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## ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

# Synthesis and Antioxidative Properties of Some 3,4-Dihydropyrimidin-2(1*H*)ones (-thiones)

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**Abstract**—3,4-Dihydropyrimidinones (-thiones) were prepared by ternary condensation of various aromatic aldehydes with ethyl acetoacetate and urea (thiourea) in the presence of trichloroacetic acid in ethanol.

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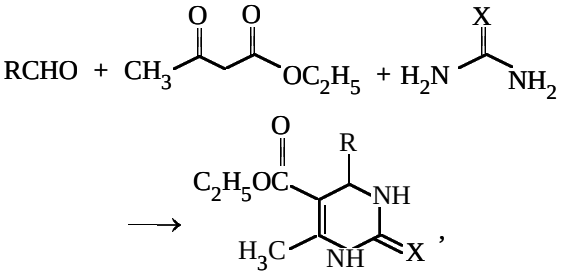
Dihydropyrimidinones attract growing interest due to their therapeutical and pharmacological activity [1]. Some functional derivatives of dihydropyrimidinones exhibit a broad spectrum of biological activity, including antiviral, antitumor, and antibacterial activity. Furthermore, 4-aryldihydropyrimidinones are powerful blockators of calcium channels and antihypertonic, α-adrenergic, and neuropeptide antagonists [2].

The simplest and direct route to dihydropyrimidinones, suggested for the first time by Biginelli and involving ternary condensation of an aldehyde, a β-keto ester, and urea, often gives the desired product in a low yield, especially with aliphatic aldehydes [3]. Higher yields can be obtained by performing the reaction in several steps, but in this case the process is not so simple as the one-step Biginelli reaction. Therefore, the Biginelli reaction continues to attract the attention of researchers looking for facile and efficient procedures for preparing dihydropyrimidinones.

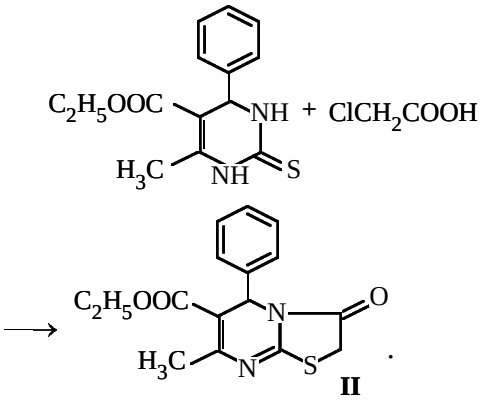
Somewhat improved procedures for preparing dihydropyrimidinones were reported in [4–6]. However, despite their potential significance, these methods are characterized by long reaction time, low selectivity, and problems with isolation of the products from the reaction mixture.

Thus, it is important to develop alternative one-pot procedures for preparing 3,4-dihydropyrimidin-2(1*H*)-ones.

Here we report on a new procedure for preparing 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) in the presence of trichloroacetic acid. We obtained 3,4-dihydropyrimidinones (-thiones) in high yield by the reaction of various aldehydes with ethyl acetoacetate and urea (thiourea) in the presence of $CCl_3COOH$ as catalyst. The reaction required refluxing in ethanol for 2–4 h.



where X = O, R = $CH_3$ (**I**), 2-HO-5-$BrC_6H_3$ (**IV**), 1-naphthyl (**V**); X = S, R = 2-$HOC_6H_4$ (**III**);



**II**

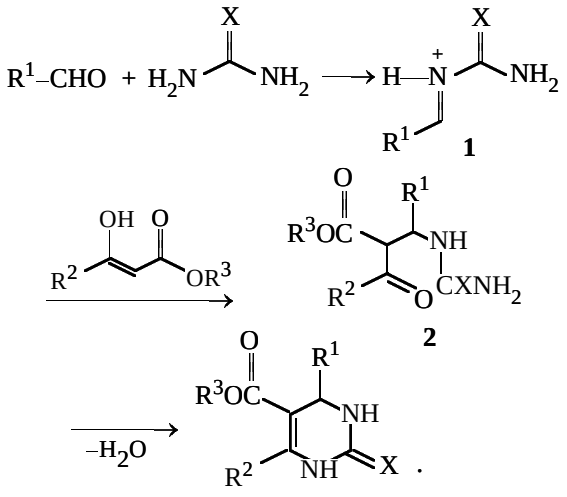
The reaction progress was monitored by TLC on Silufol UV-254 plates.

The suggested procedure ensures higher product yields (60–80%). The product can be readily isolated from the reaction mixture by filtration and washing with ethanol and water; recrystallization or chromatographic purification is not required.

**Table 1.** Physicochemical characteristics and spectral data for the compounds prepared

| Compound no. | Yield, % | $R_f$ | mp, °C | Found, %/Calculated, % | | | | Empirical formula | IR spectrum, $\nu$, $cm^{-1}$ | $^1H$ NMR spectrum, $\delta$, ppm |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S | | | |
| **I** | 65 | 0.72 | 194–196 | 54.50/54.54 | 7.02/7.07 | 14.22/14.14 | –/– | $C_9H_{14}N_2O_3$ | NH (3200) C=O (1648) | 1.09 d (3H, $CH_3$), 1.28 t (3H, $CH_3$), 2.15 s (3H, $CH_3$), 3.86 d (2H, $CH_2O$), 4.06 s (1H, CH), 7.19 s (1H, NH), 8.97 s (1H, NH) |
| **II** | 60 | 0.36 | 192–193 | 60.80/69.75 | 5.15/5.06 | 8.92/8.86 | 10.10/10.12 | $C_{16}H_{16}N_2SO_3$ | C=O (1630) | 1.17 t (3H, $CH_3$), 2.35 s (3H, $CH_3$), 3.90 s (2H, $CH_2S$), 4.30 d (2H, $CH_2O$), 5.35 s (1H, CH), 7.50–7.70 s (5H, Ar) |
| **III** | 80 | 0.54 | 215–216 | 57.65/57.53 | 5.51/5.47 | 9.62/9.58 | 10.87/10.95 | $C_{14}H_{16}N_2O_3S$ | NH (3225) C=O (1700) | 1.30 t (3H, $CH_3$), 2.35 s (3H, $CH_3$), 4.36 d (2H, $CH_2O$), 4.90 s (1H, CH), 7.10–7.60 m (4H, Ar), 9.40 s (1H, NH), 9.75 s (1H, OH) |
| **IV** | 75 | 0.27 | 190–191 | 49.59/49.55 | 4.50/4.42 | 8.27/8.25 | –/– | $C_{14}H_5N_2O_4Br$ | NH (3175) C=O (1635) | 1.30 t (3H, $CH_3$), 2.57 s (3H, $CH_3$), 4.25 d (2H, $CH_2O$), 5.70 s (1H, CH), 7.00–7.70 m (4H, Ar), 8.00 s (1H, NH), 9.41 s (1H, NH), 10.4 s (1H, OH) |
| **V** | 7 | 0.21 | 210–212 | 66.31 | 5.47 | 8.63 | – | $C_{18}H_{18}N_2O_3$ | NH (3250) C=O (1640) | 1.21 t (3H, $CH_3$), 2.60 s (3H, $CH_3$), 4.42 d (2H, $CH_2O$), 5.60 (1H, CH), 8.10–9.75 m (7H, $C_{10}H_7$), 8.05 s (1H, NH), 9.91 s (1H, NH) |

The mechanism of formation of dihydropyrimidinones (-thiones) was studied for a long time; the majority of researchers today agree with the following transformation sequence suggested by Kappe [7]:



First, protonated imine **1** is formed; it subsequently reacts with the enol form of the keto ester to give ureide **2**. This is followed by cyclization with the release of a water molecule.

The structures of the compounds were confirmed by IR, $^1H$, and $^{13}C$ NMR spectroscopy.

The physicochemical characteristics and spectral properties of the compounds are given in Table 1.

To evaluate the antioxidative power of **I**–**V** in elementary steps of cumene oxidation, we studied the reactions of **I**–**V** with cumylperoxy radicals (CPRs) and cumyl hydroperoxide (CHP).

The capability of **I**–**V** to terminate oxidation chains by the reaction with CPRs was evaluated using as example the cumene oxidation at 60°C, initiated with azobis(isobutyronitrile) in a concentration of $2 \times 10^{-2}$ M. We found that compounds **I**–**V** actively terminate oxidation chains by reacting with CPRs (Fig. 1).

From the duration of the induction period $\tau_{ind}$, we calculated the stoichiometric coefficient of inhibition *f*, equal to the number of oxidation chains terminated on one inhibitor molecule and its transforma-

tion products:

$$f = \tau_{ind} W_i / [In]_0,$$

where $W_i$ is the initiation rate and $[In]_0$ is the initial concentration of the inhibitor In.

From the kinetics of the oxygen uptake, we calculated the rate constants of the reactions of **I**–**V** with CPR, $k_7$ [8, 9]. To this end, the kinetic curves of the oxygen uptake $[O_2]$–$\tau$ were linearized in the coordinates $[O_2]^{-1}$–$\tau^{-1}$, and $k_7$ was calculated from the line slope: $\tan\alpha = fk_7[In]_0/(k_2[RH]W_i)$ [9, 10], hence, $k_7 = (\tan\alpha)k_2[RH]W_1/(f[In]_0)$, where $k_2$ is the chain initiation rate [8, 9], equal to 1.51 l mol$^{-1}$ s$^{-1}$, [RH] = 7.17 M.

The high antioxidative activity and the kinetic parameters of the reactions involving **I**–**V** were also confirmed in experiments on autooxidation of cumene at 110°C (Fig. 2).

Table 2 shows that the parameter $f$ for **I**–**V** varies from 0.5 to 4.22, and the rate constants $k_7$ of the reactions of the inhibitors with CPR vary from $2.01 \times 10^4$ to $2.92 \times 10^4$ l mol$^{-1}$ s$^{-1}$. The transformation products of **I**–**V** formed in the reactions with CPR also exhibit certain inhibiting effect; the oxidation rate after the induction period is somewhat lower than in the uninhibited oxidation (Fig. 1).

The reactions of **I**–**V** with CHP were performed in chlorobenzene in a nitrogen atmosphere at 110°C. All these compounds decompose CHP. The kinetic curves of CHP decomposition under the action of **I**–**V** (the curve obtained with **I** is shown as example in Fig. 3) are S-shaped, which is characteristic of an autocatalytic process. The reaction has a certain induction period in which the CHP consumption is insignificant; this is followed by its catalytic decomposition, and then, as the CHP is consumed, the reaction rate decreases.

Apparently, the inhibitor first reacts with CHP, and the resulting transformation product catalytically decomposes CHP. To determine the reaction stoichiometry, CHP was taken in excess.

The catalytic factor $\nu$ is the number of CHP molecules decomposed by one inhibitor molecule; it was calculated as $\nu = ([ROOH]_0 - [ROOH]_\infty)/[In]_0$, where $[ROOH]_0$ and $[ROOH]_\infty$ are, respectively, the initial and final concentrations of CHP, and $[In]_0$ is the initial inhibitor concentration.

Our experiments showed that one molecule of **I**–**V** can decompose up to several ten thousands of CHP molecules. Presumably, compounds **I**–**V** exert a combined inhibiting effect, terminating the oxidation chains in the reaction with CHP and catalytically decomposing CHP.

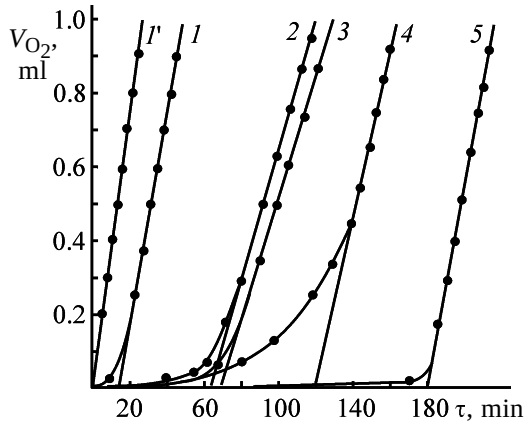



**Fig. 1.** Kinetic curves of initiated oxidation of cumene in the presence of **I**–**V** (curves *1*–*5*, respectively). 60°C; [AIBN] = $2 \times 10^{-2}$ M. ($V_{O_2}$) Oxygen volume and ($\tau$) time; the same for Fig. 2. [InH], M: (*1*′) 0 and (*1*–*5*) $5 \times 10^{-5}$; the same for Fig. 2.

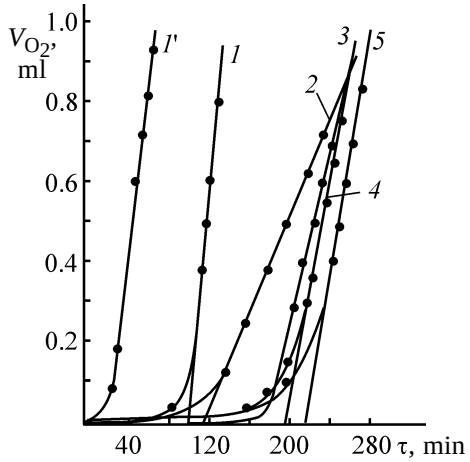



**Fig. 2.** Kinetic curves of cumene autooxidation in the presence of **I**–**V** (curves *1*–*5*, respectively) at 110°C.

## EXPERIMENTAL

The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker-300 NMR spectrometer (300 MHz for $^1$H), and the IR spectra, on a Specord 75-R spectrometer (mulls in mineral oil). To check the purity of the compounds prepared and monitor the reaction progress, we used TLC on Silufol UV-254 plates (eluent isopropyl alcohol–hexane, 1 : 1).

**3,4-Dihydropyrimidin-2(1*H*)-ones (-thiones).** A round-bottomed flask equipped with a reflux condenser and a power-driven stirrer was charged with appropriate aldehyde (1.25 mol), ethyl acetoacetate (1.90 mol), urea or thiourea (1.25 mol), $CCl_3COOH$

**Table 2.** Kinetic parameters of the reactions of **I**–**V** with cumylperoxy radicals ($k_7$, $f$, 60°C, [AIBN] = $2 \times 10^{-2}$ M) and of the decomposition of cumyl hydroperoxide ($k$, ν, 110°C)

| Compound | $T$ = 60°C | | $T$ = 110°C | | | |
|---|---|---|---|---|---|---|
| | $f$ | $k_7 \times 10^{-4}$, l mol$^{-1}$ s$^{-1}$ | $k$, l mol$^{-1}$ s$^{-1}$ | ν | $[In]_0$, M | τ, min |
| **I** | 0.5 | 2.01 | 11 | 20 000 | $5 \times 10^{-5}$ | 100 |
| **II** | 1.54 | 2.3 | 33 | 27 000 | $5 \times 10^{-5}$ | 120 |
| **III** | 1.68 | 2.92 | 18.5 | 22 000 | $5 \times 10^{-5}$ | 180 |
| **IV** | 2.88 | 2.4 | 20.8 | 25 000 | $5 \times 10^{-5}$ | 200 |
| **V** | 4.32 | 2.85 | 16.6 | 30 000 | $5 \times 10^{-5}$ | 220 |

(25 mg), and 95% ethanol (10 ml). The mixture was stirred for 2–4 h. The reaction progress was monitored by TLC. After the reaction completion, the mixture was cooled to room temperature, and the crystalline product was filtered off, washed with ethanol, dried, and recrystallized from aqueous ethanol (1 : 3).

Cumyl hydroperoxide was purified [10] and then distilled.

Chlorobenzene and cumene were purified by a common procedure based on sulfonation of impurities with concentrated sulfuric acid [11, 12]. The CHP concentration was determined by iodometric titration [10] of samples taken at regular intervals.

Experiments on CHP decomposition were performed in chlorobenzene at 110°C in a glass bubbler in an inert gas atmosphere; the CHP concentration was varied in the range 0.16–0.64 M, and the concentrations of **I**–**V**, in the range $(1–5) \times 10^{-4}$ M.

Experiments on the initiated oxidation of cumene were performed on a manometric unit [12]. As initiator we used AIBN (initiation rate $1 \times 10^{-5}$ l mol$^{-1}$ s$^{-1}$ at 60°C [13]; initiator concentration $2 \times 10^{-2}$ M in all the experiments). The concentrations of **I**–**V** were $(1–5) \times 10^{-4}$ M.

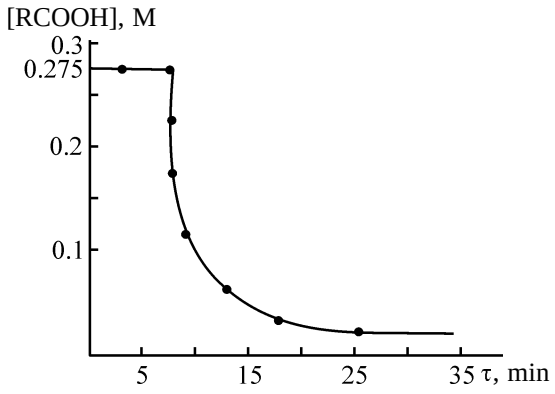



**Fig. 3.** Kinetic curve of CHP decomposition in the presence of **I**. 110°C; $[In]_0 = 1 \times 10^{-4}$ and $[CHP]_0 = 0.275$ M. (τ) Time.

## CONCLUSION

3,4-Dihydropyrimidinones (-thiones) exhibiting high antioxidative power were prepared by ternary condensation.

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