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A SIMPLE SYNTHESIS OF 2',5'-DISUBSTITUTED-SPIRO [DIHYDROACRIDINE 9(10H), 4'-THIAZOLINES] BY THE REACTION OF CORRESPONDING 3-(ACRIDIN-9-YL)-THIOUREAS WITH METHYL BROMOACETATE AND BROMOACETONITRILE

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Abstract : A convenient method has been devised for the preparation of the spirodihydro-acridinethiazolines **5a-j** by the treatment of thioureas **3a-e** with methyl bromoacetate and bromoacetonitrile via non-isolable isothioureas **4a-j** and their subsequent cyclization with methanolic sodium methoxide.
Key words : isothiocyanatoacridine, acridinylthiourea, spirodihydroacridinethiazoline

In our previous paper we have reported the synthesis of a new type of spiro heterocycles, 2'-alkoxy and 2'-methylthio-5'-alkyloxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazolines] by the cyclization of corresponding thiocarbonimidates[1] and dithiocarbamates[2], with methyl bromoacetate.

In a view of biological activities of thiazolines[3] and acridines[4], the obtained results lead us to prepare other interesting spiro compounds with an expectation, that these would reveal biological activities.

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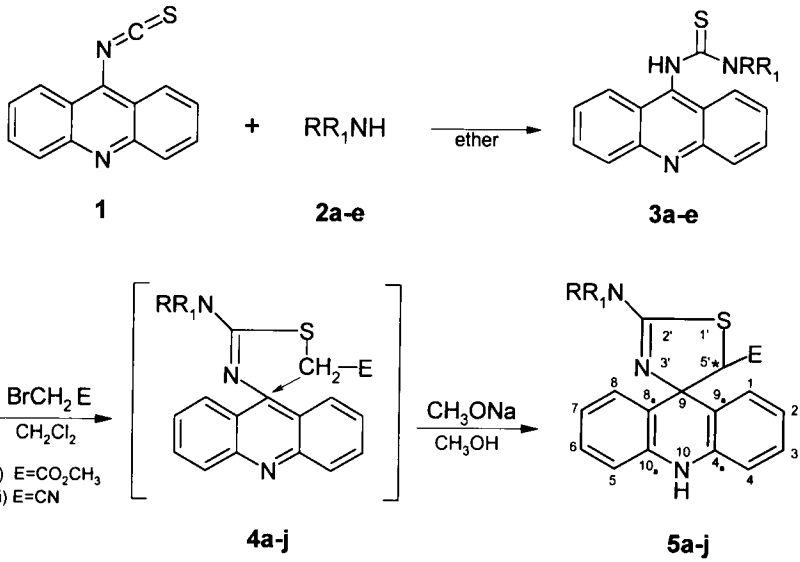

2,3	R	R_1
a	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$
b	CH_3	C_6H_5
c	$(CH_2)_2O(CH_2)_2$	
d	$(CH_2)_5$	
e	CH_3	C_6H_{11}

4,5	R	R_1	E
a	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	CO_2CH_3
b	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	CN
c	CH_3	C_6H_5	CO_2CH_3
d	CH_3	C_6H_5	CN
e	$(CH_2)_2O(CH_2)_2$		CO_2CH_3
f	$(CH_2)_2O(CH_2)_2$		CN
g	$(CH_2)_5$		CO_2CH_3
h	$(CH_2)_5$		CN
i	CH_3	C_6H_{11}	CO_2CH_3
j	CH_3	C_6H_{11}	CN

Scheme 1

To extend our previous work, we whish to report a new, simple synthesis of 2'-(dialkyl(aryl)amino)-5'-substituted-spiro[dihydroacridine 9(10H), 4'-thiazolines].

In the series of spirodihydroacridinethiazolines **5a-j** there are the alkoxy[1] and alkylthio[2] substituents in 2'-possition of thiazoline nucleus replaced by an amino group (NRR_1). The starting 3-(acridin-9-yl)-1,1-disubstituted-thioureas **3a-e**, are obtained via the reaction of secondary amines **2a-e** with 9-isothiocyanatoacridine[5] **1**. On the

reaction of acridinyl thioureas including primary amine residue will be reported elsewhere[6].

By the treatment of **3a-e** with halogenocarbonyl compounds, namely methyl bromoacetate and bromoacetonitrile in dichloromethane, the non-isolable isothioureas **4a-j** have been obtained, which in alkaline medium subsequently afforded the corresponding spiro compounds **5a-j** (scheme1).

Due to the presence of a stereogenic center at the 5'-carbon in the thiazoline ring of the spiroderivatives **5a-j** a non-equivalence of corresponding protons and carbon atoms of both benzene rings in the dihydroacridine skeleton confirms their spiro structure.

EXPERIMENTAL

NMR spectra where recorded on a Tesla BS 587 (80MHz) and Jeol NMR-EX 270 (^{1}H-270.17 MHz , ^{13}C-67.94 MHz) spectrometers. The chemical shift are given in the ppm (δ scale) using tetramethylsilane as internal standard. ^{13}C signal multiplicities were determined from DEPT spectra. Mass spectra were measured on a MAT 8500 EI (70 eV) and microanalysis on a Perkin-Elmer 2400 analyzer. IR spectra were obtained on a Specord 75 IR. The melting points are uncorrected.

General procedure for the preparation of 3-(acridin-9-yl)-1,1-disubstituted-thioureas 3a-e

Amine **2a-e** (1.1 mmol) was added dropwise to a stirred solution of 9-isothiocyanato-acridine **1** 0.236g (1 mmol) in ether (30 mL). The reaction mixture was stirred at room temperature until a pale yellow precipitate deposited. This was collected on filter, washed with ether and dried.

3-(Acridin-9-yl)-1,1-dipropyl-thiourea (2a)

M.p.192-197 °C; yield 95%. For $C_{20}H_{23}N_3S$ (337.489) calculated: 71.18% C, 6.87% H, 12.45% N, found: 70.02% C, 6.77% H, 12.31% N. ^{1}H NMR ($CDCl_3$): 10.82 (bs, 1H, NH), 7.87-6.71(m ,8H, AcrH), 4.08 and 3.53 (t, 2H, CH_2), 2.02 and 1.68 (dt, 2H, CH_2), 1.12 and 0.83 (t, 3H, CH_3).

3-(Acridin-9-yl)-1,1-methylphenyl-thiourea (2b)

M.p. 186-191 °C; yield 93%. For $C_{21}H_{17}N_3S$ (343.452) calculated: 73.44% C, 4.99% H, 12.29% N, found: 72.52% C, 4.91% H, 12.11% N. ^{1}H NMR ($CDCl_3$): 10.87 (bs, 1H, NH), 7.87-6.72 (m, 13H, ArH), 4.08 and 3.58 (s, 3H, NCH_3).

3-(acridin-9-yl)-1-morpholino-thiourea (2c)

M.p. 230-235 °C; yield 96%. For $C_{18}H_{17}N_3OS$ (323.418) calculated: 66.85% C, 5.29% H, 12.99% N, found: 66.05% C, 5.20% H, 12.81% N. ^{1}H NMR ($(CD_3)_2SO$): 11.35 (bs, 1H, NH), 8.29-7.10 (m, 8H, AcrH), 4.49-3.25 (m, 8H).

3-(acridin-9-yl)-1-piperidino-thiourea (2d)

M.p. 231-236 °C; yield 95%. For $C_{19}H_{19}N_3S$ (321.446) calculated: 70.99% C, 5.96% H, 13.07% N, found: 69.97% C, 5.91% H, 12.98% N. ^{1}H NMR ($(CD_3)_2SO$): 11.33 (bs, 1H, NH), 8.24-7.01 (m, 8H, AcrH), 4.50-3.87 and 4.01-3.38 (m, 4H, NCH_2), 1.87-1.13 (m, 6H, CH_2).

3-(acridin-9-yl)-1,1-methylcyclohexyl-thiourea (2e)

M.p. 205-209 °C; yield 92%. For $C_{21}H_{23}N_3S$ (349.499) calculated: 72.17% C, 6.63% H, 12.02% N, found: 71.07% C, 6.57% H, 11.85% N. ^{1}H NMR ($CDCl_3$): 10.87 (bs, 1H, NH), 7.85-6.69 (m, 8H, AcrH), 5.75-5.25 and 4.50-4.01 (m, 1H, NCH), 3.58 and 3.08 (s, 3H, NCH_3), 2.25-0.98 (m,10H).

General procedure for the preparation of 2'-(dialkyl(aryl)amino)- 5'-substituted-spiro[dihydroacridine 9(10H), 4'-thiazolines] 5a-j.

To a suspension of 3-(acridin-9-yl)-1,1-disubstituted-thiourea **3a-e** (1mmol) in dichloromethane (20mL) methyl bromoacetate 0.2g (1.3 mmol) and bromoacetonitrile 0.13g (1.11 mmol), resp. was added dropwise. The reaction mixture was intensively stirred at room temperature for 2h until thiourea **3a-e** has disappeared (monitored by thin-layer chromathography, eluent benzene-acetone 5:2, UV detection at 336 nm). After evaporation of the solvent a suspension of sodium methoxide (0.13g, 1.31 mmol) in dry methanol (20mL) was added. The stirring was continued for another 20 min and the reaction mixture poured into H_2O.

The precipitated product was collected by filtration, dried and crystallized from chloroform-heptane.

2'-Dipropylamino-5'-methoxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5a)

M.p. 150-152 °C; yield 85%. For $C_{23}H_{27}N_3O_2S$ (409.552) calculated : 67.45 % C, 6.64% H, 10.26% N, found: 66.26% C, 6.55% H, 10.04% N. IR ($CHCl_3$): 3433, 1730, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.71 (m, 8H, AcrH), 6.49 (bs, 1H, NH), 4.18 (s, 1H, H-5'), 3.49 (q, 2H), 3.14 (s, 3H, OCH_3), 1.77 (dt, 2H), 0.99 (t,3H). ^{13}C NMR ($CDCl_3$): 170.3 (C=O), 162.7 (C-2'), 138.8, 137.7 (C_{4a}, C_{10a}), 124.2, 121.4 (C_{8a}, C_{9a}), 128.2, 128.0, 127.5, 126.0, 120.6, 120.3, 113.9, 113.1 (d, AcrH), 80.7 (C-9), 64.8 (q, OCH_3), 53.1 (t, NCH_2), 52.0 (d, C-5'), 21.6 (t, CH_2), 11.2 (q, CH_3). MS(70ev): m/z(%) 409 (M^+, 18), 305(80), 262 (100), 237(64), 220(75).

2'-Dipropylamino-5'-cyano-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5b)

M.p. 190-193 °C; yield 85%. For $C_{22}H_{24}N_4S$ (376.525) calculated : 70.18 % C, 6.42% H, 14.88% N, found: 69.16% C, 6.35% H, 14.68% N. IR ($CHCl_3$): 3435, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.71 (m, 8H, AcrH), 6.49 (bs, 1H, NH), 4.20 (s, 1H, H-5'), 3.46 (q, 2H), 1.81 (dt, 2H), 1.00 (t,3H). ^{13}C NMR ($CDCl_3$): 160.9 (C-2'), 138.3, 138.0 (C_{4a}, C_{10a}), 122.5, 121.1 (C_{8a}, C_{9a}), 129.1, 128.6, 127.1, 125.9, 121.2, 120.8, 114.1, 113.8 (d, AcrH), 117.1 (CN), 80.3 (C-9), 53.3 (t, NCH_2), 50.2 (d, C-5'), 21.6 (t, CH_2), 11.3 (q, CH_3). MS(70ev): m/z(%) 376 (M^+,14), 306(11), 305(77), 261(14), 260(100).

2'-Methylphenylamino-5'-methoxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5c)

M.p. 95-97 °C; yield 80%. For $C_{24}H_{21}N_3O_2S$ (415.516) calculated : 69.37 % C, 5.09% H, 10.11% N, found: 68.26% C, 5.05% H, 10.01% N. IR ($CHCl_3$): 3435, 1730, 1633 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.72 (m, 13H, ArH), 6.50 (bs, 1H, NH), 4.20 (s, 1H, H-5'), 3.68 (s, 2H, NCH_3), 3.18 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 170.1 (C=O), 162.9 (C-2'), 145.7 (C_{ipso}), 138.7, 137.7 (C_{4a}, C_{10a}), 123.7, 120.9 (C_{8a}, C_{9a}), 129.9, 128.4, 128.1, 127.7, 127.6, 127.0, 126.0, 120.8, 120.5, 114.0, 113.2, (d, ArH), 80.8 (C-9), 65.8 (q, OCH_3), 52.1 (d, C-5'), 41.5 (t, NCH_3). MS(70ev): m/z(%) 415 (M^+, 17), 311(65), 296(96), 234(100), 205(90), 179(16), 155(11).

2'-methylphenylamino-5'-cyano-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5d)

M.p. 185-188 °C; yield 75%. For $C_{23}H_{18}N_4S$ (382.488) calculated : 72.22 % C, 4.74% H, 14.65% N, found: 71.06% C, 4.61% H, 14.41% N. IR ($CHCl_3$): 3435, 1633 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.72 (m, 13H, ArH), 6.40 (bs, 1H, NH), 4.02 (s, 1H, H-5'), 3.52 (s, 2H, NCH_3). ^{13}C NMR ($CDCl_3$): 161.1 (C-2'), 150.6 (C_{ipso}), 138.2, 137.9 (C_{4a}, C_{10a}), 122.4, 120.6 (C_{8a}, C_{9a}), 128.8, 128.5, 128.0, 127.1, 126.3, 125.9, 125.1, 120.6, 120.2, 113.5, 113.3, (d, ArH), 116.8 (CN), 80.6 (C-9), 51.0 (d, C-5'), 41.4 (t, NCH_3). MS(70ev): m/z(%) 382(M^+, 34), 372(23), 311(100), 296(90), 235(15), 234(57), 205(83), 179(12).

2'-morpholino-5'-methoxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5e)

M.p. 238-239 °C; yield 80%. For $C_{21}H_{21}N_3O_3S$ (395.482) calculated : 63.77 % C, 5.35% H, 10.63% N, found: 62.56% C, 5.25% H, 10.51% N. IR (KBr): 3440, 1730, 1610 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): 8.95 (bs, 1H, NH), 7.40-6.82 (m, 8H, AcrH), 4.14 (s, 1H, H-5'), 3.80 (t, 4H, OCH_2), 3.65 (t, 4H, NCH_2), 3.18 (s, 3H, OCH_3). ^{13}C NMR ($(CD_3)_2SO$): 169.2 (C=O), 163.8 (C-2'), 138.7, 137.6 (C_{4a}, C_{10a}), 123.5, 120.6 (C_{8a}, C_{9a}), 128.5, 128.2, 127.5, 125.9, 120.8, 120.5, 114.1, 113.2 (d, AcrH), 80.7 (C-9), 66.5 (t, OCH_2), 65.0 (q, OCH_3), 52.1 (d, C-5'), 49.2 (t,NCH_2) . MS(70ev): m/z(%) 395(M^+, 38), 291(100), 246(11), 237(74), 219(14), 206(64), 205(100), 179(18), 123(13).

2'-morpholino-5'-cyano-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5f)

M.p. 291-293 °C; yield 75%. For $C_{20}H_{18}N_4OS$ (362.455) calculated : 66.27 % C, 5.01% H, 15.46% N, found: 65.76% C, 4.91% H, 15.29% N. IR (KBr): 3435, 1612 cm^{-1}. ^1H NMR ($(CD_3)_2SO$): 8.95 (bs, 1H, NH), 7.41-6.83 (m, 8H, AcrH), 4.15 (s, 1H, H-5'), 3.80 (t, 4H, OCH_2), 3.66 (t, 4H, NCH_2).

2'-piperidino-5'-methoxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5g)

M.p. 220-224 °C; yield 75%. For $C_{22}H_{23}N_3O_2S$ (393.509) calculated : 67.15 % C, 5.89% H, 10.67% N, found: 66.06% C, 5.79% H, 10.49% N. IR ($CHCl_3$): 3435, 1730, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.69 (m, 8H, AcrH), 6.47 (bs, 1H, NH), 4.22 (s, 1H, H-5'), 3.65 (t, 4H, NCH_2), 3.14 (s,3H,OCH_3), 1.84-1.61 (m, 6H). ^{13}C NMR

($CDCl_3$): 170.2 (C=O), 163.2 (C-2'), 138.7, 137.6 (C_{4a}, C_{10a}), 124.0, 121.0 (C_{8a}, C_{9a}), 128.2, 128.0, 127.5, 126.0, 120.6, 120.3, 114.0, 113.1 (d, AcrH), 80.5 (C-9), 64.9 (t, OCH_3), 52.1 (d, C-5'), 50.3 (t, NCH_2), 25.6, 24.5 (t, CH_2). MS(70ev): m/z(%) 393(M^+, 35), 289(100), 260(13), 237(93), 220(18), 206(89), 179(33).

2'-piperidino-5'-cyano-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5h)

M.p. 285-2874 °C; yield 75%. For $C_{21}H_{20}N_4S$ (360.483) calculated : 69.97 % C, 5.59% H, 15.54% N, found: 68.76% C, 5.42% H, 15.41% N. IR ($CHCl_3$): 3436, 1615 cm^{-1}. ^1H NMR ($CDCl_3$): 7.63-6.66 (m, 8H, AcrH), 6.48 (bs, 1H, NH), 4.21 (s, 1H, H-5'), 3.66 (t, 4H, NCH_2), 1.85-1.62 (m, 6H).

2'-methylcyclohexylamino-5'-methoxycarbonyl-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5i)

M.p. 146-149 °C; yield 65%. For $C_{24}H_{27}N_3O_2S$ (421.563) calculated : 68.38 % C, 6.45% H, 9.97% N, found: 67.26% C, 6.39% H, 9.76% N. IR ($CHCl_3$): 3435, 1730, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-6.70 (m, 8H, AcrH), 6.45 (bs, 1H, NH), 4.19 (s, 1H, H-5'), 3.87 (dd, 1H, NCH), 3.15 (s, 3H, OCH_3), 3.14 (s, 3H, NCH_3), 2.04-1.26 (m, 10H). ^{13}C NMR ($CDCl_3$): 170.2 (C=O), 163.4 (C-2'), 138.8, 137.7 (C_{4a}, C_{10a}), 124.1, 121.1 (C_{8a}, C_{9a}), 128.2, 128.0, 127.5, 126.0, 120.6, 120.3, 113.9, 113.1 (d, AcrH), 80.3 (C-9), 77.2 (d, NCH), 64.4 (q, OCH_3), 52.0 (d, C-5'), 32.7 (q, NCH_3), 30.5, 25.6, 25.4 (t, CH_2), 11.2 (q, CH_3). MS(70ev): m/z(%) 421(M^+, 5), 348(11), 317(36), 237(60), 234(100).

2'-methylcyclohexylamino-5'-cyano-spiro[dihydroacridine 9(10H), 4'-thiazoline] (5j)

M.p. 195-198 °C; yield 72%. For $C_{23}H_{24}N_4S$ (388.536) calculated : 71.10 % C, 6.23% H, 14.42% N, found: 70.98% C, 6.14% H, 14.33% N. IR ($CHCl_3$): 3440, 1618 cm^{-1}. ^1H NMR ($CDCl_3$): 7.62-6.69 (m, 8H, AcrH), 6.46 (bs, 1H, NH), 4.19 (s, 1H, H-5'), 3.88 (dd, 1H, NCH), 3.14 (s, 3H, NCH_3), 2.05-1.27 (m, 10H).

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