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

P. KRISTIAN, I. CHOMČA, J. BERNÁT, and J. IMRICH

Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, SK-041 67 Košice

Received 9 April 1998

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], acridinyldithiocarbamates *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 bromoacetylbromide corresponding 1,3-thiazolidine-2,4-diones *IV*, too [6].

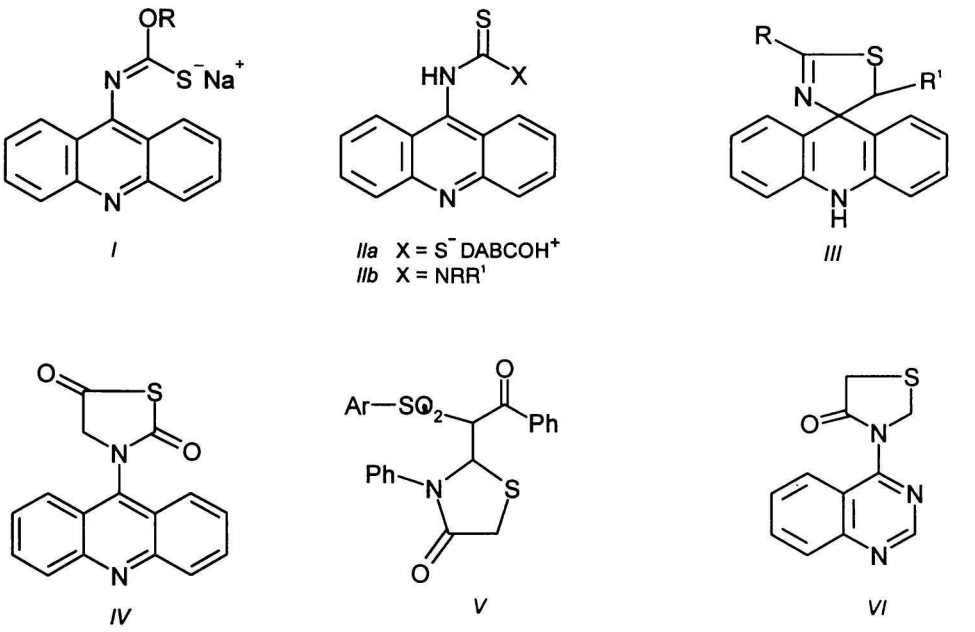
Recently, 2-(benzoyl-arylsulfonyl-methylene)-3-phenyl-1,3-thiazolidin-4-ones *V* were synthesized by the treatment with ethyl bromoacetate of nonisolable potassium sulfide salts obtained *via* nucleophilic addition of acidic arylsulfonylacetophenones to phenyl isothiocyanates [2]. Also some new quinazolinyl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

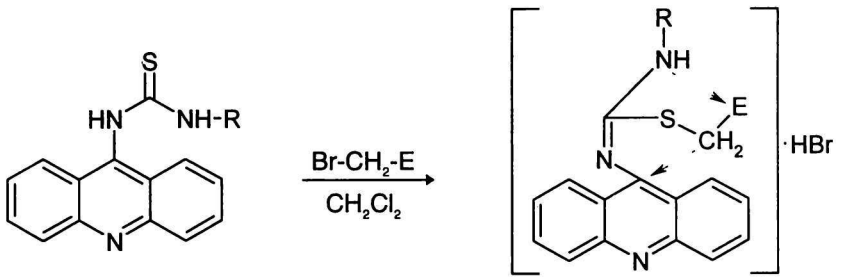
The high antibacterial activity of acridines [8, 9] prompted us to introduce the acridine moiety into the thiazolidinone and thiazolidine rings. As suitable intermediates for this purpose we used 1-(acridin-9-yl)-3-disubstituted thioureas *VIIa*—*VIIe* [10] containing primary, secondary, and tertiary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

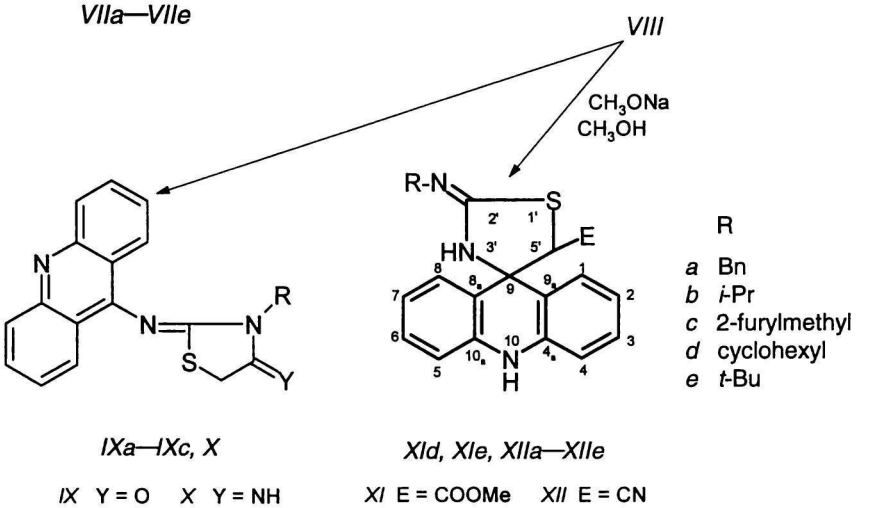
We found out that thioureas *VIIa*—*VIIc* afforded with methyl bromoacetate 3-substituted-2-(acridin-9-yl)imino-1,3-thiazolidin-4-ones *IXa*—*IXc*, whereas thioureas *VIId, VIIe* with N-3 bound to secondary or tertiary carbon, cyclized to 2′-substituted imino-5′-methoxycarbonylspiro[9,10-dihydroacridine-9,4′-thiazolidines] *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, isothioureas *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 SCH_2—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 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.







Scheme 1

More pronounced differences were observed in ^{1}H NMR spectra, where thiazolidinones *IX* possess a typical singlet of 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 (^{1}H), 67.94 MHz (^{13}C), compounds *IXb, IXc*), and Varian VXR-300 (300 MHz (^{1}H), 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*, *VIId*, 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 $C_{19}H_{15}N_3OS$ (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), $\tilde{\nu}$/cm^{-1}: 3210, 1620, 1560. ^{1}H NMR spectrum ((CD$_3$)$_2$SO), δ: 11.53 (s, 1H, NH), 6.91—8.19 (m, 10H, H$_{acridinyl}$, 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, φ_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 $C_{23}H_{17}N_3OS$ (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), $\tilde{\nu}$/cm^{-1}: 1720, 1630. ^{1}H 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$_2$S).

IXb: Yield 78 %, m.p. = 164—167 °C. For $C_{19}H_{17}N_3OS$ (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), $\tilde{\nu}$/cm^{-1}: 1723, 1633. ^{1}H 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$_2$S), 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) [M$^{+\cdot}$], 293 (57) [M$^{+\cdot}$ − C_3H_6], 219 (49) [Acr—N=C=NH$^+$].

IXc: Yield 85 %, m.p. = 157—159 °C. For $C_{21}H_{15}N_3O_2S$ (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), $\tilde{\nu}$/cm^{-1}: 1723, 1630. ^{1}H 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$_2$N), 3.88 (s, 2H, CH$_2$S). ^{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$_2$N), 33.3 (CH$_2$S).

XId: Yield 75 %, m.p. = 181—183 °C. For $C_{23}H_{25}N_3O_2S$ (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), $\tilde{\nu}$/cm^{-1}: 3440, 1735. ^{1}H NMR spectrum ($CDCl_3$), δ: 6.70—7.61 (m, 8H, H$_{acridinyl}$), 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 $C_{21}H_{23}N_3O_2S$ (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), $\tilde{\nu}$/cm^{-1}: 3435, 1735. ^{1}H 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, H$_{acridinyl}$), 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 (C$_{acridinyl}$), 128.5, 128.2, 127.4, 126.0, 120.7, 120.4, 114.1, 113.8 (CH$_{acridinyl}$), 81.2 (C-9), 63.8 (CH-5′), 53.6 (C, *t*-Bu), 52.4 (CH$_3$O), 29.1 (CH$_3$, *t*-Bu).

XIIa: Yield 45 %, m.p. = 131—134 °C. For $C_{23}H_{18}N_4S$ (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), $\tilde{\nu}$/cm^{-1}: 3436, 2210, 1615. ^{1}H 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 $C_{19}H_{18}N_4S$ (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), $\tilde{\nu}$/cm^{-1}: 3430, 2210, 1620.

^{1}H NMR spectrum ($CDCl_3$), δ: 6.70—7.75 (m, 8H, $H_{acridinyl}$), 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 $C_{21}H_{16}N_4OS$ (M_r = 372.45) w_i(calc.): 67.72 % C, 4.33 % H, 15.04 % N; w_i(found): 67.36 % C, 4.24 % H, 14.95 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3438, 2210, 1615. ^{1}H NMR spectrum ($CDCl_3$), δ: 6.79—7.71 (m, 9H, $H_{acridinyl}$, CH_{furyl}), 6.50 (s, 1H, NH-10), 6.32— 6.41 (m, 2H, $CH_{2\,furyl}$), 4.73 (s, 2H, $CH_{2\,furyl}$), 4.24 (s, 1H, CH-5′).

XIId: Yield 78 %, m.p. = 170—172 °C. For $C_{22}H_{22}N_4S$ (M_r = 374.51) w_i(calc.): 70.56 % C, 5.92 % H, 14.96 % N; w_i(found): 70.27 % C, 5.84 % H, 14.81 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3433, 2210, 1620. ^{1}H NMR spectrum ($CDCl_3$), δ: 6.51—7.75 (m, 8H, $H_{acridinyl}$), 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 $C_{20}H_{20}N_4S$ (M_r = 348.47) w_i(calc.): 68.94 % C, 5.78 % H, 16.08 % N; w_i(found): 68.47 % C, 5.69 % H, 15.99 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3436, 2210, 1620. ^{1}H 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, $H_{acridinyl}$), 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′-C=N), 138.2, 137.9, 122.0, 120.8 ($C_{acridinyl}$), 129.2, 128.7, 127.1, 125.9, 121.3, 120.9, 114.2, 113.9 ($CH_{acridinyl}$), 117.0 (CN), 81.3 (C-9), 54.2 (C, *t*-Bu), 49.5 (CH-5′), 29.0 (CH_3, *t*-Bu).

Acknowledgements. This study was supported by the Grant Agency for Science of the Slovak Ministry of Education (Reg. No. 96/5195/553). The authors thank to Dr. T. Liptaj and Dr. N. Prónayová from the Faculty of Chemical Technology, Slovak University of Technology, Bratislava for the measurement of NMR spectra of compounds XIc and XIIe.

REFERENCES

1. Wobig, D., *Liebigs Ann. Chem. 1992*, 415.
2. Sherif, S. M., *Monatsh. Chem. 127,* 557 (1996).
3. Bernát, J., Kristian, P., Imrich, J., Mazagová, D., Černák, J., Bušová, T., and Lipkowski, J., *Synth. Commun. 25,* 3973 (1995).
4. Kristian, P., Bernát, J., Imrich, J., Danihel, I., Suchár, G., Chomča, I., Hočová, S., Bušová, T., Guspanová, J., and Linden, A., *Molecules 1,* 191 (1996).
5. Bernát, J., Chomča, I., Kristian, P., and Voss, G., *Synth. Commun.*, in press.
6. Imrich, J., Bernát, J., Kristian, P., Bušová, T., and Hočová, S. *Collect. Czech. Chem. Commun. 61,* 432 (1996).
7. Deshmukh, M. B. and Deshmukh, D. S., *J. Indian Chem. Soc. 72,* 847 (1995).
8. Acheson, R. M., *Acridines,* p. 666. Wiley, New York, 1973.
9. Antonini, I., Polucci, P., Jenkins, T. C., Kelland, L. R., Menta, E., Pescalli, N., Stefanska, B., Mazerski, J., and Martelli, S., *J. Med. Chem. 40,* 3749 (1996).
10. Mazagová, D., Sabolová, D., Kristian, P., Imrich, J., Antalík, M., and Podhradský, D., *Collect. Czech. Chem. Commun. 59,* 203 (1994).
11. Kristian, P., *Chem. Zvesti 15,* 641 (1961).