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STEREOSELECTIVE SYNTHESIS OF NEW SPIRO-FUSED HETEROCYCLIC SYSTEMS, 2,3,4,4a,5.6-HEXAHYDRO-6H-SPIRO[BENZO[*c*]QUINOLIZINE-5,4'-PYRAZOL]-5'-ONES

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The synthesis of 2,3,4,4a,5,6-hexahydro-6H-spiro[benzo[c]quinolizine-5,4'-pyrazol]-5'-ones has been achieved by the reaction of 2-piperidinobenzaldehydes with 2-aryl-5-methyl-2,4-dihydropyrazol-3-one via the "tert-amino effect" mechanism.

Keywords: pyrazol-3-one, spiroheterocycles, quinolizine, *tert*-amino effect, Knoevenagel condensation.

The term "*tert*-amino effect" was proposed by Meth-Cohn and Suschitzky [1] for the general reaction of cyclization of some derivatives of *ortho*-substituted N,N-dialkylanilines. The cyclization which occurs at the unsaturated α-carbon atom of the dialkylamino group, was described for compounds with an unsaturated (A=B) *ortho* substituent, including at least one heteroatom (nitroso-, azo-, azomethino-, nitro-, amino-, or carbonyl functions) [2]. Professor Reinhoudt's group established that cyclization also took place with N,N-dialkylanilines with a vinyl substituent in the *ortho* position [3]. This reaction is an original method for the formation of a C–C bond with an unactivated NCH_2 group [4].

We have shown previously [5-8] that the Knoevenagel condensation occurs in tandem with cyclization *via* the *tert*-amino effect mechanism when 2-dialkylaminobenzaldehydes react with cyclic CH-active compounds (derivatives of 1,3-cyclohexandione, Meldrum's acid, barbituric acid) [9]. These reactions were shown to occur stereoselectively [4, 10-12].

The aim of the current work was to investigate the reaction of 2-piperidinobenzaldehydes **1a-d** with 2-aryl-5-methyl-2,4-dihydropyrazol-3-ones **2a-c**. The reactions were carried out in boiling butanol. 3'-Methyl-1'-phenyl-2,3,4,4a,5,6-hexahydro-6H-spiro[benzo[*c*]quinolizine-5,4'-pyrazol]-5'-ones **3a-j** (Table 1) were formed as a result. The reaction products contain two asymmetric centers, so it is consequently possible to form two diastereoisomers. It was shown that the reaction proceeded stereoselectively and led predominantly to a single diastereomer (up to 95-98%).

In the ^{1}H NMR spectrum of the basic reaction product (Table 2) the signal of the proton on the carbon atom 4a appears as a doublet of doublets in the 3.13-3.18 ppm region. This proton interacts with a large coupling constant of 11.2-11.5 Hz with the axial hydrogen in position 4 and with a small coupling constant of 2.3-2.5 Hz with the equatorial hydrogen in the same position. Hence the hydrogen in position 4a occupies an axial position.

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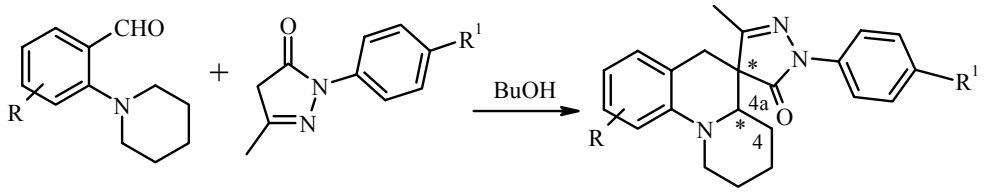

1a–d **2a–c** **3a–j**

1 a R = H, **b** R = Cl-4, **c** R = Br-5, **d** R = CF_3-5; **2 a** R^1 = H, **b** R^1 = Cl, **c** R^1 = CO_2Et; **3 a-c** R = H, **a** R^1 = H, **b** R^1 = Cl, **c** R^1 = CO_2Et; **d** R = Cl-9, R^1 = H, **e-g** R = Br-8, **e** R^1 = H, **f** R^1 = Cl, **g** R^1 = CO_2Et; **h-j** R = CF_3-8, **h** R^1 = H, **i** R^1 = Cl, **j** R^1 = CO_2Et

The signal of the proton in position 4a of the minor isomer is observed as a doublet with J = 10 Hz and is shifted to weak field in comparison with the proton of the major isomer. It is possible that the proton of the major isomer falls within the shielding cone of the anisotropic carbonyl group, as a result of which its signal is shifted to strong field. It is most likely that the oxygen atom of the keto group of the minor product lies in the axial position.

Thus we have developed a stereoselective method for the synthesis of new heterocyclic system, 1'-aryl-3'-methyl-2,3,4,4a,5,6-hexahydro-6H-spiro[benzo[*c*]quinoliizine-5,4'-pyrazol]-5'-one.

TABLE 1. Characteristics of Compounds **3a-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Mass spectrum, *m/z* (*I*, %)	Yield, %
		C	H	N			
3a	$C_{22}H_{23}N_3O$	76.52 / 76.49	6.79 / 6.71	12.25 / 12.16	95	345 (100)	85
3b	$C_{22}H_{22}ClN_3O$	69.85 / 69.56	6.07 / 5.84	11.23 / 11.06	122	381 (31), 379 (100)	85
3c	$C_{25}H_{27}N_3O_3$	72.11 / 71.92	6.77 / 6.52	10.34 / 10.06	123	417 (98)	90
3d	$C_{22}H_{22}ClN_3O$	69.66 / 69.56	5.98 / 5.84	11.38 / 11.06	76	381 (38), 379 (100)	87
3e	$C_{22}H_{22}BrN_3O$	62.35 / 62.27	5.54 / 5.23	10.12 / 9.90	96	425 (100), 423 (97)	85
3f	$C_{22}H_{21}BrClN_3O$	57.98 / 57.60	4.87 / 4.61	9.17 / 9.16	180	461 (22), 459 (100), 457 (97)	77
3g	$C_{25}H_{26}BrN_3O_3$	60.67 / 60.49	5.37 / 5.28	8.77 / 8.46	113	497 (100), 495 (98)	76
3h	$C_{23}H_{22}F_3N_3O$	66.94 / 66.82	5.52 / 5.36	10.28 / 10.16	109		78
3i	$C_{23}H_{21}ClF_3N_3O$	61.78 / 61.68	5.01 / 4.73	9.55 / 9.38	168		82
3j	$C_{26}H_{26}F_3N_3O_3$	64.48 / 64.32	5.51 / 5.40	9.02 / 8.65	97		75

Table 2. ^{1}H NMR Spectra of Compounds **3a-j**

Compound	Chemical shifts, δ, ppm., (SSCC, *J*, (Hz)							
	H-1 (e), br. d	H-1 (a)	H-2 (e)	H-2 (a)	H-3 (e)	H-3 (a), m	H-4 (e)	H-4 (a), dddd
3a	4.09 (12.0)	2.67 (dd, 12.0, 11.8)	1.79 (br. d, 11.0)	1.54 (br. d, 10.8)	1.56 (br. d, 9.8)	1.35-1.41	1.78 (br. d, 12.0)	1.04 (12.3, 11.6, 11.5, 3.3)
3b	4.09 (11.3)	2.60-2.80 (m)	1.65-1.89 (m)	1.25-1.65 (m)				1.02 (12.2, 11.9, 11.2, 3.5)
3c	4.10 (11.9)	2.64 (dd, 11.9, 9.5)	1.68-1.88 (m)	1.68-1.88 (m)	1.35-1.55 (m)		1.34-1.29 (m)	1.03 (12.5, 11.6, 11.5, 3.2)
3d	4.02 (11.5)	2.76 (br. d, 5.8)	1.78 (br. d, 15.4)	1.57 (br. d, 10.5)	1.55 (br. d, 10.1)	1.34-1.45	1.75 (br. d, 12.1)	1.05 (12.6, 11.5, 3.0, 11.3)
3e	4.03 (12.3)	2.63-2.73 (m)	1.76 (br. d, 14.2)	1.58 (br. d, 12.5)	1.55 (br. d, 11.9)	1.33-1.47	1.77 (br. d, 14.8)	1.01 (12.4, 11.8, 3.0, 11.3)
3f	4.03 (11.6)	2.60-2.78 (m)	1.65-2.00 (m)	1.20-1.65 (m)			1.65-2.00 (m)	1.02 (12.2, 11.9, 3.5, 11.6)
3g	4.10 (11.4)	2.66 (dd, 9.6, 10.8)	1.68-1.88 (m)	1.35-1.55 (m)			1.68-1.88 (m)	1.06 (12.5, 11.6, 10.8, 3.2)
3h	4.13 (12.0)	2.63-2.75 (m)	1.70-1.87 (m)	1.25-1.68 (m)			1.70-1.87 (m)	1.00 (12.5, 12.0, 11.3, 3.6)
3i	4.15 (12.5)	2.70-3.00 (m)	1.70-2.00 (m)	1.25-1.75 (m)			1.70-2.00 (m)	1.03 (12.6, 12.0, 11.5, 3.0)
3j	4.09 (11.3)	3.00-3.15 (m)	1.76-2.00 (m)	1.35-1.60 (m)			1.76-2.00 (m)	1.02 (12.6, 11.7, 11.0, 3.1)

Table 2 (continued)

Compound	Chemical shifts, δ, ppm., (SSCC, *J*, (Hz)										
	H-4(a), dd	H-6 (e), d	H-6 (a), d	H-7	H-8	H-9	H-10	CH_3, s	ArH_2-*o*, d	ArH_2-*m*	ArR^2-*p*
3a	3.14 (11.5, 2.5)	3.27 (16.3)	2.71 (16.3)	7.02 (d, 7.0)	7.10 (dd, 7.3, 7.0)	6.67 (dd, 7.3, 7.0)	6.95 (d, 7.0)	1.90	7.88 (8.3)	7.38 (dd, 8.3, 8.5)	7.13 (1H, t, *J* = 8.5, ArH)
3b	3.14 (11.2, 2.5)	3.26 (16.5)	2.71 (16.5)	6.92 (d, 7.6)	7.09 (dd, 7.6, 7.6)	6.67 (dd, 7.6, 6.3)	6.83 (d, 6.3)	1.90	7.90 (9.0)	7.38 (d, 9.0)	
3c	3.14 (11.5, 2.5)	3.19 (16.5)	2.88 (16.5)	7.04 (d, 7.8)	7.13 (dd, 7.6, 7.8)	6.71 (dd, 7.6, 7.2)	7.02 (d, 7.2)	2.05	8.00 (s)		4.32 (2H,q, *J* = 7.2, OCH_2);1.33 (3H, t, *J* = 7.2, CH_3)
3d	3.18 (11.3, 2.6)	3.19 (16.8)	2.72 (16.8)	6.95 (d, 9.0)	6.90 (dd, 9.0, 2.8)		6.65 (d, 2.8)	1.90	7.88 (8.0)	7.38 (dd, 7.8, 8.0)	7.15 (1H, t, *J* = 7.8, ArH)
3e	3.13 (11.3, 2.5)	3.22 (17.3)	2.73 (d, 17.3)	7.21-7.12 (m)		7.21-7.12 (m)	6.88 (d, 9.3)	1.91	7.88 (8.0)	7.38 (dd, 7.8, 8.0)	7.14 (1H, t, *J* = 7.8, ArH)
3f	3.13 (11.6, 2.4)	3.23 (16.5)	2.76 (16.5)	7.11 (s)		7.19 (d, 8.9)	6.90 (d, 8.9)	1.90	7.90 (9.1)	7.38 (d, 9.1)	
3g	3.18 (11.6, 2.4)	3.24 (16.5)	2.77 (16.5)	7.11 (s)		7.19 (d, 9.0)	6.89 (d, 9.0)	2.05	8.02 (s)		4.32 (2H,q, *J* = 7.2, OCH_2); 1.33 (3H, t, *J* = 7.2, CH_3)
3h	3.15 (11.3, 2.5)	3.26 (15.5)	2.83 (15.5)	7.06 (d, 8.9)	7.12-7.21 (m		7.12-7.21 (m)	1.89	7.88 (7.6)	7.50-7.20 (3H, m)	
3i	3.25 (11.5, 2.1)	3.26 (15.3)	2.86 (15.3)	7.26 (s)		7.39 (d, 9.7)	7.08 (d, 9.7)	1.91	7.92 (8.8)	7.42 (d, 8.8)	
3j	3.22 (11.0, 2.8)	3.28 (16.5)	2.83 (16.5)	7.26 (s)		7.37 (d, 9.7)	7.08 (d, 9.7)	1.91	8.02 (s)		4.33 (2H,q, *J* = 7.0, OCH_2) 1.39 (3H, t, *J* = 7.0, CH_3)

EXPERIMENTAL

The course of reactions and the purity of the compounds synthesized were monitored by TLC on Silufol UV-254 plates with (1:10) and (1:5) ethyl acetate–hexane eluents. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with Bruker WM-250 (250 MHz) and Bruker DRX-500 (500 MHz) spectrometers and mass spectra with a Varian MAT 311A with an ionizing current of 70eV with direct injection of the sample into the source.

Preparation of 2-Dialkylamino Derivatives of Benzaldehyde 1a-d. (General Method). Piperidine (15.55 mmol) and potassium carbonate (2.17 g, 15.55 mmol) were added to a solution of the corresponding 2-fluorobenzaldehyde (14.14 mmol) in DMSO (8.0 ml). The mixture was boiled for 5 h and the end of the reaction was determined by TLC. The reaction mixture was cooled to room temperature, water (75 ml) was added, and the product was extracted with ethyl acetate (3 × 60 ml). The combined extracts were washed with ammonium chloride solution. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuum. The products were crystallized from ethanol.

2-Piperidinobenzaldehyde (1a). Yield 87%; mp 95°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.19 (1H, s, CHO); 7.66 (1H, dd, *J* = 6.1, *J* = 1.5, ArH); 7.40-7.55 (1H, m, ArH); 7.00-7.15 (2H, m, ArH); 2.87-3.05 (4H, m, 2CH_2); 1.30-1.81 (6H, m, 3CH_2). Found, %: C 76.21; H 8.03; N 7.55. $C_{12}H_{15}NO$. Calculated, %: C 76.16; H 7.99; N 7.40.

4-Chloro-2-piperidinobenzaldehyde (1b). Yield 94%, oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.15 (1H, s, CHO); 7.74 (1H, d, *J* = 2.5, ArH); 7.61 (2H, dd, *J* = 9.2, *J* = 2.3, 2ArH); 7.18 (1H, d, *J* = 9.2, ArH); 3.00-3.04 (4H, m, 2CH_2); 1.32-1.86 (6H, m, 3CH_2). Found, %: C 64.65; H 6.39; N 6.35. $C_{12}H_{14}ClNO$. Calculated, %: C 64.43; H 6.31; N 6.26.

5-Bromo-2-piperidinobenzaldehyde (1c). Yield 53%; mp 75°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.10 (1H, s, CHO); 7.72 (1H, d, *J* = 2.3, ArH); 7.59 (2H, dd, *J* = 8.8, *J* =2.8, 2ArH); 7.07 (1H, d, *J* =8.5, ArH); 3.08 (4H, m, 2CH_2); 1.30-1.81 (6H, m, 3CH_2). Found, %: C 53.86; H 5.29; N 5.31. $C_{12}H_{14}BrNO$. Calculated, %: C 53.75; H 5.26; N 5.22.

2-Piperidino-5-trifluoromethylbenzaldehyde (1d). Yield 78%; mp 82°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.10 (1H, s, CHO); 7.90 (1H, s, ArH); 7.73 (2H, d, *J* = 8.6, ArH); 7.25 (1H, d, *J* = 8.6, ArH); 3.13-3.18 (4H, m, 2CH_2); 1.50-1.88 (6H, m, 3CH_2). Found, %: C 60.82; H 5.55; N 5.55. $C_{13}H_{14}F_3NO$. Calculated, %: C 60.70; H 5.49; N 5.44.

Preparation of 1'-Aryl-3'-methyl-2,3,4,4a,5,6-hexahydro-6H-spiro[benzo[*c*]quinolizine-5,4'-pyrazole]-5'-ones 3a-j. (General Method). 2-Aryl-5-methyl-2,4-dihydropyrazol-3-one **2a-c** (2.3 mmol) was added to a solution of benzaldehyde **1a-d** (2.3 mmol) in butanol (20 ml) and the reaction mixture was boiled for 3 h. The end of the reaction was determined by TLC. The reaction mixture was then cooled to room temperature, the solvent was evaporated in vacuum and the residue was extracted with ethanol. The physicochemical and spectroscopic characteristics are cited in Tables 1 and 2.

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