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Desulfurization of 2-Thioxo-1,2,3,4-tetrahydropyrimidin-4-ones with Oxiranes and 2-Haloacetonitriles

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Abstract—A procedure was developed for the synthesis of tetrahydropyrimidine-2,4-diones by desulfurization of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones with oxiranes or 2-haloacetonitriles in polar solvents in the presence of a base.

It is known that 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one derivatives differently react with different alkylating agents. In most cases, the reaction gives the corresponding 2-alkylsulfanylpyrimidin-6(1*H*)-ones or 2-alkylsulfanyl-1-alkylpyrimidin-4(1*H*)-ones, while 2-chloroacetic acid reacts with 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones in an aqueous solution to afford tetrahydropyrimidine-2,4-diones.

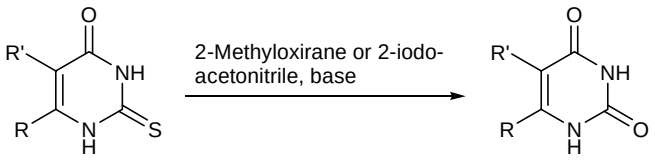
We found that 2-methyloxirane and 2-iodoacetonitrile are also capable of effecting desulfurization of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one derivatives with formation of 1,2,3,4-tetrahydropyrimidine-2,4-diones (Scheme 1). The reactions were performed using the following base–solvent systems (which are typically used for alkylation of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones): K_2CO_3–DMFA, NaH–DMFA, NaOMe–MeOH, KOH–EtOH, and NaOH–H_2O. The yield of the resulting pyrimidine-2,4-dione derivatives was quantitative, regardless of the base used.

While studying desulfurization of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones **Ia**–**Ie** we showed that 2-phenyloxirane and 2-ethyloxirane also equally effective in this reaction, and the corresponding 1,2,3,4-tetrahydropyrimidine-2,4-diones **IIa**–**IIe** were formed in quantitative yield. Presumably, the reason is that the examined oxirane derivatives possess an endocyclic methylene group which is not shielded with respect to nucleophilic attack. Both protic polar solvents (H_2O, MeOH, EtOH) and aprotic dimethylformamide ensured quantitative formation of pyrimidinediones **IIa**–**IIe**. This suggests that the solvent does not participate in the reaction with initially formed 2-[(2-hydroxyalkyl)sulfanyl]pyrimidinone and that oxirane acts as source of oxygen.

Desulfurization of compounds **Ia**–**Ie** with 2-iodoacetonitrile (as well as with 2-bromo- and 2-chloroacetonitrile) resulted in quantitative formation of pyrimidinediones **IIa**–**IIe** only when the reaction was carried out in an alcoholic medium. The reaction in DMF in the presence of K_2CO_3 was accompanied by strong tarring. Treatment of **Ia**–**Ie** with 2-iodoacetonitrile in aqueous sodium hydroxide afforded compounds **IIa**–**IIe** in a poor yield, and the conversion of initial 2-thioxopyrimidinones was not complete. These data indicate that the process should be performed in a protic solvent which is likely to promote cleavage of the initially formed 2-(cyanomethylsulfanyl) derivative. The low yield of pyrimidine-2,4-diones in the reaction in water may be due to heterogeneous conditions and concurrent hydrolysis of 2-iodoacetonitrile.

It should be noted that the maximal yield of compounds **II** in the reactions with both substituted oxiranes and 2-haloacetonitriles was observed only when the amount of base was equal to or greater than equimolar. Reduction of the amount of base leads to proportional decrease in the conversion (according to the HPLC data). Therefore, the base acts as a reagent rather than catalyst.

Scheme 1.



Ia–Ie **IIa–IIe**

R = R' = H (**a**); R = Me, R' = H (**b**); R = $PhCH_2$, R' = H (**c**); R = 2,6-$F_2C_6H_3CH_2$, R' = H (**d**); R = H, R' = Me (**e**).

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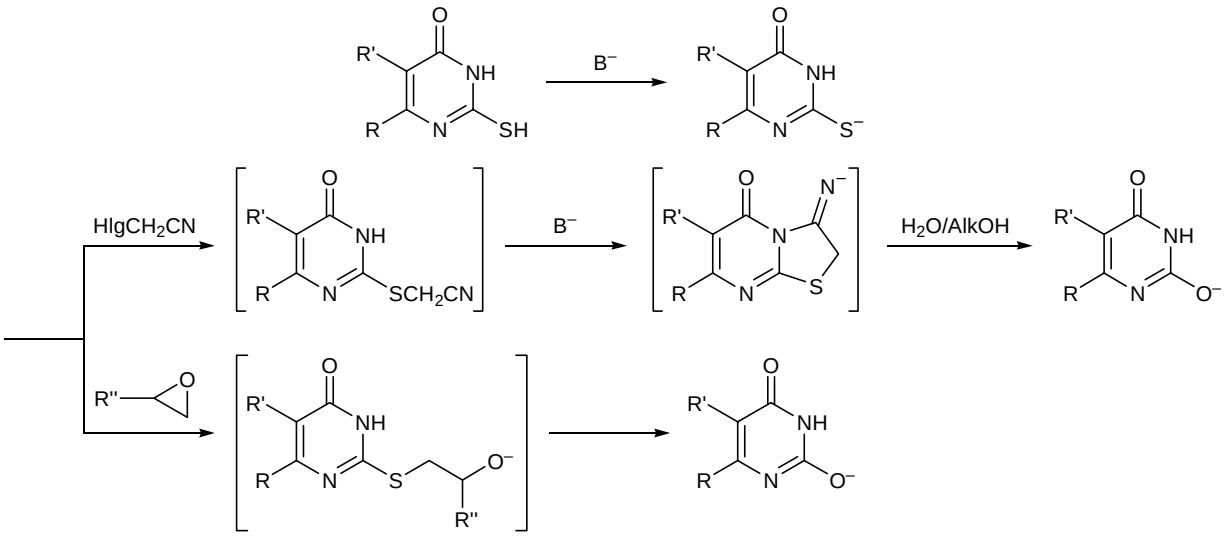
Scheme 2.



R" = Me, Et, Ph; B is a base; Hlg = Cl, Br, I.

Desulfurization of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones with 2-haloacetonitriles and oxiranes was not reported previously. On the other hand, the reaction of sodium thiosulfate and thiourea with oxiranes is known to give the corresponding thiiranes [4]. Here, the source of sulfur is sodium thiosulfate or thiourea. Presumably, the examined reactions of 2-thioxopyrimidinones **I** follow an analogous mechanism. Unlike compounds **I**, there is no need of deprotonating thiourea to ensure its nucleophilic attack on oxirane ring.

There are published data indicating that cyanomethyl esters readily undergo hydrolysis [5]. Therefore, we presumed that 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one reacts with 2-iodoacetonitrile in the presence of a base to give initially 2-(cyanomethylsulfanyl)pyrimidin-6(1*H*)-one whose solvolysis leads to formation of the corresponding pyrimidinedione (Scheme 2).

Ethyl 2-bromoacetate and 2-bromo-1,1-dimethoxyethane are known to react with 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones to afford 2-(ethoxycarbonylmethylsulfanyl)pyrimidin-6(1*H*)-ones [6] and 2-(2,2-dimethoxyethylsulfanyl)pyrimidin-6(1*H*)-ones [7], respectively. Therefore, the only 2-haloacetic acid derivatives capable of desulfurizing 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones are 2-haloacetic acids themselves or the corresponding nitriles.

Thus the observed desulfurization of 2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ones by the action of oxiranes and 2-haloacetonitriles may be rationalized in terms of a strong ability of the initially formed 2-(2-hydroxyalkyl)- and 2-(cyanomethylsulfanyl)pyrimidin-6(1*H*)-ones to undergo solvolysis (intra- or intermolecular, respectively).

EXPERIMENTAL

The mass spectra (electron impact, 70 eV) were recorded on a Varian MAT-111 spectrometer with direct sample admission into the ion source. The melting points were determined on a MelTemr 3.0 apparatus at a heating rate of 10 deg/min. HPLC analysis was performed on a Waters ALC/GPC-244 chromatograph under the following conditions: compound **IId**: 125×3-mm column, stationary phase Inertsil ODS (5 μm), eluent MeCN–H_2O (10:10, by volume) + 5 ml of 1 N H_2SO_4; flow rate 0.1 ml/min, UV detector with a diode matrix (λ 280 nm); compounds **IIa**–**IIc** and **IIe**: 250×4.6-mm column, stationary phase Licrosphere RP8, eluent MeCN–MeOH (67:33), flow rate 0.3 ml/min. The IR spectra were obtained in KBr on a Perkin–Elmer 580 instrument. TLC analysis was performed using Sorbfil plates; eluent CH_2Cl_2–MeOH (19:1); spots were visualized under UV light or by treatment with iodine vapor.

1,2,3,4-Tetrahydropyrimidine-2,4-diones IIa–IIe. *a.* Compound **Ia**–**Ie**, 10 mmol, was dissolved on heating under stirring in 11 ml of a 1 N aqueous solution of sodium hydroxide. The solution was cooled to room temperature, 11 mmol of 2-substituted oxirane was added, and the mixture was stirred until initial compound **I** disappeared (TLC, after acidification). The mixture was neutralized with 1 N hydrochloric

acid, and the precipitate was filtered off, washed with water (25 ml), and dried. The yield of **IIa**–**IIe** was almost quantitative.

1,2,3,4-Tetrahydropyrimidine-2,4-dione (IIa). mp 335°C (decomp.) [8].

6-Methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (IIb). mp 300°C (decomp.) [8].

6-Benzyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (IIc). mp 262–263.5°C [9].

6-(2,6-Difluorobenzyl)-1,2,3,4-tetrahydropyrimidine-2,4-dione (IId). mp >300°C (decomp.; from AcOH). IR spectrum: ν(C=O) 1660 cm^{-1}. Mass spectrum, *m*/*z* (I_{rel}, %): 238 (32) M^+, 219 (0.1), 195 (0.8), 175 (14), 152 (8) 127 (27), 68 (100). Found, %: C 55.42; H 3.48; F 15.90; N 11.71. M^+ 238. $C_{11}H_8F_2N_2O_2$. Calculated, %: C 55.47; H 3.49; F 15.95; N 1 1.76. *M* 238.20.

5-Methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (IIe). mp >336°C (decomp.) [9].

b. A mixture of 5 mmol of compound **Ia**–**Ie**, 5 ml of anhydrous DMF, and 0.69 g (5 mmol) of K_2CO_3 was stirred for 45 min at 90–100°C. The mixture was then cooled to 20°C, 5.5 mmol of 2-substituted oxirane was added, and the mixture was stirred until initial compound **I** disappeared (TLC). The mixture was diluted with 100 ml of water and neutralized with 1 N hydrochloric acid, and the precipitate was filtered off, washed with 25 ml of water on a filter, and dried. The reaction of **Ia**–**Ie** with oxiranes in DMF in the presence of NaH was carried out in a similar way. Yield of **IIa**–**IIf** nearly quantitative.

c. Compound **Ia**–**Ie**, 5 mmol, was dissolved under stirring in a solution of 0.32 g (6 mmol) of sodium methoxide in 20 ml of methanol, 5.5 mmol of 2-haloacetonitrile was added, and the mixture was stirred until initial compound **I** disappeared (TLC, after acidification). The mixture was neutralized with 1 N hydrochloric acid, and the precipitate was filtered off, washed with 5 ml of methanol, and dried. The reaction of **Ia**–**Ie** with 2-haloacetonitriles in ethanol in the presence of KOH was carried out in a similar way. Yield of **IIa**–**IIe** nearly quantitative.

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