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2-BROMO-1-PHENYLETHYLIDENEMALONONITRILE IN THE SYNTHESIS OF THIENO[3,2-*b*]PYRIDINES AND THIAZOLO[4,5-*b*]PYRIDINES

V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, V. N. Nesterov, Yu. T. Struchkov,* and V. P. Litvinov

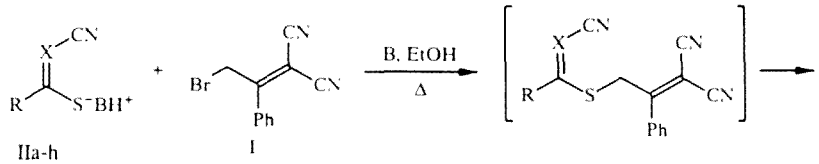
A novel regioselective synthesis of thieno[3,2-b]pyridines and thiazolo[4,5-b]pyridines from 2-bromo-1-phenylethylidenemalononitrile is proposed. In the case of the thiazolo[4,5-b]pyridines, the intermediate 5-(2,2-dicyano-1-phenylvinyl)thiazoles were separated. Formation of the thiazolo[4,5-b]pyridines was confirmed by x-ray analysis.

Substituted thienopyridines and thiazolopyridines are of considerable interest because many of them show a broad spectrum of biological activity. The known methods for preparing such compounds are generally typified by a multistage synthesis or hard to obtain starting materials [1-3]. We propose a novel, convenient method for the regioselective synthesis of substituted thienopyridines and thiazolopyridines from 2-bromo-1-phenyl-ethylidenemalononitrile (I) using a cascade reaction strategy developed previously for the preparation of pyridothienopyridines and pyridothienopyrimidines [4-6].

Adducts of malononitrile (cyanamide) with isothiocyanates or sulfur hydrocarbons (IIa-h) react with dinitrile I to form substituted thieno[3,2-*b*]pyridines or thiazolo[4,5-*b*]pyridines (IIIa-h). The mechanism of the process may be thought of as consecutive stages of alkylation at sulfur, closing of the thiophene or thiazole ring by a Thorpe–Ziegler reaction resulting in the appropriately substituted (IV) and a subsequent Thorpe–Guareschi reaction completing the synthesis of the bicyclic system III.

As a result of the reaction of malononitrile I with piperidine 1-(R-amino)-2,2-dicyanoethylene-1-thiolates IIa-c (formed in ethanol solution from equimolar amounts of the sodium salt and pyridine) there were obtained 2-amino-6-(R-amino)-3,7-dicyano-4-phenylthieno[3,2-*b*]pyridines (IIIa-c). Further, the intermediate 4-amino-2-(R-amino)-3-cyano-5-(2,2-dicyano-1-phenyl-vinyl)thiophenes (IVa-c) could not be separated, probably because of the rapid cyclization of the latter to give IIIa-c.

In the case of a similar reaction using the piperidinium salts of N-substituted N′-cyanothioureas IId-f (prepared from the corresponding sodium salts and piperidine), the intermediate thiazoles (IVd-f) could be separated and were bright yellow or orange compounds, moderately soluble in ethanol. The high stability of thiazoles IVd-f when compared with the corresponding thiophenes is evidently due to the lower nucleophilicity of the amino group with the introduction into the ring of the nitrogen atom in place of the C–CN fragment. By refluxing these compounds in alcohol in the presence of catalytic amounts of piperidine or by holding without solvent at a temperature above 190°C, there occurs a further cyclization to form 5-amino-2-(R-amino)-7-phenyl-6-cyanothiazolo[4,5-*b*]pyridines IIId-f. These colorless or light yellow compounds are almost insoluble in ethanol.



IIa-h I

*Deceased.

A. D. Zelinski Institute of Organic Synthesis, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 413-419, March, 1996. Original article submitted December 22, 1995.

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TABLE 1. Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum in DMSO–D_6, δ, ppm	Yield, %
		C	H	N				
IIIa	$C_{21}H_{13}N_5S$	69.02 68.65	3.29 3.57	19.22 19.06	260...262	3445, 3341, 3316, 3197 (NH), 2217 (CN), 1635, 1600, 1533	6,91 (2H, s, NH_2), 7,21 (1H, m, *p*-H_{NPh}), 7,38 (4H, m, *o*-H_{NPh} and *m*-H_{NPh}), 7,55 (5H, s, H_{CPh}), 10,46 (1H, br. s, NHR)	72,0
IIIb	$C_{17}H_{13}N_5S$	64.08 63,93	4.04 4,10	21.89 21,93	287...289	3458, 3275, 3184, 2978 (NH), 2210 (CN), 1632, 1588, 1575, 1543, 1522	1,19 (3H, t, CH_3), 3,31 (2H, q, CH_2), 6,88 (2H, s, NH_2), 7,59 (5H, m, H_{Ph}), 8,97 (1H, c, NHR)	81,5
IIIc	$C_{18}H_{13}N_5S$	65.38 65.24	3.71 3,95	21.21 21,13	275...277	3460, 3340, 3303, 3159 (NH), 2211 (CN), 1634, 1549, 1527	3,92 (2H, d, $-CH_2-$), 5,20 (2H, m, $-CH_2$), 5,82 (1H, m, $-CH-$), 6,87 (2H, s, NH_2), 7,55 (5H, s, H_{Ph}), 9,27 (1H, s, NHR)	85,0
IIId	$C_{19}H_{13}N_5S$	66.71 66,45	3.86 3,82	20.49 20,39	310...311	3422, 3284, 3180 (NH), 2212 (CN), 1611, 1599, 1540, 1502	6,78 (2H, s, NH_2), 7,00...7,80 (10H, m, H_{Ph}), 10,96 (1H, s, NHR)	59,0
IIIe	$C_{15}H_{13}N_5S$	60.78 61,00	4.51 4,44	23.85 23,71	294...295	3493, 3352, 3170, 2972 (NH), 2220 (CN), 1609, 1553, 1523, 1449	1,20 (3H, t, CH_3), 3,40 (2H, q, CH_2), 6,28 (2H, s, NH_2), 7,55 (5H, m, H_{Ph}), 8,58 (1H, s, NHR)	67,0
IIIf	$C_{16}H_{13}N_5S$	62.48 62,52	4.13 4,26	22.91 22,78	236...238	3461, 3295, 3103 (NH), 2217 (CN), 1642, 1595, 1580, 1523	4,01 (2H, d, $-CH_2-$), 5,17 (2H, m, $-CH_2$), 5,87 (1H, m, $-CH-$), 6,63 (2H, s, NH_2), 7,55 (5H, s, H_{Ph}), 8,95 (1H, s, NHR)	70,0
IIIg	$C_{16}H_{10}N_4S_2$	59.75 59,61	3.06 3,13	17.51 17,38	286...288	3460, 3312, 3170 (NH), 2238, 2215 (CN), 1681, 1545, 1538, 1367	2,76 (3H, s, CH_3), 7,23 (2H, s, NH_2), 7,61 (5H, s, H_{Ph})	88,0
IIIh	$C_{14}H_{10}N_4S_2$	56.53 56,36	3.14 3,38	18.91 18,78	216...218	3481, 3272, 3140 (NH), 2210 (CN), 1632, 1553, 1531, 1496	2,78 (3H, s, CH_3), 6,79 (2H, s, NH_2), 7,60 (5H, m, H_{Ph})	74,5
IVd	$C_{19}H_{13}N_5S$	66.39 66,45	3.80 3,82	20.25 20,39	*	3466, 3359, 3278, 3083 (NH), 2212, 2198 (CN), 1621, 1601, 1560, 1536	6,43† (1H, s, NH_2), 7,05...7,69 (10H, m, H_{Ph}), 11,25 (1H, s, NHR)	93,0
IVe	$C_{15}H_{13}N_5S$	61.12 61,00	4.55 4,44	23.92 23,71	*	3453, 3300, 3244, 3118, 3042 (NH) 2213, 2196 (CN), 1641, 1587	1,17 (3H, t, CH_3), 3,40 (2H, q, CH_2), 6,60† (1H, s, NH_2), 7,46 (5H, m, H_{Ph}), 9,31 (1H, s, NHR)	96,0
IVf	$C_{16}H_{13}N_5S$	62.58 62,52	4.20 4,26	22.94 22,78	*	3448, 3297, 3160, 3119 (NH), 2210, 2191 (CN), 1636, 1576, 1457	4,01 (2H, d, $-CH_2-$), 5,20 (2H, m, $-CH_2$), 5,87 (1H, m, $-CH-$), 6,62† (1H, s, NH_2), 7,51 (5H, m, H_{Ph}), 9,48 (1H, s, NHR)	96,0

*For IVd-f the melting points recorded were those for cyclization to IIId-f formed on heating.

†Due to exchange process, the signal is broadened and has a lower intensity.

TABLE 2. Valence Angles ω (deg.) in IIIf

Angle	ω	Angle	ω
C(2)—S(1)—C(7a)	81.0(2)	C(6)—C(7)—C(8)	127.5(4)
C(2)—N(3)—C(3a)	109.2(4)	C(7a)—C(7)—C(8)	118.5(4)
C(3a)—N(4)—C(5)	116.3(4)	S(1)—C(7a)—C(3a)	116.2(4)
C(2)—N(17)—C(18)	123.2(13)	S(1)—C(7a)—C(7)	126.9(3)
C(2)—N(17)—C(18a)	122.3(11)	C(3a)—C(7a)—C(7)	116.9(4)
S(1)—C(2)—N(3)	122.2(4)	C(7)—C(8)—C(9)	125.5(4)
S(1)—C(2)—N(17)	114.4(3)	C(7)—C(8)—C(13)	115.1(4)
N(3)—C(2)—N(17)	123.3(4)	C(9)—C(8)—C(13)	119.4(4)
N(3)—C(3a)—N(4)	119.8(4)	C(8)—C(9)—C(10)	124.3(5)
N(3)—C(3a)—C(7a)	111.3(4)	C(9)—C(10)—C(11)	116.0(5)
N(4)—C(3a)—C(7a)	128.8(5)	C(10)—C(11)—C(12)	119.4(6)
N(4)—C(5)—N(16)	115.4(4)	C(11)—C(12)—C(13)	125.8(7)
N(4)—C(5)—C(6)	117.5(4)	C(8)—C(13)—C(12)	115.1(5)
N(16)—C(5)—C(6)	127.1(5)	N(15)—C(14)—C(6)	174.7(4)
C(5)—C(6)—C(7)	126.5(4)	N(17)—C(18)—C(19)	111.4(19)
C(5)—C(6)—C(14)	111.2(4)	N(17)—C(18a)—C(19a)	102.9(13)
C(7)—C(6)—C(14)	122.1(4)	C(18)—C(19)—C(20)	126.2(20)
C(6)—C(7)—C(7a)	114.0(4)	C(18a)—C(19a)—C(20a)	126.3(26)

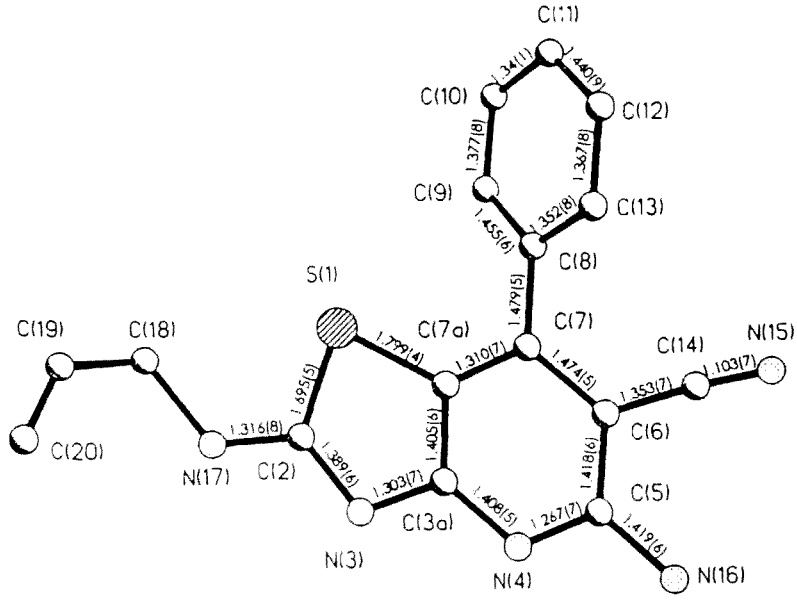
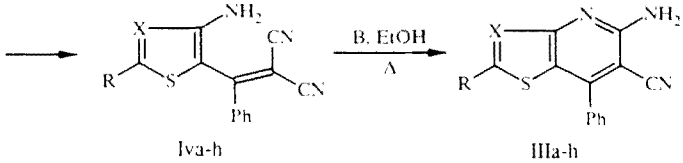


Fig. 1. Overall view and bond lengths for the IIIf molecule.



IVa-h IIIa-h

B = piperidine; I—IV a R = NHPh, X = C—CN, b R = NHEt, X = C—CN, c R = $NHCH_2CH{=}CH_2$, X = C—CN, d R = NHPh, X = N, e R = NHEt, X = N, f R = $NHCH_2CH{=}CH_2$, X = N, g R = SCH_3, X = C—CN, h R = SCH_3, X = N

Piperidine 1-methylmercapto-2,2-dicyanoethylene-1-thiolate IIg (obtained in ethanol solution using equal amounts of the corresponding sodium dithiolate and methyl iodide with further consecutive additions of equimolar amounts of acetic acid and piperidine) reacts with dinitrile I to form 2-amino-3,7-dicyano-6-methylmercapto-4-phenylthieno[3,2-*b*]pyridine IIIg.

TABLE 3. Atomic Coordinates ($\times 10^4$, for H $\times 10^3$) in IIIf

Atom	x	y	z
S(1)	1825(1)	2407(2)	8106(1)
N(3)	601(2)	3093(5)	7127(2)
N(4)	647(2)	3996(5)	5913(2)
N(15)	2272(2)	4875(6)	5033(2)
N(16)	703(2)	4883(7)	4745(2)
N(17)	797(2)	2200(6)	8447(3)
C(2)	1007(2)	2559(6)	7866(3)
C(3a)	951(2)	3431(5)	6694(3)
C(5)	1019(2)	4303(6)	5527(2)
C(6)	1695(2)	4024(5)	5913(2)
C(7)	2016(2)	3410(5)	6726(2)
C(7a)	1616(2)	3150(5)	7109(2)
C(8)	2717(2)	3072(5)	7133(2)
C(9)	3111(3)	3622(7)	7924(3)
C(10)	3769(3)	3329(9)	8281(4)
C(11)	4044(3)	2463(9)	7859(4)
C(12)	3650(3)	1912(8)	7080(4)
C(13)	2999(3)	2193(6)	6710(3)
C(14)	2037(2)	4474(6)	5451(2)
C(18)	1257(12)	1561(49)	9281(18)
C(18a)	1226(9)	1239(48)	9206(18)
C(19)	1043(7)	5(19)	9460(15)
C(19a)	740(11)	5538(19)	9492(9)
C(20)	499(15)	-522(31)	9194(17)
C(20a)	735(12)	-807(23)	9718(11)
H(161)	93(2)	507(5)	452(2)
H(162)	20(3)	530(6)	451(3)
H(17)	31(2)	247(6)	826(2)
H(9)	291(2)	424(5)	818(2)
H(10)	408(3)	383(8)	870(3)
H(11)	449(2)	229(6)	809(2)
H(12)	381(3)	137(6)	684(3)
H(13)	271(2)	174(6)	624(3)

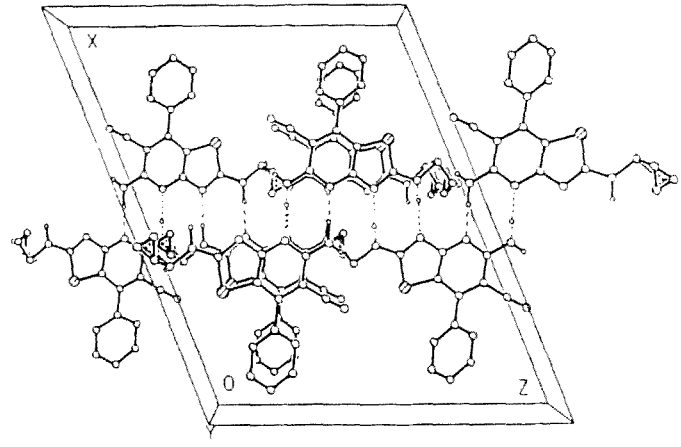


Fig. 2. AC projection of crystalline IIIf, dotted lines show the N–H-N intermolecular bonds.

Reaction of piperidine S-methyl-N-cyaniminodithiocarbonate IIh (obtained similarly to thiolate IIg) with I gives 2-amino-6-methylmercapto-4-phenyl-3-cyanothiazolo[4,5-*b*]pyridine IIIh. The structure of the products obtained was supported by PMR and IR spectra (see Table 1) and x-ray crystallography on IIIf (see Table 1).

The IR spectra of the 2-amino-6-(R-amino)-3,7-dicyano-4-phenylthieno[3,2-*b*]pyridines IIIa-c have broad absorption bands at 2210-2220 cm^{-1} corresponding closely to two cyano group signals.

The PMR spectra show singlet signals for the protons of the amino group at 6.9 ppm and the NHR proton at $\delta > 8.9$.

The IR spectra of 4-amino-2-(R-amino)-5-(2,2-dicyano-1-phenylvinyl)thiazoles IVd-f show signals for two cyano groups at 2150-2210 cm^{-1}, typical of a dicyanoethenyl fragment. The spectra of the corresponding thiazolo[4,5-*b*]pyridines IIId-f show only one signal near 2210 cm^{-1}, assigned to the CN group in the pyridine ring.

The PMR spectra of thiazoles IVd-f have broadened singlet signals at 6.1-7.0 ppm for the thiazole amino group protons and a sharp singlet at $\delta > 8.5$ for the NHR group proton. The analogous thiazolo[4,5-*b*]pyridines IIId-f show two sharp singlets at 6.5-6.9 ppm and 8.7-11.3 ppm which are assigned to the NH_2 and NHR groups respectively.

The most convincing evidence for these structures comes from the x-ray structural analysis of IIIf. A general view of the molecule with basic bond lengths is given in Fig. 1 (the numbering of the atoms differs from IUPAC recommendations) and valence angles are given in Table 2. The bond lengths in IIIf have conventional values [7]. The thiazolopyrimidine unit is planar to an accuracy of 0.006 Å. Short non-bonded intra-molecular contacts at S_1-C_9 (3.119(5) Å) and C_{13}-C_{14} (3.140(8) Å) (sum of van der Waal radii for S and C 3.50 Å, double the C radius 3.40 Å) serve to twist the phenyl substituent by 49.6° out of the plane of the bicycle.

In the crystal the intermolecular hydrogen bonds $N_{16}-H_{162}$-N_4 (−x, 1 − y, 1 − z) [N_{16}-N_4 2.925(6), $N_{16}-H_{162}$, 1.10(5), H_{162}-N_4 1.85(5) Å, angle $N_{16}-H_{162}$-N_4 178(3)°, $N_{17}-H_{17}$-N_3 (−x, y, 1.5 − z) N_{17}-N_3 2.962(6), $N_{17}-H_{17}$ 1.03(5), H_{17}-N_3 1.93(5) Å, angle $N_{17}-H_{17}$-N_3 176(3)°] assemble molecule IIIf into curved bands along the ac plane (Fig. 2). Analysis of the crystalline molecular packing showed that other shortened intermolecular contacts were absent.

We have developed a novel method for the regioselective synthesis of substituted thieno[3,2-*b*]pyridines and thiazolo[4,5-*b*]pyridines which opens up broader possibilities for preparing potentially biologically active compounds.

EXPERIMENTAL

Melting points were measured on a Kofler stage, IR spectra on a Specord M-80 instrument for KBr tablets, and PMR spectra on a Bruker WM-200 instrument for DMSO-D_6 solutions. C, H, and N elemental analyses were measured on a Perkin-Elmer C, H, N analyzer. The parameters for III and IV are given in Table 1.

2-Bromo-1-phenylethylidenemalononitrile I was prepared using the method reported in [8].

X-ray Structural Investigation of IIIf. Crystals of IIIf are monoclinic, at 20°C a = 21.903(2), b = 8.366(3), c = 17.991(4) Å, β = 110.56(2)°, V = 3087(3) $Å^3$, d_{calc} = 1.323 g/cm^3, Z = 8, space group c2/c. Unit cell parameters and intensities of 2713 independent reflections were measured on a Siemens P3/PC four circle automatic diffractometer (λMoKα, graphite monochromator, $\theta/2\theta$ scanning to θ_{max} = 28°). The structure was solved by a direct method revealing all nonhydrogen atoms and refined using a least squares full matrix method in the anisotropic approximation for 1855 reflections with $I > 3\sigma(I)$. Atoms C_{18}, C_{19}, and C_{20} were randomized in two positions in line with rotation of the allyl substituent around the $N_{17}-C_{18}$ bond. According to the least squares refinement, the population densities at C_{18}, C_{18a}, C_{19}, C_{19a}, C_{20}, and C_{20a} were 0.50 and 0.50 respectively. All hydrogen atoms except those bound to the latter six carbon atoms were directly revealed in difference synthesis and refined isotropically. The final value of the difference factor was R = 0.065 (R_w = 0.065). All calculations were carried out using the SHELXTL PLUS program (PC version). Atomic coordinates are given in Table 3 (atomic thermal parameters can be obtained from the authors).

2-Amino-6-(R-amino)-3,7-dicyano-4-phenylthieno[3,2-*b*]-pyridines (IIIa-c). Acetic acid (2 mmole) was added to a solution of sodium 1-(R-amino)-2,2-dicyanoethylene-1-thiolate (2 mmole) in alcohol (20 ml) and piperidine (2 mmole) was added after 2 min. The mixture was heated to 50°C and (2-bromo-1-phenylethylidene)malonodinitrile (I, 2 mmole) was then added. The precipitated products (IIIa-c) were filtered and washed with ethanol and hexane and dried in air.

4-Amino-2-(R-amino)-5-(2,2-dicyano-1-phenylethenyl)thiazoles (IVd-f) as described above from the sodium salt of N-substituted N′-cyanothioureas (2 mmole) in alcohol (15 ml) to give IVd-f.

5-Amino-2-(R-amino)-7-phenyl-6-cyanothiazolo[4,5-*b*]pyridines (IIId-f). Piperidine (2-3 drops) were added to a solution of thiazoles IVd-f (2 mmole) in alcohol (30 ml) heated to 50°C. The product was refluxed until precipitation of the products IIId-f began. The precipitate was filtered and washed with acetone and hexane and dried in air.

2-Amino-3,7-dicyano-6-methylmercapto-4-phenylthieno[3,2-*b*]pyridine (IIIg). Methyl iodide (2 mmole) was added to a solution of sodium 2,2-dicyano-1,1-dithiolate (2 mmole) in ethanol (20 ml) heated to 60-65°C. The mixture was held for

30 min at 30-40°C and there were added successively acetic acid (2 mmole), piperidine (2 mmole), and 2-dinitrile I (2 mmole). The precipitated product IIIg was filtered and washed with ethanol and hexane and dried in air.

2-Amino-6-methylmercapto-4-phenyl-3-cyanothiazolo[4,5-*b*]pyridine (IIIh) as described above for IIIg from sodium S-methyl-N-cyaniminodithiocarbonate to give IIIh.

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