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Synthesis of some thiazolyldithiocarbamates and their predictive physicochemical properties

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Abstract
Thiazole scaffolds are well known for their physiological properties and found immense use in the field of agriculture and medicine. The Dithiocarbamate are the oldest known broad-spectrum fungicides. In the present communication an attempt has been made to synthesize thiazolyldithiocarbamate compounds having both thiazole as well as Dithiocarbamate moieties. The reaction has been carried out using 2-amino-4-arylthiazoles as precursors the products obtained were characterized by spectral analysis. The thiazolyldithiocarbamates were studied for their physicochemical properties using ChemAxon online webserver. The outcome of the studies has been discussed in this paper.

Keywords: Thiazole, dithiocarbamate synthesis, physicochemical properties, spectral analysis, chemaxon

Introduction
The thiazoles are known to be associated with diverse biological activities ranging from medicinal [1, 2] to agriculture [3, 4]. The thiazole derivatives are well known agrochemicals and are used as herbicides, fungicides and insecticides. Some examples are Benzoline (herbicide), Metasulfovax (fungicide) and Thiacloprid (insecticide). Similarly, Dithiocarbamate [5, 6] are widely used in agriculture [7, 8] as fungicides (Thiram).
Keeping this in view, it was of interest to synthesize compounds having thiazole ring system along with Dithiocarbamate group. The attempt was made to synthesize thiazolyldithiocarbamate [9] compounds as they may have potential pesticidal properties.
The present paper describes the synthesis of some thiazolyldithiocarbamates using 2-amino-4-arylthiazoles (1a-1c) as precursors. Compounds 1a-1c were treated with carbon disulphide to give corresponding potassium thiazolyldithiocarbamates (2a-2c), which on further treatment with dimethyl sulphate gave the final product as methyl thiazolyldithiocarbamate derivatives (3a-3c). The reaction sequence has been summarized in Figure 1.

Experimental
Some reagents were used as obtained from commercial suppliers. The 1H NMR spectra were recorded on Perkin Elmer R-32 (90 MHz) instrument using TMS as internal standard and $CDCl_3$ as solvent. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. Elemental analysis (C, H and N) was taken with Heraeus CHN-rapid analyser and the data showed good agreement between the experimentally determined values and the theoretically calculated values.

Synthesis of 2-amino-4-aryl-1, 3-thiazoles (1a-1c) [10-12]
2-Amino-4-phenyl-1, 3-thiazole (1a; General procedure)
Acetophenone (2.0 g) in dry benzene (25 mL was refluxed with thiourea (2.5 g) and iodine (4.2 g) for 36 hrs. and the solvent was distilled off. The residue obtained was treated with liquor ammonia. The solid so obtained was filtered, washed with water, dried and crystallised from ethanol to obtain white crystalline 2-Amino-4-phenyl-1, 3-thiazole (1a). Yield (68%, 2.0 g); M.P. 152-153 °C, lit. M.P. 153-154 °C.

2-Amino-4-(4′-methylphenyl)-1, 3-thiazole (1b)
4-Methy1acetophenone (2.5 g) in dry benzene (50 mL) was refluxed with thiourea (2.0 g) and iodine (3.3 g) for 36 hrs to obtain 2-amino-4-(4′-methylphenyl)-1, 3-thiazole (1b). Yield (73%, 2.6 g); M.P. 124-125 °C, lit. M.P. 123-124 °C.

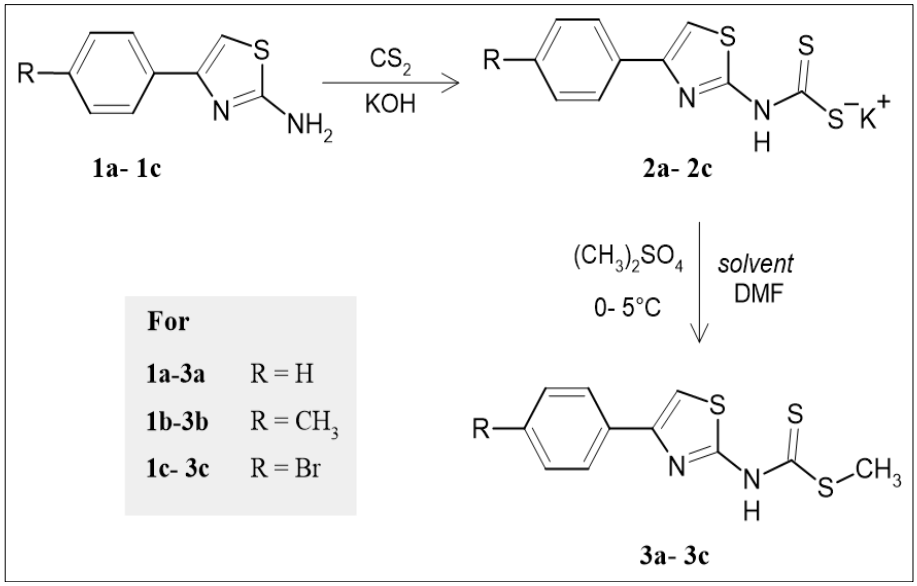

Fig 1: Synthesis of Methyl N-(4-arylthiazol-2-yl) Dithiocarbamate (3a-3c) from 2-amino-4-aryl-1, 3-thiazoles (1a-1c)

2-Amino-4-(4′-methylphenyl)-1, 3-thiazole (1b)
4-Methy1acetophenone (2.5 g) in dry benzene (50 mL) was refluxed with thiourea (2.0 g) and iodine (3.3 g) for 36 hrs to obtain 2-amino-4-(4′-methylphenyl)-1, 3-thiazole (1b). Yield (73%, 2.6 g); M.P. 124-125 °C, lit. M.P. 123-124 °C.

2-Amino-4-(4′-bromophenyl)-1, 3-thiazole (1c)
4-Bromoacetophenone (2.5g) in dry benzene (50 mL) was refluxed with thiourea (2.0 g) and iodine (3.5g) for 40 hrs. to obtain 2-amino-4-(4′-bromophenyl)-1, 3-thiazole (1c) as light-yellow prisms. Yield (75%, 2.4 g); M.P. 176-177 °C, lit. M.P. 177 °C.

Synthesis of Potassium N-(4-arylthiazol-2-yl) Dithiocarbamate (2a-2c)
Potassium N-(4-phenylthiazol-2-yl) Dithiocarbamate (2a; *General procedure*)
Potassium hydroxide (0.64g) and carbon disulphide (1.0 mL) were added to solution of 2-amino-4-phenyl-1, 3-thiazole (1a, 2.0 g) in dimethylformamide (10mL). The mixture was stirred for 30 minutes. Then, ethyl acetate (20mL) and ether (200mL) were added. The solid separated was filtered, washed with ether and crystallized from tetrahydrofuran-petroleum ether to give 2a as pale-yellow crystals. Yield (70%, 2.3 g).

IR (υ cm^{-1} KBr): 990 (C---S stretching).

Potassium N-[4-(4′-(methylphenyl) thiazol-2-yl) Dithiocarbamate (2b)
Potassium hydroxide (0.58g) and carbon disulphide (0.8 mL) were added to solution of 2-Amino-4-(4′-methylphenyl)-1, 3-thiazole (1b, 2.0 g) in dimethylformamide (10 mL) to obtain 2b as pale-yellow prisms Yield (87%, 2.8 g).

IR (υ cm^{-1} KBr): 995 (C---S stretching).

Potassium N-[4-(4′-(bromophenyl) thiazol-2-yl) Dithiocarbamate (2c)
Potassium hydroxide (0.44g) and carbon disulphide (0.5 mL) were added to solution of 2-amino-4-(4′-bromophenyl)-1, 3-thiazole (1c, 2.0 g) in dimethylformamide (10 mL) to obtain 2c as pale-yellow prisms. Yield (76%, 2.2 g).

IR (υ cm^{-1} KBr): 995 (C---S stretching).

Synthesis of methyl N-(4-arylthiazol-2yl) dithiocarbamate (3a-3c)
Methyl N-(4-phenylthiazol-2yl) dithiocarbamate (3a, *General procedure*)
Dimethyl sulphate (0.35 ml) was added to a well stirred solution of potassium N-(4-phenylthiazol-2-yl) Dithiocarbamate (2a; 1.0 g) in dimethylformamide (15 mL). The stirring was continued for 2 hrs. maintaining temperature at 0-5ºC. Then water (50 mL) was added to it and extracted with ether. The ether layer was washed with water, dried (over sodium sulphate) and distilled. The residue thus obtained, was purified by column chromatography. It was further crystallised from benzene-petroleum ether to give 3a as light-yellow shining needles. Yield (71%, 0.64 g); M.P. 137-138 °C. 1H NMR ($CDCl_3$) δ: 2.52(s, 3H, SCH_3), 7.06 (s, 1H, H-5), 7.25-7.44 (m, 3H, H3′, H-4′ and H5′), 7.56-7.72 (m, 2H, H-2′ and H-6′). IR (υ cm^{-1} KBr): 1300(C=S stretching); Elemental analysis: Found, C 49.60, H3.78, N 10.54%; $C_{11}H_{10}N_2S_3$, Formula weight: 266.4; requires C 49.62, H 3.76; N 10.53%.

Methyl N-4-(4′-methylphenylthiazol-2-yl) Dithiocarbamate (3b)
Dimethyl sulphate (0.56 mL) was added to a well stirred solution of potassium N-(4-(4'-methylphenylthiazol-2-yl) Dithiocarbamate (2b, 1.0 g) in dimethylformamide (15 mL). Stirring this for 2 hrs.at 0-5 °C gave 3b as light-yellow shining crystals. Yield (81%, 0.75g); M.P. 110-111 °C. 1H NMR ($CDCl_3$) δ: 2.37(s, 3H, CH_3), 2.62(s,3H, S CH_3), 7.0 (s,1H, H-5), 7.12 (d, J =9Hz, 2H, H-3′ and H-5′), 7.60 (d, J=9Hz, 2H, H-2′ and H6′). IR (υ cm^{-1} KBr): 1300(C=S stretching); Elemental analysis: Found, C 51.29, H4.12, N 10.05%, $C_{12}H_{12}N_2S_3$, Formula weight: 280.4 requires C 51.43, H 4.29; N 10.00%.

Methyl N-4-(4′-bromophenylthiazol-2-yl) Dithiocarbamate (3c)
Dimethyl sulphate (0.3 mL) was added to a well stirred solution of potassium N-4-(4′-bromophenylthiazol-2-yl) Dithiocarbamate (2c; 1.0 g) in dimethylformamide (15 mL). Stirring this for 2 hrs.at 0-5 °C gave 3c as pale-yellow shining crystals. Yield (83%, 0.78g); M.P. 190-191 °C. 1H NMR ($CDCl_3$) δ: 2.74 (s,3H, SCH_3), 7.1 (s,1H, H-5), 7.5 (d, J=9Hz, 2H, H-3′ and H-5′), 7.64 (d, J=9Hz, 2H, H-2′ and H6′). IR (υ

cm^{-1} KBr):1300(C=S stretching); Elemental analysis: Found, C 38.10, H2.55, N 8.00%, $C_{11}H_9BrN_2S_3$, Formula weight: 345.3; requires C 38.26, H 2.61; N 8.12%.

Table 1: Physicochemical Properties of Methyl N-(4-arylthiazol-2-yl) Dithiocarbamate (3a-3c)

Physicochemical Properties	Compounds(3a-3c) Methyl N-(4-arylthiazol-2yl) Dithiocarbamate		
	3a (R=H)	3b (R=CH_3)	3c (R=Br)
Molecular formula	$C_{11}H_{10}N_2S_3$	$C_{12}H_{12}N_2S_3$	$C_{11}H_9BrN_2S_3$
Molar mass	266.4	280.4	345.3
TPSA Å²	110.55	110.55	110.55
log S	-5.32	-5.82	-6.33
logP	4.85	5.36	5.62
logD (pH 7.4)	4.79	5.31	5.56
Strongest Acidic pka	8.21	8.21	8.21
Strongest Basic Pka	0.98	0.98	0.98

Result and Discussion

Synthesis of methyl N-(4-arylthiazol-2yl) Dithiocarbamate (3a-3c) was carried out in two steps. The reaction of 2-amino-4-aryl-1, 3-thiazoles (1a-1c) was carried out with carbon disulphide in presence of potassium hydroxide to give corresponding potassium thiazolyldithiocarbamates (2a-2c), which on further treatment with dimethyl sulphate gave the final product as methyl thiazolyldithiocarbamate derivatives (3a-3c). The synthesized compounds (3a-3c) were characterized by elemental analysis and spectral studies. For study of physicochemical properties Chem Axon online web server was used.

Physicochemical Properties

For synthesized compounds (3a-3c) the study of physicochemical properties, like logP (octanol/water partition coefficient), logD (distribution coefficient), logs (intrinsic solubility), pKa (acidic and basic), was carried out using Chem Axon online web server. The outcome has been summarized in Table 1.

All methyl N-(4-arylthiazol-2yl) Dithiocarbamate derivatives (3a-3c), have been found to have strongest acidic pka value as 8.21 and strongest basic pka as 0.98. All compounds have same TPSA value of 110.55 Å². The logP and log D (at pH 7.4) values were found to be highest for compound 3c and lowest for 3a. This indicates an increased lipophilic character of 3c (R=Br) compared to 3a (R=H) and 3b (R=CH_3). Thus, for compounds 3a-3c, the lipophilic character follows the order 3c >3b >3a (Table 1). The logs values indicate very poor solubility for all the compounds.

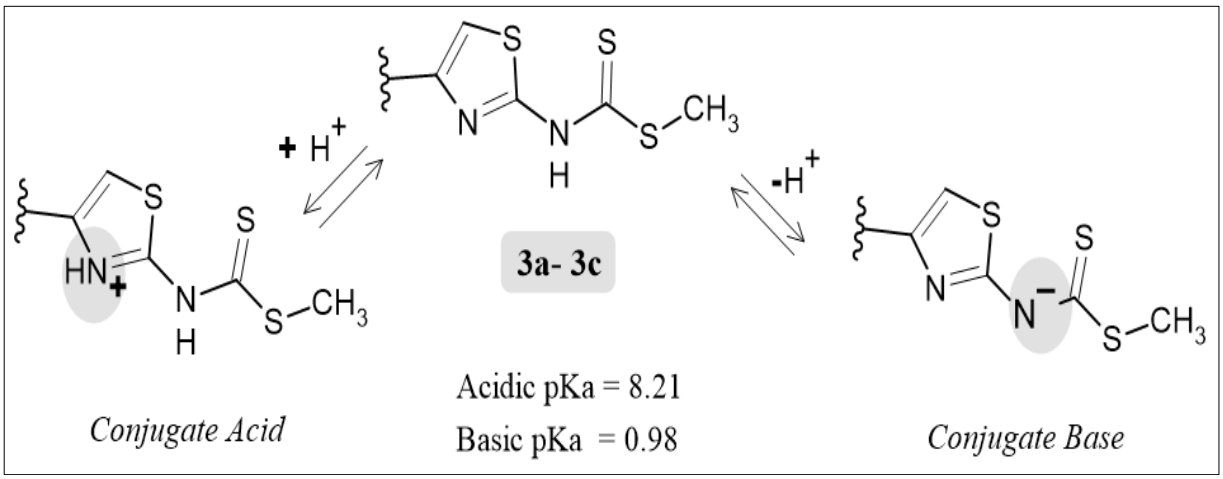

Fig 2: Strongest acidic and strongest basic pKa for Methyl N-(4-arylthiazol-2-yl) dithiocarbamate

Conclusion

The 2-amino-4-arylthiazoles were treated with carbon disulphide followed by dimethyl sulphate, to synthesise methyl thiazolyldithiocarbamate derivatives. The synthesized compounds were characterized by spectral analysis and studied for their physicochemical properties. All compounds were found to have same TPSA value and showed same acidic and basic pKa. Compounds were found to have high lipophilic character and very poor solubility.

Note

The synthetic part of this paper is an unpublished work from the Ph.D. thesis (1986) of the author (Bhupinder Mehta), carried out in Chemistry Department University of Delhi. The research work has been further extended for studies of physicochemical properties by incorporating recently developed cheminformatic tools and updated literature.

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