SYNTHESIS OF 3-SUBSTITUTED 5,6-DIPHENYLPYRIMIDIN-4-ONES FROM DIPHENYLCYCLOPROPENONE AND N-SUBSTITUTED AMIDE OXIMES

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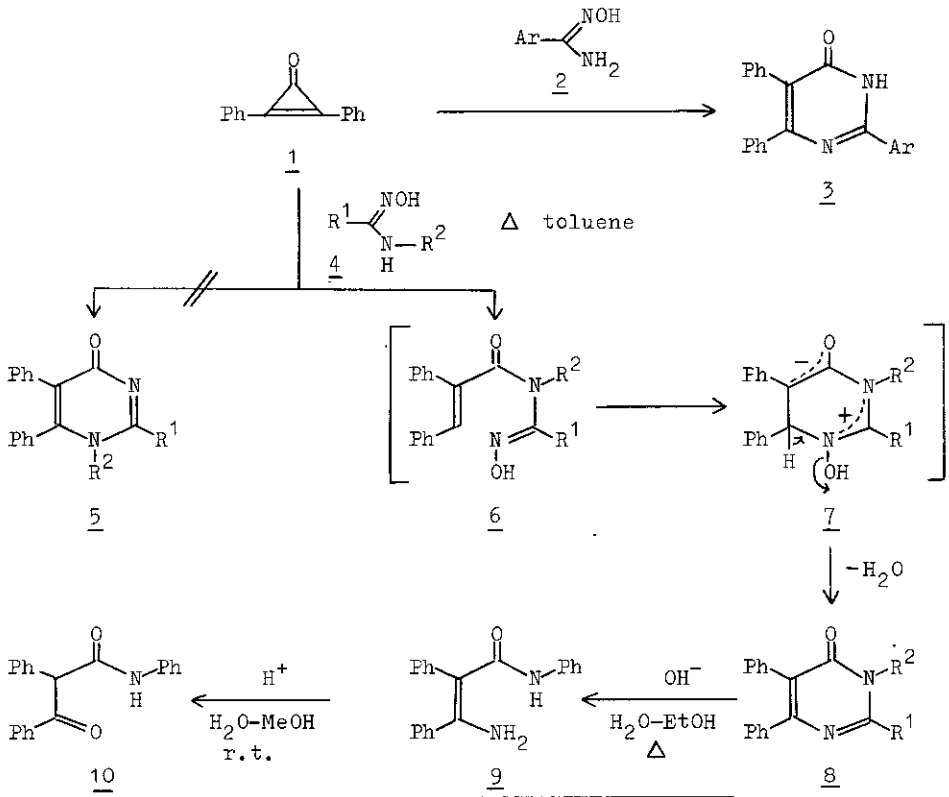
Abstract —— 3-Substituted 5,6-diphenylpyrimidin-4-ones were prepared regioselectively from diphenylcyclopropenone and N-substituted amide oximes.

Diphenylcyclopropenone (1) is a readily available and useful synthon for heterocycles.[1,2] There have been some reports about the formation of two isomeric pyrimidin-4-ones 5 and 8 from 1. 1-Substituted pyrimidin-4-ones 5 were formed on treatment of 1 with benzo[c]cinnolinium-5-(N-benzimido-imides)[3], N-imidoyl sulfoximides[4], or N-phenylbenzamidines.[3,5] On the other hand, isomeric 3-substituted pyrimidin-4-ones 8 were obtained from 1 and N-imidoyl sulfimides.[6] These reactions, however, do not seem preparative because of the low yields[4], two step operations in the experiments[3,5], or limited availability of the reagents.[3,4,6] In a previuos report[7], we described a facile and general synthesis of 2-aryl-5,6-diphenylpyrimidin-4-ones (3) from 1 and arylamide oximes 2. As a continuation of this work, we have examined the reaction of 1 with N-substituted amide oximes 4 and found a method to introduce substituents on the 3-position of pyrimidin-4-ones regioselectively.

Treatment of 1 with N-phenylformamide oxime (4a) in refluxing toluene afforded an addition-dehydration product. The structure of the product was presumed to be either 1,5,6-triphenylpyrimidin-4-one (5a) or 3,5,6-triphenylpyrimidin-4-one (8a) on the basis of the spectral and analytical data. The structure, however, was finally found to be 8a as follows; Alkaline hydrolysis of the product in refluxing aqueous ethanol gave a ring-opened product 9, which was further hydrolyzed in the presence of sulfuric acid in aqueous methanol at room temperature to yield the known β-ketoamide 10.[8] Moreover, the IR spectrum of



4-8	R^1	R^2
a	H	C_6H_5-
b	H	4-MeO-C_6H_4-
c	H	4-Me-C_6H_4-
d	H	4-Cl-C_6H_4-
e	C_6H_5-	C_6H_5-
f	C_6H_5-	4-Me-C_6H_4-
g	H	H

the product from 1 and 4e was identical with that of the authentic 8e[9], but not with that of the authentic 5e.[3] Thus, regioselective formation of 3-substituted pyrimidin-4-ones 8 from 1 and 4 has been established and the physical and spectral data of these pyrimidinones are shown in the Table. 2,4-Unsubstituted derivative 8g was also obtained.

The tentative reaction pathway is shown in the Scheme. Intramolecular

Table. 3-Substituted 5,6-diphenylpyrimidin-4-ones (8)

Product	Yield %	mp °C	MS (M^+) m/e	IR (KBr) cm^{-1}	NMR (Solvent) δ
8a	69	206-207 (MeOH)	324	1650, 1600, 1580, 1565, 1525, 1490	8.20 (s, 1H), 7.20-7.47 (m, 15H) ($CDCl_3$)
8b	46	180-181 (MeOH)	354	1655, 1600, 1580, 1565, 1515, 1505	8.23 (s, 1H), 6.89-7.43 (m, 14H), 3.82 (s, 3H) ($CDCl_3$)
8c	64	188-189 (MeOH)	338	1645, 1600, 1585, 1565, 1530, 1505	8.21 (s, 1H), 7.23-7.31 (m, 14H), 2.43 (s, 3H) ($CDCl_3$)
8d	60	241-242 ($MeOH-CHCl_3$)	357	1640, 1590, 1580, 1565, 1515, 1480	9.01 (s, 1H), 6.87-7.17 (m, 14H) (CF_3COOH)
8e	76	298-300 (DMF)	400	1650, 1605, 1575, 1545, 1530, 1500	
8f	50	264-266 ($MeOH-CHCl_3$)	414	1655, 1580, 1550, 1525, 1510, 1490	7.05-7.53 (m, 19H), 2.28 (s, 3H) ($CDCl_3$)
8g	77	254-257 (MeOH)	248	2650, 1620, 1595, 1560, 1520, 1485	8.92 (s, 1H), 6.92 (s, 10H) (CF_3COOH)

Satisfactory microanalytical data (C ±0.40%, H ±0.16%) were obtained.

conjugate addition of nitrogen atom of oxime 6 affords resonance-stabilized zwitterion intermediate 7, which extrudes water, giving 8.

EXPERIMENTAL

Starting amide oximes 4[10]: N-Arylamide oximes 4b-d were prepared according to the literature method for 4a[11]. Thus, treatment of 4g[11] (3.0 mmol) and arylamine hydrochloride (3.0 mmol) in refluxing ethanol (9 ml) for several hours gave N-arylamide oximes in 50-60% yields. 4b: mp 135-137°C. 4c: mp 138-140°C. 4d: mp 152-154°C.

3-Substituted 5,6-diphenylpyrimidin-4-ones 8: A general procedure. A mixture of 1 (3.0 mmol) and 4 (3.0 mmol) in toluene (9 ml) was refluxed for 3-5 h.

After cooling, the precipitates were collected by filtration, washed with a small amount of methanol, and recrystallized to give 8.

N-Phenyl-3-amino-2,3-diphenyl-2-propene-1-carboxamide (9): A mixture of 8 (970 mg, 3.0 mmol) in aqueous ethanol (30 ml, water:ethanol=1:9) containing 1% potassium hydroxide was refluxed for 10 h. After evaporation of the solvent, the residue was washed with water and recrystallized from methanol to give 9 (580 mg, 61% yield), white plates, mp 124-126°C. IR (KBr) cm^{-1}: 3450, 3400, 1635, 1585, 1570, 1510, 1480. MS m/e: 314 (M^+). Anal. Calcd. for $C_{21}H_{18}ON_2$: C, 80.23; H, 5.77. Found: C, 80.54; H, 5.87.

N-Phenyl-2,3-diphenylpropan-3-one-1-carboxamide (10): A mixture 9 (314 mg, 1.0 mmol) in aqueous methanol consisting of methanol (10 ml) and 10% sulfuric acid (10 ml) was stirred at room temperature for 2 h. The precipitates were collected by filtration and recrystallized from methanol to give 10 (222 mg, 71% yield), mp 168-169°C (lit.[8] mp 168-169°C). IR (KBr) cm^{-1}: 3250-3030, 1670, 1655, 1590, 1545, 1490. MS m/e: 315 (M^+).

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