IMIDAZOLIDES OF PIPERIDONE CARBOXYLIC ACIDS: SYNTHESIS AND PHYSICAL PROPERTIES

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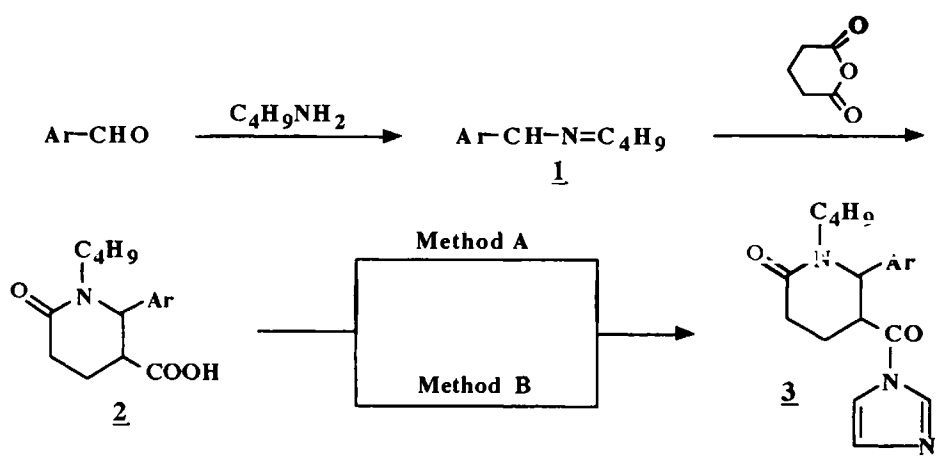
Abstract:

The condensation of arylidene n-butylamines with glutaric anhydride giving *N*-Butyl-2-aryl-3-carboxy-piperidin-6-ones 2 compounds has been carried out in satisfying yields. Trans acids derivatives were obtained by fractional cristallization. Eight new imidazolides of piperidonic-carboxylic acids 3 were synthesized from 2 by two simple methods.

Introduction

Our interest in the title compounds was generated by the pharmacological investigations of imidazolide and piperidone derivatives. Imidazole ring has been increasingly incorporated into structures synthesized for their potential biological activities: antifungal (1), antiparasitic agents (2), antithromboxane synthetase (3,4) and aromatase inhibitors (5,6,7). The piperidone-carboxylic acids 2a-h have been prepared by condensation of arylidene n-butylamines and glutaric anhydride in refluxing toluene or xylene (Scheme 1).



Method A: 1/ $SOCl_2$ / $CHCl_3$, 80°C 4h
2/ Imidazole / CH_3CN, reflux 3h

Method B: 1,1'-carbonyldiimidazole, THF, reflux 3h

Scheme 1

The main reaction provided trans-1-butyl-2-aryl-3-carboxy-piperidin-6-ones in satisfying yields (Table 1). The corresponding imidazolides of piperidone-carboxylic acids 3a-h were obtained by two simple methods. The appropriate acidic chloride was refluxed with three molar excess of imidazole in anhydrous acetonitrile under nitrogen (method A). The other reaction constituted the preferred synthetic way (method B): the reaction of free carboxylic acids, with *N,N'*-carbonyldiimidazole in equimolar proportions, in anhydrous tetrahydrofuran at room temperature gave imidazolides in good yields (Table 2).

Experimental

M.p.s were determined in open capillary tubes on a Buchi micro-melting-point apparatus and are uncorrected. IR spectra were recorded for KBr discs using a Perkin-Elmer 1320 spectrometer. ^1H NMR spectra were determined on a Bruker AC 200 MHz spectrophotometer using tetramethylsilane as an internal standard (chemical shifts in ppm).

General procedure for the preparation of 1-N-butyl-2-aryl-3-carboxy-piperidin-6-ones 2a-h.

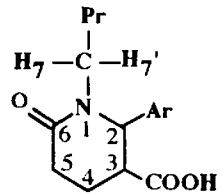
Arylidene n-butylamines 1 (0.05 mol) and glutaric anhydride (0.05 mol) were heated in refluxing toluene (or xylene) for 24 h. The solvent was reduced under vacuum. Analytically pure trans acid derivatives were obtained from the diastereomeric mixture by fractional cristallization (Table 1). I.R: ν_{max} /cm^{-1} (KBr) 1725, 1710, 1600 and 1580.

1-N-Butyl-2-aryl-3-imidazolide-6-oxo-piperidines 3 a-h

Method A : In a round bottom flask fitted with a magnetic stirrer, a condenser, and a nitrogen inlet, thionyl chloride (100 ml) was added to carboxypiperidines 2 (0.03 mol) dissolved in 100 ml of $CHCl_3$. The mixture was heated for 4 h at 80°C on an oil bath, then evaporated under vacuum. The residue was treated with dry benzene and evaporated to dryness. The crude precipitate was washed with dry diethyl ether and allowed to react with imidazole (0.09 mol) in 150 ml of CH_3CN without further purification. The mixture was refluxed 3 h with stirring under a nitrogen atmosphere. The solvent was evaporated in vacuo and the imidazolides purified by cristallization (Table 2). I.R: ν_{max} /cm^{-1} (KBr) 1730, 1725, 1640 and 1625.

Method B: A mixture of carboxypiperidinones 2 (0.01 mol) and carbonyldiimidazole (0.013 mol) in 30 ml of anhydrous THF was refluxed for 3 h under a nitrogen atmosphere on an oil bath. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ (50 ml) and treated with a $NaHCO_3$ saturated solution (50 ml). The organic layers were washed with water (3 x 20 ml) and dried on anhydrous Na_2SO_4. Evaporation of the solvent and cristallization of the residue provided the imidazolides having satisfactory spectral and elemental analysis data. The protection of the amino group of 2f with carbobenzoxychloride before reaction with carbonyldiimidazole (method B) was needded to obtain 3f in good yield. The deprotection was easily realized by catalytic hydrogenation (H_2, Pd/C).

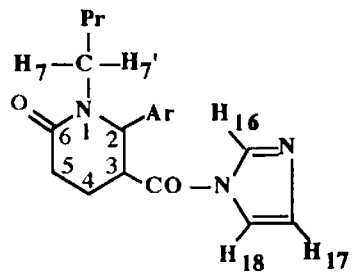
Table 1: 1-*N*-butyl-2-aryl-3-carboxy-piperidin-6-ones



N°	Ar	Recryst. solvent (*)	Yield (%)	M.p. (°C)	^{1}H nmr (δ ppm, CDC 3)								
					Arom	H2 (d)	H7 (m)	H3 (m)	2H5(m)	H7' (m)	H4 (m)	H4' (m)	J2-3 (Hz)
2 a	C_6H_5	a	72	170	7.3 (m, 5H)	5.1	4.0	2.9	2.6	2.4	2.1	1.8	2.8
2 b	4-NO_2 C_6H_4	b	40	173	8.3 (d, 2H) 7.4 (d, 2H)	5.3	4.0	2.9	2.6	2.4	2.1	1.8	2.9
2 c	4-Cl C_6H_4	c	60	140	7.4 (d, 2H) 7.1 (d, 2H)	5.1	4.0	2.8	2.6	2.4	2.1	1.9	3.0
2 d	4-F C_6H_4	d	45	124	7.1 (m, 4H)	5.1	4.0	2.8	2.6	2.4	2.1	1.9	3.3
2 e	4-NH_2 C_6H_4	e	98	164	6.8 (d, 2H) 6.5 (d, 2H)	4.7	3.7	2.7	2.3	2.3	1.8	1.8	4.4
2 f	4-C_5H_5N	f	40	185	8.6 (d, 2H) 7.3 (d, 2H)	5.2	4.0	2.9	2.6	2.4	2.1	1.8	3.3
2 g	2,4-Cl_2 C_6H_3	g	40	214	7.6 (d, H) 7.5 (d, H) 7.2 (d, H)	5.3	3.7	2.8	2.8	2.2	1.9	1.6	2.3
2 h	4-CN C_6H_4	h	40	137	7.2 (d 2H) 7.3 (d 2H)	5.2	4.0	2.8	2.6	2.4	2.1	1.8	2.9

(*) a: 2-propanone; b: ethyl acetate; c: ethanol 45°; d: diethyl ether; e: chloroform; f: diethyl ether / ethanol (70/30); g: ethanol 50°; h: ethanol 30°

Table 2: Imidazolides of piperidonic acids



N°	Ar	Method	Yield (%)	M.p. (°C)	^{1}H nmr (δ ppm, $CDCl_3$)								
					Arom	H_{16} (s)	H_2 (d)	H_7 (m)	H_3 (m)	$2H_5$ (m)	$H_{7'}$ (m)	$H_4H_{4'}$ (m)	J_{2-3} (Hz)
3 a	C_5H_5	A, B	53	145	7.20 (m, 7H)	8.00	5.00	4.00	3.45	2.64	2.45	2.16	5.5
3 b	4-NO_2 C_6H_4	A, B	54	177	8.25 (d, 2H); 7.45 (d, 2H); 7.37 (d, H_{18}); 7.09 (d, H_{17})	8.06	5.17	4.05	3.40	2.63	2.35	2.15	5.4
3 c	4-Cl C_6H_4	B	80	155	7.35 (d, 2H); 7.20 (d, 2H); 7.38 (d, H_{18}); 7.09 (d, H_{17})	8.07	5.00	4.02	3.38	2.61	2.44	2.15	5.8
3 d	4-F C_6H_4	B	81	143	7.25 (d, 4H); 7.34 (d, H_{18}); 7.03 (d, H_{17})	8.02	4.99	3.95	3.35	2.61	**2.45**	2.17	5.9
3 e	4-NH_2 C_6H_4	B	45	180	7.33 (d, H_{18}); 7.04 (d, H_{17}); 6.97 (d, 2H); 6.63 (d, 2H)	7.90	4.83	3.97	3.45	2.50	2.50	2.13	6.2
3 f	4-C_5H_5N	B	60	180	8.66 (d, 2H); 7.37 (d, H_{18}); 7.15 (d, H_{17}); 7.18 (d, 2H)	8.07	5.04	4.05	3.36	2.58	2.35	2.15	4.9
3 g	2,4-Cl_2 C_6H_3	B	75	130	7.47 (d, H_{14}); 7.44 (d, H_{18}); 7.30 (dd, H_{15}); 7.16 (d, H_{12}); 7.13 (d, H_{17})	8.12	5.31	4.05	3.52	2.48	2.35	2.10	2.8
3 h	4-CN C_6H_4	B	60	150	7.67 (d, 2H); 7.40 (m, 3H); 7.06 (d, H_{17})	8.04	5.10	4.00	3.60	2.57	2.35	2.15	5.4

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