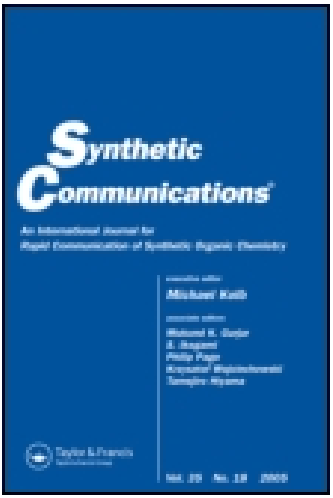

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Synthesis of Novel 3,5-Disubstituted-4-isothiazolecar

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Synthesis of Novel 3,5-Disubstituted-4-isothiazolecarbonitriles

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ABSTRACT

α-Cyano-β-enaminones, obtained by regioselective acylation of β-enaminonitriles, were smoothly converted to thiones which on oxidative cyclization afforded 3,5-disubstituted-4-isothiazolecarbonitriles in good to excellent yields.

Key Words: α-Cyano-β-thioenaminones; β-Enaminonitriles; Lawesson's reagent; 3,4,5-Trisubstitutedisothiazoles.

INTRODUCTION

Mononuclear isothiazoles were unknown until 1956 when Adam and Slack[1] obtained isothiazole-4,5-dicarboxylic acid by the oxidation of

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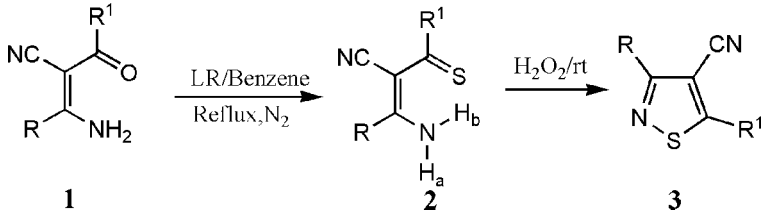
5-aminobenz[d]isothiazole. Since then synthesis, properties and applications of isothiazoles have been extensively reviewed.[2] Isothiazole containing penicillins and cephalosporins competed quite successfully with ampicillin.[3,4] Isothiazole analogs were also synthesized and tested in vitro for muscaranic receptor activity and M1 efficacy.[5] Isothiazole derivatives are also known to act as estrogen synthetase inhibitors.[6] Isothiazole derived compounds are also used as protectors for polymers, dyes, detergents, and leather goods, for decontamination of pigments, latexes, food stuffs, and stabilizer for photomaterials.[7] Further to these applications, isothiazoles have also been reported to exhibit insecticidal,[8] fungicidal,[9] and insect repellant[10] activities.

The most frequently used methods for construction of isothiazole ring consists of cyclization of compounds containing preformed N–C–C–C–S fragments. Thus, various isothiazole derivatives are prepared either by the oxidative cyclization of 2-aminoalk-1-enethiocarboxyamides[11,12] or thioacylation of suitably substituted enamines followed by oxidative ring closure.[13] But these methods suffer from the lack of variants particularly at C-5 and generally result in poor yields. Thioenaminones were converted to isothiazoles[14] by treatment with hydroxylamine-O-sulfonic acid (HAS). But this approach is severely limited to 5-aryl substituents only as the enaminones[15] were prepared from aryl methyl ketones. In addition, this approach does not allow incorporation of nitrile function at C-4.

Recent observation[16] that 3-methylthio-5-aryl-4-isothiazolecarbonitriles show good activity against polio1 and ECHO 9 prompted us to develop a general method for synthesis of 4-isothiazolecarbonitriles with built-in scope for variation of substituents at C-3 and C-5 positions of isothiazole ring. In spite of limitations thioenaminones appear to be attractive precursor for synthesis of isothiazoles in view of their easy availability and simplicity of oxidative cyclization. It occurred to us that limitations inherently associated with thioenaminones prepared from aryl methyl ketones can be easily removed if thioenaminones are prepared from α-acyl-β-enaminonitriles. However, a severe constraint to this apparently simple approach is the lack of a general procedure for regioselective preparation of C-acyl enaminonitriles.[17] Recently, we have described[18,19] regioselective acylation of enaminonitriles with a variety of acid chlorides in the presence of an added organic base. Herein, we report preparation of a series of 3,5-disubstituted-4-isothiazolecarbonitriles **3** via oxidative cyclization of α-cyano-β-thioenaminones **2** (Sch. 1) derived from α-cyano-β-enaminones **1**.[19] The structures of all these compounds **2a–l** and **3a–l** are firmly secured by elemental and spectral analyses. In our case, thionation is best achieved by Lawesson's reagent (LR).[20] *m*-Chloroperbenzoic acid, hydrogen peroxide, and bromine were also used for oxidative cyclization of thioenaminone **2e**, whereby isothiazole **3e** was obtained in 84%, 82%, and 78% yields, respectively. Although hydrogen



Scheme 1.

peroxide took longer time it was preferred over other reagents in view of its easy availability, operational simplicity, and comparable yield with *m*-chloroperbenzoic acid.

In conclusion, ready availability of diversely substituted thioenaminonitriles **2a–l** (Table 1) offers an excellent opportunity to prepare 3,5-disubstituted-4-isothiazolecarbonitriles **3a–l** with excellent control of regiospecificity. In view of the inherent flexibility incorporated in the synthetic design, substituents at C-5 of isothiazole can be alkyl groups **3a–c**, phenoxyalkyl groups **3d–e**, heteroaromatic groups **3g–h**, as well as aryl group **3f**. Variation in the nature of C-5 substituents can also occur in the form of conjugated double bond and triple bond unsaturation in the side chain, **3i** and **3j** which by themselves can generate new functionality. Furthermore, variation of substituent at C-3 can also be achieved by choice of appropriate enamines, **3k** and **3l**. It is pertinent

Table 1. Compounds **2a–l** prepared.

Compound	R	R^1	M.p. (°C)	Yield[a] (%)
2a	CH_3	CH_3	152–154	70
2b	CH_3	CH_2CH_3	130–131	68
2c	CH_3	$CH_2CH_2CH_3$	64–65	65
2d	CH_3	$CH_2OC_6H_5$	115–116	75
2e	CH_3	$CH_2OC_6H_3Cl_2(2,4)$	156–157	78
2f	CH_3	*p*-$NO_2C_6H_4$	205–207	58
2g	CH_3	2-Furyl	131–132	62
2h	CH_3	2-Thienyl	139–141	64
2i	CH_3	$(CH{=}CH)_2{-}C_6H_5$	176–177	48
2j	CH_3	$C{\equiv}C{-}C_6H_5$	193–195	45
2k	C_6H_5	CH_3	179–180	55
2l	*p*-$CH_3OC_6H_4$	CH_3	190–192	59

[a]Yields of isolated products.

to note that 5-alkenylisothiazoles were recently prepared[21] from 3,4,5-tribromoisothiazoles by cross coupling with terminal alkynes in poor to moderate yield contaminated with undesirable byproducts. In conjunction with Krebs' work[22] which allows introduction of various nucleophilic substituents at C-5 of 3-phenyl-5-thioalkylisothiazole-4-carbonitriles, the present work offers unlimited opportunity for direct introduction of various non-nucleophilic substituents at C-5 position of 4-cyanoisothiazoles.

When compared with the literature documented methods[12,14,23–25] for preparation of 4-cyano/carboxyisothiazoles, the present procedure allows an extremely simple and highly flexible synthesis of cyanoisothiazoles with novel variants at C-5 position which are otherwise difficult to prepare in good to excellent yields.

EXPERIMENTAL

Melting points were determined in open capillaries. Solid compounds were crystallized from ethyl acetate-pet. ether (60–80°). IR spectra were taken in Hitachi 270-30 spectrometer, ^{1}H NMR and ^{13}C NMR spectra were recorded in Bruker DPX-300 and DPX-400 spectrometers using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded in JEOL JMS 600 and ANY I 08-LCMS spectrometers. Elemental analyses were done in PERKIN-ELMER 240C Elemental Analyzer. Reported yields were of isolated materials.

α-Cyano-β-enaminones[19] and LR[26] were prepared following procedures described earlier.

General Procedure for the Preparation of α-Cyanothioenaminones (2)

A mixture of cyanoenaminone (0.01 mol), LR (0.005 mol), and dry benzene (40 mL) were refluxed slowly under nitrogen (4–6 hr). The course of the reaction was monitored by TLC. Benzene was distilled off. The yellow mass thus obtained was purified by column filtration (silica gel, 60–120 mesh, 5–10% ethyl acetate–pet. ether). Removal of solvent gave solid materials which on crystallization from a suitable solvent afforded pure products.

General Procedure for the Preparation of Isothiazoles (3)

To a solution of thioenaminone (0.001 mol) in ether (10 mL), hydrogen peroxide (30% w/v, 10 mL) was added with continuous stirring at room

temperature. On completion of addition of hydrogen peroxide stirring was allowed to continue for 48 hr. The course of the reaction was monitored by TLC. The reaction mixture was extracted with ether (3×10 mL) and washed sequentially with water, dilute sodium bicarbonate solution and brine. Organic layer was dried over anhydrous sodium sulphate. Removal of the solvent afforded the desired product. The solid material thus obtained was crystallized from suitable solvent and the liquid material was purified by column filtration (silica gel, 60–120 mesh, 5–10% ethyl acetate-pet. ether) and the purity of the liquid compounds were determined by observing single GC peak.

Representative Spectral Data of Selected Compounds

2c. Yellow crystal. IR (KBr): cm^{-1} 3320, 2940, 2198, 1632, 1225. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.0 (t, J 7.4 Hz, 3H, CH_3), 1.8 (m, 2H, CH_2CH_3), 2.45 (s, 3H, C≡CCH_3), 3.15 (t, J 7.4 Hz, 2H, $CH_2CH_2CH_3$), 6.75 (bs, 1H, NH_a), 13.5 (bs, 1H, NH_b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.96, 24.22, 24.94, 54.25, 97.02, 118.83, 169.95, 224.2. m/z (%): 168 (M^+, 98), 135 (100). Anal. calcd for $C_8H_{12}N_2S$ (168.25): C, 57.11; H, 7.19; N, 16.65. Found: C, 57.23; H, 7.20; N, 16.58.

2e. Yellow crystal. IR (KBr): cm^{-1} 3357, 2940, 2208, 1626, 1211. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.48 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 6.80 (d, J 8.75 Hz, 1H, Ar6′H), 6.88 (bs, 1H, NH_a), 7.11 (dd, J 1.38 and 8.75 Hz, 1H, Ar5′H), 7.37 (d, J 1.38 Hz, 1H, Ar3′H), 13.46 (bs, 1H, NH_b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.42, 78.51, 96.50, 115.18, 117.56, 123.50, 126.58, 127.35, 130.16, 152.42, 171.04, 211.99. m/z (%): 300 (M^+, 10.70), 302 (7.5), 304 (1.54), 139 (100). Anal. calcd for $C_{12}H_{10}Cl_2N_2OS$ (301.18): C, 47.85; H, 3.35; N, 9.03. Found: C, 47.76; H, 3.37; N, 9.11.

2g. Red crystal. IR (KBr): cm^{-1} 3209, 2853, 2195, 1636, 1581, 1427, 1304, 1259. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.53 (s, 3H, CH_3), 6.54 (dd, J 1.7 and 3.5 Hz, 1H, β-H of furan ring), 6.80 (bs, 1H, NH_a), 7.47 (d, J 3.5 Hz, 1H, β'-H of furan ring), 7.66 (d, J 1.7 Hz, 1H, α-H of furan ring). 13.69 (bs, 1H, NH_b). m/z (%): 192 (M^+, 13), 191 (100). Anal. calcd for $C_9H_8N_2SO$ (192.17): C, 56.25; H, 4.20; N, 14.58. Found: C, 56.64; H, 4.24; N, 14.62.

2i. Red solid. IR (KBr): cm^{-1} 3256, 2914, 2194, 1670, 1574, 1445, 1265. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.53 (s, 3H, CH_3), 7.14 (d, J 15.3 Hz, 1H, CH-Ph), 7.29–7.64(m, 8H, CH=CH–CH= and ArH), 10.35 (bs, 1H, NH_a), 13.37 (bs, 1H, NH_b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.40, 96.67, 119.14, 127.28, 127.96, 128.82, 128.95, 135.24, 136.36, 140.62, 143.39, 172.36,

202.37. m/z (%): 254 (M^+, 100). Anal. calcd. for $C_{15}H_{14}N_2S$ (254.27): C, 70.84; H, 5.95; N, 11.02. Found: C, 69.98; H, 6.02; N, 11.06.

3,5-Dimethyl-4-isothiazolecarbonitrile (3a). White crystal. Yield: 70%. M.p.: 55°C (literature[13] 56°C). IR (KBr): cm^{-1} 3660, 2948, 2224, 1668, 1530, 1502. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.57 (s, 3H, *C*═*CCH*$_3$), 2.71 (s, 3H, CH_3). m/z (%): 138 (M^+, 100). Anal. calcd for $C_6H_6N_2S$ (138.18): C, 52.15; H, 4.38; N, 20.27. Found: C, 51.93; H, 4.40; N, 20.31.

5-Ethyl-3-methyl-4-isothiazolecarbonitrile (3b). Liquid. Yield 64%. B.p.: 80–84°C/7 mm. IR (neat): cm^{-1} 3294, 2960, 2226, 1624,1423, 1373. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, J 7.0 Hz, 3H, *CH*$_3$), 2.57 (s, 3H, *C*═*CCH*$_3$), 3.10 (q, J 7.0 Hz, 2H, *CH*$_2$$CH_3$). m/z (%): 152 (M^+, 82), 137 (100). Anal. calcd for $C_7H_8N_2S$ (152.21): C, 55.23; H, 5.29; N, 18.40. Found: C, 55.34; H, 5.32; N, 18.45.

3-Methyl-5-propyl-4-isothiazolecarbonitrile (3c). Liquid. Yield 67%. B.p.: 112–114°C/7 mm. IR ($CHCl_3$): cm^{-1} 3432, 2942, 2226, 1520, 1435, 1364. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04 (t, 3H, J 7.0 Hz, *CH*$_3$), 1.99 (m, 2H, *CH*$_2$$CH_3$) 2.53 (s, 3H, C═C*CH*$_3$), 2.98 (t, J 7.0 Hz, 3H, *CH*$_2$$CH_2CH_3$). m/z (%): 166 (M^+, 100). Anal. calcd for $C_8H_{10}N_2S$ (166.24): C, 57.80; H, 6.06; N, 16.85. Found: C, 58.03; H, 6.10; N, 16.88.

3-Methyl-5-(phenoxymethyl)-4-isothiazolecarbonitrile (3d). White crystal. Yield 77%. M.p.: 91–92°C. IR (KBr): cm^{-1} 2994, 2226, 1591, 1484, 1368. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.66 (s, 3H, *CH*$_3$), 5.42 (s, 2H, *CH*$_2$), 6.96–7.35 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.04, 63.63, 106.40, 112.43, 114.69, 122.33, 129.71, 157.11, 167.83, 173.74. m/z (%): 230 (M^+, 100). Anal. calcd for $C_{12}H_{10}N_2OS$ (230.28): C, 62.58; H, 4.38; N, 12.16. Found: C, 61.98; H, 4.41; N, 12.13.

5-((2,4-Dichlorophenoxy)methyl)-3-methyl-4-isothiazolecarbonitrile (3e). White crystal. Yield 82%. M.p.: 145°C. IR (KBr): cm^{-1} 3445, 2224, 1542, 1485, 1364. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.63 (s, 3H, *CH*$_3$), 5.47 (s, 2H, *CH*$_2$), 6.95 (d, J 8.76 Hz, 1H, Ar6′*H*), 7.24 (dd, J 2.3 and 8.76 Hz, 1H, Ar5′*H*), 7.42 (d, J 2.3 Hz, 1H, Ar3′*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.13, 65.24, 107.5, 112.33, 115.22, 124.67, 127.85, 128.11, 130.55, 151.68, 167.96, 172.52. m/z (%): 298 (M^+, 27), 300 (24), 302 (7), 156 (100). Anal. calcd. for $C_{12}H_8Cl_2N_2OS$ (299.17): C, 48.17; H, 2.69; N, 9.36. Found: C, 48.31; H, 2.72; N, 9.39.

3-Methyl-5-(4-nitrophenyl)-4-isothiazolecarbonitrile (3f). White crystal. Yield 56%. M.p.: 119–120°C. IR (KBr): cm^{-1} 3468, 2202, 1597, 1529, 1405. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.71 (s, 3H, *CH*$_3$), 7.24 and 8.40 (d, J 8.73 Hz, each 2H, Ar-H). m/z (%): 245 (M^+, 100). Anal. calcd for $C_{11}H_7N_3O_2S$ (245.25): C, 53.87; H, 2.88; N, 17.13. Found: C, 54.11; H, 2.91; N, 17.15.

5-(Furan-2-yl)-3-methyl-4-isothiazolecarbonitrile (3g). White crystal. Yield 60%. M.p.: 68–69°C. IR (KBr): cm^{-1} 3114, 2218, 1578, 1474, 1386.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.62 (s, 3H, *CH_3*), 6.64 (dd, *J* 1.8 and 3.9 Hz, 1H, *β-H* of furan ring), 7.30 (dd, *J* 3.9 Hz, 1H, *β′-H* of furan ring), 7.60 (d, *J* 1.8 Hz, 1H, *α-H* of furan ring). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.13, 102.13, 112.29, 112.95, 113.87, 143.90, 145.06, 162.34, 168.17. *m/z* (%): 191 (MH^+, 100). Anal. calcd. for $C_9H_6N_2OS$ (190.21): C, 56.82; H, 3.18; N, 14.73. Found: C, 56.65; H, 3.15; N, 14.77.

5-(Thiophen-2-yl)-3-methyl-4-isothiazolecarbonitrile (3h). White crystal. Yield 69%. M.p.: 77°C. IR (KBr): cm^{-1} 3212, 2222, 1612, 1543, 1440, 1362. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.63 (s, 3H, *CH_3*), 7.19 (dd, *J* 3.73 and 5.10 Hz, 1H, *β′-H* of thiophene ring), 7.58 (dd, *J* 1.00 and 5.10 Hz, 1H, *β-H* of thiophene ring), 7.70 (dd, *J* 1.00 and 3.73 Hz, 1H, *α-H* of thiophene ring). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.35, 104.33, 114.08, 128.20, 128.68, 129.95, 133.60, 167.23, 168.82. *m/z* (%): 206 (M^+, 100). Anal. calcd. for $C_9H_6N_2S_2$ (206.28): C, 52.40; H, 2.93; N, 13.58. Found: C, 52.62; H, 2.95; N, 13.61.

3-Methyl-5-((1E,3E)-4-phenylbuta-1,3-dienyl)-4-isothiazolecarbonitrile (3i). Light yellow crystal. Yield 72%. M.p.: 145–146°C. IR (KBr): cm^{-1} 3452, 3025, 2222, 1606, 1486, 1373. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (s, 3H, *CH_3*), 6.90 (d, *J* 16 Hz, 1H, *CH*═CH–CH═CH–C_6H_5), 7.12–7.20 (m, 2H, ═*CH*–*CH*═), 7.31–7.49 (m, 6H, *CH*–*C_6H_5*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.22, 113.72, 118.10, 126.91, 127.14, 128.46, 128.88, 129.12, 135.97, 138.65, 139.34, 168.19, 172.39. *m/z* (%): 252 (M^+, 44), 251 (100). Anal. calcd. for $C_{15}H_{12}N_2S$ (252.32): C, 71.40; H, 4.79; N, 11.10. Found: C, 70.86; H, 4.83; N, 11.14.

3-Methyl-5-(2-phenyl-ethynyl)-4-isothiazolecarbonitrile (3j). White crystal. Yield 66%. M.p.: 165–167°C. IR (KBr): cm^{-1} 3455, 3018, 2227, 1607, 1444. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.74 (s, 3H, *CH_3*), 7.21–7.58 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.94, 113.20, 115.19, 126.30, 126.66, 129.61, 131.51, 134.41, 151.62, 162.89, 177.18. *m/z* (%): 224 (M^+, 100). Anal. calcd for $C_{13}H_8N_2S$ (224.27): C, 69.62; H, 3.59; N, 12.49. Found: C, 70.21; H, 3.61; N, 12.60.

5-Methyl-3-phenyl-4-isothiazolecarbonitrile (3k). White crystal. Yield 73%. M.p.: 76°C (literature[13] 77°C). IR (KBr): cm^{-1} 3312, 2970, 2216, 1486, 1435. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.78 (s, 3H, *CH_3*), 7.48–8.03 (m, 5H, Ar*H*). *m/z* (%): 200 (M^+, 100). Anal. calcd for $C_{11}H_8N_2S$ (200.25): C, 65.97; H, 4.03; N, 13.99. Found: C, 66.32; H, 3.98; N, 13.79.

3-(4-Methoxyphenyl)-5-methyl-4-isothiazolecarbonitrile (3l). White crystal. Yield 70%. M.p.: 87–88°C. IR (KBr): cm^{-1} 3274, 2218, 1684, 1506, 1487. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.76 (s, 3H, *CH_3*), 3.86 (s, 3H, O*CH_3*), 7.00 (d, *J* 8.84 Hz, 2H, Ar2′*H*), 7.99 (d, *J* 8.84 Hz, 2H, Ar3′*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.11, 55.31, 106.92, 114.16, 125.71, 129.03, 132.50, 161.19, 167.00, 174.61. *m/z* (%): 230 (M^+, 100). Anal. calcd for $C_{12}H_{10}N_2OS$ (230.28): C, 62.58; H, 4.38; N, 12.16. Found: C, 61.86; H, 4.41; N, 12.21.

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