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

Monika Jochheim,[a] Harald G. Krug,[a] Richard Neidlein,[a]* and Claus Krieger [b]

a) Pharmazeutisch-Chemisches Institut, Im Neuenheimer Feld 364, 69120 Heidelberg, Germany

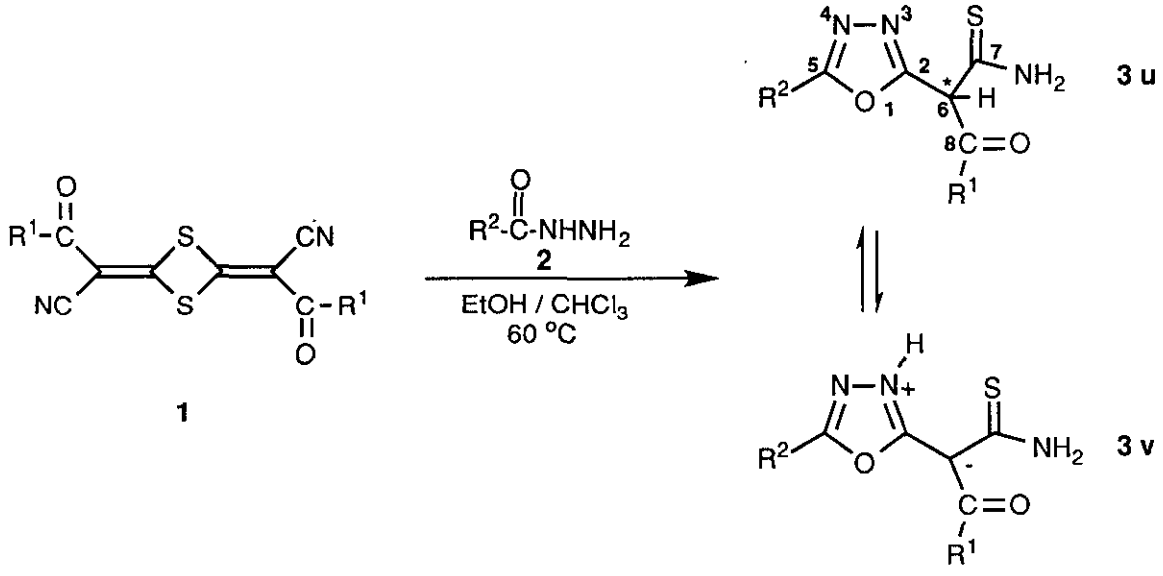
b) Max-Planck-Institut für Medizinische Forschung, Abteilung Organische Chemie, Jahnstraße 29, 69120 Heidelberg, Germany

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 5*H*-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-l] we reported syntheses of different phosphono and phosphino-substituted heterocycles and the reaction of 1,3-dithietane-2,4-diylidenebis(cyanomethyl-phosphonates) 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
3.1a	OEt	Ph
3.1b	OEt	C_6H_4-Cl-p
3.1c	OEt	C_6H_4-NO_2-p
3.1d	OEt	C_6H_4-OMe-p
3.1e	OEt	CH=CHC_6H_5
3.2f	OMe	C_6H_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 nitrogen[3] (3.35 Å).

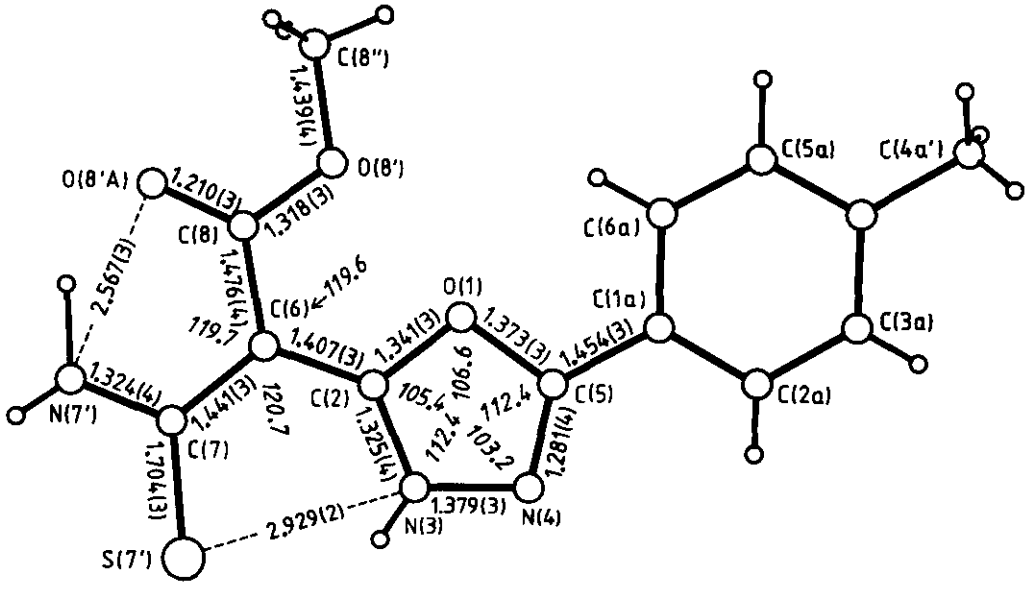


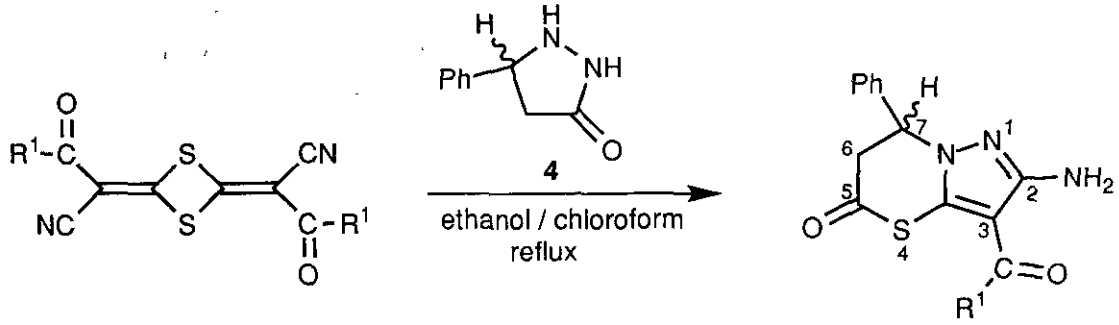
Figure 1: Perspective view, atom labelling, selected bond distances (in Å) and bond angles (in °) of **3.2f**

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 ^{1}H nmr spectrum (DMSO-d_6) the presence of the single tautomer (**3.1a u**) was indicated by the presence of the H-6 proton which occured 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 $CDCl_3$ 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-one[6] (**4**) was prepared from 3-phenylacrylic acid ethyl ester and hydrazine hydrate (ethanol, reflux) and falsely described in the older literature[7] as 3-phenylacrylic acid hydrazide.



1 **5**

compound	R^1
5.1	OEt
5.2	OMe

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.

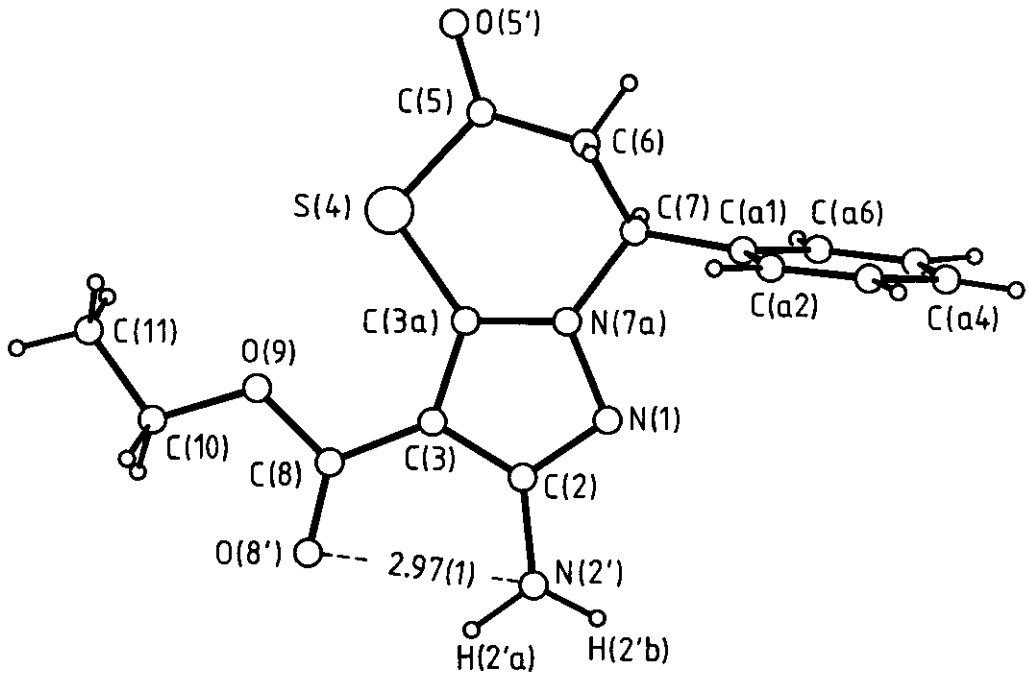
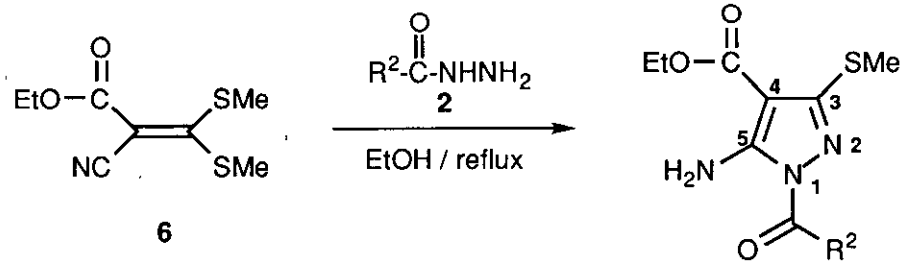


Figure 2: Perspective view and atom labelling of **5.1**

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



compound	R^2
7a	Ph
7b	C_6H_4-Cl-p
7c	C_6H_4-NO_2-p
7d	C_6H_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.

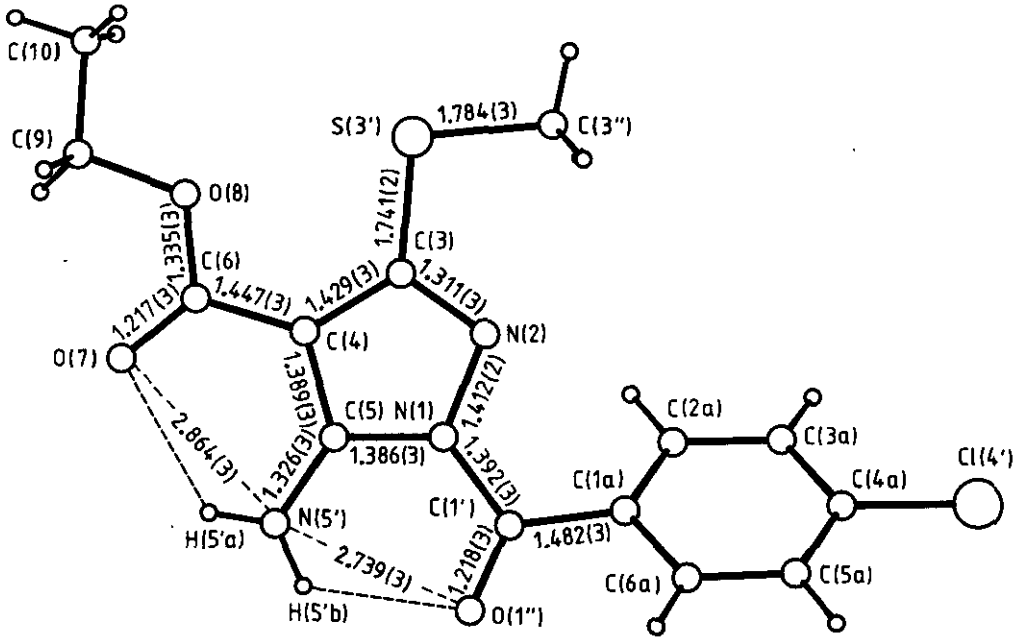


Figure 3: Perspective view, atom labelling and selected bond distances (in Å) of **7b**

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 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 hydrazide[6] (**2e**), 5-phenylpyrazolidin-3-one[6,7] (**4**) and 2-cyano-3,3-bis(methylsulfanyl)acrylic acid ethyl ester[11] (**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, DMSO-d_6) δ = 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.26, 4.28 (2 x q, $^3J_{HH}$ = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 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}C-Nmr (75.43 MHz, DMSO-d_6) δ = 13.7 (q, $OCH_2\underline{C}H_3$), 56.2 (d, CH), 62.0 (t, $O\underline{C}H_2CH_3$), 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 $C_{13}H_{13}N_3O_3S$: 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}H-Nmr (299.95 MHz, DMSO-d_6) δ = 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.24, 4.26 (2 x q, $^3J_{HH}$ = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.71 (s, 1H, CH), 7.70 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-3', H-5'), 8.00 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-2', H-6'), 9.69 (br, 1H, NH), 10.13 (br, 1H, NH). ^{13}C-Nmr (62.89 MHz, DMSO-d_6) δ = 13.8 (q, $OCH_2\underline{C}H_3$), 56.4 (d, CH), 62.1 (t, $O\underline{C}H_2CH_3$), 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 $C_{13}H_{12}N_3O_3ClS$: 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}H-Nmr (299.95 MHz, DMSO-d_6) δ = 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.24, 4.27 (2 x q, $^3J_{HH}$ = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.77 (s, 1H, CH), 8.26 (d, $^3J_{HH}$ = 9.0 Hz, 2H, H-2', H-6'), 8.46 (d, $^3J_{HH}$ = 9.0 Hz, 2H, H-3', H-5'), 9.73 (br, 1H, NH), 10.17 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, DMSO-d_6) δ = 13.7 (q, $OCH_2\underline{C}H_3$), 56.2 (d, CH), 62.1 (t, $O\underline{C}H_2CH_3$), 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) ν = 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 (CH_3CN) λ_{max} (log ε) = 214 (4.08, sh), 281 (4.36), 343 (3.61, sh). *Anal.* Calcd for $C_{13}H_{12}N_4O_5S$: 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). ^{1}H-Nmr (299.95 MHz, DMSO-d_6) δ = 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.86 (s, 3H, OCH_3), 4.22, 4.25 (2 x q, $^3J_{HH}$ = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 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). ^{13}C-Nmr (75.43 MHz, DMSO-d_6) δ = 13.8 (q, $OCH_2\underline{C}H_3$), 55.5 (q, OCH_3), 56.3 (d, CH), 62.0 (t, $O\underline{C}H_2CH_3$), 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) ν = 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 (CH_3CN) λ_{max} (log ε) = 270 (4.42), 303 (4.04, sh), 318 (3.95, sh). *Anal.* Calcd for $C_{14}H_{15}N_3O_4S$: 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). ^{1}H-Nmr (299.95 MHz, DMSO-d_6) δ = 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.23, 4.25 (2 x q, $^3J_{HH}$ = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.66 (s, 1H, CH), 7.37, 7.59 (2 x d, $^3J_{HH}$ = 16.5 Hz, 2H, C$\underline{H}$=C$\underline{H}$-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). ^{13}C-Nmr (75.43 MHz, DMSO-d_6) δ = 14.1 (q, $OCH_2\underline{C}H_3$), 56.6 (d, CH), 62.3 (t, $O\underline{C}H_2CH_3$), 110.0 (d,

CH=CH-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, CH=CH-Ph), 160.3 (s, C-2), 164.8 (s, C-5, CO), 194.7 (s, CS). Ir (KBr, tablet) ν = 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 $C_{15}H_{15}N_3O_3S$: 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}H-Nmr (299.95 MHz, DMSO-d_6) δ = 2.40 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.71 (s, 1H, CH), 7.43 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H-3', H-5'), 7.88 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H-2', H-6'), 9.70 (br, 1H, NH), 10.15 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, DMSO-d_6) δ = 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) ν = 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 $C_{13}H_{13}N_3O_3S$: 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 $P\bar{1}$ (# 2 Int. Tables) were obtained by recrystallization from ethanol: $C_{13}H_{13}N_3O_3S$, 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, α = 109.95 (2) °, β = 93.86 (2) °, γ = 104.58 (2) °, V = 667.2 (8) Å^3, Z = 2, D_x = 1.450 g cm^{-3}, μ = 2.416 cm^{-1} (Mo Kα), F_{000} = 304 e. Intensity data were collected using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å) (Enraf-Nonius CAD4) and applying the ω-2θ-scan technique (crystal size: 0.20 mm x 0.20 mm x

0.30 mm). Up to sin $\theta/\lambda \leq 0.62$ Å^{-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-5*H*-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-5*H*-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}H-Nmr (299.95 MHz, $CDCl_3$) $\delta = 1.36$ (t, $^3J_{HH} = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 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, CH_2) - ($\delta_M = 5.71$, $^3J_{HH} = 3.5$ Hz, $^3J_{HH} = 5.5$ Hz; 1H, CH)], 4.31 (q, $^3J_{HH} = 7.1$ Hz, 2H, $OC\underline{H}_2CH_3$), 4.83 (br, 2H, NH_2), 7.00 - 7.36 (m, 5H, H-2', H-3', H-4', H-5', H-6'). ^{13}C-Nmr (75.43 MHz, $CDCl_3$) $\delta = 14.3$ (q, $OCH_2\underline{C}H_3$), 47.1 (t, C-6), 60.1 (d, C-7), 60.4 (t, $O\underline{C}H_2CH_3$), 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) ν = 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 $C_{15}H_{15}N_3O_3S$: 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, α = 110.32 (2) °, β = 90.63 (6) °, γ = 94.18 (6) °, V = 755 (2) $Å^3$, Z = 2, D_x = 1.396 g cm^{-3}, μ = 2.195 cm^{-1} (*Mo* Kα), F_{000} = 332 e.

Intensity data were collected using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å) (Enraf-Nonius CAD4) and applying the ω-2θ-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-5*H*-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. ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = ABM-signal [(δ_A = 3.37, $^2J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 3.5 Hz - δ_B = 3.51, $^2J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 5.5 Hz; 2H, CH_2) - (δ_M = 5.71, $^3J_{HH}$ = 3.5 Hz, $^3J_{HH}$ = 5.5 Hz; 1H, CH)], 3.84 (s, 3H, OCH_3), 4.85 (br, 2H, NH_2), 7.01 - 7.37 (m, 5H, H-2', H-3', H-4', H-5', H-6'). ^{13}C-Nmr (75.43 MHz, $CDCl_3$) δ = 47.1 (t, C-6), 51.3 (q, OCH_3), 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 (CH_3CN) λ_{max} (log ε) = 206 (4.25), 263 (4.07), 290 (3.58, sh). *Anal.* Calcd for $C_{14}H_{13}N_3O_3S$: 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-1*H*-pyrazole-4-carboxylic acid ethyl ester (**7a**)

- 2.47 g (81 %) **7a** were obtained as colorless crystals, mp 90 - 92 °C. ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.42 (s, 3H, SCH_3), 4.31 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.33 (br, 2H, NH_2), 7.42 - 7.58 (m, 3H, H-3', H-4', H-5'), 8.13 - 8.16 (m, 2H, H-2', H-6'). ^{13}C-Nmr (62.89 MHz, $CDCl_3$) δ = 13.0 (q, SCH_3), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 60.1 (t, $CO_2\underline{C}H_2CH_3$), 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, $\underline{C}O_2CH_2CH_3$), 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 (CH_3CN) λ_{max} (log ε) = 207 (4.35), 227 (4.27, sh), 245 (4.37), 270 (4.11, sh). *Anal.* Calcd for $C_{14}H_{15}N_3O_3S$: 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-1*H*-pyrazole-4-carboxylic acid ethyl ester (**7b**)

- 3.12 g (91 %) **7b** were obtained as colorless crystals, mp 144 - 146 °C. ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.42 (s, 3H, SCH_3), 4.31 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.32 (br, 2H, NH_2), 7.40 - 7.45 (m, 2H, H-3', H-5'), 8.10 - 8.15 (m, 2H, H-2', H-6'). ^{13}C-Nmr (75.43 MHz, $CDCl_3$) δ = 13.0 (q, SCH_3), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 60.1 (t, $CO_2\underline{C}H_2CH_3$), 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, $\underline{C}O_2CH_2CH_3$), 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 (CH_3CN) λ_{max} (log ε) = 212 (4.35), 250 (4.39), 274 (4.13, sh). *Anal.* Calcd for $C_{14}H_{14}N_3O_3ClS$: 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 $P2_1/c$ (# 14 Int. Tables) were obtained by recrystallization from ethanol: $C_{14}H_{14}N_3O_3ClS$, 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) $Å^3$, Z = 4, D_x = 1.410 g cm^{-3}, μ = 3.755 cm^{-1} (Mo Kα), F_{000} = 704 e.
Intensity data were collected using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å) (Enraf-Nonius CAD4) and applying the ω-2θ-scan technique (crystal size: 0.15 mm x 0.20 mm x 0.40 mm). Up to sin $\theta/\lambda \leq 0.62$ $Å^{-1}$ 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)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**7c**)

- 3.20 g (91 %) **7c** were obtained as yellow crystals, mp 156 - 158 °C. ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.39 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.40 (s, 3H, SCH_3), 4.33 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 7.34 (br, 2H, NH_2), 8.30 (s, 4H, H-2', H-3', H-5', H-6'). ^{13}C-Nmr (75.43 MHz, $CDCl_3$) δ = 13.0 (q, SCH_3), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 60.3 (t, $CO_2\underline{C}H_2CH_3$), 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, $\underline{C}O_2CH_2CH_3$), 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 (CH_3CN) λ_{max} (log ε) = 240 (4.47). *Anal.* Calcd for $C_{14}H_{14}N_4O_5S$: 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-methylsulfanyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (**7d**)

- 3.12 g (92 %) **7d** were obtained as colorless crystals, mp 159 - 160 °C. ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.47 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 4.32 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 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}C-Nmr (75.43 MHz, $CDCl_3$) δ = 13.0 (q, SCH_3), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 55.4 (q, OCH_3), 60.0 (t, $CO_2\underline{C}H_2CH_3$), 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, $\underline{C}O_2CH_2CH_3$, 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 $C_{15}H_{17}N_3O_4S$: 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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