Reaction of 1-Phenyl-2-methylamino-3-hydroxy-3-(p-bromophenyl)propan-1-one Hydrochloride with Acetonitrile. A 2.7-g (10 mmole) sample of the amino hydroxy ketone and 10 ml (200 mmole) of dry acetonitrile were placed in an ampul, the contents were purged with argon, and the ampul was sealed and heated at 100°C for 15 h. It was then opened, and the hydrochloride was precipitated with ether and removed by filtration. p-Bromobenzaldehyde was not detected in the solution by TLC.

Deuteration of trans-1,2-Dimethyl-4-(p-bromophenyl)-5-benzoyl-2-imidazoline (XXII). A 0.1-g sample of imidazoline XXII and 0.03 g of sodium methoxide were placed in an ampul and dissolved in 1 ml of deuteromethanol. After 10 min, the degree of conversion was 90%. The deuterium exchange was monitored from the PMR spectra.

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PYRIMIDINES.

73.* SYNTHESIS OF ACETYLPYRIMIDINES

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UDC 547.853.1:542.957.2

It is shown that the use of benzene as the solvent in the preparation of 2- and 4-acetylpyrimidines from cyanopyrimidines via the Grignard reaction makes this reaction a practical method for the preparation of pyrimidinyl ketones. Preparatively convenient methods for the preparation of 4-acetylpyrimidine from 4-ethylpyrimidine through the α-oximino derivative and 5-acetylpyrimidine from 4,6-dichloro derivatives of pyrimidine are proposed.

Up until now, little study has been devoted to ketones of the pyrimidine series, which are not very easy to obtain. They are primarily obtained via the Grignard reaction from cyanopyrimidines or by homolytic acylation [2]. Although a related series, viz., acetylpyrimidines, has been described in the literature, experimental data are not available in all cases; in addition, the syntheses are multistep processes and give the products in low

*See [1] for communication 72.

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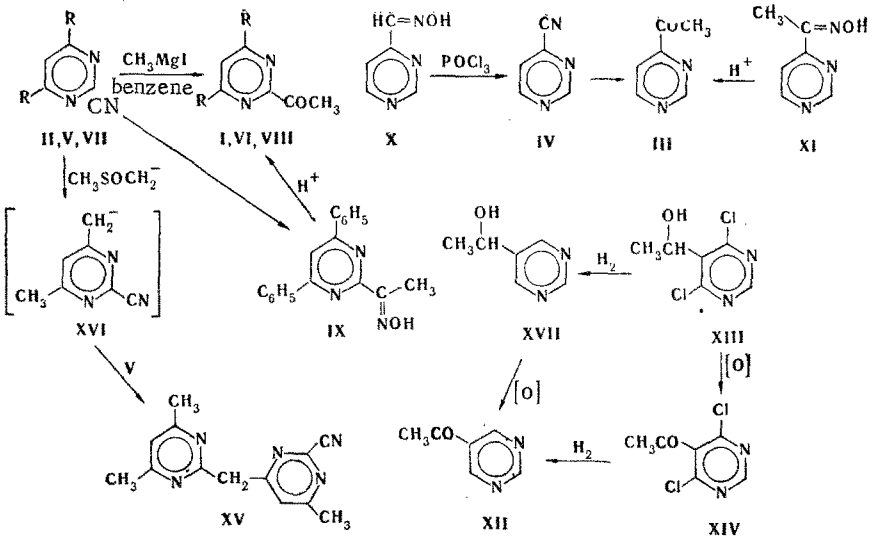
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 958-962, July, 1981. Original article submitted October 13, 1980.

0009-3122/81/1707-0710$07.50

yields. This is particularly the case for pyrimidines with an acetyl group in the 2 position. Thus contradictory data exist relative to unsubstituted 2-acetylpyrimidine (I): Cervinka and co-workers [3] report the preparation of I without presenting the experimental conditions and cite [4], in which ketone I was not obtained by the reaction of 2-cyanopyrimidine (II) and methylmagnesium iodide in ether. A limited number of 4,6-disubstituted 2-acetylpyrimidines have been synthesized in 7-38% yields via homolytic acylation [2, 5]. The preparation of 4-acetylpyrimidine (III) from 4-cyanopyrimidine (IV) by the reaction with a Grignard reagent in ether was described in several papers [3, 4, 6]; at 20°C [4] the yield of ketone III was only 20%, whereas, according to patent data [6], the compound was obtained in 53% yield at −10 to 15°C. The poor reproducibility when this reaction is carried out in ether and the extremely cumbersome method for the preparation of starting nitrile IV [4] make this method preparatively inconvenient.

It has been noted that better yields are sometimes obtained in the preparation of ketones from nitriles by means of the Grignard reaction when benzene rather than ether is used as the solvent [7, 8]. In fact, we obtained 2-acetylpyrimidine in 50% yield by the reaction of nitrile II in benzene with an ether solution of methylmagnesium iodide at 20°C. 2-Acetyl-4,6-dimethylpyrimidine (VI) was obtained smoothly and in high yield (86%) when 2-cyano-4,6-dimethylpyrimidine (V) was subjected to this reaction. Ketone VI was obtained in 38% yield in [5] by homolytic acylation. Rapid darkening of the reaction mixture was observed when 2-cyano-4,6-diphenylpyrimidine (VII) was heated with methylmagnesium iodide in benzene with subsequent decomposition with water, and, although the formation of the ketone was always established by chromatography, its yield varied markedly (0-50%). However, ketone VIII can be readily isolated from the reaction mixture in 70% yield in the form of oxime IX.

In [4] one of the unsuccessful features in the synthesis of 4-acetylpyrimidine from nitrile IV was the preparation of the latter from 4-methylpyrimidine through the carboxylic acid, which readily undergoes decomposition during isolation. We have shown that by using 4-methylpyrimidine as the precursor, nitrile IV is more conveniently obtained by dehydration of the corresponding oxime X, i.e., by the usual method that has been well developed in the aromatic series. We further showed that cyanopyrimidine IV on reaction in benzene with an ether solution of methylmagnesium iodide forms ketone III in a yield that is twice the yield obtained in ether under the same conditions [4]. However, we assumed that the hydrolysis of 4-(α-oximino) ethylpyrimidine (XI), which is readily obtained from the accessible 4-ethylpyrimidine [9], may be the simplest and most rapid method for the preparation of acetylpyrimidine III. In tests of the various methods we found that in the case of hydrolysis with concentrated HCl the yield of the ketone is only 14%, and only oxidative hydrolysis with nitrous acid [10] made it possible to obtain 4-acetylpyrimidine in yields higher than 60%.



I, II R=H; V, VI R=CH_3; VII, VIII R=C_6H_5

According to the data in [11], the synthesis of 5-acetylpyrimidine (XII) is realized by dechlorination of 2,4-dichloro-5-acetylpyrimidine. As a result, the overall yield of

the five-step synthesis on the basis of acetoacetic ester through 5-acetyluracil, which is obtained in 30% yield, is only 5%. We have shown that the synthesis of pyrimidine XII through 4,6-dichloro-5-(α-hydroxyethyl)pyrimidine (XIII) via its dechlorination and subsequent oxidation is more convenient and less time-consuming and gives the product in ∿30% overall yield (based on malonic ester). Reversing the order of the last two steps (initial oxidation of XIII and subsequent dechlorination of XIV) gives ketone XII in lower yield.

Thus we have proposed preparatively convenient methods for the preparation of isomeric acetylpyrimidines in 50-80% yields.

An attempt to use the modified method for the synthesis of ketones from nitriles through the imino sulfoxides [12] for the preparation of 2-acetylpyrimidines was unsuccessful. In the case of acetylpyrimidine I starting nitrile II vanished in the reaction mixture after 1 h, but we were unable to isolate the individual reaction products. Cyanopyrimidine VII reacts with the methylsulfinyl carbanion (the dimsyl anion) much more slowly, and up to 50% of starting compound can be isolated from the reaction mixture even after 3 h. As in the preceding case, the corresponding ketone was not found, and only 2-hydroxy-4,6-diphenylpyrimidine was obtained in low yield [13]. Dipyrimidinylmethane XV was obtained rather than ketone VI in the reaction of nitrile V with the dimsyl anion. Pyrimidine V, being a conjugated electrophile, can undergo nucleophilic attack at several centers, and it may be assumed that the dimsyl anion upon reaction with methylpyrimidine V does not attack it at the carbon atom of the nitrile group but, displaying the properties of a hard base, reacts with the proton of the activated CH_3 group to give pyrimidinylmethyl anion XVI. The latter may either add to the C≡N group or replace it via aromatic nucleophilic substitution, depending on the acceptor capacity of the substrate and the solvating properties of the medium. Similar transformations with the formation of arylpyridylmethanes have also been described for pyridylmethyl anions in the reaction of the latter with cyano- or fluorobenzonitriles [14]. Favorable conditions for alkylation are also present for the sufficiently electron-acceptor pyrimidine ring in the case under consideration.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60A spectrometer with hexamethyldisiloxane as the internal standard. The molecular masses were determined by mass spectrometry with a high-resolution MS-902 spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a $CHCl_3$—alcohol system (30:1).

2-Acetylpyrimidine (I). A 5-ml (12.5 mmole) sample of a 2.5 N solution of CH_3MgI in ether was added at 4-5°C in the course of 20 min to a solution of 1.05 g (10 mmole) of cyanopyrimidine II [15] in 30 ml of absolute benzene, and the mixture was maintained at 20°C for 30 min. It was then poured into 100 ml of ice water with vigorous stirring, and the aqueous mixture was acidified with 10 ml of 10% HCl and allowed to stand for 10 min. The benzene was separated, and the aqueous solution was neutralized to pH 7 with solid $NaHCO_3$ and extracted with CH_2Cl_2 (six 25-ml portions). The extract was dried with $MgSO_4$ and evaporated to give 1.17 g of crude pyrimidine I, which darkened rapidly on standing. It was sublimed at 100-110°C (2-3 mm) to give 0.6 g (49%) of the ketone in the form of white needles with mp 52°C (mp 52°C [3]) and R_f 0.11. UV spectrum, λ_{max} (log ε): 218 (4.02) and 290 nm (2.50). PMR spectrum ($CDCl_3$): 2.72 (3H, s, CH_3), 7.49 (1H, t, 5-H of the pyrimidine ring, $J_{5-4,6}$ = 5 Hz), and 8.90 ppm (2H, d, 4,6-H of the pyrimidine ring, $J_{4,6-5}$ = 5 Hz).

2-Acetyl-4,6-dimethylpyrimidine (VI). A 24-ml (0.06 mole) sample of a 2.5 N solution of CH_3MgI in ether was added with ice cooling in the course of 30 min to a solution of 3 g (0.023 mole) of cyanopyrimidine V [16] in 120 ml of absolute benzene, after which the mixture was refluxed for 4 h, cooled, and poured with stirring over 150 g of finely crushed ice. The benzene was separated, and the aqueous layer was acidified with 25 ml of 4 N HCl. It was then neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (six 50-ml portions), the organic layer was dried with $MgSO_4$ and evaporated, and the resulting yellow oily product was extracted with hot hexane (four 20-ml portions). The hexane was evaporated to give 2.90 g (86%) of a colorless crystalline product that readily sublimed at 120-140°C (3 mm) to give a substance with mp 39-41°C [bp 70-72°C (3 mm) [2, 5]] and R_f 0.30. Found: C 64.3; H 6.87; N 18.9%. $C_8H_{10}N_2O$. Calculated: C 64.0; H 6.67; N 18.7%. IR spectrum ($CHCl_3$): 1718 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 236 nm (3.87). PMR spectrum (CCl_4): 2.73 (6H, s, CH_3), 2.82 (3H, s, CH_3CO), and 7.40 ppm (1H, s, 5-H of the pyrimidine ring).

2-Acetyl-4,6-diphenylpyrimidine (VIII). A) A 4-ml (10 mmole) sample of a 2.5 N solution of CH_3MgI in ether was added with ice cooling in the course of 20 min to a solution of 1.29 g (5 mmole) of cyanopyrimidine VII [17] in 80 ml of absolute benzene, after which the mixture was stirred at 20°C for 25 min and refluxed for 5 h (until starting VII, with R_f 0.57 vanished, according to TLC). The mixture was then cooled and poured with stirring into cold 1 N HCl, and the benzene layer was separated. The aqueous layer was neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$ (two 50-ml portions). The extract was dried with $MgSO_4$ and evaporated, and the resulting dark oily product began to crystallize when ether was added. The precipitate was removed by filtration and washed with ether to give 0.75 g (55%) of ketone VIII with mp 147-150°C (from alcohol) and R_f 0.25. IR spectrum (KBr): 1710 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 2.84 (3H, s, CH_3), 7.42-7.70 (6H, m, aromatic m- and p-H), and 8.25-8.40 ppm (5H, aromatic o-H and pyrimidine ring 5-H). Found: C 79.2; H 5.29; N 10.1%. $C_{18}H_{14}N_2O$. Calculated: C 79.0; H 5.12; N 10.2%.

B) A 0.5-g sample of oxime IX was refluxed with 3 ml of concentrated HCl until it dissolved (after 2-3 h), and the solution was cooled and neutralized with dry $NaHCO_3$ and filtered to give 0.3 g of ketone VIII with mp 145-149°C.

2-(α-Oximinoethyl)-4,6-diphenylpyrimidine (IX). The reaction mixture obtained by a method similar to that in the preceding experiment was refluxed for 2.5 h, after which it was cooled and poured into a cold solution of 10 g of $NH_2OH \cdot HCl$ in 30 ml of water with vigorous stirring. The precipitate was separated and washed successively with alcohol, benzene, and alcohol to give 1.02 g (70%) of oxime IX with mp 260-262°C (from alcohol) and R_f 0.60 [$CHCl_3$—alcohol (10:1)]. Found: N 14.5%; M 289. $C_{18}H_{15}N_3O$. Calculated: N 14.5%; M 289.

4-Acetylpyrimidine (III). A) A suspension of 5 g (0.036 mole) of oximinoethylpyrimidine XI [18] in 100 ml of HCl (1:1) was stirred for 15 min, after which it was cooled to 0°C and treated with a solution of 20 g of $NaNO_2$ in 30 ml of water in the course of 4 h. The mixture was allowed to stand overnight, after which it was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (six 50-ml portions). The extract was dried with $MgSO_4$ and evaporated, and the residue was sublimed at 70°C (3 mm) to give 3 g (67%) of ketone III with mp 65-67°C (mp 67°C [3, 4]) and R_f 0.48. IR spectrum (KBr): 1710 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 2.67 (3H, s, CH_3), 7.93 (1H, d, pyrimidine ring 5-H, J_{5-6} = 5 Hz), 9.03 (1H, d, pyrimidine ring 6-H, J_{6-5} = 5 Hz), and 9.44 ppm (1H, s, pyrimidine ring 2-H). UV spectrum, λ_{max} (log ε): 202 (3.98) and 264 nm (3.60).

B) A 5-ml (12.5 mmole) sample of a 2.5 N solution of CH_3MgI in ether was added dropwise in the course of 10 min to a cooled (to 5°C) solution of 1.05 g (10 mmole) of cyanopyrimidine IV in 30 ml of absolute benzene, and the yellow-green suspension was stirred for 45 min without cooling. The mixture was then poured with stirring over 100 g of ice, and 10 ml of 4 N $NaHCO_3$ solution was added. The benzene was separated, and the aqueous layer was allowed to stand for 10 min, after which it was neutralized with solid $NaHCO_3$ and extracted with methylene chloride (six 30-ml portions). The extract was dried with $MgSO_4$ and evaporated to give 0.6 g (49%) of light-yellow crystalline ketone III, which was identical to the product obtained in experiment A.

4-Cyanopyrimidine (IV). A 37-ml sample of $POCl_3$ was added to a suspension of 20 g (0.163 mole) of pyrimidine-4-aldoxime [19] in 100 ml of $CHCl_3$, after which the excess solvent was removed by vacuum distillation, ice was added to the residue, and the mixture was triturated thoroughly. The resulting solution was neutralized and evaporated, and the residue was separated with a column filled with silica gel (elution with chloroform). The fractions that gave one spot with R_f 0.46 [chloroform—alcohol (10:1)] on a Silufol UV-254 plate were evaporated to give 6.8 g (40%) of a light-yellow oil that crystallized rapidly. Sublimation at 60°C (5 mm) gave a product with mp 31-32°C (mp 31°C [3, 4]).

5-Acetylpyrimidine (XII). A) From 4,6-Dichloro-5-acetylpyrimidine (XIV). A solution of 0.1 g (0.52 mmole) of pyrimidine XIV [20] in 5 ml of alcohol was hydrogenated in the presence of 0.05 g of 10% Pd/C and 0.05 g of MgO for 8 h, after which the precipitate was removed by filtration and washed with alcohol, and the alcohol solutions were evaporated. The residual oil was dissolved in 4 ml of water, and the solution was neutralized with 4 N HCl and extracted with ether (five 4-ml portions). The ether solutions were dried with $MgSO_4$ and evaporated, and the residue was sublimed at 70°C (2 mm) to give 0.022 g (34%) of ketone XII with mp 87-88°C (mp 88°C [11]) and R_f 0.57. IR spectrum (KBr): 1700 cm^{-1} (C=O) US spectrum, λ_{max} (log ε): 222 (4.11), 289 nm (2.75). PMR spectrum ($CDCl_3$): 2.62 (3H, s, CH_3), 9.20 (2H, s, pyrimidine ring 6-H), and 9.36 ppm (1H, s, pyrimidine ring 2-H).

B) From 5-(α-Hydroxyethyl)pyrimidine (XVII). A solution of 6.5 g (0.034 mole) of pyrimidine XIII [20] in 110 ml of absolute alcohol was hydrogenated in the presence of 1.3 g of 10% Pd/C and 3.25 g of MgO with gentle refluxing until hydrogen absorption ceased (∿12 h). The precipitate was removed by filtration and washed with alcohol, and the solutions were evaporated. The residue was dissolved in 150 ml of water, and the solution was acidified to pH 5 with 4 N HCl and extracted with hot chloroform for 24 h. The chloroform solution was dried with $MgSO_4$ and evaporated to give 3.33 g (79%) of pyrimidine XVII in the form of a colorless oil, which was subsequently used without additional purification. According to the data in [3], this compound has bp 90°C (0.1 mm). PMR spectrum ($CDCl_3$): 1.50 (3H, d, CH_3, J_{CH_3-H} = 6 Hz), 5.00 (1H, q, $\diagdown\!\!\diagup CH$, J_{CH-CH_3} = 6 Hz), 5.44 (broad, 1H, OH), 8.75 (2H, s, pyrimidine ring 4,6-H), and 9.0 ppm (1H, s, pyrimidine ring 2-H). A mixture of 3.23 g (0.026 mole) of alcohol XVII and 30 g of active MnO_2 was stirred for 3 h in 250 ml of methylene chloride, and the resulting precipitate was removed by filtration and washed repeatedly with methylene chloride. The combined solutions were evaporated to give 2.33 g (73%) of colorless crystalline pyrimidine XII, which was identical to the compound obtained in experiment A.

2'-Cyano-4,4',6-trimethyl-2,4'-dipyrimidinylmethane (XV). A 0.24-g (10 mmole) sample of NaH was dissolved with stirring in 10 ml of absolute DMSO until hydrogen evolution ceased and a homogeneous greenish mass formed while maintaining a bath temperature of ∿70°C. The mixture was then cooled with cold water and treated dropwise with stirring with a solution of 1.33 g (10 mmole) of cyanopyrimidine V in 8 ml of absolute DMSO. The reaction mixture immediately turned dark-red. The mixture was cooled for 30 min, after which it was poured over 200 g of ice, and the aqueous mixture was neutralized with concentrated HCl and extracted with ether (six 50-ml portions). The extract was washed with water (three 150-ml portions), dried with $MgSO_4$, and evaporated to give 1.13 g (94%) of dipyrimidinylmethane XV with R_f 0.11 and mp 99-100°C (from hexane). PMR spectrum ($CDCl_3$): 2.38 (6H, s, 4,6-CH_3), 2.48 (3H, s, 4'-CH_3), 4.33 (2H, s, CH_2), 6.92 (1H, s, pyrimidine ring 5-H), and 7.34 ppm (1H, s, pyrimidine ring 5'-H). Found: C 63.5; H 5.4; N 29.2%; M 239. $C_{13}H_{13}N_5$. Calculated: C 65.4; H 5.5; N 29.3%; M 239.

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