

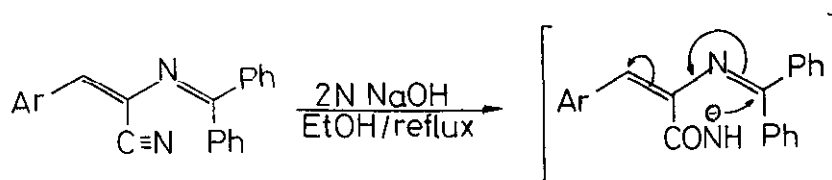
A SYNTHESIS OF 2,2,4-TRISUBSTITUTED 2H-IMIDAZOL-5-ONES FROM 3-CYANO-1,1,4-TRIARYL-2-AZA-1,3-DIENES

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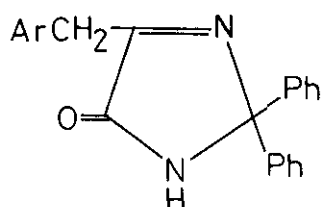
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Abstract - A series of 4-arylmethyl-2,2-diphenyl-2H-imidazol-5-ones (2a-r) are prepared via intramolecular cyclization from 4-aryl-3-cyano-1,1-diphenyl-2-aza-1,3-butadienes (1a-r) in aq. NaOH - ethanol system.

The synthesis of imidazoles¹⁻³ is of continuing interest since many compounds of this type play important roles in biologically significant processes and possess a variety of pharmacological activities. Although much attention has been focused to the chemistry of 2- and 4-oxo-imidazole derivatives^{3,4} because of their numerous uses as insecticides, fungicides, and pharmacologically active substances, little work has been done on 2H-imidazol-5-ones. Only a few reports are available in the literature, dealing both with their synthesis^{5,6} and structures.^{7,8} Some 2,2,4-trisubstituted 2H-imidazol-5-ones are prepared by oxidation of the corresponding 2H-imidazol-5-thiones,⁵ which in turn are obtained by reaction of acetophenones, ammonia and excess sulfur,⁹ or by condensation of ketones and aldehydes with α -oxothionamides.^{5,10} Another approach to the 2,2,4-trisubstituted 2H-imidazol-5-ones is the reaction of the amide of phenylglyoxylic acid with acetophenone and ammonia,⁵ as well as peracid oxidation of 2,2,4-trisubstituted 2H-imidazoles,⁶ or the reaction of their N-oxides with sodium cyanide in DMSO.⁶ In this paper we report



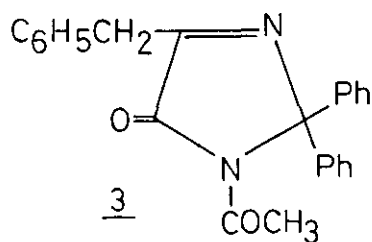
1a-r



2a-r

2	Ar
<u>a</u>	C ₆ H ₅
<u>b</u>	1-C ₁₀ H ₇
<u>c</u>	2-C ₁₀ H ₇
<u>d</u>	2-Furyl
<u>e</u>	3-Pyridyl
<u>f</u>	2-BrC ₆ H ₄
<u>g</u>	4-BrC ₆ H ₄
<u>h</u>	2-ClC ₆ H ₄
<u>i</u>	4-ClC ₆ H ₄

2	Ar
<u>j</u>	2,4-Cl ₂ C ₆ H ₃
<u>k</u>	2-FC ₆ H ₄
<u>l</u>	4-FC ₆ H ₄
<u>m</u>	2-CH ₃ C ₆ H ₄
<u>n</u>	4-CH ₃ C ₆ H ₄
<u>o</u>	2,4-(CH ₃) ₂ C ₆ H ₃
<u>p</u>	2-CH ₃ OC ₆ H ₄
<u>q</u>	4-CH ₃ OC ₆ H ₄
<u>r</u>	2,4-(CH ₃) ₂ C ₆ H ₃



a new synthesis of 2,2,4-trisubstituted 2H-imidazol-5-ones (2) starting from the 2-aza-1,3-butadienes (1) (Scheme). Refluxing a mixture of 1, which was easily prepared by condensation of N-diphenylmethyleamino-acetonitrile with aromatic aldehydes,¹¹ 2N sodium hydroxide and ethanol until dissolution of all solids (1-5 h), resulted in the 4-arylmethyl-2,2-diphenyl-2H-imidazol-5-ones 2 (Table 1). The reactions involve hydrolysis of the cyano function to the corresponding amide, which then undergoes intramolecular cyclization to afford the compounds (2). The ¹H nmr spectra show singlet for the methylene group in the region 3.82-4.32 ppm and broad NH singlet signal at δ 9.20-10.50 ppm. In the ir spectra they have the NH absorption at 3164-3193 cm⁻¹ and 3436-3439 cm⁻¹, the C=O at 1710-1720 cm⁻¹, and the C=N at 1627-1636 cm⁻¹. In addition, compounds (2) can be easily acylated. Thus, refluxing 2a with excess of acetic anhydride gave amide derivative (3) in 77 % yield. As can be seen from Table 1, the yields of the prepared 2,2,4-trisubstituted 2H-imidazol-5-ones (2a-r) are modest. Attempts to improve the yield of 2a by varying the molar ratio of reactants, the concentration, and the solvent (CH₂Cl₂, DMF), gave similar results, or failed. However, despite the moderate yield, the method provides a direct route to these compounds from readily available starting materials.

EXPERIMENTAL

Melting points were taken on a Boetius micro melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 983 G spectrophotometer in chloroform solutions. The ¹H nmr spectra were obtained on Tesla BS 487-C (80 MHz) spectrometer in CDCl₃ solutions using TMS as internal standard. The azadienes (1a-r) were prepared according to published procedure.¹¹

Table 1. 4-Arylmethyl-2,2-diphenyl-
2H-imidazol-5-ones (2)

Com- pound	Reaction time (h)	Yield (%)	mp(°C) ^a
<u>2a</u>	2	58	188-189
<u>2b</u>	5	53	169-170
<u>2c</u>	5	49	231-232 ^b
<u>2d</u>	1	50	170-172
<u>2e</u>	1	26	188-190 ^c
<u>2f</u>	2	50	180-181
<u>2g</u>	5	42	200-201
<u>2h</u>	2	47	188-190
<u>2i</u>	1	31	183-184
<u>2j</u>	23	38	189-191
<u>2k</u>	1	42	183-185
<u>2l</u>	2	44	179-181
<u>2m</u>	5	35	131-132
<u>2n</u>	2	47	179-180
<u>2o</u>	3	57	194-196
<u>2p</u>	5	53	158-159
<u>2q</u>	5	48	179-180
<u>2r</u>	3	57	171-172

^a Recrystallized from ethanol unless
stated otherwise.

^b From ethyl acetate.

^c From acetone.

Table 2. Spectroscopic Data and Analyses of Compounds 2a-r

Com- pound	Ir(CHCl ₃) ν, cm ⁻¹	¹ H nmr (CDCl ₃) δ, ppm	Molecular Formula	Calcd/Found (%)		
				C	H	N
<u>2a</u>	3439,3184 1711,1630	3.95 (s, 2H), 7.00-7.40 (m, 15H), 9.30 (br s, 1H)	C ₂₂ H ₁₈ N ₂ O	80.95 80.90	5.59 5.82	8.59 8.39
<u>2b</u>	3439,3171 1710,1630	4.32 (s, 2H), 6.80-7.75 (m, 17H), 10.50 (br s, 1H)	C ₂₆ H ₂₀ N ₂ O	82.95 82.60	5.35 5.61	7.44 7.24
<u>2c</u>	3439,3183 1720,1627	^a 4.06 (s, 2H), 7.00-7.90 (m, 17H), 10.87 (br s, 1H)	C ₂₆ H ₂₀ N ₂ O	82.95 82.65	5.35 5.55	7.44 7.26
<u>2d</u>	3439,3178 1720,1636	3.97 (s, 2H), 6.00-6.25 (m, 3H), 7.00-7.35 (m, 10H), 9.65 (br s, 1H)	C ₂₀ H ₁₆ N ₂ O ₂	75.93 76.23	5.10 5.26	8.86 8.46
<u>2e</u>	3439,3184 1713,1633	3.97 (s, 2H), 7.00-7.72 (m, 12H), 8.32-8.62 (m, 2H), 9.70 (br s, 1H)	C ₂₁ H ₁₇ N ₃ O	77.04 77.58	5.23 5.62	12.83 12.51
<u>2f</u>	3439,3164 1711,1632	^a 4.00 (s, 2H), 6.80-7.47 (m, 14H), 10.69 (br s, 1H)	C ₂₂ H ₁₇ BrN ₂ O	65.20 65.44	4.23 4.25	6.91 6.81
<u>2g</u>	3437,3166 1711,1630	3.85 (s, 2H), 6.87-7.34 (m, 14H), 10.21 (br s, 1H)	C ₂₂ H ₁₇ BrN ₂ O	65.20 65.44	4.23 4.38	6.91 6.84
<u>2h</u>	3439,3166 1710,1633	4.05 (s, 2H), 6.87-7.37 (m, 14H), 10.02 (br s, 1H)	C ₂₂ H ₁₇ ClN ₂ O	73.23 73.37	4.75 5.00	7.76 7.48
<u>2i</u>	3437,3172 1711,1630	3.9 ⁴ (s, 2H), 7.00-7.50 (m, 14H), 10.07 (br s, 1H)	C ₂₂ H ₁₇ ClN ₂ O	73.23 73.36	4.75 4.51	7.76 7.48
<u>2j</u>	3439,3174 1711,1635	4.04 (s, 2H), 7.00-7.45 (m, 13H), 10.24 (br s, 1H)	C ₂₂ H ₁₆ Cl ₂ N ₂ O	66.85 67.02	4.08 4.33	7.09 6.95

Table 2 (continued)

<u>2k</u>	3436,3168	4.00 (s, 2H), 6.70-7.40	$C_{22}H_{17}FN_2O$	76.73	4.97	8.13
	1711,1634	(m, 14H), 9.92 (br s, 1H)		76.42	4.93	7.91
<u>2l</u>	3437,3180	3.89 (s, 2H), 6.57-7.40	$C_{22}H_{17}FN_2O$	76.73	4.97	8.13
	1711,1631	(m, 14H), 9.84 (br s, 1H)		76.41	4.92	8.01
<u>2m</u>	3439,3168	2.39 (s, 3H), 3.95 (s, 2H), 6.89-7.40 (m, 14H), 10.09 (br s, 1H)	$C_{23}H_{20}N_2O$	81.15	5.92	8.23
	1711,1629			80.96	6.17	8.17
<u>2n</u>	3439,3182	2.27 (s, 3H), 3.87 (s, 2H), 6.81-7.39 (m, 14H), 10.02 (br s, 1H)	$C_{23}H_{20}N_2O$	81.15	5.92	8.23
	1711,1630			80.98	5.99	8.01
<u>2o</u>	3438,3170	2.31 (s, 6H), 3.91 (s, 2H), 6.75-7.40 (m, 13H), 9.20 (br s, 1H)	$C_{24}H_{22}N_2O$	81.33	6.26	7.90
	1711,1629			81.63	6.59	7.66
<u>2p</u>	3439,3182	3.57 (s, 3H), 3.95 (s, 2H), 6.59-7.41 (m, 14H), 10.35 (br s, 1H)	$C_{23}H_{20}N_2O_2$	77.51	5.66	7.86
	1711,1630			77.74	5.82	7.78
<u>2q</u>	3439,3172	3.70 (s, 3H), 3.89 (s, 2H), 6.55-7.40 (m, 14H), 10.01 (br s, 1H)	$C_{23}H_{20}N_2O_2$	77.51	5.66	7.86
	1713,1629			77.81	5.59	7.68
<u>2r</u>	3439,3193	3.52 (s, 3H), 3.70 (s, 3H), 3.82 (s, 2H), 6.15-7.27 (m, 13H), 9.68 (br s, 1H)	$C_{24}H_{22}N_2O_3$	74.59	5.74	7.25
	1713,1629			74.83	5.96	7.25

^a DMSO- d_6 used as solvent.

Preparation of the compounds (2a,b,d-r) (general procedure)

2N Sodium hydroxide solution (50 ml, 100 mmol) was added to a suspension of 1 (5 mmol) in ethanol (50 ml) and the mixture was heated under reflux until dissolution of all solids (Table 1). The solvent was evaporated under reduced pressure, water (100 ml) was added and the residue was extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with

water (100 ml), dried (Na_2SO_4), and concentrated. The residue was taken in ethanol to give the compounds (2) (Tables 1 and 2).

2,2-Diphenyl-4-(2-naphthylmethyl)-2H-imidazol-5-one (2c)

The mixture of 3-cyano-1,1-diphenyl-4-(2-naphthyl)-2-aza-1,3-butadiene (1c, 1.79 g, 5 mmol), 2N NaOH (50 ml, 100 mmol) and ethanol (50 ml) was heated under reflux for 2 h. The solvent was evaporated and the precipitate formed was collected by filtration and recrystallization from ethanol.

Acetylation of compound 2a: preparation of N-acetyl-4-benzyl-2,2-diphenyl-2H-imidazol-5-one (3)

A solution of 2a (0.50 g, 1.5 mmol) in acetic anhydride (5.10 g, 50 mmol) was heated under reflux for 2 h. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (3 x 25 ml). After drying (Na_2SO_4), the solvent was evaporated and the residue was taken up in ethanol to give, after recrystallization from ethanol-water, 0.43 g (77%) of 3: mp 111-112°C; ir (nujol): 1640 (C=N), 1710, 1745 (C=O) cm^{-1} ; ^1H nmr (CDCl_3): 2.47 (s, 3H, CH_3CO), 3.94 (s, 2H, CH_2), 6.92-7.30 (m, 15H, arom.); Anal. Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.97; H, 5.73; N, 7.51.

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