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SYNTHESIS OF CONDENSED 3-CYANOPYRIDIN-2(1*H*)-ONES BASED ON THE SMILES REARRANGEMENT

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Condensed 3-cyanopyridin-2(1H)-ones have been synthesized via an intramolecular nucleophilic substitution (Smiles rearrangement). The X-ray structural analysis revealed the existence of intermolecular hydrogen bonding.

Keywords: isoquinoline, pyrano[3,4-*c*]pyridine, pyridin-2(1*H*)-one, pyridine-2(1*H*)-thione, Smiles rearrangement.

The 3-cyanopyridin-2(1*H*)-ones are of both theoretical and practical interest. In particular, they are synthons for annelated heterocyclic systems [1-4] while 3-cyanopyridin-2(1*H*)-ones show cardiotonic and inotropic activity as phosphodiesterase inhibitors [5-7].

We have previously prepared 5-cyanopyrano[3,4-*c*]pyridin-6(7*H*)-ones which contain alkyl and aryl substituents in position 8 [8]. With the aim of introducing cyclic amine fragments into the pyridine ring, we have developed a method for preparing condensed 3-cyanopyridin-2(1*H*)-ones through Smiles rearrangement.

We have used the condensed 3-cyanopyridin-2(1*H*)-thiones **1a-i** [9-12] as starting materials. Initially, we unsuccessfully attempted to carry out preparation of the condensed 3-cyanopyridin-2(1*H*)-ones *via* nucleophilic substitution of the *S*-methyl and *S*-benzyl derivatives of the 3-cyanopyridine-2(1*H*)-thiones **2j-m** [10-14] using an aqueous alcoholic solution of sodium hydroxide. Subsequently this task was achieved using the 2-hydroxyethylsulfanyl derivatives **2a-i** which underwent a Smiles rearrangement using sodium hydroxide under analogous conditions to give the 3-cyanopyridin-2(1*H*)-ones **3a-i**.

Rearrangement of the 2-hydroxyethylsulfanyl derivatives **2a-i** occurred in the presence of a tenfold excess of sodium hydroxide in quite good yields (65-90%) which reached 85-90% in the case of the 8-morpholino- or 8-piperidino-substituted derivatives **3a**,**b**,**e**,**h** (Table 1). Decreasing the amount of base caused a decrease in the product yield. The cleavage product - thiirane (**4**) is also formed in the reaction mixture and may

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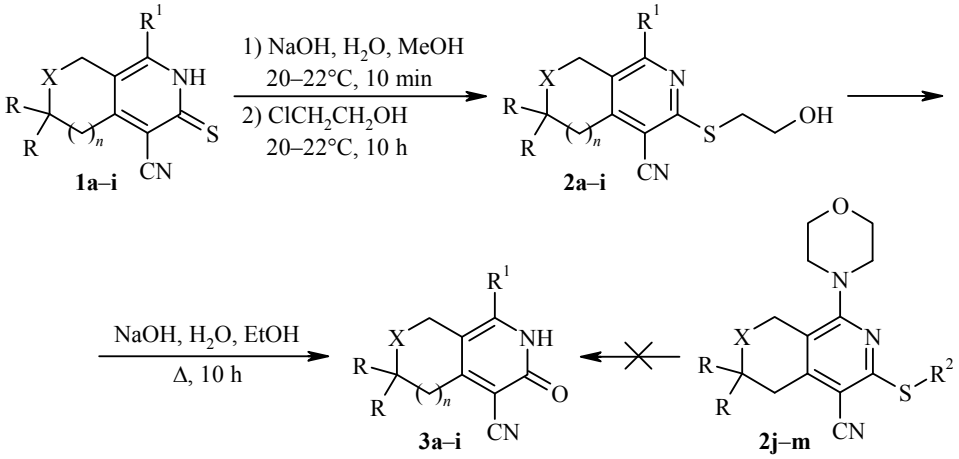

1–3 a X = O, *n* = 1, R = Me, R^1 = morpholin-4-yl; **1–3 b** X = O, *n* = 1, R = Me, R^1 = piperidin-1-yl; **1–3 c** X = O, *n* = 1, R = Me, R^1 = pyrrolidin-1-yl; **1–3 d** X = NMe, *n* = 1, R = H, R^1 = morpholin-4-yl; **1–3 e** X = CH_2, *n* = 1, R = H, R^1 = morpholin-4-yl; **1–3 f** X = CH_2, *n* = 1, R = H, R^1 = piperidin-1-yl; **1–3 g** X = CH_2, *n* = 1, R = H, R^1 = pyrrolidin-1-yl; **1–3 h** X = CH_2, *n* = 0, R = H, R^1 = morpholin-4-yl; **1–3 i** X = CH_2, *n* = 0, R = H, R^1 = pyrrolidin-1-yl; **2j**,**k** X = O, R = Me; **l**,**m** X = CH_2, R = H; **2j**,**l** R^2 = Me; **k**,**m** R^2 = CH_2Ph

polymerize under basic conditions [15, 16]. A similar O–S Smiles rearrangement is observed in furazan and furoxazan derivatives [17]. The patent [18] reports the preparation of the pyridin-2(1*H*)-one **3a** using 2-bromoethanol without isolation of the 2-hydroxyethyl derivative **2a** under more forcing conditions (heating at 135ºC) without a study of the reaction chemistry. However, in the patent, the melting point, IR and mass spectra, and elemental analysis are absent with only a questionable ^{1}H NMR spectrum. The proposed intramolecular nucleophilic substitution reaction mechanism is presented in the following scheme.

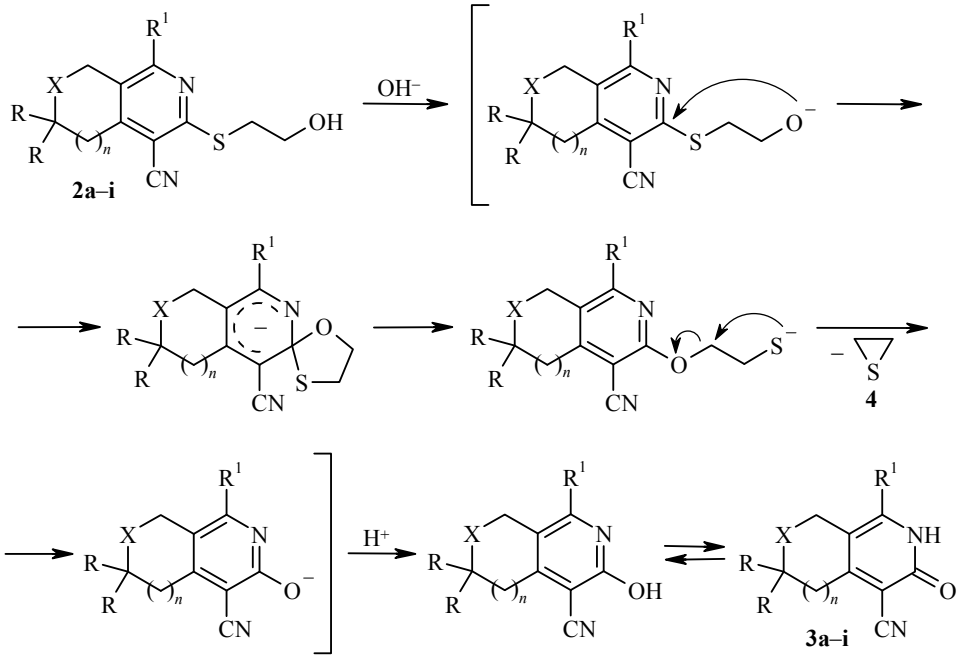

TABLE 1. Physicochemical Characteristics of Compounds **2**, **3a-i**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, %
		C	H	N	S		
2a	$C_{17}H_{23}N_3O_3S$	58.22 / 58.43	6.71 / 6.63	11.85 / 12.02	8.95 / 9.18	138-140	92
2b	$C_{18}H_{25}N_3O_2S$	62.07 / 62.22	7.38 / 7.25	11.78 / 12.09	9.45 / 9.23	151-152	75
2c	$C_{17}H_{23}N_3O_2S$	61.08 / 61.23	6.77 / 6.95	12.47 / 12.60	9.52 / 9.62	148-150	89
2d	$C_{16}H_{22}N_4O_2S$	57.65 / 57.46	6.74 / 6.63	16.91 / 16.75	9.70 / 9.59	192-194	74
2e	$C_{16}H_{21}N_3O_2S$	60.07 / 60.16	6.78 / 6.63	13.33 / 13.15	9.77 / 10.04	108-110	70
2f	$C_{17}H_{23}N_3OS$	64.58 / 64.32	7.51 / 7.30	13.07 / 13.24	9.86 / 10.10	124-126	77
2g	$C_{16}H_{21}N_3OS$	63.58 / 63.34	7.10 / 6.98	13.61 / 13.85	10.45 / 10.57	142-144	80
2h	$C_{15}H_{19}N_3O_2S$	59.06 / 58.99	6.46 / 6.27	13.88 / 13.76	10.67 / 10.50	128-130	70
2i	$C_{15}H_{19}N_3OS$	62.18 / 62.25	6.80 / 6.62	14.63 / 14.52	11.21 / 11.08	165-167	73
3a	$C_{15}H_{19}N_3O_3$	62.12 / 62.27	6.43 / 6.62	14.70 / 14.52	—	280-282	85
3b	$C_{16}H_{21}N_3O_2$	66.72 / 66.88	7.46 / 7.37	14.71 / 14.62	—	244-245	90
3c	$C_{15}H_{19}N_3O_2$	65.82 / 65.91	6.88 / 7.01	15.26 / 15.37	—	255-257	73
3d	$C_{14}H_{18}N_4O_2$	61.42 / 61.30	6.57 / 6.61	20.53 / 20.42	—	225-227	69
3e	$C_{14}H_{17}N_3O_2$	65.02 / 64.85	6.77 / 6.61	16.38 / 16.20	—	253-254	88
3f	$C_{15}H_{19}N_3O$	70.25 / 70.01	7.23 / 7.44	16.50 / 16.33	—	>360	65
3g	$C_{14}H_{17}N_3O$	69.31 / 69.11	7.21 / 7.04	17.35 / 17.27	—	272-273	65
3h	$C_{13}H_{15}N_3O_2$	63.51 / 63.66	6.32 / 6.16	17.28 / 17.13	—	228-230	88
3i	$C_{13}H_{15}N_3O$	68.21 / 68.10	6.65 / 6.59	18.45 / 18.33	—	>360	73

It is known from the literature that 2-hydroxypyridines are in tautomeric equilibrium with 2-pyridones [19]. The IR spectra of compounds **3a-i** show amide carbonyl stretching vibration bands at 1640-1650 cm^{-1}, a nitrile group at 2210-2215 cm^{-1}, and weak NH group vibrations at 3110-3150 cm^{-1}. The ^1H NMR spectra recorded in DMSO-d_6 show the NH group protons as broad signals in the region 10.31-11.45 ppm (Table 2).

According to X-ray structural analysis, the crystalline form of compound **3a** exists in the pyridone form (Fig. 1).

The pyran ring has a "half chair" conformation with the C(1), C(4), C(5), and C(10) atoms in a single plane (the maximum deviation being 1.0144(29) Å) with deviations from this plane for the O(2) and C(3) atoms of 0.3160(30) and 0.4788(30) Å, respectively (Fig. 1). It was found that the morpholine ring also has a "half chair" conformation with deviations from the mean plane formed by C(16), C(17), C(19), and C(20) of 0.6560(33) and 0.6795(22) Å, respectively, for the O(18) and N(15) atoms. From the study it was found clearly that an intermolecular hydrogen bond exists between the N(8)–H(8) and O(21) atoms such that the molecule occurs as a dimeric pair. The length of the donor-acceptor bond is 2.756 Å (Fig. 2).

Thus, we have developed a method for the preparation of condensed 3-cyanopyridin-2(1*H*)-ones. X-ray structural analysis and other physicochemical methods have confirmed the structure of the compounds synthesized.

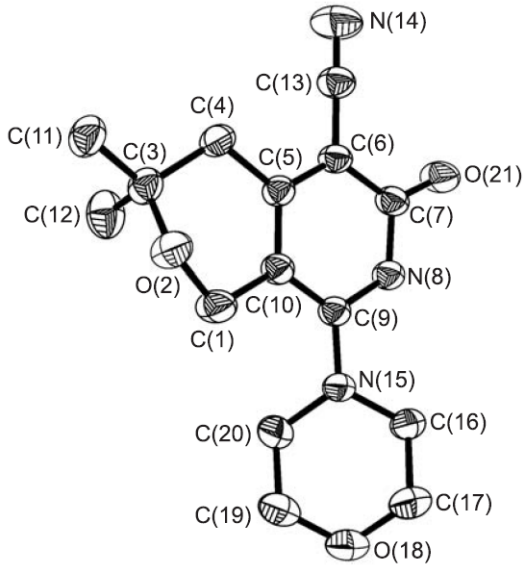

Fig. 1. Structure of the compound **3a** molecule with representation of atoms with thermal vibration ellipsoids of 50% probability.

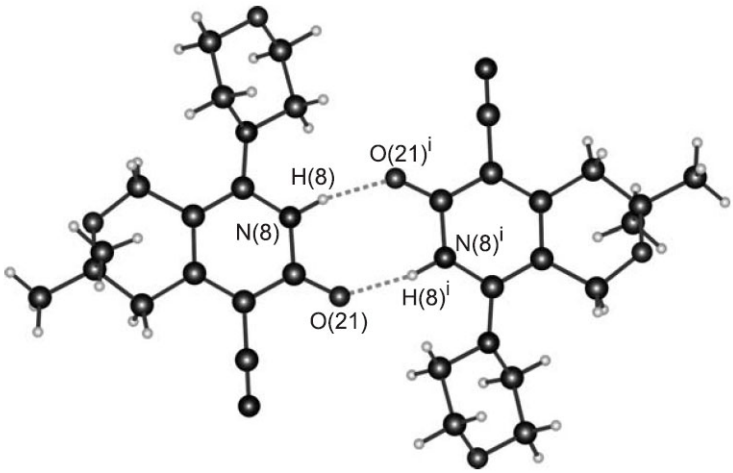

Fig. 2. Structure of the dimeric pair of the compound **3a** molecule formed with the aid of the intermolecular hydrogen bonds (symmetry notation [i: -*x*, 1-*y*, 1-*z*]).

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer using vaseline oil. ^{1}H NMR spectra were recorded on a Mercury 300 instrument (300 MHz) using DMSO-d_6 with TMS as standard. Mass spectra were recorded on an MKh-1320 instrument through direct introduction of the sample into the ion source (EI, 50 eV). Elemental analysis was performed on a Euro EA 3000 Elemental Analyzer. Melting points were recorded on a Boetius micro hot stage apparatus.

8-R^{1}-6-(2-Hydroxyethylsulfanyl)-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitriles 2a-c, 3-(2-hydroxyethylsulfanyl)-7-methyl-1-morpholino-5,6,7,8-tetrahydro[2,7]-naphthyridine-4-carbonitrile (2d), 1-R^{1}-3-(2-hydroxyethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles 2e-g, and

1-R[1]-3-(2-hydroxyethylsulfanyl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitriles 2h,i (General Method). A solution of compound **1a-i** (0.01 mol) in MeOH (20 ml) was added to a solution of NaOH (0.4 g, 0.01 mol) in water (10 ml). The mixture was stirred at 20-22ºC for 10 min to the formation of a clear solution followed by the dropwise addition of 2-chloroethanol (0.8 g, 0.01 mol). The solution was stirred at 20-22ºC for 10 h, and the crystals formed were filtered off, washed with water, and recrystallized from EtOH.

TABLE 2. ^{1}H NMR spectra of Compounds **2**, **3a-i**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
2a	1.30 (6H, s, 3-C(CH$_3$)$_2$); 2.68 (2H, s, 4-CH$_2$); 3.26 (2H, t, ^3J = 6.8, SCH$_2$CH$_2$); 3.26-3.31 (4H, m, N(CH$_2$)$_2$); 3.62 (2H, t, ^3J = 6.8, CH$_2$OH); 3.70–3.76 (4H, m, (CH$_2$)$_2$O); 4.47 (2H, s, 1-CH$_2$); 4.63 (1H, br. s, OH)
2b	1.29 (6H, s, 3-C(CH$_3$)$_2$); 1.65-1.72 (6H, m, 3,4,5-CH$_2$ piperidine); 2.66 (2H, s, 4-CH$_2$); 3.23-3.27 (6H, m, N(CH$_2$)$_2$, SCH$_2$CH$_2$); 3.63 (2H, t, ^3J = 6.7, CH$_2$OH); 4.45 (2H, s, 1-CH$_2$); 4.55 (1H, br. s, OH)
2c	1.28 (6H, s, 3-C(CH$_3$)$_2$); 1.90-2.01 (4H, m, N(CH$_2$CH$_2$)$_2$); 2.60 (2H, s, 4-CH$_2$); 3.26 (2H, t, ^3J = 6.8, SCH$_2$CH$_2$); 3.58-3.68 (6H, m, N(CH$_2$)$_2$, CH$_2$OH); 4.56 (1H, br. s, OH); 4.71 (2H, s, 1-CH$_2$)
2d	2.41 (3H, s, NCH$_3$); 2.65 (2H, t, ^3J = 6.0, 4-CH$_2$); 2.88 (2H, t, ^3J = 6.0, 3-CH$_2$); 3.23-3.31 (8H, m, 1-CH$_2$, N(CH$_2$CH$_2$)$_2$O, SCH$_2$CH$_2$); 3.62 (2H, q, ^3J = 6.4, CH$_2$OH); 3.72-3.77 (4H, m, (CH$_2$)$_2$O); 4.62 (1H, t, ^3J = 5.7, OH)
2e	1.65-1.77 (2H, m) and 1.83–1.93 (2H, m, 6,7-CH$_2$); 2.51 (2H, t, ^3J = 6.1, 8-CH$_2$); 2.82 (2H, t, ^3J = 6.4, 5-CH$_2$); 3.22-3.33 (6H, m, N(CH$_2$)$_2$, SCH$_2$CH$_2$); 3.58-3.71 (6H, m, (CH$_2$)$_2$O, CH$_2$OH); 4.58 (1H, br. s, OH)
2f	1.62-1.74 (8H, m) and 1.79-1.86 (2H, m, 6,7-CH$_2$, 3,4,5-CH$_2$ piperidine); 2.50 (2H, t, ^3J = 6.1, 8-CH$_2$); 2.79 (2H, t, ^3J = 6.6, 5-CH$_2$); 3.21-3.32 (6H, m, N(CH$_2$)$_2$, SCH$_2$CH$_2$); 3.62 (2H, t, ^3J = 6.7, CH$_2$OH); 4.25 (1H, br. s, OH)
2g	1.61-1.70 (2H, m) and 1.70-1.79 (2H, m, 6,7-CH$_2$); 1.87–1.97 (4H, m, N(CH$_2$CH$_2$)$_2$); 2.62 (2H, t, ^3J = 5.9, 8-CH$_2$); 2.71 (2H, t, ^3J = 6.3, 5-CH$_2$); 3.22 (2H, t, ^3J = 6.7, SCH$_2$CH$_2$); 3.56-3.65 (6H, m, N(CH$_2$)$_2$, CH$_2$OH); 4.48 (1H, t, ^3J = 5.6, OH)
2h	2.05-2.15 (2H, m, 6-CH$_2$); 2.86-2.95 (4H, m, 5,6-CH$_2$); 3.22 (2H, t, ^3J = 6.9, SCH$_2$CH$_2$); 3.57-3.63 (6H, m, N(CH$_2$)$_2$, CH$_2$OH); 3.68-3.73 (4H, m, (CH$_2$)$_2$O); 4.59 (1H, br. s, OH)
2i	1.94-2.00 (4H, m, N(CH$_2$CH$_2$)$_2$); 2.00-2.11 (2H, m, 6-CH$_2$); 2.83 (2H, t, ^3J = 7.6, 7-CH$_2$); 3.13 (2H, t, ^3J = 7.3, 5-CH$_2$); 3.23 (2H, t, ^3J = 6.8, SCH$_2$CH$_2$); 3.61 (2H, t, ^3J = 6.8, CH$_2$OH); 3.69-3.75 (4H, m, N(CH$_2$)$_2$); 4.48 (1H, br. s, OH)
3a	1.28 (6H, s, 3-C(CH$_3$)$_2$); 2.66 (2H, s, 4-CH$_2$); 3.18-3.23 (4H, m, N(CH$_2$)$_2$); 3.68-3.73 (4H, m, (CH$_2$)$_2$O); 4.43 (2H, s, 1-CH$_2$); 11.45 (1H, br. s, NH)
3b	1.28 (6H, s, 3-C(CH$_3$)$_2$); 1.63-1.70 (6H, m, 3,4,5-CH$_2$ piperidine); 2.64 (2H, s, 4-CH$_2$); 3.13-3.19 (4H, m, N(CH$_2$)$_2$); 4.38 (2H, s, 1-CH$_2$); 11.29 (1H, br. s, NH)
3c	1.27 (6H, s, 3-C(CH$_3$)$_2$); 1.88-1.99 (4H, m, N(CH$_2$CH$_2$)$_2$); 2.58 (2H, s, 4-CH$_2$); 3.54-3.60 (4H, m, N(CH$_2$)$_2$); 4.63 (2H, s, 1-CH$_2$); 10.31 (1H, br. s, NH)
3d	2.38 (3H, s, NCH$_3$); 2.62 (2H, t, ^3J = 6.0, 4-CH$_2$); 2.86 (2H, t, ^3J = 6.0, 3-CH$_2$); 3.18-3.22 (6H, m, 1-CH$_2$, N(CH$_2$CH$_2$)$_2$O); 3.69-3.74 (4H, m, (CH$_2$)$_2$O); 11.20 (1H, br. s, NH)
3e	1.63-1.72 (2H, m) and 1.72-1.85 (2H, m, 6,7-CH$_2$); 2.45 (2H, t, ^3J = 5.8, 8-CH$_2$); 2.78 (2H, t, ^3J = 6.5, 5-CH$_2$); 3.17-3.22 (4H, m, N(CH$_2$)$_2$); 3.68-3.72 (4H, m, (CH$_2$)$_2$O); 11.17 (1H, br. s, NH)
3f	1.60-1.71 (8H, m) and 1.75-1.84 (2H, m, 6,7-CH$_2$, 3,4,5-CH$_2$ piperidine); 2.41 (2H, t, ^3J = 5.9, 8-CH$_2$); 2.76 (2H, t, ^3J = 6.5, 5-CH$_2$); 3.13-3.18 (4H, m, N(CH$_2$)$_2$); 11.12 (1H, br. s, NH)
3g	1.61-1.69 (2H, m) and 1.71-1.80 (2H, m, 6,7-CH$_2$); 1.88-1.96 (4H, m, N(CH$_2$CH$_2$)$_2$); 2.55 (2H, t, ^3J = 6.1, 8-CH$_2$); 2.71 (2H, t, ^3J = 6.5, 5-CH$_2$); 3.51-3.62 (4H, m, N(CH$_2$)$_2$); 10.60 (1H, br. s, NH)
3h	2.02-2.12 (2H, m, 6-CH$_2$); 2.83 (2H, t, ^3J = 7.0, 7-CH$_2$); 2.83 (2H, t, ^3J = 7.7, 5-CH$_2$); 3.47-3.53 (4H, m, N(CH$_2$)$_2$); 3.64-3.69 (4H, m, (CH$_2$)$_2$O); 11.05 (1H, br. s, NH)
3i	1.82-1.98 (6H, m, 6-CH$_2$, N(CH$_2$CH$_2$)$_2$); 2.70 (2H, t, ^3J = 7.7, 7-CH$_2$); 3.01 (2H, t, ^3J = 7.2, 5-CH$_2$); 3.56–3.67 (4H, m, N(CH$_2$)$_2$); 10.44 (1H, br. s, NH)

Compounds **2a-i**. IR spectrum, ν, cm^{-1}: 1560-1570 (C=C Ar), 2200-2205 (CN), 3450-3500 (OH).

8-R^1-3,3-Dimethyl-6-oxo-3,4,6,7-tetrahydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitriles 3a-c, 7-methyl-1-morpholino-3-oxo-2,3,5,6,7,8-hexahydro[2,7]naphthyridine-4-carbonitrile (3d), 1-R^1-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles 3e-g, and 1-R^1-3-oxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitriles 3h,i (General Method). 50% Aqueous NaOH solution (8 g, 0.1 mol) was added to a solution of compound **2a-i** (0.01 mol) in EtOH (50 ml). The mixture was refluxed for 10 h. After cooling, the white precipitate of the thiirane (**4**) polymer was filtered off. The filtrate was diluted with water and washed with chloroform to remove unreacted starting compound **2a-i**. The aqueous layer was acidified with HCl and the precipitated crystals of compound **3a-i** were filtered off, washed with water, and recrystallized from a mixture of chloroform and ethanol (1:2).

Compounds **3a-i**. IR spectrum, ν, cm^{-1}: 1640-1650 (C=O), 2210-2215 (CN), 3110-3150 (NH). Compound **3a**. Mass spectrum, *m*/*z* (I_{rel}, %): 289 $[M]^+$ (100), 288 (17), 274 (20), 258 (33), 244 (14), 231 (24).

Thiirane (**4**) polymer. Yield 0.5 g (83%, alone preparation of compound **3a**), white powder, mp 160-162ºC. Mass spectrum, *m*/*z* (I_{rel}, %): 60 $[M]^+$ (100), 59 (21), 58 (52), 45 (75), 28 (23).

X-ray Structural Study of Compound 3a. Crystals of compound **3a** ($C_{15}H_{19}N_3O$, *M* 289.34) are monoclinic and were prepared by crystallization from chloroform. At 20ºC: *a* 6.7098(13), *b* 12.620(3), *c* 17.826(4) Å; β 99.05(3)º; *V* 1490.6(5) $Å^3$, *Z* 4, space group $P2_1/c$. Parameters were measured on an Enraf-Nonius CAD-4 automatic diffractometer for 22 reflections with $12.77< \theta <14.77$. The intensities of 4675 reflections were measured in the range $0 \le h \le 9$, $-17 \le k \le 0$, $-25 \le l \le 24$; θ_{max} 30º (MoKα radiation, graphite monochromator). All of the calculations were carried out using the SHELXTL program package [20]. After averaging of symmetrically equivalent reflections, the array contained 4338 independent reflections (R_{int} 0.016) of which 2919 had $I > 2\sigma(I)$. The structure was solved by the direct method and the hydrogen atom coordinates were determined from the difference Fourier syntheses. The structure was refined in full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms and the isotropic approximation for hydrogen atoms. The final probability factors were *R* 0.052, *S* 1.018. The crystallographic data for compound **3a** has been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 917444).

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