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 (SiO_2) led to alkyl 2-(dialkylamino)-4-phenylthiazole-5-carboxylates in fairly high yields. The structures of the products were confirmed by their IR, ^{1}H- and ^{13}C-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 B_1 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 SiO_2 powder in the conversion of *S*-vinylated *N*-benzoylisothiourea 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*

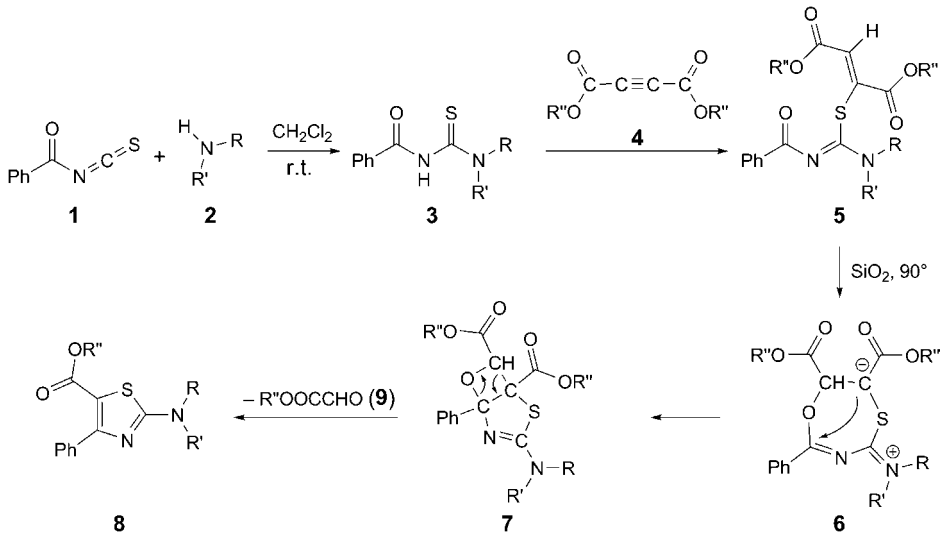

Table 1. *Synthesis of Alkyl 2-(Dialkylamino)-4-phenylthiazole-5-carboxylates* **8** (see *Scheme*)

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	$(CH_2)_2O(CH_2)_2$		Me	84
h	$(CH_2)_2O(CH_2)_2$		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 SiO_2 at 90° after 1 h. In this last step, we also used MgO, ZnO, or CuO, MnO_2, $Al_2(SO_4)_3$, Al_2O_3, $Cu(NO_3)_2$, Na_2CO_3, $NaHCO_3$, $NaHSO_4$, $FeSO_4$, $Mn(NO_3)_2$, or $Cu(NO_3)_2$ powder instead of SiO_2 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		$(CH_2)_2O(CH_2)_2$	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		$(CH_2)_2O(CH_2)_2$	Me	**k**	Bn	Bn	Me

The structures of products **8** were confirmed by their IR and ^{1}H- and ^{13}C-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 ^{1}H-NMR spectrum ($CDCl_3$) of **8c** consisted of a *d* for the two Me_2CH groups (δ(H) 1.42, ^3J(H,H) = 6.9 Hz), a *s* for the MeO group (δ(H) 3.74), a *m* for the two Me_2CH 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 ^{1}H-decoupled ^{13}C-NMR spectrum of **8c** showed 11 distinct resonances; a partial assignment of these resonances is given in the *Exper. Part*. The ^{1}H- and ^{13}C-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

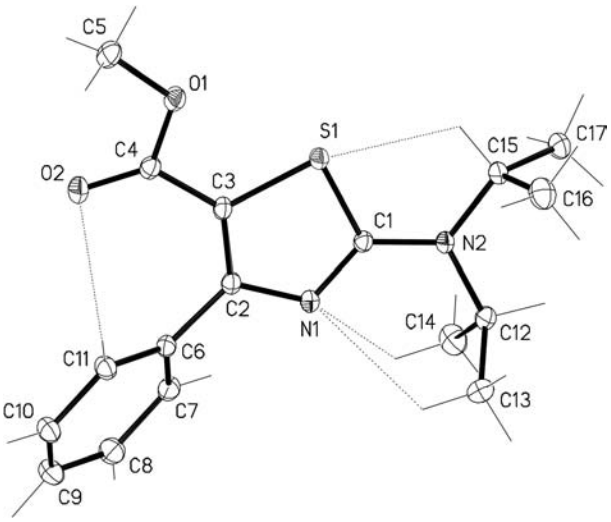

Fig. 1. *X-Ray crystal structure of compound* **8c**, *showing intramolecular C–H ··· O/N/S H-bonds forming S(7), S(6), and S(5) motifs, respectively* (dotted lines). Arbitrary atom numbering; 50% probability ellipsoids.

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	$-10 \le h \le 11$
Crystal color, habit	colorless, block		$-22 \le k \le 22$
Crystal dimensions [mm]	$0.55 \times 0.47 \times 0.41$		$-27 \le l \le 26$
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-sp^2 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

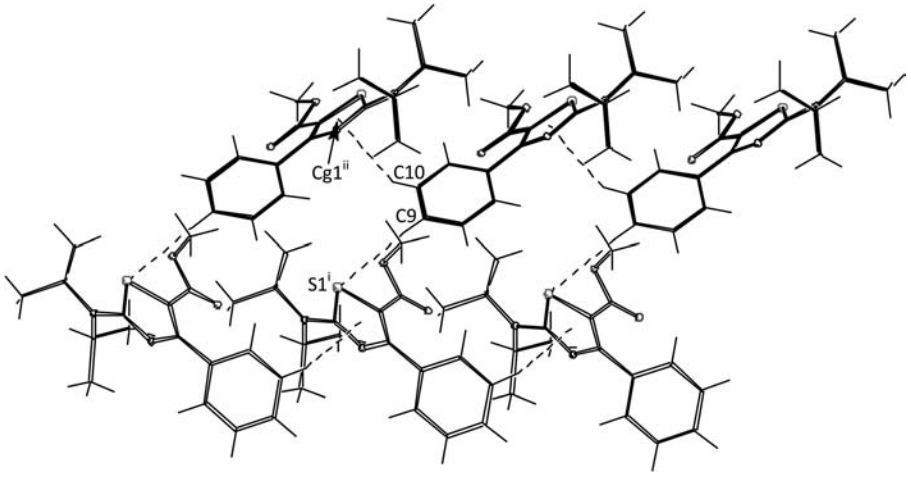

Fig. 2. *Arrangement of the molecules within the layers parallel to the (001) plane in the crystal of* **8c**. Intermolecular C–H ··· S and C–H ··· π contacts are shown with dashed lines. Intramolecular interactions are omitted for clarity. Symmetry codes are given in *Table 6*.

Table 6. *Geometry of Proposed C–H···π Close Contacts for* **8c**

D–H···A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
C(9)–H(9)···S(1)^{i}	0.98(2)	2.90(2)	3.869(2)	170(1)
C(11)–H(11)···O(2)	0.97(2)	2.48(2)	2.949(2)	110(1)
C(13)–H(13C)···N(1)	0.99(2)	2.58(2)	3.134(2)	115(1)
C(14)–H(14A)···N(1)	0.98(2)	2.52(2)	3.067(2)	115(1)
C(15)–H(15)···S(1)	1.00(2)	2.39(2)	2.984(2)	118(1)
C(10)–H(10)···*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)···π[*Cg*(1)]^{ii} contacts. At the same time, the benzene moiety forms a C(9)–H(9)···S(1)^{i} contact with the neighboring, 2_1-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 (SiO_2) powder. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-DRX-300-Avance* spectrometer; at 300.13 (^1H) and 75.467 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si 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_a 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*.

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[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}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}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}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}C-NMR: 43.28 ((CH_2)$_2$N); 63.79 ((CH_2)$_2$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}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}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}H-NMR: 4.54 (br. *s*, NH); 4.75 (br, 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}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 (3C); 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-ynedioate **4** (0.142 g,1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 2 min. The mixture was stirred for 1h at r.t. The solvent was evaporated and the viscous residue purified by FC (SiO_2, petroleum ether/AcOEt 10:2): product **5**.

Dimethyl (2Z)-2-{[(Benzoylimino)(diethylamino)methyl]thio}but-2-enedioate (**5a**): Viscous oil. IR (KBr): 3059, 2876, 2949, 1727, 1628, 1546, 1314, 1249, 1203. ^{1}H-NMR: 1.26–1.35 (*m*, 2 *Me*CH2); 3.58, 3.79 (2 *s*, 2 MeO); 3.68–3.79 (*m*, 2 MeC*H*$_2$); 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}C-NMR: 12.45, 13.22 (2 *Me*CH$_2$, Et$_2$N); 45.61, 45.77 (2 Me*C*H$_2$); 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 (2Z)-2-{[(Benzoylimino)(morpholin-4-yl)methyl]thio}but-2-enedioate (**5g**): Viscous oil. IR (KBr): 3059, 2654, 2856, 1726, 1545, 1253, 1203. ^{1}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}C-NMR: 48.89 ((CH_2)$_2$N); 52.30, 53.40 (2 MeO); 66.36 ((CH_2)$_2$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 (2Z)-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}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}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 (2Z)-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}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}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}H-NMR: 1.26 (*t*, ^3J = 6.9, 2 *Me*CH_2); 3.54 – 3.57 (*m*, 2 Me*C*H_2); 3.73 (*s*, MeO); 7.39 (br., 3 arom. H); 7.75 (br., 2 arom. H). ^{13}C-NMR: 12.49 (2 *Me*CH_2); 45.46 (2 Me*C*H_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 $C_{15}H_{18}N_2O_2S$ (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}H-NMR: 1.23 – 1.31 (*m*, 3 *Me*CH_2); 3.56 (*q*, ^3J = 7.2, 2 Me*C*H_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}C-NMR: 12.49 (2 *Me*CH_2N); 14.28 (*Me*CH_2O); 45.41 (2 Me*C*H_2N); 60.38 (Me*C*H_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 $C_{16}H_{20}N_2O_2S$ (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}H-NMR: 1.42 (*d*, ^3J = 6.9, 2 *Me*CH_2); 3.74 (*s*, MeO); 3.91 – 3.96 (*m*, 2 $(Me)_2C$*H*); 7.37 – 7.45 (*m*, 3 arom. H); 7.81 – 7.84 (*m*, 2 arom. H). ^{13}C-NMR: 20.02 (*Me*$_2$CH); 51.15 (MeO); 51.44 (2 Me$_2$*C*H); 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 $C_{17}H_{22}N_2O_2S$ (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}H-NMR: 1.27 (*t*, ^3J = 7.1, *Me*CH_2); 1.42 (*d*, ^3J = 6.9, *Me*$_2$CH); 3.91 – 3.95 (*m*, 2 Me$_2$C*H*); 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}C-NMR: 14.34 (*Me*CH_2); 20.04 (2 *Me*$_2$CH); 51.14 (Me*C*H_2); 60.31 (2 Me$_2$*C*H); 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 $C_{18}H_{24}N_2O_2S$ (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}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}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 $C_{16}H_{18}N_2O_2S$ (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}H-NMR: 1.25 (*t*, ^3J = 7.0, *Me*CH_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}C-NMR: 14.25 (*Me*CH_2); 23.76, 25.13, 49.17 (5 CH_2 (pip)); 60.46 (Me*C*H_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 $C_{17}H_{20}N_2O_2S$ (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}H-NMR: 3.59 – 3.62 (*m*, $(CH_2)_2$N); 3.75 (*s*, Me); 3.82 – 3.83 (*m*, $(CH_2)_2$O); 7.39 (br, 3 arom. H); 7.72 (br, 2 arom. H). ^{13}C-NMR: 51.74 (Me); 47.99 ($(CH_2)_2$N); 66.04 ($(CH_2)_2$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. ^{1}H-NMR: 1.27 (*t*, $^3J = 7.2$, *Me*CH_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 (*Me*CH_2); 47.98 ($(CH_2)_2N$); 60.70 (Me*C*H_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. ^{1}H-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. ^{1}H-NMR: 1.25 (*t*, $^3J =$ 7.0, *Me*CH_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 (*Me*CH_2); 37.89 (MeN); 55.93 (CH_2N); 60.55 (Me*C*H_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. ^{1}H-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. ^{1}H-NMR: 1.25 (*t*, $^3J =$ 7.1, *Me*CH_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 (*Me*CH_2); 53.32 $(CH_2)_2N$); 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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