The Use of an Unusual Rearrangement Sequence for the Syntheses of 3-(1-Aminoalkylidene)-3*H*-thiophen-2-ones and two Examples of their Surprising Electrophilic-Induced Dimerization Reactions

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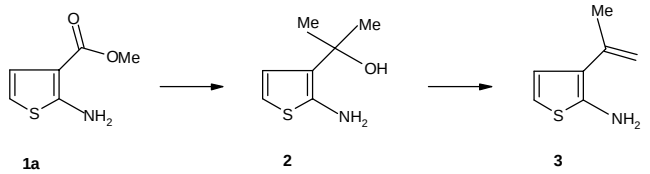
Abstract. The reaction of 2-amino-3-carbomethoxythiophene (**1a**) and 2-amino-3-carboethoxy-4,5-dimethylthiophene (**1b**) with methyl- or ethylmagnesium chloride leads to new 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones **4a**–**d** in good yields (60–87%). Treatment of the compounds **4a** and **4c** with catalytic amounts of *p*-TsOH in boiling $CHCl_3$ afforded the (±)-4,4'-bis-(1-aminoalkylidene)-3',4'-4*H*,2'*H*-[2,3']bithiophenyl-5,5'-diones **9a** and **9b** as new interesting heterocycles in preparatively useful yields (60–65%).

Some years ago, we were interested in larger amounts of 2-amino-3-isopropenylthiophene (**3**), which seemed to be a useful intermediate for the syntheses of more complex, thiophene-ring containing heterocycles with potential fungicidal activity. In one of our planned synthesis strategies, this molecule should be available by reaction of an excess of methylmagnesium chloride with 2-amino-3-carbomethoxythiophene **1a** followed by acid catalyzed dehydration of the resulting 2-(2-amino-thiophen-3-yl)propan-2-ol (**2**).



1a **2** **3**

Scheme 1 First planned synthesis of 2-amino-3-isopropenylthiophene (**3**)

Studying the reaction of 4–5 equivalents of methylmagnesium chloride with 2-amino-3-carbomethoxythiophene **1a**, we were surprised to find that we could not isolate 2-(2-aminothiophen-3-yl)propan-2-ol (**2**) or 3-acetyl-2-aminothiophene; instead 3-(1-aminoethylidene)-3*H*-thiophen-2-one (**4a**) was obtained as sole product in 60% yield. As 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones turned out to be unknown, a more thorough investigation on the reaction of alkyl Grignard reagents with 2-amino-3-carboalkoxythiophenes was initiated in our laboratories. In this paper, we report for the first time on our results concerning this interesting reaction. Additionally, the electrophilic induced dimerization reactions of the compounds **4a** and **4c** are discussed.

Results and Discussion

As simple thiophene model compounds, we chose 2-amino-3-carbomethoxythiophene (**1a**) [1] and 2-amino-3-carboethoxy-4,5-dimethylthiophene (**1b**), which is commercially available (Maybridge). The reaction of these two aminothiophenes with methyl- and ethylmagnesium chloride in a mixture of THF and dioxane was carefully studied. As our investigations showed, in all cases 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones **4a**–**d** were obtained in good to very good yields (60–87%) by using the same simple general procedure (see Scheme 2) for all the compounds. The structures of **4a**–**d** were assigned on the basis of ^{1}H- and ^{13}C NMR experiments. The structural assignment of **4a** is discussed in detail. The most information is obtained from the fully coupled ^{13}C NMR spectrum. The methyl group shows vicinal couplings to the NH_2 group, namely a coupling of 8 Hz with the NH proton trans to it (absorbing at 9.62 ppm) and a coupling of 4 Hz with the NH proton *cis* to it (absorbing at 8.80 ppm, distinction checked by a low power decoupling experiment). The observation of these couplings [2] prove that the methyl group and the NH_2 group are attached to the same C atom which absorbs at 163.5 ppm as shown by a HMBC correlation [3] (see Figure 1) with the methyl protons. The C atom β to the NH_2 group appears at 106.8 ppm (also shown by a HMBC correlation to the methyl protons). Contrarily, the carbonyl C atom at 190.7 ppm shows no HMBC correlation to the methyl protons and no quartett structure in the fully coupled ^{13}C NMR spectrum, thereby excluding a methyl ketone moiety. The two olefinic C atoms C-4 and C-5 can be easily distinguished by their one bond $^1J_{CH}$ coupling constants [4] (see Experimental Part). Their HMBC correlations shown in Figure 1 complete the structural assignment.

In the literature, only the reaction of a single 2-amino-3-carboalkoxythiophene (2-amino-3-carboethoxy-4,5,6,7-

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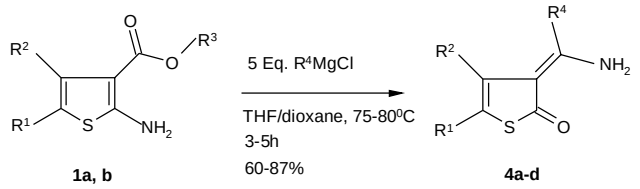


	R^1	R^2	R^3
1a	H	H	Me
1b	Me	Me	Et

	R^1	R^2	R^4
4a	H	H	Me
4b	Me	Me	Me
4c	H	H	Et
4d	Me	Me	Et

Scheme 2 Preparation of 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones

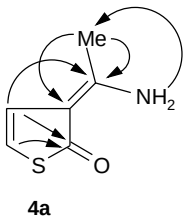


Fig. 1 HMBC correlations used in the structure elucidation of **4a** (the correlation between the NH_2 protons and the methyl C atom was established by selective decoupling)

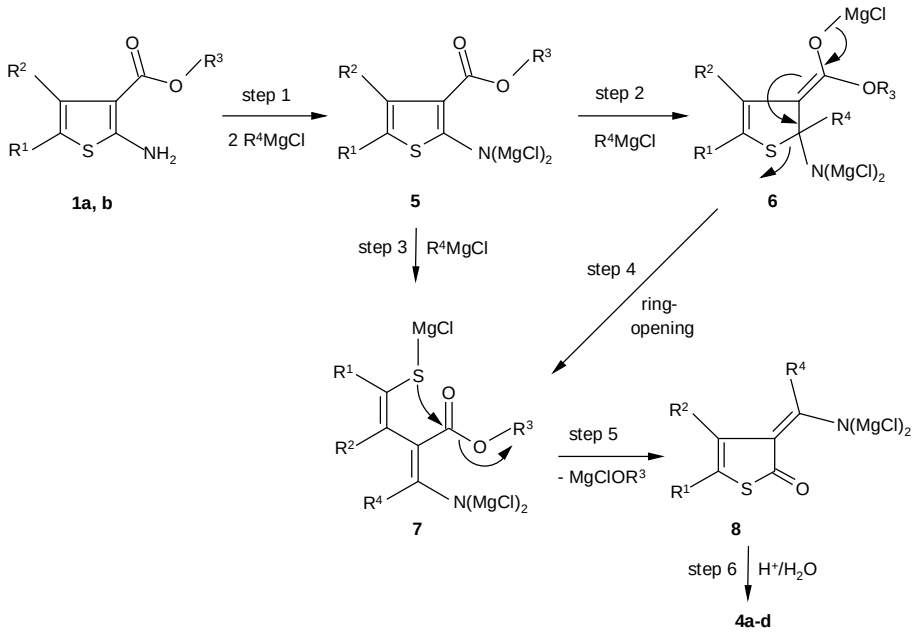
tetrahydrobenzo[*b*]thiophene) with Grignard reagents (benzyl- and phenylmagnesium halides) was hitherto reported [5]. The two different Grignard reactions gave 3-(1-aminophenylmethylene)-3*H*-4,5,6,7-tetrahydrobenzo[b]thiophen-2-one and 3-(1-amino-2-phenylethylidene)-3*H*-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-one, respectively, in low yields (20–25%). Evidence for the proposed structure of the new compounds was not given nor were mechanistical details discussed by the authors.

A possible mechanism for the formation of **4a–d** is given in Scheme 3 [6].

In the first step, the dimagnesium salt **5** is formed, which after 1,4-addition of the alkyl Grignard reagent to the nitrogen-bearing C-2-atom gave the intermediate **6**. This intermediate, after ring-opening led to the mercapto compound **7**, which after cyclization (loss of R^3OMgCl) gave the dimagnesium salts **8** of the 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones, which were hydrolyzed (NH_4Cl/H_2O) to the final products **4a–d**. For the formation of **7**, an alternative mechanism via attack of the Grignard reagent at C-2 under immediate ring-opening (step 3 in Scheme 3) should also be taken into account. The results of our investigations show that the reactions of alkyl Grignard reagents with 2-amino-3-carboalkoxythiophenes afford a general and useful access to 3-(1-aminoalkylidene)-3*H*-thiophen-2-ones with varied substitution pattern. With the unsubstituted thiophen-2-ones **4a** and **4c** two very interesting compounds for further chemical transformations were obtained.

Electrophilic Induced Dimerization Reactions of Compounds 4a and 4c

Taking the ^1H NMR spectra of **4a** and **4c** in $CDCl_3$, we always observed signals in the spectrum, corresponding to a side product. After storing the NMR-solutions at room temperature for several days, in each case we observed a defined mixture of starting material and a new compound. Assuming that an acid catalyzed process was responsible for the formation of the new compound ($CHCl_3$ always contains traces of HCl!), we heated compounds **4a** and **4c** in the presence of an additional acid (catalytic amounts of *p*-TsOH) for several hours at reflux temperature (Scheme 4). After work-up and chromatographic purification, we obtained two new compounds **9a** and **9b** in preparative useful yields (60–65%). The



Scheme 3 Proposed mechanism for the formation of 3*H*-thiophen-2-ones **4a–d**

structure elucidation of **9a** and **9b** uses the same methods as described for **4a**. In **9a**, the fully coupled ^{13}C spectrum already gives a strong indication of the site of the bond between the two heterocyclic rings: The signal at 35.5 ppm is a triplet with a $^1J_{CH}$-coupling constant of 144 Hz, proving it to be the signal of an SCH_2 group as the $^1J_{CH}$ -coupling constant of a C–CH_2–C would be around 127 Hz [7]. Furthermore, the single remaining olefinic =CH shows a $^1J_{CH}$ coupling constant of 163 Hz, a coupling too small for an olefinic C atom attached to an S atom [4]. Finally, the HMBC correlations over two and three bonds presented in figure 2 prove the junction to be between C-2 and C-3'.

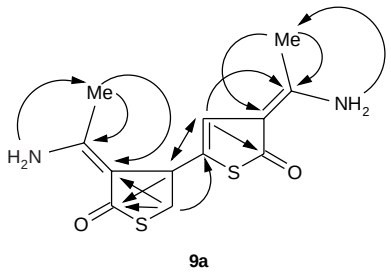
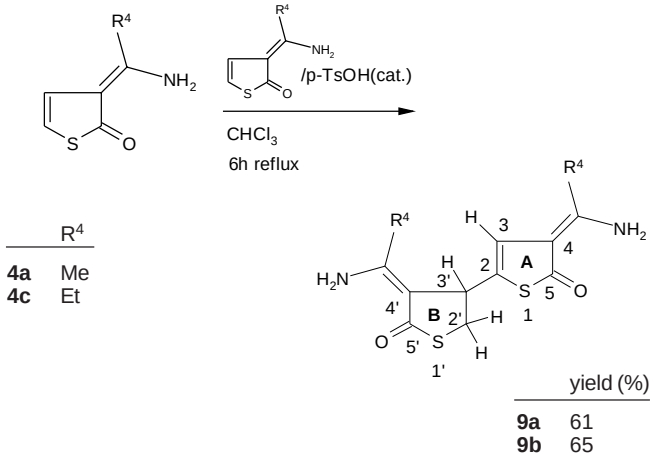


Fig. 2 HMBC correlations used in the structure elucidation of **9a**

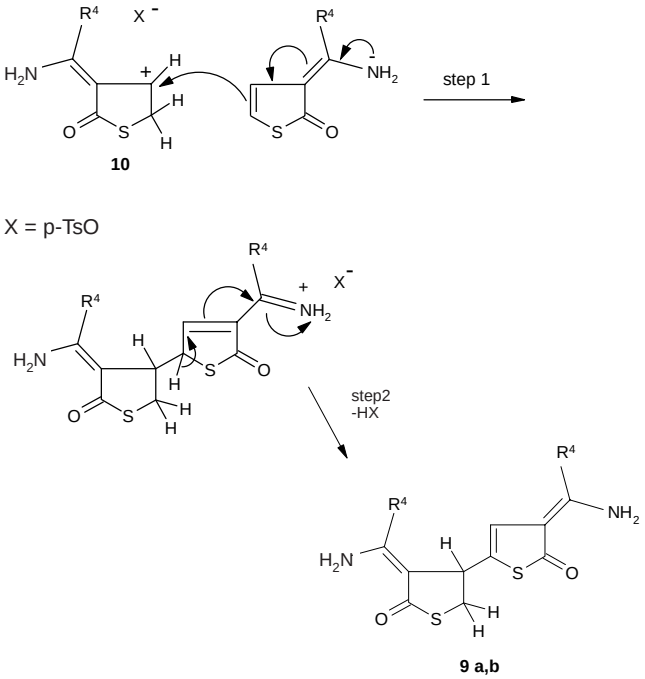
From the mechanistic point of view, the formation of the racemic 4,4'-(1-aminoalkylidene)-3',4'-dihydro-4*H*,2'*H*-[2,3']bithiophenyl-5,5'-diones **9a** and **9b** can be explained by an electrophilic- induced dimerization reaction, in which the cation **10** (see Scheme 5) acts as the electrophile. For the formation of cation **10**, we used acids like *p*-TsOH and methane sulfonic acid. The best yields were obtained by using *p*-TsOH (methane sulfonic acid catalyzed reactions gave more polymeric side products!).



	yield (%)
9a	61
9b	65

Scheme 4 Preparation of 4,4'-bis(1-aminoalkylidene)-3',4'-dihydro-4*H*,2'*H*-[2,3']bithiophenyl-5,5'diones **9a** and **9b**

The substitution reaction in the two cases investigated, only takes place at the C-5-position of **4a** and **4c**, which can be easily explained by assuming an enamine-type reaction of **4a** and **4c** with the cation **10** in the first step of the reaction (see Scheme 5).



Scheme 5 Electrophilic induced dimerization reactions of the compounds **4a** and **4c**

Our first results concerning other electrophilic reactions of **4a** and **4c**, such as nitration, acylation and chlorination showed that these reactions always afforded the 5-substituted products [8]. This selectivity may allow us to use the compounds **4a** and **4c** as useful intermediates for the synthesis of more complex thiophene-ring containing heterocycles with potential biological activity. A more thorough investigation on reactions of the compounds **4a** and **4c** with electrophiles is in progress in our laboratories.

Experimental

Melting points were measured on a Büchi B-510-apparatus and are uncorrected. The NMR-spectra were measured with a Varian Unity 500 spectrometer. Chemical shifts are reported in ppm referenced to TMS (^1H NMR) or the residual solvent signal of $CDCl_3$ or DMSO-D_6 (^{13}C NMR). IR-spectra were recorded by using a Bruker IFS 88 spectrometer. MS were obtained on a Finnigan MAT 212/SS spectrometer. TLC was performed on Merck silica gel 60F-254.

Synthesis of 3-(1-Aminoalkylidene)-3*H*-thiophen-2-ones 4a–d (General Procedure)

At room temperature, 0.03 mol of 2-amino-3-carboalkoxythiophene (**1a** or **1b**) was dissolved in 120 ml of absolute dioxane. Then the flask was cooled to 10 °C and 0.15 mol of a ca.

2.8 molar THF solution of methyl- or ethylmagnesium chloride solution (Fluka or Merck) was added slowly (ca. 30 minutes) under vigorous stirring and a constant N_2-stream in such a manner that the internal temperature remained constant at 8–10 °C. Then the mixture was heated at 75–80 °C for 3–5 hours. After cooling to 5 °C, 100 ml of a saturated aqueous ammoniumchloride solution was added slowly in such a manner, that the internal temperature remained constant at 5–10 °C. After completion of the quenching process, 400 ml EtOAc was added and the water phase extracted. After three more extractions with EtOAc, the combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by flash-chromatography (SiO_2, *n*-hexane-EtOAc 1:1). The best yields were obtained when work-up and purification were performed on the same day (60–87%).

3-(1-Aminoethylidene)-3H-thiophen-2-one (**4a**)

Slightly yellowish crystals, yield 60%, *m.p*. 117–118 °C (recrystallized from TBME). – IR (KBr): ν/cm^{-1} = 3 354, 3 268, 3 106, 1 637, 1 601, 1 478, 1 378, 1 211, 1 196, 1 106, 1 094, 862, 723, 710. – ^{1}H NMR (DMSO-D_6): δ/ppm = 2.22 (s, CH_3), 6.13 (d, *J* = 7.0, H-5), 6.61 (d, *J* = 7.0, H-4), 8.80 (s (br), 1H, NH), 9.62 (s(br), 1 H,NH). – ^{13}C NMR (DMSO-D_6): δ/ppm: 19.7 (CH_3), 106.8 (C-3), 107.4 ($^1J_{CH}$ = 188, C-5), 121.4 ($^1J_{CH}$ = 167, C-4), 163.5 (imino-C), 190.7 (C-2). – MS: *m/z* (%) = 141(84)[M$^+$], 124(62), 112(46), 96(54), 68(100).

C_6H_7NOS	Calcd.:	C 51.04	H 5.00	N 9.92	S 22.71
(141.19)	Found:	C 51.16	H 4.99	N 10.0	S 22.31.

3-(1-Aminoethylidene)-4,5-dimethyl-3H-thiophen-3-one (**4b**)

Slightly orange powder, yield 87%, *m.p*. 177–178 °C (recrystallized from TBME/EtOAc 3:1). – IR (KBr): ν/cm^{-1} = 3 328, 3 162, 3 114, 1 592, 1 480, 1 368, 1 228, 1 155, 1 074, 992, 731. – ^{1}H NMR (DMSO-D_6): δ/ppm = 2.02 (s, CH_3), 2.04 (s, CH_3), 2.33 (s, olefinic-CH_3), 8.42 (s(br), NH), 10.28 (s(br), NH). – ^{13}C NMR (DMSO-D_6): δ/ppm = 13.2 (C-4-$\underline{CH_3}$), 15.1 (C-5-$\underline{CH_3}$), 21.0 (olefinic-CH_3), 108.4 (C-3), 112.6 (C-5), 124.7 (C-4), 163.0 (imino-C), 190.7 (C-2). – MS: *m/z* (%) = 169 (100) [M$^+$], 152 (42), 124 (26), 82 (32).

$C_8H_{11}NOS$	Calcd.:	C 56.77	H 6.55	N 8.28
(169.25)	Found:	C 56.52	H 6.59	N 8.27.

3-(1-Aminopropylidene)-3H-thiophen-2-one (**4c**)

Slightly yellowish powder, yield 64%, *m.p*. 95–96 °C (recrystallized from TBME). – IR (KBr): ν/cm^{-1} = 3 266, 3 116, 3 076, 2 980, 1 647, 1 589, 1 528, 1 477, 1 377, 1 310, 1 241, 1 190, 1097, 840. – ^{1}H NMR (DMSO-D_6): δ/ppm = 1.17 (t, *J* = 7.8, $CH_2\underline{CH_3}$), 2.53 (q, *J* = 7.8, $\underline{CH_2}CH_3$), 6.16 (d, *J* = 7.0, H-5), 6.66 (d, *J* = 7.0, H-4), 8.74 (s(br), NH), 9.64 (s(br), NH). – ^{13}C NMR (DMSO-D_6): δ/ppm = 13.0 ($CH_2\underline{CH_3}$), 26.7 ($\underline{CH_2}CH_3$), 105.7 (C-3), 107.7 (C-5), 121.0 (C-4), 168.4 (imino-C), 191.2 (C-2). – MS: *m/z* (%) = 155 (100) [M$^+$], 138 (18), 126 (16), 110 (44), 82 (58).

C_7H_9NOS	Calcd.:	C 54.17	H 5.84	N 9.02
(155.22)	Found:	C 54.21	H 5.80	N 8.92.

3-(1-Aminopropylidene)-4,5-dimethyl-3H-thiophen-2-one (**4d**)

Slightly orange powder, yield 62%, *m.p*. 159–160 °C (recrystallized from TBME/EtOAc 3:1). – IR (KBr): ν/cm^{-1} = 3 263, 3 115, 2 970, 1 640, 1 573, 1 487, 1 306, 1 240, 1 218, 1 155, 1 078, 804. – ^{1}H NMR (DMSO-D_6): δ/ppm = 1.18 (t, *J* = 7.8, $CH_2\underline{CH_3}$), 2.03 (s, CH_3), 2.06 (s, CH_3), 2.62 (q, *J* = 7.8, $\underline{CH_2}CH_3$), 8.33 (s(br), NH), 10.34 (s(br),NH). – ^{13}C NMR (DMSO-D_6): δ/ppm = 13.3 (C-4-$\underline{CH_3}$), 13.6 ($CH_2\underline{CH_3}$), 14.6 (C-5-CH_3), 26.0 ($\underline{CH_2}CH_3$), 107.4 (C-3), 113.3 (C-5), 123.6 (C-4), 191.4 (C-2). – MS: *m/z* (%) = 183 (100) [M$^+$], 166 (44), 165 (16), 123 (20), 105 (10).

$C_9H_{13}NOS$ (183.27)					
Calcd.:	C 58.98	H 7.15	N 7.64	O 8.73	S 17.50
Found:	C 58.74	H 6.99	N 7.74	O 8.90	S 17.24.

Synthesis of the Compounds 9a and 9b (General Procedure)

In a 100 ml round bottom flask equipped with a Soxhlet-extraction apparatus filled with molecular sieves(4 Å) a solution of 4.0 mmol of **4a** or **4c** and a catalytic amount of freshly crystallized TsOH in 80 ml of absolute $CHCl_3$ was heated at reflux temperature for 6 hours. After cooling, the $CHCl_3$ solution was washed twice with water and after drying of the organic phase (Na_2SO_4), the solvent was removed under reduced pressure. The residue was in each case purified by flash-chromatography (SiO_2, *n*-hexane-EtOAc 1:4).

(±)-4,4'-Bis-(1-aminoethylidene)-3',4'-dihydro-4H-2'H-[2,3'] bithiophenyl-5,5'-dione (**9a**)

Orange crystals, yield 61%, *m.p*. 179–180 °C (recrystallized from EtOAc/*n*-hexane 4:1). – IR (KBr): ν/cm^{-1} = 3 313, 3 161, 1 601, 1 498, 1 225, 1 185, 1 110, 845. – ^{1}H NMR (DMSO-D_6): δ/ppm = 1.84 (s, CH_3), 2.16 (s, CH_3), 2.96 (dd, *J* = 11.2, 1.5, 1H, H-2'), 3.59 (dd, *J* = 11.2, 7.8, 1H, H-2'), 4.26 (d(br), *J* = 7.8, H-3'), 6.34 (s, H-3), 7.55 (s(br) 1H, NH(ring B), 8.61 (s(br), 2H, NH), 9.39 (s(br), 1H, NH). – ^{13}C NMR (DMSO-D_6): δ/ppm = 19.8 (CH_3(ring A)), 20.0 (CH_3(ring B)), 35.3 ($^1J_{CH}$ = 144, C-2'), 42.6 ($^1J_{CH}$ = 133, C-3'), 100.6 (C-4'), 107.0 (C-4), 116.2 ($^1J_{CH}$ = 163, C-3), 128.6 (C-2), 157.6 (imino-C(ring B)), 162.1 (imino-C(ring A)), 190.3 (C-5), 192.7 (C-5'). – MS: *m/z* (%) = 282 (100) [M$^+$], 236 (24), 208 (38), 141 (42), 124 (28).

$C_{12}H_{14}N_2O_2S_2$	Calcd.:	C 51.04	H 5.00	N.9.92
(282.39)	Found:	C 50.97	H 5.00	N 9.79.

(±)-4,4'-Bis-(1-aminopropylidene)-3',4'-dihydro-4H,2'H-[2,3'] bithiophenyl-5,5'-dione (**9b**)

Colourless crystals, yield 65 %, *m.p*. 188–189 °C (recrystallized from EtOAc/*n*-hexane 4:1). – IR (KBr): ν/cm^{-1} = 3 361, 3 287, 3 189, 1 589, 1 504, 1 382, 1 220, 1 174, 1 070, 950. – ^{1}H NMR (DMSO-D_6): δ/ppm = 0.99 (t, *J* = 7.6, $CH_2\underline{CH_3}$), 1.14 (t, *J* = 7.6, $CH_2\underline{CH_3}$), 2.12 (m, 2H, $\underline{CH_2}CH_3$(ring B)), 2.43 (q, *J* = 7.6, $\underline{CH_2}CH_3$(ring A)), 2.97 (dd, *J* = 11.3, 1.4, 1H, H-2'), 3.59 (dd, *J*= 11.3, 7.8, 1H, H-2'), 4.32 (d(br), *J* = 7.8, H-3'), 6.38 (s, H-3), 7.45 (s(br), 1H, NH), 8.55 (s(br), 1H, NH), 8.68 (s(br), 1H, NH), 9.39 (s(br), 1H, NH). – ^{13}C NMR (DMSO-D_6): δ/ppm = 12.2 ($CH_2\underline{CH_3}$ (ring B)), 12.9 ($CH_2\underline{CH_3}$ (ring A)), 26.7 ($\underline{CH_2}CH_3$ (ring B)), 26.8 ($\underline{CH_2}CH_3$ (ring A)), 35.4 (C-2'), 42.4 (C-3'), 99.9 (C-4'), 105.9 (C-4), 115.8 ($^1J_{CH}$ = 163, C-3), 129.3 (C-2), 162.3 (imino-C (ring B)), 166.9 (imino-C (ring A)), 190.9 (C-5), 193.4 (C-5'). – MS: *m/z* (%) = 310 (100) [M$^+$] , 264 (24), 155 (44).

$C_{14}H_{18}N_2O_2S_2$ (310.44)					
Calcd.:	C 54.17	H 5.84	N 9.02	O 20.66	S 10.31
Found:	C 54.16	H 5.85	N 8.90	O 20.52	S 10.33.

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