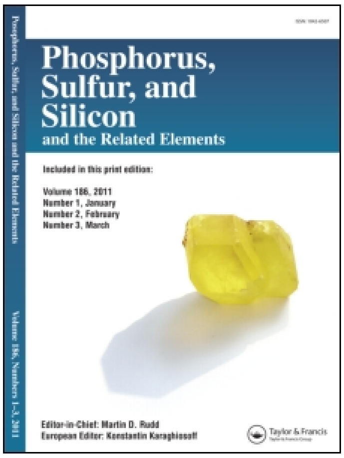

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KETOKETEN gem-DITHIOLS IN ORGANIC SYNTHESIS: SYNTHESIS OF NEW THIOPYRANS AND 1,3-DITHIOLANE DERIVATIVES

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KETOKETEN gem-DITHIOLS IN ORGANIC SYNTHESIS: SYNTHESIS OF NEW THIOPYRANS AND 1,3-DITHIOLANE DERIVATIVES

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3-H IIIa,b and 4-H VIIa–c thiopyrans were prepared via reaction of gem dithiols Ia,b with nitriles. The dithiolanes IXa also could be obtained from reaction of Ia,b with cinnamoylidene anilines.

Key words: Thiopyrans and dithiolanes, ketoken gem-dithiol, oxoketoken dithiols

INTRODUCTION

Thiols and gem-dithiols are versatile reagents that have been extensively used in the synthesis of sulfur heterocycles.[1–6] Addition of the thiol group of α,B-unsaturated nitriles[7] and nitriles[8] α,B-unsaturated[9] imines has been investigated. The reaction of azomethines with excess thiol in acid medium has been used in synthetic organic sulfur chemistry.[9]

As a part of a program for synthesis of new sulfur heterocycles as potential antimicrobial and schistosomal agents, the reactivity of ketoketen gem-dithiols Ia,b towards activated nitriles has been studied. The work has resulted in developing a route for synthesis of polyfunctionally substituted thiopyrans whose synthetic approaches are rather lined. Moreover, a synthesis of dithiolanes could be achieved. Compounds Ia,b were readily obtained via reacting methyl ketones with carbon disulfide in a basic medium as described in the literature.[10,11] It has been found that Ia reacts with ethyl cyanoacetate and with malononitrile to yield condensation products via water elimination. These were formed as IIIa,b rather than the other possible isomeric acyclic adducts IIa,b. Structures IIIa,b were based on ^{1}H.nmr which revealed thiopyran 2-thione H-3[12] at δ4.5 ppm and NH_2 signal at δ6.8 ppm.

Formation of IIIa,b is assumed to proceed via condensation of active methylene reagent with a keto-carbonyl function to yield the unisolable intermediate IIa,b. Subsequent cyclization via addition of the sulfur nucleophile to the cyano group has precluded condensation with a ketocarbonyl reaction, although this can not be ruled out completely.

Compound Ia reacted with cinnamonitriles IVa,c and Ib with IVb and gave thiopyran 4-H derivatives VIIa–c. Formation of 4-H thiopyran derivatives VIIa–c is assumed to proceed via the addition of active methylene in the tautomeric form to acyclic Michael products VIa–c which cyclize into VIIIa–c via addition of the sulfur nucleophile to the cyano group. Structure VIIa–c was established for reaction products based on ^{1}H nmr which revealed thiopyran 4-H at δ4.6 ppm similar to the reported resonance of a similar system.[12] Isomeric 2-H thiopyrans are expected to have the 2-H proton resonance at a much lower field as this proton is deshielded by the sulfur atom.

Another facile and a new synthetic route for the synthesis of 4-H thiopyran could also be achieved. Thus compounds VIIa,b could be prepared by mixing Ia,b with benzaldehyde and/or anisaldehyde and active methylene reagents. It seems that IVa,b are first formed then add Ia,b. The products VIIa,b produced by this way were found identical with those obtained before.

In conjunction with this work directed for developing approaches to synthesis of dithiolanes, the behavior of gem-dithiols towards conjugated systems of the type —C=C—C=N was investigated. Addition of Ia,b to VIIIa,b resulted in the formation of Xa,b. Compounds Xa,b were formed via addition of sulfur nucleophile to the more electronegative azomethane moiety followed by addition of the second sulfur nucleophile to —C=C—, the amine salt is liberated to give the dithiolanes Xa,b via formation of intermediate IXa–c.

EXPERIMENTAL

All melting points are uncorrected and determined on an "electrothermal melting point apparatus." IR spectra (KBr) were determined on a Pye Unicam infrared Spectrophotometer 633791. ^1H nmr ($CDCl_3$) spectra were measured on "Varian Instrument Division EM 390 90 MHz Spectrometer."

(1) *Synthesis of Ketoketen gem-dithiols Ia,b*: Equimolar amounts of each of 4-acetylbiphenyl and/or 2-acetyl furan (0.01 mol) and carbon disulfide (0.01 mol) in dry benzene (100 ml) were added to potassium tert butoxide (0.02 mol) in dry benzene (100 ml) with vigorous shaking. Water (500 ml) was then added with shaking. The benzene layer was extracted and washed with water twice. Neutralization of the aqueous solution with cold concentrated hydrochloric acid yielded a yellow solid which was collected and purified via salt formation and acidification.

(a) 3,3-Dimercapto 1-(4-biphenyl)2-propen-1-one Ia, (yield 82%) m.p. 121°C. Analysis for $C_{15}H_{12}OS_2$ (272).

Calcd: C, 66.17; H, 4.41; S, 23.53%. Found: C, 66.2; H, 4.4; S, 23.5%. ^1H nmr: δ7.2 (s1H, $C\underline{H}{=}C$), 7.4–8.1 (m9H, biphenyl), 5.6 (s1H, $S\underline{H}$).

(b) 3,3-Dimercapto 1(2-furyl)2-propen-1-one Ib, (yield 74%) m.p. 83°C Analysis for $C_7H_6O_2S_2$ (186).

Calcd: C, 45.16; H, 3.22; S, 34.4%. Found: C, 45.2; H, 3.2; S, 34.5%. ^1H nmr δ5.4 (s1H, $S\underline{H}$), 7.1 (s1H, $C\underline{H}{=}C$), 7.2–7.4 (3H, furan).

(2) *Reaction of Ia with active methylene reagents; synthesis of H-3 thiopyran derivatives IIIa,b*: A mixture of the gem-dithiol Ia (0.01 mol), malononitrile and/or ethylcyanoacetate (0.1 mol) in absolute ethanol (100 ml) and sodium ethoxide (0.01 mol) was heated under reflux for 3 hours. After cooling and neutralization with cold dilute hydrochloric acid (15%) the separated products IIIa,b were collected and recrystallized from ethanol.

Analysis for IIIa (yield 57%), m.p. 242°C, $C_{20}H_{17}NO_2S_2$ (367.25).

Calcd: C, 65.41; H, 4.66; S, 17.43%. Found: C, 65.4; H, 4.6; S, 17.5%. IR: 1690 cm^{-1} (C=O), 3500–3300 cm^{-1} (NH_2). ^1H nmr: δ2.3–2.4 (t3H, $C\underline{H}_3$), 3.4–3.5 (q2H, $C\underline{H}_2$), 4.3–4.4 (s1H, 3H thiopyran), 8.5 (2H, NH_2) and 7.4–7.9 (m9H, biphenyl).

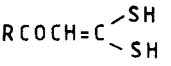
Analysis for IIIb (yield 52%), m.p. 296°C, $C_{18}H_{12}N_2S_2$ (320.3)

Calcd: C, 67.5; H, 3.77; S, 19.98%. Found: C, 67.6; H, 3.8; S, 20.1%. IR: 2225 cm^{-1} (νCN); 3450–3320 cm^{-1} (νNH_2). ^1H nmr: δ4.4–4.5 (s1H, 3H-thiopyran), 7.4–7.8 (m9H, biphenyl).

Reaction of Ia,b with cinnamylidenemalononitriles IVa–c synthesis of 4-H thiopyranes VIIa–c.

Method 1: A mixture of Ia,b and IVa–c (0.01 mol) in ethanol (B.D.H.) (100 ml) and triethylamine (in catalytic amount) was heated under reflux for 5 hours. After concentrating the solvent to a third of its volume and cooling, the separated products were collected and recrystallized from dimethylformamide.

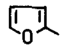
VIIa in the form of pale brown crystals (yield 66%) m.p. 254°C. VIIa, Analysis for $C_{27}H_{23}NO_3S_2$ (473.45).

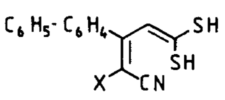


I

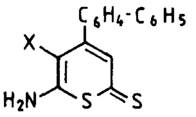
a, R = -C_6H_5-C_6H_4

b, R =





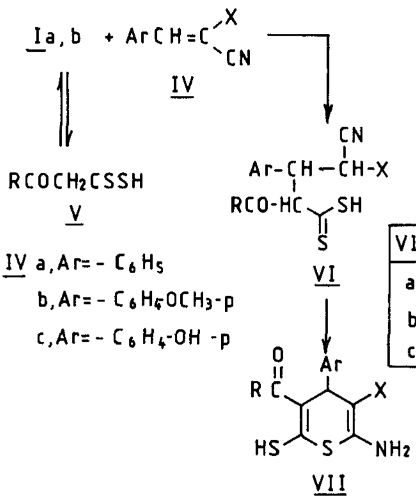
II



III

a, X = -$CO_2C_2H_5$

b, X = -CN

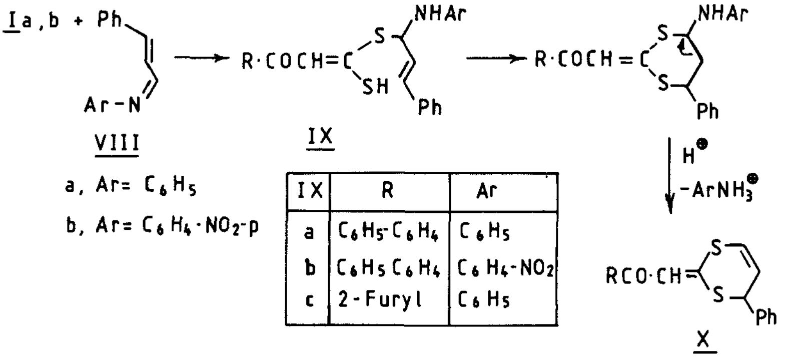


IV a, Ar = -C_6H_5

b, Ar = -C_6H_4-OCH_3-p

c, Ar = -C_6H_4-OH -p

VII	R	Ar	X
a	C_6H_5-C_6H_4	C_6H_5	$CO_2C_2H_5$
b	2-Furyl	$C_6H_4OCH_3$	CN
c	C_6H_5-C_6H_4	C_6H_4OH	$CO_2C_2H_5$



VIII a, Ar = C_6H_5

b, Ar = C_6H_4·NO_2-p

IX	R	Ar
a	C_6H_5-C_6H_4	C_6H_5
b	$C_6H_5C_6H_4$	C_6H_4-NO_2
c	2-Furyl	C_6H_5

X

a, R = C_6H_5-C_6H_4

b, R = 2-Furyl

Calcd: C, 68.49; H, 4.89; S, 13.51%. Found C, 68.5; H, 4.9; S, 13.6%. IR: 1710 cm^{-1} (νCO), 1660 cm^{-1} (νCO) and 3530–3430^{-1} (NH_2). ^1H nmr: δ2.3–2.5 (t3H, CH_3), 3.5 (q2H, CH_2), 4.5 (s1H, 4-H thiopyran), 4.6 (s1H, SH), 8.9 (s2H, NH_2), and at 7.2–7.9 (m14H, C_6H_5–C_6H_4 and C_5H_5).

VIIb in the form of pale brown crystals (yield 71%), m.p. 181°C. Analysis for $C_{18}H_{14}N_2O_3S_2$ (370).

Calcd: C, 58.37; H, 3.78; N, 7.56; S, 17.29%. Found: C, 58.4; H, 3.8; N, 7.5; S, 17.3%. IR: 1680 cm^{-1} (νCO), 2210 cm^{-1} (ν-CN), 2560 cm^{-1} (νSH) and at 3440–3350 cm^{-1} (ν-NH_2). ^1H nmr: δ2.3 (s3H-CH_3), 4.6 (s1H, 4-H-thiopyran), 6.6 (s2H, NH_2)–6.9 (s1H, CO—CH); 7.1 (m3H, Furan)–7.8 (m4H, C_6H_4).

VIIc in the form of brown crystals, m.p. 276°C (yield 67%). Analysis for $C_{27}H_{23}NO_4S_2$ (489).

Calcd: C, 66.25; H, 4.7; S, 13.08%. Found: C, 66.3; H, 4.7; S, 13.1%. IR: 1710 cm^{-1} (νC=O ester), 1680 cm^{-1} (νCO), 2540 cm^{-1} (νSH), 3600 cm^{-1} (νOH). ^{1}H nmr: δ3.5 (t3H, $C\underline{H}_3$), 3.2–3.4 (q2H-$C\underline{H}_2$), 6.3 (s2H, NH_2). 7.2–7.9 (m14H, C_6H_5, C_6H_5–C_6H_4), 4.6 (s1H, 4-H thiopyran), 10.1 (s1H, $O\underline{H}$).

Method 2: Equimolar amounts of Ia, ethyl cyanoacetate and benzaldehyde or of Ib, malononitrile and *p*-anisaldehyde (0.01 mol) in ethanol 100 ml (BDH) and triethylamine (91 ml) were treated under reflux for 5 hours, then the reactions were completed as in method 1. The products found were idential to VIIa,b.

Reactions of Ia with VIIIa,b and Ib with VIIIc; synthesis of 1,3 dithiolanes Xa,b: A mixture of equimolar amounts of the dithol Ia and VIIIa,b and of the dithiol Ib and VIIIc (0.01 mol) in ethanol (100 ml) and triethylamine (1 ml) were heated under reflux for 6 hours. After cooling and acidification with cold conc. HCl and recrystallization from benzene in the form of pale yellow crystals (yield 63%). The reaction of Ia with VIIIa and VIIIb were found to possess identical M.P., 152°C, Xa.

Xa. Analysis of $C_{24}H_{18}OS_2$ (236.39)

Calcd: C, 74.6; H, 4.69; S, 16.56%. Found: C, 74.6; H, 4.6; S, 16.5%. IR: 1665 cm^{-1} (νCO). ^{1}H nmr: δ5.4 (s1H, 4H dithiolan), 7.2 (s1H, CO—$C\underline{H}$), 7.4–7.6 (d2H, $C\underline{H}$—$C\underline{H}$, cyclic) and at 7.6–8.0 (m14H, $C_6\underline{H}_5$ and $C_6\underline{H}_5$–$C_6\underline{H}_4$).

Xb. Yellowish crystals from acetone m.p. 214°C (yield 58%). Analysis for $C_{16}H_{12}S_2O_2$ (300.25).

Calcd: C, 64.00; H, 4.02; S, 21.31%. Found: C, 63.8; H, 3.9; S, 21.5%. IR: 1670 cm^{-1} (νC=O). ^{1}H nmr: δ7.4 (m3H Furan), 7.8–8.1 (m5H, $C_6\underline{H}_5$), 7.0 (s1H, CO—$C\underline{H}$), 6.8 (d2H, $C\underline{H}$=$C\underline{H}$ cyclic), 5.1 (s1H, 4H-dithiolan).

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