

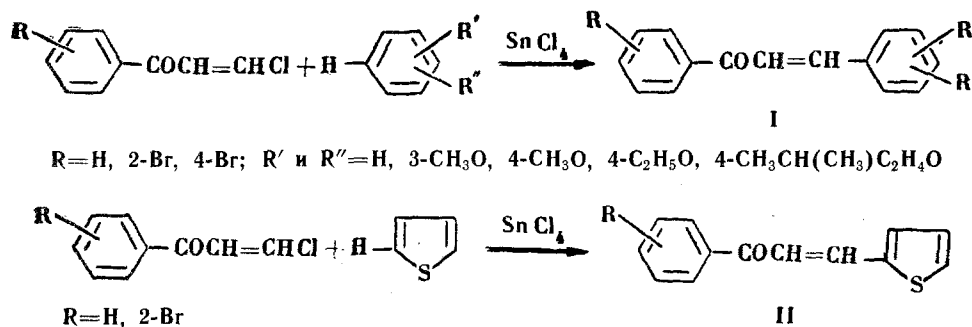
A SYNTHESIS OF CHALCONES AND THEIR THIOPHENE ANALOGS
BASED ON β -CHLOROVINYLKETONES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2, pp. 215-219, 1965

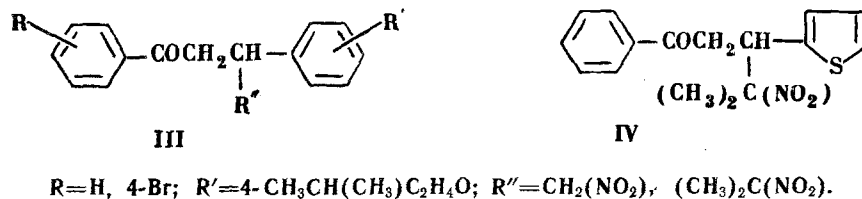
A newly developed synthesis [1-3] of chalcones (arylstyryl ketones), based on condensing aryl- β -chlorovinylketones with ethers of mono- and dihydric phenols in the presence of stannic chloride, is extended. A number of chalcones not previously described are obtained in good yield and derivatives prepared. Hitherto undescribed nitroketones are obtained by addition of nitromethane and 2-nitropropane to an activated double bond of the chalcones and a thiophene analog of a chalcone.

Previous papers have been concerned with a new method of synthesizing chalcones, α, β -unsaturated ketones, based on condensing aryl- β -chlorovinylketones with aromatic compounds in the presence of stannic chloride. The present paper gives new data on the synthesis of chalcones and thiophene analogs by condensing aryl- β -chlorovinylketones with thiophene in the presence of stannic chloride. The α, β -unsaturated ketones of the thiophene series are of interest on account of their physiological activity and possible use as starting materials in organic syntheses [5, 6].



α, β -Unsaturated ketones, containing both a benzene and a thiophene ring, are most frequently obtained by crotonic condensation of the appropriate aldehydes with alkyl ketones containing an active methyl or methylene group, in the presence of acid or alkaline catalysts [4, 5]. The starting aldehydes and alkyl ketones containing a thiophene ring are comparatively inaccessible compounds, which restricts their use in organic synthesis. Thiophene analogs of chalcones have now been obtained by directly condensing thiophene with aryl- β -chlorovinylketones. In view of the easy accessibility of thiophene, as compared with aldehydes and alkyl ketones containing a thiophene ring, direct ketovinilation of thiophene is a simple and convenient method of synthesizing thiophene analogs of chalcones. The chalcones and thiophene analogs prepared were characterized as 2,4-dinitrophenylhydrazones.

Nitromethane can be added at the double bond in different ways, depending on the way in which the reaction is carried out [7]. Treatment of a chalcone with nitromethane using a molar ratio of 1:30 gave nitroketone III, an addition product of one molecule of nitromethane and one molecule of chalcone. Reaction of the chalcones and thiophene analog of a chalcone with 2-nitropropane at a molar ratio of 1:1.5 gave the nitroketones III and IV, addition products derived from one molecule of 2-nitropropane and one molecule of α, β unsaturated ketones.



With one exception, the resultant chalcones and their thiophene analogs are crystalline and variously colored. The nitroketones are crystalline and colorless. The disappearance of color is due to breaking of the conjugated chain through disappearance of the double bond.

To determine the mode of condensation of phenyl- β -chlorovinylketone with phenylisoamyl ether, the resultant phenyl (p-isoamyloxystyryl)ketone was oxidized with excess alkaline hydrogen peroxide [8]. Benzoic and 4-isoamyloxybenzoic acids were isolated from the oxidation products, so that the phenyl- β -chlorovinylketone condenses at the p position in phenyl isoamyl ether.



R	R'	Yield, %	Mp, °C	Crystal color and shape	Mol. formula	Found, %			Calc., %			2, 4-dinitrophenylhydrazones			
						C	H	Br	C	H	Br	Mp, °C	Mol. formula	N, % Found	N, % Calc.
H	4-C ₆ H ₁₁ O	48	54.5 ^a	Pale yellow needles	C ₂₀ H ₂₂ O ₂	81.43; 81.46	7.54; 7.58		81.56	7.57		120 ^b	C ₂₆ H ₂₆ N ₄ O ₅	11.73; 11.37	11.78
4-Br	4-C ₆ H ₁₁ O	40	90.5 ^a	Pale yellow needles	C ₂₀ H ₂₁ BrO ₂	64.40; 64.21	5.71; 5.55	21.19; 21.08	64.30	5.67	21.45	145 ^b	C ₂₆ H ₂₅ BrN ₄ O ₅	10.40; 10.50	10.42
2-Br	4-C ₆ H ₁₁ O	44	yellow viscous oil bp 218-220° (0.2 mm)		C ₂₀ H ₂₁ BrO ₂	64.00; 64.12	6.14; 6.16	21.30; 21.54	64.30	5.67	21.45	157-158 ^b	C ₂₆ H ₂₅ BrN ₄ O ₅	10.52; 10.32	10.42
2-Br	4-C ₂ H ₅ O	60	91.5 ^a	Pale yellow plates	C ₁₇ H ₁₅ BrO ₂	61.91; 61.89	5.00; 4.83	24.34; 24.01	61.64	4.56	24.14	172-173 ^b	C ₂₃ H ₁₉ BrN ₄ O ₅	11.07; 11.23	10.96
2-Br	3,4-(CH ₃ O) ₂	54	103.5 ^d	Yellow plates	C ₁₇ H ₁₅ BrO ₃	58.47; 58.57	4.55; 4.64	23.01	58.80	4.37	23.01	150 ^c (decomp.)	C ₂₃ H ₁₉ BrN ₄ O ₆	10.10; 9.96	10.62
2-Br	4-CH ₃ O	50	71 ^a	Pale yellow needles	C ₁₆ H ₁₃ BrO ₂	60.03; 60.20	4.59; 4.46	25.60; 25.49	60.58	4.13	25.19	225 ^b	C ₂₂ H ₁₇ BrN ₄ O ₅	11.69; 11.84	11.30

a from ethanol; b from ethanol and ethyl acetate; c from nitromethane; d from methanol.

EXPERIMENTAL*

Phenyl(p-isoamyloxystyryl)ketone. A solution of 12 g (0.072 mole) phenyl-β-chlorovinylketone and 14 g (0.085 g) phenylisoamyl ether in 50 ml dry benzene is cooled with ice-salt, and with vigorous stirring 18.8 g (0.072 mole) stannic chloride are added dropwise over 1 hr. After maintaining the reaction conditions for 1 hr 30 min more, 50 ml ether and 50 ml water are added. The benzene-water layer is separated off, and the aqueous layer extracted with benzene. The united ether-benzene extracts are repeatedly washed with a 5% soda solution, then with water, and dried over calcium chloride. After the solvent has been removed under somewhat reduced pressure, on cooling the residue gives fine orange crystals. A 2,4-dinitrophenylhydrazone was prepared in the usual way. All the other chalcones (table) were prepared similarly.

Oxidation of phenyl(p-isoamyloxystyryl)ketone. 6 g (0.15 mole) NaOH in 10 ml methanol are added to 3 g (0.01 mole) ketone in 75 ml methanol, and 80 ml 30% hydrogen peroxide added dropwise with vigorous stirring, bath temperature 45-50°. At the end of oxidation the mixture is made acid with sulfuric acid, and from the precipitate formed, benzoic and 4-isoamyloxybenzoic acids, the latter melting at 141° are isolated (from methanol).

2-Nitro-2-methyl-3-(p-isoamyloxyphenyl)-5-phenylpentan-5-one. This is prepared by mixing 0.7 g (0.0023 mole) phenyl(p-isoamyloxystyryl)ketone with 0.3 g (0.0038 mole) 2-nitropropane and 0.5 ml diethylamine and heating for 2 hr 30 min on a steam bath. When the diethylamine and excess 2-nitropropane have been distilled off under somewhat reduced pressure, the residual oil crystallizes. Colorless crystals melting at 77.5° (from ethanol). Yield 0.74 g (81%). Found: C 72.49, 72.69; H 7.59, 7.64; N 3.66, 4.09%, calculated for C₂₃H₂₉NO₄: C 72.03; H 7.62; N 3.66%.

4-Nitro-3-(p-isoamyloxyphenyl)-1-phenylbutan-1-one. This is prepared in a way similar to the above, from 1 g (0.0034 mole) phenyl(p-isoamyloxystyryl)ketone, 6.3 g (0.1 mole) nitromethane, and 0.5 ml diethylamine. Colorless cubic crystals melting at 58° (from ethanol). Yield 1 g (85%). Found: C 70.30, 70.27; H 7.59, 7.68; N 4.31, 4.59%, calculated for C₂₁H₂₅NO₄: C 70.95; H 7.09; N 3.94%.

2-Nitro-2-methyl-3-(p-isoamyloxyphenyl)-5-(p-bromophenyl)pentan-5-one. This is prepared similarly from 1 g (0.003 mole), p-bromophenyl-(p-isoamyloxystyryl)ketone, 0.4 g (0.0045 mole) 2-nitropropane, and 0.5 ml diethylamine. Colorless cubes melting at 78° (from ethanol). Yield 0.8 g (67%). Found: C 59.97, 59.91; H 7.42, 7.21; N 2.78, 2.85%, calculated for C₂₃H₂₈BrNO₄: C 59.74; H 7.10; N 3.03%.

1-Thienyl-3-phenylpropen-3-one. This is prepared, using conditions similar to those used in preparing the chalcones, from 5 g (0.03 mole) phenyl-β-chlorovinylketone, 3.34 g (0.04 mole) thiophene, and 7.8 g (0.03 mole) stannic chloride in 50 ml dry benzene, with good cooling (ice + salt), in a stream of nitrogen. The oil left on removal of

* With S. D. Rynkevich

the solvents crystallizes when cooled with dry ice. Small pale yellow needles, melting at 58-59° (from petrol ether). Yield 2.9 g (45%).

2-Nitro-2-methyl-3(α -thienyl)-5-phenylpentan-5-one. A mixture of 1 g (0.005 mole) 1-thienyl-3-phenylpropen-3-one, 0.75 g (0.008 mole) 2-nitropropane, and 0.5 ml diethylamine is heated for 2 hr 30 min on a steam bath. A thick oil, which crystallizes on cooling, is obtained. Pale gray needles melting at 103° (from ethanol). Yield 1.3 g (91%). Found: C 62.93, 63.13; H 6.05, 6.07; N 4.63, 4.50; S 10.59, 10.66%, calculated for $C_{16}H_{17}NO_3S$: C 63.34; H 5.65; N 4.62; S 10.57%.

1-Thienyl-3-(o-bromophenyl)propen-3-one. This is prepared from 8 g (0.03 mole) o-bromophenyl- β -chlorovinylketone, 3.34 g (0.04 mole) thiophene, and 7.8 g (0.03 mole) stannic chloride in 50 ml dry benzene. The condensation is carried out in a stream of nitrogen. After the solvents have been taken off under somewhat diminished pressure, the residue is vacuum-distilled. The main fraction, boiling at 179-180°(0.2 mm), is completely crystallized in the receiver. Pale yellow crystals melting at 31° (from methanol-petrol ether). Yield 4.1 g (43.3%). Found: C 53.18, 52.90; H 3.46, 3.49; Br 26.84; S 11.18, 11.01%, calculated for $C_{13}H_9BrOS$: C 53.25; H 3.12; Br 27.25; S 10.93%.

2,4-Dinitrophenylhydrazone. Bright red crystals, melting at 217° (from ethyl acetate-ethanol). Found: N 11.29; 11.39%, calculated for $C_{13}H_9BrN_4O_4S$: N 11.60%.

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17 October 1963

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