

**SYNTHESIS AND ALKYLATION OF
PIPERIDINIUM 4,5-*trans*-3-CYANO-6-HYDROXY-
4-(2-IODOPHENYL)-6-METHYL-5-(2-METHYLPHENYL)-
CARBAMOYL-1,4,5,6-TETRAHYDROPYRIDINE-2-THIOLATE.
MOLECULAR AND CRYSTAL STRUCTURE OF
3-(2-IODOPHENYL)-2-(4-PHENYL-
2-THIAZOLYL)ACRYLONITRILE**

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The reaction of o-iodobenzaldehyde, cyanothioacetamide, and N-acetoacetyl-o-toluidine in the presence of piperidine gave piperidinium 4,5-trans-3-cyano-6-hydroxy-4-(2-iodophenyl)-6-methyl-5-(2-methylphenyl)carbamoyl-1,4,5,6-tetrahydropyridine-2-thiolate used in the synthesis of substituted 4,5-trans-2-alkylthiotetrahydropyridines and 2-(2-thiazolyl)acrylonitriles. The structure of 3-(2-iodophenyl)-2-(4-phenyl-2-thiazolyl)acrylonitrile was studied using X-ray diffraction structural analysis.

Keywords: N-acetoacetyl-o-toluidine, o-iodobenzaldehyde, 3-(2-iodophenyl)-2-(4-phenyl-2-thiazolyl)acrylonitrile, cyanothioacetamide, condensation, X-ray diffraction structural analysis.

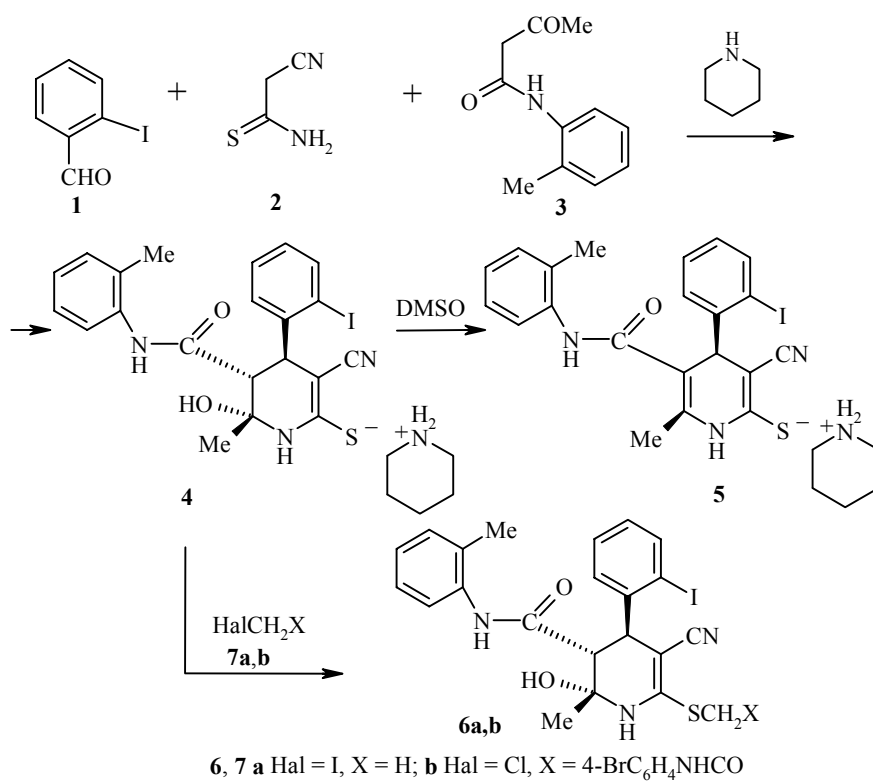
Substituted sulfur-containing tetrahydropyridines have not been extensively studied [1]. In light of the biological activity of these heterocycles [2], there is interest in developing convenient stereoselective methods for their preparation.

We are the first to report the preparation of substituted piperidinium tetrahydropyridine-2-thiolate (**4**) by the reaction of o-iodobenzaldehyde (**1**), cyanothioacetamide (**2**), and N-acetoacetyl-o-toluidine (**3**) in the presence of piperidine. Thiolate **4** is stable in the crystalline state but, in contrast to its thienyl analog [3], it readily converts to dehydration product **5** upon dissolution, which makes analysis of the structure of this salt by ¹H NMR spectroscopy impossible. The steric selectivity of this synthetic method may be evaluated relative to derivative **6** obtained by the reaction of thiolate **4** with halides **7** in ethanol.

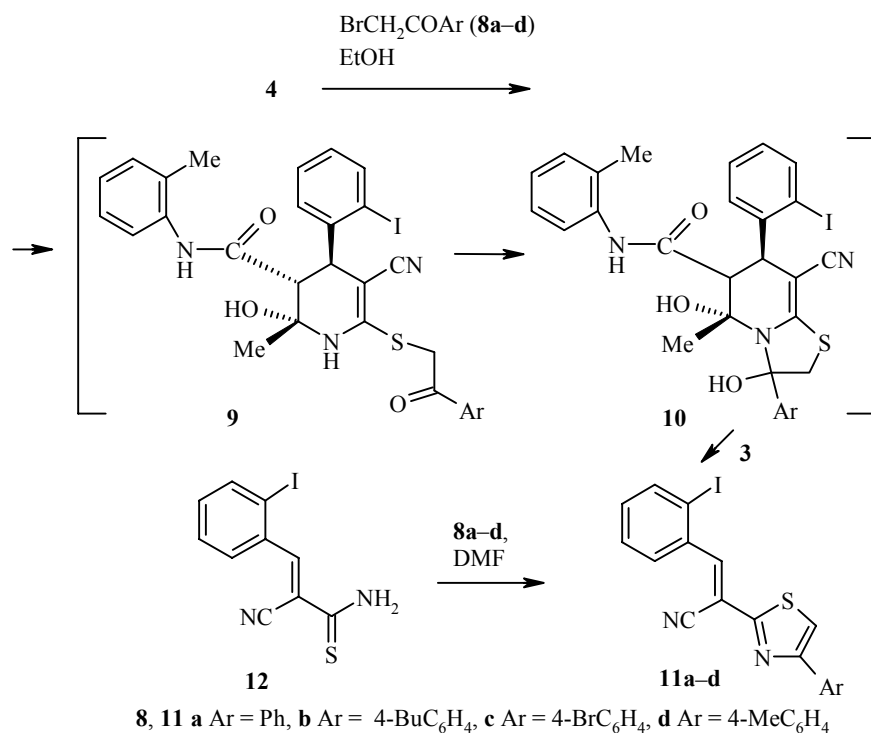
The ¹H NMR spectra of **6** show signals for all the indicated substituents and NH group (see Experimental). The signals for 4-H and 5-H appear as doublets at 4.50-4.56 and 2.84-2.90 ppm, respectively with ³J = 11.8-12.3 Hz. According to the Karplus-Conroy equation [4], at the above ³J values the φ_{C(4)H-C(5)H} torsion angle is 160-165°, indicating *trans*-equatorial arrangement of the Ar and ArNHCO groups. The OH group presumably occupies an axial position, which was noted for isostructural analogs of **4** and **6** [5].

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The alkylation of salt **4** by bromides **8** in ethanol at 20°C leads to recyclization of the tetrahydropyridine ring and, through intermediates **9** and **10**, to thiazoles **11**, which were also obtained independently from **12** and **8** in DMF according to a reported procedure [6]:



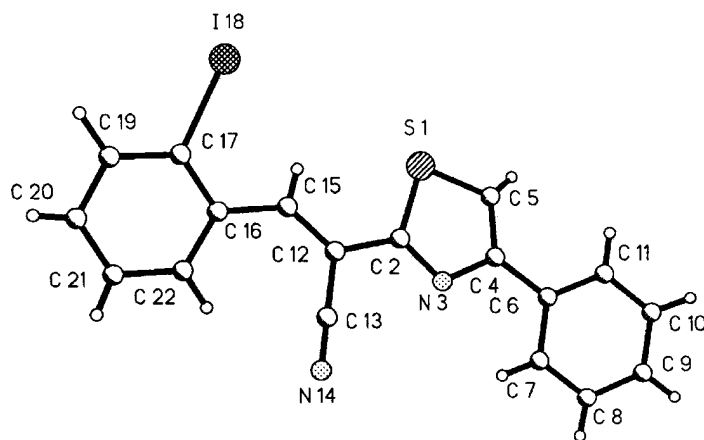


Fig. 1. General view of **11a** molecule.

TABLE 1. Bond Lengths (d) in **11a**

Bond	d , Å	Bond	d , Å
I ₍₁₈₎ -C ₍₁₇₎	2.096(5)	C ₍₈₎ -C ₍₉₎	1.382(8)
S ₍₁₎ -C ₍₅₎	1.701(5)	C ₍₉₎ -C ₍₁₀₎	1.356(9)
S ₍₁₎ -C ₍₂₎	1.729(4)	C ₍₁₀₎ -C ₍₁₁₎	1.392(8)
N ₍₃₎ -C ₍₂₎	1.289(6)	C ₍₁₂₎ -C ₍₁₅₎	1.342(6)
N ₍₃₎ -C ₍₄₎	1.378(5)	C ₍₁₂₎ -C ₍₁₃₎	1.440(6)
N ₍₁₄₎ -C ₍₁₃₎	1.137(6)	C ₍₁₅₎ -C ₍₁₆₎	1.459(6)
C ₍₂₎ -C ₍₁₂₎	1.479(6)	C ₍₁₆₎ -C ₍₁₇₎	1.389(7)
C ₍₄₎ -C ₍₅₎	1.365(7)	C ₍₁₆₎ -C ₍₂₂₎	1.393(7)
C ₍₄₎ -C ₍₆₎	1.463(6)	C ₍₁₇₎ -C ₍₁₉₎	1.392(8)
C ₍₆₎ -C ₍₁₁₎	1.388(6)	C ₍₁₉₎ -C ₍₂₀₎	1.368(11)
C ₍₆₎ -C ₍₇₎	1.398(7)	C ₍₂₀₎ -C ₍₂₁₎	1.367(11)
C ₍₇₎ -C ₍₈₎	1.385(8)	C ₍₂₁₎ -C ₍₂₂₎	1.386(8)

An X-ray diffraction structural analysis of **11a** was carried out to elucidate the direction of the recyclization and establish the structure of its products unequivocally. Product **11a** is the *E*-isomer relative to the C₍₁₂₎=C₍₁₅₎ bond. A general view of the this molecule is shown in Fig. 1 and the bond lengths and angles are given in Table 1.

The substituted thiazole ring in **11a** is rigorously planar and the deviation of individual atoms is only ± 0.002 Å. The dihedral angle between the heterocyclic and phenyl (C₍₆₎⋯C₍₁₁₎) substituents is 163° , which indicates slight twisting about the C₍₄₎-C₍₆₎ bond. The C₍₂₎-C₍₁₂₎=C₍₁₅₎-C₍₁₆₎ fragment with mean deviation of the atoms from the mean plane equal to ± 0.014 Å lies in the plane of the heterocycle (the corresponding dihedral angle is only 2.5°), while the *o*-iodophenyl substituent is twisted relative to this chain by 155.5° . The slight distortion in molecular planarity probably should be attributed to intramolecular nonbonding contacts: S₍₁₎⋯H₍₁₅₎, 2.74(5) Å; C₍₁₃₎⋯C₍₂₂₎, 3.045(8) Å; C₍₁₃₎⋯H₍₂₂₎, 2.47(5) Å, I₍₁₈₎⋯H₍₁₅₎, 2.81(5) Å (the corresponding sums of the van der Waals radii are 2.91, 3.54, 2.87, and 3.13 Å respectively [7]).

TABLE 2. Bond Angles (ω) in **9a**

Angle	ω , deg	Angle	ω , deg
C ₍₅₎ -S ₍₁₎ -C ₍₂₎	88.6(2)	C ₍₆₎ -C ₍₁₁₎ -C ₍₁₀₎	120.5(5)
C ₍₂₎ -N ₍₃₎ -C ₍₄₎	111.2(4)	C ₍₁₅₎ -C ₍₁₂₎ -C ₍₁₃₎	123.5(4)
N ₍₃₎ -C ₍₂₎ -C ₍₁₂₎	123.1(4)	C ₍₁₅₎ -C ₍₁₂₎ -C ₍₂₎	123.4(4)
N ₍₃₎ -C ₍₂₎ -S ₍₁₎	115.1(3)	C ₍₁₃₎ -C ₍₁₂₎ -C ₍₂₎	113.0(4)
C ₍₁₂₎ -C ₍₂₎ -S ₍₁₎	121.8(3)	N ₍₁₄₎ -C ₍₁₃₎ -C ₍₁₂₎	177.8(5)
C ₍₅₎ -C ₍₄₎ -N ₍₃₎	113.8(4)	C ₍₁₂₎ -C ₍₁₅₎ -C ₍₁₆₎	130.4(4)
C ₍₅₎ -C ₍₄₎ -C ₍₆₎	126.4(4)	C ₍₁₇₎ -C ₍₁₆₎ -C ₍₂₂₎	117.1(5)
N ₍₃₎ -C ₍₄₎ -C ₍₆₎	119.8(4)	C ₍₁₇₎ -C ₍₁₆₎ -C ₍₁₅₎	120.6(4)
C ₍₄₎ -C ₍₅₎ -S ₍₁₎	111.2(3)	C ₍₂₂₎ -C ₍₁₆₎ -C ₍₁₅₎	122.2(5)
C ₍₁₁₎ -C ₍₆₎ -C ₍₇₎	118.2(5)	C ₍₁₆₎ -C ₍₁₇₎ -C ₍₁₉₎	121.7(5)
C ₍₁₁₎ -C ₍₆₎ -C ₍₄₎	121.7(4)	C ₍₁₆₎ -C ₍₁₇₎ -I ₍₁₈₎	122.3(4)
C ₍₇₎ -C ₍₆₎ -C ₍₄₎	120.0(4)	C ₍₁₉₎ -C ₍₁₇₎ -I ₍₁₈₎	116.1(4)
C ₍₈₎ -C ₍₇₎ -C ₍₆₎	120.7(5)	C ₍₂₀₎ -C ₍₁₉₎ -C ₍₁₇₎	119.1(6)
C ₍₉₎ -C ₍₈₎ -C ₍₇₎	119.6(5)	C ₍₂₁₎ -C ₍₂₀₎ -C ₍₁₉₎	121.0(6)
C ₍₁₀₎ -C ₍₉₎ -C ₍₈₎	120.6(6)	C ₍₂₀₎ -C ₍₂₁₎ -C ₍₂₂₎	119.6(6)
C ₍₉₎ -C ₍₁₀₎ -C ₍₁₁₎	120.4(5)	C ₍₂₁₎ -C ₍₂₂₎ -C ₍₁₆₎	121.5(6)

Conjugation in the heterocycle in this molecule gives rise to significant redistribution of bond lengths, which are in accord with the values established for thiazoles. The other bond lengths and angles have the expected values [8].

A short intermolecular contact is found in the crystal: C₍₅₎-H₍₅₎⋯N₍₁₄₎ (1 + x, y, 1 + z), C₍₅₎⋯N₍₁₄₎, 3.448(7) Å; C₍₅₎-H₍₅₎, 0.82(5) Å; H₍₅₎⋯N₍₁₄₎, 2.64(5) Å; C₍₅₎-H₍₅₎⋯N₍₁₄₎, 174(3)°.

TABLE 3. Coordinates ($\times 10^4$) and Isotropic Equivalent Temperature Parameters for Non-hydrogen Atoms and Isotropic Temperature Parameters for Hydrogen Atoms in **11a**

Atom	x	y	z	$U_{(eq)}$
1	2	3	4	5
I ₍₁₈₎	-5(1)	1725(1)	1317(1)	69(1)
S ₍₁₎	4367(2)	285(1)	2497(1)	46(1)
N ₍₃₎	3484(4)	-496(1)	414(4)	34(1)
N ₍₁₄₎	-324(6)	-353(2)	-3351(5)	53(1)
C ₍₂₎	3028(5)	-22(2)	577(5)	33(1)
C ₍₄₎	4968(5)	-651(2)	1855(5)	36(1)
C ₍₅₎	5619(6)	-272(2)	3101(6)	44(1)
C ₍₆₎	5722(6)	-1175(2)	1917(6)	37(1)
C ₍₇₎	5263(7)	-1466(2)	389(6)	47(1)
C ₍₈₎	5999(8)	-1957(2)	420(8)	54(1)
C ₍₉₎	7176(8)	-2166(2)	1981(8)	59(1)
C ₍₁₀₎	7643(8)	-1889(2)	3476(8)	59(1)
C ₍₁₁₎	6922(7)	-1393(2)	3460(7)	51(1)
C ₍₁₂₎	1493(5)	249(2)	-780(5)	31(1)
C ₍₁₃₎	495(6)	-84(2)	-2233(5)	36(1)
C ₍₁₅₎	1053(6)	749(2)	-652(6)	37(1)
C ₍₁₆₎	-354(6)	1079(2)	-1881(6)	39(1)
C ₍₁₇₎	-969(7)	1518(2)	-1313(7)	46(1)
C ₍₁₉₎	-2287(9)	1844(2)	-2465(10)	66(2)

TABLE 3 (continued)

1	2	3	4	5
C ₍₂₀₎	-2970(9)	1733(3)	-4203(10)	72(2)
C ₍₂₁₎	-2377(9)	1310(3)	-4818(8)	68(2)
C ₍₂₂₎	-1076(8)	985(2)	-3663(7)	52(1)
H ₍₅₎	6573(88)	-264(25)	3947(85)	7(2)
H ₍₇₎	4475(74)	-1323(22)	-586(73)	5(2)
H ₍₈₎	5796(79)	-2121(24)	-551(82)	6(2)
H ₍₉₎	7712(72)	-2499(24)	2024(71)	5(1)
H ₍₁₀₎	8334(86)	-2056(26)	4505(85)	7(2)
H ₍₁₁₎	7280(76)	-1204(23)	4458(76)	5(2)
H ₍₁₅₎	1695(63)	917(19)	282(64)	3(1)
H ₍₁₉₎	-2747(90)	2166(28)	-2043(87)	8(2)
H ₍₂₀₎	-3868(97)	1923(29)	-4757(92)	8(2)
H ₍₂₁₎	-2757(91)	1210(27)	-5898(92)	7(2)
H ₍₂₂₎	-589(71)	703(23)	-4086(68)	5(1)

EXPERIMENTAL

The IR spectra were taken on an IKS-29 spectrophotometer for vaseline mulls. The mass spectra were taken on a Kratos MS-30 mass spectrometer with direct sample inlet into the source. The ¹H NMR spectra were registered on a Bruker AM-300 spectrometer for **4** and **6** and Bruker WP-100 SY spectrometer for **11** in DMSO-d₆ with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 3:5 acetone–hexane as the eluent.

Piperidinium 4,5-trans-3-Cyano-6-hydroxy-4-(2-iodophenyl)-6-methyl-5-(2-methylphenyl)carbamoyl-1,4,5,6-tetrahydropyridine-2-thiolate (4). A sample of cyanothioacetamide **2** (2 g, 20 mmol) was added with stirring to a mixture of *o*-iodobenzaldehyde **1** (4.64 g, 20 mmol) and three drops of piperidine in ethanol (30 ml) at about 20°C. After 5 min, N-acetoacetyl-*o*-toluidine **3** (3.83 g, 20 mmol) was added and, then, piperidine (2.47 ml, 25 mmol) was added. After 30 min, the precipitate formed was filtered off and washed with acetone to give 11 g (93%) salt **4**; mp 171-173°C. IR spectrum, ν , cm⁻¹: 3150-3330 (NH, OH), 2164 (CN), 1680 (CO). As a result of rapid dehydration of thiolate **4** in DMSO or CDCl₃, the ¹H NMR spectrum shows signals for 1,4-dihydropyridine-2-thiolate **5**: 1.55-1.68 (6H, m, 3CH₂); 1.78 (3H, s, 6-Me); 2.06 (3H, s, 2'-Me); 3.02 (4H, m, CH₂NCH₂); 4.81 (1H, s, 4-H); 7.06 m, 7.42 m, and 7.71 d (8H, H_{Ar}); 7.65 (1H, s, NH); 8.36 (1H, s, CONH) (the signals for the NH₂⁺ group protons are not seen due to deuterioexchange). Electron impact mass spectrum at 70 eV, m/z (I_{rel} , %): 58 (21), 107 (100), 224 (30), 252 (99), 253 (36), 254 (30), 358 (90), 359 (34). The [M⁺] peak is lacking. Found, %: C 53.24; H 5.57; N 9.83; S 5.19. C₂₆H₃₁IN₄O₂S. Calculated, %: C 52.88; H 5.29; N 9.49; S 5.43.

4,5-trans-3-Cyano-6-hydroxy-4-(2-iodophenyl)-6-methyl-2-X-methylthio-5-(2-methylphenyl)-carbamoyl-1,4,5,6-tetrahydropyridines (6a,b). A mixture of salt **4** (1.77 g, 3 mmol) and corresponding halide **7** (3 mmol) in 30 ml 80% aq. ethanol was stirred at 20°C until the starting reagents were entirely dissolved and filtered through a paper filter. After 12 h, the fine crystalline precipitate formed in the filtrate was filtered off and washed with 80% aq. ethanol and hexane.

Yield of **6a** 1.71 g (75%); mp 196-198°C. IR spectrum, ν , cm⁻¹: 3180-3390 (NH, OH), 2174 (CN), 1650 (CO). ¹H NMR spectrum, δ , ppm, J (Hz): 1.60 (3H, s, 6-Me); 1.90 (3H, s, 2'-Me); 2.49 (3H, s, SMe); 2.84 (1H, d, ³ J = 11.8, 5-H); 4.50 (1H, d, ³ J = 11.8, 4-H); 6.10 (1H, s, OH); 7.10 m, 7.38 m, and 7.81 d (8H_{Ar}); 7.71 (1H, s, NH); 9.25 (1H, s, CONH). Electron impact mass spectrum at 70 eV, m/z (I_{rel} , %): 58 (49), 77 (26), 107 (100), 165 (31), 266 (40), 372 (27). The [M⁺] peak is lacking. Found, %: C 50.41; H 4.76; N 8.46; S 6.29. C₂₂H₂₂IN₃O₂S. Calculated, %: C 50.87; H 4.27; I 24.43; N 8.09; S 6.17.

Yield of **6b** 1.66 g (77%); mp 232-233°C. IR spectrum, ν , cm^{-1} : 3180-3330 (NH, OH), 2175 (CN), 1650 (CO). ^1H NMR spectrum, δ , ppm, J (Hz): 1.61 (3H, s, 6-Me); 1.90 (3H, s, 2'-Me); 2.90 (1H, d, $^3J = 12.3$, 5-H); 3.91 (2H, s, SCH_2); 4.48 (1H, d, $^3J = 12.3$, 4-H); 6.17 (1H, s, OH); 7.09 m, 7.37 d, 7.58 q, 7.81 d (12 H_{Ar}); 8.29 (1H, s, NH); 9.27 (1H, s, 5-CONH); 10.48 (1H, s, 2- SCH_2CONH). Electron impact mass spectrum at 70 eV, m/z (I_{rel} , %): 58 (78), 65 (54), 77 (75), 91 (91), 107 (76), 133 (90), 171 (85), 173 (61), 197 (99), 199 (89), 220 (58), 239 (55), 266 (82), 326 (49), 393 (44). The $[\text{M}^+]$ peak is lacking. Found, %: C 48.91; H 3.22; N 8.13; S 4.75. $\text{C}_{29}\text{H}_{26}\text{BrIN}_4\text{O}_3\text{S}$. Calculated, %: C 48.55; H 3.65; N 7.81; S 4.47.

2-(4-Aryl-2-thiazolyl)-3-(2-iodophenyl)acrylonitriles (11a-d). A. These compounds were obtained identically to sulfides **6** using corresponding bromides **8a-d**.

B. Thiazoles **11a-d** were obtained according to a reported procedure [6] using **12** (0.94 g, 3 mmol) and **8a-d** (3 mmol).

Yield of thiazole **11a** 0.85 g (68%) (A); 0.88 g (71%) (B); mp 112-114°C. ^1H NMR spectrum, δ , ppm: 7.42 m, 8.02 m (9H, H_{Ar}); 8.30 (1H, s, H_{Het}); 8.36 (1H, s, $\text{CH}=\text{C}$). Found, %: C 52.45; H 2.82; N 6.97; S 8.01. $\text{C}_{18}\text{H}_{11}\text{IN}_2\text{S}$. Calculated, %: C 52.91; H 2.68; N 6.76; S 7.74.

Yield of thiazole **11b** 1.12 g (79%) (A); 1.20 g (85%) (B); mp 77-78°C. ^1H NMR spectrum, δ , ppm: 0.89 (3H, t, Me); 1.29 m, 1.52 m, and 2.60 t (6H, 3 CH_2); 7.28 m, 7.60 t, 7.90 d, and 8.03 d (8 H_{Ar}); 8.23 (1H, s, H_{Het}); 8.29 (1H, s, $\text{CH}=\text{C}$). Found, %: C 56.44; H 4.35; N 5.63; S 7.03. $\text{C}_{22}\text{H}_{19}\text{IN}_2\text{S}$. Calculated, %: C 56.18; H 4.07; N 5.96; S 6.82.

Yield of thiazole **11c** 1.32 g (89%) (A); 1.30 g (88%) (B); mp 155-157°C. ^1H NMR spectrum, δ , ppm: 7.27 m, 7.62 t, and 8.01 t (8 H_{Ar}); 8.28 (1H, s, H_{Het}); 8.39 (1H, s, $\text{CH}=\text{C}$). Found, %: C 43.37; H 2.31; N 5.82; S 6.81. $\text{C}_{18}\text{H}_{10}\text{BrIN}_2\text{S}$. Calculated, %: C 43.84; H 2.04; N 5.68; S 6.50.

Yield of thiazole **11d** 0.86 g (67%) (A); 1.05 g (82%) (B); mp 95-97°C. ^1H NMR spectrum, δ , ppm: 2.33 (3H, s, Me); 7.27 m, 7.60 t, 7.94 d, and 8.07 d (8 H_{Ar}); 8.20 (2H, d, H_{Het} and $\text{CH}=\text{C}$). Found, %: C 53.45; H 3.17; N 6.81; S 7.62. $\text{C}_{19}\text{H}_{13}\text{IN}_2\text{S}$. Calculated, %: C 53.28; H 3.06; N 6.54; S 7.49.

X-ray Diffraction Structural Analysis of 3-(2-Iodophenyl)-2-(4-phenyl-2-thiazolyl)acrylonitrile (11a). The unit cell parameters of monoclinic crystals of **11a** at 20°C: $a = 8.141(3)$, $b = 25.506(8)$, $c = 8.419(3)$ Å; $V = 1598.5(9)$ Å³; $d_{\text{calc}} = 1.721$ g/cm³; $Z = 4$; space group $P2_1/n$. The unit cell parameters and intensities of 3495 independent reflections were measured on Siemens P3/PC automatic four-circle diffractometer using $\lambda\text{MoK}\alpha$ radiation, graphite monochromator, and $\theta/2\theta$ scanning to $\theta_{\text{max}} = 27^\circ$. The structure was solved by the direct method, which revealed all the nonhydrogen atoms and refined by the full-matrix method of least squares in anisotropic approximation for the nonhydrogen atoms. All the hydrogen atoms were found objectively in the Fourier difference map and refined isotropically. The final $R_1 = 0.052$ for 2980 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.127$ for 3436 independent reflections. All the calculations were carried out using the SHELXTL PLUS and SHELXL-93 (PC version) programs. The coordinates and isotropic equivalent temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms are given in Table 3.

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