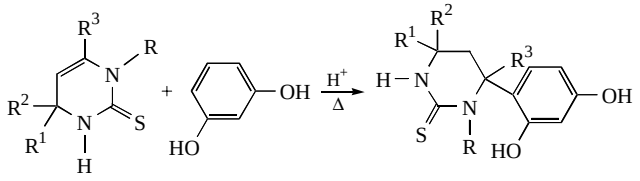
Reactions of resorcinol with substituted 3,4-dihydro-2(1*H*)-pyrimidinethiones

Sergei I. Filimonov

Department of Organic Chemistry, Yaroslavl State Technical University, 150023 Yaroslavl, Russian Federation.
Fax: +7 0852 44 0729; e-mail: z55@yaroslavl.ru

Acid-catalysed alkylation of resorcinol by substituted tetrahydropyrimidinethiones has been examined.

The interaction between pyrimidinethiones and phenolic compounds was first examined by Zigeuner *et al.*[1–2] It was found that pyrimidinethiones formed a product of addition at the 6-position of the pyrimidine ring upon boiling with a tenfold excess of 2,6-dimethylphenol in methanol with concentrated hydrochloric acid as a catalyst. Moreover, Zigeuner *et al.*[1] noted that, when the reaction was performed with 2,4-xylenol under the same conditions, the main reaction product was 2,2-bis(4-hydroxy-3,5-dimethylphenyl)propane.



1a–l **2a–l**

a $R^1 = R^2 = R^3 = Me$, R = H
b $R^1 = R^2 = R^3 = R = Me$
c $R^1 = R^2 = R^3 = Me$, R = Ph
d $R^1 = R^2 = R^3 = Me$, R = C_6H_4Me-*p*
e $R^1 = R^2 = R^3 = Me$, R = C_6H_4OMe-*p*
f $R^1 = R^2 = R^3 = Me$, R = C_6H_4Cl-*m*
g $R^1 = R^2 = R^3 = Me$, R = $C_6H_4CF_3$-*m*
h $R^1 = R = H$, $R^2 = Ph$, $R^3 = Me$
i $R^1 = R = H$, $R^2 = R^3 = Ph$
j $R^1 = R = H$, $R^2 = Ph$, $R^3 = C_6H_4OMe$-*p*
k $R^1 = R = H$, R^2 = 2-Fur, $R^3 = C_6H_4OMe$-*p*
l $R^1 = R = H$, $R^2 = Ph$, $R^3 = Et$

In this study, the reaction of resorcinol addition to pyrimidinethiones **1** has been examined. It is well known[3] that rearrangement products, corresponding 1,3-thiazines and aminodihydro-2(1*H*)-pyridinethiones, can be formed when the reaction is performed under the above conditions[1] (heating with a strong mineral acid). Thermal reactions (zinc chloride catalyst, temperature up to 140 °C) were unsuccessful (the yields were low). Thus, the reaction conditions were changed. The interaction of compounds **1** with resorcinol was examined at temperatures from 40 °C to the boiling temperatures of nonpolar solvents (chloroform, trichloroethylene and toluene) using sulfonic acids as catalysts. The products were separated as a precipitate or oil in 45–90% yields.† It is likely that the reaction is reversible, and complete alkylation can be performed not always even with a large excess of resorcinol. As a rule, a precipitate (oil) separated from the reaction mixture contained up to 80% of the target product, 10–20% of resorcinol and 5–15% of the starting pyrimidinethione (according to HPLC data).

† IR spectra were measured on a Bruker IFS-88 spectrometer in the range 700–4000 cm^{-1} using suspensions of substances in Vaseline oil. ^1H NMR spectra of test compounds were recorded on a Bruker AM-300 spectrometer at 300 MHz using 3–5% solutions in [$^2H_6$]DMSO. The chemical shifts of protons were measured with reference to an internal standard of HMDS (0.055 ppm). Mass spectra were measured on a MX-1321 mass spectrometer with direct sample injection at 100–150 °C with an ionisation energy of 70 eV. Reversed-phase high-performance liquid chromatography was performed on a Perkin-Elmer instrument (mobile phase: acetonitrile–water, 70:30; stationary phase: C-18).

Starting compounds **1** were synthesised according to published procedures.[1,2]

The reaction time of the resorcinol alkylation by compounds **1** depends on the structure of the substituent R. The reaction rate depends on the capability of the substituent R to stabilise the intermediate carbocation. Compounds **1** in which R = H exhibited the highest rate of the reaction with resorcinol. The reaction rate dramatically decreased in the order R = H, Me, Ph and C_6H_4Me-*p*. In the case of R = $C_6H_4NO_2$-*p*, the reaction does almost not proceed under the specified conditions. The effect of the substituent R^3 is not so evident; the reaction time was insignificantly shortened in the order Me, Et and Ph, C_6H_4OMe-*p*. Compound **2k** (R^2 = 2-Fur) is an exception, probably, because of its low solubility.

The catalyst amount has almost no effect on the reaction time; an amount equal to 10% of the weight of the pyrimidine-thione reactant is sufficient. With higher concentrations, the amount of by-products increases thus decreasing the yield and making the purification difficult. Methanesulfonic acid was tested as a catalyst; however, it did not exhibit considerable advantages.

To decide on a solvent, its capability of dissolving the starting pyrimidinethione should be taken into account. For active compounds with R = H, the reaction proceeded with approximately equal ease in toluene, chloroform or trichloroethylene. In contrast, for compounds with R = Ph, the target product was almost not formed in toluene, and the reaction time was halved when the reaction was performed in trichloroethylene. In this case, the reaction temperature exerted a considerable effect.

The IR spectra of resorcinol-substituted pyrimidinethiones did not exhibit bands due to double bonds in the pyrimidine ring in the region 1700–1630 cm^{-1}. Not always clearly defined signals (as a rule, as doublets) appear in the regions 3400–3250 and 1000–900 cm^{-1}, which are indicative of the presence of hydroxyl groups in the molecule.

The ^1H NMR spectra of resorcinol-substituted pyrimidinethiones **2**‡ exhibit a spin–spin interaction constant of 13–14 Hz, which is typical of the gem-protons 5-H_e/5-H_a. Mixtures of rotational isomers (50:50) were detected for compounds with unsymmetrical substituents R (R = *m*-ClC_6H_4 and *m*-$CF_3C_6H_4$); in this case, the signals of OH, 5-H_a and 6-Me were split into doublets. On this basis, the most downfield signal (split) of a hydroxyl proton can be attributed to the OH group in the α-position with respect to the pyrimidine ring, and the most upfield signal should be attributed to the 6-Me group.

Table 1 Physico-chemical properties of compounds **2**.

	Empirical formula	MW	mp/°C	R.T./ min[a]	Reaction time/h[b]	Yield (%)
2a	$C_{13}H_{18}N_2O_2S$	266.36	211–213	0.86	1	90
2b	$C_{14}H_{20}N_2O_2S$	280.4	207–209	0.82	1.5	86
2c	$C_{19}H_{22}N_2O_2S$	342.46	210–212	0.99	10	74
2d	$C_{20}H_{24}N_2O_2S$	356.48	225–226	1.07	18	65
2e	$C_{20}H_{24}N_2O_3S$	372.48	217–218	0.96	6	60
2f	$C_{19}H_{21}ClN_2O_2S$	376	212–214	0.97	8	72
2g	$C_{20}H_{21}F_3N_2O_2S$	410.45	221–222	1.02	10	76
2h	$C_{17}H_{18}N_2O_2S$	312.4	210–212	0.90	4	53
2i	$C_{22}H_{20}N_2O_2S$	376.47	240–242	0.96	3	55
2j	$C_{23}H_{22}N_2O_3S$	406.50	188–190	0.86	2	71
2k	$C_{21}H_{20}N_2O_4S$	396.46	193–195	1.00	4	50
2l	$C_{18}H_{20}N_2O_2S$	328.43	145–147	0.83	1.5	74

[a]HPLC (retention time). [b]The reaction time for syntheses in chloroform.

Compounds **2h**–**2l** were isolated as mixtures of the stereoisomers different in the spatial orientation of resorcinol at carbon in the 6-position. The arrangement of the R^2 substituent is always equatorial, as evidenced by a large spin–spin interaction constant of 11–12 Hz of vicinal protons 4-H_a/5-H_a equal to 11–12 Hz. The ratio between the isomers depended on the separation procedure; however, isomers with more upfield chemical shifts of hydroxyl proton signals were predominant.

‡ *General procedure for the synthesis of substituted tetrahydro-6-(2,4-dihydroxyphenyl)-2(1H)-pyrimidinethiones* **2**. A suspension containing a pyrimidinethione (0.01 mol), resorcinol (0.015 mol) and 0.1 g of toluenesulfonic acid in 20–30 ml of chloroform was boiled for 1–20 h until the formation of a precipitate (oil), which was separated and purified as follows: (i) the precipitate (oil) was dissolved in isopropanol (acetone) on heating; next, the solution was cooled and poured into water with intense stirring; (ii) the oil or solid precipitate was purified by crystallization from acetone–chloroform or acetone–benzene.

2a: ^{1}H NMR, δ: 9.11 (s, 1H, OH), 8.78 (s, 1H, OH), 7.83 (s, 1H, NH), 7.68 (s, 1H NH), 6.88 (d, 1H, H^{12}_{Rz}, *J* 8.5 Hz), 6.23 (d, 1H, H^{9}_{Rz}, *J* 1.8 Hz), 6.16 (dd, 1H, H^{11}_{Rz}, *J* 8.5 and 1.8 Hz), 3.0 (d, 1H, 5-H_e, *J* 13.3 Hz), 1.53 (d, 1H, 5-H_a, *J* 13.3 Hz), 1.55 (s, 3H, 4-Me_e), 1.19 (s, 3H, 4-Me_a), 0.63 (s, 3H, 6-Me). IR, ν/cm^{-1}: 3358, 3290, 3180, 1614, 1604, 981, 940.

2b: ^{1}H NMR, δ: 9.46 (s, 1H, OH), 9.17 (s, 1H, OH), 9.89 (s 1H, NH), 6.4 (d, 1H, H^{11}_{Rz}, *J* 8.0 Hz), 6.32 (s, 1H, H^{9}_{Rz}), 6.18 (d, 1H, H^{12}_{Rz}, *J* 8.0 Hz), 3.3 (s, 3H, NMe), 2.89 (d, 1H, 5-H_e, *J* 13.5 Hz), 1.73 (d, 1H, 5-H_a, *J* 13.5 Hz), 1.68 (s, 3H, 4-Me_e), 1.12 (s, 3H, 4-Me_a), 0.58 (s, 3H, 6-Me). IR, ν/cm^{-1}: 3330, 3200, 1598, 1520, 1500, 975.

2c: ^{1}H NMR, δ: 9.28 (s, 1H, OH), 8.98 (s, 1H, OH), 8.09 (s, 1H, NH), 7.7–7.3 (m, 6H, H_{Ar}), 6.26 (d, 1H, H^{9}_{Rz}, *J* 1.5 Hz), 6.24 (dd, 1H, H^{11}_{Rz}, *J* 8.5 and 1.5 Hz), 3.12 (d, 1H, 5-H_e, *J* 13.4 Hz), 1.88 (d, 1H, 5-H_a, *J* 13.4 Hz), 1.40 (s, 3H, 4-Me_e), 1.37 (s, 3H, 4-Me_a), 0.63 (s, 3H, 6-Me). IR, ν/cm^{-1}: 3350, 3320, 975.

2d: ^{1}H NMR, δ: 9.55 (s, 1H, OH), 9.35 (s, 1H, OH), 8.2 (s, 1H, NH), 7.2–7.0 (m, 6H, H_{Ar}), 6.32 (s, 1H, H^{9}_{Rz}), 6.23 (d, 1H, H^{11}_{Rz}, *J* 8 Hz), 3.12 (d, 1H, 5-H_e, *J* 13.8 Hz), 2.37 (s, 3H, Me_{Ar}), 2.0 (d, 1H, 5-H_a, *J* 13.8 Hz), 1.37 (s, 3H, 4-Me), 1.30 (s, 3H, 4-Me), 0.63 (s, 3H, 6-Me). IR, ν/cm^{-1}: 3384, 3377, 3190, 1619, 1606, 980, 961. MS, *m*/*z*: 356 (50) [M$^+$], 341, 246, 231, 217, 205, 191, 175, 149, 107, 91, 58, 40.

2e: ^{1}H NMR, δ: 9.43 (s, 1H, OH), 9.13 (s, 1H, OH), 8.12 (s, 1H, NH), 7.05 (m, 3H, H_{Ar}), 6.8 (dd, 2H, H_{Ar}, *J* 9 Hz,) 6.32 (s, 1H, H_{Rz}), 6.27 (d, 1H, H_{Rz}, *J* 8.3 Hz), 3.73 (s, 3H, OMe), 2.0 (d, 1H, 5-H_e, *J* 13.5 Hz), 1.9 (d, 1H, 5-H_a, *J* 13.5 Hz), 1.27 (s, 3H, 4-Me), 1.23 (s, 3H, 4-Me), 0.58 (s, 3H, 6-Me). IR, ν/cm^{-1}: 3500, 3350, 1619, 1599, 1523, 1500, 1160, 990, 920.

2f: ^{1}H NMR, δ: 9.55 (s, 1H, OH), 9.25 (s, 1H, OH), 8.38 (s, 1H, NH), 7.3 (m, 3H, H_{Ar}), 7.05 (m, 2H, H_{Ar}) 6.32 (m, 2H, H_{Rz}), 3.02 (d, 1H, 5-H_e, *J* 14.0 Hz) , 1.95 (t, 1H, 5-H_a, *J* 14.0 Hz), 1.32 (s, 3H, 4-Me), 1.26 (s, 3H, 4-Me), 0.6 (d, 3H, 6-Me). IR, ν/cm^{-1}: 3300, 3200, 980, 940.

2g: ^{1}H NMR, δ: 9.35 (s, 1H, OH), 9.03 (s, 1H, OH), 8.36 (s, 1H, NH), 7.7–7.3 (m, 4H, H_{Ar}), 7.04 (dd, H, H^{12}_{Rz}, *J* 8.0 Hz), 6.32 (s, H, H^{9}_{Rz}), 6.28 (d, H, H^{12}_{Rz}, *J* 8.0 Hz), 3.1 (d, 1H, 5-H_e, *J* 13.9 Hz), 1.92 (t, 1H, 5-H_a, *J* 13.9 Hz), 1.3 (s, 6H, 4-Me), 0.6 (s, 3H, 6-Me), a mixture of rotational isomers with OH, Ar and NH doublets. IR, ν/cm^{-1}: 3260, 3030, 1605, 1595, 970, 915. MS, *m*/*z*: 412 (1.5) [M$^+$], 411 (5.9), 285 (5.6), 261 (6.1), 259 (15.9), 203 (99), 191 (25.9), 182 (22), 175 (100), 161 (20), 150 (23), 145 (22), 135 (14.9).

References

1 G. Zigeuner, A. Frank, H. Dujmovits and W. Adam, *Monatsh. Chem*., 1970, **101**, 1415.

2 G. Zigeuner, W. B. Lintschinger and F. Wode, *Monatsh. Chem*., 1975, **106**, 1219.

3 G. Zigeuner, W. B. Lintschinger, A. Fuchsgruber and K. Kollmann, *Monatsh. Chem*., 1976, **107**, 155.

Received: 16th April 1999; Com. 99/1477

2i (a mixture of two diastereoisomers in the ratio ~60:40): ^{1}H NMR, δ: major isomer, 9.38 (s, 1H, OH), 9.10 (s, 1H, OH), 8.20 (1H, NH), 7.76 (s, 1H, NH), 7.4–7.1 (m, 11H, H_{Ar} + H_{Rz}), 6.38 (d, 1H, H_{Rz}, *J* 8.0 Hz), 6.32 (s, 1H, H_{Rz}), 4.4 (dd, 1H, 4-H, *J* 11.5 and 2.9 Hz), 3.1 (dd, 1H, 5-H, *J* 13.5 Hz and 2.9 Hz), 2.1 (dd, 1H, 5-H, *J* 13.5 and 11.5 Hz); minor isomer, 9.72 (s, 1H, OH), 8.93 (s 1H, OH), 8.28 (s, 1H, NH), 7.53 (s, 1H, NH), 6.22 (d, 1H, H_{Rz}), 6.15 (d, 1H, H_{Rz}), 3.84 (dd, 1H, 4-H), 2.64 (dd, 1H, 5-H), 2.38 (t, 1H, 5-H). IR, ν/cm^{-1}: 3415, 3300, 3200, 1615, 1600, 978.

2h (a mixture of two diastereoisomers in the ratio ~85:15): ^{1}H NMR, δ: major isomer, 9.47 (s, 1H, OH), 9.18 (s, 1H, OH), 8.4 (s, 1H, NH), 8.0 (s, 1H, NH), 7.40–7.15 (m, 5H, H_{Ar}), 6.9 (d, 1H, H^{12}_{Rz}, *J* 8.0 Hz), 6.35 (s, 1H, H^{9}_{Rz}), 6.23 (d, 1H, H^{11}_{Rz}, *J* 8.0 Hz), 3.78 (dd, 1H, 4-H, *J* 11.5 and 3.0 Hz), 2.98 (dd, 1H, 5-H_e, *J* 12.6 and 3.0 Hz), 1.58 (dd, 1H, 5-H_a, *J* 12.6 and 11.5 Hz), 1.53 (s, 3H, 6-Me); minor isomer, 9.8 (s, 1H, OH), 9.12 (s 1H, OH), 8.23 (s, 1H, NH), 8.12 (s, 1H, NH), 6.22 (d, 1H, H_{Rz}), 6.15 (d, 1H, H_{Rz}), 4.23 (dd, 1H, 4-H), 2.9 (dd, 1H, 5-H), 1.7 (t, 1H, 5-H). IR, ν/cm^{-1}: 3350, 3120, 1615, 1595, 975.

2j (a mixture of two diastereoisomers in the ratio ~60:40): ^{1}H NMR, δ: major isomer, 9.7 (s, 1H, OH), 9.08 (s, 1H, OH), 8.28 (s, 1H, NH), 8.15 (s, 1H, NH), 7.4–6.15 (m, 12H, H_{Ar} + H_{Rz}), 3.88 (dd, 1H, 4-H, *J* 11.8 and 3.0 Hz), 3.76 (s, 3H, OMe), 2.6 (dd, 1H, 5-H, *J* 13.2 and 3.0 Hz), 2.35 (dd, 1H, 5-H, *J* 13.2 and 11.8 Hz); minor isomer, 9.32 (s, 1H, OH), 9.1 (s, 1H, OH), 8.25 (s, 1H, NH), 7.68 (s, 1H, NH), 4.32 (dd, 1H, 4H, *J* 11.8 and 3.0 Hz), 3.72 (s, 3H, OMe), 3.12 (dd, 1H, 5-H, *J* 13.2 and 3.0 Hz), 2.1 (dd, 1H, 5-H, *J* 13.2 and 11.8 Hz). IR, ν/cm^{-1}: 3250, 3380, 1603, 1540, 1040, 978. MS, *m*/*z*: 406 [M$^+$], 396, 330, 296, 253, 236, 219, 177, 165, 148, 134, 110, 104, 82, 76, 53, 39.

2k (a mixture of two diastereoisomers in the ratio ~95:5): ^{1}H NMR, δ: 9.32 (s, 1H, OH), 9.09 (s, 1H, OH), 8.16 (1H, NH), 7.69 (s, 1H, NH), 7.45 (s, 1H, 3-H_{Fu}), 7.13 (m, 3H, H_{Ar} + H_{Fu}), 6.78 (d, 2H, H_{Ar}, *J* 9.5 Hz), 6.3 (m, 4H, H_{Rz} + H_{Fu}), 4.35 (dd, 1H, 4-H, *J* 11.1 and 3.0 Hz), 3.72 (s, 3H, OMe), 3.15 (dd, 1H, 5-H, *J* 13.9 and 3.0 Hz), 2.38 (dd, 1H, 5-H, *J* 13.9 and 11.1 Hz). IR, ν/cm^{-1}: 3440, 3250, 1618, 1598, 1036, 1018, 982, 930.

2l (a mixture of two diastereoisomers in the ratio ~90:10): ^{1}H NMR, δ: 9.25 (s, 1H, OH), 8.95 (s, 1H, OH), 7.75 (s, 1H, NH), 7.7 (s, 1H, NH), 7.4–7.15 (m, 5H, H_{Ar}), 6.9 (d, 1H, H^{12}_{Rz}), 6.35 (d, 1H, H^{9}_{Rz}), 6.23 (dd, 1H, H^{5}_{Rz}), 3.9 (dd, 1H, 4-H, *J* 11.6 and 3.0 Hz), 2.9 (dd, 1H, 5-H, *J* 12.6 and 3.0 Hz), 1.78 (dd, 1H, 5-H, *J* 11.6 and 12.6 Hz), 2.03 (m, 1H, CH_2), 1.87 (m, 1H, CH_2), 0.78 (t, 3H, Me).