SYNTHESIS OF THIENO[3,2-*d*][1,2,3]THIADIAZOLES. NEW MECHANISTIC ASPECTS OF THE HURD-MORI REACTION

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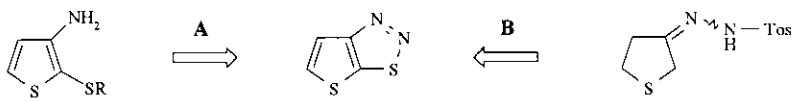
Abstract - The synthesis of new thieno[3,2-*d*][1,2,3]thiadiazole derivatives is described. A modified reaction mechanism of the Hurd-Mori reaction is presented showing better agreement with the obtained results.

In recent years 1,2,3-thiadiazoles have attracted some attention for pharmaceutical use[1] as well as precursors for highly reactive intermediates (e.g. thioketenes and alkynethiolate salts).[2] In the course of our studies towards the synthesis of various types of new annelated 1,2,3-thiadiazoles,[3] we were interested in methyl thieno[3,2-*d*][1,2,3]thiadiazolecarboxylates as new potential plant activators. For the construction of the parent ring system two synthetic approaches are reported in the literature: the first one is the cyclization by diazotation of 3-amino-2-thio-substituted thiophenes (path A in Scheme 1),[4] the second one (path B in Scheme 1) is the annelation *via* the Hurd-Mori reaction.[5]

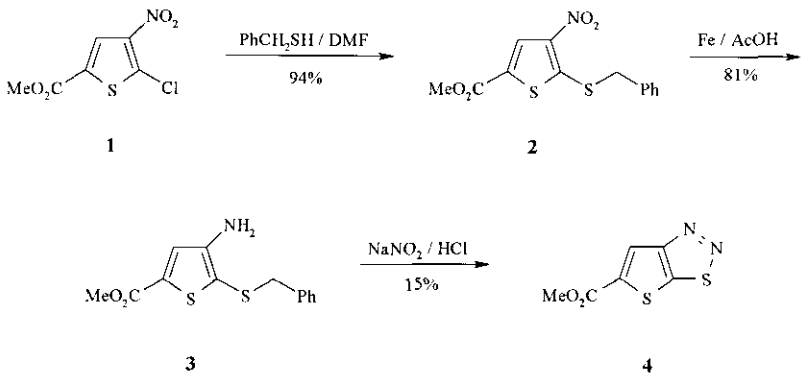


Scheme 1

Ohno *et al.*[6] prepared the methyl thieno[3,2-*d*][1,2,3]thiadiazole-6-carboxylate starting with the tosyl hydrazone of methyl tetrahydro-4-oxothiophene-3-carboxylate. The most remarkable feature of this reaction was the unexpected aromatization in the course of the cyclization. Therefore the authors proposed a plausible reaction mechanism which was able to explain the observed aromatization as a result of an elimination of 4-toluenesulfinic acid and subsequent ring rearrangement.

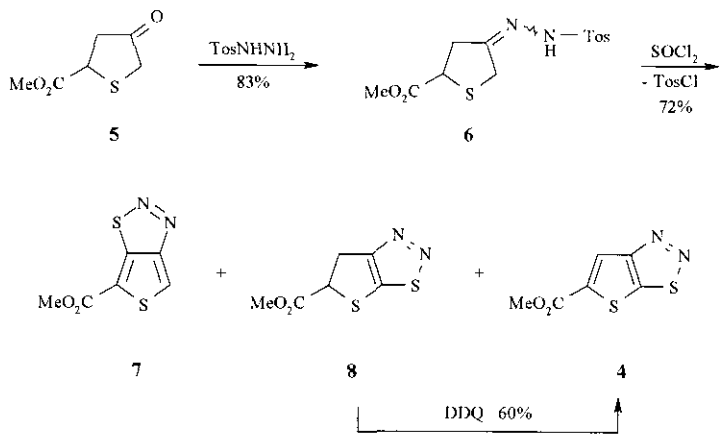
In our first attempts to build-up the unknown methyl thieno[3,2-*d*][1,2,3]thiadiazole-5-carboxylate (**4**) we started with the diazotation approach first. The reaction sequence started with the synthesis of the 4-nitro-5-phenylmethylthio- substituted thiophene (**2**) which was obtained from methyl 5-chloro-4-nitro-thiophene-2-carboxylate (**1**)[7] by nucleophilic substitution. This nitro compound was then reduced with iron

powder in acetic acid to the amine (**3**). The diazotation with sodium nitrite was carried out according to a protocol published by Gewald *et al.*[8] However, after chromatographic purification the target compound (**4**) was isolated in only 15% yield (Scheme 2).



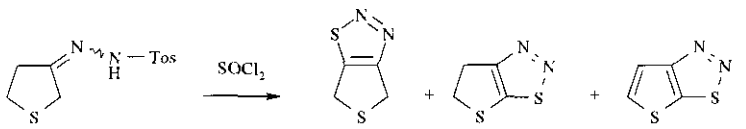
Scheme 2

As a consequence of this disappointing result we continued our synthetic work with the Hurd-Mori reaction: Thus, methyl tetrahydro-4-oxothiophene-2-carboxylate (**5**) (easily prepared from dimethyl tetrahydro-4-oxothiophene-2,3-dicarboxylate (**13**) by hydrolysis, decarboxylation and esterification[10]) was converted with 4-toluenesulfonylhydrazine to the hydrazone (**6**), which was obtained as a mixture of the *E*- and *Z*-isomers in a ratio of 45:55. The cyclization of **6** with an excess of $SOCl_2$ under standard conditions[5] yielded a 1:2.6-mixture of the 1,2,3-thiadiazoles (**7**) and (**8**) beside traces of **4** as well as tosyl chloride instead of 4-toluenesulfinic acid as described by Ohno *et al.*[6] The 5,6-dihydrothienothiadiazole (**8**) was identified using the NMR data tabulated in Table 1 and by its successful DDQ-oxidation to **4**. (Scheme 3).



Scheme 3

When we compare this product distribution with the cyclization of the tosylhydrazone (**9**) which was already investigated by Rovira *et al.*[11] we can see that in both cases [3,2-*d*]-annelation is preferred by 3:1 to the [3,4-*d*]-annelation (Scheme 4). This can be explained with the electronic influence of the sulfur atom to the regioselectivity of the Hurd-Mori reaction.[12] However, the presence of the ester functionality effects the aromatization of the [3,4-*d*] isomer (**7**) but decreases the aromatization tendency of the [3,2-*d*]-isomers (**8**:**4** = 2.6 : 0.15 *vs.* **11**:**12** = 2:1).

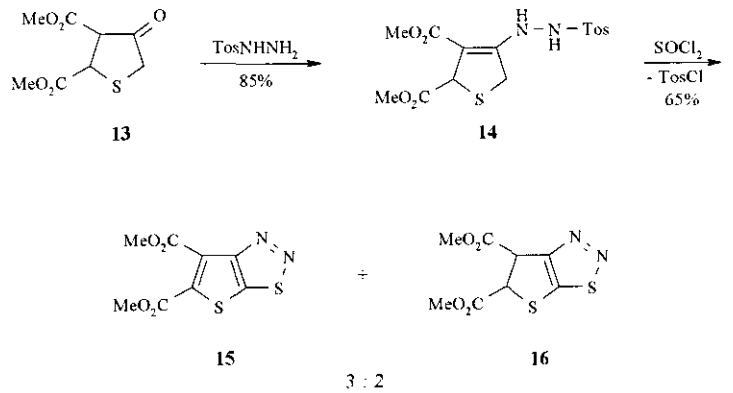


9 **10** **11** **12**

1 : 2 : 1

Scheme 4

trans-Dimethyl tetrahydro-4-oxothiophene-2,3-dicarboxylate (**13**)[9] was condensed with 4-toluenesulfonylhydrazine to the corresponding hydrazone, which appears completely in its tautomeric form (**14**). In the next step **14** was treated with an excess of $SOCl_2$ in CH_2Cl_2 at room temperature for 17 h. After working up the reaction mixture we isolated again tosyl chloride and a 3:2 mixture of **15** and the *trans*-dihydro product (**16**). (Scheme 5) The formation of tosyl chloride and **16** is in disagreement with the mechanism suggested by Ohno *et al.*[6] Our attempt to increase the amount of **15** by stirring the isolated mixture of **15** and **16** with $SOCl_2$ in CH_2Cl_2 failed. So we had an experimental evidence that the formation of the full aromatized product (**15**) must be a result of the cyclization sequence and not of a subsequent reaction, e.g. oxidation by air, dehydrogenation or some addition-elimination reactions.



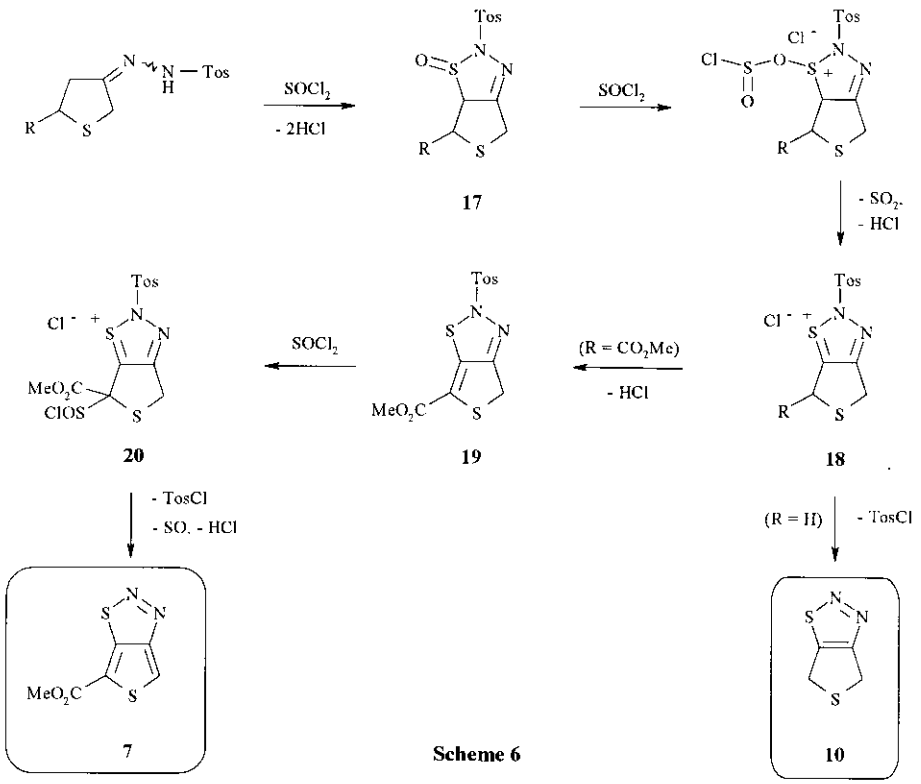
13 **14**

15 : **16**

3 : 2

Scheme 5

A mechanistic model of the Hurd-Mori reaction which explains the influence of the ester group on the aromatization of the [3,4-*d*]-isomer as well as the formation of tosyl chloride as a by-product is shown in Scheme 6. The first intermediate is the *N*-tosyldihydrothiadiazole *S*-oxide (**17**)[13] which undergoes a Pummerer-like rearrangement to the *N*-tosylthiadiazolium chloride (**18**) with $SOCl_2$. In the case R=H, **18** affords the thiadiazole (**10**) just by elimination of tosyl chloride, however, when R=CO_2Me elimination of HCl is favored. Electrophilic attack of $SOCl_2$ on the the push-pull-substituted double bond then leads to the sulfinyl chloride (**20**) which forms **7** *via* elimination of tosyl chloride, HCl, and sulfur oxide.

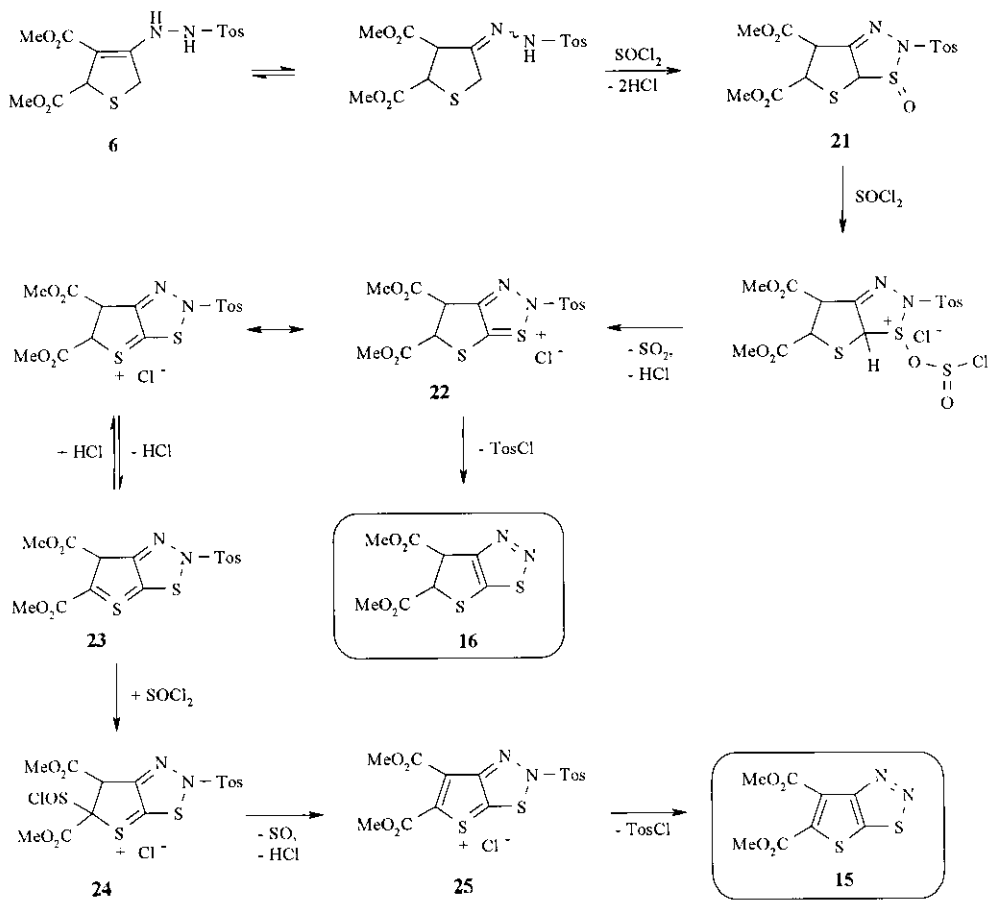


Scheme 6

Finally, we would like to suggest a model, which can probably explain the formation of the thieno[3,2-*d*][1,2,3]thiadiazoles (**15**) and (**12**) beside **16** and **11**. In Scheme 7 we have outlined the mechanism exemplified for the reaction of **14**.

The first intermediate is again the *N*-tosyldihydrothiadiazole *S*-oxide (**21**) which undergoes a *Pummerer*-like rearrangement to **22.** This intermediate can either eliminate tosyl chloride forming the dihydro-thienothiadiazole (**16**) or HCl forming the thiocarbonyl ylide intermediate (**23**) which is stabilized due to the *push-pull* substituents providing a charge stabilization.[14]

The formation of thiocarbonyl ylides under reaction conditions of the *Pummerer*-rearrangement is well known and used for the synthesis of thieno[3,4-*c*]thiophenes.[15] Thiocarbonyl ylide (**23**) can again react with $SOCl_2$ in a 1,3-addition forming the sulfinyl chloride (**24**) which forms **25** *via* a *syn*-elimination.[16] The last step is the loss of tosyl chloride leading to **15**.



Scheme 7

Table 1: Spectroscopic Properties of Thieno[3.2-*d*][1.2,3]thiadiazoles (**4-16**) in ($CDCl_3$):

Compd	^{1}H NMR	^{13}C NMR
4	4.00 (s, 3H, OMe), 8.45 (s, 1H, H-6)	52.9 (q, OMe), 122.3 (d, C-6), 141.4 (s, C-5), 149.1 (s, C-3a), 161.6 (s, CO), 168.1 (s, C-6a)
7	4.00 (s, 3H, OMe), 8.55 (s, 1H, H-4)	52.8 (q, OMe), 114.5 (s, C-6a), 122.2 (d, C-4), 144.0 (s, C-6), 161.1 (s, C-6a), 169.3 (s, CO)
8	3.70 (**ABX**, J=16 Hz, J~9 Hz, 1H, H-6A), 3.80 (s, 3H, OMe), 3.95 (**ABX**, J=16 Hz, J~6 Hz, 1H, H-6B), 5.25 (**ABX**, J~9 Hz, J~6 Hz, 1H, H-5)	28.3 (t, C-6), 52.8 (q, OMe), 58.0 (d, C-5), 151.2 (s, C-3a), 165.6 (s, C-6a), 169.7 (s, CO)
15	3.95 (s, 3H, OMe), 4.05 (s, 3H, OMe)	53.2 (q, OMe), 53.4 (q, OMe), 127.3 (s, C-6), 139.8 (s, C-5*), 147.8 (s, C-3a*), 160.3 (s, CO), 162.4 (s, CO), 165.5 (s, C-6a)
16	3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe), 5.08 (d, J= 6 Hz, 1H, H-6), 5.68 (d, J=6 Hz, 1H, H-5),	46.0 (d, C-6), 53.4 (q, OMe), 53.5 (q, OMe), 60.7 (d, C-5), 152.4 (s, C-3a), 162.0 (s, C-6a), 168.9 (s, CO), 169.1 (s, CO)

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are not corrected. All column chromatographic purifications were accomplished on silica gel 60 (Merck).

NMR spectra were recorded on a Bruker AC 200 FT-NMR spectrometer and are expressed in δ-values (ppm) downfield to TMS used as internal standard. Significant ^{1}H NMR data are tabulated in the following order: δ, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; b, broad), coupling constant(s) in Hz, number of protons, and assignments.

Methyl 4-Nitro-5-[(phenylmethyl)thio]thiophene-2-carboxylate (2):

A solution of 14.59 g (65.8 mmol) methyl 5-chloro-4-nitrothiophene-2-carboxylate (**1**)[7] in 50 mL of dry DMF was dropped into a cooled solution of 8.18 g (65.8 mmol) phenylmethylmercaptan and 18.19 g (131.6 mmol) K_2CO_3 in 20 mL of DMF. After stirring for 5 h at rt the reaction mixture was poured on ice. The precipitate was filtered, washed with cold MeOH, and dried in *vacuo* to obtain 19.2 g (94%) yellow crystals. An analytical sample was prepared by recrystallization from diisopropyl ether, mp 151-152°C; ^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3H, $COOCH_3$), 4.30 (s, 2H, SCH_2), 7.35-7.50 (m, 5H, arom.H), 8.22 (s, 1H, H-3); ^{13}C-NMR ($CDCl_3$): δ = 39.9 (t, SCH_2), 52.7 (q, $COO\underline{C}H_3$), 127.8 (d, C-3), 128.4 (d, C-4'), 128.9 (d, C-3'), 129.1 (d, C-2'), 133.3 (s, C-2), 141.3 (s, C-1'), 145.7 (s, C-4), 154.1 (s, C-5), 160.5 (s, $\underline{C}OOCH_3$). Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 50.47; H, 3.58; N, 4.53. Found: C, 50.55; H, 3.38; N, 4.50.

Methyl 4-Amino-5-[phenylmethylthio]thiophene-2-carboxylate (3):

A cooled solution of 10.00 g (32.32 mmol) of nitrothiophene (**2**) in 50 mL of AcOH was treated with 10.83 g (193.9 mmol) of Fe-powder in small portions. After stirring for 4 h at 5°C the reaction mixture was poured in water. The aqueous solution was neutralized with $NaHCO_3$ and extracted twice with ether. The organic layer was dried over Na_2SO_4 to obtain 7.43 g (81%) of beige crystals, mp 60-62°C; ^{1}H-NMR ($CDCl_3$): δ = 3.45 (br s, 2H, NH_2), 3.85 (s, 5H; SCH_2 + $COOCH_3$), 7.10-7.20 (m, 2H, arom.H), 7.20-7.30 (m, 4H, arom.H + H-3); ^{13}C-NMR ($CDCl_3$): δ = 42.2 (t, SCH_2), 52.1 (q, $COO\underline{C}H_3$), 111.9 (s, C-5), 124.6 (d, C-3), 127.3 (d, C-4'), 128.5 (d, C-3'), 128.8 (d, C-2'), 133.8 (s, C-2), 137.7 (s, C-1'), 150.1 (d, C-4), 162.0 (s, $\underline{C}OOCH_3$). Anal. Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01. Found: C, 56.39, H, 4.71, N, 4.89.

Methyl Thieno[3,2-*d*][1,2,3]thiadiazole-5-carboxylate (4):

A solution of 1.23 g (17.9 mmol) of $NaNO_2$ in 10 mL of water was dropped slowly in a cooled suspension of 5.00 g (17.9 mmol) of aminothiophene (**3**) in 70 mL of AcOH and 25 mL conc. HCl. After stirring for 90 min at 0°C the green, homogeneous solution was poured in water. The aqueous phase was neutralized with $NaHCO_3$ and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated to dryness. After chromatographic purification on 150 g silica gel using light petroleum and ethyl acetate (20:1) as the eluent and recrystallization from diisopropyl ether 0.55 g (72 %) of beige crystals were

obtained, mp 132-133°C. Anal. Calcd for $C_6H_4N_2O_4S_2$: C, 35.99; H, 2.01; N, 13.99. Found: C, 36.21; H, 2.00; N, 14.07.

General Procedure for the Preparation of the Hydrazones (6) and (14):

A solution of the ketone (**5** or **13**) and one equiv. of 4-toluenesulfonylhydrazine in dry MeOH (2 mL/mmol ketone) was stirred for 4 h at rt. The precipitate was filtered, washed with cold MeOH, and dried in *vacuo*. An analytical sample was prepared by recrystallization from MeOH.

(*E*)/(*Z*)-Methyl Tetrahydro-4-[2-[4-methylphenylsulfonyl]-2-hydrazinyl-1-ylidene]thiophene-2-carboxylate (6): This compound was obtained as colorless crystals (83%), mp 171-173°C; ^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3H, CH_3), 2.50-3.10 (m, 2H, H-3a+H-3b), 3.40-3.75 (m, 5H, H-5a+H-5b+OCH_3), 3.80-4.05 (m, 1H, H-2), 7.35 (d, 2H, J=8 Hz, H-3'+H-5'), 7.85 (d, 2H, J=8 Hz, H-2'+H-6'), 7.95 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 21.6 (q, CH_3), 29.7 (t, C-3_E), 32.4 (t, C-3_Z), 35.5 (t, C-5_Z), 39.1 (t, C-5_E), 43.3 (d, C-2_E), 44.4 (d, C-2_Z), 52.6 (q, $COOCH_{3E}$), 52.8 (q, $COOCH_{3Z}$), 128.0 (d, C-2'+C-6'), 129.7 (d, C-3'+C-5'), 135.0 (s, C-1'), 144.4 (s, C-4'), 161.4 (s, C-4_Z) 161.5 (s, C-4_E), 172.3 (s, $\underline{C}OOCH_3$). Anal. Calcd for $C_{13}H_{16}N_2O_4S_2$: C, 47.55; H, 4.91; N, 8.53. Found: C, 47.82; H, 4.90; N, 8.59.

Dimethyl 2,5-Dihydro-4-[4-methylphenylsulfonyl]hydrazothiophene-2,3-dicarboxylate (14): This compound was obtained as colorless crystals (85%), mp 169-172°C; ^{1}H NMR ($CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.68 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $COOCH_3$), 4.05 (s, 2H, H-5a+H-5b), 4.69-4.73 (m, 1H, H-2), 6.45 (br s, 1H, NH), 7.40 (d, 2H, J=8 Hz, H-3'+H-5'), 7.78 (d, 2H, J=8 Hz, H-2'+H-6'), 8.80 (br s, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$): δ = 21.6 (q, CH_3), 36.0 (t, C-5), 50.3 (d, C-2), 51.3 (q, $COO\underline{C}H_3$) 52.6 (q, $COO\underline{C}H_3$), 96.3 (s, C-3), 128.1 (d, C-2'+C-6'), 130.0 (d, C-3'+C-5'), 132.7 (s, C-1'), 145.2 (s, C-4'), 163.1 (s, C-4), 166.2 (s, $\underline{C}OOCH_3$), 173.5 (s, $\underline{C}OOCH_3$). Anal. Calcd for $C_{15}H_{18}N_2O_6S_2$: C, 46.62; H, 4.70; N, 7.25. Found: C, 46.85; H, 4.45; N, 7.24.

Methyl Thieno[3,4-*d*][1,2,3]thiadiazole-6-carboxylate (7) and methyl 5,6-dihydrothieno[3,2-*d*][1,2,3] thiadiazole-5-carboxylate (8):

A solution of 1.00 g (3.04 mmol) of **6** in 20 mL of dry CH_2Cl_2 was treated with 4.5 mL (62 mmol) of $SOCl_2$ in one portion. After stirring for 17 h at rt the mixture was concentrated in *vacuo*. The oily residue was chromatographed on 50 g silica gel using light petroleum and ethyl acetate (10:1) as the eluent to obtain 0.12 g (20%) of **7** (colorless crystals) and 0.32 g (50%) of **8** (pale yellow liquid which darkens within a few hours), respectively. An analytically pure sample of **7** was prepared by crystallization from diisopropyl ether, mp 104-106°C. Anal. Calcd for $C_6H_4N_2O_4S_2$: C, 35.99; H, 2.01; N, 13.99. Found: C, 36.21; H, 2.20; N, 13.99.

Aromatization of 8 to 4 with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ):

A solution of 150 mg (0.74 mmol) of **8** and 336 mg (1.48 mmol) of DDQ in 20 mL of dry benzene was heated under reflux for 10 days. After evaporating the solvent the residue was chromatographed on 20 g of silica gel using light petroleum and ethyl acetate (15:1) as the eluent to obtain 90 mg (60%) of **4.**

Dimethyl Thieno[3,2-*d*][1,2,3]thiadiazole-5,6-dicarboxylate (15):

A solution of 3.50 g (9.10 mmol) of **14** in 50 mL of dry CH_2Cl_2 was treated with 13.2 mL (182 mmol) of $SOCl_2$ in one portion. After stirring for 17 h at rt the mixture was concentrated in *vacuo*. The oily residue was chromatographed on 120 g of silica gel using light petroleum and ethyl acetate (3:1) as the eluent to obtain a 3:2 mixture of **15** and **16** in 65% yield. An analytically pure sample of **15** (0.40 g, 17%) was prepared by recrystallization from THF, mp 127-129°C. Anal. Calcd for $C_8H_6N_2O_4S_2$: C, 37.20; H, 2.34; N, 10.85. Found: C, 37.46; H, 2.34; N, 11.01.

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