

A Convenient Synthesis of Polyfunctionally Substituted (Acridin-9-yl)imino-1,3-thiazolidin-4-ones and Spiro[9,10-dihydroacridine-9,4'-thiazolidines]

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1-(Acridin-9-yl)-3-disubstituted thioureas react with methyl bromoacetate and bromoacetonitrile, respectively, depending on a substituent bulkiness, to polyfunctionally substituted (acridin-9-yl)imino-1,3-thiazolidin-4-ones and spiro[9,10-dihydroacridine-9,4'-thiazolidines]. Reactions represent the simple and convenient way to synthesize the title compounds with possible antibacterial activity. Based on their spectral data, the structure of products is discussed.

A great variety of compounds bearing the NCS fragment undergo heterocyclization upon cyclocondensation with α -halocarbonyl compounds [1, 2]. We have successfully used this convenient approach for the synthesis of hitherto unreported polyfunctionally substituted thiazolines and spiro acridines of biological interest [3–5]. As synthons for these reactions salts of acridinylthiocarbonimidates *I* [3], acridinylthiocarbamates *IIa* [4], and acridinylthioureas *IIb* [5] were utilized together with methyl bromoacetate and bromoacetonitrile in the role of α -halocarbonyl reagent. The reaction products usually were polyfunctionally substituted spiro[9,10-dihydroacridine-9,4'-thiazolidines] *III*, only *O*-alkyl-*N*-substituted thiocarbonimidates *I* afforded with bromoacetyl bromide corresponding 1,3-thiazolidine-2,4-diones *IV*, too [6].

Recently, 2-(benzoyl-arylsulfonyl-methylene)-3-phenyl-1,3-thiazolidin-4-ones *V* were synthesized by the treatment with ethyl bromoacetate of nonisolable potassium sulfide salts obtained *via* nucleophilic addition of acidic arylsulfonylacetophenones to phenyl isothiocyanates [2]. Also some new quinazolinyl thiazolidines *VI* showed promising antibacterial activity when compared with streptomycin as a standard [7].

The high antibacterial activity of acridines [8, 9] prompted us to introduce the acridine moiety into the thiazolidinone and thiazolidine rings. As suitable intermediates for this purpose we used 1-(acridin-9-yl)-3-disubstituted thioureas *VIIa–VIIe* [10] containing primary, secondary, and tertiary alkyl rest. The compounds *VIIa–VIIe* reacted with methyl bromoacetate or bromoacetonitrile to give nonisolable isothiureas *VIII* (Scheme 1). The presence of hydrogen atom attached to N-3 of isothiurea *VIII* allowed its subsequent cyclocondensation to 2-(acridin-9-yl)imino-1,3-thiazolidin-4-ones *IXa–IXc*. Such a re-

action is not possible with thioureas formed from secondary amines [5]. Depending on the bulkiness of alkyl substituent and α -halocarbonyl reagent, spiro[9,10-dihydroacridine-9,4'-thiazolidines] *XId, XIe* and *XIIa–XIIe* were also obtained.

We found out that thioureas *VIIa–VIIc* afforded with methyl bromoacetate 3-substituted-2-(acridin-9-yl)imino-1,3-thiazolidin-4-ones *IXa–IXc*, whereas thioureas *VIIId, VIIe* with N-3 bound to secondary or tertiary carbon, cyclized to 2'-substituted imino-5'-methoxycarbonylspiro[9,10-dihydroacridine-9,4'-thiazolidines] *XId* and *XIe*. The rise of spiro compounds *XId* and *XIe* is preferred in this case probably due to the steric hindrance of bulky substituent R (cyclohexyl, *tert*-butyl) which prevents a nucleophilic attack of N-3 to carbonyl group necessary for the thiazolidinone *IX* formation (Scheme 1).

Using the second reagent, bromoacetonitrile, isothiureas *VIII* arisen *in situ* from thioureas *VIIa–VIIe* cyclized exclusively to 2'-substituted imino-5'-cyanospiro[9,10-dihydroacridine-9,4'-thiazolidines] *XIIa–XIIe*. Because of increased acidity of $\text{SCH}_2\text{—CN}$ protons the cyclization reaction is facilitated and we did not observe the formation of incidental 1,3-thiazolidin-4-imines *X* which might be expected as products of addition of NH—R fragment to cyano group.

Different structures of thiazolidinones *IX* and spiro compounds *XI, XII* were confirmed by spectral methods. Whereas in IR spectra of thiazolidinones the C=O band at $\tilde{\nu} = 1723 \text{ cm}^{-1}$ and band of exocyclic C=N group at $\tilde{\nu} = 1630 \text{ cm}^{-1}$ are observed, in spiro compounds *XId, XIe* ester C=O band at $\tilde{\nu} = 1735 \text{ cm}^{-1}$ and endocyclic C=N band at 1615 cm^{-1} are found. In spiro compounds *XIIa–XIIe* the band at 2210 cm^{-1} corresponds to a cyano group.

Scheme 1

More pronounced differences were observed in ^1H NMR spectra, where thiazolidinones *IX* possess a typical singlet of CH_2 group at $\delta = 3.77\text{--}4.15$, replaced in spiro compounds *XI*, *XII* by H-5' singlet in the range $\delta = 4.11\text{--}4.25$. Moreover, signals of NH ($\delta = 6.47\text{--}6.51$) and OCH_3 protons ($\delta = 3.14$, in *XI*) occur. Other

spectral data including mass and ^{13}C NMR spectra of selected derivatives support proposed structures. A nonequivalence of protons and carbons of acridinyl side rings in high-resolution NMR spectra of *XIe*, *XIIe* confirms the presence of chiral centre C-5' in a rigid structure of spiro compound.

EXPERIMENTAL

NMR spectra were recorded on a Tesla BS 587 (80 MHz), Jeol NMR-EX 270 (270.17 MHz (^1H), 67.94 MHz (^{13}C), compounds *IXb*, *IXc*, and Varian VXR-300 (300 MHz (^1H), 75 MHz (^{13}C), compounds *XIe*, *XIIe*) spectrometers. The chemical shifts are given in δ scale using tetramethylsilane as an internal standard. ^{13}C signals were assigned using DEPT spectra. Mass spectra were measured on a MAT 8500 (EI, 70 eV) spectrometer and microanalysis was done on a Perkin—Elmer CHN 2400 analyzer. IR spectra were obtained on a Specord 75 IR spectrophotometer. The melting points are uncorrected.

Starting thioureas *VIIa*, *VIIb*, *VIIc*, and *VIIe* were prepared by reaction of 9-isothiocyanatoacridine [11] with corresponding amines in chloroform [10]. Analogously was prepared 1-(acridin-9-yl)-3-furfurylthiourea (*VIIc*): yield 95 %, m.p. = 168—170 °C. For $\text{C}_{19}\text{H}_{15}\text{N}_3\text{OS}$ ($M_r = 333.41$) w_i (calc.): 68.44 % C, 4.53 % H, 12.60 % N; w_i (found): 68.07 % C, 4.43 % H, 12.49 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3210, 1620, 1560. ^1H NMR spectrum ($(\text{CD}_3)_2\text{SO}$), δ : 11.53 (s, 1H, NH), 6.91—8.19 (m, 10H, $\text{H}_{\text{acridinyl}}$, H-5_{furyl}, NH), 6.30—6.52 (m, 2H, H-3_{furyl}, H-4), 4.84 (d, $J = 6.1$ Hz, 2H, CH_2).

3-Substituted 2-(Acridin-9-yl)imino-1,3-thiazolidin-4-ones *IXa*—*IXc* and 2',5'-Disubstituted Spiro[9,10-dihydroacridine-9,4'-thiazolidines] *XId*, *XIe*, *XIIa*—*XIIe*

To a suspension of thiourea *VII* (1 mmol) in dichloromethane (30 cm^3) methyl bromoacetate (0.2 g; 1.3 mmol) or bromoacetonitrile (0.13 g; 1.11 mmol) was added slowly with stirring which continued until thiourea disappeared (*ca.* 2 h, detected by TLC chromatography, eluent benzene—acetone, $\varphi_r = 5:2$). After evaporation of solvent a methanolic solution (20 cm^3) of sodium methoxide (0.13 g; 1.31 mmol) was added and stirring continued for 25 min. Reaction mixture was then poured into water (50 cm^3), a precipitate formed was filtered off, dried and recrystallized from the mixture chloroform—cyclohexane.

IXa: Yield 70 %, m.p. = 214—216 °C. For $\text{C}_{23}\text{H}_{17}\text{N}_3\text{OS}$ ($M_r = 383.474$) w_i (calc.): 72.04 % C, 4.47 % H, 10.96 % N; w_i (found): 71.87 % C, 4.41 % H, 10.79 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 1720, 1630. ^1H NMR spectrum (CDCl_3), δ : 7.41—8.91 (m, 13H, H_{aryl}), 5.32 (s, 2H, CH_2 benzyl), 4.15 (s, 2H, CH_2S).

IXb: Yield 78 %, m.p. = 164—167 °C. For $\text{C}_{19}\text{H}_{17}\text{N}_3\text{OS}$ ($M_r = 335.43$) w_i (calc.): 68.03 % C, 5.11 % H, 12.53 % N; w_i (found): 67.87 % C, 5.01 % H, 12.43 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 1723, 1633. ^1H NMR spectrum (CDCl_3), δ : 8.21 (d, $J = 8.9$ Hz, 2H, H-4, H-5), 7.87 (d, $J = 8.6$ Hz, 2H, H-1, H-8), 7.76 (dd, $J = 8.9$, 6.5 Hz, 2H, H-3, H-6), 7.47 (dd, $J = 8.6$, 6.5 Hz, 2H, H-2, H-7), 5.11 (m, $J = 6.9$ Hz, 1H, CHN),

3.77 (s, 2H, CH_2S), 1.76 (d, $J = 6.9$ Hz, 6H, 2CH_3). ^{13}C NMR spectrum (CDCl_3), δ : 172.5 (C=O), 157.6 (C=N), 151.6 (C-4a, C-10a), 150.6 (C-9), 131.5, 130.8, 126.2, 124.7 (CH-1 to CH-8), 118.7 (C-8a, C-9a), 49.5 (CH), 34.1 (CH_2), 20.1 (2CH_3). Mass spectrum, m/z ($I_r/\%$): 335 (100) [$\text{M}^{+\bullet}$], 293 (57) [$\text{M}^{+\bullet} - \text{C}_3\text{H}_6$], 219 (49) [$\text{Acr}-\text{N}=\text{C}=\text{NH}^+$].

IXc: Yield 85 %, m.p. = 157—159 °C. For $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ ($M_r = 373.44$) w_i (calc.): 67.54 % C, 4.05 % H, 11.25 % N; w_i (found): 67.27 % C, 4.01 % H, 11.19 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 1723, 1630. ^1H NMR spectrum (CDCl_3), δ : 8.21 (ddd, $J = 8.8$, 1.1, 0.7 Hz, 2H, H-4, H-5), 7.82 (ddd, $J = 8.4$, 1.5, 0.7 Hz, 2H, H-1, H-8), 7.76 (ddd, $J = 8.8$, 6.5, 1.5 Hz, 2H, H-3, H-6), 7.44 (ddd, $J = 8.4$, 6.5, 0.7 Hz, 2H, H-2, H-7), 7.51 (dd, $J = 1.7$, 0.9 Hz, 1H, H-5'), 6.56 (dd, $J = 3.3$, 0.9 Hz, 1H, H-3'), 6.45 (dd, $J = 3.3$, 1.7 Hz, 1H, H-4'), 5.30 (s, 2H, CH_2N), 3.88 (s, 2H, CH_2S). ^{13}C NMR spectrum (CDCl_3), δ : 170.8 (C=O), 156.0 (C=N), 150.2 (C-2'), 149.4 (C-4a, C-10a), 148.5 (C-9), 142.7 (C-5'), 130.4, 129.5, 125.1, 123.7 (CH-1 to CH-8), 117.6 (C-8a, C-9a), 110.7, 110.1 (C-3', C-4'), 39.3 (CH_2N), 33.3 (CH_2S).

XId: Yield 75 %, m.p. = 181—183 °C. For $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$ ($M_r = 407.54$) w_i (calc.): 62.78 % C, 6.18 % H, 10.31 % N; w_i (found): 61.26 % C, 6.11 % H, 10.21 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3440, 1735. ^1H NMR spectrum (CDCl_3), δ : 6.70—7.61 (m, 8H, $\text{H}_{\text{acridinyl}}$), 6.48 (s, 1H, NH-10), 4.21 (s, 1H, CH-5'), 3.65—3.95 (m, 1H, cyclohexyl), 3.14 (s, 3H, OCH_3), 1.21—2.04 (m, 10H, cyclohexyl).

XIe: Yield 75 %, m.p. = 193—196 °C. For $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$ ($M_r = 381.50$) w_i (calc.): 66.12 % C, 6.08 % H, 11.01 % N; w_i (found): 65.97 % C, 5.99 % H, 10.98 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3435, 1735. ^1H NMR spectrum (CDCl_3), δ : 7.48 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.29 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.22 (overlapped signal, 1H), 7.18 (overlapped signal, 1H), 6.97 (ddd, $J = 7.7$, 7.3, 1.1 Hz, 1H), 6.92 (ddd, $J = 7.9$, 7.2, 1.2 Hz, 1H), 6.89 (dd, $J = 7.9$, 1.1 Hz, 1H), 6.84 (dd, $J = 7.9$, 1.2 Hz, 1H, $\text{H}_{\text{acridinyl}}$), 6.49 (s, 1H, NH-10), 4.11 (s, 1H, CH-5'), 3.14 (s, 3H, OCH_3), 1.57 (s, 9H, *t*-Bu). ^{13}C NMR spectrum (CDCl_3), δ : 170.5 (COO), 2'-C=N not detected, 139.1, 137.8, 121.7, 120.5 ($\text{C}_{\text{acridinyl}}$), 128.5, 128.2, 127.4, 126.0, 120.7, 120.4, 114.1, 113.3 ($\text{CH}_{\text{acridinyl}}$), 81.2 (C-9), 63.8 (CH-5'), 53.6 (C, *t*-Bu), 52.4 (CH_3O), 29.1 (CH_3 , *t*-Bu).

XIIa: Yield 45 %, m.p. = 131—134 °C. For $\text{C}_{23}\text{H}_{18}\text{N}_4\text{S}$ ($M_r = 382.49$) w_i (calc.): 72.23 % C, 4.74 % H, 14.65 % N; w_i (found): 72.00 % C, 4.71 % H, 14.59 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3436, 2210, 1615. ^1H NMR spectrum (CDCl_3), δ : 6.78—7.75 (m, 13H, H_{aryl}), 6.50 (s, 1H, NH-10), 4.75 (s, 2H, CH_2 benzyl), 4.25 (s, 1H, CH-5').

XIIb: Yield 50 %, m.p. = 169—173 °C. For $\text{C}_{19}\text{H}_{18}\text{N}_4\text{S}$ ($M_r = 334.45$) w_i (calc.): 68.24 % C, 5.42 % H, 16.75 % N; w_i (found): 67.76 % C, 5.33 % H, 16.69 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3430, 2210, 1620.

^1H NMR spectrum (CDCl_3), δ : 6.70—7.75 (m, 8H, $\text{H}_{\text{acridinyl}}$), 6.47 (bs, 1H, NH-10), 4.01—4.27 (m, 1H, CHN), 4.19 (s, 1H, CH-5'), 1.32 (d, 6H, 2CH_3).

XIIc: Yield 45 %, m.p. = 150—152 °C. For $\text{C}_{21}\text{H}_{16}\text{N}_4\text{OS}$ ($M_r = 372.45$) $w_i(\text{calc.})$: 67.72 % C, 4.33 % H, 15.04 % N; $w_i(\text{found})$: 67.36 % C, 4.24 % H, 14.95 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3438, 2210, 1615. ^1H NMR spectrum (CDCl_3), δ : 6.79—7.71 (m, 9H, $\text{H}_{\text{acridinyl}}$, CH_{furyl}), 6.50 (s, 1H, NH-10), 6.32—6.41 (m, 2H, CH_2furyl), 4.73 (s, 2H, CH_2furyl), 4.24 (s, 1H, CH-5').

XIId: Yield 78 %, m.p. = 170—172 °C. For $\text{C}_{22}\text{H}_{22}\text{N}_4\text{S}$ ($M_r = 374.51$) $w_i(\text{calc.})$: 70.56 % C, 5.92 % H, 14.96 % N; $w_i(\text{found})$: 70.27 % C, 5.84 % H, 14.81 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3433, 2210, 1620. ^1H NMR spectrum (CDCl_3), δ : 6.51—7.75 (m, 8H, $\text{H}_{\text{acridinyl}}$), 6.51 (s, 1H, NH-10), 4.19 (s, 1H, CH-5'), 3.58—4.01 (m, 1H, cyclohexyl), 1.11—1.97 (m, 10H, cyclohexyl).

XIIE: Yield 78 %, m.p. = 187—190 °C. For $\text{C}_{20}\text{H}_{20}\text{N}_4\text{S}$ ($M_r = 348.47$) $w_i(\text{calc.})$: 68.94 % C, 5.78 % H, 16.08 % N; $w_i(\text{found})$: 68.47 % C, 5.69 % H, 15.99 % N. IR spectrum (KBr), $\tilde{\nu}/\text{cm}^{-1}$: 3436, 2210, 1620. ^1H NMR spectrum (CDCl_3), δ : 7.67 (d, $J = 7.7$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.21—7.33 (m, 2H), 7.07 (dd, $J = 7.8, 7.6$ Hz, 1H), 6.98 (dd, $J = 8.0, 7.6$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H, $\text{H}_{\text{acridinyl}}$), 6.51 (s, 1H, NH-10), 4.13 (s, 1H, CH-5'), 1.57 (s, 9H, *t*-Bu). ^{13}C NMR spectrum (CDCl_3), δ : 155.2 ($2'\text{-C}=\text{N}$), 138.2, 137.9, 122.0, 120.8 ($\text{C}_{\text{acridinyl}}$), 129.2, 128.7, 127.1, 125.9, 121.3, 120.9, 114.2, 113.9 ($\text{CH}_{\text{acridinyl}}$), 117.0 (CN), 81.3 (C-9), 54.2 (C, *t*-Bu), 49.5 (CH-5'), 29.0 (CH_3 , *t*-Bu).

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