

A New Synthetic Route to 3,5-Diphenyl-4-pyridones

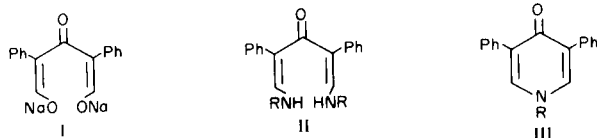
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Benary and Bitter (1) showed that when dibenzyl ketone was condensed with an excess of ethyl formate in the presence of sodium ethoxide, the sodium salt (I) was formed. This was ascertained through the formation of 1,5-dianilino-2,4-diphenylpent-1,4-dien-3-one (II, R = Ph) on acidification with aniline hydrochloride.

Being interested in confirmation of the structure of such diarylamino derivative and in the study of the action of acids and alkalis on it, a series of 1,5-diarylamino-2,4-diphenylpent-1,4-dien-3-ones (II) was obtained by the action of primary aromatic amine hydrochlorides on the sodium salt (I) (cf. Table II).



The ir spectra of II showed medium carbonyl absorption at 1640-1626 cm^{-1} and a weak associated NH band at 3080-3050 cm^{-1} (2). The nmr spectrum of 1,5-dianilino-2,4-diphenylpent-1,4-dien-3-one (II, R = Ph) showed a singlet at τ 3.04 (2 CH), a multiplet at τ 2.7 (4 Ph) and a singlet at τ -1.2 to τ -1.65 (2 NH).

1,5-Diarylamino-2,4-diphenylpent-1,4-dien-3-ones (II) could be cyclized by the action of alkali or acid to give quantitatively the corresponding *N*-aryl-3,5-diphenyl-4-pyridones (III) with elimination of a molecule of primary aromatic amine. Cyclization with alkali involves extraction of a proton from one of the NH groups, followed by a nucleophilic attack on the carbon neighboring the other NH group. This attack is favored by the formation of a partial positive charge on this carbon due to the electron withdrawal effect of the carbonyl group. Cyclization by acid seems to involve protonation of a nitrogen atom, thus increasing the chance of the adjacent carbon to be attacked by lone pair of electrons of the non-protonated one.

On the other hand, the action of ammonium chloride and the hydrochlorides of hydroxylamine, methylamine, *n*-butylamine, and *p*-hydroxyaniline on the sodium salt I led to the direct formation of the corresponding pyridones (III). This may be considered to take place through an

unstable intermediate such as II which immediately cyclizes to the pyridone probably due to the presence of electron-releasing substituents on the imino nitrogen.

The ir spectrum of 3,5-diphenyl-4-pyridone (III, R = H) showed a strong carbonyl band at 1630 cm^{-1} and a broad absorption in the region 3000-2840 cm^{-1} signifying polymeric association (3). Its nmr spectrum showed a singlet of one proton intensity at τ 1.4 (NH) and a multiplet at τ 2.7 for aromatic and ethylenic protons.

Unlike 2,6-diphenyl-4-pyridone (4), 3,5-diphenyl-4-pyridone resisted hydrolysis to 3,5-diphenyl-4-pyrone by the action of hydrochloric acid. It could be methylated by means of diazomethane or through its silver salt and methyl iodide into 1-methyl-3,5-diphenyl-4-pyridone (III, R = CH_3).

EXPERIMENTAL

Analyses were performed by Microanalysis Unit, Faculty of Science, Cairo University, Cairo. Ir spectra were measured with a Unicam SP 200 spectrophotometer for potassium bromide pellets or in nujol, uv and visible spectra were measured for ethanolic solutions with a Unicam SP 800 spectrophotometer and nmr spectra with a Varian A-60D instrument for solutions in carbon tetrachloride with TMS as internal standard.

Condensation of Dibenzyl Ketone and Ethyl Formate.

Dibenzyl ketone (5 g., 0.02 mole) and ethyl formate (4.4 g., 0.5 mole) were successively added to a suspension of sodium ethoxide (4.9 g., 0.7 mole) in dry ether and left overnight. The yellow sodium salt (I) was filtered and washed with ether. It was benzoylated with benzoyl chloride in pyridine into 2,4-diphenylpent-1,4-dien-3-one-1,5-dibenzoate (5.2 g.) which crystallized from methanol in needles, m.p. 109°.

Anal. Calcd. for $\text{C}_{31}\text{H}_{22}\text{O}_5$: C, 78.48; H, 4.64. Found: C, 78.24; H, 4.46.

1,5-Diarylamino-2,4-diphenylpent-1,4-dien-3-ones (II) (Table II).

They were prepared by treating an aqueous solution of the sodium salt (I) with the respective primary amine hydrochloride. The yellow oil which separated was extracted with ether, and the ethereal solution washed with water, dried (sodium sulfate) and evaporated. The residual oil afforded II on treatment with boiling methanol which crystallized from benzene-methanol in orange needles unless otherwise stated.

3,5-Diphenyl-4-pyridones (III) (Table III).

They were prepared according to either (a) or (b). They crystallized from methanol in needles or plates unless otherwise stated.

TABLE I
Ultraviolet and Visible Spectral Data of 1,5-Diarylamino-2,4-diphenylpent-1,4-dien-3-ones (II),
and 3,5-Diphenyl-4-pyridones (III)

No.	R	λ max/nm (ϵ)			
II	C ₆ H ₅	238 (19170)	293 (18040)	308 sh (16320)	415 (32300)
II	<i>p</i> -CH ₃ C ₆ H ₄	236 (15880)	297 (15700)		421 (25800)
II	<i>p</i> -ClC ₆ H ₄	237 sh (15510)	300 (21570)		415 (35370)
II	<i>p</i> -BrC ₆ H ₄	240 sh (22350)	300 (27130)		417 (43480)
II	<i>p</i> -IC ₆ H ₄	256 (22460)	305 (22980)		420 (36560)
II	β -naphthyl	235 sh (18450)	284 (29520)	315 (23990)	452 (43870)
III	OH	242 (26670)	298 (10530)	334 (6586)	
III	CH ₃	237 (26130)	290-307 (12690)		
III	<i>n</i> -Bu	239 (18960)	290-307 (11040)		
III	C ₆ H ₅	244 (18870)	302 (17660)		
III	<i>p</i> -CH ₃ C ₆ H ₄	245 (22840)	303 (22350)		
III	<i>p</i> -OHC ₆ H ₄	244 (29050)	303 (23140)		
III	<i>p</i> -ClC ₆ H ₄	246 (25440)	303 (23760)		
III	<i>p</i> -BrC ₆ H ₄	246 (23350)	305 (25300)		
III	<i>p</i> -IC ₆ H ₄	247 (26540)	307 (30160)		
III	β -naphthyl	244 (39250)	309 (29440)	288 sh (22150)	

TABLE II
1,5-Diarylamino-2,4-diphenylpent-1,4-dien-3-ones (II)

R	M.p., °C	Formula	C	Calcd.		Analyses				
				H	N	X	C	H	N	X
C ₆ H ₅	170 (a)	C ₂₉ H ₂₄ N ₂ O	83.63	5.80	6.73		83.79	5.69	6.65	
<i>p</i> -CH ₃ C ₆ H ₄	170	C ₃₁ H ₂₈ N ₂ O	83.75	6.35	6.30		83.64	6.21	5.97	
<i>p</i> -ClC ₆ H ₄	167	C ₂₉ H ₂₂ Cl ₂ N ₂ O	71.76	4.57	5.77	14.61	71.60	4.60	5.60	14.08
<i>p</i> -BrC ₆ H ₄	180	C ₂₉ H ₂₂ Br ₂ N ₂ O	60.64	3.86	4.88	27.84	60.70	3.99	4.99	28.10
<i>p</i> -IC ₆ H ₄	183	C ₂₉ H ₂₂ I ₂ N ₂ O	52.12	3.32	4.19	37.98	52.40	3.30	4.29	38.80
β -naphthyl (b)	204	C ₃₇ H ₂₈ N ₂ O	86.04	5.46	5.42		86.40	5.60	5.83	

(a) Lit. (1) 166°. (b) Crystallized from chloroform.

(a) An ethanolic solution of II was refluxed with 4 ml. of 5% aqueous sodium hydroxide or hydrochloric acid for 15 minutes. After dilution with water, the corresponding pyridone (III) separated in quantitative yield. The pyridones prepared by this method were (III, R = C₆H₅, *p*-CH₃C₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-IC₆H₄, and β -naphthyl).

(b) An aqueous solution of the sodium salt (I) was treated with ammonium chloride or with the required primary amine hydrochloride. The mixture was then extracted with ether which was washed with water, dried (sodium sulfate) and evaporated. The sticky oil left yielded the pyridone (III, 40-50 yield) on treatment with methanol. The pyridones prepared by this method were (III, R = H, OH, CH₃, *n*-Bu, and *p*-OHC₆H₄).

1-Methyl-3,5-diphenyl-4-pyridone (III, R = CH₃).

This compound was also prepared in 96% yield by refluxing the silver salt of 3,5-diphenyl-4-pyridone with methyl iodide and in 75% yield by treating 3,5-diphenyl-4-pyridone with diazomethane in ether.

1-Methyl-3,5-diphenyl-4-pyridone Picrate.

This compound was obtained as yellow needles (ethanol), m.p. 206°.

Anal. Calcd. for C₂₄H₁₈N₄O₈: C, 58.78; H, 3.70; N, 11.43. Found: C, 58.72; H, 3.59; N, 11.07.

1,3,5-Triphenyl-4-pyridone Picrate.

TABLE III
3,5-Diphenyl-4-pyridones (III)

R	M.p., °C	Formula	C	Calcd.		Analyses				
				H	N	X	C	Found		X
								H	N	
H (a)	396	C ₁₇ H ₁₃ NO	82.51	5.30	5.69		82.31	5.30	5.51	
OH (b)	257	C ₁₇ H ₁₃ NO ₂	77.55	4.98	5.32		77.77	4.87	4.98	
CH ₃	187	C ₁₈ H ₁₅ NO	82.75	5.79	5.36		82.64	5.93	5.51	
<i>n</i> -Bu	159	C ₂₁ H ₂₁ NO	83.12	6.98	4.62		83.38	7.03	5.03	
C ₆ H ₅	200	C ₂₃ H ₁₇ NO	85.41	5.30	4.33		85.28	5.04	4.62	
<i>p</i> -OHC ₆ H ₄ (b)	280	C ₂₃ H ₁₇ NO ₂	81.39	5.05	4.13		81.38	5.07	4.04	
<i>p</i> -CH ₃ C ₆ H ₄	138	C ₂₄ H ₁₉ NO	85.45	5.68	4.15		85.16	5.75	3.97	
<i>p</i> -ClC ₆ H ₄	160	C ₂₃ H ₁₆ ClNO	77.20	4.51	3.91	9.91	76.90	4.80	4.30	9.80
<i>p</i> -BrC ₆ H ₄	168	C ₂₃ H ₁₆ BrNO	68.68	4.01	3.48	19.86	68.69	3.97	3.61	19.53
<i>p</i> -IC ₆ H ₄	200	C ₂₃ H ₁₆ INO	61.49	3.59	3.12	28.25	61.15	3.74	3.01	28.50
β -naphthyl	102	C ₂₇ H ₁₉ NO	86.82	5.13	3.75		86.61	5.10	3.57	

(a) Crystallized from acetic acid. (b) Crystallized from benzene-methanol.

REFERENCES

- This compound was obtained as yellow needles (ethanol), m.p. 167°.
- Anal.* Calcd. for C₂₉H₂₀N₄O₈: C, 63.04; H, 3.65; N, 10.14. Found: C, 62.71; H, 3.65; N, 10.28.
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 - (3) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, 1964, p. 207.
 - (4) L. Neelakantan, *J. Org. Chem.*, **23**, 741 (1958).