An Efficient Regioselective Synthesis of 2,4-Diarylfurans

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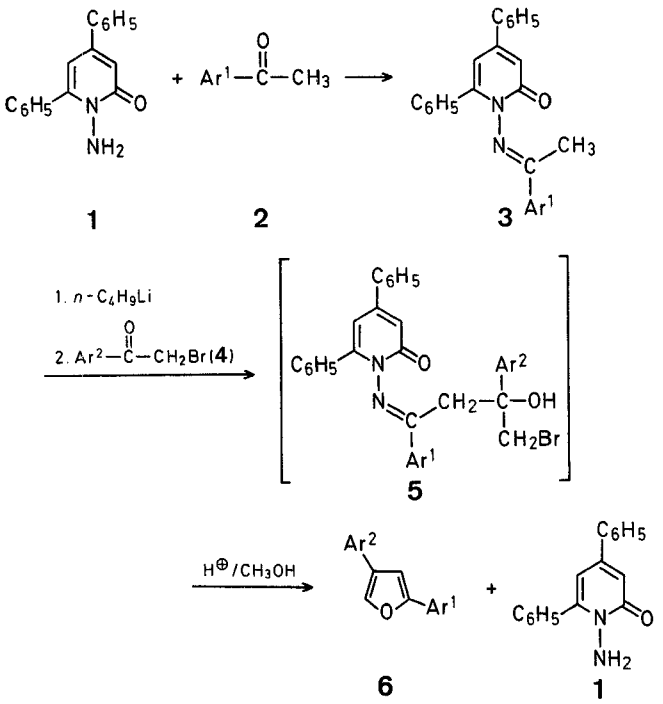
In spite of much work on the synthesis of furan derivatives[1], very few studies have been devoted to the preparation of 2,4-disubstituted furans, particularly when the substituents in positions 2 and 4 are different. Cross-coupling reactions between acyl chlorides and allyl halides in the presence of aluminium trichloride[2,3], condensation of enol ethers of β-dicarbonyl compounds with dimethylsulfonium methylide[4,5], or cyclization of acetylenic diols by action of metallic salts[6–9], allow the preparation of 2,4-disubstituted furans having different substituents. However, these methods are restricted to the aliphatic series and the two latter procedures possess obvious disadvantages, in particular, the limited availability of starting materials.

Thus, we have developed a two-step process for the preparation of 2,4-diarylfurans from aryl methyl ketones and phenacyl bromides. The reaction of 1-amino-4,6-diphenyl-2-pyridone **(1)** with aryl methyl ketones **2** gives the corresponding ketimines **(3),** which are isolated as crystalline solids in high yields. Metallation of **3** with *n*-butyllithium at −78 °C followed by addition of the appropriate phenacyl bromide **4** and treatment with methanolic hydrochloric acid yielded the corresponding furans **6** (Table 1).

Advantages of the present, simple route to 2,4-diarylfurans **6** are:

- unambiguous position of the substituents;
- good yields;
- mild and convenient reaction conditions;
- general availability of starting materials **2** and **4**;
- high yield recovery of reagent **1** for reuse.



The principal limitation involves the presence of groups in Ar^1 which are sensitive to the lithium reagent.

The conversion **3**→**6** involves attack of the carbanion derivative of **3** on the carbonyl group of the phenacyl bromide **4** to give **5** which, under acidic conditions, undergoes hydrolysis, elimination and cyclization to give **6.** In all the cases examined, the intermediates **5** have been isolated as crystalline solids (Table 2).

Ketimines 3; General Procedure:

To a solution of 1-amino-4,6-diphenyl-2-pyridone (**1**; 2.6 g, 10 mmol) in ethanol (75 ml), the appropriate aryl methyl ketone **2** (10 mmol) and aqueous hydrochloric acid (1 ml) are added. The reaction mixture is stirred under reflux for 2 h. After cooling, the precipitated solid is separated by filtration and recrystallized from ethanol.

N-(α-Methyl-benzylidenamino)-4,6-diphenyl-2-pyridone (**3a**, $Ar^1 = C_6H_5$); yield: 92%; colourless crystals; m.p. 203 °C.

$C_{25}H_{20}N_2O$	calc.	C 82.39	H 5.53	N 7.69
(364.5)	found	82.60	5.56	7.55

N-(α-4-Dimethylbenzylidenamino)-4,6-diphenyl-2-pyridone (**3b**, $Ar^1 = 4\text{-}H_3C\text{—}C_6H_4$); yield: 90%; colourless flakes; m.p. 178 °C.

$C_{26}H_{22}N_2O$	calc.	C 82.51	H 5.86	N 7.40
(378.5)	found	82.42	5.79	7.27

Table 1. Furans **6** from Ketimines **3** and Phenacyl Bromides **4**

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p.		M.S. *m/e*
6a	C_6H_5	C_6H_5	85	109–110°	110–111°[10]		—
6b	C_6H_5	4-Br—C_6H_4	86	140–142°	$C_{16}H_{11}BrO$	(299.2)	300 ($M^+ + 1$)
6c	C_6H_5	4-Cl—C_6H_4	87	130°	$C_{16}H_{11}ClO$	(254.7)	254 (M^+)
6d	C_6H_5	4-H_3CO—C_6H_4	83	132–134°	$C_{17}H_{14}O_2$	(250.3)	250 (M^+)
6e	C_6H_5	4-C_6H_5—C_6H_4	90	138–140°	$C_{22}H_{16}O$	(296.4)	296 (M^+)
6f	C_6H_5	4-O_2N—C_6H_4	82	152°	$C_{16}H_{11}NO_3$	(265.3)	265 (M^+)
6g	4-O_2N—C_6H_4	4-O_2N—C_6H_4	80	225–226°	225–226°[11]		—
6h	4-H_3C—C_6H_4	4-H_3CO—C_6H_4	82	107°	$C_{18}H_{16}O_2$	(264.3)	264 (M^+)
6i	4-H_3C—C_6H_4	4-Cl—C_6H_4	90	175°	$C_{17}H_{13}ClO$	(268.7)	268 (M^+)
6j	4-H_3C—C_6H_4	4-Br—C_6H_4	95	191°	$C_{17}H_{13}BrO$	(313.2)	314 ($M^+ + 1$)
6k	4-H_3C—C_6H_4	C_6H_5	85	133°	$C_{17}H_{14}O$	(234.3)	234 (M^+)

[a] Yield of recrystallized products.

[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.26, Br ±0.21, Cl ±0.20, N ±0.08.

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Table 2. Ketimines **5** from Ketimine **3** and Phenacyl Bromides **4**

Product No.	Ar^1	Ar^2	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]
5a	C_6H_5	C_6H_5	84	195°	$C_{33}H_{27}BrN_2O_2$ (563.5)
5b	C_6H_5	4-Br—C_6H_4	78	209–210°	$C_{33}H_{26}Br_2N_2O_2$ (642.4)
5c	C_6H_5	4-Cl—C_6H_4	75	203–205°	$C_{33}H_{26}BrClN_2O_2$ (597.9)
5d	C_6H_5	4-H_3CO—C_6H_4	80	170°	$C_{34}H_{29}BrN_2O_3$ (593.5)
5e	C_6H_5	4-C_6H_5—C_6H_4	83	210°	$C_{39}H_{31}BrN_2O_2$ (639.6)
5f	C_6H_5	4-NO_2—C_6H_4	85	187–190°	$C_{33}H_{26}BrN_3O_4$ (608.6)

[a] Yield of recrystallized product.

[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.30, N ±0.36, Br ±0.35, Cl ±0.09; exceptions: **5a** (C +0.69), **5b** (N +0.47), **5a, c** (H ±0.52).

N-(α-Methyl-4-nitrobenzylidenamino)-4,6-diphenyl-2-pyridone (**3c**, Ar^1 = 4-O_2N—C_6H_4); yield: 89%; yellow crystals; m.p. 169 °C.

$C_{25}H_{19}N_3O_3$	calc.	C 73.34	H 4.68	N 10.26
(409.4)	found	73.21	4.55	10.40

Mass spectra of all ketimines **3** show the molecular ion (M^+) and the fragment $M^+ - 15$ is the base peak. The I.R. spectra show two strong bands at ν = 1650 cm^{-1} (C=O) and ν = 1610 cm^{-1} (C=N). ^{1}H-N.M.R. spectra show a singlet at δ = 2.3 ppm attributable to the α-methyl group.

***N*-[α-(2-Aryl-3-bromo-2-hydroxy)-benzylidenamino]-4,6-diphenyl-2-pyridones 5; General Procedure:**

A solution of ketimine **3** (3 mmol) in dry tetrahydrofuran (30 ml) is cooled at −78 °C and 1.6 molar *n*-butyllithium in *n*-hexane (2.7 ml, 3 mmol) is added under nitrogen. The reaction mixture is stirred for 30 min and a solution of the appropriate phenacyl bromide **4** (3 mmol) in tetrahydrofuran (10 ml) is added. The mixture is stirred for 30 min and allowed to warm to room temperature. The solvent is removed under reduced pressure, the residual material is treated with cold methanol (10 ml), and recrystallized from 1:1 dichloromethane/ether (20 ml).

2,4-Diarylfurans 6 from 3 and 4; General Procedure:

A well-stirred solution of ketimine **3** (4 mmol) in dry tetrahydrofuran (50 ml) is cooled to −78 °C and 1.6 molar *n*-butyllithium in *n*-hexane (3.6 ml, 4 mmol) is added under nitrogen. The resultant solution is stirred for 30 min and a solution of the appropriate phenacyl bromide **4** (4 mmol) in tetrahydrofuran (10 ml) is added. The reaction mixture is stirred for 30 min and allowed to warm to room temperature. The solvent is removed under reduced pressure at room temperature, the residue is dissolved in methanol (20 ml), and hydrochloric acid (0.2 ml) is added. The solution is heated under reflux for 1 h. After cooling, the precipitated solid is separated by filtration and recrystallized from methanol to give the furans **6** (Table 1).

By concentration of the mother liquour, compound **1** is isolated as a crystalline solid in high purity; yield: 60–72%.

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