SYNTHESIS OF N,N'–BIS(ARYL)–N–(2–THIAZOLIN–2–YL)THIOUREAS[§]

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Abstract– The reaction of arylisothiocyanates with 2–chloroethylamine in pyridine led to the formation of complex *N,N'*–bis(aryl)–*N*–(2–thiazolin–2–yl)thioureas (1–3). These compounds and the mixed thioureas or ureas 8–11, show a strong chelated structure due to the presence of an intramolecular hydrogen bond.

Synthesis of 2–thiazolines or 2–aminothiazolines has been extensively employed.[1] It is of particular interest, since thiazolines can be easily transformed into thiazoles or penicillin derivatives.[2] Likewise, some important naturally occurring derivatives contain the 2–thiazoline ring.[3]

2–Haloalkylamines react with alkyl– or arylisothiocyanates to give 2–alkyl(aryl)amino–2–thiazolines.[4] This reaction involves the formation of 2–haloalkylthioureas, which undergo spontaneous intramolecular cyclization. Other reactions can occur also through 2–haloalkylthioureas giving thiazolines. Thus, 2–haloalkylthioureas must be the intermediates in the aziridine expansion into thiazolines.[5] On the other hand, haloalkylthioureas are unequivocally generated by the reaction of amines with 2–haloalkylisothiocyanates to give thiazolines.[6] The major part of this last research is patented, due to the possible biological activity of the resulting compounds. Thus, Narayanan et al.[7] reported the reaction of anions of heterocyclic amines, generated from sodium hydride, with 2–chloroethylisothiocyanate. Finally, non–heterocyclic NH groups[8] and polyethyleneimine[9] have been added to 2–chloroethylisothiocyanate. In all cases, 2–aminothiazoline derivatives are the only products isolated, although some authors[10] have reported surprisingly that haloethylthioureas are the products in the reaction of cyclopropylamines or imidazolidine–2–thiones[11] from the reaction of glycosylisothiocyanates with 2–chloroethylamine.

We have recently reported[12] that reactions of glycosylisothiocyanates with 2–chloroethylamine afford the unexpected *N,N'*–bis(glycosyl)–*N*–(2–thiazolin–2–yl)thioureas. The pathway of these reactions involves the addition of an isothiocyanate to the heterocycle intermediate, which is generated by spontaneous

[§]Dedicated respectfully to the memory of Prof. Tetsuji Kametani.

cyclization of corresponding haloalkylthioureas.

In order to generalize these results, we have explored the reaction of arylisothiocyanates with chloroethylamine in pyridine at room temperature using a double molar amount of isothiocyanate. This reaction gives in a one–step *N,N'*–bis(aryl)–*N*–(2–thiazolin–2–yl)thioureas (**1–3**). When an equimolar amount of both reagents was used, the bis(aryl)thioureas were also isolated, but in a lower yield.

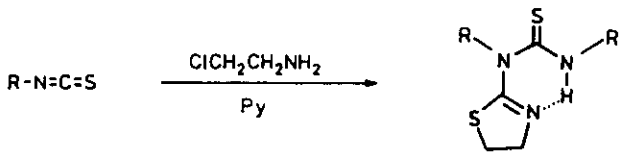
On the other hand, we have isolated the intermediates 2–aryliminothiazolidine hydrochlorides (**4–7**) by reaction of arylamines with 2–chloroethylisothiocyanate. This approach is useful, since it permits the further nucleophilic addition to an isothiocyanate or an isocyanate, giving mixed complex thioureas or ureas (**8–11**).

The most outstanding structural feature of compounds **1–3** and **8–11** is the presence of an intramolecular hydrogen bond, which is showed by the downfield chemical shift of the NH group (9–14 ppm). This hydrogen bond gives a strong conformational rigidity in these molecules. Similar chemical shifts have been observed for the NH protons of intramolecularly bonded thioureas.[13]

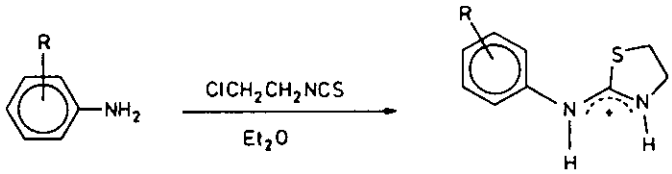
Table 1. ^{1}H–Nmr Data of Compounds (1)–(11)

compd	CH_3	S–CH_2	N–CH_2	NH	Ar
1[a]		3.01t J 7.0	4.81t J 7.0	14.07s	7.59–6.97m
2[a]		1.85t J 7.0	4.29t J 7.0	13.95s	7.54–6.59m
3[a]		3.15t J 6.8	4.85t J 6.8	13.92s	7.46–6.85m
4[b]		3.71t J 7.6	4.07t J 7.6	10.35m	7.69–7.47m
5[b]		3.64t J 7.6	3.99t J 7.6	9.93m	7.70–7.35m
6[b]	2.31s	3.60t J 6.8	3.97t J 6.8	11.48m	7.27s
7[b]	3.84s	3.57t J 7.5	3.94t J 7.5	11.09m	7.45–6.98m
8[a]	2.34s	3.11t J 7.0	4.86t J 7.0	14.12s	7.58–6.87m
9[a]	3.82s	3.10t J 7.0	4.87t J 7.0	14.39s	7.63–6.89m
10[a]	2.90d J 4.7	3.13t J 7.0	4.31t J 7.0	9.26s	7.29d J 8.7 6.87d J 8.5
11[a]	3.84s	3.13t J 7.0	4.36t J 7.0	12.29s	7.57–6.92m

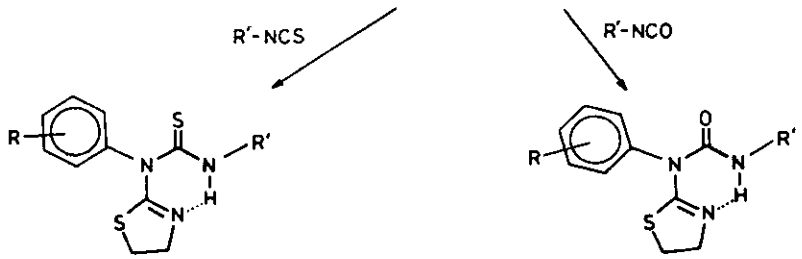
[a]In $CDCl_3$. [b]In DMSO–d_6.



1 R = C_6H_5
2 R = 4-ClC_6H_4
3 R = 4-BrC_6H_4

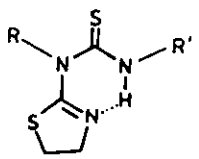


4 R = 4-Cl
5 R = 4-Br
6 R = 4-Me
7 R = 2-OMe



8 R = 4-Me, R' = Ph
9 R = 2-OMe, R' = Ph

10 R = 4-Cl, R' = Me
11 R = 2-OMe, R' = Ph



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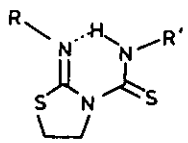

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The large differences in the chemical shifts of thiazoline methylenes by passing of intermediates **4–7** to bis(aryl)thioureas or ureas **1–3** and **8–11** ($\Delta\delta_{CH_2N-CH_2S}$ 0.36 ppm in **4**, and 2.44 ppm in **2**) should be noted. This aspect is also observed in the ^{13}C–nmr spectra.

Table 2. ^{13}C–Nmr Data of Compounds (1)–(11)

compd	CH_3	CH_2S	CH_2N	C=O	C=N	C=S	Aromatic
1[a]		24.44	54.59		158.89	178.50	147.97(1C), 138.49(1C), 129.00(2C) 128.42(2C), 125.97(2C), 124.98(2C) 124.59(1C), 121.05(1C)
2[a]		23.72	54.96		159.88	178.43	147.13(1C), 137.88(1C), 131.22(2C) 130.94(2C), 129.66(1C), 129.00(1C) 125.67(2C), 123.12(2C)
3[a]		24.67	54.89		159.64	178.58	147.00(1C), 137.59(1C), 132.28(2C) 131.68(2C), 126.31(2C), 123.05(2C) 119.35(1C), 118.45(1C)
4[b]		30.85	49.19		170.77		135.38(1C), 131.69(1C), 129.51(2C) 125.19(2C)
5[b]		30.97	49.29		170.73		135.90(1C), 132.44(1C), 132.10(1C) 125.83(1C), 125.27(1C), 120.22(1C)
6[b]	20.59	30.81	49.18		170.61		136.96(1C), 134.21(1C), 130.07(2C) 123.39(2C)
7[b]	55.89	30.78	49.21		171.58		153.48(1C), 129.90(1C), 126.62(1C) 124.66(1C), 120.78(1C), 112.86(1C)
8[a]	20.87	24.63	54.72		158.76	178.80	145.67(1C), 138.74(1C), 134.84(1C) 129.74(2C), 128.59(2C), 126.15(1C) 124.81(2C), 121.01(2C)
9[a]	55.60	24.75	54.74		158.42	178.69	151.22(1C), 139.00(1C), 136.75(1C) 129.51(1C), 128.57(1C), 126.29(1C) 126.06(1C), 125.69(1C), 124.80(1C) 121.11(1C), 120.67(1C), 111.56(1C)
10[a]	26.42	25.72	48.91	153.87	158.49		148.10(1C), 129.64(1C), 128.99(2C) 122.63(2C)
11[a]	55.60	25.62	48.65	151.46	157.79		150.85(1C), 138.36(1C), 137.56(1C) 128.77(2C), 125.75(1C), 123.34(1C) 121.10(1C), 120.63(1C), 119.88(2C) 111.51(1C)

[a]In $CDCl_3$. [b]In DMSO–d_6.

As we have recently reported for glycosylisothiocyanates,[12] we have assumed for compounds **1–3** and **8–11** that the further attack of isocyanate or isothiocyanate on the heterocyclic intermediate takes place regioselectively in the exocyclic nitrogen (**12**). These data are also based on those of Rasmussen *et al.*,[14] who have observed that structures like **13** are unstable and they undergo a slow rearrangement to **12**.

In ^{13}C–nmr experiments, resonances of heterocyclic carbon C–5 have been used in the assignment of thiazoline and thiazolidine isomeric structures.[15] In our case, the chemical shift range of this carbon is not diagnostic.

EXPERIMENTAL

Melting points were determined on an Electrothermal digital apparatus and are uncorrected. Ir spectra (KBr discs) were recorded on a Perkin–Elmer 399 instrument, nmr spectra on a Bruker AC 200–E spectrometer operating at 200 MHz (for ^1H) or 50.2 MHz (for ^{13}C) using TMS as internal reference. Chemical shifts are quoted in ppm and coupling constants in Hz. Assignments were confirmed by DEPT experiments. Elemental analyses were performed on a Perkin–Elmer 240C analyzer.

General procedure for the preparation of *N,N'*–bis(aryl)–*N*–(2–thiazolin–2–yl)thioureas

To a solution of 2–chloroethylamine hydrochloride (15.0 mmol) in pyridine (30 ml) the arylisothiocyanate (30.0 mmol) was added, and the mixture was kept at room temperature for 48 h. Then, it was poured into ice–water and the solid formed was filtered off and washed with cold water. Products were recrystallized from ethanol.

N,N'–Bis(phenyl)–*N*–(2–thiazolin–2–yl)thiourea (1). Yield: 80%; mp 123–124°C; ir (ν_{max} cm^{-1}) 3100–2720 (NH, CH), 1620 (C=N), 1545 (NH), 1600, 1495, 750 and 700 (aromatic). Anal. Calcd for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.40. Found: C, 61.18; H, 4.75; N, 13.32.

N,N'–Bis(4–chlorophenyl)–*N*–(2–thiazolin–2–yl)thiourea (2). Yield: 91%; mp 120–122°C; ir (ν_{max} cm^{-1}) 3080–2660 (NH, CH), 1625 (C=N), 1550 (NH), 1580, 1475, and 815 (aromatic). Anal. Calcd for $C_{16}H_{13}Cl_2N_3S_2$: C, 50.26; H, 3.43; N, 10.99. Found: C, 50.62; H, 3.39; N, 11.21.

N,N'–Bis(4–bromophenyl)–*N*–(2–thiazolin–2–yl)thiourea (3). Yield: 35%; mp 141–143°C; ir (ν_{max} cm^{-1}) 3140–2600 (NH, CH), 1655, 1605 (C=N), 1550 (NH), 1600, 1570, and 835 (aromatic). Anal. Calcd for $C_{16}H_{13}Br_2N_3S_2$: C, 40.78; H, 2.78; N, 8.92. Found: C, 40.85; H, 2.67; N, 8.80.

General procedure for the preparation of 2–aryliminothiazolidine hydrochlorides

2–Chloroethylisothiocyanate (10.0 mmol) was added dropwise at room temperature to a solution of arylamine (10.0 mmol) in diethyl ether (10 ml). Crystals formed were filtered off and washed with cold ether. Products were recrystallized from appropiate solvents.

2–(4–Chlorophenyl)iminothiazolidine hydrochloride (4). Yield: 60%; mp 187–189°C (dec. from ethyl acetate); ir (ν_{max} cm^{-1}) 3200–2520 (NH^+), 1630 (C=N), 1545 (NH), 1585, 1485, and 820 (aromatic). Anal. Calcd for $C_9H_{10}Cl_2N_2S$: C, 43.38; H, 4.05; N, 11.24. Found: C, 43.71; H, 4.15; N, 11.14.

2–(4–Bromophenyl)iminothiazolidine hydrochloride (5). Yield: 68%; mp 177–179°C (from 96% ethanol–ethyl acetate); ir (ν_{max} cm^{-1}) 3180–2520 (NH^+), 1640 (C=N), 1555 (NH), 1600, 1500, and 835 (aromatic). Anal. Calcd for $C_9H_{10}BrClN_2S$: C, 36.81; H, 3.43; N, 9.54. Found: C, 36.86; H, 3.37; N, 9.28.

2–(4–Tolyl)iminothiazolidine hydrochloride (6). Yield: 90%; mp 161–163°C (from 96% ethanol–ethyl acetate); ir (ν_{max} cm^{-1}) 3260–2500 (NH^+), 1645 (C=N), 1515 (NH), 1595, 1480, and 830 (aromatic). Anal. Calcd for $C_{10}H_{13}ClN_2S$: C, 52.51; H, 5.73; N, 12.25. Found: C, 52.26; H, 5.74; N, 12.16.

2–(2–Methoxyphenyl)iminothiazolidine hydrochloride (7). Yield: 82%; mp 192–194°C (from 96% ethanol–ethyl acetate); ir (ν_{max} cm^{-1}) 3200–2500 (NH^+), 1640 (C=N), 1560 (NH), 1600, 1510, and 780 (aromatic). Anal. Calcd for $C_{10}H_{13}ClN_2OS$: C, 49.07; H, 5.35; N, 11.45. Found: C, 49.14; H, 5.38; N, 11.39.

N–(4–Tolyl)–*N'*–phenyl–*N*–(2–thiazolin–2–yl)thiourea (8). To a solution of 6 (0.23 g, 1.0 mmol) in pyridine (2 ml) phenylisothiocyanate (0.12 ml, 1.0 mmol) was added, and the mixture was kept at room temperature for 24 h, then poured into ice–water. The white solid was filtered off and recrystallized from ethanol. Yield: 0.3 g, 91%; mp 107–108°C; ir (ν_{max} cm^{-1}) 3100–2720 (NH, CH), 1605 (C=N), 1550 (NH), 1600, 1510, 830, 750, and 705 (aromatic). Anal. Calcd for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.45; H, 5.41; N, 12.67.

N–(2–Methoxyphenyl)–*N'*–phenyl–*N*–(2–thiazolin–2–yl)thiourea (9). It was prepared as indicate above from 7 (0.24 g, 1.0 mmol) in pyridine (2 ml) and phenylisothiocyanate (0.12 ml, 1.0 mmol). Yield: 0.34 g, 100%; mp 111–113°C; ir (ν_{max} cm^{-1}) 3100–2660 (NH, CH), 1630 (C=N), 1575 (NH), 1600, 1505, 785, 755 and 715 (aromatic). Anal. Calcd for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23. Found: C, 59.47; H, 5.02; N, 12.13.

N–(4–Chlorophenyl)–*N'*–methyl–*N*–(2–thiazolin–2–yl)urea (10). From 4 (0.17 g, 0.7 mmol) in pyridine (10 ml) and methylisocyanate (0.04 ml, 0.7 mmol). Yield: 0.13 g, 68%; mp 132–134°C; ir (ν_{max} cm^{-1}) 3200–2900 (NH, CH), 1700, 1650 (amide), 1630 (C=N), 1555 (NH), 1600, 1495, and 840 (aromatic). Anal. Calcd for $C_{11}H_{12}ClN_3OS$: C, 48.98; H, 4.48; N, 15.58. Found: C, 49.38; H, 4.66; N, 15.25.

N–(2–Methoxyphenyl)–*N'*–phenyl–*N*–(2–thiazolin–2–yl)urea (11). From 7 (0.24 g, 1.0 mmol) in pyridine (2 ml) and phenylisocyanate (0.11 ml, 1.0 mmol). Yield: 0.32 g, 100%; mp 119–121°C; ir (ν_{max} cm^{-1}) 3100–2820 (NH, CH), 1710 (amide), 1635 (C=N), 1570 (NH), 1600, 1500, 770, 750, and 700 (aromatic). Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.39; H, 5.24; N, 12.75.

ACKNOWLEDGEMENTS

This research was supported by Dirección General de Investigación Científica y Técnica (Grant No. PB86–0255).

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Received, 24th July, 1989