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A NOVEL RING TRANSFORMATION OF 5-ACYLAMINOURACILS AND 5-ACYLAMINO-PYRIMIDIN-4(3H)-ONES INTO IMIDAZOLES

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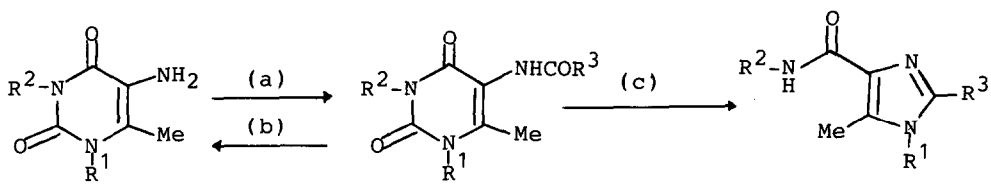
Summary 1,3-Disubstituted 5-acylamino-6-methyluracils (**2a-e**) were transformed into 1,2-disubstituted 4-alkylcarbamoyl-5-methyl-1H-imidazoles (**3a-e**) by treatment with 5% aqueous sodium hydroxide in ethanol. Similarly, reaction of 5-acylamino-6-methyl-3-phenyl-4-(3H)-pyrimidinones (**5a-d**) with 5% aqueous sodium hydroxide in ethanol gave 2-substituted 5-methyl-4-phenylcarbamoyl-1H-imidazoles (**6a-d**).

Pyrimidines are important material for the synthesis of a number of compounds which have potential biological activities, and various reactions have been studied.[1] We previously studied the ring transformation of 5-amino-4(3H)-pyrimidinones into imidazoles by the reaction with nitrous acid.[2] We now report a novel ring transformation of 5-acylaminouracils and 5-acylamino-4(3H)-pyrimidinones into imidazoles by the reaction with aqueous sodium hydroxide.

Although deacylation of 5-acetylamino-3,6-dimethyl-1-phenyluracil[3] (**2a**) with 5% hydrochloric acid proceeded to give 5-amino-3,6-dimethyl-1-phenyluracil[4] (**1a**), a novel ring transformation was observed when hydrolysis of **2a** was carried out with 5% aqueous sodium hydroxide. Namely, the reaction gave 2,5-dimethyl-4-methylcarbamoyl-1-phenyl-1H-imidazole (**3a**) in 81% yield, whose chemichal structure was determined by IR, ^{1}H-NMR and mass spectra as well as elemental analyses. Further confirmation was carried out by X-ray crystallographic analysis[5] (Fig. 1). Similarly, treatment of 1,3-disubstituted 5-acylamino-6-methyluracils[3] (**2b-e**) with 5% aqueous sodium hydroxide gave 1,2-disubstituted 4-alkylcarbamoyl-5-methyl-1H-imidazoles (**3b-e**)(Table I). The formation of these imidazoles from acylaminouracils seems to proceed by the reaction mechanism illustrated in Scheme 3. Similar transformation of 5-acylamino-6-methyl-3-phenyl-4(3H)-pyrimidinones[6] (**5a-d**) to 2- substituted 5-methyl-4-phenylcarbamoyl-1H-imidazoles (**6a-d**) was

carried out as illustrated in Scheme 2. Since **2** and **5** are readily available by the acylation of 1,3-disubstituted 5-amino-6-methyluracils[4] or 5-amino-6-methyl-3-phenyl-4(3H)-pyrimidinones[7], the ring transformation reaction above provides a convenient method for the synthesis of imidazoles.

A typical experimental procedure is as follows: A solution of 1,3-disubstituted 5-acylamino-6-methyluracils[3] (**2a-e**) or 5-acylamino-1-phenyl-6-methyl-4(3H)-pyrimidinones[6] (**5a-d**) (1 mmol) in a mixture of 5% aqueous sodium hydroxide (5 ml) and ethanol (30 ml) was refluxed for 3 h. Solvent was distilled off. Water was added to the residue to give crystals. When crystals were not obtained, the solution was neutrallized with 5% hydrochloric acid and extracted with chloroform. Evaporation of chloroform and recrystlliza-tion of the resulted solid from benzene gave 1,2-disubstituted 4-alkylcarbamoyl-5-methyl-1H-imidazoles (**3a-e**) (Table I) or 2-substituted 5-methyl-4-phenylcarbamoyl-1H-imidazoles (**6a-d**)(Table II).



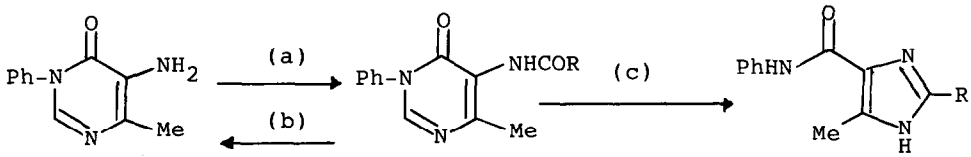
1a-e 2a-e 3a-e

(a): Ac_2O or benzoyl chloride, (b): 10% HCl-EtOH (1:1), (c): 5% NaOH/EtOH

Scheme 1

Table I. 1,2-Disubstituted 4-Alkylcarbamoyl-5-methyl-1H-imidazoles (**3a-e**)

Compound	R^1	R^2	R^3	Yield (%)	Mp (°C)	Molecular Formula	MS m/z (M^+)
3a	Ph	Me	Me	81	154-156	$C_{13}H_{15}N_3O$(229.27)	229
3b	Me	Ph	Me	70	171-173	$C_{13}H_{15}N_3O$(229.27)	229
3c	Me	Ph	Ph	73	164-166	$C_{18}H_{17}N_3O$(291.34)	291
3d	Me	Me	Me	44	169-170	$C_8H_{13}N_3O$ (167.21)	167
3e	Ph	Me	Ph	34	220-221	$C_{18}H_{17}N_3O$(291.34)	291



4 5a-d 6a-d

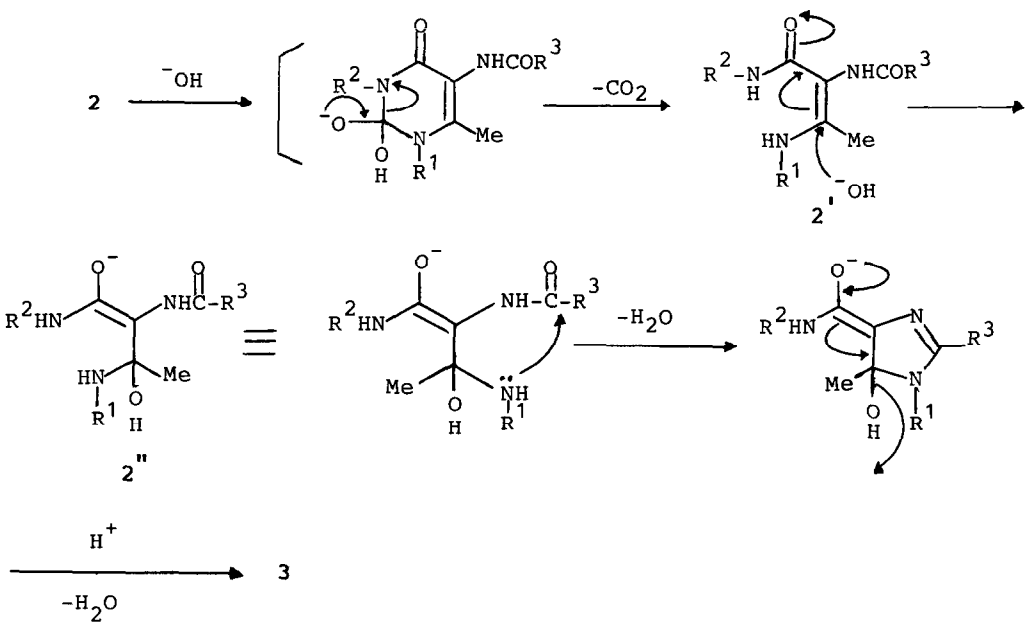
(a): Ac_2O, benzoyl chloride, propionyl chloride or butyryl chloride,
(b): 10% HCl-EtOH (1:1), (c): 5% NaOH/EtOH

Scheme 2

Table II. 2-Substituted 5-Methyl-4-phenylcarbamoyl-1H-imidazoles (6a-d)

Compound	R	Yield (%)	Mp (°)	Molecular Formula	MS m/z (M^+)
6a	Me	81	152-154	$C_{12}H_{13}N_3O$(215.25)	215
6b	Ph	84	226-229	$C_{17}H_{15}N_3O$(277.31)	277
6c	Et	57	150-151	$C_{13}H_{15}N_3O$(229.27)	229
6d	Pr	51	179-181	$C_{14}H_{17}N_3O$(243.30)	243

Reaction Mechanism: The formation of imidazoles from acylaminouracils seems to proceed as follows. Initially a pyrimidine ring opening will take place by the nucleophilic attack of a hydroxy anion to a C2-carbonyl group to give **2'**, which will undergo further nucleophilic attack of a hydroxy anion to form **2"**. Successive dehydration will give imidazoles **3**.



Scheme 3

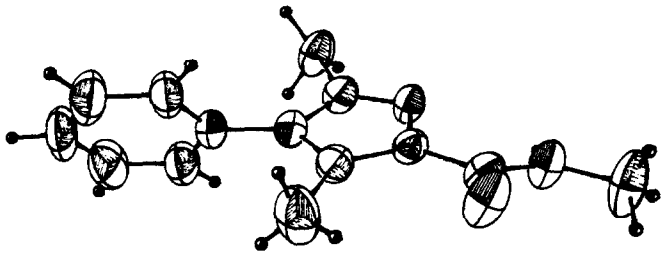


Fig. 1 ORTEP Drawing of **3a**

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References and Notes

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2) T. Ueda and J. Sakakibara, Chem. Pharm. Bull., **32**, 2863 (1984).

3) Compounds **2a-e** were prepared by the acylation of **1a-e** in 37-86% yields.

4) S. Senda, K. Hirota, and K. Banno, J. Med. Chem., **15**, 471 (1972).

5) Crystal data: monoclinic, space group $P2_1/c$, a=8.784(6), b=16.217(7), c=9.466(3) A, =108.17(5)°, v=1281.190(2) A^3, z=4. All data were collected on Enraf-Nonius CAD4 diffractometer using Mo-K radiation and a graphite monochrometer. The structure was solved by direct methods and refined by least-squares to a R factor of 0.065 for 2345 reflections.

6) Synthesis of 5-Acetylamino-6-methyl-3-phenyl-4(3H)-pyrimidinone (**5a**) was reported previously: T. Ueda, J. Sakakibara, and J. Nakagami, Chem. Pharm. Bull., **31**, 4263 (1983). Compounds **5b-d** were prepared in 72-86% yields.

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