New Synthesis of Pyrazole and Isoxazole Derivatives

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A convenient synthesis of 5-aryl-1-phenylpyrazoles and 5-arylisoxazoles, from readily available ketimine **1** dimethylformamide dimethylacetal and phenylhydrazine or hydroxylamine, is described.

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Numerous routes are available for the preparation of pyrazole [1] and isoxazole [2,3] derivatives. The classical pyrazole synthesis involves the addition of hydrazine or monosubstituted hydrazine to 1,3-dicarbonyl compounds [4,5,6,7]; the principal drawback of this method is that unsymmetrical 1,3-dicarbonyl compounds generally give two isomeric pyrazoles, even 1,3-ketoaldehydes tend to give two products in spite of considerable difference between the carbonyl groups. The second carbonyl group can be replaced by other unsaturated functions *e.g.* α,β-ethynyl ketones [8,9], and β-substituted enones [10,11]. However, these methods often result in the formation of mixtures of isomers since there can be competition between the process leading to hydrazone function and Michael-type addition of the hydrazine to the electron-deficient unsaturated linkage. Similarly the main general method for the preparation of isoxazole derivatives involves condensation reactions of 1,3-dicarbonyl compounds with hydroxylamine, however, for unsymmetrical dicarbonyl compounds the possibility of forming isomeric isoxazole derivatives is a disadvantage. Attempts to overcome the ambiguity of this method by using various β-substituted enones have been reported *e.g.* β-halo enones [12], enaminones [13,14] or acetals of α,β-acetylenic aldehydes [15].

We now report here an apparently widely applicable synthesis of 5-aryl-1-phenylpyrazoles **4** and 5-arylisoxazoles **7**, starting from ketimines **1**. Our approach is based on the treament of ketimines **1**, readily available from 1-amino-4,6-diphenyl-2-pyridone **5** with aryl methyl ketones [16], with dimethyl formamide diemtylacetal to give the corresponding enaminimines **2** which are isolated as crystalline solids in 86-98% yields (Table I). The ^{1}H-nmr spectra of **2** show two singlets at δ 6.9-7.0 and δ 2.85 ppm attributable to the methine proton and to the N-CH_3 groups. Treatment of **2** with phenylhydrazine followed by addition of methanolic hydrochloric acid yielded the *N*-amino heterocycle **5** and the corresponding pyrazoles **4** in 65-85% yields (Table II). In several cases examined, the hydrazone intermediates **3** have been isolated as crystalline solids (Table III).

On the other hand, compounds **2** react with hydroxylamine to give the corresponding isoxazoles **7** and the *N*-amino heterocycle **5**. In three cases examined, the oxime intermediates **6** have been isolated as crystalline solids in 83-94% yields (Table IV and V).

The synthesis of the isoxazoles **7** from enaminimines **2** and hydroxylamine in methanol solution provides a useful alternative to literature methods. Advantages of the present simple route to pyrazoles **4** and isoxazoles **7** are: unambiguous position of the substituent: good yields; availability of starting materials and high yield recovery of reagent **5**. The reaction seems to be quite general and is equally applicable both when the aromatic ring is substituted by electron-donating and electron-withdrawing groups.

EXPERIMENTAL

The melting points were determined with a Kofler hot stage microscope and were uncorrected. The ir spectra were recorded of mineral oil

Table I

Compounds **2**

Compound No.	Ar	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR ν (cm^{-1})	^{1}H-NMR δ (ppm)
2a	C_6H_5	95	120	$C_{28}H_{25}N_3O$ (419.5)	80.16 80.20	6.01 6.10	10.02 10.15	1650, 1625, 1545, 1490, 1370, 1350, 1285, 1110, 1090, 760, 750, 690	7.9-7.4 (16H, m), 6.95 (1H, d), 6.55 (1H, d), 4.95 (1H, d), 2.85 (6H, s)
2b	4-$H_3CC_6H_4$	86	165	$C_{29}H_{27}N_3O$ (433.6)	80.34 80.30	6.28 6.40	9.69 9.50	1650, 1610, 1530, 1490, 1390, 1350, 1280, 1100, 1090, 820, 790, 750, 700	7.7-7.35 (15H, m), 6.95 (1H, d), 6.45 (1H, s) 4.95 (1H, d), 2.85 (6H, s), 2.4 (3H, s)
2c	4-$O_2NC_6H_4$	88	232	$C_{28}H_{24}N_4O_3$ (464.5)	72.40 72.52	5.21 5.22	10.06 10.16	1650, 1640, 1550, 1515, 1350, 1300, 1120, 1095	8-7.5 (15H, m), 7 (1H, d), 6.6 (1H, d), 4.95 (1H, d), 2.85 (6H, s)
2d	4-$H_3COC_6H_4$	86	150	$C_{29}H_{27}N_3O_2$ (449.6)	77.48 77.32	6.10 6.15	9.35 9.45	1650, 1625, 1560, 1545, 1375, 1110, 850, 800, 720	7.7-7.35 (15H, m), 6.9 (1H, s), 6.65 (1H, d), 5 (1H, d), 3.7 (3H, s), 2.85 (6H, s)
2e	4-ClC_6H_4	93	126	$C_{28}H_{24}ClN_3O$ (454.0)	74.08 74.12	5.33 5.45	9.26 9.24	1650, 1620, 1540, 1500, 1400, 1355, 1290, 1110, 1090, 840, 830, 795, 765	7.8-7.2 (15H, m), 7 (1H, s), 6.6 (1H, d), 4.95 (1H, d), 2.85 (6H, s)
2f	4-BrC_6H_4	98	132	$C_{28}H_{24}BrN_3O$ (498.4)	67.47 67.55	4.85 4.92	8.43 8.24	1650, 1640, 1550, 1515, 1350, 1300, 1120, 1095, 970, 870, 820, 770, 725, 690	8-7.52 (15H, m), 6.9 (1H, s), 6.6 (1H, d), 4.95 (1H, d), 2.85 (6H, s)

Table II

5-Aryl-1-phenylpyrazoles **4**

Compound No.	Ar	Yield %	Mp or Bp/mm °C	Reported or Molecular Formula	IR ν (cm^{-1})	MS M^+
4a	C_6H_5	82	55	53-54 [17]	1600, 1500, 1450, 1385, 1230, 1130, 1070, 960, 930, 760, 700	220
4b	4-$H_3CC_6H_4$	75	55-57	$C_{16}H_{14}N_2$ (234.3)	1600, 1500, 1450, 1385, 1140, 1070, 1030, 965, 930, 830, 790, 770, 700	234
4c	4-$O_2NC_6H_4$	76	87-88	93 [18]	1600, 1515, 1500, 1460, 1360, 1340, 965, 930, 855, 800, 770, 750, 700	265
4d	4-$H_3COC_6H_4$	85	185-187/4	$C_{16}H_{14}N_2O$ (250.3)	1600, 1500, 1455, 1390, 1250, 1180, 1035, 965, 930, 840, 770, 700	250
4e	4-ClC_6H_4	80	68-70	67-69 [17]	1600, 1500, 1480, 1450, 1410, 1385, 1095, 1020, 960, 930, 835, 785, 760, 740, 695	256 (M^+ +2) 254 (M^+)
4f	4-BrC_6H_4	65	110-112	100-105 [17]	1600, 1500, 1480, 1445, 1405, 1350, 1080, 1010, 960, 925, 830, 785, 760, 690	300 (M^+ +2) 298 (M^+)

mulls with a Perkin-Elmer 457 instrument. The ^{1}H-nmr spectra were obtained on solutions in DMSO-d_6 with TMS as internal standard using a Varian FT-80 instrument. Mass spectra were obtained with a Hewlett-Packard 5980 A GC/MS system; compounds were introduced through the direct insertion probe. The electron beam energy was 70 eV and the ion source was at *c.a.* 300°. Microanalysis were performed with a Perkin-Elmer 240 instrument.

Ketimines **1**. General Procedure.

Compounds **1a-c** have been prepared according with the reported procedure [16]; compounds **1d-f** have been prepared by the following improved method:

To a solution of the appropriate aryl methyl ketone (5.7 mmoles) in dry tetrahydrofuran (20 ml), boron trifluoride etherate (5.7 mmoles) was added. The reaction mixture was heated at reflux temperature for 2 hours. Then, 1-amino-4,6-diphenyl-2-pyridone (**5**) (1.5 g, 5.7 mmoles) was added and the resultant solution was heated for 2 hours. After cooling, the solvent was removed under reduced pressure, the residual material was dissolved in dimethyl formamide (15 ml) and the solution was heated at reflux temperature for 5 hours. After cooling, the solution was poured into water and the precipitated solid was separated by filtration and recrystallized from ethanol to give **1**. By this method the following compounds were prepared.

Table III

Hydrazone Derivatives **3**

Compound No.	Ar	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR ν (cm^{-1})	MS (M^+)
3b	4-$H_3CC_6H_4$	60	125-127	$C_{33}H_{23}N_4O$ (491.6)	80.62 80.83	4.72 4.81	11.39 11.43	3190, 1645, 1600, 1485, 1450, 1370, 1250, 860, 830, 760, 740, 690	491
3c	4-$O_2NC_6H_4$	70	165-167	$C_{32}H_{20}N_5O_3$ (522.5)	73.55 73.76	3.86 3.90	13.40 13.55	3290, 1655, 1610, 1520, 1420, 1350, 1275, 875, 775, 760, 705,	522
3d	4-$H_3COC_6H_4$	65	127-129	$C_{33}H_{23}N_4O_2$ (507.6)	78.09 78.13	4.57 4.63	11.04 11.12	3230, 1645, 1605, 1590, 1565, 1500, 1460, 1270, 1180, 840, 770, 760, 705	507
3e	4-ClC_6H_4	68	155-157	$C_{32}H_{20}ClN_4O$ (512)	75.07 75.23	3.94 4.02	10.94 11.09	3290, 1640, 1600, 1565, 1490, 1370, 1260, 860, 845, 830, 760, 740, 690	514 ($M^+ + 2$) 512 (M^+)
3f	4-BrC_6H_4	72	139-141	$C_{32}H_{20}BrN_4O$ (556.5)	69.07 69.25	3.62 3.87	10.07 10.15	3290, 1650, 1605, 1570, 1380, 1265, 870, 860, 830, 765, 750, 695	557 ($M^+ + 2$) 555 (M^+)

Table IV

5-Arylisoxazoles **7**

Compound No.	Ar	Yield %	Mp or Bp/mm °C	IR ν (cm^{-1})	MS (M^+)
7a	C_6H_5	89	100-102/5 (lit [12] 91-93/3)	1600, 1550, 1500, 1460, 1400,1380, 1200, 1000, 798, 760, 700	145
7b	4-$H_3CC_6H_4$	85	57 (lit [14] 58-60)	1620, 1560, 1515, 1479, 1390, 1200, 1050, 950, 925, 890, 830, 790	159
7c	4-$O_2NC_6H_4$	88	174-176 (lit [12] 172-174)	1610, 1580, 1520, 1460, 1350, 1340, 1200, 1110, 1040, 950, 920, 880, 865, 855, 820, 760, 700	190
7d	4-$H_3COC_6H_4$	78	68-70 (lit [14] 64-65)	1610, 1510, 1460, 1370, 1300, 1250, 1175, 1025, 920, 840	175
7e	4-ClC_6H_4	92	84-86 (lit [14] 84-85)	1610, 1495, 1460, 1410, 1200, 1110, 945, 920, 885, 875, 805, 740	181 ($M^+ + 2$) 179 (M^+)
7f	4-BrC_6H_4	83	118-120 (lit [14] 114-116)	1615, 1460, 1410, 1200, 1100, 1080, 1070, 1050, 1025, 950, 890, 870, 840, 810, 725	225 ($M^+ + 2$) 223 (M^+)

Table V

Oxime Derivatives **6**

Compound No.	Ar	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR ν (cm^{-1})	MS (M^+)
6c	4-$O_2NC_6H_4$	94	205	$C_{26}H_{20}N_4O_4$ (452.4)	69.02 69.11	4.46 4.34	12.38 12.25	3200, 1640, 1560, 1520, 1350, 1170, 1110, 900, 870, 780, 760, 700	452
6e	4-ClC_6H_4	93	172-174	$C_{26}H_{20}ClN_3O_2$ (441.9)	70.67 70.60	4.56 4.62	9.51 9.32	3200, 1640, 1550, 1310, 1100, 900, 890, 850, 770, 700	444 ($M^+ + 2$) 442 (M^+)
6f	4-BrC_6H_4	83	194-196	$C_{26}H_{20}BrN_3O_2$ (486.4)	64.21 64.30	4.14 4.12	8.64 8.69	3200, 1640, 1550, 1310, 1010, 900, 890, 850, 770, 700	487 ($M^+ + 2$) 485 (M^+)

N-(α-Methyl-4-methoxybenzylidenamino)-4,6-diphenyl-2-pyridone (**1d**).

This compound was obtained in 88% yield, mp 98-100° as colourless crystals.

Anal. Calcd. for $C_{26}H_{22}N_2O_2$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.20; H, 5.45; N, 7.21.

N-(α-Methyl-4-chlorobenzylidenamino)-4,6-diphenyl-2-pyridone (**1e**).

This compound was obtained in 78% yield, mp 170-172° as colourless crystals.

Anal. Calcd. for $C_{25}H_{19}ClN_2O$: C, 75.28; H, 4.80; N, 7.02. Found: C, 75.06; H, 4.98; N, 6.91.

N-(α-Methyl-4-bromobenzylidenamino)-4,6-diphenyl-2-pyridone (**1f**).

This compound was obtained in 89% yield, mp 157-159° as colourless crystals.

Anal. Calcd. for $C_{25}H_{19}BrN_2O$: C, 67.73; H, 4.32; N, 6.32. Found: C, 67.64; H, 4.21; N, 6.58.

Mass spectra of ketimines **1d-f** show the molecular ion (M^+) and the

fragment at $M^+ - 15$ is the base peak. The ir spectra show two strong bands at 1655-1650 cm^{-1} (C=O) and 1660-1580 cm^{-1} (C=N). The ^1H-nmr spectra shows a singlet at 2.2 ppm attributable to the methyl group.

N-[α-(*N*,*N*-Dimethylaminoethenyl)arylidenamino]-4,6-diphenyl-2-pyridones **2**. General Procedure.

To a solution of ketimine **1** (2.5 mmoles) in dry dimethylformamide (15 ml), dimethylformamide dimethylacetal (0.5 ml, 3.7 mmoles) was added. The reaction mixture was stirred and heated at reflux temperature for 8 hours. After cooling, the resultant solution was poured into cooled water (50 ml) and the precipitated solid was separated by filtration and recrystallized from chloroform/hexane 1:1 (20 ml) to give the enaminimines **2** (Table I).

5-Aryl-1-phenylpyrazoles **4**. General Procedure.

To a solution of enaminimine **2** (2 mmoles) in dry methanol (15 ml), phenylhydrazine (0.3 ml, 3 mmoles) was added. The reaction mixture was stirred and heated at reflux temperature for 5 hours, then hydrochloric acid 1*N* (2.5 ml) was added. The resultant solution was heated under reflux for 1 hour. After cooling, the crystalline precipitated solid was separated by filtration and was found to be 1-amino-4,6-diphenyl-2-pyridone **5**, yield, 65-70%. From the mother liquor, the solvent was removed under reduced pressure and the residual material was washed with water/dichloromethane 1:1 (30 ml). The organic layer was dried with magnesium sulfate, filtered and concentrated to dryness to give the crude pyrazole **4** which was purified by sublimation (Table II).

N-[α-(Phenylhydrazonoethyl)arylidenamino]-4,6-diphenyl-2-pyridones **3**. General Procedure.

To a solution of enaminimine **2** (2 mmoles) in dry methanol (15 ml), phenylhydrazine (0.3 ml, 3 mmoles) was added and the reaction mixture was stirred and heated at reflux temperature for 5 hours. After cooling, the solution was neutralized with hydrochloric acid and the precipitated solid was collected by filtration and recrystallized from methanol to give **3** (Table III).

5-Aryl Isoxazoles **7**. General Procedure.

To a solution of enaminimine **2** (1.3 mmoles) in dry methanol (15 ml), hydroxylamine hydrochloride (0.26 g, 2.6 mmoles) and sodium methoxide (0.14 g, 2.6 mmoles) were added and the reaction mixture was stirred and heated at reflux temperature for 5 hours. Then, hydrochloric acid (1 ml) was added and the heating was continued for 1 hour. After cooling at 0°, the crystalline precipitated solid was filtered and identified as **5**, yield, 85-90%. From the mother liquor, the solvent was removed under reduced pressure and the residual material was washed with 1:1 water/dichloromethane (30 ml). The organic layer was dried with magnesium sulfate, filtered and concentrated to dryness to give the crude isoxazole **7**, which was purified by sublimation (Table IV).

N-[α-(Hydroxyiminoethyl)arylidenamino]-4,6-diphenyl-2-pyridones **6**. General Procedure.

To a solution of enaminimine **2** (1.2 mmoles) in dry methanol (15 ml), hydroxylamine hydrochloride (0.24 g, 2.4 mmols) and sodium methoxide (0.13 g, 2.4 mmoles) were added. The reaction mixture was stirred and heated at reflux temperature for 5 hours. After cooling at 0°, the precipitated solid was separated by filtration and recrystallized from methanol to give **6** (Table V).

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