Chemistry

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1965

SovietRxiv

Abstract

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Academician of the Academy of Sciences of the Latvian SSR S. A. Giller, L. I. Vereshchagin,
K. K. Venter, S. P. Korshunov, V. V. Tsirule, D. O. Lolya

Furyl-2- and 5-Nitrofuryl-2-acetylenic Ketones

Several years ago, furylpolyalkynyl compounds were isolated from certain species of plants and microorganisms. This aroused great interest in a new class of compounds that until now had been little studied (^{1}).

The work carried out to date in this field has been concerned mainly with elucidating the structure of natural compounds. As for synthetic investigations, with the exception of a few episodic studies ($^{2-4}$), they are almost entirely absent. Meanwhile, of particular interest, from the standpoint of studying their physicochemical and physiological properties, may be the still unknown furylalkynones, 5-nitrofurylalkynones, and their numerous derivatives, since these compounds contain a conjugated system of multiple bonds including a furan ring, an acetylenic bond, and a carbonyl group in combination with electron-donating or electron-accepting substituents. On the basis of the relationships found between structure and physiological action (^{5}), such a combination may lead to new highly active compounds possessing antifungal and antiviral properties.

We have for the first time succeeded in carrying out the synthesis of furylacetylenic ketones of type II from the corresponding carbinols I (^{6}) by oxidizing them with active manganese dioxide. In this case the yield of ketones was 70-90%. From a preparative standpoint it proved possible to oxidize the starting carbinols I without their prior purification, which is substantially important in view of their low stability and the considerable losses during distillation in vacuum. The ketones obtained in this way are listed in Table 1.

$$\text{furfural} \xrightarrow[\text{HC}\equiv\text{CR}]{C_2H_5MgBr} \text{furyl-CHOH}-\text{C}\equiv\text{CR} \longrightarrow$$

$$(I)$$

$$\xrightarrow{MnO_2} \text{furyl-CO}-\text{C}\equiv\text{CR} \xrightarrow{+HNO_3+(CH_3CO)_2O} O_2\text{N-furyl-CO}-\text{C}\equiv\text{CR}$$

$$\text{II, } R = \text{aryl, 5-bromofuryl-2} \qquad \text{III, } R = \text{aryl}$$

As already stated, 5-nitrofurylacetylenes may prove to be potential chemotherapeutic agents for the treatment of fungal and viral diseases.

The preparation of such compounds by nitration of furylacetylenic compounds had hitherto been considered unlikely because of the presence in the molecule of a reactive acetylenic bond. Nevertheless, we succeeded in carrying out the nitration of furylacetylenic ketones by a somewhat modified procedure previously proposed for the nitration of furylalkenones ([7–9]).

It was found that ketones of type II containing an unsubstituted phenyl group or electron-donating substituents in the phenyl ring are readily nitrated in acetic anhydride medium to the corresponding nitro derivatives III at a temperature of −25° without the addition of any catalysts. However, in the presence of electron-accepting substituents (II, R = p-C_6H_4—Cl; p-C_6H_4—Br; m-C_6H_4—Br; 5-bromofuryl-2), the nitration reaction is slowed to such an extent that, under the same conditions, only the starting ketone is recovered. It was found that such less reactive furan ketones can be nitrated in good yields by employing more severe reaction conditions (temperature from 0 to +5°) with the addition of small amounts of catalyst—sulfuric acid. This phenomenon is explained by the fact that the rate of nitration of ketones II depends to a greater extent on the substituent at the phenyl ring conjugated with the furan ring, which testifies to the good "conducting" properties of the acetylene π-electrons and the carbonyl group.

In all nitration experiments with ketones II, we were able to isolate only mononitro derivatives, i.e., to carry out selective nitration of the furan ring in the 5-position. For nitration of the phenyl ring, much more severe conditions are required. Such an exceptionally high reactivity of the furan ring in the 5-position (in comparison with an aromatic ring) has already been observed previously in cases of nitration of phenylfuryl- and thienylfuryl ketones ([10]) and is associated with the specific influence of the heteroatom (oxygen).

Data on 5-nitrofuryl-2-acetylene ketones III are given in Table 2.

In the IR spectra of ketones III, absorption bands are observed at 2197-2210 cm^{-1}, which is characteristic of stretching vibrations of disubstituted acetylene derivatives. The absorption bands in the ranges 1342-1356 and 1520-1538 cm^{-1} should be assigned to stretching vibrations of the nitro group attached to the furan ring, and the absorption at 1624-1648 cm^{-1} to the conjugated carbonyl group.

The absorption maxima of nitro ketones III in the UV region are found in the ranges 230-240 and 320-330 mμ, i.e., they exhibit a small bathochromic shift in comparison with the starting ketones II.

The semicarbazones of ketones III exhibit in their IR spectra the characteristic absorption bands both for —C C—bonds and for $-CONH_2$ groups, which indicates the absence of formation of cyclic structures through the acetylene bond.

The results of biological tests of the compounds obtained will be published in a separate communication.

Experimental Part

Synthesis of furylacetylene ketones II

To a solution of 0.2 g-mol of magnesium bromethylide in dry ether, with stirring and cooling to 5-10°, was added an ethereal solution of 0.1 g-mol of arylacetylene or 5-bromofuryl-2-acetylene. The reaction mixture was boiled for 5 h. Then, with ice cooling, 0.25 g-mol of furfural in ether (1:1) was added dropwise. The mixture was stirred for 1 h and left overnight. The complex was decomposed with water and NH_4Cl solution. The ether extract was washed with soda, water, and dried. The ether was distilled off, and the residue* was dissolved in 50 ml of benzene. With vigorous stirring, 0.4 g-mol of active manganese dioxide was added to the solution ([11]). The mixture was boiled for 2 h. The MnO_2 precipitate was filtered off and thoroughly washed with benzene. The solvent was distilled off in the vacuum of a water-jet pump, and the solid residue was recrystallized from aqueous alcohol.

* All the alcohols are very unstable and cannot be distilled. The exception is 1-(furyl-2′)-3-(4-methylphenyl)-propyn-2-ol-1, b.p. 159-160°/2 mm.
Found, %: C 79.01; H 5.86
$C_{14}H_{12}O_2$. Calculated, %: C 79.25; H 5.63

Table 1

Furyl-2-acetylenic ketones II

R =	Yield,* %	M.p., °C	Empirical formula	C, % calculated	C, % found	H, % calculated	H, % found	Halogen, % calculated	Halogen, % found	UV spectra (in alcohol) λmax, mμ (ε · 10^{-4})	IR spectra ν, cm^{-1} C=O	IR spectra ν, cm^{-1} — C C —
C_6H_5	85	51—52	$C_{13}H_8O_2$	79.58	79.40	4.11	4.34	—	—	226 (1.178); 315 (2.238)	1936	2200

R =	Yield,* %	M.p., °C	Empirical formula	C, % calculated	C, % found	H, % calculated	H, % found	Halogen, % calculated	Halogen, % found	UV spectra (in alcohol) λmax, mμ ($\epsilon \cdot 10^{-4}$)	IR spectra ν, cm^{-1} C=O	IR spectra ν, cm^{-1} — C C —
n-$C_6H_4CH_3$	88	93—95	$C_{14}H_{10}O_2$	79.98	79.75	4.79	4.98	—	—	231 (1.340); 319 (2.402)	1647	2205
n-$C_6H_4C_2H_5$	76	47—48.5	$C_{15}H_{12}O_2$	80.34	80.19	5.39	5.23	—	—	230 (1.839); 326 (3.043)	1630	2175
n-C_6H_4Cl	73	137—138	$C_{13}H_7ClO_2$	67.70	67.58	3.06	3.20	Cl 15.37	Cl 15.39	228 (1.400); 320 (2.456)	1636	2175
n-C_6H_4Br	83	129—130	$C_{13}H_7BrO_2$	56.76	56.67	2.56	2.36	Br 29.05	Br 29.14	230 (1.981); 316 (3.641)	1630	2185
m-C_6H_4Br	90	77—79	$C_{13}H_7BrO_2$	56.76	56.91	2.56	2.39	Br 29.05	Br 29.27	312 (2.158)	1633	2210
5-Bromofuryl-2	70	117—117.5	$C_{11}H_5BrO_3$	49.84	49.65	1.90	1.74	Br 30.15	Br 30.11	234 (0.902); 343 (2.780)	1630	2150

* Yields calculated on the starting arylacetylenes or 5-bromofuryl-2-acetylene.

Table 2

5-Nitrofuryl-2-acetylenic ketones III

R =	Yield, %	M.p., °C	Empirical formula	C, % calculated	C, % found	H, % calculated	H, % found	N, % calculated	N, % found	Halogen, % calculated	Halogen, % found	UV spectra (in alcohol) λmax, mμ ($\epsilon \cdot 10^{-4}$)	IR spectra νmax, cm^{-1} — NO_2	IR spectra νmax, cm^{-1} C=O	IR spectra νmax, cm^{-1} — C C —
C_6H_5	63	159–161	$C_{13}H_7NO_4$	64.73	64.42	2.93	3.08	5.81	5.85	—	—	230 (1.440); 329 (2.084)	1342; 1520	1624	2193
Semicarbazone	76	199	$C_{14}H_{10}N_4O_4$	—	—	—	—	18.79	19.04	—	—	—	—	—	—
n-$C_6H_4CH_3$	66	183.5–184.5	$C_{14}H_9NO_4$	65.88	66.22	3.55	3.68	5.49	5.33	—	—	231 (1.631); 338 (2.302)	1351; 1532	1630	2200
Semicarbazone	74	209.5–210.5	$C_{15}H_{12}N_4O_4$	—	—	—	—	17.94	17.97	—	—	249 (1.503); 315 (1.906)	1353; 1531*	—	2205
n-C_6H_4Cl	66	201–202	$C_{13}H_6ClNO_4$	56.64	56.79	2.19	2.56	5.08	5.28	Cl 12.86	Cl 13.12	236 (1.614); 326 (2.292)	1358; 1537	1638	2202
Semicarbazone	75	210–212	$C_{14}H_9ClN_4O_4$	—	—	—	—	16.84	16.86	—	—	253 (1.914); 315 (1.389); 356 (1.308)	1360; 1530**	—	2210
n-C_6H_4Br	65	209–210	$C_{13}H_6BrNO_4$	48.78	48.64	1.89	2.03	4.38	4.61	Br 24.96	Br 25.46	229 (2.477); 297 (2.182); 335 (3.882)	1360; 1532	1636	2202
Semicarbazone	79	205–206	$C_{14}H_9BrN_4O_4$	—	—	—	—	14.86	15.19	—	—	325 (1.921)	1356; 1538	1648	2207

R =	Yield, %	M.p., °C	Empirical formula	C, % calculated	C, % found	H, % calculated	H, % found	N, % calculated	N, % found	Halogen, % calculated	Halogen, % found	UV spectra (in alcohol) λmax, mμ, ($\epsilon \cdot 10^{-4}$)	IR spectra νmax, cm^{-1} — NO_2	IR spectra νmax, cm^{-1} C=O	IR spectra νmax, cm^{-1} C≡C
m-C_6H_4Br	69	136–137.5	$C_{13}H_6BrNO_4$	48.78	48.76	1.89	1.94	4.38	4.74	Br 24.96	Br 25.07	325 (1.921)	1356; 1538	1648	2207
Semicarbazone	86	230	$C_{14}H_9BrN_4O_4$		—	—	—	14.86	14.74	—	—	325 (1.921)	1356; 1538	1648	2207

* In the IR spectra, absorption appears at 1590 and 1710 cm^{-1}, which is characteristic of the valence vibrations of C=N and $-CONH_2$.

** In the IR spectra, the corresponding absorption is observed at 1560 and 1692 cm^{-1}.

Nitration of furylacetylene ketones II. To 9.3 ml of acetic anhydride at a temperature of 0 to +5°, 4.7 g of nitric acid (specific gravity 1.52) was slowly added with stirring. The reaction was carried out under anhydrous conditions. In the nitration of ketones II ($R = C_6H_5$; n-$C_6H_4-CH_3$), the reaction conditions were as follows: the nitrating mixture was cooled to −30°, and a solution of 0.01 g-mol of the ketone in acetic anhydride was added dropwise with good stirring (temperature within the range from −25 to −30°). After this, the mixture was kept at the same temperature for 1 h more and poured, with stirring, onto a mixture of ice and water (1:1) in a sevenfold amount relative to the acetic anhydride introduced into the reaction. A reddish-yellow oil separated; it was washed with ice water (until the acid reaction disappeared), left under water in a refrigerator until the next day, dissolved in acetone (about 12 ml), and a solution of 5 g of crystalline sodium acetate in 4 ml of water was added; the mixture was shaken at 50-60° for 10-15 min. It was cooled to room temperature, diluted with water (12 ml), and the crystals obtained were filtered off, washed with water, and dried at room temperature in vacuo over phosphorus pentoxide. Recrystallization was from alcohol or dichloroethane. The nitration conditions for II ($R = n$-C_6H_4-Cl; n-C_6H_4-Br; m-C_6H_4-Br) differed from those indicated above only in that the nitration reaction was conducted at a temperature from 0 to +5° for 3 h with the addition to the nitrating mixture of a catalyst—0.74 g (0.4 ml) of sulfuric acid (specific gravity 1.84).

Ketones III are yellow crystalline substances, sufficiently stable on storage. The melting points of these compounds are considerably higher than those of the initial non-nitrated ketones.

Under these nitration conditions, from 1-(furyl-2′)-3-(5″-bromofuryl-2″)-propyn-2-one-1 we were unable to isolate a nitration product of sufficient purity.

Our attempt to carry out the nitration of 1-(furyl-2′)-3-(*n*-chlorophenyl)-propyn-2-one-1 in sulfuric acid medium at a temperature from 0 to +5° did not give positive results, and only resinified products were isolated.

Semicarbazones of ketones III were obtained by heating ketones III for 2–4 h in an aqueous-alcoholic medium with a fourfold excess (relative to the theoretically required amount) of semicarbazide hydrochloride and were purified by recrystallization from ethyl alcohol.

Institute of Organic Synthesis
Academy of Sciences of the Latvian SSR

Institute of Petroleum and Coal-Chemical Synthesis
at Irkutsk State University
named after A. A. Zhdanov

Received
5 IV 1965

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Note: Figure translations are in progress. See original paper for figures.