PYRIDAZINES, 74.[1,2]

SYNTHESIS OF NOVEL 4,5-DISUBSTITUTED PYRIDAZINES BY HOMOLYTIC SUBSTITUTION AND STRUCTURE DETERMINATION OF UNEXPECTED REACTION PRODUCTS

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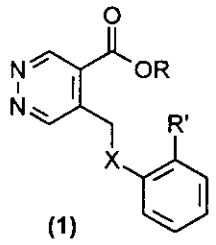
(Dedicated with best personal wishes to Professor Dr. R. Neidlein on the occasion of his 65th anniversary)

Abstract - Synthesis of the 5-aryloxymethyl-4-pyridazinecarboxylic acid derivatives (**1a-d**) and of the analogous thioethers (**1e,f**) by radical reactions in a two-phase system is reported. The stereochemical assignment of unexpected dimeric reaction products formed in the absence of an organic layer is presented.

Vicinally disubstituted pyridazines represent versatile building blocks for the exploitation of the bioisosteric potential of the 1,2-diazine system.[3] For the preparation of pyridazines bearing functionalised carbon atoms in both β-positions, homolytic substitution reactions employing nucleophilic carbon-centered radicals have been shown to be a powerful tool.[4] Here we report on investigations aimed at the synthesis of so far not accessible 4,5-disubstituted pyridazines of type (**1**) using silver ion mediated oxidative decarboxylation of phenoxyacetic acid or thiophenoxyacetic acid as source for the required substituted methyl radicals.[5]

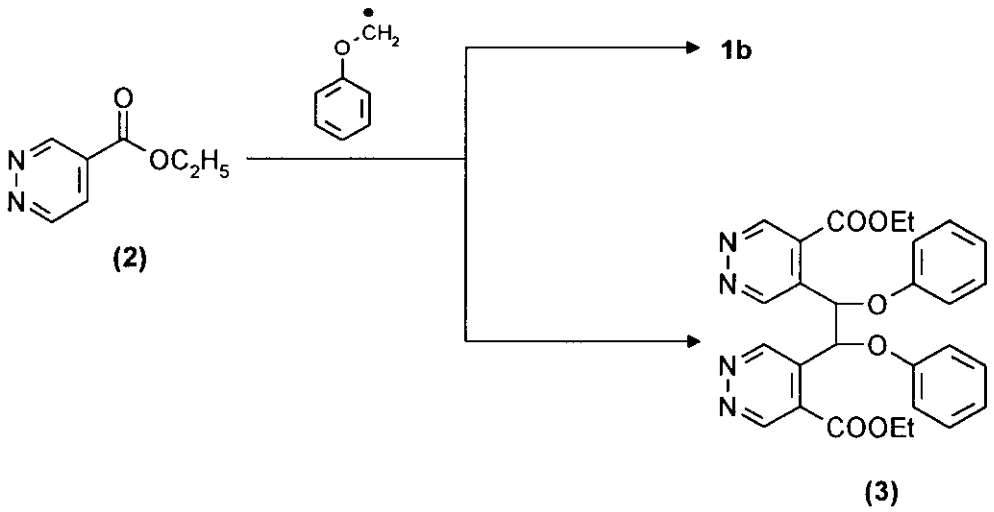


(1)

a)	X=O	R=H	R'=H
b)	X=O	R=Et	R'=H
c)	X=O	R=H	R'=Br
d)	X=O	R=Et	R'=Br
e)	X=S	R=H	R'=H
f)	X=S	R=Et	R'=H

Whereas initial attempts to prepare the free carboxylic acid (**1a**) by reaction of 4-pyridazinecarboxylic acid with phenoxymethyl radicals under conditions generally permitting smooth radicalic alkylation of the pyridazine system[6] failed, employment of the ethyl ester (**2**) gave the target compound (**1b**) albeit in extremely poor yield (< 3%) Surprisingly, the main product of this reaction (yield 20%) was found to be a dimer of **1b** as indicated by the ^{1}H- and ^{13}C-nmr data together with the mass spectrometrically determined molecular weight. In addition, another dimeric product could be isolated upon crystallisation (yield: 2 2%).

Scheme 1



(2)

(3)

In order to assign the stereochemistry of these compounds unequivocally, a X-ray structure determination of the major isomer was performed, showing the latter to be the meso compound (**3**) (see Figure 1 and Table 1). Thus, the second optically inactive dimer represents racemic **3**. To our knowledge, the formation of dimers in the course of *Minisci*-type aryloxyalkylation reaction is unprecedented.

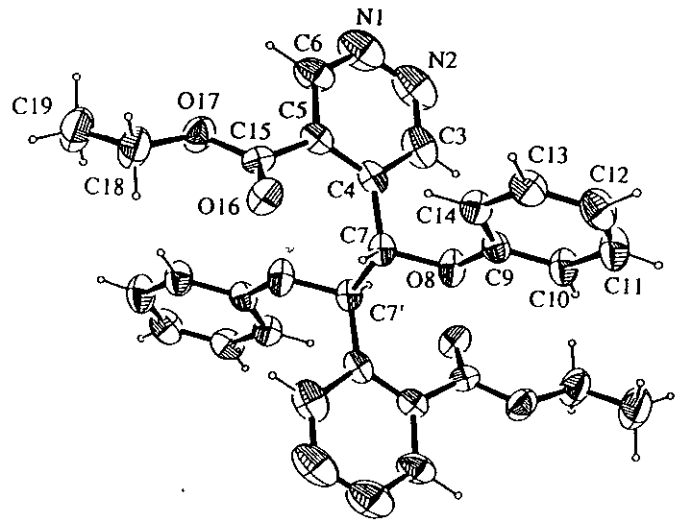


Figure 1 ORTEP-plot (30%-ellipsoids) of $C_{28}H_{26}N_4O_6$ (**meso-3**) with crystallographic atom numbering scheme The molecule is centrosymmetric. Selected bond lengths (Å)· N(1)-N(2)=1.336(5), N(1)-C(6)=1.309(5), N(2)-C(3)=1 332(5), C(3)-C(4)=1.403(4), C(4)-C(5)=1 373(3), C(5)-C(6)=1 396(4), C(4)-C(7)=1 511(3), C(5)-C(15)=1 485(3), C(7)-C(7')=1 547(3), C(7)-O(8)=1.416(2), O(8)-C(9)=1 384(2)

Table 1. Atomic coordinates and equivalent thermal displacement parameters of non-hydrogen atoms for $C_{28}H_{26}N_4O_6$ (**meso-3**). $U_{eq} = (1/3)\,\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$

	x/a	*y/b*	*z/c*	U_{eq} [Å^2]
N(1)	0.5339(3)	0.2144(2)	0 6197(6)	0.120(1)
N(2)	0.4669(3)	0.2580(2)	0.7097(4)	0 119(1)
C(3)	0.4466(2)	0.3369(3)	0.6407(5)	0.090(1)
C(4)	0.4901(2)	0.3789(1)	0.4775(3)	0.057(1)
C(5)	0 5584(2)	0.3323(1)	0 3878(3)	0 058(1)
C(6)	0 5774(2)	0.2502(2)	0.4672(5)	0.086(1)
C(7)	0.4652(1)	0.4704(1)	0.4243(4)	0.053(1)
O(8)	0 37088(9)	0 4915(1)	0.4706(2)	0 068(1)
C(9)	0.2907(1)	0.4644(1)	0 3249(3)	0 056(1)
C(10)	0 2024(2)	0 4868(2)	0.3811(5)	0.075(1)
C(11)	0.1180(2)	0 4637(2)	0 2437(6)	0.093(1)
C(12)	0 1223(2)	0 4187(2)	0 0540(5)	0 088(1)
C(13)	0.2102(2)	0 3958(2)	0.0014(5)	0 074(1)
C(14)	0.2958(2)	0 4180(2)	0 1358(4)	0 063(1)
C(15)	0.6099(2)	0 3635(1)	0.2064(3)	0.056(1)
O(16)	0 5742(1)	0 4101(1)	0 0616(2)	0 071(1)
O(17)	0 6984(1)	0.3322(1)	0 2254(3)	0.081(1)
C(18)	0.7573(2)	0.3538(3)	0 0526(6)	0.098(2)
C(19)	0 8578(3)	0 3307(3)	0.1354(10)	0.122(2)

Systematic variation of the reaction conditions did permit to suppress dimerisation of **1b** (see Table 2, entries 1, and 2); this, however, led to a further decrease of the conversion rate of **2**.

Table 2

entry	mole ratio					temperature	reaction time	ratio (1):(3)
	(2)	phenoxy-acetic acid	$(NH_4)_2S_2O_8$	$AgNO_3$	2*N*-H_2SO_4			
1	1	5	3	0.3	1 ml/mmol (2)	90°C	2 h	ca. 1:10
2	1	5	1.5	0.1	10 ml/mmol (2)	70°C	30 min	ca. 8:1
3	1	3	3	0.1	10 ml + 10 ml toluene/ mmol (2)	90°C	2 h	only (1)

Since the introduction of an aryloxymethyl substituent into the ester (**2**) should result in increased lipophilicity, the radical reaction of **2** was performed in a two-phase system (toluene/aqueous sulphuric acid) anticipating that under these conditions the initially formed target compound (**1b**) is extracted into the organic layer prior to its dimerisation.[7] In fact, under such conditions (Table 2, entry 3) we succeeded in obtaining analytically pure **1b** in satisfactory yield (72%), employment of *o*-bromophenoxymethyl radicals afforded a 42% yield of the ester (**1d**).

In a similar manner we could prepare the thio-isoster of **1b** (compound **1f**) from **2** *via* silver ion catalysed oxidative decarboxylation of thiophenoxyacetic acid in 63% yield It should be noted that attempts to prepare **1d** or **1f** in the absence of an organic layer resulted in multi-component mixtures. The carboxylic acids (**1a**, **1c**, and **1e**) became finally accessible upon alkaline hydrolysis of the corresponding esters.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected Infrared spectra (KBr pellets, NaCl plates) were recorded on a Mattson Galaxy Series FTIR 3000 spectro-

photometer. Mass spectra were obtained on a Varian MAT 44/S. ^1H and ^{13}C-nmr spectra were recorded on a Varian Gemini 200 spectrometer (^1H: 199.98 MHz, ^{13}C: 50.29 MHz). The centre of the solvent multiplet (DMSO-d_6) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2 49 ppm for ^1H and δ 39.50 ppm for ^{13}C. Reactions were monitored by tlc using Polygram SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0 25 mm layer thickness). Elemental analyses were performed by Mag. J. Theiner, Institute of Physical Chemistry, University of Vienna, Austria. We thank Doz. Dr. K.-H. Ongania, Institute of Organic Chemistry, University of Innsbruck for recording the mass spectra.

Reaction of Ethyl 4-Pyridazinecarboxylate with Phenoxymethyl Radicals under Standard Conditions

To a stirred mixture of **2** (1 52 g, 10.0 mmol), $AgNO_3$ (0.51 g, 3 0 mmol) and phenoxyacetic acid (7.61 g, 50.0 mmol) in 10 ml of 2*N* H_2SO_4 was added at 90°C a solution of $(NH_4)_2S_2O_8$ (6.85 g, 30.0 mmol) in 20 ml of water over a period of 20 min. After heating for additional 120 min the mixture was cooled to room temperature and was extracted with CH_2Cl_2 (4x 50 ml) The CH_2Cl_2 layer was washed with 2*N* NaOH (2x 50 ml), water (3x 50 ml) and saturated sodium chloride solution (1x 50 ml), dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo*. Compound (**3**) crystallised upon treatment of the residue with ether. Compound (**1b**) was obtained by filtering off the precipitate, concentrating the ether solution and cooling it to -20°C.

Separation of meso-3 and rac-3:

Meso-3 was obtained by careful fractional crystallisation of **3** from ethyl acetate The **rac-3** then became available by concentrating the ethyl acetate solution and cooling it to 4°C overnight.

meso-5,5'-(1,2-Diphenoxy-1,2-ethanediyl)-bis-4-pyridazinecarboxylic acid ethyl ester (meso-3)

Yield: 513 mg (20.0%), colourless needles, mp 212-215°C (ethyl acetate). Anal Calcd for $C_{28}H_{26}N_4O_6$: C, 65.36, H, 5.09; N, 10.89. Found: C, 65.28; H, 5.25, N, 10.68. EI-ms: m/z (rel.int.) 514 (5.6%, M^+), 135 (100%) Ir (cm^{-1}): 1725 (C=O). ^1H-Nmr (DMSO-d_6) δ: 1.32 (t, 6H, J=7.0 Hz, 2 x CH_3), 4.35 (q, 4H,

J=7.0 Hz, 2 x CH_2), 6 67 (s, 2H, 2 x CH), 6.87-7.28 (m, 10H, benzene-H), 9.38, 9.47 (s, 4H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ: 13.6 (CH_3), 62.7 (CH_2), 74.6 (CH), 115.5 (benzene C-2, C-6), 122.4 (benzene C-4), 127.5 (pyridazine C-4), 129.8 (benzene C-3, C-5), 134 3 (pyridazine C-5), 148.9, 150.3 (pyridazine C-3, C-6), 155.9 (benzene C-1), 164.1 (C=O).

Crystal structure determination of $C_{28}H_{26}N_4O_6$ (meso-3):

A prismatic crystal of $C_{28}H_{26}N_4O_6$ (**meso-3**) with dimensions of 0.20 x 0 22 x 0.94 mm was used for X-ray diffraction work with a PHILIPS PW1100 four-circle diffractometer and graphite monochromatized Mo Kα radiation Crystal data are: $C_{28}H_{26}N_4O_6$, M_r = 514.54, monoclinic, space group $P2_1/a$ (non-standard setting of No 14), a = 13.855 (3) Å, b = 15.806 (4) Å, c = 6 088 (2) Å, β = 98 49 (1)°, V = 1318 6 (6) Å^3, Z = 2, D_x = 1 296 g cm^{-3}, λ = 0.71069 Å, μ = 0 087 mm^{-1}, T = 297 K. Cell dimensions were determined from ±Θ-scans of 19 reflections (Θ = 16-21°) The intensities of 2645 reflections with Θ < 25°, $-16 \le h \le 16$, $0 \le k \le 18$, $0 \le l \le 7$, were measured by Θ-2Θ scans. Three standard reflections were monitored every two hours and showed negligible intensity variations (±0 9%) The data were corrected for LP. Absorption was small and therefore neglected. Merging yielded 2324 independent reflections, not systematically extinguished, of which 1546 had $F_O \ge 4\sigma(F_O)$.

The structure was solved with direct methods using the program *SHELX*76 [8] Structure refinement by full-matrix least-squares was carried out with the same program using weights $w = 1/[\sigma^2(F_O)^2+0.0002F_O^2]$, anisotropic temperature factors for non-hydrogen atoms, and a correction for extinction. All hydrogen atoms were located from a difference Fourier synthesis and were refined in positional parameters and isotropic temperature factors Final Refinement on F gave R = 0 045, wR = 0.043, and S = 1.63 for 1545 reflections and 225 parameters. Maximum and minimum residual densities 0 16 and -0.14 e Å^{-3}. Atomic coordinates of non-hydrogen atoms are given in Table 1 [9] A view of the molecular structure is shown in Fig 1. The molecule has a centre of inversion at x,y,z = 1/2,1/2,1/2, halfway between C(7) and C(7'). This means that **3** represents a meso-form. Bond lengths and angles in the molecule are normal The two phenoxymethylresidues [C_6H_5O-C(7)] of the molecule are essentially coplanar. They are almost exactly perpendicular to the pyridazine ring. The ethoxycarbonyl group, also approximately planar, is inclined by about 34° to the pyridazine ring.

rac-5,5'-(1,2-Diphenoxy-1,2-ethanediyl)-bis-4-pyridazinecarboxylic acid ethyl ester (rac-3)

Yield: 57 mg (2.2%), colourless crystals, mp 173-175°C (ethyl acetate). Anal. Calcd for $C_{28}H_{26}N_4O_6$: C, 65.36; H, 5.09; N, 10 89. Found: C, 65.61; H, 4.99; N, 10 91. EI-ms. m/z (rel.int.) 514 (7.3%, M^+), 94 (100%). Ir (cm^{-1}): 1721 (C=O) ^{1}H-Nmr (DMSO-d_6) δ. 1.34 (t, 6H, J=7 0 Hz, 2 x CH_3), 4.36 (q, 4H, J=7.0 Hz, 2x CH_2), 6.69 (s, 2H, 2x CH), 6.86-7.26 (m, 10H, benzene-H), 9.28, 9.45 (s, 4H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ· 13.6 (CH_3), 62.7 (CH_2), 73 9 (CH), 115.3 (benzene C-2, C-6), 122.2 (benzene C-4), 127.6 (pyridazine C-4), 129.8 (benzene C-3, C-5), 133 9 (pyridazine C-5), 149.0, 150 6 (pyridazine C-3, C-6), 156 1 (benzene C-1), 164.0 (C=O)

General Procedure for the Reaction of Ethyl 4-Pyridazinecarboxylate with Aryloxy(thio)methyl Radicals in a Two-Phase System:

2 (1.52 g, 10.0 mmol), $AgNO_3$ (0.170 g, 1.0 mmol) and phenoxyacetic acid (4.56 g, 30 0 mmol), 2-bromo-phenoxyacetic acid (6.96 g, 30.0 mmol) or thiophenoxyacetic acid (5.05 g, 30 0 mmol), respectively, were suspended in 100 ml of 2*N* H_2SO_4 and 100 ml of toluene and the mixture was heated to 90°C. Under vigorous stirring a solution of $(NH_4)_2S_2O_8$ (6.85 g, 30.0 mmol) in 20 ml of water was added dropwise during 10 min and heating was continued for 60 min. After cooling to room temperature the organic layer was separated, washed with 2*N* NaOH (2x 50 ml), water (3x 50 ml) and saturated sodium chloride solution (1x 50 ml). It then was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residues obtained were treated as follows:

Ethyl 5-phenoxymethyl-4-pyridazinecarboxylate (1b)

The residue was recrystallised from ether to yield 1.86 g (72 0%) of colourless needles, mp 67-68°C. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65 11; H, 5.46; N, 10 85 Found C, 65.37; H, 5.23, N, 10 91. Ms (DCI; isobutane): m/z (rel.int) 259 (100%, M^++1). Ir (cm^{-1}): 1719 (C=O) ^{1}H-Nmr (DMSO-d_6) δ: 1.32 (t, 3H, J=7.1 Hz, CH_3), 4.37 (q, 2H, J=7.1 Hz, CH_2), 5.53 (s, 2H, CH_2), 6 99-7.37 (m, 5H, benzene-H), 9.49, 9 58 (s, 2H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ: 13.8 (CH_3), 62.1 (CH_2), 64 4 (CH_2), 114.7 (benzene C-2, C-6), 121.4 (benzene C-4), 125.9 (pyridazine C-4), 129.6 (benzene C-3, C-5), 136.4 (pyridazine C-5), 148 8, 150.4 (pyridazine C-3, C-6), 157 5 (benzene C-1), 163.9 (C=O)

Ethyl 5-(2-bromophenoxymethyl)-4-pyridazinecarboxylate (1d)

The residue was recrystallised from ether to yield 1.41 g (41.8%) of colourless needles, mp 95.5-97°C Anal. Calcd for $C_{14}H_{13}N_2O_3Br$ C, 49.87; H, 3 89; N, 8.31. Found: C, 50.01; H, 3.81, N, 8 31 EI-ms: m/z (rel.int.) 338/336 (0:15/0 15%, M^+), 137 (100%) Ir (cm^{-1}): 1723 (C=O). ^{1}H-Nmr (DMSO-d_6) δ: 1.33 (t, 3H, J=7.1 Hz, CH_3), 4.38 (q, 2H, J=7.1 Hz, CH_2), 5.62 (s, 2H, CH_2), 6.97-7.67 (m, 4H, benzene-H), 9.52, 9.68 (s, 2H, pyridazine-H) ^{13}C-Nmr (DMSO-d_6) δ: 13.7 (CH_3), 62.2 (CH_2), 65.4 (CH_2), 111.1 (benzene C-2,), 113.8 (benzene C-6), 122.9 (benzene C-4), 125.6 (pyridazine C-4), 129.1 (benzene C-5), 133.1 (benzene C-3), 136.0 (pyridazine C-5), 148.9, 150.2 (pyridazine C-3, C-6), 153 7 (benzene C-1), 163.7 (C=O).

Ethyl 5-thiophenoxymethyl-4-pyridazinecarboxylate (1f)

The resulting yellow oil was washed with ether to yield 1.73 g (63.1%) of a light yellow oil. Owing to limited stability no satisfactory elemental analyses could be obtained from this compound. Ir (cm^{-1}): 1726 (C=O). ^{1}H-Nmr (DMSO-d_6) δ 1 32 (t, 3H, J=7.1 Hz, CH_3), 4.32 (q, 2H, J=7.1 Hz, CH_2), 4.51 (s, 2H, CH_2-S), 7.28 (s, 5H, benzene-H), 9.20, 9 33 (s, 2H, pyridazine-H) ^{13}C-Nmr (DMSO-d_6) δ: 13.7 (CH_3), 32 3 (CH_2-S), 62.1 (CH_2), 126.5 (pyridazine C-4), 127.5 (benzene C-4), 129.1 (benzene C-2, C-6), 131 0 (benzene C-3, C-5), 133.1, 137 5 (pyridazine C-5, benzene C-1), 149.2, 153.2 (pyridazine C-3, C-6), 164.0 (C=O).

Hydrolysis of the Esters 1b, 1d, 1f to the Acids 1a, 1c, 1e

A solution of **1b** (3.10 g, 12 0 mmol), **1d** (337 mg, 1 0 mmol) or **1f** (173 mg, 0.63 mmol), respectively, and sodium hydroxide (3 equivalents) in 50% ethanol (10-120 ml) was heated under reflux for 2 h. After removing ethanol *in vacuo* the solution was acidified with 2*N* HCl at 0°C. The separated solid was filtered, washed with water, light petroleum and dried

5-Phenoxymethyl-4-pyridazinecarboxylic acid (1a)

2.55 g (92.2%), colourless crystals, mp 197°C (decomp.). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.36; H, 4.38; N, 12 14 EI-ms· m/z (rel.int.) 230 (11.1%, M^+), 94 (100%). Ir (cm^{-1}): 1719 (C=O). ^{1}H-Nmr (DMSO-d_6) δ: 5.55 (s, 2H, CH_2), 6.94-7.36 (m, 5H, benzene-H), 9.47,

9.55 (s, 2H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ· 64.5 (CH_2), 114.8 (benzene C-2, C-6), 121.4 (benzene C-4), 126.5 (pyridazine C-4), 129.7 (benzene C-3, C-5), 136 8 (pyridazine C-5), 149 2, 150.3 (pyridazine C-3, C-6), 157.6 (benzene C-1), 165.5 (C=O).

5-(2-Bromophenoxymethyl)-4-pyridazinecarboxylic acid (1c)

271 mg (87.7%), buff white crystals, mp >230°C (decomp). Anal Calcd for $C_{12}H_9N_2O_3Br$ x 0.25 H_2O: C, 45 96; H, 3.05; N, 8.93. Found: C, 45.75, H, 2 94; N, 8 86. EI-ms: m/z (rel.int.) 310/308 (2 6/2 6%, M^+), 44 (100%). Ir (cm^{-1}). 1703 (C=O). ^{1}H-Nmr (DMSO-d_6) δ· 5.64 (s, 2H, CH_2), 6 93-7.67 (m, 4H, benzene-H), 9.49, 9.67 (s, 2H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ: 65 6 (CH_2), 111.2 (benzene C-2,), 114 0 (benzene C-6), 122.9 (benzene C-4), 126 1 (pyridazine C-4), 129.2 (benzene C-5), 133 1 (benzene C-3), 136.5 (pyridazine C-5), 149.2, 149 9 (pyridazine C-3, C-6), 153.7 (benzene C-1), 165 3 (C=O)

5-Thiophenoxymethyl-4-pyridazinecarboxylic acid (1e)

65 mg (41 9%), buff white crystals, mp 172-174°C Anal. Calcd for $C_{12}H_{10}N_2O_2S$ x 0.1 H_2O. C, 58.10; H, 4 14; N, 11 29 Found: C, 58.10; H, 3.93; N, 10.82 EI-ms· m/z (rel.int.) 246 (4 3%, M^+), 43 (100%). Ir (cm^{-1}): 1717 (C=O) ^{1}H-Nmr (DMSO-d_6) δ. 4.54 (s, 2H, CH_2), 7 29 (s, 5H, benzene-H), 9.14, 9 34 (s, 2H, pyridazine-H). ^{13}C-Nmr (DMSO-d_6) δ: 32.0 (CH_2), 127.3 (benzene C-4), 127.4 (pyridazine C-4), 129 1 (benzene C-2, C-6), 130.6 (benzene C-3, C-5), 133.5, 137.6 (pyridazine C-5, benzene C-1), 149.6, 153.1 (pyridazine C3, C-6), 165.6 (C=O)

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