On the Reaction of 2-Chloroethylisothiocyanate with Aromatic Amines

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The reaction of aromatic amines with 2-chloroethylisothiocyanate **2** to give 2-arylaminothiazolines **1** was investigated. The course of this reaction was found to depend on the electronic nature of the amine and the reaction conditions. With arylamines that are relatively electron-rich, good yields of the thiazolines **1** were obtained. With electron-poor amines, adducts **4**, in which two equivalents of **2** reacted with the amine, accompanied **1**. The relative amounts of 2:1 adducts increased as the arylamine became progressively more electron deficient. With 3,4-dichloroaniline, the yields of the 2:1 adducts were promoted by the presence of triethylamine.

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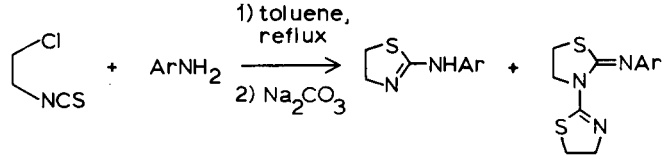
Due to the interesting activity of 2-arylaminothiazolines **1** as acaricides, fungicides and herbicides, considerable attention has been focused on this class [1]. In connection with a synthesis program directed to the discovery of novel herbicidal molecules, we required a series of thiazolines **1** with various substitutions on the aromatic ring. These compounds are usually prepared by the acid-catalyzed cyclization of *N*-hydroxyethyl-*N'*-arylthioureas derived from the coupling of ethanolamines with arylisothiocyanates [2]. To avoid the preparation of an isothiocyanate of each arylamine of interest, we chose the more convenient route utilizing 2-chloroethylisothiocyanate **2** and the appropriate aromatic amine [3]. Treatment of primary anilines with 2-haloalkylisothiocyanates has been reported to give 2-arylaminothiazolines [1a,3b], though the generality of the process with respect to the arylamine has not been investigated. We report herein that the outcome of this reaction is highly dependent on the reaction conditions and the electronic nature of the arylamine.

The coupling of arylamines with **2** was typically effected by heating equimolar amounts of the reactants in toluene until precipitate formation was complete [1a]. Addition of aqueous sodium carbonate resulted in dissolution of the solid and the products were then isolated from the organic phase. With relatively electron-rich anilines such as *p*-toluidine **3a**, good yields of the desired 1:1 adducts **1** were obtained (Table I). However, with electron-poor aromatic amines, yields of **1** were lower and significant amounts of the products **4**, in which two equivalents of **2** had reacted with **3**, were formed. The yields of the 2:1 adducts became greater as the aryl group became more electron deficient, until with 2-aminopyridine **3e**, no 1:1 adduct was formed.

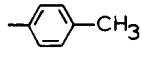
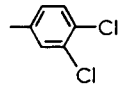
Assignment of the *N*-thiazolinyl-2-iminothiazolidine structure shown for **4** was based on the spectral data and combustion analyses of the compounds, as well as independent synthesis. When **1c** [4] was treated sequentially with **2** and aqueous sodium carbonate, it was converted exclusively to **4c**, thus fixing the 2-aryliminothiazolidine substructure and ruling out other possible larger ring isomers. The unsymmetrical structure **4** as opposed to the alternative isomer **5** was indicated by the presence of four distinct methylene signals in the proton nmr spectrum and four aliphatic and two imino carbon resonances in the ^{13}C nmr spectrum.

To determine the nature of the precipitates which form in these reactions, that resulting from heating a toluene solution of **2** and **3c** was isolated and found to be freely

TABLE I

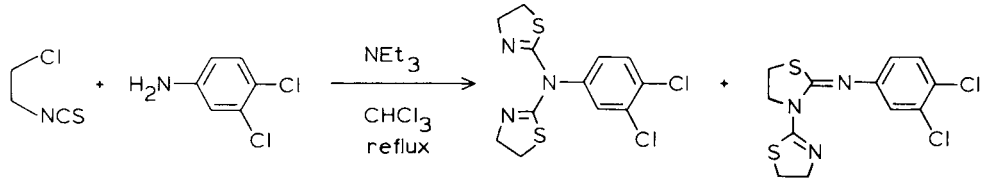


2 3 a-e 1 a-e 4 a-e

entry	Ar	%1	%4 *
a		79	9
b		66	9
c		38	30
d		23	44
e		0	73

* Yields of **4** are based on **2** as limiting reagent.

SCHEME



2 3c 5 4c

water soluble. Neutralization with aqueous carbonate yielded 26% of unreacted **3c**, 38% of **1c** and 12% of **4c**. An additional 18% of **4c** was obtained from the supernatant liquid. Thus the solids are a mixture of the hydrochloride salts of the aniline and 1:1 and 2:1 adducts. We did not detect any of the chloroethylthiourea precursor to **1a**.

When the coupling of **2** and **3c** was conducted in the presence of triethylamine as a proton acceptor, the reaction took an entirely different course, as shown in the Scheme. Under these conditions, the symmetrical 2:1 adduct **5** was produced along with **4c** with only a small amount of **1c** being observed. This result reveals the superior nucleophilicity of **1c** to **3c** and also demonstrates the degree to which **1c** is protected as a hydrochloride in the absence of base [5]. Treatment of **1c** with **2** and triethylamine also gave **5** and **4c** in 46% and 40% yields, respectively.

In conclusion, this study has identified those primary arylamine substrates for which reaction with 2-chloroethylisothiocyanate constitutes a useful route to 2-arylaminothiazolines. It appears that the electronic nature of the aryl ring substituents influences the product types obtained. The more electropositive substituents favor the 1:1 adducts **1**; the more electronegative favor 2:1 adducts **4**. Since product mixtures are likely to result with electron-deficient arylamines, the arylisothiocyanate route [2] would be the preferred method of obtaining thiazolines of that type.

EXPERIMENTAL

Proton nmr spectra were obtained at 60 MHz on a Varian EM-360L spectrometer using tetramethylsilane as an internal standard. Carbon nmr spectra were recorded at 22.5 MHz on a JEOL FX-90Q spectrometer. Infrared spectra were obtained on Perkin-Elmer 299-B or Beckman Acculab spectrophotometers. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All reactions were conducted under a nitrogen atmosphere. Flash chromatography [6] was done on Woelm silica, 32-63 μm. Melting points are uncorrected.

General Procedure for Reaction of 2-Chloroethylisothiocyanate **2** with Aromatic Amines.

A solution of 25 mmoles of the arylamine in 35 ml of toluene was stirred at room temperature or reflux. A solution of 25 mmoles of **2** [7] in 10 ml of toluene was then added dropwise and the mixture was heated at reflux for 45 minutes to 3.5 hours and allowed to cool. A solution of 5.30 g (50 mmoles) of sodium carbonate in 30 ml of water was added and the heterogeneous mixture was stirred for 15 minutes. The phases were then separated and the aqueous layer was extracted with dichloromethane or chloroform. The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated. The crude products were then flash chromatographed using mixtures of ethyl acetate and hexane or dichloromethane and acetone. Analytical samples were prepared by recrystallization. The yields in Table I refer to chromatographed products which were homogeneous on thin layer chromatography.

Physical constants and spectral data of the compounds prepared in this manner are as follows:

N-(4-Methylphenyl)-4,5-dihydro-2-thiazolamine (**1a**).

Compound **1a** had mp 128.5-130.5° from cyclohexane (lit [8] mp 131°); ir (chloroform): ν 3420, 1640, 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.8-7.2 (m, 5H), 3.70 (t, J = 7 Hz, 2H), 3.21 (t, J = 7 Hz, 2H), 2.28 (s, 3H).

Anal. Calcd. for $C_{10}H_{12}N_2S$: C, 62.47; H, 6.29; N, 14.57. Found: C, 62.34; H, 6.33; N, 14.54.

2-(4-Methylphenylimino)-3-(4,5-dihydrothiazol-2-yl)thiazolidine (**4a**).

Compound **4a** had mp 112-114° from cyclohexane; ir (chloroform): ν 2990, 2950, 1640, 1590 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.22 (d, J = 9 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 4.33 (t, J = 7 Hz, 2H), 4.03 (t, J = 7 Hz, 2H), 3.20 (t, J = 7 Hz, 4H), 2.35 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}N_3S_2$: C, 56.29; H, 5.45; N, 15.15. Found: C, 56.69; H, 5.68; N, 15.18.

N-(3-Bromophenyl)-4,5-dihydro-2-thiazolamine (**1b**).

Compound **1b** had mp 108-110.5° from cyclohexane (lit [1c] 106-107°); ir (chloroform): ν 3420, 1635, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.9-7.4 (m, 4H), 6.60 (bs, 1H), 3.75 (t, J = 7 Hz, 2H), 3.30 (t, J = 7 Hz, 2H).

Anal. Calcd. for $C_9H_9BrN_2S$: C, 42.05; H, 3.50; N, 10.89. Found: C, 42.31; H, 3.72; N, 10.85.

2-(3-Bromophenylimino)-3-(4,5-dihydrothiazol-2-yl)thiazolidine (**4b**).

Compound **4b** had mp 191-193° dec; ir (chloroform): ν 2960, 1645, 1590 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.7-7.4 (m, 4H), 4.30 (t, J = 7 Hz, 2H), 4.00 (t, J = 7 Hz, 2H), 3.0-3.4 (m, 4H).

Anal. Calcd. for $C_{12}H_{12}BrN_3S_2$: C, 42.11; H, 3.53; N, 12.28. Found: C, 42.19; H, 3.63; N, 12.40.

N-(3,4-Dichlorophenyl)-4,5-dihydro-2-thiazolamine (**1c**).

Compound **1c** had mp 134-135° from toluene (lit [1c] 131-132°); ir (potassium bromide): ν 3420, 3140, 3100, 2860, 1620, 1580 cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 8.55 (bs, 1H, exchangeable with deuterium oxide), 7.6-7.8 (m, 1H), 7.1-7.5 (m, 2H), 3.97 (t, J = 7 Hz, 2H), 3.30 (t, J = 7 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 163.04, 148.95,

132.46, 130.48, 126.36, 123.41, 121.16, 48.00, 31.31.

Anal. Calcd. for $C_9H_6Cl_2N_2S$: C, 43.75; H, 3.23; N, 11.33. Found: C, 43.69; H, 3.34; N, 11.30.

2-(3,4-Dichlorophenylimino)-3-(4,5-dihydrothiazol-2-yl)thiazolidine (**4c**).

Compound **4c** had mp 163-164° dec from toluene; ir (chloroform): ν 2980, 1640, 1590 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.35 (d, J = 9 Hz, 1H), 7.08 (d, J = 2 Hz, 1H), 6.80 (dd, J = 2, 9 Hz, 2H), 4.30 (t, J = 7 Hz, 2H), 3.97 (t, J = 7 Hz, 2H), 3.23 (t, J = 7 Hz, 2H), 3.18 (t, J = 7 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 157.67, 155.70, 148.79, 132.56, 130.59, 127.36, 123.36, 120.94, 57.34, 51.36, 33.94, 26.79.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3S_2$: C, 43.39; H, 3.31; N, 12.64. Found: C, 43.31; H, 3.37; N, 12.62.

N-(3-Pyridinyl)-4,5-dihydro-2-thiazolamine (**1d**).

Compound **1d** had mp 128-133° from toluene; ir (chloroform): ν 3430, 1635 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.1-8.5 (m, 2H), 7.0-7.6 (m, 2H), 6.90 (bs, 1H), 3.72 (t, J = 6 Hz, 2H), 3.27 (t, J = 6 Hz, 2H).

Anal. Calcd. for $C_8H_9N_3S$: C, 53.61; H, 5.06. Found: C, 53.73; H, 5.12.

2-(3-Pyridinylimino)-3-(4,5-dihydrothiazol-2-yl)thiazolidine (**4d**).

Compound **4d** had mp 111-113.5° from cyclohexane/toluene; ir (chloroform): ν 2960, 1635, 1585 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.1-8.5 (m, 2H), 7.0-7.5 (m, 2H), 4.33 (t, J = 7 Hz, 2H), 3.98 (t, J = 7 Hz, 2H), 3.25 (t, J = 7 Hz, 2H), 3.20 (t, J = 7 Hz, 2H).

Anal. Calcd. for $C_{11}H_{12}N_4S_2$: C, 49.98; H, 4.58. Found: C, 50.36; H, 4.73.

2-(2-Pyridinylimino)-3-(4,5-dihydrothiazol-2-yl)thiazolidine (**4e**).

Compound **4e** had mp 101-103.5° from cyclohexane; ir (chloroform): ν 2980, 1610, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.40 (dd, J = 2, 5 Hz, 1H), 7.63 (ddd, J = 2, 8, 8 Hz, 1H), 6.8-7.4 (m, 2H), 4.28 (t, J = 7 Hz, 2H), 4.00 (t, J = 7 Hz, 2H), 3.17 (t, J = 7 Hz, 2H), 3.15 (t, J = 7 Hz, 2H).

Anal. Calcd. for $C_{11}H_{12}N_4S_2$: C, 49.98; H, 4.58; N, 21.19. Found: C, 50.36; H, 4.71; N, 21.32.

Reaction of 3,4-Dichloroaniline **3c** with **2** in the Presence of Triethylamine.

A stirred solution of 4.05 g (25 mmoles) of **3c** and 3.5 ml (2.5 g, 25 mmoles) of triethylamine in 30 ml of chloroform was cooled in an ice bath. A solution of 3.04 g (25 mmoles) of **2** in 5 ml of chloroform was added dropwise, the ice bath was removed, and stirring was continued for 2 hours. The reaction mixture was then heated to reflux for 3 hours and allowed to stir at room temperature overnight. The resulting brown solution was diluted with dichloromethane, washed with water and the organic layer dried over anhydrous magnesium sulfate and concentrated. The residue was flash chromatographed using 3:1 v/v ethyl acetate-hexane as the eluent. Early fractions contained 1.78 g of a mixture of **1c** and **5** as a tan solid, mp 130-135.5°. Recrystallization from toluene-hexane at low temperature followed by recrystallization from cyclohexane gave 0.93 g (22%) of pure **5** as colorless needles, mp 133-136.5° dec; ir (chloroform): ν 2995, 1625, 1600, 1470, 1320 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.62 (d, J = 10 Hz, 1H), 7.53 (d, J = 2 Hz, 1H), 7.28 (dd, J = 2, 10 Hz, 1H), 4.17 (t, J = 7 Hz, 4H); 3.30 (t, J = 7 Hz, 4H); ^{13}C nmr (deuteriochloroform): δ 160.63, 141.42, 133.30, 132.89, 131.08, 130.72, 128.47, 59.94, 34.83.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3S_2$: C, 43.39; H, 3.31; N, 12.64. Found: C, 43.44; H, 3.55; N, 12.45.

The mother liquors from the above recrystallizations were carefully chromatographed using 1:1 v/v ethyl acetate-hexane. A 0.10 g (1.6%) sample of **1c** was obtained in pure form with the remainder of the material (0.4 g) eluting as an approximately 1:1 mixture of **1c** and **5** (^1H nmr analysis).

Later fractions from the initial chromatography contained 1.60 g (35%) of **4c** as a white solid, mp 161-164°. The ^1H nmr spectrum of this material was identical to that of the previously prepared sample and the two samples coeluted on thin layer chromatography (Rf = 0.58 with 3:1 v/v ethyl acetate-hexane as the eluent).

Preparation of **1c** from 3,4-Dichlorophenyl Isothiocyanate and Ethanolamine.

Following the procedure of Fanta and Deutsch [9], 8.0 g (39 mmoles) of 3,4-dichlorophenyl isothiocyanate was treated with 2.43 g (40 mmoles) of ethanolamine in 30 ml of dichloromethane. The resulting thiourea was heated to reflux in 100 ml of 6*N* hydrochloric acid for 3 hours, cooled and the solution made basic with a solution of 25 g of sodium hydroxide in 50 ml of water. Extraction with dichloromethane, drying over anhydrous magnesium sulfate and concentration gave 8.09 g of a white solid. The crude product was recrystallized from toluene to give 7.16 g (74%) of **1c** as colorless prisms, mp 133-136°. The ^1H nmr spectrum of this sample was superimposable with that of the sample prepared from **3c** and **2**.

Reaction of **1c** with **2**.

A. With Sodium Carbonate Added Sequentially.

A solution of 2.01 g (8.1 mmoles) of **1c** and 1.24 g (10.2 mmoles) of **2** in 30 ml of toluene was stirred and heated to reflux for 2 hours. At this point a white precipitate had separated and the reaction mixture was allowed to cool to room temperature. A solution of 1.62 g (15.3 mmoles) of sodium carbonate in 20 ml of water was added and the mixture was stirred until dissolution of the solid was complete. The phases were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2.71 g of a pale yellow solid. The crude product was flash chromatographed using initially 1:1 and then 3:1 v/v ethyl acetate-hexane as the eluent. Early fractions contained 0.08 g of a tan solid, mp 104-115°. This was analyzed by ^1H nmr and tentatively designated as a mixture of **1c** and **5**, approximately 3:2 respectively. Later fractions furnished 2.18 g (81%) of **4c** as a white solid, mp 162-165° dec. The ir and ^1H nmr spectra of this product were identical with those of the previously prepared samples.

B. With Triethylamine.

To a stirred solution of 2.00 g (8.1 mmoles) of **1c** and 1.5 ml (1.1 g, 11 mmoles) of triethylamine in 25 ml of chloroform was added 1.60 g (13.2 mmoles) of **2** in 10 ml of chloroform. After heating to reflux for 3 hours and standing at room temperature for 21 hours, the orange reaction mixture was diluted with dichloromethane and washed with water. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give 2.68 g of a tan solid. This was flash chromatographed using initially 1:1 and then 2:1 v/v ethyl acetate-hexane as the eluent. Early fractions contained 1.25 g (46%) of **5** as a white solid, mp 135-137.5° dec. Further elution furnished 1.08 g (40%) of **4c** as a white powder, mp 162.5-164° dec. Comparison of ir and ^1H nmr spectral data with that of the previously prepared samples confirmed the structural assignments.

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