One-Pot, Pseudo-Five-Component Synthesis of Bis[2-(arylimino)-1,3-thiazolidin-4-ones]

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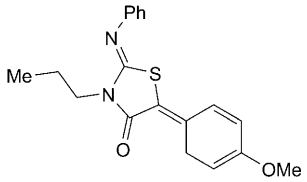
Synthesis and characterization of bis[2-(arylimino)-1,3-thiazolidin-4-ones] are described. The one-pot, pseudo-five-component reaction of an aliphatic diamine, isothiocyanatobenzene, and dialkyl but-2-ynedioate at room temperature in anhydrous CH_2Cl_2 gives the title compound in relatively high yield. Under the same conditions, aromatic 1,2-diamines yield 2-(arylimino)-*N*-(enaminoaryl)-1,3-thiazolidin-4-ones in a pseudo-four-component reaction. Their structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of cyclization is proposed (*Scheme 3*).

1. Introduction. – The multi-component coupling reactions are emerging as a useful tool for synthesizing small, drug-like molecules with several levels of structural diversity [1]. They are also welcome in the context of economic and practical considerations. Moreover, multicomponent coupling strategies offer significant advantages over conventional linear-type syntheses [2].

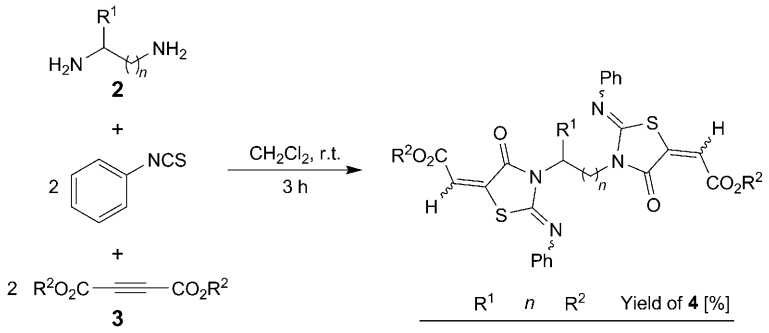
Among small-molecule heterocyclic compounds, thiazolidine is a recognized scaffold for potential drugs and drug candidates. Anticonvulsant, sedative, antidepressant, anti-inflammatory, antihypertensive, antihistaminic, and antiarthritic activities are a few among many biological responses shown by this scaffold [3]. In particular, 2-imino-1,3-thiazolidin-4-ones are known to possess remarkable hypnotic, antitubercular, and cardiovascular activities [4–6]. For example, 5-(4-methoxycyclohexa-2,4-dien-1-ylidene)-2-(phenylimino)-3-propyl-1,3-thiazolidin-4-one (**1**) is known to have potent anti-inflammatory (COX inhibitor) activity [7]. This diversity in the biological response profiles of thiazolidine derivatives has attracted the attention of many researchers to explore this skeleton.



1 (Anti-inflamatory agent)

2. Results and Discussion. – Some of our previous works included the use of aliphatic and aromatic diamines to synthesize important heterocycles of potential synthetic and pharmacological interest [8]. In continuation, we investigated the synthesis of bis(2-arylimino-1,3-thiazolidin-4-ones) and 2-(arylimino)-*N*-(enaminoaryl)-1,3-thiazolidin-4-ones from various diamines. Thus, the reaction of aliphatic diamines **2** and isothiocyanatobenzene in the presence of dialkyl but-2-ynedioate **3** proceeded spontaneously at 25° in anhydrous CH_2Cl_2 and furnished bis(2-arylimino-1,3-thiazolidin-4-ones) **4** within 3 h in 80–85% yields (*Scheme 1*).

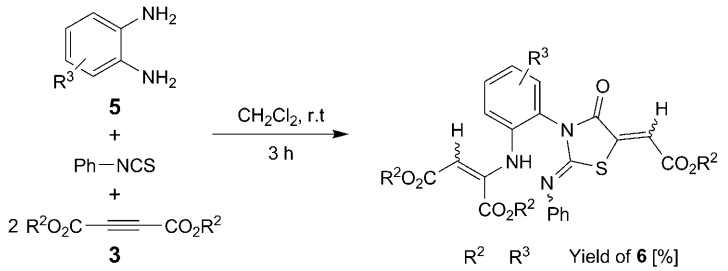
Scheme 1. *Synthesis of the Bis(2-arylimino-1,3-thiazolidin-4-ones)* **4**



	R^1	*n*	R^2	Yield of **4** [%]
4a	H	1	Me	80
4b	H	1	Et	82
4c	H	2	Me	82
4d	H	2	Et	80
4e	Me	1	Me	85
4f	Me	1	Et	80

When benzene-1,2-diamines **5** and isothiocyanatobenzene in dry CH_2Cl_2 were allowed to react in the presence of **3** at room temperature, compound **6**, as a yellow powder, was formed in nearly quantitative yield (*Scheme 2*). This product was identified as dimethyl 2-({2-[5-(2-methoxy-2-oxoethylidene)-4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]phenyl}amino)but-2-enedioate.

Scheme 2. *Synthesis of 2-(Arylimino)*-N-*(enaminoaryl)-1,3-thiazolidin-4-ones* **6**



	R^2	R^3	Yield of **6** [%]
6a	Me	H	75
6b	Et	4-Me	70

The structures of compounds **4a**–**4f**, **6a**, and **6b** were deduced from their elemental analysis, IR, and ^{1}H- and ^{13}C-NMR spectra.

The mass spectrum of the symmetric **4a** displayed the molecular-ion peak at *m*/*z* 550. Two fragment-ion peaks at *m*/*z* 288 ($[M-262]^+$) and 263 ($[M-287]^+$) are in agreement with two important structural parts of **4a**. The fragment-ion peak at *m*/*z* 288 resulted from dissociation of the CH_2–N bond along with a transfer of an H-atom between the two fragments (*m*/*z* 261 and 289). The fragment-ion peak at *m*/*z* 263 ($[M-288+1]^+$) is related to the protonation of the fragment with the mass 262. The IR spectrum of **4a** showed four sharp adsorptions at 1709, 1691, 1635, and 1608 cm^{-1} which are ascribed to NC=O, CO_2R, C=N, and C=C, respectively. The ^{1}H-NMR spectrum of **4a** exhibited three sharp *singlet*s arising from MeO groups (3.81 ppm), CH_2 groups of the diamine (4.45 ppm), and the =CH group (6.89 ppm). The Ph moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed eleven distinct resonances in agreement with the symmetric structure. The characteristic C-atom signals of the 2-(arylimino)-1,3-thiazolidin-4-one ring are attributed to NC=O, NC=N, and S*C*=C, and they appeared at 165.20, 151.22, and 141.18 ppm, respectively. It is important to note that the molecular structures of product **4a**–**4d** are symmetric.

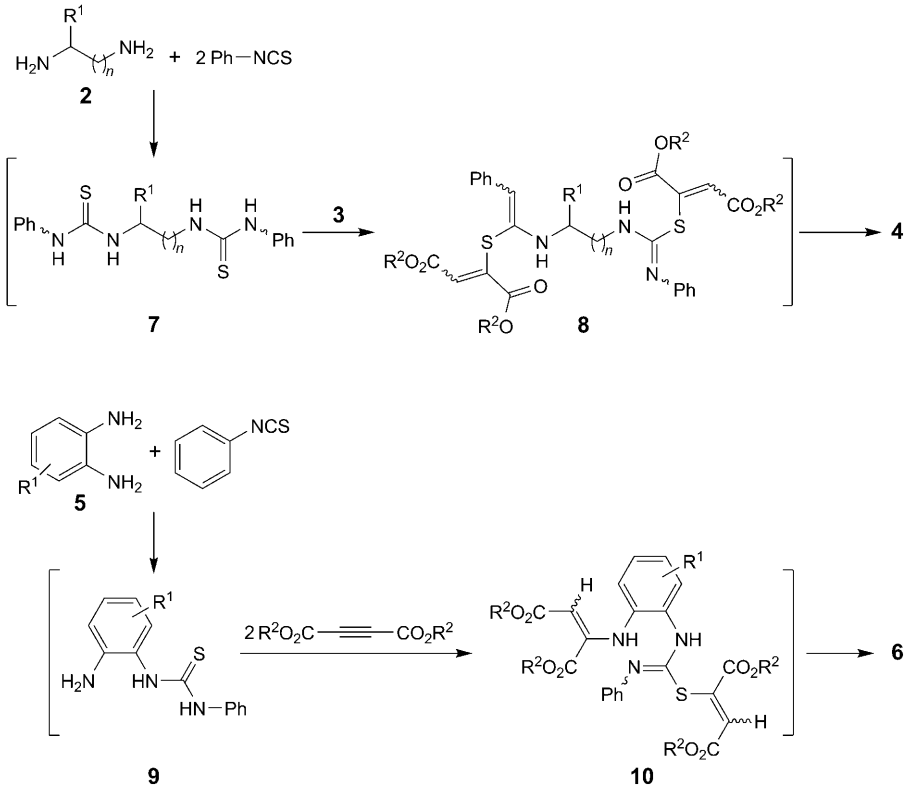
The ^{1}H-NMR spectrum of **6a** showed six *singlet*s at 3.60, 3.73, 3.84, 5.55, 7.03, and 9.54 ppm arising from three MeO groups, two CH groups (NC=*C*H and SC=*C*H), and a NH group. The ^{13}C-NMR spectrum of **6a** showed 22 prominent peaks assigned to the proposed structure. Signals for NC=O, NC=N, and S*C*=CH appeared at 164.07, 150.82, and 148.06 ppm, respectively, indicating the presence of the thiazolidine ring. The enaminone moiety gave rise to characteristic signals at 95.73 (NC=*C*H), 138.66 (N*C*=CH), and 164.22, 166.29 ppm (2 *C*O_2Me).

Although we have not established the mechanism of the reaction in an experimental manner, an explanation is proposed in *Scheme 3*. First, the aliphatic diamine **2** readily reacts with 2 equiv. of isothiocyanatobenzene to produce bis-thiourea **7**, which is converted to the intermediate **8** in the presence of dialkyl but-2-ynedioate **3**. Finally, product **4** is obtained *via* an intramolecular cyclocondensation [9] in 80–85% yields. On the other hand, benzene-1,2-diamine **5** reacts with only 1 equiv. of isothiocyanatobenzene to produce thiourea **9** (in a separate reaction, **9** was isolated and characterized). In the presence of 2 equiv. of dialkyl but-2-ynedioate **3**, **9** is converted to intermediate **10** that finally afforded 2-(arylimino)-*N*-(enaminoaryl)-1,3-thiazolidin-4-one **6** *via* an intramolecular cyclocondensation in 70–75% yield.

The difference of the two reactions is related to the reactivity of aliphatic and aromatic diamines. Aliphatic diamines are more reactive than aromatic diamines, and, at first step, the aliphatic diamine **2** readily reacts with 2 equiv. of isothiocyanatobenzene to produce bis-thiourea **7**, whereas the benzene-1,2-diamine **5** reacts with only 1 equiv. of phenyl isothiocyanate to produce thiourea **9**. Another reason can be a steric factor.

In summary, we have described an efficient and simple one-pot multicomponent reaction for the synthesis of bis(2-arylimino-1,3-thiazolidin-4-ones) from aliphatic diamines, isothiocyanatobenzene, and dialkyl but-2-ynedioates. In addition, we have shown that benzene-1,2-diamine produces a 2-(arylimino)-*N*-(enaminoaryl)-1,3-thiazolidin-4-one under the same conditions. The use of easily accessible starting materials,

Scheme 3. *Proposed Mechanism for the Formation of Bis(2-arylimino-1,3-thiazolidin-4-ones)* **4** *and* N-*(Enaminoaryl)-2-imino-1,3-thiazolidin-4-ones* **6**



the simple experimental procedure and purification, neutral conditions, using the substrates in the reaction without any prior activation or modification, short reaction times, and relatively good yields with both diamine types are the advantages of the present method.

Experimental Part

General. Aliphatic diamines, benzene-1,2-diamines, dialkyl but-2-ynedioates, and isothiocyanatobenzene were obtained from *Merck* (Germany) and *Fluka* (Switzerland). Column chromatography: *Merck* silica gel (SiO_2; 230–240 mesh). M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$, with a *Bruker DRX-500 AVANCE* spectrometer at 500.13 and 125.75 MHz, resp. EI-MS: *FINNIGAN-MAT 8430* mass spectrometer operating at an ionization potential of 20 eV. Elemental analyses: *Herpes CHN–O–Rapid* analyzer.

Preparation of Compounds **4a**–**4f**. *General Procedure* (exemplified for **4a**). Dimethyl but-2-ynedioate (**3a**; 2 mmol) was added slowly to a magnetically stirred 5-ml flat bottom flask containing a mixture of diamine **2** (1 mmol) and isothiocyanatobenzene (2 mmol) in 3 ml of CH_2Cl_2 at r.t. The mixture was stirred for 3 h to completion of the reaction (monitored by means of TLC). The solvent was removed, and the product was separated by CC with hexane/AcOEt 6 : 1.

Dimethyl 2,2′-{Ethane-1,2-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4a**). Yield: 0.44 g (80%). Yellow powder. M.p. 135–138° (dec.). IR (KBr): 1709 (2 CO_2Me), 1635 (2 NCO), 1608 (2 C=N), 1584 (2 C=C), 1206, 1190 (2 C–O). ^{1}H-NMR (500.1 MHz): 3.81 (*s*, 2 MeO); 4.45 (*s*, 2 CH_2); 6.89 (*s*, 2 =CH); 6.93 (*d*, *J* = 7.3, 4 H); 7.17 (*t*, *J* = 7.5, 2 H); 7.33 (*t*, *J* = 7.6, 4 H). ^{13}C-NMR (125.7 MHz): 40.46; 52.44; 116.34; 120.99; 125.25; 129.35; 141.18; 147.1; 151.22; 165.20; 166.17. EI-MS: 550 (8, M^+), 518 (21), 491 (19), 458 (56), 288 (100), 275 (39), 263 (47), 201 (42), 117 (25), 104 (14), 91 (10), 77 (30). Anal. calc. for $C_{26}H_{22}N_4O_6S_2$ (550.60): C 56.72, H 4.03, N 10.18; found: C 56.78, H 4.01, N 10.15.

Diethyl 2,2′-{Ethane-1,2-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4b**). Yield: 0.47 g (82%). Yellow powder. M.p. 160–162°. IR (KBr): 1721 (2 CO_2Et), 1697 (2 NCO), 1647 (2 C=N), 1610 (2 C=C), 1189, 1147 (2 C–O). ^{1}H-NMR (500.1 MHz): 1.31 (*t*, *J* = 7.1, 2 *Me*CH_2); 4.23 (*q*, *J* = 7.1, 2 MeCH_2O); 4.45 (*s*, 2 CH_2N); 6.88 (*s*, 2 =CH); 6.94 (*d*, *J* = 7.4, 4 H); 7.15 (*t*, *J* = 7.4, 2 H); 7.31 (*t*, *J* = 7.6, 4 H). ^{13}C-NMR (125.7 MHz): 14.14; 40.43; 61.66; 116.81; 121.01; 125.2; 129.32; 140.93; 147.14; 151.4; 165.25; 165.78. EI-MS: 579 (2, $[M+1]^+$), 578 (2, M^+), 532 (24), 505 (44), 486 (32), 301 (100), 289 (38), 276 (76), 201 (48), 117 (13), 104 (61), 91 (32), 77 (30). Anal. calc. for $C_{28}H_{26}N_4O_6S_2$ (578.65): C 58.12, H 4.53, N 9.68; found: C 58.15, H 4.50, N 9.70.

Dimethyl 2,2′-{Propane-1,3-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4c**). Yield: 0.46 g (82%). Yellow powder. M.p. 160–162°. IR (KBr): 1727 (2 CO_2Me), 1693 (2 NCO), 1648 (2 C=N), 1616 (2 C=C), 1203, 1155 (2 C–O). ^{1}H-NMR (500.1 MHz): 2.31–2.34 (*m*, CH_2); 3.79 (*s*, 2 MeO); 4.11 (*t*, *J* = 7.1, 2 CH_2N); 6.89 (*s*, 2 =CH); 6.96 (*d*, *J* = 7.3, 4 H); 7.17 (*t*, *J* = 7.4, 2 H); 7.34 (*t*, *J* = 7.7, 4 H). ^{13}C-NMR (125.7 MHz): 25.75; 40.57; 52.44; 116.15; 121.08; 125.24; 129.34; 141.51; 147.14; 150.79; 164.84; 166.20. EI-MS: 564 (7, M^+), 532 (6), 505 (1), 472 (35), 302 (100), 287 (35), 263 (6), 117 (16), 104 (6), 91 (5), 77 (27). Anal. calc. for $C_{27}H_{24}N_4O_6S_2$ (564.63): C 57.44, H 4.28, N 9.92; found: C 57.46, H 4.25, N 9.95.

Diethyl 2,2′-{Propane-1,3-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4d**). Yield: 0.47 g (80%). Yellow powder. M.p. 147–150°. IR (KBr): 1721 (2 CO_2Me), 1688 (2 NCO), 1642 (2 C=N), 1612 (2 C=C), 1193, 1152 (2 C–O). ^{1}H-NMR (500.1 MHz): 1.30 (*t*, *J* = 7.1, 2 *Me*CH_2); 2.32–2.34 (*m*, CH_2); 4.12 (*t*, *J* = 7.1, 2 CH_2N); 4.26 (*q*, *J* = 7.1, 2 MeCH_2O); 6.89 (*s*, 2 =CH); 6.98 (*d*, *J* = 7.4, 4 H); 7.18 (*t*, *J* = 7.4, 2 H); 7.35 (*t*, *J* = 7.9, 4 H). ^{13}C-NMR (125.7 MHz): 14.13; 25.78; 40.55; 61.64; 116.63; 121.08; 125.20; 129.32; 141.24; 147.17; 150.94; 164.92; 165.84. EI-MS: 592 (10, M^+), 546 (6), 519 (1), 501 (35), 316 (100), 301 (24), 277 (18), 117 (14), 104 (27), 91 (31), 77 (49), 59 (11), 41 (7). Anal. calc. for $C_{29}H_{28}N_4O_6S_2$ (592.68): C 58.77, H 4.76, N 9.45; found: C 58.75, H 4.79, N 9.44.

Dimethyl 2,2′-{Propane-1,2-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4e**). Yield: 0.48 g (85%). Yellow powder. M.p. 140–142°. IR (KBr): 1729 (2 CO_2Me), 1696 (2 NCO), 1640 (2 C=N), 1611 (2 C=C), 1199, 1116 (2 C–O). ^{1}H-NMR (500.1 MHz): 1.78 (*d*, *J* = 7.1, *Me*CH); 3.79 (*s*, MeO); 3.81 (*s*, MeO); 4.08 (*dd*, *J* = 13.6, 3.0, 1 H); 4.97–5.07 (*m*, 1 H); 5.38–5.47 (*m*, 1 H); 6.85 (*s*, =CH); 6.89 (*s*, =CH); 6.91–6.92 (*m*, 4 H); 7.12–7.18 (*m*, 2 H); 7.31 (*t*, *J* = 7.7, 4 H). ^{13}C-NMR (125.7 MHz): 15.41; 44.18; 49.84; 52.36; 52.45; 115.95; 116.46; 120.88; 120.94; 125.12; 125.20; 129.34; 129.39; 141.05; 141.27; 147.10; 147.44; 150.87; 151.20; 164.94; 165.20; 166.18; 166.26. EI-MS: 564 (8, M^+), 550 (9), 532 (10), 505 (13), 472 (36), 302 (100), 287 (48), 263 (19), 117 (14), 104 (11), 91 (39), 77 (75), 59 (16), 41 (7). Anal. calc. for $C_{27}H_{24}N_4O_6S_2$ (564.63): C 57.44, H 4.28, N 9.92; found: C 57.41, H 4.30, N 9.90.

Diethyl 2,2′-{Propane-1,2-diylbis[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl-5-ylidene]}diethanoate (**4f**). Yield: 0.47 g (80%). Yellow powder. M.p. 141–143°. IR (KBr): 1719 (2 CO_2Et), 1695 (2 NCO), 1640 (2 C=N), 1610 (2 C=C), 1200, 1117 (2 C–O). ^{1}H-NMR (500.1 MHz): 1.32 (*t*, *J* = 7.1, 2 *Me*CH_2); 1.77 (*d*, *J* = 7.2, *Me*CH); 4.07 (*dd*, *J* = 14.0, 3.0, 1 H); 4.23 (*q*, *J* = 7.1, 2 MeCH_2O); 4.98–5.08 (*m*, 1 H); 5.37–5.48 (*m*, 1 H); 6.84 (*s*, =CH); 6.88 (*s*, =CH); 6.91 (*d*, *J* = 7.8, 4 H); 7.15 (*t*, *J* = 7.2, 2 H); 7.31 (*t*, *J* = 7.4, 4 H). ^{13}C-NMR (125.7 MHz): 14.14; 15.42; 44.14; 49.79; 61.55; 61.68; 116.41; 116.93; 120.90; 120.96; 125.08; 125.17; 129.28; 129.33; 140.79; 141.02; 147.16; 147.40; 151.05; 151.45; 164.99; 165.27; 165.81; 165.90. EI-MS: 592 (7, M^+), 577 (15), 546 (17), 519 (22), 500 (58), 316 (100), 301 (62), 277 (19), 117 (26), 104 (18), 91 (13), 77 (37). Anal. calc. for $C_{29}H_{28}N_4O_6S_2$ (592.68): C 58.77, H 4.74, N 9.45; found: C 58.75, H 4.71, N 9.43.

Dimethyl 2-({2-[5-(2-Methoxy-2-oxoethylidene)-4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]phenyl}-amino)but-2-enedioate (**6a**). Yield: 0.37 g (75%). Yellow powder. M.p. 159–161°. IR (KBr): 1734, 1697 (3 CO_2Me), 1673 (NCO), 1641 (C=N), 1612, 1600 (2 C=C), 1275, 1208 (2 C–O). ^{1}H-NMR (500.1 MHz): 3.60 (*s*, MeO); 3.73 (*s*, MeO); 3.84 (*s*, MeO); 5.55 (*s*, NC=CH); 7.03 (*s*, =CH); 7.09–7.11 (*m*, 3 H); 7.18 (*t*, *J* = 7.5, 1 H); 7.34–7.37 (*m*, 3 H); 7.39–7.44 (*m*, 2 H); 9.54 (*s*, NH). ^{13}C-NMR (125.7 MHz): 51.26; 52.52; 52.63; 95.73; 116.77; 121.25; 124.42; 125.25; 126.03; 128.20; 129.15; 129.44; 130.22; 138.66; 141.43; 147.33; 148.06; 150.82; 164.07; 164.22; 166.29; 169.27. EI-MS: 495 (5, M^+), 462 (6), 436 (9), 403 (100), 351 (4), 337 (21), 292 (26), 261 (7), 240 (41), 157 (12), 121 (11), 93 (11), 77 (22). Anal. calc. for $C_{24}H_{21}N_3O_7S$ (495.50): C 58.18, H 4.27, N 8.48; found: C 58.15, H 4.29, N 8.51.

Diethyl 2-({2-[5-(2-Ethoxy-2-oxoethylidene)-4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]-4-methyl-phenyl}amino)but-2-enedioate (**6b**). Yield: 0.39 g (70%). Red liquid. IR (KBr): 1730, 1710 (3 CO_2Me), 1668 (NCO), 1642 (C=N), 1611 (NC=C), 1605 (SC=C), 1267, 1195 (2 C–O). ^{1}H-NMR (500.1 MHz): 0.97 (*t*, *J* = 7.0, *Me*CH_2O); 1.27 (*t*, *J* = 7.0, *Me*CH_2O); 1.30 (*t*, *J* = 7.0, *Me*CH_2O); 2.34 (*s*, *Me*); 4.04 (*q*, *J* = 7.0, MeC*H*$_2O$); 4.16 (*q*, *J* = 7.0, MeC*H*$_2O$); 4.25 (*q*, *J* = 7.1, MeC*H*$_2O$); 5.53 (*s*, NC=CH); 6.89 (*s*, 1 H); 6.98 (*s*, =CH); 7.07–7.17 (*m*, 2 H); 7.24–7.32 (*m*, 5 H); 9.50 (*s*, NH). ^{13}C-NMR (125.7 MHz): 13.99; 14.12; 14.30; 21.17; 59.92; 61.66; 61.86; 95.78; 117.06; 120.99; 125.08; 126.62; 128.14; 128.95; 129.04; 130.83; 138.41; 140.46; 141.26; 147.47; 148.50; 151.18; 163.88; 164.08; 165.89; 168.90. EI-MS: 551 (8, M^+), 504 (7), 478 (10), 459 (100), 393 (5), 365 (20), 308 (25), 275 (8), 254 (40), 185 (14), 135 (10), 108 (10), 77 (20). Anal. calc. for $C_{28}H_{29}N_3O_7S$ (551.61): C 60.97, H 5.30, N 7.62; found: C 60.95, H 5.32, N 7.65.

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