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Chemistry

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Abstract

Full Text

Chemistry

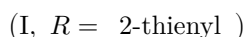
G. N. Dorofeenko, V. I. Dulenko

Synthesis of 1,3-Disubstituted 5,6,7,8-Tetrahydroisochromylum Salts

(Presented by Academician M. I. Kabachnik on 29 I 1964)

Pyrylium salts constitute a very interesting, but as yet little-studied, class of heterocyclic compounds. The high reactivity of the pyroxonium nucleus has made it possible to develop methods for converting pyrylium salts into various heterocyclic and aromatic compounds ⁽¹⁾. Recently the number of works in this area of organic synthesis has increased. A significant achievement was the discovery, in 1959, of the bisacylation reaction of olefins ⁽²⁾. The mechanism of this reaction consists in the intermediate formation of β,γ -unsaturated ketones, whose further acylation gives unsaturated 1,5-diketones that cyclize, with elimination of water, to pyrylium salts ^(3,4,5).

We have found that, upon acylation of readily available products of the crotonic condensation of cyclohexanone with acetone and acetophenone—cyclohexenylacetone ⁽⁶⁾ (I, R = CH₃) and cyclohexenylacetophenone ⁽⁷⁾ (I, R = Ph), which are β,γ -unsaturated ketones—with acid anhydrides in the presence of hydrochloric acid, substituted 5,6,7,8-tetrahydroisochromylum salts are formed. Subsequently, the crotonic condensation of cyclohexanone with heterocyclic ketones—2-acetothienone and 2-methyl-5-acetylfuran—was studied, as a result of which cyclohexenylacetothienone was obtained



and 2-methyl-5-cyclohexenylacetylfuran



These compounds



like other products of the crotonic condensation of cyclohexanone, are β,γ -unsaturated ketones; therefore, on acylation they readily and rapidly form substituted pyrylium salts, which, under the action of ammonia, are converted into the corresponding 1,3-disubstituted 5,6,7,8-tetrahydroisoquinolines:



Study of the acylation of compounds I with acid anhydrides in the presence of hydrochloric acid showed that cyclohexenylacetone, cyclohexenylacetophenone, and cyclohexenylacetothienone form salts of 5,6,7,8-tetrahydro-

Table 1

R	R'	Yield, %	m.p., °C	C found, %	H found, %	Cl found, %	C calc., %	H calc., %	Cl calc., %	Picrate m.p., °C	N found, %	N calc., %
CH ₃	CH ₃	80	79	50.34	5.81	13.37	50.29	5.76	13.50	124	14.28	14.35
			—							—		
			80.5							125		
CH ₃	C ₂ H ₅	85	99	52.29	6.48	12.87	52.08	6.19	12.81	97	13.84	13.86
			—							—		
			100							98		
CH ₃	C ₃ H ₇	75	59	54.03	6.76	12.22	53.70	6.59	12.20	115	13.32	13.40
			—							—		
			60							116		
CH ₃	iso-C ₃ H ₇	79	130	53.97	6.78	12.18	53.70	6.59	12.20	160	13.49	13.40
			—							—		
			132							161		
CH ₃	iso-C ₄ H ₉	75	97	55.70	7.10	12.26	55.17	6.95	11.63	139	12.81	12.96
			—							—		
			98							140		
CH ₃	C ₅ H ₁₁	45	—	—	—	—	—	—	—	105	12.64	12.56
			—							—		
			50*									
Ph	CH ₃	90	198	59.11	5.25	11.03	59.17	5.28	10.92	175	12.24	12.39
			—							—		
			200							176		
Ph	C ₂ H ₅	84	204	60.43	5.79	10.43	60.27	5.65	10.47	152	11.93	12.01
			—							—		
			205							154		
Ph	C ₃ H ₇	87	207	61.30	6.08	10.28	61.28	6.00	10.05	139	11.70	11.66
			—							—		
			210							140		
Ph	iso-C ₃ H ₇	83	215	61.12	6.10	10.18	61.28	6.00	10.05	162	11.57	11.66
			—							—		
			216							163		
Ph	C ₄ H ₉	75	189	62.03	6.37	9.75	62.20	6.32	9.61	141	11.20	11.33

R	R'	Yield, m.p.,		C	H	Cl	C	H	Cl	Picrate	N	N
		%	°C	found,	found,	found,	calc.,	calc.,	calc.,		m.p.,	found,
Ph	iso-C ₄ H ₉	85	219	62.04	6.30	9.91	62.20	6.32	9.61	130	22.37	11.33
		—	—	—	—	—	—	—	—	—	—	—
			220							131		
Ph	C ₅ H ₁₁	65	142	62.96	6.76	9.27	63.07	6.62	9.31	—	—	—
		—	—	—	—	—	—	—	—	—	—	—
5-methylfuryl	(C ₂ H ₅) ₂ CH	70	162	63.09	6.73	9.13	63.07	6.62	9.31	137	10.68	11.02
		—	—	—	—	—	—	—	—	—	—	—
			164							139		
5-methylfuryl	PhCH ₂	45	182	65.48	5.20	8.56	65.91	5.28	8.85	—	—	—
		—	—	—	—	—	—	—	—	—	—	—
5-methylfuryl	CH ₃	50	142	54.91	5.34	10.83	54.80	5.21	10.79	182	—	—
		—	—	—	—	—	—	—	—	—	—	—
			55							183		
5-methylfuryl	C ₃ H ₇	40	152	57.25	6.13	9.61	57.22	5.93	9.94	164	11.40	11.57
		—	—	—	—	—	—	—	—	—	—	—
			45							166		

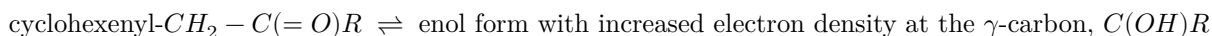
R	R'	Yield, m.p.,		C	H	Cl	S	C	H	Cl	S	Picrate	N	N
		%	°C	found,	found,	found,	found,	calc.,	calc.,	calc.,	calc.,	m.p.,	found,	calc.,
thienyl	CH ₃	90	200	50.45	4.79	10.71	9.73	50.83	4.57	10.72	9.69	198	12.23	12.22
		—	—	—	—	—	—	—	—	—	—	—	—	—
			201											
thienyl	C ₂ H ₅	86	188	52.35	4.81	10.42	9.42	50.25	4.97	10.28	9.29	160	11.81	11.86
		—	—	—	—	—	—	—	—	—	—	—	—	—
			190									162		
thienyl	C ₃ H ₇	81	213	53.51	5.31	9.79	8.86	53.55	5.34	9.88	8.94	138	11.38	11.52
		—	—	—	—	—	—	—	—	—	—	—	—	—
			214											
thienyl	isb-C ₃ H ₇	77	207	53.71	5.41	9.84	8.90	53.55	5.34	9.88	8.94	155	11.53	11.52
		—	—	—	—	—	—	—	—	—	—	—	—	—
			210									157		
thienyl	isb-C ₄ H ₉	77	225	54	5.61	9.43	8.51	54.76	5.68	9.51	8.60	142	11.27	11.20
		—	—	—	—	—	—	—	—	—	—	—	—	—
			227	68								144		
thienyl	C ₅ H ₁₁	60	97	55.66	5.68	9.06	8.30	55.86	5.99	9.16	8.29	167	—	10.89
		—	—	—	—	—	—	—	—	—	—	—	—	—
			99									168		
thienyl	(C ₂ H ₅) ₂ CH	70	173	55.73	6.04	8.97	8.13	55.86	5.99	9.16	8.29	145	10.83	10.89
		—	—	—	—	—	—	—	—	—	—	—	—	—
			174									147		

* The yield of 5,6,7,8-tetrahydroisoquinoline is given (b.p. 301–303°), since the salt could not be isolated in the crystalline state.

** Phenylacetic acid chloride was used as the acylating agent.

...isochromylium in high yield (65–90%), whereas 2-methyl-5-cyclohexenylacetylfuran is partly resinified during the reaction, which is connected with the acidophobic character of the furan nucleus; therefore the yield of pyrylium salts is 40–55%.

The high reactivity of β,γ -unsaturated ketones can probably be explained by the ease of enolization of the carbonyl group, which contributes to an increase of electron density at the γ -carbon atom:



In the acylation of cyclohexenylacetoacetic acid, only polymerization products were isolated.

All the 5,6,7,8-tetrahydroisochromylium salts obtained by us, except for one ($R = R' = \text{CH}_3$) (4), were previously unknown. They are colorless or slightly colored crystals, sparingly soluble in acetone, alcohol, and water. Solutions of salts containing thiophene and furan nuclei as substituents fluoresce blue and yellow-green. The 5,6,7,8-tetrahydroisoquinolines corresponding to the salts, identified as picrates, are currently being tested for physiological activity.

Experimental Part

Preparation of the starting substances. Cyclohexenylacetone and cyclohexenylacetoacetic acid were obtained by alkaline condensation of cyclohexanone with acetoacetic ester (6), and cyclohexenylaceto-

phenone was synthesized from cyclohexanone and acetophenone (7). In a similar manner, the condensation of cyclohexanone with 2-acetothienone and 2-methyl-5-acetylfuran was carried out for the first time. Cyclohexenylacetothienone (yield 30%), b.p. 150–152°/6 mm; d_{20}^{20} 1.1286; n_D^{20} 1.5773; MR_D 60.5; MR_{calcd} = 59.9.

Found, %: C 69.91; H 6.72; S 15.47

$C_{12}H_{14}OS$. Calculated, %: C 69.56; H 6.84; S 15.54

2-Methyl-5-cyclohexenylacetylfuran (yield 10%), b.p. 180–182°/22 mm; n_D^{20} 1.5445.

Found, %: C 75.91; H 7.81

$C_{13}H_{16}O_2$. Calculated, %: C 76.43; H 7.90

Semicarbazone, m.p. 166–168°.

Found, %: N 15.83

$C_{14}H_{19}N_3O$. Calculated, %: N 16.08

Carrying out the reaction. To 0.01 g-mole of I is added a freshly prepared mixture of 0.05 g-mole of the acid anhydride and 0.01 g-mole of 70% $HClO_4$; the mixture is stirred well and left at room temperature for 20-30 min. The reaction mixture is diluted with ether, the pyrylium salt is filtered off, washed well with ether, and dried. In the acylation of cyclohexenylacetone the salts obtained usually do not crystallize immediately; therefore they are reprecipitated with ether from *n*-propyl alcohol. Salts contaminated with resin are washed on the filter with a mixture of acetone and ether.

The conversion of the salts into 5,6,7,8-tetrahydroisoquinolines was carried out by passing gaseous ammonia through a suspension of the salt in ethyl alcohol. The picrates were recrystallized from alcohol. The experimental data are given in Table 1.

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