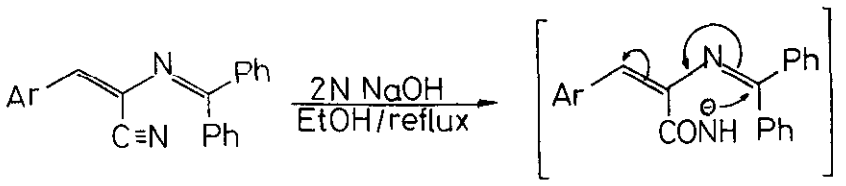
A SYNTHESIS OF 2,2,4-TRISUBSTITUTED 2H-IMIDAZOL-5-ONES FROM 3-CYANO-1,1,4-TRIARYL-2-AZA-1,3-DIENES

Veneta Dryanska

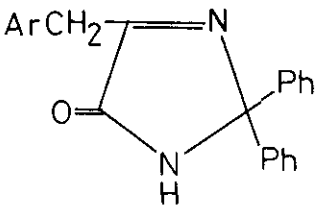
Department of Chemistry, University of Sofia,
Sofia 1126, Bulgaria

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 imidazoles[1-3] 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



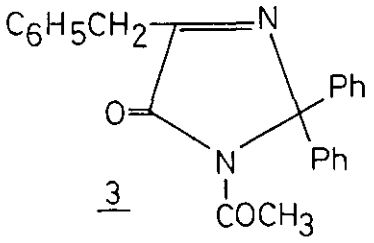
1a-r



2a-r

2	Ar
a	C_6H_5
b	1-$C_{10}H_7$
c	2-$C_{10}H_7$
d	2-Furyl
e	3-Pyridyl
f	2-BrC_6H_4
g	4-BrC_6H_4
h	2-ClC_6H_4
i	4-ClC_6H_4

2	Ar
j	2,4-$Cl_2C_6H_3$
k	2-FC_6H_4
l	4-FC_6H_4
m	2-$CH_3C_6H_4$
n	4-$CH_3C_6H_4$
o	2,4-$(CH_3)_2C_6H_3$
p	2-$CH_3OC_6H_4$
q	4-$CH_3OC_6H_4$
r	2,4-$(CH_3)_2C_6H_3$



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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-diphenylmethyleneamino-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 ^{1}H 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 (CH_2Cl_2, 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 ^{1}H nmr spectra were obtained on Tesla BS 487-C (80 MHz) spectrometer in $CDCl_3$ 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)

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

Compound	Ir($CHCl_3$) ν, cm^{-1}	^1H nmr ($CDCl_3$) δ, ppm	Molecular Formula	Calcd/Found (%) C	H	N
2a	3439,3184 1711,1630	3.95 (s, 2H), 7.00-7.40 (m, 15H), 9.30 (br s, 1H)	$C_{22}H_{18}N_2O$	80.95 80.90	5.59 5.82	8.59 8.39
2b	3439,3171 1710,1630	4.32 (s, 2H), 6.80-7.75 (m, 17H), 10.50 (br s, 1H)	$C_{26}H_{20}N_2O$	82.95 82.60	5.35 5.61	7.44 7.24
2c	3439,3183 1720,1627	[a]4.06 (s, 2H), 7.00-7.90 (m, 17H), 10.87 (br s, 1H)	$C_{26}H_{20}N_2O$	82.95 82.65	5.35 5.55	7.44 7.26
2d	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)	$C_{20}H_{16}N_2O_2$	75.93 76.23	5.10 5.26	8.86 8.46
2e	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)	$C_{21}H_{17}N_3O$	77.04 77.58	5.23 5.62	12.83 12.51
2f	3439,3164 1711,1632	[a]4.00 (s, 2H), 6.80-7.47 (m, 14H), 10.69 (br s, 1H)	$C_{22}H_{17}BrN_2O$	65.20 65.44	4.23 4.25	6.91 6.81
2g	3437,3166 1711,1630	3.85 (s, 2H), 6.87-7.34 (m, 14H), 10.21 (br s, 1H)	$C_{22}H_{17}BrN_2O$	65.20 65.44	4.23 4.38	6.91 6.84
2h	3439,3166 1710,1633	4.05 (s, 2H), 6.87-7.37 (m, 14H), 10.02 (br s, 1H)	$C_{22}H_{17}ClN_2O$	73.23 73.37	4.75 5.00	7.76 7.48
2i	3437,3172 1711,1630	3.94 (s, 2H), 7.00-7.50 (m, 14H), 10.07 (br s, 1H)	$C_{22}H_{17}ClN_2O$	73.23 73.36	4.75 4.51	7.76 7.48
2j	3439,3174 1711,1635	4.04 (s, 2H), 7.00-7.45 (m, 13H), 10.24 (br s, 1H)	$C_{22}H_{16}Cl_2N_2O$	66.85 67.02	4.08 4.33	7.09 6.95

Table 2 (continued)

2k	3436,3168 1711,1634	4.00 (s, 2H), 6.70-7.40 (m, 14H), 9.92 (br s, 1H)	$C_{22}H_{17}FN_2O$	76.73 76.42	4.97 4.93	8.13 7.91
2l	3437,3180 1711,1631	3.89 (s, 2H), 6.57-7.40 (m, 14H), 9.84 (br s, 1H)	$C_{22}H_{17}FN_2O$	76.73 76.41	4.97 4.92	8.13 8.01
2m	3439,3168 1711,1629	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 80.96	5.92 6.17	8.23 8.17
2n	3439,3182 1711,1630	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 80.98	5.92 5.99	8.23 8.01
2o	3438,3170 1711,1629	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 81.63	6.26 6.59	7.90 7.66
2p	3439,3182 1711,1630	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 77.74	5.66 5.82	7.86 7.78
2q	3439,3172 1713,1629	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 77.81	5.66 5.59	7.86 7.68
2r	3439,3193 1713,1629	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 74.83	5.74 5.96	7.25 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 $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.97; H, 5.73; N, 7.51.

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