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

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1-(Acradin-9-yl)-3-disubstituted thioureas react with methyl bromoacetate and bromoacetoni-
trile, 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 repre-
sent 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 cycloco-
densation with α-halocarbonyl compounds [1, 2]. We
have successfully used this convenient approach for the
synthesis of hitherto unreported polyfunctionally sub-
tituted thiazolines and spiro acridines of biological
interest [3–5]. As synthons for these reactions salts
of acridinylthiocarbonimides I [3], acridinyldithio-
carbamates IIa [4], and acridinylthioureas IIb [5] were
utilized together with methyl bromoacetate and bro-
moacetonitrile in the role of α-halocarbonyl reagent.
The reaction products usually were polyfunctionally
substituted spiro[9,10-dihydroacridine-9,4'-thiazolidi-
es] III, only O-alkyl-N-substituted thiocarbonimi-
dates I afforded with bromoacetylbromide corre-
sponding 1,3-thiazolidine-2,4-diones IV, too [6].

Recently, 2-(benzoyl-arsulfonyl-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 addi-
tion of acidic arylsulfonylacetylenes to phenyl
isothiocyanates [2]. Also some new quinazolinyli-
thiazolines 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] con-
taining primary, secondary, and tertiary alkyl rest.
The compounds VIIa–VIIe reacted with methyl bro-
moacetate or bromoacetonitrile to give nonisolable
isothioureas VIII (Scheme 1). The presence of hy-
drogen atom attached to N-3 of isothiourea VIII al-
low 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–VIIe 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'-thia-
zolidines] 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 (cyco-
hexyl, tert-butyl) which prevents a nucleophilic attack
of N-3 to carbonyl group necessary for the thiazolidi-
one IX formation (Scheme 1).

Using the second reagent, bromoacetonitrile, iso-
thioureas VIII arised 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 SCH2—
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 meth-
ods. Whereas in IR spectra of thiazolidinones the
C=O band at \( \tilde{\nu} = 1723 \) cm\(^{-1}\) and band of exocyclic
C=N group at \( \tilde{\nu} = 1630 \) cm\(^{-1}\) are observed, in spiro
compounds XId, XIe ester C=O band at \( \tilde{\nu} = 1735 \)
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.
More pronounced differences were observed in $^1$H NMR spectra, where thiazolidinones $IX$ possess a typical singlet of $\text{CH}_2$ group at $\delta = 3.77-4.15$, replaced in spiro compounds $XI$, $XII$ by H-5$'$ singlet in the range $\delta = 4.11-4.25$. Moreover, signals of NH ($\delta = 6.47-6.51$) 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 (13C)), compounds IXb, IXc, and Varian VXR-300 (300 MHz (1H), 75 MHz (13C)), compounds XIf, XIIe spectrometers. The chemical shifts are given in δ scale using tetramethylsilane as an internal standard. 13C 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, VIIId, 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 (VIIe): yield 95%, m.p. = 168—170°C. For C19H15N3OS (M = 333.41) w1(calc.): 68.44 % C, 4.53 % H, 12.60 % N; w1(found): 68.07 % C, 4.43 % H, 12.49 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 3210, 1620, 1560. 1H NMR spectrum (CDCl3): δ: 11.53 (s, 1H, NH), 6.91—8.19 (m, 10H, H1-cyclic, H-5furyl, NH), 6.30—6.52 (m, 2H, H-3furyl, H-4), 4.84 (d, J = 6.1 Hz, 2H, CH2).

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] XIf, XIf

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; 1.1 mmol) was added slowly with stirring which continued until thiourea disappeared (ca. 2 h, detected by TLC chromatography, eluent benzene—acetone, ϕx = 5:2). After evaporation of solvent a melaninic 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—acyclohexane.

IXa: Yield 70%, m.p. = 214—216°C. For C23H17N3O3S (M = 383.474) w1(calc.): 72.04 % C, 4.47 % H, 10.96 % N; w1(found): 71.87 % C, 4.41 % H, 10.79 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 1720, 1630. 1H NMR spectrum (CDCl3), δ: 7.41—8.91 (m, 13H, Haryl), 5.32 (s, 2H, CH2benzyl), 4.15 (s, 2H, CH2S).

IXb: Yield 78%, m.p. = 164—167°C. For C19H17N3O3S (M = 335.43) w1(calc.): 68.03 % C, 5.11 % H, 12.53 % N; w1(found): 67.87 % C, 5.01 % H, 12.43 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 1723, 1633. 1H NMR spectrum (CDCl3), 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-2, H-7), 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, CH2S), 1.76 (d, J = 6.9 Hz, 6H, 2CH3). 13C NMR spectrum (CDCl3), 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 (CH2), 20.1 (2CH3). Mass spectrum, m/z (I (%)): 335 (100) [M+], 293 (57) [M+ 2—C6H6], 219 (49) [Acr—N=C—NH2].

IXc: Yield 85%, m.p. = 157—159°C. For C21H15N3O2S (M = 373.44) w1(calc.): 67.54 % C, 4.05 % H, 11.25 % N; w1(found): 67.27 % C, 4.01 % H, 11.19 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 1723, 1630. 1H NMR spectrum (CDCl3), δ: 8.21 (d, 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, CH2N), 3.88 (s, 2H, CH2S). 13C NMR spectrum (CDCl3), 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 (CH1 to CH-10), 117.6 (C-8a, C-9a), 110.7, 110.1 (C-3′, C-4′), 39.3 (CH2N), 33.3 (CH2S).

XIf: Yield 75%, m.p. = 193—196°C. For C23H23N3O3S (M = 381.50) w1(calc.): 66.12 % C, 6.08 % H, 10.31 % N; w1(found): 61.26 % C, 6.11 % H, 10.21 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 3440, 1735. 1H NMR spectrum (CDCl3), δ: 6.70—7.61 (m, 8H, Haryl), 6.48 (s, 1H, NH-10), 4.21 (s, 1H, CH-5′), 3.65—3.95 (m, 1H, cyclohexyl), 3.14 (s, 3H, OCH3), 1.21—2.04 (m, 10H, cyclohexyl).

XIf: Yield 75%, m.p. = 131—134°C. For C23H23N3O3S (M = 382.49) w1(calc.): 72.23 % C, 4.74 % H, 14.65 % N; w1(found): 72.00 % C, 4.71 % H, 14.59 % N. IR spectrum (KBr), ν/cm\(^{-1}\): 3436, 2210, 1615. 1H NMR spectrum (CDCl3), δ: 6.78—7.75 (m, 13H, Haryl), 6.50 (s, 1H, NH-10), 4.75 (s, 2H, CH2benzyl), 4.25 (s, 1H, CH-5′).
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