Polarized Ketene Dithioacetals; 60.[1] Synthesis of Novel 6-Aryl-5-bis(methylthio)methyl-3(2*H*)-pyridazinones

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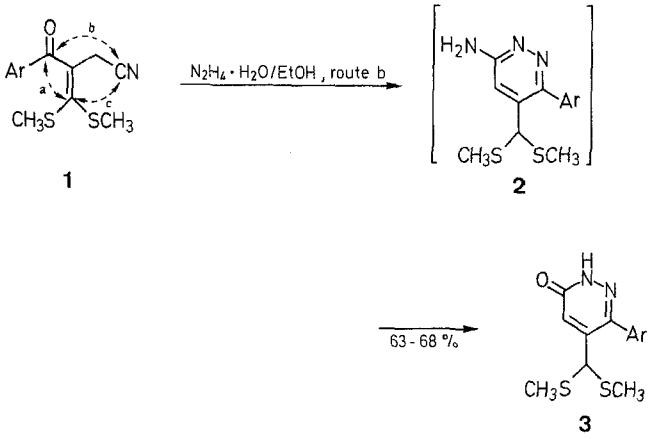
4-Aryl-3-bis(methylthio)methylene-4-oxobutanenitriles **1a–e** undergo cyclocondensation with hydrazine hydrate to give novel 6-aryl-5-bis(methylthio)methyl-3(2*H*)-pyridazinones **3a–e** in good yields. The reaction of ketene dithioacetal **1b** with hydroxylamine afforded only the open-chain amidoxime **4**.

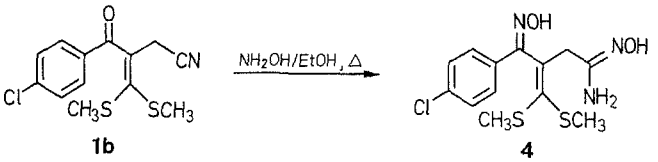
The acyl- and α-cyanoalkylketene dithioacetals have been shown by us as useful 1,3-electrophilic fragments which react with binucleophiles to yield a wide variety of heterocycles.[2] However, the dithioacetals **1** derived from β-aroylpropionitrile possess additional 1,4-electrophilic sites in addition to its 1,3-electrophilic reactivity. They can therefore react with binucleophiles (or nucleophiles) through either of the routes a, b or c depending upon the relative electrophilicities of reactive centers and other factors. Thus, when **1** were reacted with alkylamines, the corresponding 1-substituted 2-amino-4-aroyl-5-methylthiopyrroles were obtained in good yields.[3] However, **1** can react with hydrazine hydrate to give either substituted pyrazole (route a) or the corresponding pyridazine derivatives (routes b or c). We have observed that pyridazine formation (route b) is preferred over pyrazole ring closure. We report our results in the present communication.

When **1a** was refluxed with excess of hydrazine hydrate in ethanol the reaction mixture showed (TLC) formation of only one product (68%) which after isolation was characterized as 5-bis(methylthio)methyl-6-phenyl-3(2*H*)-pyridazinone (**3a**). The 3(2*H*)-pyridazinone **3a** is presumably formed by cyclocondensation of hydrazine hydrate at carbonyl and nitrile groups (route b) to give the 3-aminopyridazine **2a** followed by its hydrolysis under experimental conditions. The other substituted 3 (2*H*)-pyridazinones **3b–e** were similarly obtained in 63–67% overall yields (Table).



1 2 3

When **1b** was reacted with either one or four equivalents of hydroxylamine hydrochloride, the product isolated was identified as amidoxime **4**. Our attempts to isolate any of the five or six membered heterocyclic compounds like oxazine,[4] isoxazole,[5] or cyclic nitrone[6] from this reaction were however not successful.



1b 4

Formation of novel pyridazinone derivatives from reaction of **1** and hydrazine hydrate is of considerable interest in view of the various pharmacological properties exhibited by these class of compounds especially in central nervous system and cardiovascular area.[7,8]

The desired ketene dithioacetals **1a–e** were prepared according to our earlier reported procedure.[3]

6-aryl-5-bis(methylthio)methyl-3(2*H*)-pyridazinones 3a–e; General Procedure:

A solution of **1** (5 mmol) and $N_2H_4 \cdot H_2O$ (0.28 g, 5.5 mmol) in EtOH (15 mL) is refluxed for 15–16 h. The solvent is removed under vacuum and the residue poured onto ice-cold water (15 mL), extracted with $CHCl_3$ (3 × 15 mL), dried (Na_2SO_4) and concentrated to give the crude 3(2*H*)-pyridazinones **3**, which are purified by column chromatography over silica gel column, using benzene/hexane (1:2) as eluent and crystallized from benzene/hexane (Table).

3-Bis(methylthio)methylene-4-(4-chlorophenyl)-4-oxobutanamide Dioxime (4):

A solution of **1b** (1.4 g, 5 mmol) and NH_2OH [generated from $NH_2OH \cdot HCl$ (1.40 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in water (5 mL), neutral to litmus] in ethanol (20 mL) is refluxed for 1 h. The mixture is poured onto ice-cold water (20 mL). the precipitated product is filtered, washed with water and crystallized from MeOH to give **4** as white crystals; yield 1.52 g (88%); mp 167–168 °C.

$C_{13}H_{16}ClN_3O_2S_2$	calc.	C 45.14	H 4.66	N 12.15
(345.9)	found	45.50	5.06	12.00

Table. 6-Aryl-5-bis(methylthio)methyl-3(2*H*)-pyridazinones **3a–e** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ	MS (70eV)[e] m/z (M^+)
3a	68	153–154	$C_{13}H_{14}N_2OS_2$ (278.4)	3100, 3185, 3250 (w), 1655 (s)	2.10 (s, 6H, SCH_3); 4.62 [s, 1H, $-CH(SCH_3)_2$]; 7.28 (s, 1H, H-4); 7.60 (s, 5H$_{arom}$); 12.60 (s, 1H, NH, exchangeable with D_2O)[f]	278
3b	63	165–166	$C_{13}H_{13}ClN_2OS_2$ (312.9)	3100, 3200, 3250 (w), 1655 (s), 3370, 1670[h]	2.08 (s, 6H, SCH_3); 4.52 [s, 1H, $-CH(SCH_3)_2$]; 7.28 (s, 1H, H-4); 7.52 (s, 4H$_{arom}$); 12.55 (s, 1H, NH, exchangeable with D_2O)[f,g]	312, 314
3c	65	162–163	$C_{14}H_{16}N_2O_2S_2$ (308.4)	3105, 3200, 3250 (w), 1660 (s)	2.06 (s, 6H, SCH_3); 3.80 (s, 3H, OCH_3); 4.58 [s, 1H, $-CH(SCH_3)_2$]; 6.83–7.72 (m, 5H$_{arom}$ + H-4); 12.65 (br s, 1H, NH-exchangeable with D_2O)[f]	308
3d	67	171–172	$C_{14}H_{16}N_2OS_2$ (292.4)	3100, 3185, 3240 (w), 1655 (s)	1.98 (s, 6H, SCH_3); 2.32 (s, 3H, CH_3); 4.52 [s, 1H, $-CH(SCH_3)_2$]; 7.15 (s, 1H, H-4); 7.10–7.50 (m, 4H$_{arom}$); 12.60 (s, 1H, NH, exchangeable with D_2O)[f]	292
3e	66	148–149	$C_{13}H_{13}BrN_2OS_2$ (357.3)	3110, 3190, 3242 (w), 1655 (s)	2.05 (s, 6H, SCH_3); 4.48 [s, 1H, $-CH(SCH_3)_2$]; 7.15 (s, 1H, H-4); 7.48 (s, 4H$_{arom}$); 12.80 (br, NH, exchangeable with D_2O)[f]	356, 358

[a] Yield of pure isolated products.
[b] Satisfactory microanalyses obtained C ±0.28, H ±0.31, N ±0.26.
[c] Recorded on a Perkin-Elmer 297 spectrophotometer.
[d] Recorded on a Varian EM-390 spectrometer.
[e] Recorded on a Jeol-D 300 mass spectrometer.
[f] The δ value for the NH proton is very similar to that reported for other pyridazinones.[9]
[g] ^{13}C-NMR ($CDCl_3$/TMS): δ = 13.90 (SCH_3); 50.85 [$CH(SCH_3)_2$]; 126.50 (C-1′ of 4-chlorophenyl); 128.82, 130.35 (CH, aromatic); 132.83 (C–Cl); 135.51 (HC-4); 144.39 (C-5); 146.48 (C-6); 162.05 (C=O).
[h] Recorded in CH_2Cl_2.

IR (KBr): ν = 3350 (w, NH), 1660 cm^{-1} (s, C=O).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.00 (s, 3H, SCH_3); 2.31 (s, 3H, SCH_3); 3.30 (s, 2H, CH_2); 5.15 (br s, 2H, NH_2, exchangeable with D_2O); 7.35–7.74 (dd, A_2B_2, 4H$_{arom}$); 8.90 (s, 1H, OH, exchangeable with D_2O).

^{13}C-NMR (DMSO-d_6): δ = 16.18 (q, SCH_3); 16.21 (q, SCH_3); 35.47 (t, CH_2); 127.70; 128.01 (d, CH, arom); 132.85 [s, C=C(SCH$_3$)$_2$]; 133.90 (s, C-1 of phenyl); 136.00, 136.18 (s, C-4′ of *p*-chlorophenyl and ArC=NOH); 149.50 (s, H_2NC=NOH); 154.77 [s, C=C(SCH$_3$)$_2$].

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(1) Part 59; Chakrasali, R. T., Ila, H., Junjappa, H. *Synthesis* **1988**, 87.
(2) For a recent review, see: Dieter R. K. *Tetrahedron* **1986**, *42*, 3029.
(3) Apparao, S., Ila, H., Junjappa, H. *Synthesis* **1981**, 65.
(4) El-Kohly, I. E-S., Mostafa Fuid-Alla, H., Mishrikey, M. M. *J. Heterocycl. Chem.* **1980**, *17*, 541.
(5) Zvilichovsky, G., David, M. *J. Org. Chem.* **1983**, *48*, 575.
(6) Blatt, A. H. *J. Am. Chem. Soc.* **1936**, *58*, 590.
Blatt, A. H. *J. Am. Chem. Soc.* **1934**, *56*, 2774.
Knott, E. B. *J. Chem. Soc.* **1947**, 1196.
(7) Taoufik, J., Couquelet, J. D., Couquelet, J. M., Carby, A. *J. Heterocycl. Chem.* **1984**, *21*, 305 and references cited therein.
(8) Tišler, M., Stanovnik, B., in: *Comprehensive Heterocyclic Chemistry*, Vol. 3, Boulton, A. J., McKillop, A. (eds.), Pergamon Press, Oxford, 1984, pp. 1–56.
(9) Exinger, A., Wermuth, C. G. *Synthesis* **1974**, 817.

Errata:

– Baldo, M. A., Chessa, G., Marangoni, G., Pitteri, B. *Synthesis* **1987**, 720. On p. 722, line 6, "degree of functionalization" should read "yield of binding". On the same page in the preparation of bis-hydrazone **5**, line 8, "solid product" should read "oil".

– Singh, L. W., Ila, H., Junjappa, H. *Synthesis* **1988**, 89. On p. 90 in the ^{1}H-NMR data for dioxime **4**, line 2, "N_2" should read "NH_2".

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- Burger, K., Hübl, D., Geith, K. *Synthesis* **1988**, 194. On p. 196 in the table, for entries **4l**, **4m**, and **4n**, Y = O, and *Nu* = Cl, Br, and C_6H_5, respectively.

- Tolstikov, A.G., Khakhalina, N.V., Spirikhin, L.V. *Synthesis* **1988**, 221. In the title and abstract, benzyl esters should read benzyl ethers.

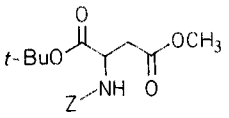
- Gupta, A.K., Ila, H., Junjappa, H. *Synthesis* **1988**, 284. Compounds **4** are 1,6-dioxo-1,2,3,6-tetrahydropyrano[3,4-*c*]pyrroles; compounds **9** are 1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridines.

- Keshavarz-K., M., Cox, S.D., Angus, R.O., Jr., Wudl, F. *Synthesis* **1988**, 641. On p. 642 the IR spectra shown in Figures 2 and 3 should be interchanged.

- Rodriguez, J., Waegell, B. *Synthesis* **1988**, 534. On p. 535, the first line of the general procedure should read: "DMAP (0.92 g, 7.5 mmol) and then α,β-unsaturated aldehyde **1** (0.1 mol)..."

- Zbiral, E., Drescher, M. *Synthesis* **1988**, 735. On p. 738 in the last procedure, the name for compounds **14** should read: (5-Oxo-5,6-dihydroimidazo[1,2-*c*]pyrimidin-3-yl)methylphosphonsäuren.

- Valerio, R.M., Alewood, P.F., Johns, R.B. *Synthesis* **1988**, 786. On p. 787 formula **2** should be:



Also on p. 787 in the reaction of **5** in the scheme on the right side, the reagent should be:

- Garrigues, B., Mulliez, M. *Synthesis* **1988**, 810. The title should read: Salts of *N*-(Sulfoalkyl)ureas and -thioureas.

- Yokoyama, M., Watanabe, S., Seki, T. *Synthesis* **1988**, 879. On p. 880 the name of compound **3a** in the first procedure should be azido(2-benzyloxyethoxy)methane.