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Synthesis and Properties of Unique Mesoionic 1,3-Thiazolium-4-olates

B. Zaleska[1,*], **D. Ciez**[1], and **H. Falk**[2]

[1] Department of Organic Chemistry, Jagiellonian University, PL-30060 Kraków, Poland
[2] Institute of Chemistry, Johannes Kepler University, A-4040 Linz, Austria

Summary. N-bridged 1,3-thiazolium-4-olates were synthesized by reaction of 3-substituted 3-aminothioacrylanilides with bromoacetic acid ethyl ester in refluxing xylene. Their structural aspects were investigated by means of mass, NMR, and absorption spectroscopy. They display an unusual ring-chain tautomeric equilibrium, which is governed by the nature of the solvents and the *pH* value.

Keywords. Substituted 1,3-Thiazolium-4-olates; Ring-chain Tautomerism; Synthesis; Absorption Spectra; Solvatochromism.

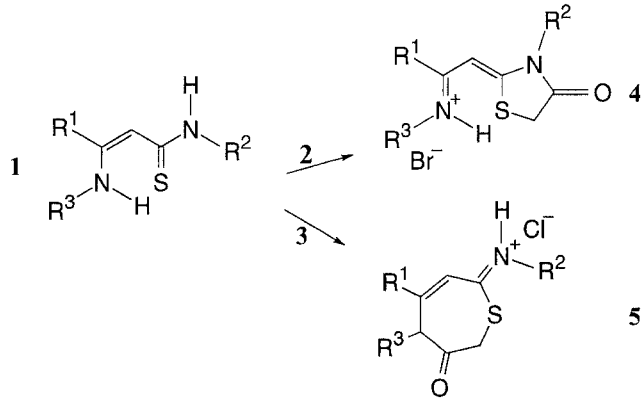
Synthese und Eigenschaften einzigartiger Mesoionischer 1,3-Thiazolium-4-olate

Zusammenfassung. N-verbrückte 1,3-Thiazolium-4-olate wurden durch Reaktion von 3-substitutierten 3-Aminothioacrylaniliden mit Bromessigsäureethylester in siedendem Xylol synthetisiert. Ihre strukturellen Aspekte wurden mit Hilfe von Massen-, NMR- und Absorptionsspektroskopie untersucht. Sie zeigen ein ungewöhnliches Ring-Ketten-Tautomeriegleichgewicht, das durch die Natur des Lösungsmittels und den *pH*-Wert gesteuert wird.

Introduction

Thiazolium-4-olates have been investigated over the years because of their pharmacological activity [1, 2, 3]. The common method of preparation of these systems involves S-alkylation of N-monosubstituted thioamides with α-haloacids, followed by cyclodehydration [4, 5]. Previously, it has been shown that certain derivatives of 3-aminothioacrylanilides (**1**; $R^1 = CH_3 = Ar$) behaved as polyfunctional binucleophiles. Accordingly, the reaction with 1,2-bielectrophiles resulted in the ready formation of heterocyclic systems like **4** and **5**, depending on whether ethyl-bromoacetoate (**2**) or chloroacetyl chloride (**3**) had been used as reagents in refluxing toluene [6, 7].

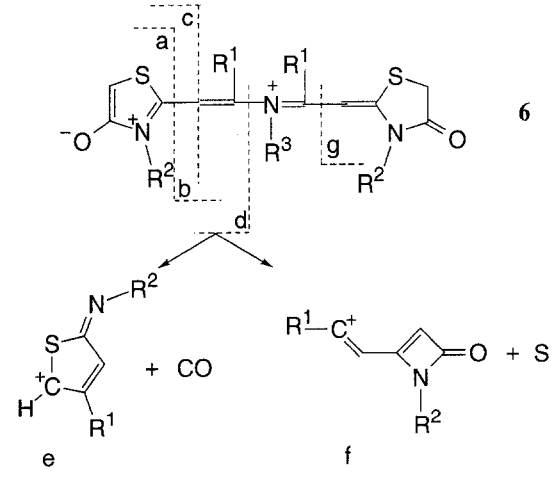
During these studies it has been observed that a very sparingly soluble and intensely colored by-product was formed in the reactions involving **2**. Its yield has been found to be strongly dependent on the nature of the different residues R^1–R^3 and to some extent also on the reaction conditions. The formation, structural aspects, and spectroscopic properties of these products are reported in the present paper.



	a	b	c	d	e	f
R^1	CH_3	CH_3	CH_3	C_6H_5	C_6H_5	C_6H_5
R^2	C_6H_5	4-CH_3–C_6H_5	C_6H_5	C_6H_5	4-CH_3–C_6H_5	C_6H_5
R^3	C_6H_5	C_6H_5	4-CH_3–C_6H_5	C_6H_5	C_6H_5	4-CH_3–C_6H_5

Results and Discussions

Using refluxing xylene in the reaction of **1d**–**1f** (R^1 = aryl) with **2** instead of toluene resulted in enhanced amounts of by-products **6d**–**6f** which could be readily isolated in about five percent yield due to their insolubility in common organic solvents. Under these conditions, **1a**–**1c** ($R^1 = CH_3$) provided yields of compounds **6a**–**6c** up to sixty percent. Obviously, the course of this reaction was critically dependent on the steric requirements of the substituent R^1.



Scheme 1

The molecular formula of the deep blue colored compounds **6** was established by elemental analysis and mass spectroscopy. Besides the diagnostic M^+ ions in the electron impact mass spectra of **6**, several characteristic fragmentation ions could be

observed. Thus, loss of one thiazolium-4-olate ring (a) and formation of typical ions (b–f) by α- and β-cleavages of the thiazolidin-4-one ring [7] as well as cleavage of the thiazolidone ring (g) as illustrated in Scheme 1 could be observed and led to the formulation of the constitutions of **6** as given in the formulae.

Additional evidence came from the IR spectra, which displayed peaks characteristic for the C=O group of the 1,3-thiazolidin-4-one ring at 1708 cm^{-1} and the C=N moiety of the 1,3-thiazolium-olate ring at 1601 cm^{-1}. Due to the low solubility of compounds **6** in common NMR solvents, a reliable ^{13}C NMR spectrum could be obtained only in the case of **6b**. It displayed eight methyl signals in the range of 18.3–23.6 ppm, two CH_2 groups at 30.9 and 33.03 ppm, =CH-vinylic carbon signals at 102.2–104.1 ppm, and two =CH-groups of the 1,3-thiazolium-4-olate ring. Carbonyl carbon atom resonances were observed at 169.0, 170.5, and 175.4 ppm. These assignments could be confirmed by means of a DEPT experiment. The ^1H NMR spectrum of the same compound displayed the same relative numbers of signal groups, *i.e.* eight methyl signals, two CH_2 signals characteristic of the thiazolidin-4-one ring, two plus two vinylic proton signals, and one pair of resonances in the region of 6.9 ppm, which is typical for 1,3-thiazolium-4-olates.

These data corroborated the constitutional assignment, but pointed to an equilibrium mixture of at least two diastereomers or tautomers of **6** constituting a unique and novel chromophoric system consisting of a mesoionic structure linked *via* an ionic spacer to a heterocyclic ring system.

With regard to the mechanistic implications of the formation of compounds **6** in the reaction between **1** and **2** in boiling xylene, the reaction of 3-amino-thioacrylanilides with hydrochloric acid may serve as a lead. It has been shown that this reaction proceeded in an intermolecular cyclization of two molecules of **1** with elimination of one molecule of amine [8]. Obviously, this cyclization reaction must have involved an intermediate with an N-spacer. Thus, in the case of $2 \cdot \mathbf{1} + 2 \cdot \mathbf{2}$, in a first step an open chain S-alkylated product may form which then eliminates one molecule amine from position 3 of the 3-aminothioacrylic acid derivative. Finally, ring closure of the N-chainspaced intermediate could form the mesoionic system **6**. This reaction sequence would be strongly dependent on the steric requirements in the regions forming the spacer between the two rings.

Investigation of the chromophoric system of compounds **6** by means of their absorption spectra led to a surprise: it turned out that the absorption spectra of **6** in a series of solvents displayed apparently a rather strong solvatochromic effect. As an

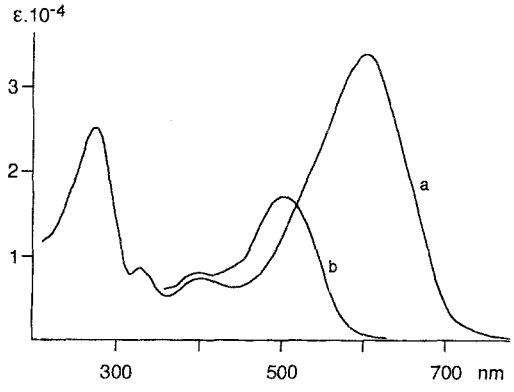


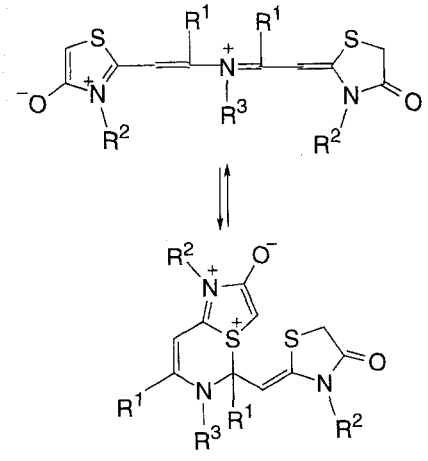
Fig. 1. Absorption spectra of **6a**$^+$Br$^-$ in dichloromethane (a) and acetone (b)

example, Fig. 1 illustrates the UV/Vis spectrum of **6a**$^+$Br$^-$ in two extreme aprotic solvents. From an inspection of the different absorption spectra of compounds **6a–6f** and their spectroscopic behavior in solvent mixtures it became clear that for **6** the phenomenon was rather an equilibrium between two species absorbing with rather broad absorption bands in the regions of 500 and 600 nm, and not a continuous shift of absorption wavelengths due to different solvent properties as would be characteristic of a true solvatochromic effect. In addition, it turned out that in solutions of 80% dimethylsulfoxide/water brought to different *pH* values two species could be found to be in equilibrium. For the example of **6a**, the first one absorbed at 525 nm (rel. intensity: 0.85; *pH*: 7), the other one at 600 nm (rel. intensity: 1.00; *pH*: 1.8) with an isosbestic point at 545 nm (relative intensity: 0.75). Spectrophotometric titration of this system resulted in an apparent pK_a of 4.7 ± 0.1.

With respect to the nature of the two species one could *a priori* think of diastereomers, addition equilibria, or tautomers. The first possibility is a rather restricted one. Orienting force field calculations [9] showed that the diastereomer with the residues pointing as far as possible from each other would be considerably stabilized against the other ones. Moreover, the observed shifts of absorption bands would not correlate with diastereomeric species.

With respect to addition equilibria, protonation might occur at the oxygen of the 1,3-thiazolium-4-olate ring, which could explain the titration experiment described above. However, we were not able to isolate a compound like **6a**$^+$Br$^-$HCl. Thus, a protonation equilibrium was not considered as an explanation of the two-species phenomena.

An addition equilibrium of the corresponding anion in aprotic solvents to the unsaturated positions between the bridge-N$^+$ and the thiazolidone ring would be another possibility to consider. Such an equilibrium should be strongly dependent on the nucleophilicity of the anion. However, the absorption spectra of **6a**$^+$Br$^-$, **6a**$^+$CN$^-$, and **6a**$^+$NO$_3^-$ displayed only marginally shifted long wavelength absorption bands at 504, 495, and 499 nm, thus ruling out an addition equilibrium of this kind.



Scheme 2

These results left to propose an equilibrium between tautomers. With respect to proton tautomerism, the two terminal rings of **6** would be candidates. However, the ^{1}H NMR spectra did not indicate an equilibrium involving the protons at the thiazolidone or the thiazolinolate rings. Thus, valence tautomerism, *i.e.* in the case of **6**, an unusual ring chain tautomerism between **6** and **6′** as shown in the formulae of Scheme 2 was inevitable to invoke. This hypothesis was found to be in accordance with the NMR and mass spectroscopic data acquired so far for compounds **6**. In addition, PPP-type calculations [10] of the chromophoric systems of **6** and **6′**, indicated, that the latter one should be bathochromically shifted with respect to the first one by about 70 nm, which agreed with the observed shifts. Given the constitution of **6′**, which in contrast to **6** displayed a basic nitrogen atom in the six-ring, it became obvious that the equilibrium point could be shifted to the side of **6′** in acidic medium. This was nicely corroborated by the titration experiment leading to an apparent $pK_a = 4.7$ as described above.

Experimental

Melting points are uncorrected. NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer at 500 MHz (^{1}H) or 125 MHz (^{13}C) using *TMS* as internal standard. IR spectra of the compounds dispersed in KBr pellets were recorded with a Bruker IFS 48 FT instrument. UV/Vis spectra were recorded on HP-8451A and Hitachi-U-3210 instruments. Mass spectra were obtained using a Finnigan INCOS-500 mass spectrometer. Microanalyses were carried out with a Perkin-Elmer 240B apparatus; the results agreed satisfactorily with the calculated ones (C, H, N, S).

General Procedure for the Preparation of Bis((1-methyl-2-(1′,3′-thiazolidin-4′-one))-vinyl)-aniline bromides (**6**)

Ethylbromoacetate (2.3 ml, 21 mmol) was added dropwise to a boiling solution of *β*-aminothiocrotonic anilide (**1a–c**; 5.3 g, 20 mmol) or *β*-aminothiocinnamic anilide (**1d–f**; 6.6 g, 20 mmol) in 60 ml of xylene and kept refluxing for 5 h. After cooling the precipitate was filtered off and purified in a Soxhlet apparatus with acetone for 20 h. Products **6**, which were insoluble in acetone, were obtained as deep blue powders with a gold lustre.

6a ($C_{30}H_{26}N_3O_2S_2Br$; M = 604.6)

Yield: 3.7 g (62%); m.p.: 254 °C; IR (KBr): $\tilde{\nu} = 1703$ (C=O), 1676 (C–O$^-$), 1595 (C=N), 1484, 1359, 1271, 1142, 690, 586 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.45$ (s, CH_3), 2.53 (s, CH_3), 2.80 (s, CH_3), 2.99 (s, CH_3), 4.03 (s, CH_2), 4.04 (s, CH_2), 5.32 (s, =CH-), 5.59 (s, =CH-), 6.95–7.58 (m, aromatic H) ppm; MS (70 eV): *m/z* (%) = 523 (2) [M$^+$–H], 449 (2) [M$^+$–H–SCH_2CO], 406 (4) [M$^+$–H–PhNCO], 348 (5) [b], 308 (3), 307 (4), 276 (5), 265 (2), 233 (7), 216 (17) [d], 189 (8) [c], 188 (5) [e], 184 (5) [f], 175 (9) [a], 135 (8), 119 (7), 118 (7) [Ph–N$^+$=C–Me], 93 (100), 82 (40), 80 (41), 77 (21); UV/Vis (CH_2Cl_2): $\lambda_{max}(\varepsilon) =$ 592 (34000), 414 (7400), 339 (7900), 275 (23000) nm; UV/Vis ($CHCl_3$): $\lambda_{max}(\varepsilon) = 583$ (36000), 390 (9500), 338 (11000), 275 (34000) nm; UV/Vis (*DMSO*): $\lambda_{max}(\varepsilon) = 531$ (32000), 274 (36000) nm; UV/Vis (*DMF*): $\lambda_{max}(\varepsilon) = 522$ (34000) nm; UV/Vis (pyridine): $\lambda_{max}(\varepsilon) = 518$ (24000) nm; UV/Vis (*THF*): $\lambda_{max}(\varepsilon) = 502$ (24000), 278 (34000) nm; UV/Vis (MeOH): $\lambda_{max}(\varepsilon) = 501$ (17000), 204 (64000) nm; UV/Vis (acetone): $\lambda_{max}(\varepsilon) = 490$ (16000) nm.

6b ($C_{32}H_{30}N_3O_2S_2Br$; M = 632.6)

Yield: 3.2 g (54%); m.p.: 268 °C; IR (KBr): $\tilde{\nu} = 1708$ (C=O), 1681 (C–O$^-$), 1601 (C=N), 1508, 1362, 1274, 1144, 764, 559 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.17$ (s, *p*-tolyl CH_3), 2.33 (s, *p*-tolyl CH_3), 2.34 (s, *p*-tolyl

CH_3), 2.36 (s, *p*-tolyl CH_3), 2.44 (s, CH_3), 2.52 (s, CH_3), 2.64 (s, CH_3), 2.80 (s, CH_3), 4.01 (s, CH_2), 4.02 (s, CH_2), 5.34 (s, =CH-), 5.60 (s, =CH-), 6.88–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.31$ (C_6H_4–CH_3), 21.18 (C_6H_4–CH_3), 21.34 (C_6H_4–CH_3), 21.38 (C_6H_4–CH_3), 21.40 (CH_3), 21.48 (CH_3), 23.06 (CH_3), 23.66 (CH_3), 30.9 (CH_2), 33.0 (CH_2), 95 (br, =CH-), 102.2 (=CH-), 103.2 (=CH-), 104.5 (=CH-), 104.7 (=CH-), 169.0 (C–O^-), 170.5 (C=O), 175.4 (C=O) ppm; DEPT 135 ($CDCl_3$ + pyridine-d_5 + CD_3COCD_3): $\delta = 16.39$ (C_6H_4–CH_3), 20.50 (C_6H_4–CH_3), 20.66 (C_6H_4–CH_3), 21.73 (C_6H_4–CH_3), 22.01 (CH_3), 22.04 (CH_3), 29.18 (CH_3), 29.24 (CH_3), 32.32 (CH_2), 96.78 (=CH-), 96.95 (=CH-), 102.20 (=CH-), 103.26 (=CH-), 104.06 (=CH-), 104.15 (=CH-), 114.62 (*p*-CH, aromatic carbon), 117.92 (*p*-CH, aromatic carbon), 126.99, 127.06, 127.13, 127.33, 127.36, 128.50, 129.73, 129.80, 129.82, 130.02, 130.05 (*o*- and *m*-CH, aromatic carbons) ppm; MS (70 eV): *m/z* (%) = 551 (3) [M^+–H], 509 (2) [M^+–H–CH_2CO], 476 (3) [M^+–H–SCH_2CO], 362 (2) [b], 322 (1), 280 (1), 248 (2), 230 (7) [d], 203 (5) [c], 202 (2), 198 (2) [f], 189 (1) [a], 149 (3), 133 (3), 118 (2) [Ph–N^+=C–Me], 105 (8), 93 (6), 77 (3); UV/Vis (CH_2Cl_2): $\lambda_{max}(\varepsilon) = 584$ (33000), 415 (7700), 336 (8100), 252 (14000) nm; UV/Vis ($CHCl_3$): $\lambda_{max}(\varepsilon) = 585$ (45000), 405 (12000), 334 (16000), 278 (58000) nm; UV/Vis (*DMSO*): $\lambda_{max}(\varepsilon) = 526$ (27000), 274 (67000) nm; UV/Vis (*DMF*): $\lambda_{max}(\varepsilon) = 513$ (16000) nm; UV/Vis (pyridine): $\lambda_{max}(\varepsilon) = 518$ (28000), 308 (14000) nm; UV/Vis (*THF*): $\lambda_{max}(\varepsilon) = 497$ (20000), 277 (34000) nm; UV/Vis (MeOH): $\lambda_{max}(\varepsilon) =$ 491 (16000) nm; UV/Vis (acetone): $\lambda_{max}(\varepsilon) = 490$ (13000) nm.

6c ($C_{31}H_{28}N_3O_2S_2Br$; M = 618.6)

Yield: 3.0 g (51%); m.p.: 260 °C; IR (KBr): $\tilde{\nu} = 1706$ (C=O), 1679 (C–O^-), 1594 (C=N), 1493, 1309, 1274, 1144, 610, 588 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.24$ (s, *p*-tolyl CH_3), 2.45 (s, *p*-tolyl CH_3), 2.33 (s, CH_3), 2.52 (s, CH_3), 2.80 (s, CH_3), 2.98 (s, CH_3), 4.01 (s, CH_2), 4.03 (s, CH_2), 5.38 (s, =CH-), 5.59 (s, =CH-), 6.95–7.49 (m, aromatic H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.49$ (C_6H_4–CH_3), 20.54 (C_6H_4–CH_3), 22.36 (CH_3), 22.83 (CH_3), 23.37 (CH_3), 23.39 (CH_3), 33.12 (CH_2), 93.1 (=CH-), 101.0 (=CH-), 102.6 (=CH-), 162.3 (C–O^-), 170.8 (C=O) ppm; MS (70 eV): *m/z* (%) = 348 (3), 322 (2), 290 (4), 248 (4), 216 (19) [d], 198 (4), 189 (13) [c], 184 (7) [f], 144 (4), 132 (5) [Tol-N^+=C–Me], 106 (28), 82 (17), 80 (80), 77 (19); UV/Vis (CH_2Cl_2): $\lambda_{max}(\varepsilon) = 585$ (29000), 334 (6400), 252 (12000) nm; UV/Vis ($CHCl_3$): $\lambda_{max}(\varepsilon) = 577$ (45000), 404 (11000), 336 (13000), 268 (20000) nm; UV/Vis (*DMSO*): $\lambda_{max}(\varepsilon) = 530$ (33000), 269 (16000) nm; UV/Vis (*DMF*): $\lambda_{max}(\varepsilon) = 521$ (34000) nm; UV/Vis (pyridine): $\lambda_{max}(\varepsilon) = 520$ (28000), 307 (14000) nm; UV/Vis (*THF*): $\lambda_{max}(\varepsilon) = 517$ (30000), 277 (33000) nm; UV/Vis (MeOH): $\lambda_{max}(\varepsilon) =$ 506 (31000), 205 (94000) nm; UV/Vis (acetone): $\lambda_{max}(\varepsilon) = 502$ (33000) nm.

6d ($C_{40}H_{30}N_3O_2S_2Br$; M = 728.7)

Yield: 0.36 g (5%); m.p.: 329 °C; IR (KBr): $\tilde{\nu} = 1711$ (C=O), 1676 (C–O^-), 1594 (C=N), 1496, 1366, 1201, 1071, 844, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.63$ (s, CH_2), 5.38 (br s, =CH-), 5.52 (s, =CH-), 6.46 (br s, =CH-), 6.59 (br s, =CH-), 6.90–7.47 (m, aromatic H) ppm; MS (70 eV): *m/z* (%) = 541 (4), 521 (9), 510 (13), 497(5), 478 (10), 453 (14), 439 (3), 370 (8), 338 (17), 328 (4), 296(40), 295 (59), 278 (46) [d], 251 (100) [e], 246 (9) [f], 193 (7), 190 (9), 180 (15) [Ph-N^+=C-Ph], 135 (24), 119 (48), 91 (22), 77 (59).

6e ($C_{42}H_{34}N_3O_2S_2Br$; M = 756.8)

Yield: 0.36 g (5%); m.p.: 291 °C; IR (KBr): $\tilde{\nu} = 1708$ (C=O), 1676 (C–O^-), 1608 (C=N), 1486, 1366, 1201, 1047, 854, 645 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.28$ (s, CH_3), 2.34 (s, CH_3), 2.35 (s, CH_3), 2.36 (s, CH_3), 3.58 (s, CH_2), 3.60 (s, CH_2) 5.35 (br s, =CH-), 5.50 (s, =CH-), 6.37 (br s, =CH-), 6.42 (br s, =CH-), 6.85–7.43 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.70$ (CH_3), 19.86 (CH_3), 19.93 (CH_3), 20.02 (CH_3), 31.7 (CH_2), 102.1 (=CH-), 163.1 (C–O^-), 169.4 (C=O) ppm; MS (70 eV): *m/z* (%) = 581 (3), 549 (7), 512 (8), 466 (7), 422 (8), 398 (11), 384(10), 342(8), 310 (11), 292(7) [d], 265(100) [e], 233 (5), 211 (8), 193 (15), 180 (19) [Ph–N^+=C–Ph], 172 (8), 161 (12), 147 (17), 135 (38), 128 (11), 119 (82), 91 (57), 77 (64).

5f ($C_{41}H_{32}N_3S_2O_2Br$; M = 742.8)

Yield: 0.42 g (6%); m.p.: 291 °C; IR (KBr): $\tilde{\nu}$ = 1708 (C=O), 1676 (C–O^-), 1594 (C=N), 1493, 1366, 1201, 1047, 844, 610 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.17 (s, CH_3), 3.63 (s, CH_2), 5.32 (br s, =CH-), 5.51 (s, =CH-), 6.35 (br s, =CH-), 6.50 (br s, =CH-), 6.80–7.58 (m, aromatic H) ppm; MS (70 eV): *m/z* (%) = 553 (2), 526 (9), 494(6), 466 (13), 435(9), 384 (2), 370 (6), 342 (8), 310 (16), 278 (12) [d], 268 (7), 251 (100) [e], 246 (9) [f], 233 (8), 207 (15), 194 (18) [Tol–N^+=C–Ph], 160 (12), 147 (29), 135 (30), 119 (41), 105 (27), 91 (38), 77 (63).

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