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Syntheses of 4-Aryliminoparabanic Acids and 2-Arylimino-2,3-dihydro-1,4-thiazine Derivatives *via* 2-N,N′-Diarylamidinothiazolium Salts[1,2]

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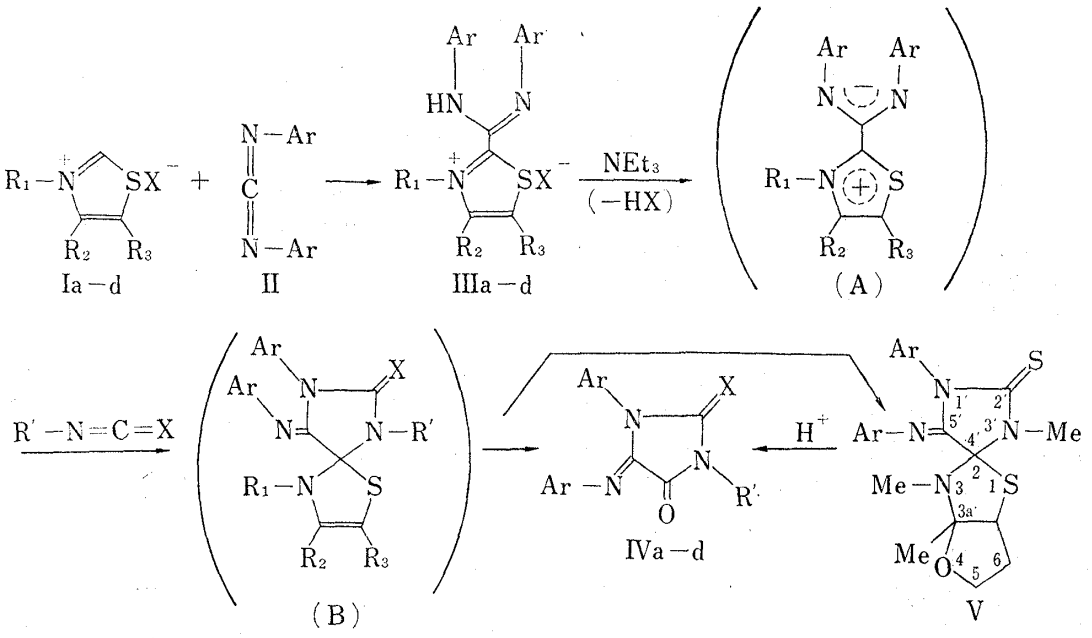
1,3-Dipolar addition reaction of 2-(N,N′-diarylamidino)thiazolium salts with heterocumulenes such as isocyanate and isothiocyanate yielded 4-aryliminoparabanic acid derivatives. On the other hand, action of alkali upon the 2-amidinothiazolium salts afforded 2-arylimino-2,3-dihydro-1,4-thiazin-3-one derivatives providing a new ring expansion reaction of thiazolium salts to 1,4-thiazine derivatives.

Previously, it was reported that 2-amidinothiazolium salts could easily be obtained by reaction of carbodiimides with some thiazolium salts and that the zwitterion species produced by deprotonation of 2-amidinothiazolium salt was suggested to be a reactive 1,3-dipole.[4] This paper deals with the 1,3-dipolar addition reaction of 2-amidinothiazolium salts with some heterocumulenes, and a base-induced ring enlargement reaction of 2-amidinothiazolium salts leading to 2,3-dihydro-1,4-thiazine derivatives is also described.

Reaction of 3,4-dimethylthiazolium iodide (Ia) with di-*p*-tolyl carbodiimide (II; Ar= *p*-tolyl) gave 2-(N,N′-di-*p*-tolylamidino)-3,4-dimethylthiazolium iodide (IIIa) in good yield. Action of methyl isothiocyanate upon IIIa in the presence of excess triethylamine (NEt_3) in N,N-dimethylformamide (DMF) afforded 1-*p*-tolyl-2-thioxo-3-methyl-5-(*p*-tolylimino)-imidazolidin-4-one (IVa), mp 134—136°, in 55% yield. Structure assignment for IVa was made on the basis of elemental analysis ($C_{18}H_{17}ON_3S$) and spectroscopic evidences as follows. IVa showed infrared (IR) bands at 1732 cm^{-1} (C=O), 1640 cm^{-1} (C=N) and 1155 cm^{-1} (C=S), and an ultraviolet (UV) maximum at 318 mμ ($\log \varepsilon$=4.02). Nuclear magnetic resonance (NMR) spectrum of IVa exhibited signals due to eight aromatic protons in the region τ 2.5—3.4[m], a N-methyl at τ 6.62[s] and two tolyl methyls at τ 7.62[s] and τ 7.70[s]. Reaction of ethyl isocyanate with IIIa gave 1-*p*-tolyl-3-ethyl-5-(*p*-tolylimino)-imidazolidine-2,4-dione (IVb) as an oil which showed IR bands at 1790 cm^{-1} and 1740 cm^{-1} and NMR signals corresponding to a N-ethyl and two tolyl groups (see Experimental) supporting its structure. Reactions of phenyl isothiocyanate and phenyl isocyanate with IIIa also gave the corresponding aryliminoparabanic acid derivatives IVc, mp 188—189°, and IVd, mp 125—126°, respectively. The structures of these products were confirmed by comparison of their spectroscopic data with those of IVa and IVb respectively (see Experimental). These products IVa—c are considered to be formed *via* 1,3-dipolar addition of the heterocumulenes with zwitterion species (A) giving cycloadduct (B) followed by decomposition of the strained spiro Δ^4-thiazoline ring of B. In the case of the reaction of 2-(N,N′-di-*p*-tolylamidino)-3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide (IIIb)[4] with methyl isothiocyanate, a stable cycloadduct (V) (C_{24}-$H_{28}ON_4S_2$, mp 209—211°) was obtained in 54% yield. NMR spectrum of V exhibited, in addition to two N-methyl signals at τ 6.70[s] and τ 7.76[s], a C-methyl signal at τ 9.10[s] and complex multiplet in the region τ 5.5—7.8 corresponding to the cyclic $-\dot{C}HCH_2CH_2O-$ system,

1) This paper constitutes Studies on Pyrimidine Derivatives and Related Compounds LXXXIV. Part LXXXIII: A. Takamizawa and S. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 305 (1974).
2) A part of this work was reported preliminarily in A. Takamizawa and S. Matsumoto, *Tetrahedron Letters*, **1968**, 4027.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **22**, 299 (1974).

which are the characteristic signals observed for the compound with 3a-methylperhydrofuro[2,3-*d*]thiazole ring system.[5] The structure of V was thus assigned as spiro {3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-[1′-*p*-tolyl-3′-methyl-5′-(*p*-tolylimino)-imidazolidine-2′-thione]}. On heating in glac. AcOH at 100°, V was decomposed to give IVa in 28% yield.

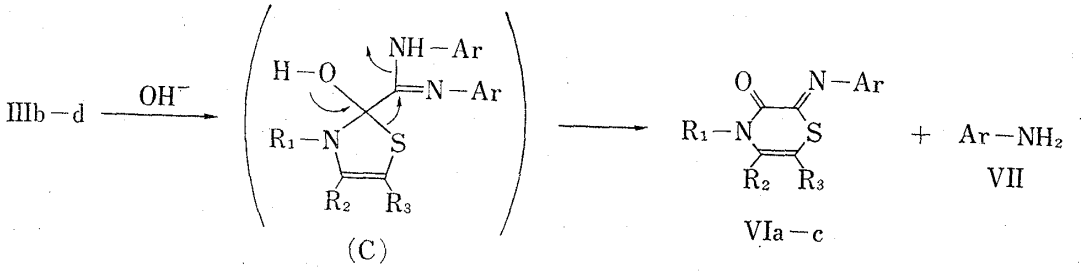


I,III	R_1	R_2	R_3	X	IV	R′	X
a	Me	Me	H	I	a	Me	S
b	Me	Me	CH_2CH_2OH	I	b	Et	O
c	$CH_2C_6H_5$	Me	CH_2CH_2OH	Br	c	Ph	S
d	Me	H	H	I	d	Ph	O

(Ar=*p*-tolyl)

Chart 1

In attempts to isolate the zwitterion species (A) from 2-amidinothiazolium salts, we found a new ring enlargement reaction yielding 2,3-dihydro-1,4-thiazine derivatives. Although IIIb was recovered unchanged on the treatment with NEt_3 in the absence of heterocumulene, when aqueous Na_2CO_3 was added to an aqueous ethanolic solution of IIIb the mixture first displayed a dark orange coloring indicative of the formation of zwitterion, then



VI	R_1	R_2	R_3
a	Me	Me	CH_2CH_2OH
b	$CH_2C_6H_5$	Me	CH_2CH_2OH
c	Me	H	H

(Ar=*p*-tolyl)

Chart 2

5) A. Takamizawa, K. Hirai, Y. Hamashima, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968).

it rapidly turned out to a pale yellow solution from which 2-(*p*-tolylimino)-4,5-dimethyl-6-(2-hydroxyethyl)-2,3-dihydro-1,4-thiazin-3-one (VIa) and *p*-toluidine (VII; Ar=*p*-tolyl) were isolated. VIa was identified with the authentic specimen which has been prepared by the action of aqueous NaOH upon the (1: 1) adduct of 3,4-dimethyl-5-(2-hydroxy)ethylthiazolium iodide (Ib) with *p*-tolyl isothiocyanate.[6] Similarly, action of aqueous Na_2CO_3 upon 2-(N,N'-di-*p*-tolylamidino)-3-benzyl-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide (IIIc)[4] and 2-(N,N'-di-*p*-tolylamidino)-3-methylthiazolium iodide (IIId) afforded corresponding 2,3-dihydro-1,4-thiazine derivatives VIb, mp 164—165°, and VIc, mp 155—156°, respectively. These products are considered to be formed by the addition-elimination mechanism *via* an intermediate (C) as shown in the Chart 2. It has been hitherto reported that 1,4-thiazine derivatives could be synthesized from 2-methyl-3-phenacylthiazolium salt[7] or from the adduct of dialkyl acylphosphonate with thiazolium salt[8] by the action of alkali respectively. In addition to the previously reported reaction,[6] the present results provide a further example of the ring expansion of 2-substituted thiazolium salts leading to 1,4-thiazine derivatives.

Experimental

All melting points were determined in capillaries and uncorrected. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane as an internal standard. UV spectra were taken on a Hitachi EPS-3 spectrophotometer in 99% EtOH. IR spectra were taken on a Japan Spectroscopic Company IR-S spectrophotometer in nujol mull unless otherwise indicated. Column chromatographies were carried our by using SiO_2 (Davision, grade 950).

2-(N,N'-Di-*p*-tolylamidino)-3,4-dimethylthiazolium Iodide (IIIa)——To a solution of 3,4-dimethylthiazolium iodide (Ia) (1.21 g) in DMF (20 ml) was added NEt_3 (1.0 g) and stirred for 10 min at room temperature, then di-*p*-tolyl carbodiimide (DTCD) (1.11 g) was added to the mixture and stirred for 4 hr at 40°. Precipitated yellow crystals were collected and recrystallized from MeOH–acetone to give IIIa (1.27 g, 54.5%) as yellow prisms, mp 226—227°. *Anal.* Calcd. for $C_{20}H_{22}N_3SI$: C, 51.51; H, 4.75; N, 9.01; S, 6.55; I, 27.85. Found: C, 51.95; H, 4.86; N, 8.96; S, 6.40; I, 27.31. NMR (d_6-DMSO, τ): 6.00 (3H, s, N-CH_3), 7.50 (3H, d, J=1 Hz, C_4–CH_3).

2-(N,N'-Di-*p*-tolylamidino)-3-methylthiazolium Iodide (IIId)——3-Methylthiazolium iodide (Id) (1.5 g) and DTCD (1.5 g) were allowed to react in DMF (25 ml) in the presence of NEt_3 (1.5 g) according to the same procedure as employed for the preparation of IIIa. After concentration of the reaction mixture *in vacuo*, the resulting crystalline residue was washed with MeOH and recrystallized from MeOH to give IIId (1.8 g, 60%) as yellow prisms, mp 196—197°. *Anal.* Calcd. for $C_{19}H_{20}N_3SI$: C, 50.78; H, 4.49; N, 9.35; S, 7.14; I, 28.24. Found: C, 50.83; H, 4.42; N, 9.80; S, 7.35; I, 28.53.

1-*p*-Tolyl-2-thioxo-3-methyl-5-(*p*-tolylimino)-imidazolidine-4-one (IVa)——To a suspension of IIIa (463 mg) in DMF (40 ml) was added NEt_3 (150 mg) and methyl isothiocyanate (731 mg), and the mixture was stirred for 4 hr at 50°. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave a residue to which acetone was added and the recovered IIIa (24 mg) was removed by filtration. The filtrate was then concentrated *in vacuo* to leave an oily residue which was chromatographed with benzene. The benzene eluate gave IVa (177 mg, 55%) as yellow prisms, mp 134—136°. *Anal.* Calcd. for $C_{18}H_{17}ON_3S$: C, 66.86; H, 5.30; N, 13.00; S, 9.90. Found: C, 66.71; H, 5.03; N, 13.04; S, 10.10. UV λ_{max} mμ (log ε): 318 (4.02). IR ν_{max} cm^{-1}: 1732 (C=O), 1640 (C=N), 1155 (C=S). NMR ($CDCl_3$, τ): 2.5—3.4^m (8H, 2×Ar), 6.62^s (3H, N–CH_3), 7.62^s and 7.70 (each 3H, 2×Ar–CH_3).

1-*p*-Tolyl-3-ethyl-5-(*p*-tolylimino)-imidazolidine-2,4-dione (IVb)——To a suspension of IIIa (463 mg) in DMF (40 ml) in a sealed tube was added NEt_3 (150 mg) and ethyl isocyanate (1.0 g), and the mixture was stirred for 4 hr at room temperature. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave an oily residue which was chromatographed with $CHCl_3$. The $CHCl_3$ eluate gave IVb (72 mg, 22.4%) as a pale yellow oil. *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.97; N, 13.08. Found: C, 70.92; H, 6.04; N, 12.88. IR ν_{max}^{film} cm^{-1}: 1790 (C=O).

6) A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **22**, 293 (1974).
7) D.J. Adams and M. Wharmby, *Tetrahedron Letters*, **1969**, 3063.
8) A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968); A. Takamizawa, Y. Hamashima, H. Sato, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 1356 (1969).

1740 (C=O). NMR ($CDCl_3$, τ): 6.47^q (2H, $-\underline{CH_2}-CH_3$), 7.67^s and 7.73^s (each 3H, $2\times Ar-CH_3$), 8.75^t (3H, $-CH_2-\underline{CH_3}$).

1-*p*-Tolyl-2-thioxo-3-phenyl-5-(*p*-tolylimino)-imidazolidin-4-one (IVc)——To a suspension of IIIa (463 mg) in DMF (20 ml) was added NEt_3 (150 mg) and phenyl isothiocyanate (500 mg), and the mixture was stirred for 4 hr at 50°. After concentration *in vacuo*, the reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave an oily residue which was chromatographed with benzene. The benzene eluate afforded IVc (58 mg, 15%) as yellow prisms, mp 188—189°. *Anal.* Calcd. for $C_{23}H_{19}ON_3S$: C, 69.85; H, 7.39; N, 10.63; S, 8.09. Found: C, 69.71; H, 7.21; N, 10.54; S, 7.88. UV λ_{max} mμ (log ε): 325 (4.04). IR ν_{max} cm^{-1}: 1740 (C=O), 1635 (C=N), 1150 (C=S).

1-*p*-Tolyl-3-phenyl-5-(*p*-tolylimino)-imidazolidine-2,4-dione (IVd)——To a suspension of IIIa (463 mg) in DMF (20 ml) was added NEt_3 (150 mg) and phenyl isocyanate (357 mg), and the mixture was stirred for 4 hr at 50°. After evaporation of DMF *in vacuo*, the residue was extracted with $CHCl_3$. From the $CHCl_3$ extract, N,N'-diphenyl urea (42 mg) was precipitated and it was removed by filtration, and the filtrate was dried over abs. Na_2SO_4 and concentrated to leave a residue which was chromatographed with ether. The ether eluate afforded IVd (118 mg, 31%) as pale yellow prisms, mp 125—126°. *Anal.* Calcd. for $C_{23}H_{19}O_2N_3$: C, 74.78; H, 5.18; O, 8.66; N, 11.38. Found: C, 74.93; H, 5.10; O, 8.76; N, 11.71. IR ν_{max} cm^{-1}: 1785 (C=O), 1735 (C=O), 1675 (C=N).

Spiro{3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4'-[1'-methyl-3'-*p*-tolyl-5'-(*p*-tolylimino)-imidazolidine-2'-thione]} (V)——To a suspension of 2-(N,N'-di-*p*-tolylamidino)-3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide (IIIb)[4] (500 mg) in DMF (10 ml) was added NEt_3 (300 mg) and methyl isothiocyanate (219 mg), and the mixture was stirred for 2 hr at 40—45°. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave a crystalline residue from which the recovered IIIb (132 mg) was removed by filtration. The filtrate was concentrated *in vacuo* to give an oily residue which was chromatographed with $CHCl_3$. The $CHCl_3$ eluate afforded V (180 mg, 54%) as pale yellow prisms, mp 209—211°. *Anal.* Calcd. for $C_{24}H_{28}ON_4S_2$: C, 63.70; H, 6.24; N, 12.38; S, 14.14. Found: C, 63.97; H, 6.29; N, 12.41; S, 14.56. IR ν_{max} cm^{-1}: 1680 (C=N). NMR ($CDCl_3$, τ): 5.5—7.8^m (5H, $-\dot{C}HCH_2-CH_2O-$), 6.70^s and 7.66^s (each 3H, $2\times N-CH_3$), 9.10^s (3H, $C_{3a}-CH_3$).

Acid-hydrolysis of V——V (120 mg) was dissolved in glac. AcOH (5 ml), and the mixture was heated for 4 hr at 100°. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated to leave an oily mixture which was submitted to preparative thin-layer chromatography using a SiO_2 plate with $CHCl_3$ and an yellow zone (*Rf ca.* 0.5) was cut to give IVa (24 mg, 28%).

2-(*p*-Tolylimino)-4,5-dimethyl-5-(2-hydroxyethyl)-2,3-dihydro-1,4-thiazin-3-one (VIa)——To a solution of IIIb (300 mg) in 50% aq. EtOH (40 ml) was added saturated aq. Na_2CO_3 solution (10 ml). The reaction mixture first displayed dark orange coloring and it turned out to a pale yellow solution. After stirring for 30 min at room temperature, the reaction mixture was allowed to stand for 2 hr. EtOH was removed by evaporation *in vacuo* and the aqueous residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave a crystalline residue which was recrystallized from MeOH to give VIa (150 mg, 79%) as yellow prisms, mp 161—162°. VIa thus obtained was identified with the authentic specimen[6] by IR comparison. The mother liquor of VIa was concentrated *in vacuo* and the residue was dissolved in ether and extracted with 10% aq. HCl solution. The acid layer was neutralized by addition of 10% aq. Na_2CO_3 solution and extracted with ether. The ether layer was washed with H_2O, dried over abs. K_2CO_3 and concentrated to give a crystalline residue (15 mg) which was identified with *p*-toluidine by IR comparison.

2-(*p*-Tolylimino)-4-benzyl-5-methyl-6-(2-hydroxyethyl)-2,3-dihydro-1,4-thiazin-3-one (VIb)——To a solution of 2-(N,N'-di-*p*-tolylamidino)-3-benzyl-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide (IIIc)[4] (240 mg) in 50% aq. EtOH (40 ml) was added saturated aq. Na_2CO_3 solution (10 ml), and the mixture was stirred for 2 hr at room temperature. EtOH was removed by evaporation *in vacuo* to leave an aqueous residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2CO_3 and concentrated *in vacuo* to leave an yellow oil which was crystallized by addition of acetone and recrystallized from MeOH to give VIb (110 mg, 62%) as yellow prisms, mp 164—165°. *Anal.* Calcd. for $C_{21}H_{22}O_2N_2S$: C, 68.81; H, 6.05; N, 7.64; S, 8.75. Found: C, 68.31; H, 6.12; N, 7.64; S, 8.94. IR ν_{max} cm^{-1}: 1650 (C=O), 1635 (C=N). UV λ_{max} mμ (log ε): 227 (4.21), 268 (4.04), 372 (3.91). NMR ($CDCl_3$, τ): 2.6—3.3^m (9H, aromatic protons), 4.76^s (2H, $-\underline{CH_2}-C_6H_5$), 6.38^t and 7.56^t (each 2H, $-CH_2CH_2O-$), 7.65^s and 7.93^s (each 3H, C_5-CH_3 and/or $Ar-CH_3$).

2-(*p*-Tolylimino)-4-methyl-2,3-dihydro-1,4-thiazin-3-one (VIc)——To a solution of 2-(N,N'-di-*p*-tolyl)-amidino-3-methylthiazolium iodide (IIId) (320 mg) in 50% aq. EtOH (40 ml) was added saturated aq. Na_2CO_3 solution (5 ml), and the mixture was stirred for 30 min at 60—70° then for 1 hr at room temperature. After evaporation of EtOH *in vacuo*, the resulting aqueous residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried over abs. Na_2SO_4 and concentrated *in vacuo* to leave an oily residue which was chromatographed by SiO_2 column with AcOEt. The AcOEt eluate afforded VIc (32 mg, 20%) as yellow

prisms, mp 155—156°. *Anal.* Calcd. for $C_{12}H_{12}ON_2S$: C, 62.09; H, 5.20; N, 12.02; S, 13.80. Found: C, 61.93; H, 5.21; N, 11.69; S, 13.61. IR ν_{max} cm^{-1}: 1656 (C=O, C=N). UV λ_{max} mμ: 226, 271, 357. NMR ($CDCl_3$, τ): 3.55[d] and 4.43[d] (each 1H, J=8 Hz, N–CH=CH–S), 6.60[s] (3H, N–CH_3), 7.66[s] (3H, Ar–CH_3).