STUDIES ON AZINETHIONES: A NOVEL SYNTHESIS OF BIS(AZINYL) TRITHIOCARBONATES AND MULTI-FUSED THIENOAZINES

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Abstract- A study of the reactivity of azinethione series toward carbon disulphide has been carried out which resulted in a synthesis of bis(azinyl)-trithiocarbonates. Reaction of 4-methylazinethiones with *N*-bromosuccinimide affords in one pot reaction unexpected multifused heterocyclic compounds.

Azinethiones and their derivatives[1,2] constitute an important class of heterocyclic compounds of considerable interest due to its diversity of chemical transformations and their uses as active ingredients of fungicidal and antimicrobial agents.[3-5] These bifunctional compounds, containing thione (thiol) with an endocyclic nitrogen atom in a vicinal position, have turned out to be precursors for the synthesis of inaccessible annelated heterocyclic systems. Extensive work has been prompted on the synthesis and chemistry of azinethiones and their condensed systems.[1,2] Although ß-enaminonitriles have been widely utilized in heterocyclic syntheses,[6-9] little have been reported on the utility of these versatile reagents as building blocks for azinethione systems.

In previous work we have reported[9] the synthesis of ammonium 1,1,3-tricyano-2-methylprop-2-enide (**3**) as a reagent in heterocyclic synthesis. In connection with this study, we report herein our work which has resulted in development of a methodology for the synthesis of bis(azinyl)trithiocarbonates and condensed thienoazines. Thus, it has been found that compound (**3**), readily obtainable from the reaction of malononitrile (**1**) with ß-aminocrotononitrile (**2**),[9] reacts readily with equimolar proportion of phenyl isothiocyanate to afford exclusively and in excellent yield (93%) the acyclic 1 : 1 adduct 1,1,3-tricyano-2-methyl-*N*-phenylthioacrylamide (**4**), the structure of which was established according to its analytical and

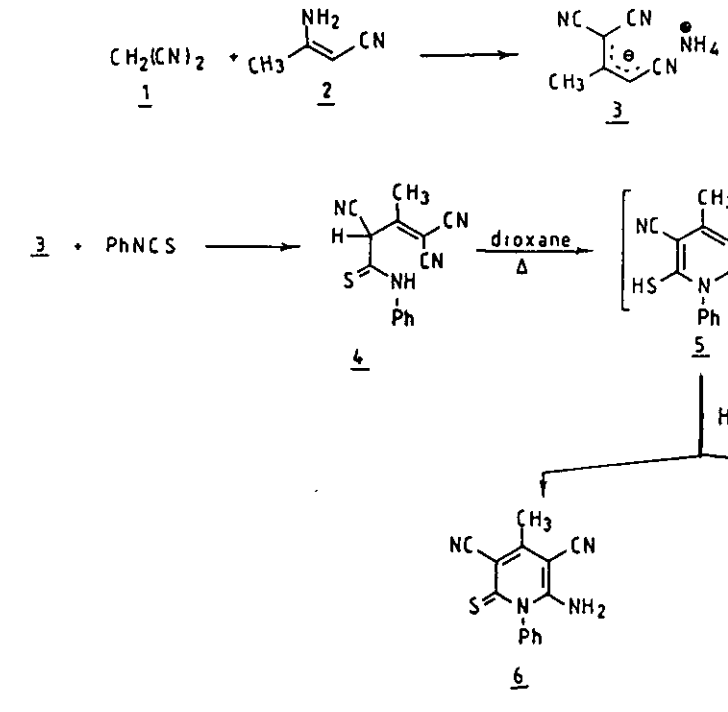
spectroscopic data. Compound (**4**) cyclized readily under reflux in dioxane to yield the corresponding 6-aminopyridine derivative (**6**). In contrast, it was found that under acidic conditions compound (**4**) cyclized into the pyridinone (**7**). Formation of **6** and **7** would proceed *via* intermediacy of the imine (**5**).

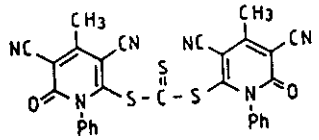
Treatment of the pyridinethione (**7**) with carbon disulphide in the presence of triethylamine and lead (II) acetate afforded the bis(pyridinyl) trithiocarbonate derivative (**8**). This synthetic methodology of bis(azinyl) trithiocarbonates could be generalized using a variety of azinethiones (**9-11**)[2,10] to get **12a-c,** respectively (Scheme 1). Attempts to react compound (**6**) with carbon disulphide, using the same methodology, was failed. This indicates that the thiol forms in azinethione compounds are responsible for formation of the trithiocarbonates. On the other hand, compound (**6**) reacted with CS_2 in presence of NaH followed by subsequent treatment with excess methyl iodide to give the final isolable product pyrido[2,3-*d*]pyrimidine derivative (**15**). Structure (**15**) was preferred for the reaction product on the basis of spectroscopic data. Thus, the ir spectrum revealed the presence of SCH_3 (υ_{max} 860 cm^{-1}) and the absence of an imine group absorption band. The isomeric structure (**14**) would be expected to show imine group at υ (*ca* 1700 - 1670 cm^{-1}).[11] ^{1}H-Nmr spectrum showed beside the aromatic protons, three singlet signals attributed to three CH_3 groups at δ = 2.11, 3.13 and 3.32 ppm.

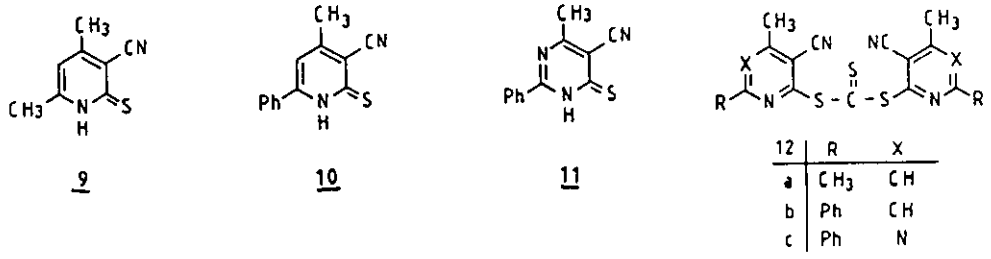
During our studies on alkylazinethiones we found unexpected formation of multifused heterocyclic species in one pot reaction. Thus, treatment of the pyridinethione (**9**) with *N*-bromosuccinimide in boiling carbon tetrachloride led exclusively to the multifused ring system (**18**) in reasonable yield (64%). Compound (**18**) was assumed to be formed *via* intermediacy of the bromoalkyl derivative (**16**) which reacted with compound (**9**) to form the thienopyridine intermediate (**17**) *via* HBr elimination. The latter, in turn, subsequently underwent intramolecular cyclization to form the final isolable product (**18**) (Scheme 2). This synthetic methodology could be generalized by using the pyridinethione (**10**) and pyrimidinethione (**11**) to get the multifused heterocyclic systems (**19a**) and (**b**), respectively.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (KBr) on a Pye Unicam SP-1000 Spectrophotomer. ^{1}H-Nmr spectra were recorded on a Varian ^{1}H-Gemini 200 MHz and a Varian EM-300 MHz Spectrometers with DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed as δ (ppm) units. Ms spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 eV. Microanalytical data were determined on a Perkin-Elmer 240 C microanalyser.

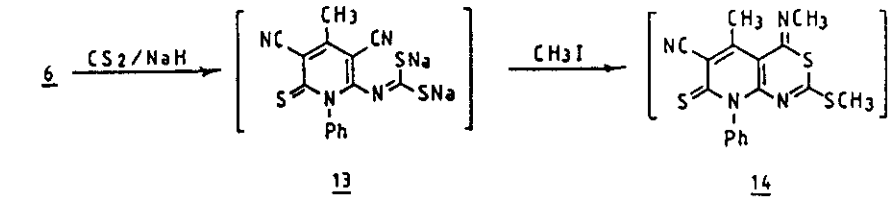




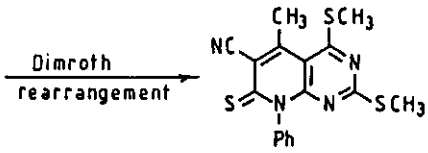


12	R	X
a	CH_3	CH
b	Ph	CH
c	Ph	N

Scheme 1



13 14



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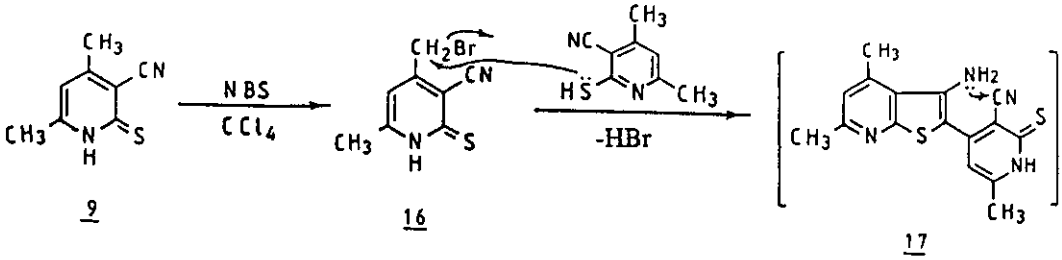
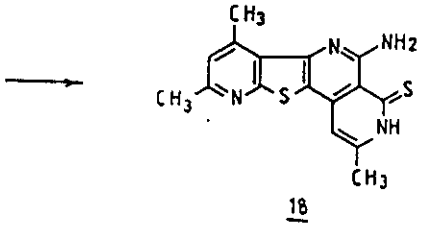
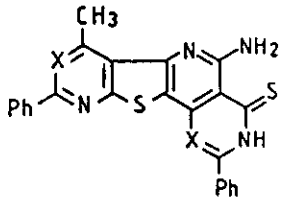


9 16 17



18



19	X
a	CH
b	N

Scheme (2)

Ammonium 1,1,3-tricyano-2-methylprop-2-enide (**3**) was prepared according to our previously reported procedures.[9]

2-Methyl-1,1,3-tricyano-*N*-phenylthioacrylamide (**4**). To a solution of **3** (1.45 g, 0.01 mol) in acetone (30 ml), phenyl isothiocyanate (1.35 g, 0.01 mol) was added. The reaction mixture was refluxed for 3 h, cooled at room temperature, and poured onto water (30 ml) whereby the resulting solid product was filtered off and recrystallized from ethanol to afford yellow crystals: yield 2.4 g (93%), mp 192°C. Ms (m/z = 266, 35%). -Ir: υ =3340 (NH), 2220, 2216, 2208 (3 CN). -^{1}H-Nmr: δ (ppm) = 1.92 (s, 3H, CH_3), 3.65 (s, 1H, CH), 6.98-7.29 (m, 5H, C_6H_5), 11.23 (br s, 1H, NH, exchangeable). Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.13; H, 3.78; N, 21.03; S, 12.04. Found: C, 63.0; H, 3.5; N, 20.8; S, 11.9.

6-Amino-1,2-dihydro-4-methyl-1-phenyl-2-thioxopyridine-3,5-dicarbonitrile (**6**). A solution of **4** (2.66 g, 0.01 mol) in dioxane (30 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 5 min. The reaction mixture was cooled at room temperature, triturated with water and neutralized with dilute hydrochloric acid (25%). The resulting solid product was collected by filtration and recrystallized from dioxane to afford yellow crystals: yield 1.9 g (74%), mp 260°C. -Ir: υ = 3450-3380 (NH_2), 2220, 2212 (2 CN). -^{1}H-Nmr: δ (ppm) = 2.31 (s, 3H, CH_3), 6.95-7.31 (m, 5H, C_6H_5), 8.33 (br s, 2H, NH_2, exchangeable). Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.13; H, 3.78; N, 21.03; S, 12.04. Found: C, 63.1; H, 3.6; N, 20.9; S, 12.0.

1,6-Dihydro-2-mercapto-4-methyl-6-oxo-1-phenylpyridine-3,5-dicarbonitrile (**7**). A solution of **4** (2.66 g, 0.01 mol) in glacial acetic acid (30 ml) was refluxed for 5 min. The solid product, which was obtained by evaporation under vacuum and trituration with water, was collected by filtration and recrystallized from dioxane to afford pale yellow crystals: yield 2.2 g (82%), mp >300°C. Ms (m/z = 267, 24%). -Ir υ = 2218, 2212 (2 CN), 1705 (CO). -^{1}H-Nmr: δ (ppm) = 2.28 (s, 3H, CH_3), 3.23 (s, 1H, SH, exchangeable), 6.98-7.25 (m, 5H, C_6H_5). Anal. Calcd for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72; S, 11.99. Found: C, 62.8; H, 3.1; N, 15.7; S, 11.8.

Bis(azinyl) trithiocarbonates (8) and (12a-c). General procedure: Equimolar amount (0.01 mol) of the appropriate azinethione (**7**) or (**9-11**) and triethylamine in dry dioxane (30 ml) where stirred in an ice bath at 0-5°C for 30 min. A solution of carbon disulphide (0.76 g, 0.01 mol) in dry dioxane (10 ml) was

then added to the reaction mixture dropwise in about 1 h and stirring was continued for an additional 1 h at 0-5°C. The solvent was then distilled off under vacuum whereby an orange oilly product was obtained.

The obtained oilly product (0.01 mol) in dry dioxane (10 ml) was added dropwise to a well stirred mixture of the appropriate azinethione (0.01 mol), $Pb(OAc)_2$ (3.89 g, 0.01 mol) and dilute HCl (25%, 7.3 ml) in dioxane (20 ml) at 0-5°C. The reaction mixture was left aside at room temperature overnight, evaporated under vacuum, and neutralized with NaOH solution (2N) (pH = 7). The solid product so formed, in each case, was filtered off and recrystallized from the proper solvent.

Bis(3,5-dicyano-1,6-dihydro-4-methyl-6-oxo-1-phenylpyridin-2-yl) trithiocarbonate (8): yellow crystals from dilute dioxane, 71%, mp >300°C. Ms (m/z = 576, 16%). -Ir: υ = 2220, 2212 (2 CN), 1708 (CO). -^{1}H-Nmr: δ (ppm) = 2.23 (s, 6H, 2 CH_3), 6.88-7.42 (m, 10H, 2 C_6H_5). Anal. Calcd for $C_{29}H_{16}N_6O_2S_3$: C, 60.40; H, 2.79; N, 14.57; S, 16.68. Found: C, 60.1; H, 2.7; N, 14.4; S, 16.5.

Bis(3-cyano-4,6-dimethyl-3-cyanopyridin-2-yl) trithiocarbonate (12a): yellow crystals from dilute dioxane, 68%, mp 220°C. -Ir: υ = 2218, 2210 (2 CN). -^{1}H-Nmr: δ (ppm) = 2.10 (s, 6H, 2 CH_3), 2.25 (s, 6H, 2 CH_3), 6.71 (s, 2H, pyridine protons). Anal. Calcd for $C_{17}H_{14}N_4S_3$: C, 55.11; H, 3.80; N, 15.12; S, 25.96. Found: C, 55.0; H, 4.1; N, 15.0; S, 25.8.

Bis(3-cyano-4-methyl-6-phenylpyridin-2-yl) trithiocarbonate (12b): yellow crystals from dilute dioxane, 70 %, mp > 300°C. -Ir: υ = 2220, 2212 (2 CN). -^{1}H-Nmr: δ (ppm) = 2.15 (s, 6H, 2 CH_3), 6.72 (s, 2H, pyridine protons), 7.12-7.52 (m, 10H, 2 C_6H_5). Anal. Calcd for $C_{27}H_{18}N_4S_3$: C, 65.56; H, 3.66; N, 11.32; S, 19.44. Found: C, 65.4; H, 3.8; N, 11.2; S, 19.4.

Bis(5-cyano-6-methyl-2-phenylpyrimidin-6-yl) trithiocarbonate (12c): yellow crystals from dioxane, 64%, mp 157°C. -Ir: υ = 2216, 2210 (2 CN). -^{1}H-Nmr: δ (ppm) = 2.22 (s, 6H, 2 CH_3), 6.91-7.29 (m, 6H, arom. protons), 7.61-7.82 (m, 4H, arom. protons). Anal. Calcd for $C_{25}H_{16}N_6S_3$: C, 60.46; H, 3.24; N, 16.92; S, 19.36. Found: C, 60.3; H, 3.1; N, 16.8; S, 19.1.

7,8-Dihydro-2,4-dimethylthio-5-methyl-8-phenyl-7-thioxopyrido[2,3-d]pyrimidine-6-carbonitrile (15) : To a solution of **6** (2.66 g, 0.01 mol) in dry benzene (20 ml) and DMF (5 ml) containing sodium hydride (0.48 g, 0.02 mol) was added carbon disulphide (0.76 g, 0.01 mol). The reaction mixture was refluxed on a boiling water bath for 2 h. After cooling at room temperature, methyl iodide (2.8 g,

0.02 mol) was added and the reaction mixture was refluxed for an additional 30 min. The residue obtained on evaporation under vacuum, was triturated with ethanol and neutralized with dilute HCl (25%). The solid product formed was filtered off and recrystallized from DMF to afford reddish-brown crystals, yield 2.2 g (59%), mp 265°C. -Ir : υ = 2220 (CN), 860 (SCH_3). -^{1}H-Nmr: δ (ppm) = 2.11 (s, 3H, CH_3), 3.13 (s, 3H, SCH_3), 3.32 (s, 3H, SCH_3), 6.85-7.32 (m, 5H, C_6H_5). Anal. Calcd for $C_{17}H_{14}N_4S_3$: C, 55.11; H, 3.81; N, 15.12; S, 25.96. Found: C, 55.0; H, 3.7; N, 14.9; S, 25.9.

Multi-fused heterocycles (18) and (19a,b). General procedure : To a solution of the appropriate azinethione (**9-11**) (0.01 mol) in carbon tetrachloride (30 ml) containing benzoyl peroxide as initiator (0.1 g), was added *N*-bromosuccinimide (1.77 g, 0.01 mol). The reaction mixture was heated under reflux for 12 h, then filtered off to remove any insoluble materials. The solid product formed on evaporation under vacuum was recrystallized from dioxane.

5-Amino-3,4-dihydro-2,7,9-trimethylthieno[2,3-*b*]pyrido[2`,3`:3,2]-2,7-naphthyridine-4-thione (18): yellow crystals, 64%, mp >300°C. Ms (m/z = 326, 28%). -Ir : υ = 3380-3200 (NH, NH_2). -^{1}H-Nmr: δ (ppm) = 2.11 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 8.13 (br s, 2H, NH_2, exchangeable), 11.43 (br s, 1H, NH, exchangeable). Anal. Calcd for $C_{16}H_{14}N_4S_2$: C, 58.87; H, 4.32; N, 17.16; S, 19.64. Found: C, 58.6; H, 4.3; N, 17.0; S, 19.6

5-Amino-3,4-dihydro-2,9-diphenyl-7-methylthieno[2,3-*b*]pyrido[2`,3`:3,2]-2,7-naphthyridine-4-thione (19a): yellow crystals, 68%, mp > 300°C. -Ir : υ = 3400-3225 (NH, NH_2). -^{1}H-Nmr: δ (ppm) : 2.18 (s, 3H, CH_3), 6.82-7.51 (m, 10H, 2 C_6H_5), 7.83 (br s, 2H, NH_2, exchangeable), 11.81 (br s, 1H, NH, exchangeable). Anal. Calcd for $C_{26}H_{18}N_4S_2$: C, 69.30; H, 4.02; N, 12.43; S, 14.23. Found: C, 69.1; H, 4.0; N, 12.4; S, 14.2.

5-Amino-3,4-dihydro-2,9-diphenylthieno[2,3-*d*]pyrimido[2`,3`:3,2]pyrido[3,4-*d*]-pyrimidine-4-thione (19b): colorless crystals, 60%, mp 265°C. -Ir : υ = 3380-3250 (NH, NH_2).-^{1}H-Nmr: δ (ppm) = 2.21 (s, 3H, CH_3), 3.91 (br s, 2H, NH_2, exchangeable), 6.83-8.1 (m, 10H, 2 C_6H_5), 11.43 (br s, 1H, NH, exchangeable). Anal. Calcd for $C_{24}H_{16}N_6S_2$: C, 63.69; H, 3.56; N, 18.56; S, 14.17. Found: C, 63.6; H, 3.3; N, 18.4; S, 14.0.

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