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Abstract

Full Text

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

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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 = CH_3) 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-tetrahydroisochromylium 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

$$(\text{I},\ R = \ \text{2-thienyl}\ )$$

and 2-methyl-5-cyclohexenylacetylfuran

$$(\text{I},\ R = \text{2-methyl-5-furyl})\,.$$

These compounds

$$\text{I}:\quad \text{cyclohexenyl-CH}_2\text{COR}$$

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:

$$\text{cyclohexenyl-CH}_2\text{COR} \xrightarrow{\text{R'CO}^+\text{ClO}_4^-} \text{acylated intermediate} \xrightarrow{-\text{H}_2\text{O}} \text{tetrahydroisochromylium perchlorate} \xrightarrow{\text{NH}}$$

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 – 80.5	50.34	5.81	13.37	50.29	5.76	13.50	124 – 125	14.28	14.35
CH_3	C_2H_5	85	99 – 100	52.29	6.48	12.87	52.08	6.19	12.81	97 – 98	13.84	13.86
CH_3	C_3H_7	75	59 – 60	54.03	6.76	12.22	53.70	6.59	12.20	115 – 116	13.32	13.40
CH_3	iso-C_3H_7	79	130 – 132	53.97	6.78	12.18	53.70	6.59	12.20	160 – 161	13.49	13.40
CH_3	iso-C_4H_9	75	97 – 98	55.70	7.10	12.26	55.17	6.95	11.63	139 – 140	12.81	12.96
CH_3	C_5H_{11}	45 – 50*	–	–	–	–	–	–	–	105	12.64	12.56
Ph	CH_3	90	198 – 200	59.11	5.25	11.03	59.17	5.28	10.92	175 – 176	12.24	12.39
Ph	C_2H_5	84	204 – 205	60.43	5.79	10.43	60.27	5.65	10.47	152 – 154	11.93	12.01
Ph	C_3H_7	87	207 – 210	61.30	6.08	10.28	61.28	6.00	10.05	139 – 140	11.70	11.66
Ph	iso-C_3H_7	83	215 – 216	61.12	6.10	10.18	61.28	6.00	10.05	162 – 163	11.57	11.66
Ph	C_4H_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	C found, %	H found, %	Cl found, %	C calc., %	H calc., %	Cl calc., %	Picrate m.p., °C	N found, %	N calc., %
Ph	iso-C_4H_9	85	219 – 220	62.04	6.30	9.91	62.20	6.32	9.61	130 – 131	22.37	11.33
Ph	C_5H_{11}	65	142	62.96	6.76	9.27	63.07	6.62	9.31	–	–	–
5-methylfuryl	$(C_2H_5)_2CH$	74	162 – 164	63.09	6.73	9.13	63.07	6.62	9.31	137 – 139	10.68	11.02
5-methylfuryl	$PhCH_2$	45**	182	65.48	5.20	8.56	65.91	5.28	8.85	–	–	–
5-methylfuryl	CH_3	50 – 55	142 – 143	54.91	5.34	10.83	54.80	5.21	10.79	182 – 183	–	–
5-methylfuryl	C_3H_7	40 – 45	152	57.25	6.13	9.61	57.22	5.93	9.94	164 – 166	11.40	11.57

R	R′	Yield, %	m.p., °C	C found, %	H found, %	Cl found, %	S found, %	C calc., %	H calc., %	Cl calc., %	S calc., %	Picrate m.p., °C	N found, %	N calc., %
thienyl	CH_3	90	200 – 201	50.45	4.79	10.71	9.73	50.83	4.57	10.72	9.69	198	12.23	12.22
thienyl	C_2H_5	86	188 – 190	52.35	4.81	10.42	9.42	50.25	4.97	10.28	9.29	160 – 162	11.81	11.86
thienyl	C_3H_7	81	213 – 214	53.51	5.31	9.79	8.86	53.55	5.34	9.88	8.94	138	11.38	11.52
thienyl	iso-C_3H_7	77	207 – 210	53.71	5.41	9.84	8.90	53.55	5.34	9.88	8.94	155 – 157	11.53	11.52
thienyl	iso-C_4H_9	77	225 – 227	54 – 68	5.61	9.43	8.51	54.76	5.68	9.51	8.60	142 – 144	11.27	11.20
thienyl	C_5H_{11}	60	97 – 99	55.66	5.68	9.06	8.30	55.86	5.99	9.16	8.29	167 – 168	–	10.89
thienyl	$(C_2H_5)_2CH$	70	173 – 174	55.73	6.04	8.97	8.13	55.86	5.99	9.16	8.29	145 – 147	10.83	10.89

* 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:

$$\text{cyclohexenyl-}CH_2 - C(=O)R \rightleftharpoons \text{ enol form with increased electron density at the } \gamma\text{-carbon, } C(OH)R$$

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 ($R = R' = CH_3$) ([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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Note: Figure translations are in progress. See original paper for figures.