Application of the Hurd-Mori-Reaction for the Synthesis of Tricyclic Annelated 1,2,3-Thiadiazoles

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The synthesis of methyl naphtho[1,2-*d*][1,2,3]thiadiazole-4-carboxylate **1a** as well as the corresponding thienobenzo[1,2,3]thiadiazoles **1b** and **1c** is reported using the Hurd-Mori reaction in the key step. Treatment of the readily available tosylhydrazones **10a-c** with thionyl chloride surprisingly affords the fully aromatic products **1a-c**, instead of the expected annelated 4,5-dihydro[1,2,3]thiadiazoles **2a-c**. Based on these results a mechanism for the aromatization step with thionyl chloride is proposed.

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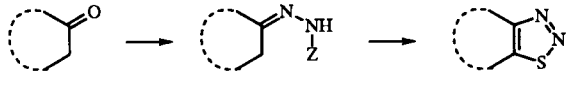
Various 1,2,3-thiadiazole derivatives are of interest for pharmaceutical use [1] as well as useful intermediates in the area of organic synthesis [2]. In the course of our research work we were interested in functionalized tricyclic annelated 1,2,3-thiadiazoles **1a-c** as potential fungicides. The retrosynthetic analysis was leading to the methodology developed by Hurd and Mori [3] *via* the 4,5-dihydro intermediates **2a-c**. This generally applicable reaction allows the annelation of the 1,2,3-thiadiazole ring during a one-pot reaction simply by treatment of *N*-acyl- or *N*-tosylhydrazones bearing an adjacent α-methyl or α-methylene group with thionyl chloride (Scheme 1).

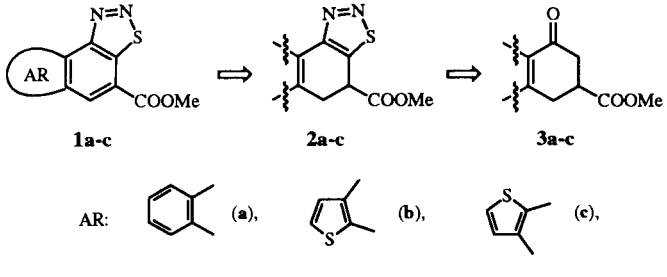
Scheme 1



Z = CH_3CO, H_2NCO, EtOCO, Tos

For the synthesis of the *N*-tosylhydrazones **10a-c** readily available γ-oxoesters **3a-c** are the logical starting products (Scheme 2).

Scheme 2



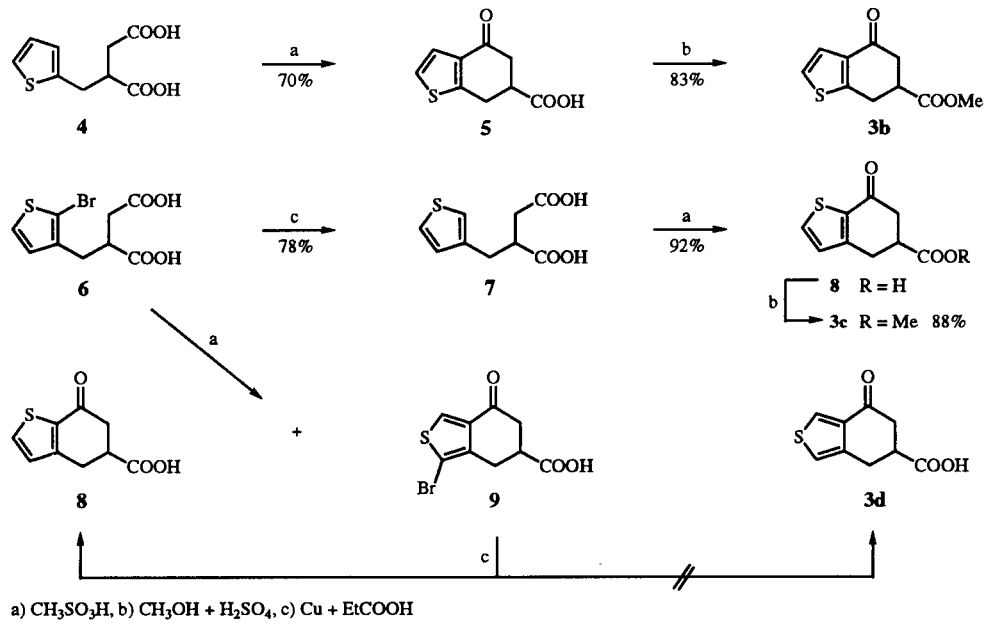
The preparation of methyl 1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylate **3a** is described in the literature [4] and the build-up of the oxoesters **3b** and **3c** was easily accomplished in a straightforward sequence starting from known compounds (Scheme 3).

Friedel-Crafts cyclization of (2-thienylmethyl)butanedioic acid **4** [5] in methanesulfonic acid led to 4,5,6,7-tetrahydro-4-oxobenzo[*b*]thiophene-6-carboxylic acid **5** which was transformed to the ester **3b**. The oxoester **3c** was obtained in good yield by reductive debromination of [3-(2-bromothienyl)methyl]butanedioic acid **6** [6] with freshly precipitated copper [7] in propanoic acid [8] followed by cyclization of the obtained (3-thienylmethyl)butanedioic acid **7** and subsequent esterification. As the more common method with zinc and acetic acid was not successful in the present case, the modification with copper in propionic acid was a very useful alternative to the sodium amalgam debromination described in the literature [6].

Having in mind to synthesize the third possible isomer **3d** also by starting from **6** we tried to use the bromine in 2-position to force the cyclization reaction into the 4-position of the thiophene ring. However, Friedel-Crafts acylation led to a 5:1 mixture of the expected bromo acid **9** accompanied by some **8** formed probably by an *ipso*-substitution, not unusual in thiophene chemistry [9]. Extending the reaction time did not affect the ratio of **8** and **9** but increasing decomposition was observed instead. Since **8** and **9** could not be separated, we tried the debromination with copper and subsequent esterification expecting a better chance for a chromatographic separation of the isomeric esters. Unexpectedly, after reduction of the mixture of **8** and **9** only the known *b*-annelated isomer **8** was isolated in good yields, obviously resulting from a *retro*-Friedel-Crafts reaction followed by recyclization (Scheme 3).

The *N*-tosylhydrazones **10a-c** were easily prepared from the corresponding γ-oxoesters **3a-c** and (*p*-toluenesulfonyl)hydrazine by refluxing in methanol. When the hydrazones **10a-c** were treated with twenty equivalents of thionyl chloride at room temperature in all three cases the fully aromatic thiadiazoles **1a-c** were obtained in a one pot reaction in good yields without any of the expected dihydro thiadiazoles **2a-c** (Scheme 4). This result was rather surprising as the analogous reaction of 1-tetralone (*p*-toluenesulfonyl)hydrazone according to the literature [10] results exclusively in the formation of 4,5-dihydronaphtho[1,2-*d*][1,2,3]thiadiazole **13**. Consequently, the

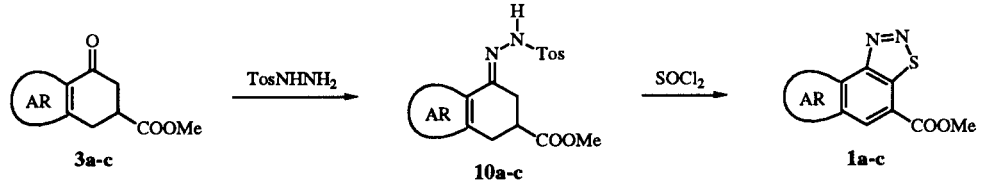
Scheme 3

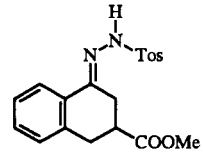
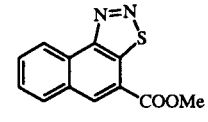
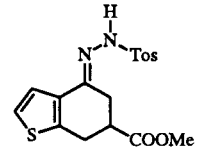
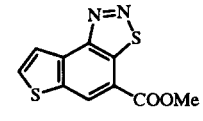
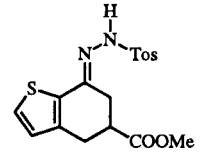
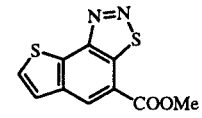


presence of the ester functionality seems to be responsible for the observed aromatization.

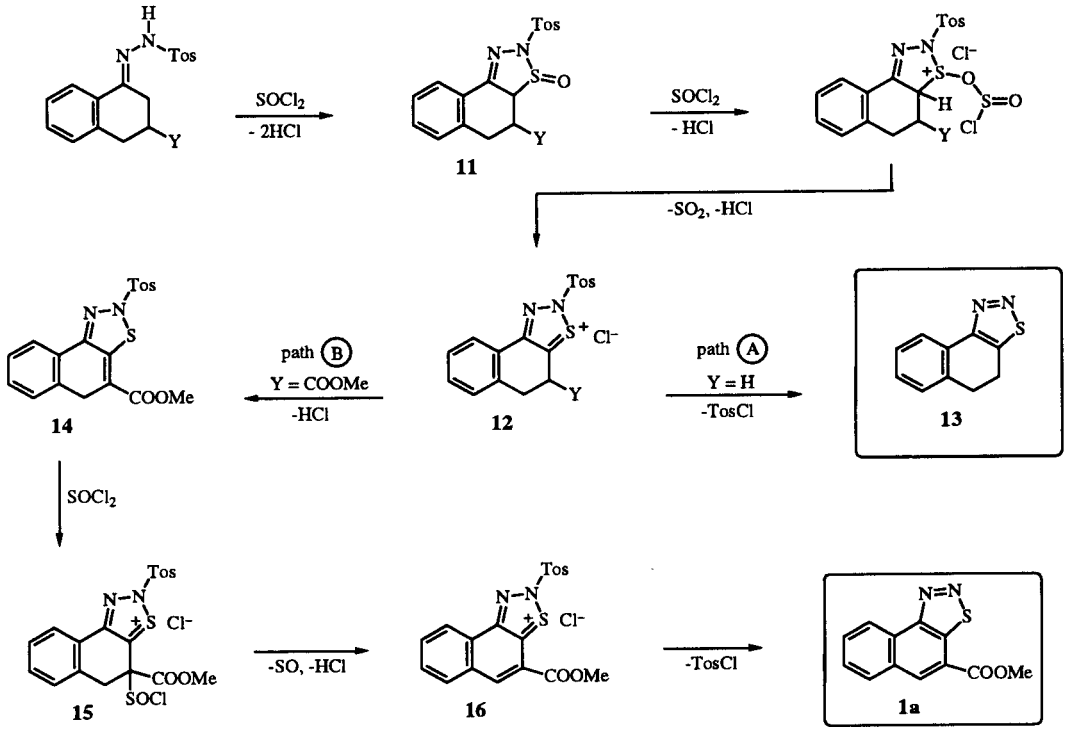
In Scheme 5 we propose a mechanistic model based on the mechanism of Britton *et al.* [1a], which probably can explain the influence of the substituent Y on the reaction sequence. The first intermediate is the *N*-tosyldihydrothiadiazole *S*-oxide **11** [11] which undergoes with thionyl chloride a Pummerer-like rearrangement to *N*-tosylthiadia-

Scheme 4



Compound	Structure	Yield	Compound	Structure	Yield
10a		90%	**1a**		73%
10b		91%	**1b**		94%
10c		87%	**1c**		90%

Scheme 5



zolium chloride **12**. If Y = H (path A), **12** leads to the dihydrothiadiazole **13** *via* elimination of tosyl chloride which can be isolated as a by-product. However when Y = $COOCH_3$ (path B) elimination of hydrogen chloride is probably favored and **14** is formed. Electrophilic attack of thionyl chloride on the push-pull-substituted double bond in the intermediate **14** leads to the sulfinyl chloride **15** which forms **16** *via* a *syn*-elimination [12]. The last step is again the loss of tosyl chloride leading finally to the aromatic product **1a**.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. All column chromatographic purifications were accomplished on silica gel 60 (E. Merck). The nmr spectra were determined with a Bruker AC 200 FT-NMR spectrometer and are expressed in parts per million (ppm) downfield to tetramethylsilane (internal standard). Significant ^1H nmr data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; b, broad), coupling constant(s) in Hz, number of protons, and assignments.

(3-Thienylmethyl)butanedioic Acid (**7**).

A mixture of [3-(bromothienyl)methyl]butanedioic acid **6** (20.00 g, 68.23 mmoles) and freshly precipitated copper (18.00 g, 283.24 mmoles) in 180 ml propanoic acid was heated under reflux for 72 hours. The hot solution was filtered and the residue was washed with propanoic acid. After evaporation the green solid was dissolved in 2*N* hydrochloric acid and extracted with diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, treated with charcoal and evaporated to dryness. After crystalization of the residual oil the product was filtered off and washed with dichloromethane to obtain 11.30 g (52.74 mmoles, 78%) pale yellow crystals, mp 135-138°; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.28 (ABX, ^2J = 16 Hz, 1H, ThC*H*H), 2.43 (ABX, ^2J = 16 Hz, 1H, ThCH*H*), 2.68-3.00 (m, 3H, C*H*COOH+CH_2COOH), 6.97 (d, $J_{H\text{-}4'\text{-}H\text{-}5'}$ = 5 Hz, 1H, H-4'), 7.18 (d, $J_{H\text{-}2'\text{-}H\text{-}5'}$ = 3 Hz, 1H, H-2'), 7.47 (dd, $J_{H\text{-}5'\text{-}H\text{-}4'}$ = 5 Hz, $J_{H\text{-}5'\text{-}H\text{-}2'}$ = 3 Hz, 1H, H-5'), 12.25 (bs, 2H, COOH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 31.6 (t, Th*C*H_2), 35.2 (t, *C*H_2COOH), 42.0 (d, *C*HCOOH), 122.3 (d, C-2'), 126.2 (d, C-5'), 128.7 (d, C-4'), 139.1 (s, C-3'), 173.2 (s, CH_2*C*OOH), 175.5 (s, CH*C*OOH).

General Procedure for the Preparation of Carboxylic Acids **5** and **8**.

A solution of (thienylmethyl)butanedioic acid **4** or **7** (9.00 g, 42.00 mmoles) in 60 ml of methanesulfonic acid was heated for 90 minutes at 70°. After cooling, the mixture was poured on ice and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness to give **5** and **8**, respectively.

4,5,6,7-Tetrahydro-4-oxobenzo[*b*]thiophene-6-carboxylic Acid (**5**).

This compound was obtained as beige crystals, 70%, mp 132-134°; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.60-2.80 (m, 2H, H-5a+H-5b), 2.20-3.40 (m, 3H, H-6+H-7a+H-7b), 7.25 (d, J = 5 Hz, 1H, H-3), 7.40 (d, J = 5 Hz, 1H, H-2), 12.60 (bs, 1H, COOH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 27.2 (t, C-7), 39.3 (t, C-5), 40.5 (d, C-6), 123.8 (d, C-3), 124.6 (d, C-2), 136.4 (s, C-3a), 153.7 (s, C-7a), 174.1 (s, COOH), 190.5 (s, C-4).

4,5,6,7-Tetrahydro-7-oxobenzo[*b*]thiophene-5-carboxylic Acid (**8**).

This compound was obtained as beige crystals, 92%, mp 162-164°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.68-2.87 (m, 2H, H-6a+H-6b), 2.99-3.38 (m, 3H, H-4a+H-4b+H-5), 7.16 (d, J = 5 Hz, 1H, H-3), 8.00 (d, J = 5 Hz, 1H, H-2), 11.25 (bs, 1H, COOH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 28.0 (t, C-4), 39.6 (t, C-6), 40.5 (d, C-5), 128.9 (d, C-3), 134.9 (d, C-2), 135.2 (s, C-7a), 150.7 (s, C-3a), 174.5 (s, COOH), 189.7 (s, C-7).

General Procedure for the Preparation of the Oxoester **3b** and **3c**.

A solution of the carboxylic acid **5** or **8** and methanesulfonic acid (0.1 ml/g) in dry methanol (10 ml/g) was heated under reflux for 17 hours. After cooling, the reaction mixture was concentrated *in vacuo*. The mixture was diluted with ether, washed with saturated aqueous sodium hydrogencarbonate and dried over anhydrous sodium sulfate. The ether was removed by rotary evaporation and the residue was microdistilled (Büchi GKR-51 apparatus) (130°, 0.05 mbar) to give **3b** and **3c**, respectively.

Methyl 4,5,6,7-Tetrahydro-4-oxobenzo[*b*]thiophene-6-carboxylate (**3b**).

This compound was obtained as white solid, 83%, mp 74-75°; ^{1}H nmr (deuteriochloroform): δ 2.70-2.95 (m, 2H, H-5a+H-5b), 3.25-3.43 (m, 3H, H-6+H-7a+H-7b), 3.75 (s, 3H, $COOCH_3$), 7.13 (d, J = 6 Hz, 1H, H-2), 7.39 (d, J = 6 Hz, 1H, H-3); ^{13}C nmr (deuteriochloroform): δ 27.6 (t, C-7), 39.5 (t, C-5), 41.3 (d, C-6), 52.2 (q, $COOCH_3$), 123.7 (d, C-3), 124.5 (d, C-2), 136.7 (s, C-3a), 152.9 (s, C-7a), 172.7 (s, $COOCH_3$), 190.1 (s, C-4).

Anal. Calcd. for $C_{10}H_{10}O_3S$ (210.25): C, 57.13; H, 4.79. Found: C, 57.07; H, 4.59.

Methyl 4,5,6,7-Tetrahydro-7-oxobenzo[*b*]thiophene-5-carboxylate (**3c**).

This compound was obtained as white solid, 88%, mp 78-80°; ^{1}H nmr (deuteriochloroform): δ 2.82-2.91 (m, 2H, H-6a+H-6b), 3.05-3.38 (m, 3H, H-5+H-4a+H-4b), 3.75 (s, 3H, $COOCH_3$), 7.00 (d, J = 6 Hz, 1H, H-3), 7.67 (d, J = 6 Hz, 1H, H-2); ^{13}C nmr (deuteriochloroform): δ 28.1 (t, C-4), 39.6 (t, C-6), 41.0 (d, C-5), 51.9 (q, $COOCH_3$), 127.9 (d, C-3), 134.4 (d, C-2), 135.6 (s, C-7a), 149.6 (s, C-3a), 172.9 (s, $COOCH_3$), 189.0 (s, C-7).

Anal. Calcd. for $C_{10}H_{10}O_3S$ (210.25): C, 57.13; H, 4.79. Found: C, 57.05; H 4.67.

General Procedure for the Preparation of the Hydrazones **10a-c**.

A mixture of oxoester **3** and one equivalent *p*-toluenesulfonylhydrazide in methanol (10 ml/g) was heated under reflux for four hours. On cooling the crystalline product was collected and dried under vacuum to give **10a**, **10b** and **10c** in 90, 91 and 87% yield, respectively. The products were pure enough for further reactions. An analytical sample was prepared by recrystallization from methanol.

Methyl 1,2,3,4-Tetrahydro-4-[2-[(4-methylphenyl)sulfonyl]-2-hydrazinyl-1-yliden]-2-naphthalenecarboxylate (**10a**).

This compound was obtained as colorless crystals, mp 179-184°; ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 2.45-2.62 (m, 1H), 2.75-3.12 (m, 4H), 3.70 (s, 3H, $COOCH_3$), 7.10-7.38 (m, 5H, arom H), 7.68 (bs, 1H, NH), 7.85-8.03 (m, 3H, arom H); ^{13}C nmr (deuteriochloroform): δ 21.6 (q, CH_3), 27.6 (t, C-1*), 31.7 (t, C-3*), 38.4 (d, C-2), 52.2 (q, $COOCH_3$), 124.9 (d, C-6), 127.0 (d, C-8), 128.1 (d, C-2'+C-6'), 128.4 (d, C-5), 129.6 (d, C-3'+C-5'), 129.9 (d, C-7), 131.0 (s, C-4a), 135.4 (s, C-1'), 136.9 (s, C-8a), 144.1 (s, C-4'), 150.3 (s, C-4), 173.8 (q, $COOCH_3$).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S$ (372.45): C, 61.27; H, 5.41; N, 7.52. Found: C, 61.05; H, 5.21; N, 7.73.

Methyl 4,5,6,7-Tetrahydro-4-[2-[(4-methylphenyl)sulfonyl]-2-hydrazinyl-1-yliden]-6-benzo[*b*]thiophenecarboxylate (**10b**).

This compound was obtained as colorless crystals, mp 193-195°; ^{1}H nmr (deuteriochloroform): δ 2.38-2.55 (m, 4H), 2.85-3.25 (m, 4H), 3.70 (s, 3H, $COOCH_3$), 7.05 (d, J = 6 Hz, 1H, H-3), 7.30-7.45 (m, 3H, H-2+H-3'+H-5'), 7.55 (bs, 1H, NH), 7.90 (d, J = 8 Hz, 2H, H-2'+H-6'); ^{13}C nmr (deuteriochloroform): δ 21.6 (q, CH_3), 26.3 (t, C-5*), 26.9 (t, C-7*), 39.7 (d, C-6), 52.3 (q, $COOCH_3$), 123.4 (d, C-3*), 123.9 (d, C-2*), 128.2 (d, C-2'+C-6'), 129.5 (d, C-3'+C-5'), 133.3 (s, C-3a), 135.2 (s, C-1'), 141.6 (s, C-7a), 144.1 (s, C-4'), 148.8 (s, C-4), 173.1 (s, $COOCH_3$).

Anal. Calcd. for $C_{17}H_{18}N_2O_4S_2$ (378.47): C, 53.95; H, 4.79; N, 7.40. Found: C, 54.16; H, 4.59; N, 7.54.

Methyl 4,5,6,7-Tetrahydro-7-[2-[(4-methylphenyl)sulfonyl]-2-hydrazinyl-1-yliden]-5-benzo[*b*]thiophenecarboxylate (**10c**).

This compound was obtained as colorless crystals, mp 190-191°; ^{1}H nmr (deuteriochloroform): δ 2.40-2.60 (m, 4H), 2.75-3.18 (m, 4H), 3.70 (s, 3H, OCH_3), 6.82 (d, J = 5 Hz, 1H, H-3), 7.20-7.38 (m, 4H, H-2+H-3'+H-5'+NH), 7.90 (d, J = 8 Hz, 2H, H-2'+H-6'); ^{13}C nmr (deuteriochloroform): δ 21.6 (q, CH_3), 27.0 (t, C-6*), 27.8 (t, C-4*), 39.6 (d, C-5), 52.3 (q, $COOCH_3$), 127.3 (d, C-3), 128.3 (d, C-2'+C-6'), 128.4 (d, C-2), 129.4 (d, C-3'+C-5'), 133.4 (s, C-7a), 135.1 (s, C-1'), 141.4 (s, C-3a), 144.1 (s, C-4'), 149.5 (s, C-7), 173.5 (s, $COOCH_3$).

Anal. Calcd for $C_{17}H_{18}N_2O_4S_2$ (378.47): C, 53.95; H, 4.79; N, 7.40. Found: C, 53.96; H, 4.99; N, 7.47.

Methyl Naphtho[1,2-*d*][1,2,3]thiadiazol-4-carboxylate (**1a**).

A solution of **10a** (1 20 g, 3.22 mmoles) in 10 ml dry dichloromethane was treated with thionyl chloride (4.7 ml, 64 mmoles) in one portion and stirred for 17 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the oily residue was chromatographed on 50 g of silica gel using light petroleum:ethyl acetate (9:1, v/v) giving 0.57 g (2.33 mmoles, 73%) of beige crystals of the desired compound, mp 161-163°; ^{1}H nmr (deuteriochloroform): δ 4.13 (s, 3H, $COOCH_3$), 7.80 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 1H, H-7*), 7.97 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 1H, H-8*), 8.17 (d, J = 8 Hz, 1H, H-6), 8.80 (s, 1H, H-5), 9.21 (d, J = 8 Hz, 1H, H-9); ^{13}C nmr (deuteriochloroform): δ 53.1 (q), 120.1 (s), 124.2 (d), 128.1 (d), 129.2 (s), 129.7 (d), 131.1 (d), 131.4 (s), 133.4 (d), 138.1 (s), 155.5 (s), 165.4 (s).

Anal. Calcd. for $C_{12}H_8N_2O_2S$ (244.27): C, 59.00; H, 3.30; N, 11.47. Found: C, 58.86; H, 3.39; N, 11.54.

General Procedure for the Preparation of the Thienobenzo-[1,2,3]thiadiazoles **1b** and **1c**.

A suspension of **10b** or **10c** in dry dichloromethane (10 ml/g) was treated with 20 equivalents of thionyl chloride in one portion. After stirring 17 hours at room temperature the mixture was concentrated *in vacuo*. The solid residue was treated with water, filtered and washed carefully with methanol to give **1b** and **1c**, respectively. An analytical sample was prepared by recrystallization from tetrahydrofurane.

Methyl Thieno[3,2-*e*]benzo[1,2,3]thiadiazol-4-carboxylate (**1b**).

This compound was obtained as beige crystals, 94%, mp 175-178°; ^{1}H nmr (deuteriochloroform): δ 4.08 (s, 3H, $COOCH_3$), 8.05 (d, $J_{H\text{-}7\text{-}H\text{-}8}$ = 6 Hz, 1H, H-7), 8.40 (dd, $J_{H\text{-}8\text{-}H\text{-}7}$ = 6 Hz,

$J_{H\text{-}8\text{-}H\text{-}5}$ < 1 Hz, 1H, H-8), 8.80 (d, $J_{H\text{-}5\text{-}H\text{-}8}$ < 1 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 53.0 (q), 118.1 (s), 122.1 (d), 125.8 (d), 133.9 (d), 136.4 (s), 138.3 (s), 138.4 (s), 152.8 (s), 165.2 (s).

Anal. Calcd. for $C_{10}H_6N_2O_2S_2$ (250.30): C, 47.99; H, 2.42; N, 11.19. Found: C, 48.11; H, 2 63; N, 11.39.

Methyl Thieno[2,3-*e*]benzo[1,2,3]thiadiazol-4-carboxylate (**1c**).

This compound was obtained as beige crystals, 90%, mp 204-207°; ^1H nmr (deuteriochloroform): δ 4.10 (s, 3H, $COOCH_3$), 7.68 (d, J = 6 Hz, 1H, H-6), 7.72 (d, J = 6 Hz, 1H, H-7), 8.78 (s, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 53.2 (q), 119.5 (s), 124.9 (d), 127.0 (d), 128.4 (d), 137.9 (s), 138.0 (s), 139.3 (s), 152.9 (s), 165.8 (s).

Anal. Calcd. for $C_{10}H_6N_2O_2S_2$ (250.30); C, 47.99; H, 2.42; N, 11.19. Found: C, 48.08, H, 2.14, N, 11.39.

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