

REACTIONS OF 1,3-DITHIETANE-2,4-DIYLIDENE BIS-(CYANOACETIC ACID ALKYL ESTERS) AND 2-CYANO-3,3-BIS(METHYLSULFANYL)ACRYLIC ACID ETHYL ESTER

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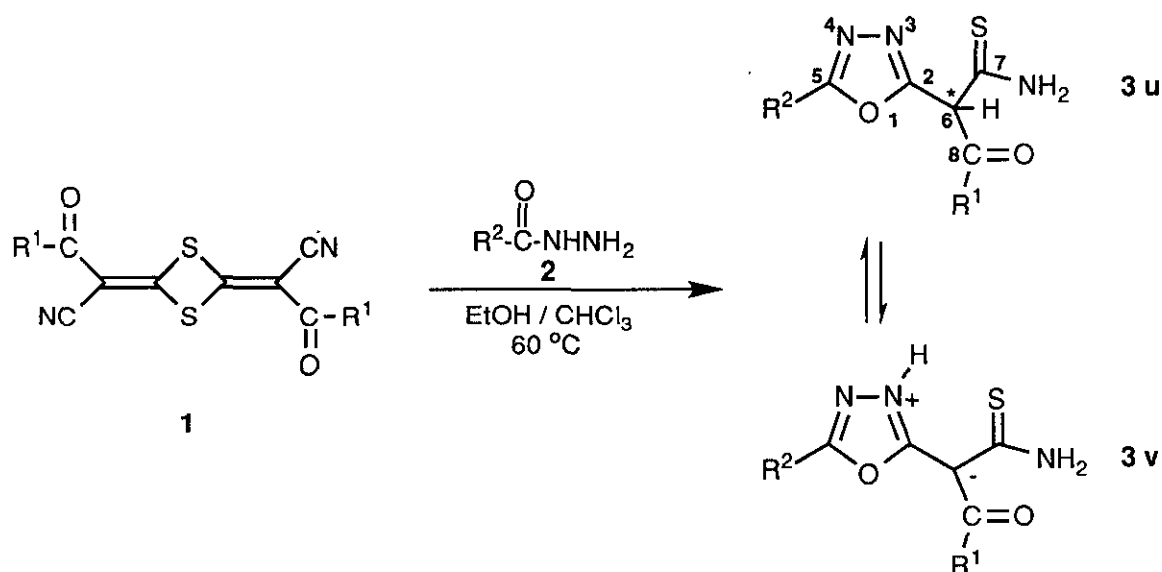
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Dedicated on 70th birthday of Heinz A. Staab, Max-Planck-Institut für Medizinische Forschung – Organische Chemie, Heidelberg

Abstract - 1,3-Dithietanes (1) react with carboxylic acid hydrazides (2) yielding substituted 1,3,4-oxadiazoles (3). The treatment of compound (1) with 5-phenylpyrazolidin-3-one (4) resulted in 5H-pyrazolo-[5,1-b][1,3]thiazines (5). Pyrazoles (7) can be obtained by the reaction of ketene-S,S-acetals (6) with carboxylic acid hydrazides (2).

In our previous papers^{1a-1} we reported syntheses of different phosphono and phosphino-substituted heterocycles and the reaction of 1,3-dithietane-2,4-diylidenebis(cyanomethylphosphonates) and phenylphosphinates with carboxylic acid hydrazides which yield tautomeric 1,3,4-oxadiazoles. One of the tautomers was confirmed by X-ray structure analysis. Our results fell under scrutiny because they contradicted with the conjecture of the resulting product with the carboxylic acid alkyl ester analogues published by K. Peseke.²

In our investigation the reaction of the 1,3-dithietanes (**1**) with carboxylic acid hydrazides (**2**) (ethanol / chloroform, 60 °C) resulted in 1,3,4-oxadiazoles (**3**) (yield: 73 - 88 % based upon **2**, Scheme 1) . These results correspond to those found with the phosphonato and phosphinato-substituted 1,3-dithietanes.^{1a}



compound	R ¹	R ²
3.1 a	OEt	Ph
3.1 b	OEt	C ₆ H ₄ -Cl-p
3.1 c	OEt	C ₆ H ₄ -NO ₂ -p
3.1 d	OEt	C ₆ H ₄ -OMe-p
3.1 e	OEt	CH=CHC ₆ H ₅
3.2 f	OMe	C ₆ H ₄ -Me-p

Scheme 1: Synthesis of 1,3,4-oxadiazoles (**3**)

The constitution of the 1,3,4-oxadiazole (**3.2f**) was proved by X-ray structure analysis (Figure 1) and should be representative for this class of compounds (**3**).

In crystalline form **3.2f** possesses the tautomeric structure (**3 v**) (Scheme 1 shows only one possible mesomeric derivative of **3 v**). The molecule (**3.2f**) is nearly planar with the exception of

the methyl protons of the methoxycarbonyl and the methylphenyl substituents respectively. The variations in the bond lengths of the oxadiazole ring which reflect the delocalization of the π -electrons are in accordance with our previous results.^{1a} An intramolecular hydrogen bond is observed between N7'-H...O8'A (2.567 (3) Å; sum of the van der Waals radii for nitrogen and oxygen:³ 2.90 Å). In addition the intramolecular S7'...N3-distance (2.929 (2) Å) is shorter than the sum of the van der Waals radii for sulfur and nitrogen³ (3.35 Å).

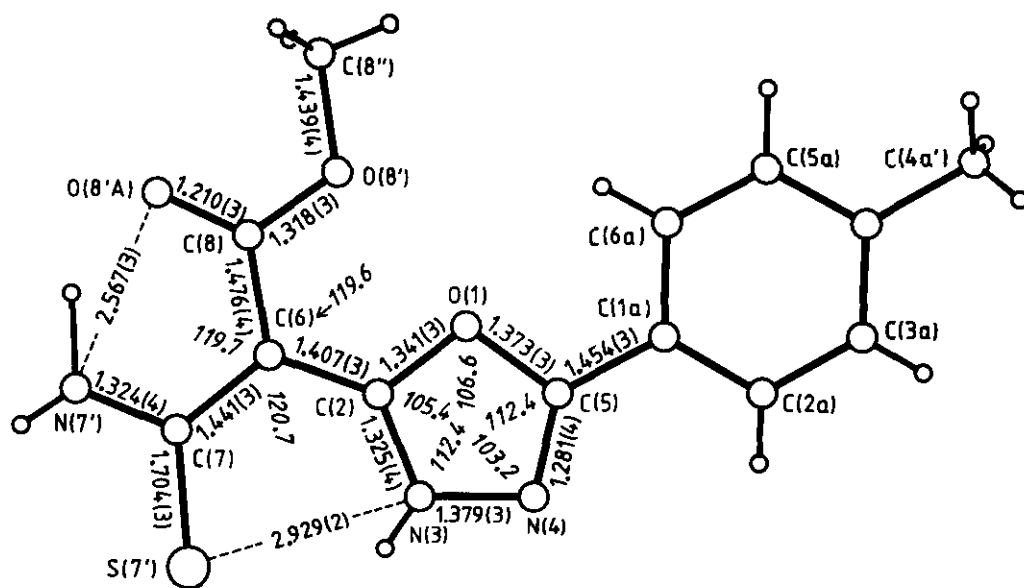


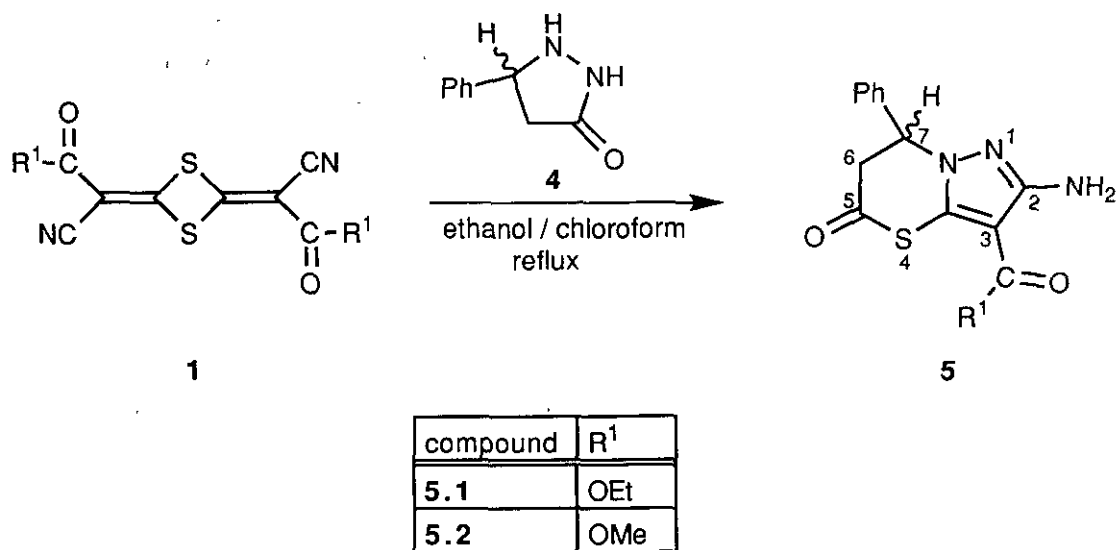
Figure 1: Perspective view, atom labelling, selected bond distances (in Å) and bond angles (in °) of **3.2f**

The presence of two tautomeric structures (**3 u**) and (**3 v**) in solution could be detected in the case of compound (**3.1a**) by nmr spectroscopy. In the ¹H nmr spectrum (DMSO-d₆) the presence of the single tautomer (**3.1a u**) was indicated by the presence of the H-6 proton which occurred as a singlet at 5.75 ppm (intensity: 1H) and two signals for the NH-protons at 9.74 ppm and 10.17 ppm. However in CDCl₃ a weak signal for the H-6 proton is found along with the expected signals for the NH-protons at 6.92 ppm, 10.40 ppm and 15.83 ppm indicating **3.1a v** as the main tautomer.

The reaction products (**3**) should mechanistically be explained by the initial nucleophilic attack on the 1,3-dithietane carbon by the β -N atom of the carboxylic acid hydrazide, subsequent tautomerism, cyclization and transformation of the cyanogroup.^{1a,4}

As seen from Scheme 1, the reaction from 1,3-dithietane (**1.1**) with 3-phenylacrylic acid hydrazide (**2e**) also yields 1,3,4-oxadiazole (**3.1e**). A consecutive reaction which is described by K. Peseke *et al.*⁵ was not observed.

The physical properties of the reaction product described by K. Peseke *et al.*⁵ were in accordance with those found in the substance obtained by the reaction of the 1,3-dithietane (**1.1**) with 5-phenylpyrazolidin-3-one (**4**) (ethanol / chloroform, reflux) (yield: 61 - 73 % based upon **2**; Scheme 2). The racemic 5-phenyl-pyrazolidin-3-one⁶ (**4**) was prepared from 3-phenylacrylic acid ethyl ester and hydrazine hydrate (ethanol, reflux) and falsely described in the older literature⁷ as 3-phenylacrylic acid hydrazide.



Scheme 2: Synthesis of 5*H*-pyrazolo[5,1-*b*][1,3]thiazines (**5**)

The X-ray structure analysis of the reaction product (**5**) (Figure 2) shows the 5*H*-pyrazolo[5,1-*b*]-[1,3]thiazine system instead of the 1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol system described by K. Peseke *et al.*⁵ In the unit cell two molecules related by inversion center are detected.

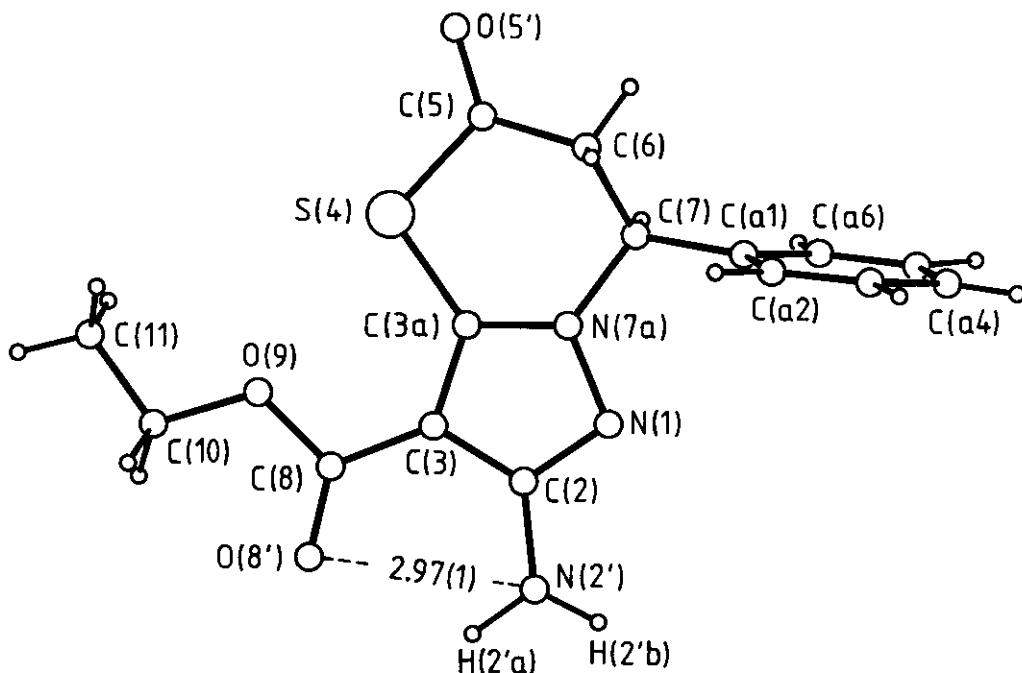
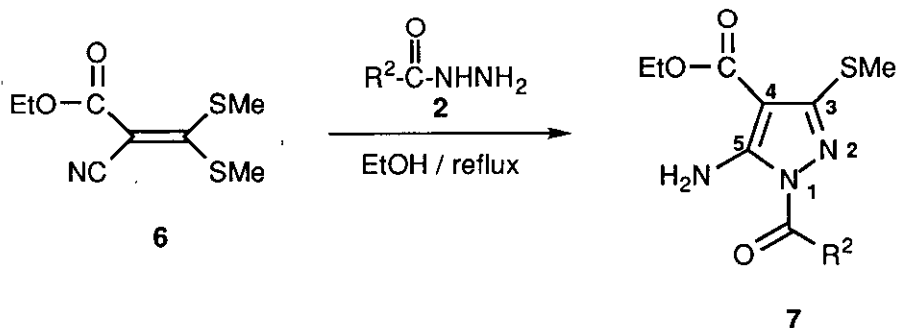


Figure 2: Perspective view and atom labelling of 5.1

After these results it was interesting to examine the constitution of the pyrazoles prepared by K. Peseke² from 2-cyano-3,3-bis(methylsulfanyl)acrylic acid ethyl ester (**6**) and carboxylic acid hydrazides (**2**).



compound	R ²
7 a	Ph
7 b	C ₆ H ₄ -Cl-p
7 c	C ₆ H ₄ -NO ₂ -p
7 d	C ₆ H ₄ -OMe-p

Scheme 3: Synthesis of pyrazoles (**7**)

From our point of view the reaction products should be 1-*R*-5-amino-3-methylsulfanyl-1*H*-pyrazole-4-carboxylic acid ethyl esters (**7**) ($R = R^2CO$, Scheme 3) and not 1-*R*-3-amino-5-methylsulfanyl-1*H*-pyrazole-4-carboxylic acid ethyl esters as proposed by K. Peseke.² We carried out the reactions under the same conditions (5 h, reflux) and isolated products with nearly the same analytical data.²

The X-ray structure analysis of compound (**7**) confirms the generation of the pyrazole ring (Figure 3) with substitution as indicated.

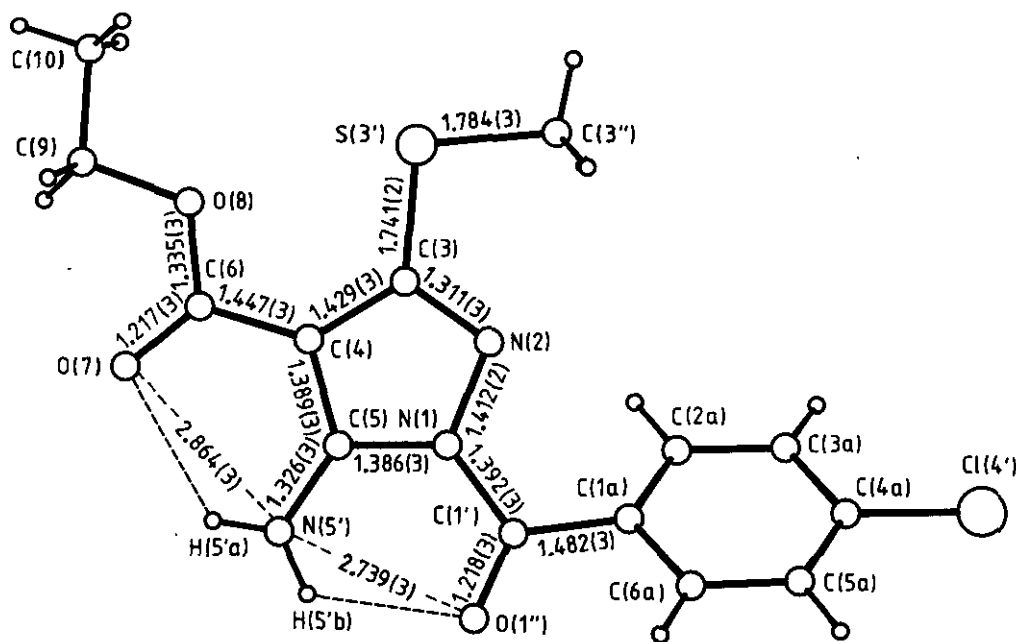


Figure 3: Perspective view, atom labelling and selected bond distances (in Å) of **7b**

In the pyrazole ring of **7b** the N1-N2, N1-C5, C3-C4 and C4-C5 bond lengths (1.412 (2) Å, 1.386 (3) Å, 1.429 (3) Å and 1.389 (3) Å) are slightly elongated compared to those of 1*H*-pyrazole (1.366 Å, 1.357 Å, 1.410 Å and 1.369 Å).⁸ However the N2-C3 bond length (1.311 (3) Å) differs somewhat in that it is shorter than the value described in the literature (1.329 Å).⁸

The N5'...O1" and N5'...O7 distances (2.739 (3) Å and 2.864 (3) Å) show typical values for N-H...O hydrogen bonds.⁹

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer ir-spectrophotometer 1600 (FTir) and are given as cm^{-1} . ^1H and ^{13}C nmr spectra were recorded on either a Bruker WM-250 (^1H -Nmr: 250.13 MHz, ^{13}C -Nmr: 62.89 MHz) or a Varian XL 300 (^1H -Nmr: 299.95 MHz, ^{13}C -Nmr: 75.43 MHz) spectrometer in CDCl_3 or $\text{DMSO}-d_6$. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane; coupling constants J are given in Hz. Ultraviolet spectra were measured with a Perkin-Elmer 320 uv-spectrophotometer in acetonitrile. Element analyses were performed on a Heraeus Vario EL CHNS apparatus.

1,3-Dithietane-2,4-diylidenebis(cyanoacetic acid alkyl esters)¹⁰ (1), 3-phenylacrylic acid hydrazide⁶ (2e), 5-phenylpyrazolidin-3-one^{6,7} (4) and 2-cyano-3,3-bis(methylsulfanyl)acrylic acid ethyl ester¹¹ (6) were prepared according to known literature procedures.

General procedure for the preparation of tautomeric derivatives of (5-*R*-[1.3.4]oxadiazol-2-yl)-thiocarbamoylacetic acid alkyl esters (3)

A hot mixture of 1,3-dithietane-2,4-diylidenebis(cyanoacetic acid alkyl ester) (1) (5.0 mmol) in 5 ml chloroform was slowly added to a stirred mixture of the corresponding carboxylic acid hydrazide (2) (10.0 mmol) in 5 ml ethanol at ca. 60 °C. The reaction mixture was then cooled to room temperature and the precipitate isolated by filtration and recrystallized from ethanol or chloroform.

(5-Phenyl-[1.3.4]oxadiazol-2-yl)thiocarbamoylacetic acid ethyl ester (3.1a)

- 2.44 g (84 %) 3.1a were obtained as colorless crystals, mp 171 - 173 °C (decomp.) (chloroform). ^1H -Nmr (299.95 MHz, $\text{DMSO}-d_6$) δ = 1.26 (t, $^3J_{\text{HH}}$ = 7.1 Hz, 3H, OCH_2CH_3), 4.26, 4.28 (2 x q, $^3J_{\text{HH}}$ = 7.1 Hz, 2H, OCH_2CH_3), 5.75 (s, 1H, CH), 7.58 - 7.70 (m, 3H, H-3', H-4', H-5'), 8.00 - 8.03

(m, 2H, H-2', H-6'), 9.74 (br, 1H, NH), 10.17 (br, 1H, NH). $^{13}\text{C-Nmr}$ (75.43 MHz, DMSO- d_6) δ = 13.7 (q, OCH_2CH_3), 56.2 (d, CH), 62.0 (t, OCH_2CH_3), 122.8 (s, C-1'), 126.3 (d, C-2', C-6'), 129.3 (d, C-3', C-5'), 131.9 (d, C-4'), 160.6 (s, C-2), 164.3, 164.4 (2 x s, C-5, CO), 194.3 (s, CS). Ir (KBr, tablet) ν = 3346 (m), 3209 (m), 2971 (w), 1655 (s), 1622 (w), 1557 (s), 1495 (s), 1482 (m), 1451 (s), 1415 (s), 1382 (m), 1322 (s), 1255 (s), 1204 (m), 1185 (m), 1108 (m), 1081 (w), 1061 (m), 1022 (m), 959 (w), 945 (s), 922 (w), 885 (m), 789 (m), 770 (m), 750 (m), 717 (w), 687 (s), 642 (m), 632 (m), 557 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 251 (4.39), 303 (4.05), 319 (3.92, sh). *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$: C, 53.60; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.54; H, 4.37; N, 14.30; S, 11.14.

[5-(4-Chlorophenyl)-[1,3,4]oxadiazol-2-yl]thiocarbamoylacetic acid ethyl ester (3.1b)

- 2.60 g (80 %) **3.1b** were obtained as yellow crystals, mp 172 - 173 °C (decomp.) (ethanol). $^1\text{H-Nmr}$ (299.95 MHz, DMSO- d_6) δ = 1.23 (t, $^3J_{\text{HH}} = 7.1$ Hz, 3H, OCH_2CH_3), 4.24, 4.26 (2 x q, $^3J_{\text{HH}} = 7.1$ Hz, 2H, OCH_2CH_3), 5.71 (s, 1H, CH), 7.70 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2H, H-3', H-5'), 8.00 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2H, H-2', H-6'), 9.69 (br, 1H, NH), 10.13 (br, 1H, NH). $^{13}\text{C-Nmr}$ (62.89 MHz, DMSO- d_6) δ = 13.8 (q, OCH_2CH_3), 56.4 (d, CH), 62.1 (t, OCH_2CH_3), 121.9 (s, C-1'), 128.3 (d, C-2', C-6'), 129.7 (d, C-3', C-5'), 137.0 (s, C-4'), 161.1 (s, C-2), 164.0, 164.6 (2 x s, C-5, CO), 194.5 (s, CS). Ir (KBr, tablet) ν = 3327 (m), 3196 (w), 2978 (w), 2904 (w), 1649 (s), 1619 (w), 1557 (s), 1419 (s), 1266 (s), 1181 (w), 1112 (w), 1095 (s), 1070 (s), 1019 (s), 959 (w), 944 (s), 885 (w), 844 (m), 829 (w), 785 (m), 752 (w), 726 (m), 696 (m), 666 (w), 639 (w), 621 (m), 561 (w), 525 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 255 (4.40), 302 (4.22), 319 (3.92, sh). *Anal.* Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_3\text{ClS}$: C, 47.93; H, 3.71; N, 12.90; S, 9.84. Found: C, 48.15; H, 3.63; N, 12.85; S, 9.82.

[5-(4-Nitrophenyl)-[1,3,4]oxadiazol-2-yl]thiocarbamoylacetic acid ethyl ester (3.1c)

- 2.97 g (88 %) **3.1c** were obtained as yellow crystals, mp 170 - 171 °C (decomp.) (ethanol). $^1\text{H-Nmr}$ (299.95 MHz, DMSO- d_6) δ = 1.25 (t, $^3J_{\text{HH}} = 7.1$ Hz, 3H, OCH_2CH_3), 4.24, 4.27 (2 x q, $^3J_{\text{HH}} = 7.1$ Hz, 2H, OCH_2CH_3), 5.77 (s, 1H, CH), 8.26 (d, $^3J_{\text{HH}} = 9.0$ Hz, 2H, H-2', H-6'), 8.46 (d, $^3J_{\text{HH}} = 9.0$ Hz, 2H, H-3', H-5'), 9.73 (br, 1H, NH), 10.17 (br, 1H, NH). $^{13}\text{C-Nmr}$ (75.43 MHz, DMSO- d_6) δ = 13.7 (q, OCH_2CH_3), 56.2 (d, CH), 62.1 (t, OCH_2CH_3), 124.5 (d, C-3', C-5'), 127.7 (d,

C-2', C-6'), 128.2 (s, C-1'), 149.1 (s, C-4'), 161.5 (s, C-2), 163.1, 164.2 (2 x s, C-5, CO), 194.0 (s, CS). Ir (KBr, tablet) $\nu = 3410$ (w), 3332 (w), 3206 (w), 2983 (w), 1663 (m), 1587 (m), 1554 (s), 1526 (s), 1420 (m), 1405 (w), 1383 (w), 1340 (m), 1318 (m), 1250 (m), 1199 (w), 1107 (w), 1074 (w), 1060 (w), 1021 (w), 1012 (w), 962 (w), 942 (w), 885 (w), 864 (w), 852 (w), 785 (w), 756 (w), 712 (w), 651 (w), 625 (w). Uv (CH₃CN) λ_{\max} (log ϵ) = 214 (4.08, sh), 281 (4.36), 343 (3.61, sh). *Anal.* Calcd for C₁₃H₁₂N₄O₅S: C, 46.43; H, 3.60; N, 16.66; S, 9.53. Found: C, 46.57; H, 3.58; N, 16.82; S, 9.76.

5-(4-Methoxyphenyl)-[1,3,4]oxadiazol-2-yl]thiocarbamoylacetic acid ethyl ester (3.1d)

- 2.75 g (86 %) **3.1d** were obtained as colorless crystals, mp 171 - 172 °C (decomp.) (chloroform). ¹H-Nmr (299.95 MHz, DMSO-d₆) $\delta = 1.23$ (t, ³J_{HH} = 7.1 Hz, 3H, OCH₂CH₃), 3.86 (s, 3H, OCH₃), 4.22, 4.25 (2 x q, ³J_{HH} = 7.1 Hz, 2H, OCH₂CH₃), 5.67 (s, 1H, CH), 7.17 (d, ³J_{HH} = 8.8 Hz, 2H, H-3', H-5'), 7.93 (d, ³J_{HH} = 8.8 Hz, 2H, H-2', H-6'), 9.69 (br, 1H, NH), 10.12 (br, 1H, NH). ¹³C-Nmr (75.43 MHz, DMSO-d₆) $\delta = 13.8$ (q, OCH₂CH₃), 55.5 (q, OCH₃), 56.3 (d, CH), 62.0 (t, OCH₂CH₃), 114.8 (d, C-3', C-5'), 115.2 (s, C-1'), 128.2 (d, C-2', C-6'), 160.1 (s, C-2), 162.0 (s, C-4'), 164.4, 164.5 (2 x s, C-5, CO), 194.5 (s, CS). Ir (KBr, tablet) $\nu = 3389$ (w), 3255 (w), 3215 (w), 2979 (w), 2837 (w), 1671 (m), 1619 (m), 1604 (m), 1544 (s), 1509 (s), 1476 (w), 1447 (w), 1429 (w), 1405 (m), 1366 (w), 1314 (s), 1304 (m), 1271 (s), 1243 (m), 1200 (w), 1175 (m), 1098 (w), 1074 (w), 1061 (m), 1030 (m), 1016 (m), 956 (w), 942 (m), 881 (w), 851 (w), 810 (w), 783 (m), 746 (w), 734 (w), 705 (w), 623 (w), 609 (w). Uv (CH₃CN) λ_{\max} (log ϵ) = 270 (4.42), 303 (4.04, sh), 318 (3.95, sh). *Anal.* Calcd for C₁₄H₁₅N₃O₄S: C, 52.33; H, 4.71; N, 13.08; S, 9.98. Found: C, 52.13; H, 4.65; N, 12.94; S, 10.07.

5-Styryl-[1,3,4]oxadiazol-2-yl]thiocarbamoylacetic acid ethyl ester (3.1e)

- 2.33 g (73 %) **3.1e** were obtained as yellow crystals, mp 169 - 171 °C (decomp.) (ethanol). ¹H-Nmr (299.95 MHz, DMSO-d₆) $\delta = 1.24$ (t, ³J_{HH} = 7.1 Hz, 3H, OCH₂CH₃), 4.23, 4.25 (2 x q, ³J_{HH} = 7.1 Hz, 2H, OCH₂CH₃), 5.66 (s, 1H, CH), 7.37, 7.59 (2 x d, ³J_{HH} = 16.5 Hz, 2H, CH=CH-Ph), 7.41 - 7.81 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 9.69 (br, 1H, NH), 10.13 (br, 1H, NH). ¹³C-Nmr (75.43 MHz, DMSO-d₆) $\delta = 14.1$ (q, OCH₂CH₃), 56.6 (d, CH), 62.3 (t, OCH₂CH₃), 110.0 (d,

$\underline{\text{C}}\text{H}=\underline{\text{C}}\text{H}-\text{Ph}$), 128.0, 129.0, 130.2 (3 x d, C-2', C-3', C-4', C-5', C-6'), 134.5 (s, C-1'), 139.2 (d, $\text{CH}=\underline{\text{C}}\text{H}-\text{Ph}$), 160.3 (s, C-2), 164.8 (s, C-5, CO), 194.7 (s, CS). Ir (KBr, tablet) $\nu = 3350$ (m), 3239 (w), 3207 (w), 3064 (w), 3025 (w), 2978 (w), 2901 (w), 1654 (s), 1553 (s), 1476 (w), 1448 (m), 1413 (s), 1384 (m), 1323 (m), 1247 (s), 1101 (w), 1066 (m), 1021 (m), 973 (w), 960 (s), 947 (s), 886 (w), 857 (w), 846 (w), 785 (m), 756 (s), 725 (w), 710 (w), 687 (s), 638 (w), 621 (w), 589 (s), 540 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 206 (4.33, sh), 215 (4.27, sh), 220 (4.24, sh), 288 (4.56), 343 (4.06). *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.79; H, 4.76; N, 13.28; S, 10.27.

[5-(4-Methylphenyl)-[1,3,4]oxadiazol-2-yl]thiocarbamoylacetic acid methyl ester (3.2f)

- 2.54 g (87 %) **3.2f** were obtained as colorless crystals, mp 186 - 187 °C (decomp.) (chloroform). $^1\text{H-Nmr}$ (299.95 MHz, DMSO-d_6) $\delta = 2.40$ (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.71 (s, 1H, CH), 7.43 (d, $^3J_{\text{HH}} = 8.1$ Hz, 2H, H-3', H-5'), 7.88 (d, $^3J_{\text{HH}} = 8.1$ Hz, 2H, H-2', H-6'), 9.70 (br, 1H, NH), 10.15 (br, 1H, NH). $^{13}\text{C-Nmr}$ (75.43 MHz, DMSO-d_6) $\delta = 21.0$ (q, CH_3), 53.0 (q, OCH_3), 56.2 (d, CH), 120.1 (s, C-1'), 126.2 (d, C-2', C-6'), 129.8 (d, C-3', C-5'), 142.1 (s, C-4'), 160.2 (s, C-2), 164.5, 164.9 (2 x s, C-5, CO), 194.2 (s, CS). Ir (KBr, tablet) $\nu = 3325$ (m), 3174 (m), 3039 (w), 2944 (w), 1660 (s), 1615 (m), 1607 (s), 1589 (s), 1545 (s), 1506 (s), 1436 (s), 1404 (s), 1322 (m), 1305 (m), 1265 (s), 1249 (s), 1205 (s), 1182 (m), 1112 (m), 1077 (m), 1064 (m), 1021 (m), 1000 (w), 971 (s), 955 (m), 933 (m), 824 (m), 783 (m), 757 (w), 724 (s), 697 (m), 667 (w), 640 (w), 621 (w), 550 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 259 (4.38), 306 (3.95), 315 (3.92, sh). *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$: C, 53.60; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.69; H, 4.65; N, 14.44; S, 11.26.

Colorless prisms of **3.2f** (triclinic) with the space group $\overline{P}1$ (# 2 Int. Tables) were obtained by recrystallization from ethanol: $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3\text{S}$, mol. weight = 291.33 g mol $^{-1}$. The unit cell parameters were $a = 7.228$ (2) Å, $b = 8.373$ (2) Å, $c = 12.294$ (4) Å, $\alpha = 109.95$ (2) °, $\beta = 93.86$ (2) °, $\gamma = 104.58$ (2) °, $V = 667.2$ (8) Å 3 , $Z = 2$, $D_x = 1.450$ g cm $^{-3}$, $\mu = 2.416$ cm $^{-1}$ (Mo K α), $F_{000} = 304$ e. Intensity data were collected using graphite-monochromated Mo-K α radiation ($\lambda = 0.7107$ Å) (Enraf-Nonius CAD4) and applying the ω -2 θ -scan technique (crystal size: 0.20 mm x 0.20 mm x

0.30 mm). Up to $\sin \theta/\lambda \leq 0.62 \text{ \AA}^{-1}$ 2610 symmetry independent reflections were measured from which 1987 with $I \geq 3.0 \sigma(I)$ were graded as observed. The structure was solved by the conventional direct method (SIR). Full matrix least-squares refinement of the atomic coordinates using anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms led to a convergence at $R = 0.055$ ($R_w = 0.066$).

General procedure for the preparation of racemic 2-amino-5-oxo-7-phenyl-6,7-dihydro-5H-pyrazolo[5.1-b][1.3]thiazine-3-carboxylic acid alkyl esters (5)

A mixture of 1,3-dithietane-2,4-diylidenebis(cyanoacetic acid alkyl ester) (1) (1.0 - 1.5 mmol) and 5-phenylpyrazolidin-3-one (4) (2.0 - 3.0 mmol) in 4 ml ethanol / chloroform (1:1) was refluxed for 15 - 30 min. After cooling to room temperature the precipitate was filtered and recrystallized from ethanol.

2-Amino-5-oxo-7-phenyl-6,7-dihydro-5H-pyrazolo[5.1-b][1.3]thiazine-3-carboxylic acid ethyl ester (5.1)

- 460 mg (73 %) 5.1 were obtained as colorless crystals, mp 190 - 194 °C. $^1\text{H-Nmr}$ (299.95 MHz, CDCl_3) $\delta = 1.36$ (t, $^3J_{\text{HH}} = 7.1$ Hz, 3H, OCH_2CH_3), ABM-signal [$(\delta_A = 3.37$, $^2J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HH}} = 3.5$ Hz - $\delta_B = 3.51$, $^2J_{\text{HH}} = 15.7$ Hz, $^3J_{\text{HH}} = 5.5$ Hz; 2H, CH_2) - ($\delta_M = 5.71$, $^3J_{\text{HH}} = 3.5$ Hz, $^3J_{\text{HH}} = 5.5$ Hz; 1H, CH)], 4.31 (q, $^3J_{\text{HH}} = 7.1$ Hz, 2H, OCH_2CH_3), 4.83 (br, 2H, NH_2), 7.00 - 7.36 (m, 5H, H-2', H-3', H-4', H-5', H-6'). $^{13}\text{C-Nmr}$ (75.43 MHz, CDCl_3) $\delta = 14.3$ (q, OCH_2CH_3), 47.1 (t, C-6), 60.1 (d, C-7), 60.4 (t, OCH_2CH_3), 98.3 (s, C-3), 125.5, 129.0 (2 x d, C-2', C-3', C-5', C-6'), 128.5 (d, C-4'), 134.1 (s, C-3a), 136.0 (s, C-1'), 156.5 (s, C-2), 163.0 (s, CO), 191.1 (s, C-5). Ir (KBr, tablet) $\nu = 3445$ (m), 3279 (m), 3189 (m), 2984 (w), 2905 (w), 1679 (s), 1616 (s), 1538 (s), 1509 (s), 1473 (m), 1458 (m), 1437 (m), 1402 (m), 1372 (s), 1316 (s), 1258 (m), 1217 (s), 1192 (w), 1161 (w), 1130 (s), 1050 (m), 1020 (m), 953 (w), 923 (w), 897 (w), 872 (w), 849 (w), 805 (w), 787 (w), 768 (s), 702 (s), 677 (w), 638 (w), 622 (w), 615 (w), 573 (w), 536 (w), 512 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 264 (4.14), 294 (3.56, sh). *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.89; H, 4.78; N, 13.27; S, 10.20.

By recrystallization from ethanol / ethyl acetate colorless triclinic needles of **5.1** with the space group $P\bar{1}$ (# 2 Int. Tables) were obtained: $C_{15}H_{15}N_3O_3S$, mol. weight = 317.37 g mol⁻¹. The unit cell parameters were $a = 5.503$ (6) Å, $b = 11.662$ (6) Å, $c = 12.582$ (4) Å, $\alpha = 110.32$ (2) °, $\beta = 90.63$ (6) °, $\gamma = 94.18$ (6) °, $V = 755$ (2) Å³, $Z = 2$, $D_x = 1.396$ g cm⁻³, $\mu = 2.195$ cm⁻¹ (Mo K α), $F_{000} = 332$ e.

Intensity data were collected using graphite-monochromated Mo-K α radiation ($\lambda = 0.7107$ Å) (Enraf-Nonius CAD4) and applying the ω -2 θ -scan technique (crystal size: 0.10 mm x 0.10 mm x 0.30 mm; slightly twinned). Up to $\sin \theta/\lambda \leq 0.53$ Å⁻¹ 1844 symmetry independent reflections were measured from which 908 with $I \geq 3.0 \sigma(I)$ were graded as observed. The structure was solved by the conventional direct method (SIR). Full matrix least-squares refinement of the atomic coordinates using anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms led to a convergence at $R = 0.092$ ($R_w = 0.098$).

2-Amino-5-oxo-7-phenyl-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]thiazine-3-carboxylic acid methyl ester (5.2)

- 552 mg (61 %) **5.2** were obtained as yellow crystals, mp 167 - 170 °C. ¹H-Nmr (299.95 MHz, CDCl₃) δ = ABM-signal [($\delta_A = 3.37$, ²J_{HH} = 15.7 Hz, ³J_{HH} = 3.5 Hz - $\delta_B = 3.51$, ²J_{HH} = 15.7 Hz, ³J_{HH} = 5.5 Hz; 2H, CH₂) - ($\delta_M = 5.71$, ³J_{HH} = 3.5 Hz, ³J_{HH} = 5.5 Hz; 1H, CH)], 3.84 (s, 3H, OCH₃), 4.85 (br, 2H, NH₂), 7.01 - 7.37 (m, 5H, H-2', H-3', H-4', H-5', H-6'). ¹³C-Nmr (75.43 MHz, CDCl₃) δ = 47.1 (t, C-6), 51.3 (q, OCH₃), 60.1 (d, C-7), 98.1 (s, C-3), 125.5, 129.0 (2 x d, C-2', C-3', C-5', C-6'), 128.5 (d, C-4'), 134.2 (s, C-3a), 136.2 (s, C-1'), 156.5 (s, C-2), 163.3 (s, CO), 191.0 (s, C-5). Ir (KBr, tablet) ν = 3454 (m), 3197 (m), 3119 (w), 2948 (w), 1694 (s), 1615 (s), 1569 (w), 1538 (s), 1511 (s), 1458 (m), 1430 (s), 1401 (m), 1361 (w), 1333 (s), 1297 (m), 1262 (w), 1216 (m), 1190 (m), 1125 (s), 1097 (s), 1051 (w), 1002 (w), 955 (w), 914 (w), 892 (w), 844 (w), 784 (s), 768 (m), 697 (m), 634 (w), 622 (w), 612 (w), 594 (w), 570 (w), 539 (w), 513 (w). UV (CH₃CN) λ_{max} (log ϵ) = 206 (4.25), 263 (4.07), 290 (3.58, sh). Anal. Calcd for C₁₄H₁₃N₃O₃S: C, 55.43; H, 4.32; N, 13.85; S, 10.57. Found: C, 55.35; H, 4.34; N, 13.59; S, 10.84.

General procedure for the preparation of pyrazoles (7)

2-Cyano-3,3-bis(methylsulfanyl)acrylic acid ethyl ester (6) (2.18 g, 10.0 mmol) and carboxylic acid hydrazide (2) (10.0 mmol) were refluxed in ethanol (15 ml) for 5 h. After cooling to room temperature the resulting precipitate was isolated by filtration and recrystallized from ethanol.

5-Amino-1-benzoyl-3-methylsulfanyl-1H-pyrazole-4-carboxylic acid ethyl ester (7a)

- 2.47 g (81 %) **7a** were obtained as colorless crystals, mp 90 - 92 °C. ¹H-Nmr (299.95 MHz, CDCl₃) δ = 1.38 (t, ³J_{HH} = 7.1 Hz, 3H, CO₂CH₂CH₃), 2.42 (s, 3H, SCH₃), 4.31 (q, ³J_{HH} = 7.1 Hz, 2H, CO₂CH₂CH₃), 7.33 (br, 2H, NH₂), 7.42 - 7.58 (m, 3H, H-3', H-4', H-5'), 8.13 - 8.16 (m, 2H, H-2', H-6'). ¹³C-Nmr (62.89 MHz, CDCl₃) δ = 13.0 (q, SCH₃), 14.4 (q, CO₂CH₂CH₃), 60.1 (t, CO₂CH₂CH₃), 92.9 (s, C-4), 127.7 (d, C-3', C-5'), 131.3 (d, C-2', C-6'), 132.4 (s, C-1'), 132.7 (d, C-4'), 153.9 (s, C-3), 156.2 (s, C-5), 164.0 (s, CO₂CH₂CH₃), 169.4 (s, CO). Ir (KBr, tablet) ν = 3468 (m), 3347 (m), 3057 (w), 3003 (w), 2975 (m), 2929 (w), 2869 (w), 1695 (s), 1657 (m), 1606 (m), 1576 (w), 1523 (s), 1464 (w), 1447 (m), 1388 (w), 1374 (m), 1359 (m), 1332 (m), 1321 (m), 1288 (s), 1185 (m), 1170 (w), 1161 (w), 1116 (m), 1093 (w), 1036 (m), 1001 (w), 932 (m), 784 (m), 712 (m), 698 (m), 689 (w), 679 (w). Uv (CH₃CN) λ_{max} (log ε) = 207 (4.35), 227 (4.27, sh), 245 (4.37), 270 (4.11, sh). Anal. Calcd for C₁₄H₁₅N₃O₃S: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 55.22; H, 4.87; N, 13.79; S, 10.73.

5-Amino-1-(4-chlorobenzoyl)-3-methylsulfanyl-1H-pyrazole-4-carboxylic acid ethyl ester (7b)

- 3.12 g (91 %) **7b** were obtained as colorless crystals, mp 144 - 146 °C. ¹H-Nmr (299.95 MHz, CDCl₃) δ = 1.38 (t, ³J_{HH} = 7.1 Hz, 3H, CO₂CH₂CH₃), 2.42 (s, 3H, SCH₃), 4.31 (q, ³J_{HH} = 7.1 Hz, 2H, CO₂CH₂CH₃), 7.32 (br, 2H, NH₂), 7.40 - 7.45 (m, 2H, H-3', H-5'), 8.10 - 8.15 (m, 2H, H-2', H-6'). ¹³C-Nmr (75.43 MHz, CDCl₃) δ = 13.0 (q, SCH₃), 14.4 (q, CO₂CH₂CH₃), 60.1 (t, CO₂CH₂CH₃), 92.7 (s, C-4), 127.9 (d, C-3', C-5'), 130.4 (s, C-1'), 132.6 (d, C-2', C-6'), 139.0 (s, C-4'), 154.0 (s, C-3), 155.9 (s, C-5), 163.6 (s, CO₂CH₂CH₃), 167.8 (s, CO). Ir (KBr, tablet) ν = 3430 (m), 3326 (m), 3191 (w), 2984 (w), 1695 (m), 1653 (m), 1629 (m), 1605 (m), 1589 (m), 1560 (w), 1554 (w), 1528 (m), 1491 (m), 1476 (m), 1465 (w), 1457 (w), 1442 (w), 1401 (w),

1394 (w), 1378 (w), 1358 (m), 1331 (m), 1291 (s), 1187 (m), 1091 (m), 1011 (m), 941 (w), 851 (m), 836 (w), 788 (w), 781 (w), 750 (w), 729 (w), 580 (w). Uv (CH₃CN) λ_{\max} (log ϵ) = 212 (4.35), 250 (4.39), 274 (4.13, sh). *Anal.* Calcd for C₁₄H₁₄N₃O₃ClS: C, 49.49; H, 4.15; N, 12.37; S, 9.44. Found: C, 49.65; H, 4.20; N, 12.35; S, 9.45.

Colorless monoclinic needles of **7b** with the space group P2₁/c (# 14 Int. Tables) were obtained by recrystallization from ethanol: C₁₄H₁₄N₃O₃ClS, mol. weight = 339.80 g mol⁻¹. The unit cell parameters were a = 10.461 (1) Å, b = 8.194 (1) Å, c = 18.694 (3) Å, β = 92.64 (1) °, V = 1600.6 (6) Å³, Z = 4, D_x = 1.410 g cm⁻³, μ = 3.755 cm⁻¹ (Mo K α), F₀₀₀ = 704 e.

Intensity data were collected using graphite-monochromated Mo-K α radiation (λ = 0.7107 Å) (Enraf-Nonius CAD4) and applying the ω -2 θ -scan technique (crystal size: 0.15 mm x 0.20 mm x 0.40 mm). Up to $\sin \theta/\lambda \leq 0.62 \text{ \AA}^{-1}$ 3128 symmetry independent reflections were measured from which 2135 reflections with $I \geq 3.0 \sigma(I)$ were graded as observed. The structure was solved by the conventional direct method (SIR) and refined by full matrix least-squares technique using anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms (R = 0.040, R_w = 0.044).

5-Amino-3-methylsulfanyl-1-(4-nitrobenzoyl)-1H-pyrazole-4-carboxylic acid ethyl ester (7c)

- 3.20 g (91 %) **7c** were obtained as yellow crystals, mp 156 - 158 °C. ¹H-Nmr (299.95 MHz, CDCl₃) δ = 1.39 (t, ³J_{HH} = 7.1 Hz, 3H, CO₂CH₂CH₃), 2.40 (s, 3H, SCH₃), 4.33 (q, ³J_{HH} = 7.1 Hz, 2H, CO₂CH₂CH₃), 7.34 (br, 2H, NH₂), 8.30 (s, 4H, H-2', H-3', H-5', H-6'). ¹³C-Nmr (75.43 MHz, CDCl₃) δ = 13.0 (q, SCH₃), 14.4 (q, CO₂CH₂CH₃), 60.3 (t, CO₂CH₂CH₃), 93.0 (s, C-4), 122.6 (d, C-3', C-5'), 131.9 (d, C-2', C-6'), 137.7 (s, C-1'), 149.7 (s, C-4'), 155.0 (s, C-3), 155.8 (s, C-5), 163.5 (s, CO₂CH₂CH₃), 167.1 (s, CO). Ir (KBr, tablet) ν = 3451 (m), 3319 (m), 3115 (w), 2973 (w), 1700 (m), 1696 (m), 1675 (m), 1663 (m), 1648 (w), 1623 (m), 1600 (w), 1559 (w), 1526 (s), 1472 (w), 1465 (w), 1404 (w), 1376 (w), 1365 (m), 1345 (m), 1319 (m), 1293 (s), 1177 (w), 1107 (m), 1029 (w), 1013 (w), 870 (w), 851 (m), 784 (m), 716 (w), 712 (w), 702 (m). Uv (CH₃CN) λ_{\max} (log ϵ) = 240 (4.47). *Anal.* Calcd for C₁₄H₁₄N₄O₅S: C, 48.00; H, 4.03; N, 15.99; S, 9.15. Found: C, 48.14; H, 3.80; N, 15.93; S, 9.19.

5-Amino-1-(4-methoxybenzoyl)-3-methylsulfonyl-1H-pyrazole-4-carboxylic acid ethyl ester (7d)

- 3.12 g (92 %) **7d** were obtained as colorless crystals, mp 159 - 160 °C. $^1\text{H-Nmr}$ (299.95 MHz, CDCl_3) δ = 1.38 (t, $^3J_{\text{HH}}$ = 7.1 Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.47 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 4.32 (q, $^3J_{\text{HH}}$ = 7.1 Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.91 - 6.95 (m, 2H, H-3', H-5'), 7.33 (br, 2H, NH_2), 8.23 - 8.27 (m, 2H, H-2', H-6'). $^{13}\text{C-Nmr}$ (75.43 MHz, CDCl_3) δ = 13.0 (q, SCH_3), 14.4 (q, $\text{CO}_2\text{CH}_2\text{CH}_3$), 55.4 (q, OCH_3), 60.0 (t, $\text{CO}_2\text{CH}_2\text{CH}_3$), 92.6 (s, C-4), 113.0 (d, C-3', C-5'), 124.2 (s, C-1'), 133.8 (d, C-2', C-6'), 153.2 (s, C-3), 156.0 (s, C-5), 163.1, 163.7 (2 x s, $\text{CO}_2\text{CH}_2\text{CH}_3$, C-4'), 168.1 (s, CO). Ir (KBr, tablet) ν = 3436 (m), 3333 (m), 2982 (w), 1689 (s), 1649 (m), 1630 (m), 1599 (m), 1527 (m), 1490 (m), 1475 (m), 1458 (m), 1441 (w), 1391 (w), 1376 (w), 1357 (m), 1323 (m), 1291 (s), 1258 (s), 1192 (m), 1169 (m), 1116 (w), 1096 (m), 1027 (m), 1011 (m), 1003 (m), 971 (w), 951 (m), 941 (m), 868 (w), 850 (m), 835 (w), 788 (m), 770 (w), 756 (m), 631 (m), 620 (w), 545 (w). Uv (CH_3CN) λ_{max} (log ϵ) = 209 (4.34), 220 (4.32, sh), 253 (4.33), 288 (4.34). *Anal.* Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$: C, 53.72; H, 5.11; N, 12.53; S, 9.56. Found: C, 53.50; H, 5.06; N, 12.49; S, 9.30.

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