THE REACTION OF β-AMINOENONES WITH N-SUBSTITUTED UREAS

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The reaction of 2-amino-2-hepten-4-one with N-substituted ureas was described as well as 2,4-heptanedione. When the product ratios from both compounds were compared, β-aminoenones were concluded to react selectively. Also the selectivity was depend on the basicity of nitrogen of ureas.

2(1H)-Pyrimidinones are the quite interesting models related to the nucleic acids. Also 2(1H)-pyrimidinones are important intermediates in the synthesis of β-diamines.[1] It has been reported that these pyrimidinones are prepared from β-diketones and ureas in the presence of acid. For example, 2,4-pentanedione gives 1,4,6-trimethyl- (1)[2] and 1-phenyl-4,6-dimethyl-2(1H)-pyrimidinone (2)[3] by the treatment with N-methylurea and N-phenylurea, respectively. However, the two isomers are expected to be obtained from N-substituted urea and unsymmetric β-diketones. We now study the selective synthesis of 2(1H)-pyrimidinones.

Firstly, considering the shieldi g effect of phenyl group of 2, methyl group at C-6 position should be shifted. The methyl signals of 1 appeared at δ 2.33 (singlet) and 2.38 ppm (doublet), while those of 2 appeared at δ 2.40 (singlet) and 1.98 ppm (doublet), listed in Table 1. From these data, the doublet signals were assigned to be the methyl group at C-6 position. Therefore, the peak intensity ratio of C-4 and C-6 methyl protons gave the isomer ratio of 4-methyl- and 6-methyl-2(1H)-pyrimidinones.

Secondly, the reaction of N-methylurea and 2,4-heptanedione (3) was carried out in ethanol to give 1,4-dimethyl-6-propyl- (4) and 1,6-dimethyl-4-propyl-2(1H)-pyrimidinone (5). Unfortunately, the compound 4 and 5 could not separate. But the isomer ratio of 4 and 5 was found to be 1 : 0.90 from the nmr spectrum. This ratio was supported by the fact that the enol form of 3 was considered to be 1 : 1 ratio mixture of 4-hydroxy-3-hepten-2-one and 2-hydroxy-2-hepten-4-one. The nucleophiles such as Grignard reagents[4] attack regioselectively on the β-carbon of β-aminoenones, which is isoelectronic with the enol form of β-diketones. But the β-aminoenones are easily hydrolyzed to β-diketones in the presence of acid in protic solvents. Therefore, N-methylurea and 2-amino-2-hepten-4-one (6)[5] were treated in anhydrous benzene in the presence of dry hydrogen chloride. The product ratio of 4 and 5 was 1 : 2.0. Comparing with the basicity of methylamine and ammonia, the more basic nitrogen of urea prefers to attack on the β-carbon of 6 and then cyclized to pyrimidinones.

Since benzoylacetone (7) is considered to be 1-phenyl-1-hydroxy-1-buten-3-one, the main product of the reaction of 7 and N-methylurea was expected to be 6-phenyl-1,4-dimethyl-2(1H)-pyrimidinone (8). Indeed, the product ratio of 8 and 4-phenyl-1,6-dimethyl-2(1H)-pyrimidinone (9) was found to be 1 : 0.095. The compound 8 (mp 181.5-182.5°) and 9 (mp 180-182°C) were separated by the fractional recrystallization. On the contrary, 1-phenyl-3-amino-2-buten-1-one (10) gave 8 and 9 with the ratio of 1 : 0.42. In the same way, 3 and 6 were treated with N-phenylurea to give 1-phenyl-4-methyl-6-propyl- (11) (mp 126-127.5°C) and 1-phenyl-4-propyl-6-methyl-2(1H)-pyrimidinone (12) (mp 165-166°C), which were separated by silica gel column chromatography. The product ratios of 11 and 12 were 1 : 2.1 and 1 : 0.8, respectively.

From these results, the reaction of urea and β-diketones is concluded to be controled by the enol form of β-diketones and the basicity of the ureas. Since the β-aminoenones can prepare in a pure isomeric form, the reaction is also concluded to be controled selectively in the synthesis of the unsymmetric 2(1H)-pyrimidinones.

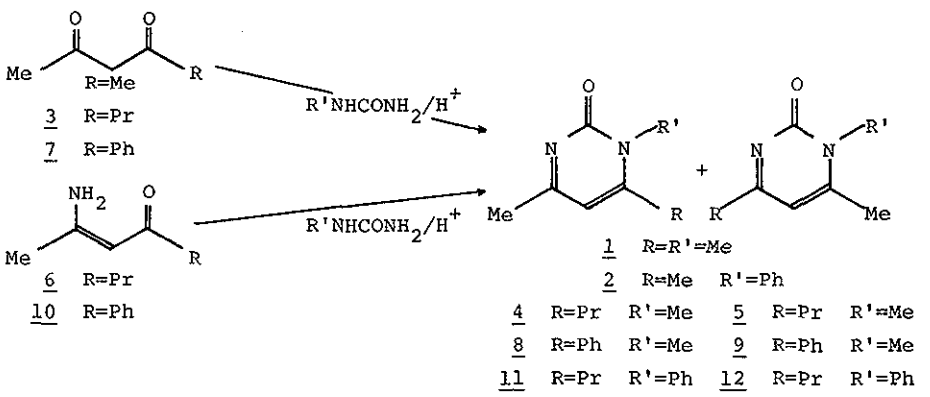

Table 1

Compound	R	R'	δ of C-4 Methyl	δ of C-6 Methyl
1	Me	Me	2.33 (s)	2.38 (d, J=0.7)
2	Me	Ph	2.40 (s)	1.98 (d, J=0.7)
4	Pr	Me	2.34 (s)	——
5	Pr	Me	——	2.40 (d, J=0.7)
8	Ph	Me	2.40 (s)	——
9	Ph	Me	——	2.42 (d, J=0.7)
11	Pr	Ph	2.41 (s)	——
12	Pr	Ph	——	1.98 (d, J=0.7)

Table 2

Compound	R	X	Isomer Ratio	Products Ratio	
3	Pr	OH	50 : 50	1 : 0.90	1 : 2.1
6	Pr	NH_2	0 : 100	1 : 2.0	1 : 0.80
7	Ph	OH	100 : 0	1 : 0.095	——
10	Ph	NH_2	0 : 100	1 : 0.42	——

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