[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE REACTION OF AMIDINES WITH α,β-UNSATURATED KETONES

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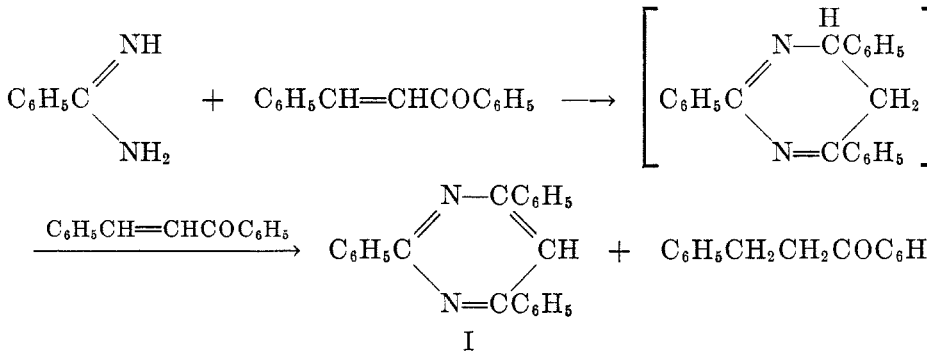
Even though the synthesis of pyrimidines has been extensively studied, their preparation by the reaction of amidines with simple α,β-unsaturated ketones has been neglected. Traube and Schwarz (1), in 1899, reported the condensation of mesityl oxide with benzamidine and with guanidine to yield 2-phenyl-4,4,6-trimethyl-4,5-dihydropyrimidine and 2-amino-4,4,6-trimethyl-4,5-dihydropyrimidine respectively. When these same bases were condensed with benzalacetone, acrolein, or cinnamaldehyde, no crystalline products were obtained. We have found that benzamidine will condense readily with α,β-unsaturated ketones of the type $C_6H_5CH{=}CHCOR$, where R does not possess an α-hydrogen, to give 6-substituted-2,4-diphenylpyrimidines. For example, the condensation of benzamidine with benzalacetophenone in an alcoholic solution of potassium hydroxide gave 2,4,6-triphenylpyrimidine in good yield.

Since the compound expected from the condensation of benzamidine with benzalacetophenone would be a dihydropyrimidine, it was apparent that oxidation of this intermediate had occurred. In fact, the yield of 2,4,6-triphenylpyrimidine obtained from the condensation of equimolar amounts of benzamidine and benzalacetophenone in an alcoholic solution of potassium hydroxide was



raised from 37% to 61% by passing dry air through the reaction mixture while it was heated under reflux. By the use of two equivalents of benzalacetophenone and omission of the stream of air, the yield of 2,4,6-triphenylpyrimidine was raised to 85%. From the residue remaining after the extraction of the pyrimidine, benzylacetophenone was isolated in 87% yield. It is, therefore, apparent that the excess benzalacetophenone accepted two atoms of hydrogen from the dihydropyrimidine and was thus reduced to benzylacetophenone. This parallels the reduction of benzalacetophenone to benzylacetophenone in the Chichibabin reaction as recently reported by Frank and Steven (2).

[1] From the Master's Thesis of Jay K. Seyler, June, 1950.

Excess potassium hydroxide is needed in this condensation. When one molar equivalent of benzamidine hydrochloride dihydrate and two molar equivalents of benzalacetophenone were treated with one molar equivalent of potassium hydroxide in alcohol and with a stream of air, the yield of 2,4,6-triphenylpyrimidine was only 16%. Doubling the quantity of potassium hydroxide raised the yield to 85% even without the use of a stream of air. The potassium hydroxide cannot be effectively replaced with sodium bicarbonate. It is probable that the dehydrogenation of the dihydropyrimidine proceeds by means of the Michael addition of the dihydropyrimidine to benzalacetophenone followed by a reverse Michael to give the pyrimidine and benzylacetophenone. This possibility will be studied in the future.

The structure of the pyrimidine (I) was established by analysis and by comparison of its properties with those previously reported for 2,4,6-triphenylpyrimidine (3, 4). In order to be certain that the compound obtained was not a dihydropyrimidine, it was also prepared by the condensation of benzamidine with α-bromobenzalacetophenone and with benzalacetophenone dibromide. In these instances, any dihydropyrimidine formed would contain bromine. The products obtained, however, were identical in all respects with that obtained from benzalacetophenone. Anker and Cook (3) reported that 2,4,6-triphenylpyrimidine could not be prepared by the condensation of benzamidine with dibenzoylmethane; they used the reaction of 2,4-diphenyl-6-chloropyrimidine with phenylmagnesium bromide for its preparation.

To further confirm the transfer of hydrogen from the dihydropyrimidine to the α,β-unsaturated ketone, two equivalents of benzal-β-acetonaphthone were condensed with benzamidine in an analogous manner. An 85% yield of 2,4-diphenyl-6-β-naphthylpyrimidine and a 61% yield of β-phenylethyl β-naphthyl ketone were obtained.

Benzamidine was also condensed successfully with benzal-α-acetonaphthone, benzal-*p*-phenylacetophenone, benzalpinacolone, and benzalpropiophenone. The products from these reactions were formulated by analogy with that obtained from benzalacetophenone; they are listed in Table I. The yields were relatively low in several cases. With benzamidine and cinnamaldehyde or styryl ethyl ketone only uncrystallizable gums were obtained. With benzalacetone, *m*-nitrobenzalacetone, dibenzalacetone, α-bromocinnamaldehyde, benzalacetone dibromide, and styryl isopropyl ketone solid products were obtained and sometimes in good yield, but they lacked the properties of the pyrimidines and proved difficult to purify. Benzalacetomesitylene also failed to react; only starting material was isolated. Apparently, attack on the carbonyl group is sterically hindered in this instance.

In the condensation of benzalpropiophenone with benzamidine, it proved necessary to bubble a stream of dry air through the reaction mixture in order to obtain the 2,4,6-triphenyl-5-methylpyrimidine, m.p. 179–179.5°. In the absence of air in methanol solution, a product, m.p. 148–150°, was isolated which was probably the dihydropyrimidine. The quantity of low-melting material obtained and the difficulty of purifying it prevented identification.

Attempts were also made to use S-alkylisothioureas in place of benzamidine in these condensations. Because of the instability of the S-alkylisothioureas in alkaline solutions, these reactions were only partially successful. Thus, S-benzylisothiourea could be condensed with benzalacetophenone or benzalacetophenone dibromide to give 2-benzylthio-4,6-diphenylpyrimidine in low yield. With benzalacetophenone, β-benzylthio-β-phenylpropiophenone was formed when sodium bicarbonate was used as the base.

EXPERIMENTAL[2]

2,4,6-Triphenylpyrimidine. To a solution of 4.80 g. (0.025 mole) of benzamidine hydrochloride dihydrate and 10.40 g. (0.050 mole) of benzalacetophenone in 50 ml. of 95% alcohol was added 2.80 g. (0.050 mole) of potassium hydroxide in 50 ml. of alcohol. The resulting mixture was heated under reflux on the steam-bath for three hours. The precipitate, which formed when the reaction mixture was cooled, was thoroughly washed with warm water to remove the inorganic salts, and then with warm alcohol. In this manner 5.86 g. of 2,4,6-triphenylpyrimidine, m.p. 183–185° was obtained. By concentration of the filtrate and crystallization of the residue from glacial acetic acid, an additional 0.84 g. of pyrimidine was obtained; total yield 6.52 g. (85%). Crystallization of this material from glacial acetic acid yielded 5.85 g. (76%) of product, m.p. 183.5–185°.

TABLE I

DESCRIPTION OF PYRIMIDINES

PYRIMIDINE	YIELD, %	M.P., °C.	EMPIRICAL FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
2,4,6-Triphenyl-	85	183.5–185°	$C_{22}H_{16}N_2$	85.7	5.2	—	85.9	5.5	—
2,4-Diphenyl-6-β-naphthyl-	85	153–154°	$C_{26}H_{18}N_2$	87.1	5.1	—	87.3	5.2	—
2,4-Diphenyl-6-α-naphthyl-	7	132–133°	$C_{26}H_{18}N_2$	87.1	5.1	7.8	87.1	5.1	8.2
2,4-Diphenyl-6-*p*-diphenyl-	43	178–179°	$C_{28}H_{20}N_2$	87.5	5.2	7.3	87.1	5.3	7.6
2,4-Diphenyl-6-*tert*-butyl-	50	90–92°	$C_{20}H_{20}N_2$	83.3	7.0	—	83.1	7.2	—
2,4,6-Triphenyl-5-methyl-	8	179–179.5°	$C_{23}H_{18}N_2$	85.7	5.6	—	85.7	6.0	—
2-Benzylthio-4,6-diphenyl-	5	147–148°	$C_{23}H_{18}N_2S$	78.0	5.1	7.9	77.9	5.3	7.9
2-α-Toluenesulfonyl-4,6-diphenyl-	—	199.5–200°	$C_{23}H_{18}N_2O_2S$	71.5	4.7	—	71.4	5.0	—

The acetic acid filtrates from the above crystallizations were combined, diluted with an equal volume of water, and then neutralized with ammonium hydroxide. The oil which formed was separated from the aqueous solution, then extracted several times with hot petroleum ether (b.p. 40–70°). The precipitate which separated when these extracts were cooled was crystallized from methyl alcohol. In this manner 3.5 g. (87%) of crude benzylacetophenone, m.p. 67–70°, was obtained [reported m.p. 72–73° (5)]. The compound was identified by the preparation of its oxime, m.p. 80–82° [reported m.p. 82° (6), 84° (7), and 87° (5)], and its semicarbazone, m.p. 141–143° [reported m.p. 140° (8) and 144° (9)].

2,4,6-Triphenylpyrimidine was also prepared in 59% yield by reacting equimolar amounts of benzamidine hydrochloride dihydrate and α-bromobenzalacetophenone in absolute alcohol containing a three-molar quantity of sodium hydroxide. It was also prepared in 60% yield by a similar method using benzalacetophenone dibromide.

[2] Microanalyses by Mr. Ralph Kelly, Mr. Harry Turner, and Mr. William Cummings.

The method used for the preparation of 2,4,6-triphenylpyrimidine is typical of the method used for the preparation of most of the other compounds.

2,4-Diphenyl-6-β-naphthylpyrimidine, m.p. 153–154°, was obtained in 85% yield by the reaction of β-acetonaphthone with benzamidine hydrochloride dihydrate under conditions similar to those described above.

From the mother liquors a 61% yield of crude, m.p. 83–88°, β-phenylethyl β-naphthyl ketone was obtained. Crystallization of the ketone from methanol gave m.p. 91–92°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.66; H, 6.19.

Found: C, 87.73; H, 6.41.

2,4,6-Triphenyl-5-methylpyrimidine. A solution of 4.80 g. (0.025 mole) of benzamidine hydrochloride dihydrate, 11.1 g. (0.050 mole) of benzalpropiophenone, and 2.80 g. (0.050 mole) of potassium hydroxide in 100 ml. of absolute alcohol was heated under reflux for 3.5 hours and a stream of dry air was passed into the solution during this time. The pyrimidine was isolated as described above. Crystallization of the product from alcohol yielded 0.60 g. (8%) of 2,4,6-triphenyl-5-methylpyrimidine, m.p. 171–179°. The analytical sample recrystallized from alcohol melted at 179–179.5°; reported, m.p. 182° (3).

Omission of the stream of air from this reaction and the use of methanol as the solvent gave, in very low yield, a lower-melting product (m.p. 148–150°) which proved difficult to purify.

2-Benzylthio-4,6-diphenylpyrimidine. A cold (0–5°) chloroform solution of benzalacetophenone dibromide, prepared by the addition of 16 g. of bromine to 15.5 g. of benzalacetophenone in 100 ml. of chloroform, was treated with a solution of 20.2 g. of S-benzylisothiourea hydrochloride in 100 ml. of water and then with a solution of 16.8 g. of potassium hydroxide in 25 ml. of water. The resulting suspension was stirred for three hours while surrounded by an ice-bath, was allowed to warm to room temperature, and finally was heated under reflux for one-half hour. The solvent was removed by distillation, and the oil which remained was dissolved in benzene. The benzene solution was extracted several times with concentrated hydrochloric acid. An oil formed in the acid extracts. This oil was dissolved in alcohol, and the resulting solution was made basic with 10% aqueous sodium hydroxide. By crystallization of the resulting precipitate from 95% alcohol, 0.80 g. (2%) of 2-benzylthio-4,6-diphenylpyrimidine, m.p. 147–148°, was obtained.

A 5% yield of this pyrimidine was obtained by the reaction of equimolar amounts of S-benzylisothiourea hydrochloride, benzalacetophenone, and potassium hydroxide in absolute alcohol.

2-α-Toluenesulfonyl-4,6-diphenylpyrimidine was prepared by the oxidation of 2-benzylthio-4,6-diphenylpyrimidine with 30% hydrogen peroxide in glacial acetic acid. The sulfone was crystallized from 95% alcohol, m.p. 199.5–200°.

β-Benzylthio-β-phenylpropiophenone. To a solution of 20.8 g. (0.10 mole) of benzalacetophenone and 20.2 g. (0.10 mole) of S-benzylisothiourea hydrochloride in 200 ml. of 84% alcohol was added 33.6 g. (0.40 mole) of sodium bicarbonate and the resulting suspension was heated under reflux for three hours. The solvent was removed by distillation and the yellow oil which remained was washed several times with warm water. By crystallization from dilute alcohol, 26.3 g. (79%) of β-benzylthio-β-phenylpropiophenone was obtained. Crystallization from methyl alcohol yielded 22.5 g. of analytically pure material, m.p. 72–73°. The reported melting point is 71° (10).

Anal. Calc'd for $C_{22}H_{20}OS$: C, 79.52; H, 6.02.

Found: C, 79.63; H, 6.13.

SUMMARY

1. Benzamidine was condensed with α,β-unsaturated ketones of the type $C_6H_5CH{=}CHCOR$, where R does not possess an α-hydrogen, to give 6-substituted-2,4-diphenylpyrimidines. Part of the α,β-unsaturated ketone was reduced in this process to the saturated ketone.

2. S-Benzylisothiourea was successfully substituted for benzamidine in one condensation, but the yield of the substituted pyrimidine was very low.

MINNEAPOLIS, MINNESOTA

REFERENCES

(1) TRAUBE AND SCHWARZ, *Ber.*, **32**, 3163 (1899).
(2) FRANK AND STEVEN, *J. Am. Chem. Soc.*, **71**, 2631 (1949).
(3) ANKER AND COOK, *J. Chem. Soc.*, 323 (1941).
(4) ASAHINA AND KURODA, *Ber.*, **47**, 1815 (1914).
(5) SCHNEIDEWIND, *Ber.*, **21**, 1323 (1888).
(6) PERKIN AND STENHOUSE, *J. Chem. Soc.*, **59**, 996 (1891).
(7) PFEIFFER, *J. prakt. Chem.*, [2] **108**, 341 (1924).
(8) MAXIM, *Compt. rend.*, **182**, 1393 (1926).
(9) SHOPPEE, *J. Chem. Soc.*, 2567 (1928).
(10) NICOLET, *J. Am. Chem. Soc.*, **57**, 1098 (1935).