SYNTHESIS AND REACTIONS OF THIOPHENE ANALOGS OF CHALCONES

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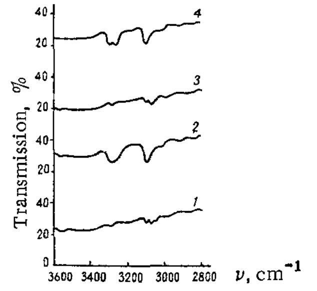
A new method of synthesizing thiophene analogs of chalcones, based on condensing aryl-β-chlorovinyl ketones with thiophene in the presence of stannic chloride, is extended. Hitherto undescribed thiophene analogs of chalcones are obtained in good yields. Addition of 2-nitropropane, nitromethane, and morpholine to the active double bond of thiophene analogs of chalcones gives γ-nitroketones and morpholine derivatives of ketones containing the benzene ring and thiophene. Oxidation with alkaline hydrogen peroxide gives an α-ketooxide of the thiophene analog of chalcone.

We have prepared thiophene analogs of chalcones I by direct condensation of thiophene with aryl-β-chlorovinyl ketones in the presence of stannic chloride condensing agent [1] in benzene or toluene solution. α,β unsaturated ketones containing the benzene and thiophene ring, find extensive application in organic synthesis [2–4].

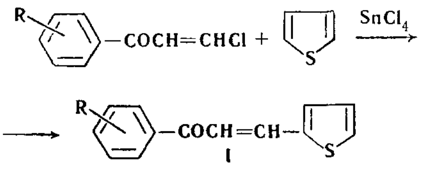


IR spectra: 1) 1-(α-Thienyl-3-(p-bromophenyl)-prop-1-en-3-one; 2) its 2,4-dinitrophenylhydrazone; 3) 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one; 4) its 2,4-dinitrophenylhydrazone.

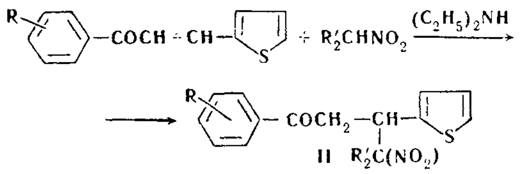
The thiophene analogs of chalcones prepared are characterized by their 2,4-dinitrophenylhydrazones (DNP). When preparing the hydrazones of α,β unsaturated ketones it is necessary to bear in mind the possibility of formation of the pyrazoline ring from an activated double bond and a —NH group taking place on heating. Hence when recrystallizing 2,4-DNPs a short heating time was used. The presence of two nitro groups in the phenylhydrazine also impedes cyclization of 2,4-DNPs to substituted pyrazolines. The IR spectra (figure) also confirms that 2,4-DNPs are formed, and not the isomeric pyrazolines. The IR spectra of the 2,4-DNPs (plots 2 and 4) have absorption bands with maxima in the 3300 cm^{-1} region, belonging to valence vibrations of the NH groups [5], present in 2,4-DNPs, and lacking with pyrazolines. The absorption bands in the 3100 cm^{-1} region belong to CH valence vibrations in the thiophene ring [5], they are also present in the spectra of the 2,4-DNPs [2,4], and in those of the starting thiophene analogs of chalcones [1, 3].

Since these vibrations do not overlap with those of other groups in the structures of the particular 2,4-DNPs, the presence of the 3300 cm^{-1} band in the spectrum confirms the existence of acyclic structures containing the NH group, i.e., of 2,4-dinitrophenylhydrazones.

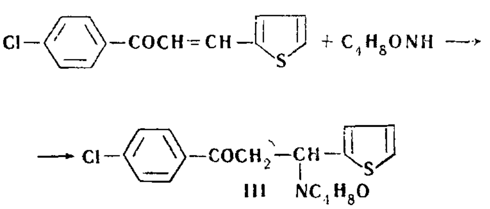
Addition of 2-nitropropane and nitromethane at the active double bond of thiophene analogs of chalcones gives γ-nitroketones II. Addition of morpholine gives β-morpholino derivatives of ketone III. Alkaline hydrogen peroxide oxidation of the thiophene analog of chalcone gives α-ketooxide IV. An α-ketooxide, γ-nitroketones and morpholino derivatives of thiophene analogs of chalcones are white crystalline compounds, while the starting thiophene analogs of chalcones are colored. The disappearance of the color is explained by interruption of the chain of conjugation benzene and thiophene rings by disturbances of the α,β double bond.

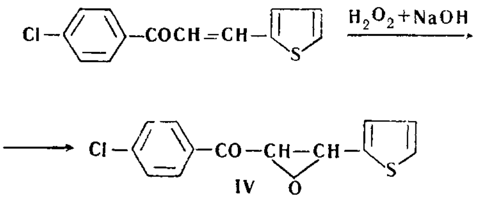


R=4-NO$_2$; 2-Cl; 3-Cl; 4-Cl

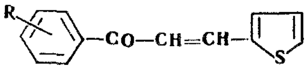


R = 4-NO$_2$; 4-Cl; R' = CH$_3$; H;





Properties of the Thiophene Analogs of Chalcones Prepared, and of their 2, 4-Dinitrophenylhydrazones



R	Compound	Mp, °C	Shape and color of crystals	Formula	Found, %				Calculated, %				Yield, %	2, 4-Dinitrophenylhydrazones			
					C	H	Cl	S	C	H	Cl	S		Mp, °C	Formula	N, %	
																Found	Calculated
4-NO_2	1-(α-Thienyl)-3-(p-nitrophenyl)prop-en-3-one	153^{2*}	Yellow needles	$C_{13}H_9NO_3S^{1*}$	60.10 60.15	3.50 3.48		12.08	60.25	3.47		12.38	77.7	140^{3*}	$C_{19}H_{13}N_5O_6S$	14.22 14 15	13.98
4-Cl	1-(α-Thienyl)-3-(p-chlorophenyl)prop-1-en-3-one	120^{3*}	Pale yellow needles	$C_{13}H_9ClOS$	62.90 62.52	3.79 4.01	14.08 13.96	12.46	62.77	3.62	14.21	12.87	79.6	179^{2*}	$C_{19}H_{13}ClN_4O_4S$	13.37 12.96	13.07
3-Cl	1-(α-Thienyl)-3-(o-chlorophenyl)prop-1-en-3-one	34^{4*}	Yellow leaflets	$C_{13}H_9ClOS$	62.68 62.62	3.68 3.80	14.75 14.50	12.47	62.77	3.62	14.21	12.87	63.1	182^{5*}	$C_{19}H_{13}ClN_4O_4S$	13.20 13.16	13.07
2-Cl	1-(α-Thienyl)-3-(m-chlorophenyl)prop-1-en-3-one	93^{4*}	Yellow needles	$C_{13}H_9ClOS$	62.70 63.00	3.54 3.36	14.18	13.01 12.81	62.77	3.62	14.21	12.87	53.4	115^{6*}	$C_{19}H_{13}ClN_4O_4S$	13.50 13.24	13.07
4-Br	1-(α-Thienyl)-3-(p-bromophenyl)-prop-1-en-3-one	129^{3*}	Yellow needles	$C_{13}H_9BrOS^{7*}$	53.12 52.85	3.57 3.57		10.75	53.25	3.12		10.93	76.3	142^{5*}	$C_{19}H_{13}BrN_4O_4S$	11.52 11.08	11.60

1*) Found: N 5.65; 5.89%. Calculated for $C_{13}H_9NO_3S$: N 5.40%.

2*–6*) Benzene, EtOH, Petrol ether, EtOH-EtOAc 1:1, Nitromethane.

7*) Found: Br 27.49; 27.32%. Calculated for $C_{13}H_9BrOS$:Br 27.25%.

EXPERIMENTAL

1-(α-Thienyl)-3-(p-nitrophenyl)prop-1-en-3-one (I, R = r-NO_2). A 3-necked flask fitted with stirrer, reflux condenser, and dropping funnel, was charged with 4 g (0.019 mole) β-chlorovinyl-p-nitrophenylketone, and 1.54 g (0.019 mole) thiophene, in 50 ml dry benzene. The flask was cooled with ice and salt to −10°, the contents stirred vigorously, and 4.8 g (0.019 mole) $SnCl_4$ added over a period of 30 min from the dropping funnel. The products were stirred for 1 hr more, then 50 ml ether and 50 ml water added. The organic layer was separated off, and the aqueous layer extracted with benzene. The bulked ether-benzene layers were washed with 5% Na_2CO_3, to remove tin completely, and then dried over $CaCl_2$. The solvent was distilled off, the residue cooled, when crystals separated in the form of yellow needles. The other thiophene analogs of chalcone were prepared similiarly. The preparations were analyzed qualitatively by thin-layer chromatography, using type TU 2962-54 grade II activity alumina as the absorbent, in the form of a non-stabilized layer on a glass plate. A 0.1 N solution of the material in ether was put on the glass plate. To advance and separate the compounds on the plate, a benzene-heptane (1:1) system of solvents was used. The visualizer was iodine. All the preparations were homogeneous. The Table gives the properties of thiophene analogs of chalcones prepared and of their 2,4-DNPs.

IR spectra of the thiophene analogs of chalcones and of their 2,4-dinitrophenylhydrazones were determined with a UR-10 spectrophotometer, tabletting with KBr (see Fig.).

2-Nitro-2-methyl-3-(α-thienyl)-5-(p-nitrophenyl)-pentan-5-one (II, R = 4-NO_2, R' = CH_3) was prepared by heating together for 2 hr 30 min on a boiling water bath a mixture of 0.2 g 1-(α-thienyl)-3-(p-nitrophenyl)prop-1-en-3-one, 1 ml 2-nitropropane, and 0.3 ml Et_2NH. After distilling off the excess 2-nitropropane and diethylamine, the substance crystallized. White crystals, mp 85° (ex EtOH). Yield 0.19 g (73%). Found: C 55.35; 55.20; H 4.32; 4.40; N 7.52; S 9.64%. Calculated for $C_{16}H_{16}N_2O_5S$: C 55.17; H 4.60; N 8.04; S 9.19%.

2-Nitro-2-methyl-3-(α-thienyl)-5-(p-chlorophenyl)pentan-5-one (II, R = 4-Cl, R' = CH_3) was prepared similarly to the compound above, starting from 0.5 g 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one, 1 ml 2-nitropropane, and 0.2 ml Et_2NH. White plates mp 94.5° (ex EtOH), yield 0.45 g (75%). Found: C 57.03; H 4.49; 4.48; Cl 10.70; 10.76; S 9.76; 9.87%. Calculated for $C_{16}H_{16}ClNO_3$: C 56.88; H 4.74; Cl 10.51; S 9.48%.

1-Nitro-2-(α-thienyl)-4-(p-chlorophenyl)butan-4-one (II, R = 4-Cl, R' = H) was prepared from 0.1 g 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one, 2 ml nitromethane, and 0.1 ml Et_2NH. White needles mp 7° (ex EtOH), yield 0.11 g (91.7%). Found: C 53.95; H 4.10; Cl 11.75; S 10.38%. Calculated for $C_{14}H_{12}ClNO_3S$: C 54.28; H 3.87; Cl 11.47; S 10.36%.

p-Chlorophenyl-[β-morpholino-β-(α-thienyl)-ethyl] ketone (III, R = C_4H_8NO) was prepared by heating together in a sealed tube in a water-bath for 5 hr 1 g (0.004 mole) 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one and 1.04 g (0.012 mole) morpholine. After evaporating excess morpholine off in a vacuum desiccator, the residue was recrystallized from petrol etherbenzene (1:1). White needles mp 67° (ex petrol ether + benzene), yield 1.1 g (81.5%). Found [$C_{17}H_{18}ClNO_2S$]: C 60.62; H 5.64; Cl 10.54; S 9.52%.

When heated for 1 hr with water on a boiling water bath, the morpholino derivative readily decomposed to give the starting heterocyclic analog of chalcone, along with morpholine. This confirmed addition of the morpholine group at the β position of the thiophene analog, since it is known [6] that β-morpholino derivatives of chalcones are readily decomposed on heating with water, into the starting ketone and morpholine.

Oxide of 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one (IV). A 3-necked flask fitted with stirrer, reflux condenser, and dropping funnel was charged with 1 g 1-(α-thienyl)-3-(p-chlorophenyl)prop-1-en-3-one 15 ml acetone, and 10 ml MeOH, the mixture vigorously stirred, heated to 30°, and 5 ml 28% H_2O_2 and 1 ml 2N NaOH added over a period of 10 min. The reaction mixture gradually turned pale, and the temperature rose spontaneously by 3°. Stirring was continued for 15 min longer after all the H_2O_2 had been added, then 10 ml water was added. A precipitate formed white plates, mp 99° (ex acetone) Yield 0.8 g (75.5%). Found: C 59.27; 59.24; H 3.41; 3.44; Cl 13.69; 13.71; S 11.67; 11.69%. Calculated for $C_{13}H_9ClO_2S$: C 58.97; H 3.40; Cl 13.42; S 12.09%.

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