SYNTHESIS OF UNSATURATED KETONES OF THE THIOPHENE SERIES

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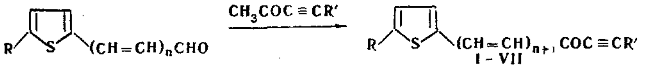
A number of unsaturated ketones containing a thiophene ring were obtained by the crotonic condensation of 2-thienyl-substituted carbonyl compounds with acetylenic ketones and aldehydes.

We have previously reported the synthesis of some thienyl ethynyl ketones by the oxidation of the corresponding secondary alcohols [1,2]. Continuing our investigations of the chemistry and biological activity of unsaturated ketones of the thiophene series, we have synthesized previously unreported thienylenyl ethynyl and thienyldi(tri)enyl ethynyl ketones of the thiophene series.

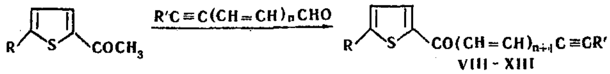
To obtain thienylenyl ethynyl ketones I-V we used the crotonic condensation of 2-formylthiophene with methyl ethynyl ketones. The corresponding thienyldi- and thienyltrienyl ethynyl ketones (VI and VII) (see Table 1) were obtained by the condensation of 2-thienylacrolein and 2-thienylpentadienal with 1-phenyl-1-butyn-3-one.



I $R=H$, $R'=CH_3$, $n=0$; II $R=H$, $R'=C_4H_9$, $n=0$; III $R=H$, $R'=C_6H_5$, $n=0$; IV $R=Br$, $R'=C_6H_5$, $n=0$; V $R=NO_2$, $R'=C_6H_5$, $n=0$; VI $R=H$, $R'=C_6H_5$, $n=1$; VII $R=H$, $R'=C_6H_5$, $n=2$

1-(2-Thienyl)-1-nonen-4-yn-3-one (II) was also obtained by alternative synthesis from an enyne alcohol prepared from 2-thienylacrolein and butylethynylmagnesium bromide and was oxidized, without isolation, with manganese dioxide at room temperature. The structure of this ketone was also confirmed by its hydrogenation over a $Pd/BaCO_3$ (5% Pd) catalyst to 1-(2-thienyl)nonan-3-one [bp 145-146° (1.5 mm), n_D^{20} 1.5064, d_4^{20} 1.0410].

Ethynylenyl ketones VIII-XIII, in which the carbonyl group is adjacent to the thiophene ring, were obtained by the condensation of 2-acetylthiophene with ethynyl and ethynylvinyl aldehydes.



VIII $R=H$, $R'=C_6H_5$, $n=0$; IX $R=Br$, $R'=C_6H_5$, $n=0$; X $R=R'=H$, $n=0$; XI $R=C_2H_5$, $R'=C_4H_9$, $n=0$; XII $R=H$, $R'=C_6H_5$, $n=1$; XIII $R=C_2H_5$, $R'=C_6H_5$, $n=1$

In contrast to thienylenyl ethynyl ketones I-VII, thienyl ethynylvinyl ketones VIII-XIII are extremely unstable. In a number of cases, they were not isolated in pure form but characterized by means of their 2,4-dinitrophenylhydrazones.

The condensation of thienylideneacetone [3] with phenylpropargyl aldehyde yielded 1-(2-thienyl)-7-phenyl-1,4-heptadien-6-yn-3-one (XIV).

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TABLE 1. Unsaturated Ketones of the Thiophene Series

Compound	Name	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %	2,4-Dinitrophenylhydrazone			
				C	H	S	C	H	S		mp, °C	empirical formula	N, %	
													found	calc.
I	1-(2-Thienyl)-1-hexen-4-yn-3-one	101—102	$C_{10}H_8OS$	68,5	4,6	18,2	68,2	4,6	18,2	50	175—176	$C_{16}H_{14}N_4O_4S$	16,0	15,7
II	1-(2-Thienyl)-1-nonen-4-yn-3-one	—[a]	$C_{13}H_{14}OS$	71,4	6,5	14,6	71,6	6,4	14,7	48	172—174	$C_{19}H_{18}N_4O_4S$	13,8	14,1
III	1-(2-Thienyl)-5-phenyl-1-penten-4-yn-3-one	76—77	$C_{15}H_{10}OS$	75,7	4,2	12,9	75,6	4,2	13,4	45	189—190	$C_{21}H_{14}N_4O_4S$	13,1	13,4
IV	1-(5-Bromo-2-thienyl)-5-phenyl-1-penten-4-yn-3-one	75—76	$C_{15}H_9BrOS$[b]	—	—	9,8	—	—	10,1	50	—	—	—	—
V	1-(5-Nitro-2-thienyl)-5-phenyl-1-penten-4-yn-3-one	139—140	$C_{15}H_9NO_3S$[c]	—	—	11,3	—	—	11,3	46	—	—	—	—
VI	1-(2-Thienyl)-7-phenyl-1,3-heptadien-6-yn-5-one	84—85	$C_{17}H_{12}OS$	77,6	4,6	12,2	77,3	4,5	12,1	41	220—222	$C_{23}H_{16}N_4O_4S$	12,4	12,6
VII	1-(2-Thienyl)-9-phenyl-1,3,5-nonatrien-8-yn-7-one	110—111	$C_{19}H_{14}OS$	78,7	4,9	10,9	78,6	4,8	11,0	43	—	—	—	—
VIII	1-(2-Thienyl)-5-phenyl-2-penten-4-yn-1-one	56—57	$C_{15}H_{10}OS$	73,5	4,2	13,6	73,6	4,2	13,4	55	215—216	$C_{21}H_{14}N_4O_4S$	13,2	13,4
IX	1-(5-Bromo-2-thienyl)-5-phenyl-2-penten-4-yn-1-one	56	$C_{16}H_9BrOS$[d]	—	—	10,0	—	—	10,1	58	—	—	—	—

[a] bp 180-181° (1 mm).

[b] Found: Br 25.7%. Calculated: Br 25.2%

[c] Found: N 5.0%. Calculated: N 4.9%.

[d] Found: Br 25.2%. Calculated: Br 25.2%.

The IR spectra of ketones I-XIV contain the characteristic frequencies of the thiophene ring (756, 1024, 1440, and 1535 cm^{-1}). The absorption band of the triple bond is distinctly displayed at 2210-2225 cm^{-1}. The absorption band at 1620-1650 cm^{-1} corresponds to the stretching vibrations of the carbonyl group, while the absorption at 1590-1618 cm^{-1} corresponds to the vibrations of the C =C bond.

EXPERIMENTAL

1-(2-Thienyl)-1-hexen-4-yn-3-one (I). A 1-ml sample of 10% aqueous NaOH was added to a cooled (to −40°) mixture of 1.34 g (0.012 mole) of 2-formylthiophene and 1 g (0.012 mole) of 2-pentyn-4-one in 30 ml of ethanol. The mixture was stirred at −40° for 3 h and neutralized with 10% acetic acid. The reaction product was extracted with ether. The extract was dried with sodium sulfate, the ether was removed by distillation, and the residue was recrystallized from alcohol to give 1.05 g (50%) of ketone I.

Ketones II-VII were similarly obtained.

1-(2-Thienyl)-5-phenyl-2-penten-4-yn-1-one (VIII). A 1-ml sample of 10% aqueous NaOH was added dropwise with stirring and cooling (at 0°) to a mixture of 1.26 g (0.01 mole) of 2-acetylthiophene and 1.3 g (0.01 mole) of phenyl-1-propyn-3-al in ethanol. The reaction was monitored by means of thin-layer chromatography on silica gel. At the end of the reaction, the reaction mixture was neutralized with 10% acetic acid, and the reaction product was extracted with ether. The extract was dried with magnesium sulfate, and the ether was evaporated. Ketone VIII was isolated from the residue by chromatography on silica gel with elution by petroleum ether−diethyl ether−benzene (3 : 1 : 1); R_f 0.27. The oil that was isolated crystallized in the cold and was recrystallized from alcohol to give 1.31 g (55%) of ketone VIII.

Compound IX was similarly obtained (see Table 1).

1-(2-Thienyl)-2-penten-4-yn-1-one (X). This compound was similarly obtained from 1.26 g (0.01 mole) of 2-acetylthiophene and 0.54 g (0.01 mole) of propynal. Chromatography on silica gel yielded 0.51 g (32%) of X as an oil that darkened rapidly in air; R_f 0.28. Ketone X formed a crystalline, light-yellow silver acetylide with an ammoniacal solution of silver nitrate. The 2,4-dinitrophenylhydrazone melted at 175-177°. Found: N 16.0%. $C_{15}H_{10}N_4O_4S$. Calculated: N 16.4%.

1-(5-Ethyl-2-thienyl)-2-nonen-4-yn-1-one (XI). This compound was similarly obtained from 1.54 g (0.01 mole) of 5-ethyl-2-acetylthiophene and 1.1 g (0.01 mole) of 2-heptyn-1-al. Chromatography on silica gel yielded 1.1 g (43%) of ketone XI as an oil that darkened rapidly in air; R_f 0.21. The 2,4-dinitrophenylhydrazone melted at 184-185°. Found: N 13.3%. $C_{21}H_{22}N_4O_4S$. Calcultaed: N 13.1%.

1-(2-Thienyl)-7-phenyl-2,4-heptadien-6-yn-1-one (XII). This compound was similarly obtained from 1.26 g (0.01 mole) of 2-acetylthiophene and 1.56 g (0.01 mole) of phenyl-2-penten-4-yn-1-al. Chromatography on silica gel yielded 0.62 g (24%) of ketone XII as a viscous oil that darkened rapidly in air; R*f* 0.26. The 2,4-dinitrophenylhydrazone melted at 128-129°. Found: N 12.5%. $C_{23}H_{16}N_4O_4S$. Calculated: N 12.6%.

1-(5-Ethyl-2-thienyl)-7-phenyl-2,4-heptadien-6-yn-1-one (XIII). This compound was similarly obtained from 1.54 g (0.01 mole) of 5-ethyl-2-acetylthiophene and 1.56 g (0.01 mole) of phenyl-2-penten-4-yn-1-al. Chromatography on silica gel yielded 0.61 g (21%) of ketone XIII as an oil that darkened rapidly in air; R*f* 0.24. The 2,4-dinitrophenylhydrazone had mp 140-141°. Found: N 11.7%. $C_{25}H_{20}N_4O_4S$. Calculated: N 11.9%.

1-(2-Thienyl)-7-phenyl-1,4-heptadien-6-yn-3-one (XIV). A 1-ml sample of 10% sodium hydroxide was added to a mixture of 1.52 g (0.01 mole) of thienylideneacetone and 1.3 g (0.01 mole) of phenyl-1-propyn-3-al in ethanol, and the mixture was stirred at +5° for 3 h. It was then neutralized with 10% acetic acid and extracted with ether. The ether extract was dried with magnesium sulfate, the ether was evaporated, and the residue was recrystallized from ethanol to give 1.72 g (65%) of a product with mp 142-143°. Found: C 77.3; H 4.6; S 12.1%. $C_{17}H_{12}OS$. Calculated: C 77.3; H 4.6; S 12.1%.

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