Synthesis of 5-Acyl-3,4-diaryl-4,5-dihydro-1,2,4-oxadiazoles

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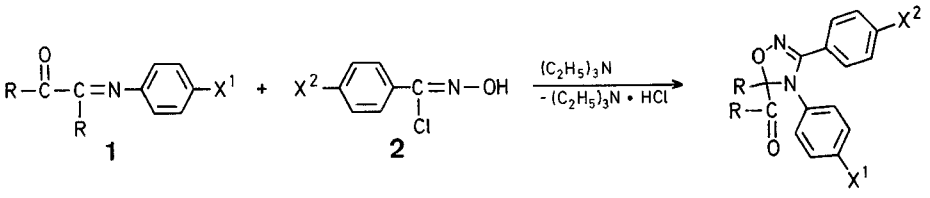
4,5-Dihydro-1,2,4-oxadiazoles are compounds of pharmacological interest[1]. They can easily be obtained by 1,3-dipolar cycloaddition of nitrile oxides and imines[2]. We describe the preparation of some new 5-substituted 5-acyl-3,4-diaryl-4,5-dihydro-1,2,4-oxadiazoles **3** achieved by the cycloaddition of nitrile oxides with monoimines **1** derived from 1,2-dicarbonyl compounds.

Appropriate iminoketones **1** were prepared according to reported methods by the reaction of benzil ($R = C_6H_5$) or biacetyl ($R = CH_3$) with *p*-substituted anilines[3] (Table). Benzonitrile



1 2 3a-w

3	R	X^1	X^2	3	R	X^1	X^2
a		H	H	l		H	Cl
b		CH_3	H	m		CH_3	Cl
c		OCH_3	H	n		OCH_3	Cl
d		$N(CH_3)_2$	H	o		$N(CH_3)_2$	Cl
e		Cl	H	p		Cl	Cl
f		Br	H	q		Br	Cl
g	H_3C	H	H	r		H	CH_3
h	H_3C	CH_3	H	s		CH_3	CH_3
i	H_3C	OCH_3	H	t		OCH_3	CH_3
j	H_3C	Cl	H	u		$N(CH_3)_2$	CH_3
k	H_3C	Br	H	v		Cl	CH_3
				w		Br	CH_3

oxide as well as its *p*-methyl and *p*-chloro derivatives were generated *in situ* from hydroxamoyl chlorides **2** according to Ref.[6]. The success of this cycloaddition depends on the higher reactivity of the imino group as a dipolarophile as compared to that of the carbonyl group. This preference has already been noted[4], but not for systems having both functional groups in the same molecule.

The regioselectivity obtained is that expected for frontier orbital control of the reaction (HOMO dipole-LUMO dipolarophile)[5].

5-Acetyl-3,4-diaryl-5-methyl- and 5-Benzoyl-3,4-diaryl-5-phenyl-4,5-dihydro-1,2,4-oxadiazoles 3a–w; General Procedure:

A mixture of the imine **1** (1 mmol) and the benzhydroxamoyl chloride **2** (1.2 mmol) is treated with freshly distilled triethylamine (1.2 mmol). For $R = C_6H_5$ the mixture is refluxed and for $R = CH_3$ it is left at room temperature. Triethylamine hydrochloride is filtered off, the solvent evaporated, and the resulting oxadiazoline is purified by silica gel chromatography using benzene as eluent (Table).

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Table. 5-Acyl-3,4-diaryl-4,5-dihydro-1,2,4-oxadiazoles **3**

3	Solvent	Time [h]	Yield [%]	m.p. [°C]	Molecular Formula[a]		I.R. (KBr)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
a	CCl_4	48	45	149–150° (methanol)	$C_{27}H_{20}N_2O_2$	(404.5)	1685	6.8–7.8 (m)
b	toluene	47	60	176–177° (ethanol)	$C_{28}H_{22}N_2O_2$	(418.5)	1685	2.0 (s); 6.6–7.8 (m)
c	benzene	48	40	173–174° (methanol)	$C_{28}H_{22}N_2O_3$	(434.5)	1690	3.5 (s); 6.6–7.7 (m)
d	toluene	48	65	198–199° (acetone)	$C_{29}H_{25}N_3O_2$	(447.5)	1690	2.8 (s); 6.6–8.0 (m)
e	toluene	48	25	155–156° (methanol)	$C_{27}H_{19}ClN_2O_2$	(438.9)	1680	6.9–8.0 (m)
f	toluene	72	50	168–169° (methanol)	$C_{27}H_{19}BrN_2O_2$	(483.4)	1680	7.0–8.1 (m)
g	toluene	6	76	94–95° (hexane/benzene)	$C_{17}H_{16}N_2O_2$	(280.3)	1720	1.46 (s); 2.46 (s); 6.9–7.6 (m)
h	toluene	5	60	80–82° (hexane/benzene)	$C_{18}H_{18}N_2O_2$	(294.4)	1720	1.45 (s); 2.26 (s); 2.45 (s); 6.8–7.6 (m)
i	toluene	7	78	oil	$C_{18}H_{18}N_2O_3$	(310.4)	1730	1.45 (s); 2.46 (s); 3.75 (s); 6.6–7.6 (m)
j	toluene	5	40	74–76°[d]	$C_{17}H_{15}ClN_2O_2$	(314.8)	1725	1.47 (s); 2.45 (s); 6.4–7.5 (m)
k	toluene	10	68	83–85° (hexane/benzene)	$C_{17}H_{15}BrN_2O_2$	(359.2)	1725	1.48 (s); 2.47 (s); 6.8–7.6 (m)
l	$CHCl_3$	8	47	137–138° (ethanol)	$C_{27}H_{19}ClN_2O_2$	(439.0)	1685	7.0–8.0 (m)
m	$CHCl_3$	6	56	144–146° (ethanol)	$C_{28}H_{21}ClN_2O_2$	(453.0)	1680	2.14 (s); 6.8–8.0 (m)
n	$CHCl_3$	7	60	153–154° (ethanol)	$C_{28}H_{21}ClN_2O_3$	(469.0)	1685	3.67 (s); 6.5–8.1 (m)
o	$CHCl_3$	6	80	136–138° (ethanol)	$C_{29}H_{24}ClN_3O_2$	(482.0)	1680	2.77 (s); 6.1–8.1 (m)
p	$CHCl_3$	7	46	130–131° (ethanol)	$C_{27}H_{18}Cl_2N_2O_2$	(473.5)	1675	6.8–8.1 (m)
q	$CHCl_3$	8	30	142–144° (ethanol)	$C_{28}H_{18}BrClN_2O_2$	(518.0)	1690	
r	$CHCl_3$	8	40	153–154° (ethanol)	$C_{28}H_{22}N_2O_2$	(418.5)	1685	2.20 (s); 6.8–8.1 (m)
s	$CHCl_3$	8	50	157–158° (ethanol)	$C_{29}H_{24}N_2O_2$	(432.5)	1685	2.10 (s); 2.27 (s); 6.7–8.1 (m)
t	$CHCl_3$	18	65	133–135° (ethanol)	$C_{29}H_{24}N_2O_3$	(448.5)	1680	2.16 (s); 3.50 (s); 6.3–8.0 (m)
u	$CHCl_3$	9	72	165–166° (ethanol)	$C_{30}H_{27}N_3O_2$	(461.6)	1680	2.20 (s); 2.77 (s); 6.2–8.1 (m)
v	$CHCl_3$	8	30	134–135° (ethanol)	$C_{28}H_{21}ClN_2O_2$	(453.0)	1680	2.27 (s); 6.9–8.1 (m)
w	$CHCl_3$	9	30	139–140° (ethanol)	$C_{28}H_{21}BrN_2O_2$	(497.4)	1675	2.24 (s); 6.7–8.1 (m)

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.20, N ±0.26, Cl ±0.30, Br ±0.20.
[b] Measured in a Perkin-Elmer spectrophotometer 257; compound **3i** was recorded as neat liquid.
[c] Measured with a Varian T-60A spectrometer.
[d] Taken for the crude product, without crystallisation.

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