1-ARYLAMINO-2,3-DIHYDRO-1*H*-IMIDAZOLE-2-THIONES FROM THE REACTION OF 1-[2-(2-ARYLHYDRAZONO)ALKYL]-PYRIDINIUM IODIDES WITH POTASSIUM THIOCYANATE§

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Abstract - The conversion of 1-[2-(2-arylhydrazono)alkyl]pyridinium iodides (**1**) with potassium thiocyanate into 1-arylamino-2,3-dihydro-1*H*-imidazole-2-thiones (**4**) is envisaged to result from the [3+2] cycloaddition reaction of intermediate arylazoalkenes (**2**) and thiocyanic acid *via* the azomethine imine cycloadducts (**3**) followed by 1,4-hydrogen shift.

Current interest in 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones has been aroused by various biological activities exhibited by a number of derivatives - both incorporated in condensed heterocycles[1] and monocyclic species.[2] The preparation of the latter mainly includes transformation of other heterocyclic systems[3] and conversion of imidazoles.[2] Few procedures involve the cyclization of acyclic precursors. The first such synthesis reported, the ring closure of a 2-thiosemicarbazide derivative of acetaldehyde diethyl acetal, dates back to one hundred years ago.[4] The structure of 1-anilino-2,3-dihydro-4,5-diphenyl-1*H*-imidazole-2-thione (**4**) (Ar, R^1, R^2 = C_6H_5) has been assigned to one of two products isolated from the reaction of 1,2-diphenyl-2-thiocyanatoethanone with phenylhydrazine.[5] Recently we have found that 1-anilino-2,3-dihydro-1*H*-imidazole-2-thiones (**4**) emerge from the reaction of α-(1-phenylhydrazino)alkanone phenylhydrazones with potassium thiocyanate in the presence of a weak acid.[6] The formation of heterocyclic products (**4**) has been envisaged to result from the [3+2] cycloaddition reaction of intermediate phenylazoalkenes (**2**) and thiocyanic acid.[7]

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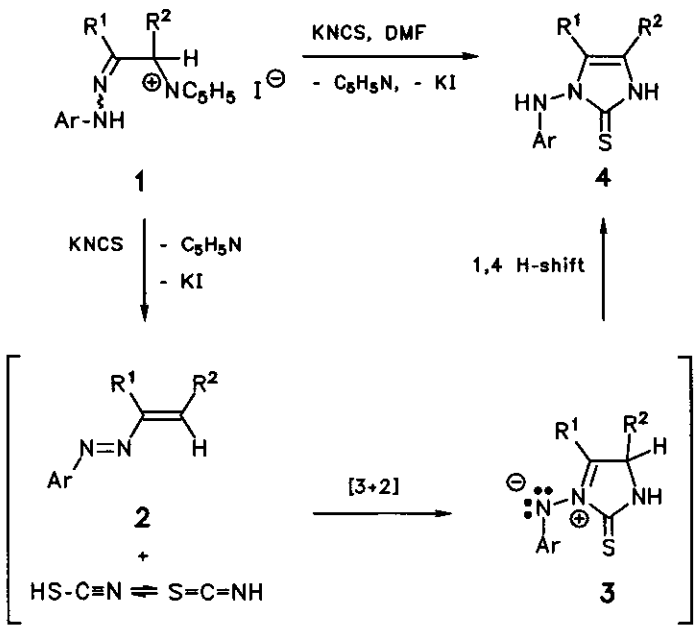
§ Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

We now report the synthesis of 1-arylamino-2,3-dihydro-1*H*-imidazole-2-thiones (**4**) by employing another precursor of arylazoalkenes(**2**),1-[2-(2-Arylhydrazono)alkyl]pyridium iodides (**1**)[8] upon reaction with potassium thiocyanate in dimethylformamide solution are converted into heterocycles (**4**) (Scheme 1). A conceivable reaction mechanism considers a base (potassium thiocyanate) induced 1,4-elimination of pyridinium iodide from **1** under concomitant generation of the arylazoalkene (**2**) and thiocyanic acid. Both *in situ* formed reactants subsequently combine in a [3+2] cycloaddition reaction. The resultant cycloadduct (**3**) (featuring an azomethine imine function) undergoes an apparent rapid stabilization by a 1,4-hydrogen shift (from ring position C-4 to the exocyclic nitrogen atom), thus affording the heteroaromatic product (**4**).



	Ar	R^1	R^2
a	C_6H_5	H	H
aa	4-ClC_6H_4	H	H
b	C_6H_5	CH_3	H
c	C_6H_5	C_2H_5	H
d	C_6H_5	$(CH_2)_4$	
e	C_6H_5	C_6H_5	H

Scheme 1

Formation of compounds (**4**) induced by nucleophilic displacement of the pyridinium substituent in **1** with the thiocyanate ion seems unlikely. In such a reaction the ambident nucleophile is expected to react with the sulfur atom as the more nucleophilic site. The cyclization of the resultant 2-(2-arylhydrazono)alkylthiocyanate should then give rise to a heterocyclic product with an endocyclic sulfur atom rather than to a product with the observed thiocarbonyl function as in structure (**4**) (*vide infra*).

In the absence of a suitable reagent capable of trapping 1-phenylazostyrene (**2e**) this compound is known to undergo rapid cyclodimerization to 1,3,6-triphenyl-6-phenylazo-1,4,5,6-tetrahydropyridazine.[9] The formation of **4e** in the presence of thiocyanic acid indicates an efficient interception of the intermediate (**2e**).

The spectral data and the chemical reactivity of compounds (**4**) are in agreement with a 5-membered heteroaromatic ring structure containing (a) a carbon-carbon double bond and (b) a thiourea moiety, with (c) an exocyclic arylamino group attached to N-1. (a) From ^{1}H- and ^{13}C-nmr evidence the carbon atoms in the heterocyclic ring are sp^2 hybridized. The α-carbon atom of **1** (sp^3) has become C-4 (sp^2) of **4**. (b) The two NH signals (exchangeable with D_2O) in the range of δ 8.8-9.1 and δ 11.8-12.4 are attributed to the arylamino substituent at N-1 and to HN-3, respectively. The downfield signal of the latter is indicative of a thiourea moiety with a strong resonance contribution of zwitterionic structures [>N–C(=S)–NH– ↔ >N–C(—S^-)=NH^+–]. The partial positive charge imposed on the ring NH group is also reflected by the typical multiplicity of ir absorptions in the range of 2500-3000 cm^{-1} (NH-associations).[10,11] This is in keeping with the solubility of compounds (**4**) in 5 % aqueous sodium hydroxide. On the other hand, a thiol function is excluded on the basis of the chemical shift of the proton signals exchangeable with D_2O (the resonance of the SH group is expected in the range of δ 2-4),[12] and by the ir absorption in the range of 1460-1500 cm^{-1} (amide II of thioureas in 5-membered rings).[11] Moreover, alkylation of compounds (**4**) provides 2-alkylthio-1*H*-imidazole derivatives and excludes any heterocyclic structure with a ring sulfur atom. (c) The electron impact mass spectra of compounds (**4**) obtained from phenylhydrazones (**1**) (Ar = C_6H_5) show the base peak at m/z 93 [$C_6H_5NH_2$] and the complementary fragment ion [M-C_6H_5NH]. This is taken as evidence for an aniline group attached to N-1 of the imidazole ring of **4** ruling out a 6-membered ring structure.

EXPERIMENTAL

Melting points (mp) were determined with a Kofler hot stage microscope (Reichert). The spectroscopic data were recorded on Beckman AccuLab 4 (ir), JEOL JNM-PMX-60 (^{1}H-nmr, 60 MHz), Bruker AM 300 (^{1}H-nmr, 300 MHz and ^{13}C-nmr, 75 MHz), Varian MAT 44S (ms). Elemental analyses were obtained at the Institut für Physikalische Chemie, University of Vienna. 1-[2-(2-phenylhydrazono)alkyl]pyridinium iodides (**1a-e**) are available as described in the literature.[8]

1-[2-[2-(4-Chlorophenyl)hydrazono]ethyl]pyridinium iodide (1aa): In a nitrogen atmosphere iodine (21.26 g, 83.8 mmol) was added to a stirred solution of acetaldehyde 4-chlorophenylhydrazone (14.13 g, 83.8 mmol) in dry pyridine (70 ml, 869 mmol) whereby the temperature rose to 60°C. After continued stirring for 12 h the solvent was removed *in vacuo*, and the dark gummy residue was repeatedly triturated with ether (3x 50 ml) until it became crystalline. Recrystallization from water and from ethanol / ether (2x) afforded slightly yellow crystals (**1aa**) (6.58 g, 21 %); mp (decomp.) 126-127°C; ir (KBr): 3175, 3160, 3070, 3020, 1635, 1595, 1515, 1490, 825 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 5.48 (2H, d, ^3J=4.0 Hz, $C\underline{H}_2$-CH=), 6.73-7.26 (4H, AA'BB', 4-ClC_6H_4), 7.46 (1H, t, ^3J=4.0 Hz, =C$\underline{H}$-CH_2), 8.16-8.28 (2H, m, H-3 and H-5 of $C_5H_5N^+$), 8.63-8.76 (1H, m, H-4 of $C_5H_5N^+$), 9.03-9.14 (2H, m, H-2 and H-6 of $C_5H_5N^+$), 10.52 (1H exchangeable with D_2O, s, HN); ^{13}C-nmr (DMSO-d_6) δ: 61.0 (CH_2), 144.5, 111.6, 128.8, 119.1 (C-1, C-2,6, C-3,5; C-4 of 4-ClC_6H_4), 145.2, 127.7, 145.8 (C-2,6, C-3,5, C-4 of $C_5H_5N^+$), 131.1 (-CH=N-); ms [m/z (%)] 254 (11), 168 (68), 166 (31), 139 (23), 128 (56), 127 (87), 111 (10), 79 (100). Anal. Calcd for $C_{13}H_{13}N_3ClI$: C, 41.79; H, 3.51; N, 11.25. Found: C, 41.83; H, 3.62; N, 11.32.

1-Anilino-2,3-dihydro-1*H*-imidazole-2-thione (4a): Typical Procedure. To a stirred solution of **1a** (1.0 g, 2.95 mmol) in dry dimethylformamide (20 ml) in a nitrogen atmosphere was added finely ground potassium thiocyanate (1.0 g, 10.3 mmol). Stirring was continued at 90°C for 2 h, and after cooling to ambient temperature water (150 ml) was added. The mixture was extracted with ether (4 x 50 ml) and the combined ether layer was washed with water (2 x 30 ml), dried (magnesium sulfate) and evaporated. The residue upon recrystallization from ethanol / water furnished slightly yellow crystals (**3a**) (0.37 g, 66 %); mp 187-189°C; ir (KBr) 3250, 3120, 3090, 1650, 1595, 1562, 1492, 1460, 731 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 6.47-7.24 (5H, m, C_6H_5), 6.95 (1H, d, J=2.6 Hz, H-5), 7.15 (1H, d, J=2.6 Hz, H-4), 8.88 (1H exchangeable, s, HN-N), 12.24 (1H exchangeable, br s, HN-C=S); ^{13}C-nmr (DMSO-d_6) δ: 113.1 (C-5), 120.3 (C-4), 147.2, 112.8, 128.8, 119.9 (C-1, C-2,6, C-3,5, C-4 of C_6H_5), 162.1 (C=S); ms [m/z (%)] 191 (90.1) [M], 158 (35.8) [M-SH], 93 (100) [$C_6H_5NH_2$], 77 (14.1) [C_6H_5]. Anal. Calcd for $C_9H_9N_3S$: C, 56.52; H, 4.74; N, 21.97; S, 16.76. Found: C, 56.46; H, 4.87; N, 21.68; S, 16.61.

1-(4-Chlorophenylamino)-2,3-dihydro-1*H*-imidazole-2-thione (4aa): Slightly yellow crystals (93 %); mp (decomp.) 235°C (ethanol / water); ir (KBr) 3140, 3080, 1589, 1570, 1489, 1462, 818, 720 cm^{-1}; ^{1}H-Nmr

(DMSO-d_6) δ: 6.47-7.26 (4H, AA'BB', 4-ClC_6H_4), 6.95 (1H, d, ^3J=2.6 Hz, H-5), 7.17 (1H, d, ^3J=2.6 Hz, HC-4), 9.10 (1H exchangeable, s, HN-N), 12.31 (1H exchangeable, br s, HN-C=S); ^{13}C-nmr (DMSO-d_6) δ: 113.8 (C-5), 120.2 (C-4), 146.2, 114.4, 128.6, 123.4 (C-1, C-2,6, C-3,5, C-4 of 4-ClC_6H_4), 162.1 (C=S); ms [m/z (%)] 226 (100) [M+1]. Anal. Calcd for $C_9H_8N_3ClS$: S, 14.21. Found: S, 14.36.

1-Anilino-5-methyl-2,3-dihydro-1*H*-imidazole-2-thione (4b): Colorless crystals (62 %); mp 209-214°C (ethanol); ir (KBr) 3300, 3110, 3080, 2920, 2790, 2710, 2570, 2480 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.97 (3H, d, ^4J=1.5 Hz, $C\underline{H}_3$-C=CH), 6.33-7.36 (6H, m, C_6H_5 and H-4), 8.66 (1H exchangeable, s, HN-N), 11.90 (1H exchangeable, br s, HN-C=S); ms [m/z (%)] 205 (66) [M], 172 (12.1) [M-SH], 113 (33.3) [M-C_6H_5NH], 93 (100) [$C_6H_5NH_2$]. Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.43; H, 5.36; N, 20.30; S, 15.50.

1-Anilino-5-ethyl-2,3-dihydro-1*H*-imidazole-2-thione (4c): Slightly yellow crystals (64 %); mp 225-230°C (methanol); ir (KBr) 3260, 3110, 3080, 2920, 2800, 2720, 2670, 2580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.06 (3H, t, ^3J=7.5 Hz, $C\underline{H}_3$-CH_2), 2.34 (2H, qd, ^3J=7.5 and ^4J=1.5 Hz, $CH_3C\underline{H}_2$-C=CH), 6.15-7.36 (6H, m, C_6H_5 and H-4), 8.62 (1H exchangeable, s, HN-N), 11.89 (1H exchangeable, br s, HN-C=S); ms [m/z (%)] 219 (47.2) [M], 186 (9) [M-SH], 127 (19.1) [M-C_6H_5NH], 93 (100) [$C_6H_5NH_2$]. Anal. Calcd for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.98; N, 19.16; S, 14.62. Found: C, 60.11; H, 5.03; N, 19.29; S, 14.72.

1-Anilino-2,3,4,5,6,7-hexahydro-1*H*-benzimidazole-2-thione (4d):[6] Slightly yellow crystals (74 %); mp 205°C (methanol).

1-Anilino-2,3-dihydro-5-phenyl-1*H*-imidazole-2-thione (4e): Colorless crystals (48 %); mp 200-203°C (methanol); ir (KBr) 3240, 3130, 3090, 3060, 2950, 2930, 2790, 2720, 2580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 6.28-7.74 (11H, m, 2 C_6H_5 and H-4), 8.95 (1H exchangeable, s, HN-N), 12.40 (1H exchangeable, br s, HN-C=S); ms [m/z (%)] 267 (46.9) [M], 234 (3) [M-SH], 175 (9.5) [M-C_6H_5NH], 117 (83.3) [M-C_6H_5NHNCS], 93 (100) [$C_6H_5NH_2$]. Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72; S, 11.98. Found: C, 67.46; H, 4.90; N, 15.74; S, 12.06.

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