone).

Dimethyl (2*Z*)-2-[[*(Benzoylimino)[bis(phenylmethyl)amino]*methyl]thio]but-2-enedioate (**5k**): Viscous oil. IR (KBr): 3060, 3030, 2948, 2926, 1724, 1631, 1534, 1313, 1252, 1199. $^1\text{H-NMR}$: 3.61, 3.81 (2 s, 2 MeO); 4.85, 4.89 (2 s, 2 CH_2); 6.84 (s, 1 olef. H); 7.34–7.45 (*m*, 12 arom. H); 7.89–7.92 (*m*, 3 arom. H). $^{13}\text{C-NMR}$: 52.30, 53.40 (2 Me); 52.99, 53.12 (2 CH_2); 127.75, 128.95, 129.43, 129.65, 131.99 (15 arom. C); 127.86 (olef. =CH); 134.90, 135.58, 136.34, 139.36, 160.69 (5 C); 163.81, 164.50 (2 C=O, ester); 172.72 (C=O, ketone).

Compounds 8a–8l: General Procedure. To a stirred soln. of benzoyl isothiocyanate (**1**; 0.163 g, 1 mmol) and secondary amine **2** (1 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise a mixture of dialkyl

but-2-ynedioate **4** (1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. Then, after 0.5 h, SiO_2 powder (2 g) was added, and the solvent was evaporated. The dry materials were heated for 1 h at 90° and then placed on top of a column of SiO_2 (10 g). The column was washed with AcOEt/light petroleum ether 2 : 10. The solvent was then evaporated: product **8**.

Methyl 2-(Diethylamino)-4-phenylthiazole-5-carboxylate (8a): Yield 250 mg (86%). White crystals. M.p. 81.4° . IR (KBr): 3054, 3025, 2974, 2934, 1710, 1600, 1511, 1481, 1331, 1263. $^1\text{H-NMR}$: 1.26 (t, $^3J = 6.9$, 2 MeCH_2); 3.54–3.57 (m, 2 MeCH_2); 3.73 (s, MeO); 7.39 (br., 3 arom. H); 7.75 (br., 2 arom. H). $^{13}\text{C-NMR}$: 12.49 (2 MeCH_2); 45.46 (2 MeCH_2); 51.61 (MeO); 127.51, 128.88, 129.80 (5 arom. C); 133.15, 134.99, 160.56, 162.47 (4 C); 169.45 (C=O). EI-MS: 290 (50, M^+), 275 (12), 261 (39), 247 (77), 229 (15), 215 (23), 201 (13), 149 (21), 133 (32), 103 (28), 89 (39), 57 (42), 42 (100). Anal. calc. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (290.38): C 62.04, H 6.25, N 9.65; found: C 61.24, H 6.14, N 8.86.

Ethyl 2-(Diethylamino)-4-phenylthiazole-5-carboxylate (8b): Yield 259 mg (85%). White crystals. M.p. 90.1° . IR (KBr): 3051, 2975, 2929, 1698, 1551, 1330, 1258. $^1\text{H-NMR}$: 1.23–1.31 (m, 3 MeCH_2); 3.56 (q, $^3J = 7.2$, 2 MeCH_2N); 4.20 (q, $^3J = 7.2$, MeCH_2O); 7.38–7.40 (m, 3 arom. H); 7.75–7.76 (m, 2 arom. H). $^{13}\text{C-NMR}$: 12.49 (2 MeCH_2N); 14.28 (MeCH_2O); 45.41 (2 MeCH_2N); 60.38 (MeCH_2O); 127.44, 128.77, 129.84 (5 arom. C); 133.44, 135.14, 160.19, 162.10 (4 C); 169.41 (C=O). EI-MS: 304 (100, M^+), 289 (12), 275 (35), 261 (80), 247 (17), 232 (27), 215 (17), 202 (12), 188 (14), 133 (23), 103 (18), 89 (33), 71 (14). Anal. calc. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (304.41): C 63.13, H 6.62, N 9.20; found: C 63.4, H 6.56, N 8.93.

Methyl 2-[Bis(1-methylethyl)amino]-4-phenylthiazole-5-carboxylate (8c): Yield 271 mg (85%). White crystals. M.p. 105.4° . IR (KBr): 3020, 2965, 2929, 1706, 1600, 1526, 13331, 1258. $^1\text{H-NMR}$: 1.42 (d, $^3J = 6.9$, 2 MeCH_2); 3.74 (s, MeO); 3.91–3.96 (m, 2 (Me) $_2\text{CH}$); 7.37–7.45 (m, 3 arom. H); 7.81–7.84 (m, 2 arom. H). $^{13}\text{C-NMR}$: 20.02 (Me_2CH); 51.15 (MeO); 51.44 (2 Me_2CH); 127.38, 128.78, 129.95 (5 arom. C); 130.86, 135.13, 160.05, 162.62 (4 C); 168.01 (C=O). EI-MS: 318 (44, M^+), 261 (28), 234 (100), 57 (38), 41 (55). Anal. calc. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (318.43): C 64.12, H 6.96, N 8.80; found: C 63.87, H 6.71, N 8.65.

Ethyl 2-[Bis(1-methylethyl)amino]-4-phenylthiazole-5-carboxylate (8d): Yield 278 mg (83%). White crystals. M.p. 90.5° . IR (KBr): 3080, 3047, 2966, 2930, 1700, 1603, 1529, 1260. $^1\text{H-NMR}$: 1.27 (t, $^3J = 7.1$, MeCH_2); 1.42 (d, $^3J = 6.9$, Me_2CH); 3.91–3.95 (m, 2 Me_2CH); 4.21 (q, $^3J = 7.1$, MeCH_2); 7.38–7.41 (m, 3 arom. H); 7.81–7.84 (m, 2 arom. H). $^{13}\text{C-NMR}$: 14.34 (MeCH_2); 20.04 (2 Me_2CH); 51.14 (MeCH_2); 60.31 (2 Me_2CH); 127.32, 128.68, 129.99 (5 arom. C); 130.87, 135.28, 159.76, 162.25 (4 C); 167.98 (C=O). EI-MS: 332 (58, M^+), 289 (100), 275 (86), 261 (18), 247 (21), 229 (15), 174 (15), 148 (35), 129 (17), 103 (28), 39 (21), 43 (24). Anal. calc. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ (332.46): C 65.03, H 7.28, N 8.43; found: C 64.21, H 6.46, N 8.01.

Methyl 4-Phenyl-2-(piperidin-1-yl)thiazole-5-carboxylate (8e): Yield 244 mg (81%). White crystals. M.p. 90.7° . IR (KBr): 3065, 2997, 2962, 2946, 1715, 1531, 1482, 1340, 1303, 1245, 1145. $^1\text{H-NMR}$: 1.67–1.72 (m, 3 CH_2 (pip)); 3.57–3.59 (m, 2 CH_2 (pip)); 3.74 (s, Me); 7.39–7.41 (m, 3 arom. H); 7.74–7.77 (m, 2 arom. H). $^{13}\text{C-NMR}$: 23.99, 25.12, 49.17 (5 CH_2); 51.53 (MeO); 127.54, 128.90, 129.76 (5 arom. C); 130.86, 134.91, 160.38, 162.44 (5 C); 170.90 (C=O). EI-MS: 302 (25, M^+), 273 (14), 246 (17), 167 (17), 149 (39), 84 (21), 58 (41), 43(100). Anal. calc. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (302.39): C 63.55, H 6.00, N 9.26; found: C 62.10, H 5.82, N 9.00.

Ethyl 4-Phenyl-2-(piperidin-4-yl)thiazole-5-carboxylate (8f): Yield 249 mg (79%). Viscous oil. IR (KBr): 3056, 2936, 2855, 1708, 1677, 1532, 1243. $^1\text{H-NMR}$: 1.25 (t, $^3J = 7.0$, MeCH_2); 1.66–1.71 (m, 3 CH_2 (pip)); 3.58–3.57 (m, 2 CH_2 (pip)); 4.20 (q, $^3J = 7.0$, MeCH_2); 7.38–7.40 (m, 3 arom. H); 7.73–7.76 (m, 2 arom. H). $^{13}\text{C-NMR}$: 14.25 (MeCH_2); 23.76, 25.13, 49.17 (5 CH_2 (pip)); 60.46 (MeCH_2); 127.49, 128.82, 129.79 (5 arom. C); 130.86, 134.10, 159.99, 162.05 (4 C); 170.84 (C=O). EI-MS: 318 (60, M^+), 275 (100), 261 (96), 299 (20), 201 (13), 174 (15), 129 (15), 104 (13), 89 (18), 43 (32). Anal. calc. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (316.42): C 64.53, H 6.37, N 8.85; found: C 64.26, H 6.21, N 8.73.

Methyl 2-(Morpholin-4-yl)-4-phenylthiazole-5-carboxylate (8g): Yield 255 mg (84%). White crystals. M.p. 130.0° . IR (KBr): 3065, 2955, 2924, 1735, 1534, 1483, 1237, 1114. $^1\text{H-NMR}$: 3.59–3.62 (m, $(\text{CH}_2)_2\text{N}$); 3.75 (s, Me); 3.82–3.83 (m, $(\text{CH}_2)_2\text{O}$); 7.39 (br, 3 arom. H); 7.72 (br, 2 arom. H). $^{13}\text{C-NMR}$: 51.74 (Me); 47.99 ($(\text{CH}_2)_2\text{N}$); 66.04 ($(\text{CH}_2)_2\text{O}$); 127.63, 129.15, 129.760 (5 arom. C); 133.48, 135.01, 160.74, 162.74 (4 C); 170.02 (C=O). EI-MS: 304 (100, M^+), 285 (6), 273 (20), 259 (18), 247 (70), 231 (13), 215 (28), 201

(8), 133 (23), 89 (28), 76 (10). Anal. calc. for $C_{15}H_{16}N_2O_3S$ (304.36): C 59.19, H 5.30, N 9.20; found: C 59.02, H 5.16, N 9.17.

Ethyl 2-(Morpholin-4-yl)-4-phenylthiazole-5-carboxylate (8h): Yield 254 mg (80%). White crystals. M.p. 90.0–91.0°. IR (KBr): 3053, 2980, 2924, 1708, 1528, 1482, 1368, 1250. 1H -NMR: 1.27 (*t*, $^3J = 7.2$, $MeCH_2$); 3.59–3.62 (*m*, $(CH_2)_2N$); 3.81–3.85 (*m*, $(CH_2)_2O$); 4.21 (*q*, $^3J = 7.2$, $MeCH_2$); 7.39–7.41 (*m*, 3 arom. H); 7.72–7.74 (*m*, 2 arom. H). ^{13}C -NMR: 14.21 ($MeCH_2$); 47.98 ($(CH_2)_2N$); 60.70 ($MeCH_2$); 66.05 ($(CH_2)_2O$); 127.56, 129.02, 129.78 (5 arom. H); 133.56, 135.31, 160.85, 162.90 (4 C); 170.41 (C=O). EI-MS: 318 (100, M^+), 304 (7), 289 (9), 273 (27), 260 (73), 246 (24), 232 (32), 215 (29), 188 (41), 133 (71), 105 (52), 39 (85), 77 (29), 56 (40). Anal. calc. for $C_{16}H_{18}N_2O_3S$ (318.39): C 60.36, H 5.70, N 8.80; found: C 60.27, H 5.61, N 8.73.

Methyl 2-[Methyl(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8i): Yield 270 mg (80%). White crystals. M.p. 77.2°. IR (KBr): 3025, 2984, 2943, 1710, 1604, 1550, 1330, 1244. 1H -NMR: 3.11 (*s*, MeN); 3.75 (*s*, MeO); 4.79 (*s*, CH_2N); 7.33–7.42 (*m*, 8 arom. H); 7.79–7.80 (*m*, 2 arom. H). ^{13}C -NMR: 37.88 (MeN); 51.61 (MeO); 55.97 (CH_2N); 127.57, 127.74, 127.86, 128.81, 129.87 (10 arom. C); 129.01, 134.77, 136.01, 160.41, 162.38 (5 C); 170.96 (C=O). EI-MS: 338 (85, M^+), 329 (47), 309 (37), 247 (11), 215 (24), 188 (14), 146 (18), 120 (15), 103 (13), 91 (100), 77 (13), 65 (17). Anal. calc. for $C_{19}H_{18}N_2O_2S$ (338.42): C 67.43, H 5.36, N 8.28; found: C 67.36, H 5.30, N 8.10.

Ethyl 2-[Methyl(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8j): Yield 271 mg (77%). White crystals. M.p. 73.2°. IR (KBr): 3059, 2983, 2926, 1702, 1605, 1550, 1331, 1242. 1H -NMR: 1.25 (*t*, $^3J = 7.0$, $MeCH_2$, EtO); 3.10 (*s*, MeN); 4.211 (*q*, $^3J = 7.0$, $MeCH_2$); 7.32–7.39 (*m*, 8 arom. H); 7.78–7.79 (*m*, 2 arom. H). ^{13}C -NMR: 14.29 ($MeCH_2$); 37.89 (MeN); 55.93 (CH_2N); 60.55 ($MeCH_2$); 127.52, 127.73, 127.83, 128.79, 129.90 (10 arom. C); 128.93, 134.89, 136.07, 160.07, 162.17 (5 C); 170.90 (C=O). EI-MS: 352 (27, M^+), 327 (13), 323 (14), 279 (8), 215 (10), 167 (26), 149 (86), 104 (100), 91 (58), 70 (54), 57 (34), 43 (48). Anal. calc. for $C_{20}H_{20}N_2O_2S$ (352.45): C 68.16, H 5.72, N 7.95; found: C 68.02, H 5.64, N 7.81.

Methyl 2-[Bis(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8k): Yield 322 mg (77%). White crystals. M.p. 107.6°. IR (KBr): 3061, 32029, 2936, 1677, 1604, 1528, 1310, 1263. 1H -NMR: 3.73 (*s*, Me); 4.72 (*s*, 2 CH_2); 7.29–7.40 (*m*, 12 arom. H); 7.80–7.3 (*m*, 3 arom. H). ^{13}C -NMR: 51.59 (Me); 53.40 (2 CH_2); 127.55, 127.89, 128.81, 129.94 (15 arom. C); 129.05, 134.68, 135.75, 160.10, 162.31 (6 C); 171.12 (C=O). EI-MS: 414 (20, M^+), 323 (82), 291 (8), 149 (4), 133 (7), 105 (6), 91 (100), 65 (12). Anal. calc. for $C_{25}H_{22}N_2O_2S$ (414.52): C 72.44, H 5.35, N 6.76; found: C 68.02, H 5.64, N 7.81.

Ethyl 2-[Bis(phenylmethyl)amino]-4-phenylthiazole-5-carboxylate (8l): Yield 321 mg (75%). White crystals. M.p. 73.1°. IR (KBr): 3060, 3028, 2978, 2912, 1708, 1534, 1481, 1331, 1237. 1H -NMR: 1.25 (*t*, $^3J = 7.1$, $MeCH_2$); 4.21 (*q*, $^3J = 7.1$, $MeCH_2$); 4.73 (*s*, $(CH_2)_2N$); 7.27–7.40 (*m*, 12 arom. H); 7.82–7.83 (*m*, 3 arom. H). ^{13}C -NMR: 14.28 ($MeCH_2$); 53.32 (CH_2N); 60.57 ($MeCH_2$); 127.50, 127.87, 127.89, 128.80, 129.98 (15 arom. C); 128.97, 134.81, 135.82, 159.78, 161.96 (6 C); 171.10 (C=O). EI-MS: 428 (3, M^+), 337 (7), 279 (4), 206 (8), 191 (15), 167 (20), 149 (66), 105 (91), 91 (73), 70 (98), 59 (97), 48 (100). Anal. calc. for $C_{26}H_{24}N_2O_2S$ (428.55): C 72.87, H 5.64, N 6.54; found: C 72.75, H 5.56, N 6.41.

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