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An Unexpected and Efficient Direct Nucleophilic C-4 Hydroxy Substitution on 2-Methoxy- and 2-Methylthio-4(3H)-pyrimidinones Bearing a Diethylamino Moiety on the C-6 Side Chain

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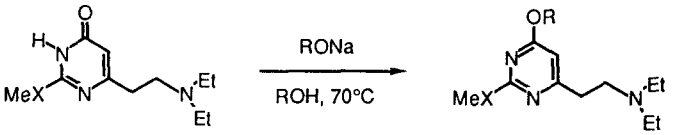
Abstract: The unexpected and efficient direct nucleophilic C-4 hydroxy (oxo) substitution by sodium alkoxides on 2-methoxy- and 2-methylthio-4(3H)-pyrimidinones bearing a diethylamino moiety on the C-6 side chain is reported. An unprecedented tandem C-6 side chain Hofmann-like elimination /C-4 pyrimidinone substitution is also reported. This provides a good method for the synthesis of new C-6 vinyl cytosine derivatives. © 1997 Elsevier Science Ltd.

Despite the fact that 2-, 4-, and 6-positions of pyrimidines are prone to direct nucleophilic attack, relatively few examples of direct removal of hydroxy (oxo) substituents are recorded. The aminolysis of pyrimidinones with the introduction of secondary or tertiary amino groups in place of the hydroxy group is possible only using appropriate phosphoramides as reagents at very high temperatures, ranging from 200°C to 300°C.[1] It is evident that both substrate and product must be exceptionally thermostable for this reaction to be practical. On the other hand, most 2,6- or 4,6-dialkoxypyrimidines are satisfactory substrates for aminolysis[2] and transalkoxylation reactions.[3] The experimental conditions are deeply affected by the presence of additional electron-withdrawing or electron-releasing groups and also by the size of the alkoxy group to be replaced.

In the course of our studies on the chemistry of uracil and pyrimidinone derivatives[4] we have found that 6-alkyl- and 5,6-dialkyl-2-methoxy-4(3H)-pyrimidinones are useful intermediates in the synthesis of the corresponding 2-alkoxy analogues[5] and 2-alkyl(and 2-aryl)amino derivatives.[6] The reaction is performed by treatment of the 2-alkoxy pyrimidinone derivatives with an excess of amide anions in refluxing tetraline or with sodium alkoxides in the appropriate alcohol. In addition, to obtain 2-alkoxy-4-substituted pyrimidines the previous activation of the C-4 position through chlorination is necessary.[6] We are reporting here that 2-methoxy- and 2-methylthio-4(3H)-pyrimidinones bearing a diethylamino moiety on the C-6 side chain, synthesized to be tested as antiviral agents,[7] do not give C-2 transalkoxylation under the usual reported conditions[5] but, unexpectedly, afford 2-methoxy-4-alkoxy- or 2-methylthio-4-alkoxy pyrimidine derivatives. An unprecedented C-6 side chain Hofmann-like elimination with the concurrent and selective migration of the

diethylamino moiety to the C-4 position of the 4(3H)-pyrimidinone ring is also reported. To the best of our knowledge, there is no precedent in the literature of direct and selective hydroxy (oxo) substitution on pyrimidine derivatives under mild experimental conditions and in the presence of seemingly more efficient leaving groups in the substrate.

When 2-methoxy-6[(2'-diethylamino)ethyl]-4(3H)-pyrimidinone **1** (1 mmol) was treated with an excess (2.0 equiv/mol) of sodium n-butoxide (prepared from dry n-butanol and Na) at 70°C in dry n-butanol (5 ml), 2-methoxy-4-butoxy-6[(2'-diethylamino)ethyl]pyrimidine **2a** was obtained as the only recovered product in 72% yield (Scheme 1).[8]



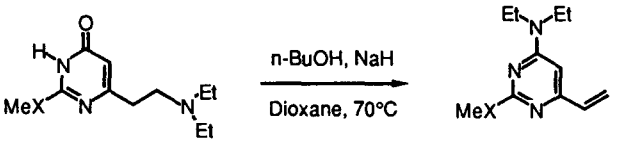
1, 3 **2a-d, 4a-d**

a: R=n-Bu. b: R=Me. c: R=Et. d: R=Bn
1, 2a-d: X=O. **3, 4a-d**: X=S

Scheme 1

To test the generality of this direct C-4 hydroxy substitution we studied further the reaction of **1** (1 mmol) with some other sodium alkoxides (2.0 equiv/mol; sodium methoxide, ethoxide, and benzyloxide) under analogous experimental conditions and the corresponding 2-methoxy-4-alkoxypyrimidine derivatives **2b-d** were obtained in acceptable yields (85%, 72%, and 70% yields, respectively) [Scheme 1].[9] It is known that alkylthiopyrimidinones easily undergo alcoholysis in alcoholic sodium alkoxide; i.e., 5-fluoromethyl-4-methylthio-2(1H)-pyrimidinone treated with methanolic sodium methoxide at 20°C for 24 hours gives the corresponding 4-methoxy-2(1H)-pyrimidinone derivative in 60% yield.[10] On the basis of these data we studied the reaction of 2-methylthio-6[(2'-diethylamino)ethyl]-4(3H)-pyrimidinone **3** with alcoholic sodium alkoxides. When compound **3** (1 mmol) was treated with an excess (2.0 equiv/mol) of sodium alkoxide (sodium methoxide, ethoxide, n-butoxide, and benzyloxide), prepared from dry alcohols and Na, at 70°C in the appropriate dry alcohol (10 ml), the corresponding 2-methylthio-4-alkoxy pyrimidine derivatives **4a-d** were obtained as the only recovered products in yields ranging from 50% to 65% (Scheme 1).[11]

Recently, Liotta and co-workers reported that the selectivity in the nucleophilic substitution on 2,4-dichloropyrimidines with alkoxides depends on the use of alkoxides prepared from Na or from NaH.[12] Interestingly, when compounds **1** (1 mmol) and **3** (1 mmol) were treated with sodium n-butoxide (1.2 equiv/mol) generated by n-butanol and NaH in dry dioxane (10 ml) at 70°C for 8 hours, the 2-methoxy- and 2-methylthio-4-diethylamino-6-vinyl pyrimidines **5** and **6** were obtained as the main products in 48% and 45% yields, respectively, (Scheme 2) in additions to very small amounts of the corresponding 4-alkoxy derivatives.[13] The reaction is operative also at room temperature even if, in this case, lower yields for **5** and **6** (11% and 9% yields, respectively) were obtained and longer reaction time (48 hours) were necessary. Compounds **5** and **6** are apparently formed through a C-6 side chain Hofmann-like elimination followed by direct and selective C-4 hydroxy (oxo) substitution by the diethylamino nucleophile. On the basis of molecular models, we can exclude an intramolecular process for the formation of compounds **5** and **6**, forbidden because of structural considerations.

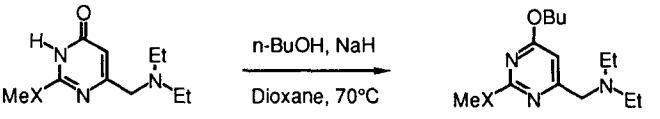


1, 3 **5, 6**

1, 5: X=O. **3, 6**: X=S

Scheme 2

On the other hand, when the reactions were performed in the presence of 6-methyl-2-methoxy-4(3H)-pyrimidinone or methyl benzoate as scavengers of the diethylamino nucleophile, compounds **5** and **6** were obtained without traces of possible cross-reaction products, showing that an intermolecular concerted process is probably operative. Moreover, when the 2-methoxy- and 2-methylthio-6-diethylaminomethyl-4(3H)-pyrimidinones **7** and **8**, lacking of the structural features necessary for the β-elimination, were treated with sodium n-butoxide (1.2 equiv/mol) generated by NaH in dry dioxane (10ml) at 70°C for 8 hours, the corresponding 4-butoxy derivatives **9** and **10** were isolated in 82% and 85% yields, respectively, as the only recovered products (Scheme 3).[11]



7, 8 **9, 10**

7, 9: X=O. **8, 10**: X=S

Scheme 3

The function of intermolecular concerted processes in the chemistry of pyrimidinone derivatives has been experimentally proven in the thermal rearrangement of 2-alkoxypyrimidines to the corresponding N-methyl pyrimidinones, in which case a concerted intermolecular four-centre mechanism has been proposed.[14] Moreover, the self association of **1** in solution at room temperature has been suggested by some infrared and ultraviolet data. In particular, in contrast to well established general IR absorption properties for 4(3H)-pyrimidinones, the absorption bands for C=O and N-H bond stretching vibrations were not present in the IR spectrum of **1** when performed in chloroform at different concentrations. On the contrary, a strong bonded O-H absorption was observed at 3200 cm^{-1}. Furthermore, preliminary UV experiments performed for **1** in cyclohexane at room temperature were characterized by the presence of a hypsochromic effect for the pyrimidinone characteristic band at 285.4 nm, as the concentration changes from 0.1 to 32 μM.

Due to the remaining activation of the C-2 position, **5** and **6** can be considered as potential entries into more substituted vinyl cytosine derivatives of difficult synthesis. Further work is in progress in our laboratory in order to generalize this reaction and to obtain the X-ray of the starting materials.

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7. The synthesis and antiviral data for compounds **1** and **3** will be reported in full elsewhere.
8. Compound **2a** was characterized by the lack of the carbonyl amide stretching at 1730 cm^{-1} in the IR spectrum. Selected data for compound **2a**- (202 mg, 72%), oil. I.R. ($CHCl_3$) ν_{max}: 3005 (C=CH), 2850 (CH), 1550 (C=C), 1100 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 0.85 (3H, m, CH_3), 1.12 (6H, t, J =7.0 Hz, CH_3), 1.28 (2H, m, CH_2), 1.47 (2H, m, CH_2), 2.86 (2H, t, J=6.5 Hz, CH_2), 3.45 (6H, m, NCH_2), 3.80 (2H, m, CH_2), 3.90 (3H, s, OCH_3), 6.0 (1H, s., CH), ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 12.82 (CH_3), 12.98 (CH_3), 19.13 (CH_2), 31.63 (CH_2), 38.20 (CH_2), 42.15 (CH_2), 53.70 (CH_2), 69.25 (CH_2), 70.70 (CH_3), 96.36 (CH), 163.14 (C), 165.62 (C), 167.80 (C); m/z 281 (M^+, 29%).
9. Selected data for compound **2b**- (203 mg, 85%), oil. I.R. ($CHCl_3$) ν_{max}: 3005 (C=CH), 2870 (CH), 1545 (C=C), 1150 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 1.15 (6H, t, J =7.3 Hz, CH_3), 2.75 (2H, t, J=6.3 Hz, CH_2), 3.50 (4H, q, J=7.3 Hz, NCH_2), 3.86 (6H, s, OCH_3), 6.1 (1H, s, CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 12.79 (CH_3), 31.63 (CH_2), 38.11 (CH_2), 42.11 (CH_2), 70.70 (CH_3), 70.85 (CH_3), 97.0 (CH),163.22 (C), 165.31 (C), 170.0 (C); m/z 239 (M^+, 31%).
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13. Selected data for compound **5**- (92 mg, 48%), oil. I.R. ($CHCl_3$) ν_{max}: 3090 (C=CH), 2870 (CH), 1560 (C=C), 1150 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ_H ppm: 1.20 (6H, t, J =7.0 Hz, CH_3), 3.55 (4H, q, J=7.0 Hz, NCH_2), 4.0 (3H, s, OCH_3), 5.45 (1H, d.d., J=2 Hz, J= 18 Hz, CH), 5.98 (1H, s, CH), 6.50 (2H, m, CH); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ_C ppm: 12.87 (CH_3), 42.20 (CH_2), 53.79 (CH_3), 94.85 (CH), 120.30 (CH_2), 135.98 (CH), 162.47 (C), 163.44 (C), 165.74 (C); m/z (M^+, 31%).
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