An Improvement in the Synthesis of Ethyl Pyrimidinecarbamates

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It is demonstrated that *N*-(ethoxycarbonyl)pyridinium chloride (**3**) is the reactive agent in the synthesis of 4-ethoxycarbonylamino-2,6-dimethylpyrimidine (**1**). A good yield (80%) of **1** may be obtained by the condensation of **3** with excess 4-amino-2,6-dimethylpyrimidine using pyridine or dimethylformamide as the solvent. A method allowing for the preparation of 4-ethoxycarbonylamino-x-hydroxypyrimidines *via* the same process is offered.

J. Heterocyclic Chem., **18**, 835 (1981).

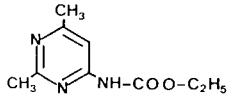
The condensation of ethyl chloroformate with amino and aminohydroxypyrimidines yields the corresponding ethyl carbamates in certain cases only. 2-Aminopyrimidine and 5-aminouracil condense with ethyl chloroformate in the cold in the presence of sodium hydroxide (1). By refluxing in benzene in the presence of excess pyrimidine, 4-aminopyrimidine reacts with ethyl chloroformate (1). Under the same experimental conditions, 4-amino-2,6-dimethylpyrimidine, cytosine, isocytosine and 4-aminouracil do not react. No explanation for these failures has, to our knowledge, been given, except in the case of cytosine where a decrease in basicity with respect to 4-aminopyrimidine might be implicated (2).

These data as well as results obtained in our laboratory with certain 4-aminopyrimidine derivatives, led us to re-examine the direct synthesis of carbamates. We find that *N*-(ethoxycarbonyl)pyridinium chloride (**3**), is an excellent reagent for the synthesis of ethyl pyrimidinecarbamates.

Results and Discussion.

With the procedure described by Dyer, *et al.* (3), we were able, unlike the authors, to isolate 4-ethoxycarbonylamino-2,6-dimethylpyrimidine (**1**) from 4-amino-2,6-dimethylpyrimidine and ethyl chloroformate. However, the yield was so low (3% with sodium hydroxide in the cold, 18% by reflux in benzene) that the authors understandably judged the method a failure.

Other procedures have also been described. The chosen pyrimidine can be reacted with ethyl pyrocarbonate in ethanol (3). We have reproduced the experiment with 4-amino-2,6-dimethylpyrimidine and isolated **1**. It was separated from 4-α,β-diethoxycarbonylamino-2,6-dimethylpyrimidine (**2**), the formation of which was not previously indicated, by chromatography on a silica gel column eluted with ethylacetate.



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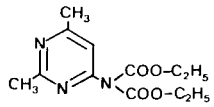


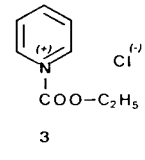
2

Baldwin and Van Der Broek (4) isolated **1** by acid catalysed desulphurization of the previously synthesized 5,7-dimethyl[1,2,4]thiadiazolo[4,3-*c*]pyrimidin-3-one.

The formation of secondary products such as **2** or complete synthesis of dimethylthiadiazolopyrimidinone (4) may easily be avoided when ethyl chloroformate is reacted with 4-amino-2,6-dimethylpyrimidine in pyridine. This procedure which has already been used in the synthesis of 2-pyrimidylurethane (5) leads to the formation of **1** with a yield of about 50%.

Various tests have established that yield is not at all or only very slightly dependent on time and temperature if the reaction is carried out under equimolar conditions in pyridine (3 hours at 20°, 43.5%; 24 hours at 20°, 51%; 24 hours at 80°, 57.6%). Pyridine plays an essential role, since there is no yield when it is replaced by sodium hydroxide or triethylamine. The yield seems limited to about 50%. The supposed formation of pyridine hydrochloride was not verified. We have determined by nmr that the precipitate formed was, in fact, the hydrochloride of 4-amino-2,6-dimethylpyrimidine. Although the presence of pyridine was indispensable.

The formation of addition compounds between pyridine and acyl halides has been described (6), a compound of this type might be in question. Synthesis of the addition compound *N*-(ethoxycarbonyl)pyridinium chloride **3** demonstrated that it was indeed the reactive entity.



3

The reaction of 4-amino-2,6-dimethylpyrimidine and compound **3** can be carried out in a solvent other than pyridine in which the pyrimidine is soluble (for example, dimethylformamide). The reaction seems easier when the mixture is homogenized by filtration of the precipitate, identified as 4-amino-2,6-dimethylpyrimidine hydro-

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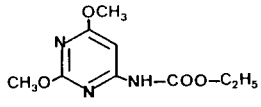
chloride, but the yield does not vary clearly. According to the method described below, a yield of approximately 80% of **1** is obtained.

The other pyrimidines which had previously failed to react might be rendered reactive. Cytosine, isocytosine and 4-aminouracil were no more reactive with *N*-(ethoxycarbonyl)pyridinium chloride than with ethyl chloroformate. These latter three compounds present a keto-enol tautomerism, the action of which at the level of the neighbouring cyclic nitrogen is well known, and might be transferred as far as the amino group. If this hypothesis is correct, the dimethoxy derivative of 4-aminouracil should react with *N*-(ethoxycarbonyl)pyridinium chloride. This does occur. The dimethoxy form of 4-aminouracil reacts with the halogenated intermediate **3** and yields 4-ethoxycarbonylamino-2,6-dimethoxypyrimidine (**4**).



4

This demonstrates that not only the acylating agent but also the type of aminopyrimidine were implicated in the literature failures to acylate pyrimidines. After methoxylation of 4-amino-x-hydroxypyrimidines, 4-ethoxycarbonylamino-x-hydroxypyrimidines can be obtained, provided that the integrity of the urethane function is preserved after demethylation.

EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and are uncorrected. ^{1}H Nmr spectra were obtained on a Jeol C 60 HL spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Ir spectra were obtained in potassium bromide discs or from film on a Perkin Elmer Ir 457 spectrophotometer. Product purity and reaction progress were checked by analytical thin layer chromatography on 2.5 × 10 cm plates coated with fluorescent silica gel (Merck 60 F 254). Elemental analysis were obtained from C.N.R.S. Laboratories, 69390, Vernaison. The technique for determination of oxygen involved a flash pyrolysis of sample according to the Schütze-Unterzaucher principle (7,8). The use of a vertical reactor described and developed by Fraisse (9,10) makes possible a complete automation of the technique.

4-Ethoxycarbonylamino-2,6-dimethylpyrimidine (**1**).

A mixture of 2 moles of 4-amino-2,6-dimethylpyrimidine and 1 mole of **3** in pyridine or dimethylformamide was heated at 80° for 24 hours with vigorous stirring. After 3 hours heating, a precipitate of 4-amino-2,6-dimethylpyrimidine hydrochloride begins to appear, m.p. 265°; nmr (DMSO-d_6): 8.9 (broad, NH_3^+, 3H), 6.5 (s, H-5, 1H), 2.4 (s, CH_3-2, 3H), 2.3 (s, CH_3-4, 3H). The precipitate was filtered as to improve contact between the reagents, and the reaction continued in a homogeneous medium. When cooled, water was added to the reaction mixture and the organic phase extracted with chloroform. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation. The crude product 4-ethoxycarbonylamino-2,6-dimethoxypyrimidine which solidified on standing was recrystallized from pentane (80% yield), m.p. 79°.

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52; O, 16.40. Found: C, 55.50; H, 6.77; N, 21.40; O, 16.54.

4-α,β-Diethoxycarbonylamino-2,6-dimethylpyrimidine (**2**).

To a solution of 4-amino-2,6-dimethylpyrimidine (5 g., 0.04 mole) in 60 ml. of refluxing ethanol was added 5.8 ml. (0.06 mole) of ethyl pyrocarbonate. After 1 hour at reflux, the precipitate of unreacted pyrimidine was filtered. The ethanol was then removed *in vacuo*. The mixture contained **1** and **2**, which were separated by chromatography on a silica gel column eluted with ethyl acetate. Compound **2** is a yellow oil (38% yield), n_D^{25} = 1.4912; ir: 1740 and 1770 ($COOC_2H_5$); nmr (deuteriochloroform): 7.6 (s, H-5, 1H), 4.2 (q, CH_2, 4H), 2.5 (s, CH_3-2, 3H), 2.4 (s, CH_3-4, 3H), 1.2 (t, CH_3, 6H).

Anal. Calcd. for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72; C, 23.95. Found: C, 53.99; H, 6.61; N, 15.67; O, 23.62.

N-(Ethoxycarbonyl)pyridinium Chloride (**3**).

To a cold stirring mixture of 9.68 ml. (0.101 mole) of ethyl chloroformate in 100 ml. of petroleum ether (−20° over solid carbon dioxide), 10 ml. of pyridine (0.122 mole) was added. The stirring was continued for 1 hour. The mixture was then filtered, precautions being taken to avoid moisture. The product was dried over phosphorus pentoxide and then rapidly used for the next synthesis, m.p. 94° dec.; ir: 2100 (pyridinium); 1640 (C=N$^+$); nmr (DMSO-d_6): 7.5-8.7 (m, pyridine, 5H), 4.5 (q, CH_2, 2H), 1.3 (t, CH_3, 3H).

Anal. Calcd. for $C_8H_{10}ClNO_2$: Cl, 18.90. Found: Cl, 19.12.

4-Ethoxycarbonylamino-2,6-dimethoxypyrimidine (**4**).

4-Amino-2,6-dimethoxypyrimidine was prepared from 4-amino-2,6-dihydroxypyrimidine and 4-amino-2,6-dichloropyrimidine (11). Compound **4** was synthesized in 60% yield in a manner similar to the preparation of **1**. However, the extraction was replaced by chromatography on a silica gel column eluted with a benzene/ethanol mixture (98/2), so that the original pyrimidine could be separated from its carbamate, m.p. 73° (hexane); ir: 3300 (NH) and 1740 ($COOC_2H_5$); nmr (deuteriochloroform): 7.7 (s, NH, 1H), 6.9 (s, H-5, 1H), 4.1 (q, CH_2, 2H), 3.8 (d, OCH_3, 6H), 1.2 (t, CH_3, 3H).

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.58; H, 5.76; N, 18.49; O, 28.17. Found: C, 47.63; H, 5.73; N, 18.38; O, 27.97.

Acknowledgement.

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