Synthesis of 4-Substituted 2-Phenylaminothiazoles from Amidines. A Convenient Route to 4-Trichloromethylthiazoles

Moisés Romero-Ortega,*,† Adriana Aviles,† Raymundo Cruz,‡ Aydee Fuentes,† Rosa María Gómez,† and Andrés Plata†

Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/ Paseo Tollocan s/n Toluca Estado de México, C.P.50000, Mexico, and Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Mexico, D.F.

romero.ortega@usa.net

Received June 22, 2000

The 2-aminothiazole moiety is frequently found in biologically active molecules that, for example, may have utility in the treatment of allergies,[1] hypertension,[2] inflammation,[3] schizophrenia,[4] as antibiotics,[5] and (HIV)[6] infections. They also exhibit some antitumoral properties.[7] In addition, Lin et al.[8] have reported that 1-phenylamino-5-aroylthiazoles exhibit good in vivo bacteriocidal activity. These compounds were prepared by the base-induced reaction of phenacyl bromide with *N*-phenylthiocarbamoylamidines which in turn were obtained from phenylthioureas and amide acetals.[8] This synthesis is limited to those thiazole derivatives bearing H, alkyl or aryl groups C-4.[9] This paper describes an alternative route to diverse *N*-phenylthiocarbamoylamidines, which as a consequence, permits the synthesis of 2-phenylamino-5-acylthiazoles bearing a wide variety of C-4 substituents.

We reasoned that the required *N*-phenylthiocarbamoylamidines[10] ought to be accessible from phenyl isothiocyanate **2** and amidines **1**, a wide variety of which are readily available. Indeed, the condensation of phenyl isothiocyanate **2** with amidine salts **1a**, **b**, **d** in a THF-50% aqueous sodium hydroxide mixture at 0 °C gave the thiocarbamoylamidines **3a**, **b**, **d** (Scheme 1) in good yields (Table 1). Because of the pronounced hydrolytic sensitivity, **3c** was generated under anhydrous conditions from formamidine acetate **1c** using triethylamine as the base. Thiocarbamoylamidine **3e** was prepared in nearly quantitative yield from free trichloroacetamidine **1e**.[11]

The reaction of *N*-thiocarbamoylbenzamidine **3a** with phenacyl bromide **4a** occurred readily at room temperature,[12] in the presence of 1 equiv of triethylamine,[13] to give 2-phenylamino-4-phenyl-5-benzoylthiazole **6a** directly in 78% yield (Table 2). The thiocarbamoylamidines **3b**−**d** were also converted into the corresponding thiazoles **6b**−**d** under identical conditions. In contrast, alkylation of the trichloroacetamidine derivative **3e** gave the intermediate S-alkylated **5e** in 95% yield. This compound exist as enol tautomeric form,[8,14] as established by ^{1}H spectroscopy, presumably as a consequence of the high electrophilicity of the trichloroacetylimino moiety. When a solution of this compound in toluene was heated at reflux temperature, ammonia was eliminated and the expected 4-tricholoromethylthiazole **6e** was formed (64%) (Scheme 2). Under the same conditions but in the presence of one equivalent of a strong base such as DBU, the loss of trichloromethide took place (loss of amide being very unfavorable) and the unexpected 4-aminothiazole **6i** was obtained instead (66%).

The alkylation of the *N*-phenylthiocarbamoylamidines **3** with ethyl bromoacetate **4b** was also studied. In all the cases examined (**3a**,**b**,**e**) the S-alkylated intermediates **5f**,**g**,**h** were readily isolable although **5g** was quite unstable. The cyclization of **5f**,**g** in toluene containing 1 equiv of DBU gave the expected thiazoles **6f**,**g**, but **5h** gave the 4-aminothiazole **6j** under these conditions. As observed for **5e**, however, heating **5h** in the absence of DBU gave the expected 4-trichloromethylthiazole **6h**.

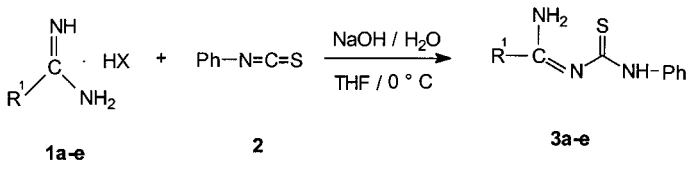
Finally, it should be noted that the processes described herein are not restricted to arylisothiocyanates. For example, ethyl isothiocyanate with benzamidine hydrochloride **1a** gives *N*-ethylthiocarbamoylbenzamidine **3f** in 85%, the reaction with phenacyl bromide **4a** gave rise to 2-(ethylamino)-4-phenyl-5-benzoylthiazole **6k** 68% (Scheme 3). A most attractive feature of this process therefore is that the substituents can be varied at will at all of the thiazole carbon atoms. Furthermore, because the trichloromethyl moiety is readily modified chemically,[15] the diversity of possible substituents in C-4 can be substantially increased. It is to be expected that this synthesis of thiazoles will find extensive utility.

* To whom correspondence should be addressed. Tel: (7) 2173890. Fax: (7)2175109.
† Universidad Autónoma del Estado de México.
‡ Universidad Nacional Autónoma de México.

(1) Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
(2) Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G.; Connolly, C. J.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. *J. Med. Chem.* **1992**, *35*, 2562.
(3) (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Waltwers, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719. (b) Clemence, F.; Le Martret, O.; Delevalle, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Dereat, R. *J. Med. Chem.* **1988**, *31*, 1453.
(4) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 1453.
(5) (a) Dridi, K.; Efrit, E. L.; Baccar, B.; Zantour, H. *Synth. Commun.* **1998**, *29*, 167 and references therein. (b) Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.
(6) Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *J. Med. Chem.* **1995**, *38*, 4929.
(7) Komar, Y.; Green, R.; Wise, D.; Worting, L. L. *J. Med. Chem.* **1988**, *23*, 501.
(8) Yang-i Lin, C. M.; Seifert, S. M.; Kang, J. P.; Lang, S. A. *J. Heterocycl. Chem.* **1979**, *16*, 1377.
(9) Hanessian, S.; Moralioglu, E. *Can. J. Chem.* **1972**, *50*, 233.
(10) Kurzer, F.; Tertink, W. *J. Chem. Soc.* **1959**, 2851.
(11) Albert, A.; Paal, B. *Chem. Ind. (London)* **1974**, 874. Trichloroacetamidine is a much weaker base ($pK_a = 6.5$) than acetamidine ($pK_a = 12.4$; ref 11).
(12) Dridi, K.; Elefrit, M. L.; Baccar, B.; Zantour, H. *Synth. Commun.* **1999**, *29*, 2019.
(13) Brindley, J. C.; Caldwell, J. M.; Meakins, G. D.; Plackett, S. J.; Price, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1153.
(14) (a) Kaye, P. T.; Meakins, G. D.; Smith, A. K.; Tirel, M. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1677. (b) Meslin, J. C.; Quiniou, H. *Tetrahedron* **1975**, *31*, 3055. (c) Meslin, J. C.; Quiniou, H. *Synthesis* **1974**, 298.
(15) (a) Romero, M.; Fuentes, A.; Gonzalez, C.; Morales, D.; Cruz, R. *Synthesis* **1999**, 225. (b) Guzman, A.; Romero, M.; Talamas, F. X.; Villena, R.; Grennhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470.

10.1021/jo0009447 CCC: $19.00
Published on Web 09/27/2000

Scheme 1



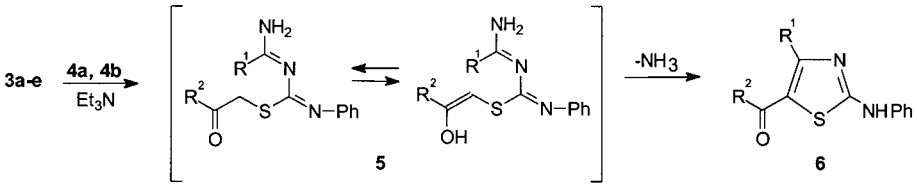
1, 3 **a**, R^1= Ph

b, R^1= Me

c, R^1= H

d, R^1= $(EtO)_2CH$

e, R^1= CCl_3



5, 6 **a**, R^1= R^2= Ph

b, R^1= Me, R^2= Ph

c, R^1= H, R^2= Ph

d, R^1= $(EtO)_2CH$, R^2= Ph

f, R^1= Ph, R^2= EtO

g, R^1= Me, R^2= EtO

Table 1. Formation of Thiocarbamoylamidines 3 from Amidines

compd	thiocarbamoylamidine **3** yield (%)
a	76
b	63
c	*a*
d	71
e	98

[a] Unstable, not purified identified by IR and ^{1}H NMR spectroscopy.

Table 2. Preparation of 2,4,5-Trisubstituted Thiazoles 6 from Thiocarbamoylamidines 3

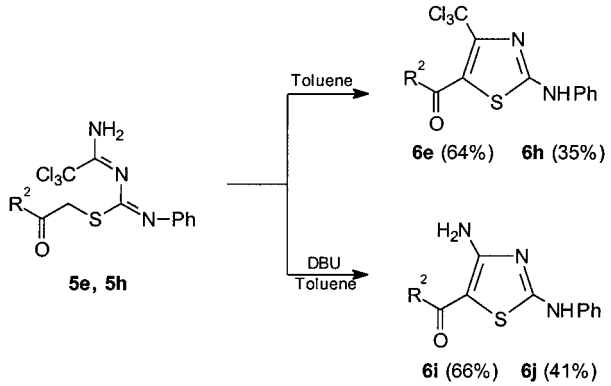
compd	S-alkylated product **5** yield (%)	2-phenylaminothiazole **6** yield (%) from **3**
a	*a*	78
b	*a*	71
c	*a*	83
d	*a*	53
e	95	64
f	75	76
g	*b*	68
h	90	35
i		66
j		41

[a] Not observed. [b] Unstable, not purified.

Experimental Section

Benzamidine hydrochloride, acetamidine hydrochloride, formamidine acetate, phenyl isothiocyanate, ethyl isothiocyanate, phenacyl bromide, ethyl bromoacetate, trichloroacetonitrile, triethylamine, and DBU were commercially available from Aldrich Chemical Co. and were used without further purification. All solvents were purified and dried prior to use.[16] Trichloroacetamidine,[11] and diethoxyacetamidine hydrobromide[17] were

Scheme 2



5 e, R^2 = Ph

h, R^2= EtO

6 e, R^2= Ph

h, R^2= EtO

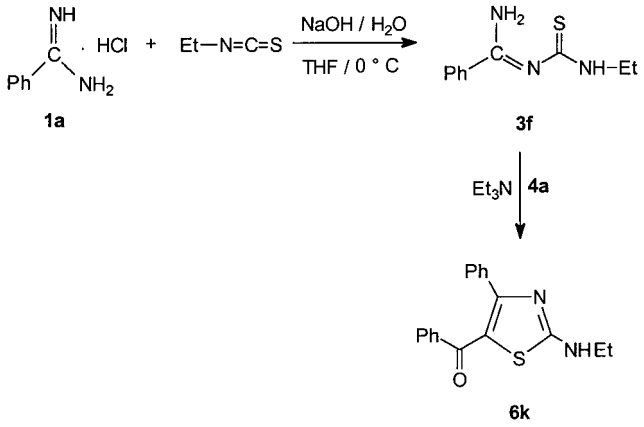
i, R^2= Ph

j, R^2= EtO

(16) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

(17) Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.

Scheme 3



prepared according to the published procedures. Melting points are uncorrected and were measured on a Mel-Temp II apparatus. ^{1}H NMR spectra were recorded on a 200 MHz spectrometer using $CDCl_3$ as solvent and are reported in (δ) ppm from internal tetramethylsilane. ^{13}C NMR spectra were also recorded in $CDCl_3$ solution. The IR spectra were measured in $CHCl_3$ solution.

Synthesis of the *N*-Phenylthiocarbamoylamidines (3). A suspension of amidine salt (1 equiv) in THF (2−5 mL/mmol amidine) was added at 0 °C to aqueous sodium hydroxide (1 equiv) and phenyl isothiocyanate **2** (1 equiv), and the reaction mixture was stirred for 1−2 h at this temperature. It was then diluted with ethyl acetate (20 mL), and the organic phase was washed with saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the crude products as solids. The pure material was obtained after crystallization from hexane−dichloromethane.

***N*-Phenylthiocarbamoylbenzamidine (3a).** Benzamidine hydrochloride **1a** was converted into the corresponding *N*-phenylthiocarbamoylbenzamidine **3a** as described in the general method. After crystallization, **3a** was obtained in 76% as yellow crystals: mp 116−118 °C; IR 3473, 3394, 1615, 1085 cm^{-1}; ^{1}H NMR δ 7.15−7.65 (m, 8 H), 7.78−7.98 (m, 2 H), 8.78 (br, 1 H, NH), 11.2 (broad, 2 H, NH_2); mass spectrum *m*/*z* 255 (20, M$^+$), 135 (100). Anal. Calcd for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.45. Found: C, 65.74; H, 5.14; N, 16.30.

***N*-Phenylthiocarbamoylacetamidine (3b).** Acetamidine hydrochloride **1b** was converted into the corresponding *N*-phenylthiocarbamoylacetamidine **3b** as described in the general method. **3b** was obtained in 63% as yellow crystals: mp 93−95 °C; IR 3437, 3389, 1618, 1102 cm^{-1}; ^{1}H NMR δ 2.17 (s, 3H), 7.11−7.48 (m, 3H), 7.61−7.64 (m, 2H); mass spectrum *m*/*z* 193 (10, M$^+$), 135 (100). Anal. Calcd for $C_9H_{11}N_3S$: C, 55.92; H, 5.73; N, 21.75. Found: C,55.63; H, 5.60; N, 21.78.

***N*-Phenylthiocarbamoylformamidine (3c).** It was not possible to obtain an analytically pure sample of this compound because of the pronounced tendency of *N*-phenylthiocarbamoylformamidine **3c** to be converted into the hydrolysis product under aqueous conditions, therefore this substance was generated and used directly without purification. Thus, to a suspension of formamidine acetate **1c** (1.2 g, 0.011 mol) in anhydrous THF (25 mL) containing anhydrous triethylamine (1.5 mL, 1.11 g, 0.011 mol) was added phenyl isothiocyanate **2** (1.3 mL, 1.48 g, 0.011 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. It was then diluted with ethyl acetate (50 mL) and the organic phase was washed with saturated sodium chloride solution, and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a residue that without purification was used for the synthesis of 2-phenylamino-5-benzoylthiazole **6c**.

***N*-Phenylthiocarbamoyldiethoxyacetamidine (3d).** Diethoxyacetamidine hydrobromide[17] **1d** was converted into the corresponding N-phenylthiocarbamoyldiethoxyacetamidine **3d** as described in general method. **3d** was obtained in 71% as yellow crystals: mp 90−92 °C; IR 3437, 3395, 2981, 2891 cm^{-1}; ^{1}H NMR δ 1.25 (t, 6H), 3.55−3.79 (m, 4H), 4.95 (s, 1H), 7.21−7.56 (m, 3H), 7.60−7.78 (m, 2H); mass spectrum *m*/*z* 281 (48, M$^+$), 135 (100). Anal. Calcd for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.80; S, 11.39. Found: C, 55.02; H, 6.77; S, 11.19.

***N*-Phenylthiocarbamoyltrichloroacetamidine (3e).** Phenyl isothiocyanate **2** (4.0 mL, 0.03 mol) was added to solution of trichloroacetamidine[11] **1e** (5 g, 0.03 mol) in dichloromethane (5 mL) at room temperature. It was stirred for 1 h. Crystallization of this solid from hexane−dichloromethane gave **3e** (98%): mp 86−87 °C; IR 3451, 3377, 1640, 1095 cm^{-1}; ^{1}H NMR δ 7.15−7.32 (m, 3H), 7.35−7.51 (m, 2H), 8.56 (broad, 1H, NH), 8.80 (broad, 2H, NH_2); mass spectrum *m*/*z* 295 (42, M$^+$), 90 (100). Anal. Calcd for $C_9H_8Cl_3N_3S$: C, 36.44; H, 2.71; Cl, 35.85; N, 14.16. Found: C, 36.14; H, 2.67; Cl, 35.69; N, 14.32.

***N*-Ethylthiocarbamoylbenzamidine (3f).** Prepared in the same manner as described for **3a** except that ethyl isothiocyanate was used instead phenyl isothiocyanate **2**. The residue was purified by column chromatography on silica gel using hexanes−ethyl acetate (9:1), **3f** was obtained in 85% as an oil: IR 3297, 2974, 2931, 1615, 1507, 1446 cm^{-1}; ^{1}H NMR δ 1.25 (t, 3H), 3.63 (q, 2H), 7.40−7.55 (m, 3H), 7.78−8.17 (m, 2H); mass spectrum *m*/*z* 207 (100, M$^+$), 163 (34), 104 (82). Anal. Calcd for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.31; N, 20.27; S, 15.47. Found: C, 57.85; H, 6.66; N, 20.12; S, 15.20.

Synthesis of the 2-Phenylamino-5-benzoylthiazoles (6) without Isolation of (5). Phenacyl bromide **4a** in acetone (1 equiv, 5 mL/ mmol) was added to a solution of the *N*-phenylthiocarbamoylamidine **3** (1 equiv) in acetone (2.5−5 mL/mmol amidine derivative) containing triethylamine (1 equiv) at room temperature. After the mixture was stirred for 5−8 h, ethyl acetate was added and the organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated in vacuo. Crystallization of the solid residue from hexane−dichloromethane gave the thiazoles **6**.

2-Phenylamino-4-phenyl-5-benzoylthiazole (6a). *N*-Phenylcarbamoylbenzamidine **3a** was converted into the corresponding 2-phenylamino-5-benzoylthiazole **6a** as described in general method. After crystallization **6a** was obtained in 78% yield: mp 201−3 °C; IR 3392, 1601, 1532 cm^{-1}; ^{1}H NMR δ 7.04−7.34 (m, 13H), 7.46−7.51 (m, 2H), 8.92 (broad, 1H); mass spectrum *m*/*z* 356 (100, M$^+$). Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N,7.85; S, 8.99. Found: C, 74.07; H, 4.47, N, 7.86; S, 8.82.

2-Phenylamino-4-methyl-5-benzoylthiazole (6b). *N*-Phenylcarbamoylacetamidine **3b** was converted into the corresponding 2-phenylamino-4-methyl-5-benzoylthiazole **6b** as described in the general method. **6b** was obtained in 71% after crystallization: mp 170−72 °C; IR 3393, 2847, 1598, 1534 cm^{-1}; ^{1}H NMR δ 2.41 (s, 3H), 7.16−7.54 (m, 8H) 7.70−7.75 (m, 2H); mass spectrum *m*/*z* 294 (70, M$^+$), 293 (100). Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N,9.51; S, 10.89. Found: C, 69.30; H, 4.86, N, 9.81; S, 11.09.

2-Phenylamino-5-benzoylthiazole (6c). Prepared in the general manner except that the thiocarbamoylformamidine **3c** was used as crude material. The pure material was obtained in 83% yield after crystallization: mp 125−6 °C; IR 3403, 1599, 1530 cm^{-1}; ^{1}H NMR δ 6.85 (s, 1H), 7.04−7.45 (m, 8H), 7.83−7.88 (m, 2H); mass spectrum *m*/*z* 280 (5, M$^+$), 252 (100). Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N,9.99; S, 11.43. Found: C, 68.70; H, 4.37, N, 9.86; S, 11.26.

2-Phenylamino-4(diethoxy)methyl-5-benzoylthiazole (6d). *N*-Phenylthiocarbamoyldiethoxyacetamidine **3a** was converted into the corresponding 2-phenylamino-4-(diethoxy)methyl-5-benzoylthiazole **6d** as described in the general method. **6d** was obtained in 53% yield after crystallization: mp 158−9 °C; IR 3288, 2976, 2928, 2895, 1599, 1557 cm^{-1}; ^{1}H NMR δ 1.23 (t, 6H), 3.65−3.81 (m, 4H), 5.69 (s, 1H), 7.24−7.58 (m, 8H), 7.77−7.82 (m, 2H); ^{13}C NMR δ 15.31, 63.62, 97.24, 120.57, 122.11, 125.07, 128.69, 129.79, 132.41, 139.34, 140.30, 157.29, 169.25, 187.56; mass spectrum *m*/*z* 382 (10, M$^+$), 307 (100). Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.94; H, 5.79; N, 7.32; S, 8.38. Found: C, 65.46; H, 5.97; N, 7.42; S, 8.70.

2-Ethylamino-4-phenyl-5-benzoylthiazole (6k). This compound was prepared in the same manner as described in the general method except that *N*-ethylthiocarbamoylbenzamidine **3f** was used. After crystallization, **6k** was obtained in 68% yield: mp 165−6 °C (hexane−dichloromethane); IR 3411, 3201, 2980, 1601, 1545, 1475 cm^{-1}; ^{1}H NMR δ 1.11 (t, 3H), 1.88 (broad, 1H), 3.15 (q, 2H), 7.02−7.28 (m, 8H), 7.40−7.48 (m, 2H); ^{13}C NMR δ 13.89, 41.34, 127.67, 127.81, 128.75, 129.13, 129.81, 131.24, 135.13, 138.46, 159.44, 172.75, 188.68; mass spectrum *m*/*z* 308 (100, M$^+$), 279 (11). Anal. Calcd for $C_{18}H_{16}N_2OS$: C,

70.10; H, 5.23; N, 9.08; S, 10.39. Found: C, 69.87, H, 5.32; N, 9.08; S, 10.50.

Phenacyl Bromide (4a)/Ethyl Bromoacetate (4b) S-Alkylation of *N*-Phenylthiocarbamoylamidines (3). General Procedure. The α-bromo carbonyl compound (1 equiv) was added slowly at room temperature to a stirred solution of the *N*-phenylthiocarbamoylamidine (**3**, 1 equiv) in anhydrous THF (2 mL) containing anhydrous triethylamine (1 equiv) maintained in a nitrogen atmosphere. The reaction mixture was stirred for an additional 2−3 h, it was then diluted with ethyl acetate (20 mL), the mixture was washed with saturated NH_4Cl solution (30 mL), and the organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo.

S-Alkylation of *N*-Phenylthiocarbamoyltrichloroacetamidine (3e) with Phenacyl Bromide (4a). 5e was obtained in 95% yield after crystallization of the solid residue from hexane−dichloromethane: mp 115−6 °C; IR 3394, 3062, 1684, 1662, 1652, 1557 cm^{-1}; ^1H NMR δ 2.65 (broad, 2H), 5.92 (s, 1H), 7.06−7.64 (m, 6H), 7.99−8.05 (m, 4H); mass spectrum *m*/*z* 413 (5, M^+), 105 (100). Anal. Calcd for $C_{17}H_{14}Cl_3N_3OS$: C, 49.23; H, 3.40; N, 10.13; S, 7.73. Found: C, 49.30; H, 3.52; N, 9.81, S, 7.73.

S-Alkylation of *N*-Phenylthiocarbamoylbenzamidine (3a) with Ethyl Bromoacetate (4b). 5f was obtained in 75% yield after column chromatography purification on silica gel using hexane−dichloromethane (8:2): mp 141−2 °C; IR 3435, 2983, 2903, 1743, 1574 cm^{-1}; ^1H NMR δ 1.17 (t, 3H), 3.90 (s, 2H), 4.10 (q, 2H), 6.47−7.51 (m, 8H), 7.86−7.90 (m, 2H); mass spectrum *m*/*z* 341 (50, M^+), 222 (100). Anal. Calcd for $C_{18}H_{19}N_3O_2S$: C, 63.32, H, 5.60; N, 12.30; S, 9.39. Found: C, 63.38; H, 5.79, N, 12.11; S, 9.63.

S-Alkylation of N-Phenylthiocarbamoyltrichloroacetamidine (3e) with Ethyl Bromoacetate (4b). 5h was obtained in 90% yield after crystallization of the solid residue from hexane−dichloromethane: mp 132−3 °C; IR 3463, 1735, 1629, 1590 cm^{-1}; ^1H NMR δ 1.24 (t, 3H), 3.91 (s, 2H), 4.15 (q, 2H), 7.01−7.40 (m, 5H); ^{13}C NMR δ 14.30, 34.56, 61.71, 95.02, 121.97, 125.19, 129.28, 146.48, 158.77, 163.83, 169.45; mass spectrum *m*/*z* 381 (10, M^+), 262 (100). Anal. Calcd for $C_{13}H_{14}Cl_3N_3O_2S$: C, 40.79; H, 3.68; N, 10.97; S, 8.37. Found: C,40.75; H, 3.75; N, 10.97; S, 8.19.

2-Phenylamino-4-trichloromethyl-5-benzoylthiazole (6e). A solution of S-alkylated compound **5e** (0.413 g, 1 mmol) in toluene (5 mL) in a nitrogen atmosphere was heated at reflux temperature for 1.5 h. The solution was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed successively with water and saturated NH_4Cl solution. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The product was then obtained from the residue by column chromatography on silica gel using hexanes−ethyl acetate (9:1). **6e** was obtained after crystallization from hexane−dichloromethane in 64% yield: mp 119 °C; IR 3391, 2360, 1659, 1597 cm^{-1}; ^1H NMR δ 7.12−7.66 (m, 7H). 7.84 (broad, 1H), 7.79−7.95 (m, 3H); ^{13}C NMR δ 92.01, 119.92, 125.14, 128.92, 130.00, 134.31, 137.91, 139.08, 149.47, 163.89, 187.94; mass spectrum *m*/*z* 396 (50, M^+). Anal. Calcd for $C_{17}H_{11}Cl_3N_2OS$: C, 51.34; H, 2.78; Cl, 26.74; N, 7.04; S, 8.32. Found: C, 51.58; H, 2.88; Cl, 26.27; N, 6.92; S, 8.32.

2-Phenylamino-4-phenyl-5-ethoxycarbonylthiazole (6f). A solution of S-alkylated compound **5f** (0.341 g, 1 mmol) in toluene (10 mL) containing DBU (0.1 mL, 0.102 g, 1 mmol) in a nitrogen atmosphere was heated at reflux temperature for 2 h. The solution was cooled to room temperature, diluted with ethyl acetate (40 mL), and washed successively with water and saturated NaCl solution. The organic phase was dried (Na_2SO_4) and evaporated in vacuo, and the product was then obtained from the residue by column chromatography on silica gel using hexanes−ethyl acetate (6:4). **6f** was obtained after crystallization from hexane-dichloromethane in 76% yield: mp 185−6 °C; IR 3434, 2978, 1729, 1523 cm^{-1}; ^1H NMR δ 1.25 (t, 3H), 4.19 (q, 2H), 7.09−7.41 (m, 8H). 7.70−7.75 (m, 2H), 8.26 (broad, 1H); mass spectrum *m*/*z* 324 (100, M^+). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.63; S, 9.88. Found: C, 66.42; H, 5.30; N, 8.67; S, 9.65.

2-Phenylamino-4-methyl-5-ethoxycarbonylthiazole (6g). Ethyl bromoacetate **4b** (0.55 mL, 0.835 g, 5 mmol) was added to a stirred solution of the *N*-phenylthiocarbamoylacetamidine **3b** (0.965 g, 5 mmol), containing triethylamine (0.7 mL, 0.5 g, 5 mmol), at room temperature. The reaction mixture was stirred for 2 h, ethyl acetate (50 mL) was added to the reaction mixture, and the organic phase was separated, washed with saturated NaCl solution, and dried (Na_2SO_4). Evaporation of the solvent in vacuo, gave a residue that was dissolved in toluene (20 mL), DBU (0.75 mL, 0.761 g, 5 mmol) was added, and the solution was then heated at 100 °C in a nitrogen atmosphere for 2 h. The solution was cooled to room temperature, diluted with ethyl acetate (50 mL), washed successively with water and saturated NaCl solution, dried (Na_2SO_4), and evaporated in vacuo. The product was then obtained from the residue by column chromatography from hexanes−ethyl acetate (8:2) **6g** was obtained after crystallization from hexane-dichloromethane in 68% yield: mp 138−9 °C; IR 3396, 2983, 2934, 1694, 1597 cm^{-1}; ^1H NMR δ 1.33 (t, 3H), 2.58 (s, 3H), 4.28 (q, 2H), 7.11−7.44 (m, 5H), 8.16 (broad, 1H); mass spectrum *m*/*z* 262 (100, M^+). Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.37; N, 10.67; S, 12.22. Found: C, 59.46; H, 5.36; N, 10.90.

2-Phenylamino-4-trichloromethyl-5-ethoxycarbonylthiazole (6h). This compound was prepared from the S-alkylated compound **5h** in the same manner as described for the synthesis of **6e**, after crystallization from hexane−dichloromethane pure **6h** was obtained in 35% yield: mp 122−3 °C; IR 3393, 1723, 1557, 1538, 1505 cm^{-1}; ^1H NMR δ 1.35 (t, 3H), 4.33 (q, 2H), 7.14−7.45 (m, 5H), 7.63 (broad, 1H); ^{13}C NMR δ 14.29, 62.08, 112.75, 119.81, 125.30, 130.06, 138.74, 154.80, 159.56, 163.73; mass spectrum *m*/*z* 364 (70, M^+), 265 (100). Anal. Calcd for $C_{13}H_{11}Cl_3N_2O_2S$: C, 42.69; H, 3.03; Cl, 29.08; N, 7.65. Found: C, 42.82; H, 3.20; Cl, 30.50; N, 7.68.

2-Phenylamino-4-amino-5-benzoylthiazole (6i). This compound was prepared from the S-alkylated compound **5e** in the same manner as described for the synthesis of **6e**, except that DBU (1 equiv) was necessary. After crystallization from hexane-dichloromethane pure **6i** was obtained in 66% yield: mp 186−8 °C (hexane−dichloromethane (lit.[18] 186−87 °C)); IR 3019, 1594, 1543, 1448 cm^{-1}; ^1H NMR δ 7.01 (broad, 2H), 7.14−7.75 (m, 10H), 8.59 (broad, 1H); ^{13}C NMR δ 120.75, 125.47, 127.38, 128.66, 129.91, 130.83, 138.51, 141.55, 164.60, 167.67, 169.84, 185.27; mass spectrum *m*/*z* 295 (100, M^+), 218 (10). Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.43; N, 14.22; S, 10.85. Found: C, 64.91, H, 4.55; N, 14.11; S, 11.10.

2-Phenylamino-4-amino-5-ethoxycarbonylthiazole (6j). This compound was prepared from S-alkylated compound **5h** in the same manner as described for the synthesis of **6h**, except that DBU (1 equiv) was necessary. After crystallization from hexane-dichloromethane pure **6j** was obtained in 41% yield: mp 144−6 °C (hexane−dichloromethane,); IR 3502, 3384, 1683, 1654, 1602, 1569 cm^{-1}; ^1H NMR δ 1.30 (t, 3H), 4.23 (q, 2H), 5.8 (broad, 2H), 7.12−7.43 (m, 5H), 8.30 (broad, 1H); ^{13}C NMR δ 14.78, 59.98, 120.25, 124.96, 129.86, 139.01, 168.17; mass spectrum *m*/*z* 263 (100, M^+), 235 (25). Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.73; H, 4.97; N, 15.95; S, 12.11. Found: C, 54.77, H, 4.93; N, 15.99; S, 12.11.

Acknowledgment. Financial support for this research from "Consejo Nacional de Ciencia y Tecnología", CONACyT (clave 25338-N) is gratefully acknowledged. We thank Dr. Horacio F. Olivo (University of Iowa) for ^{13}C NMR spectra and helpful discussions. The authors wish to thank Professor Joseph M. Muchowski from Roche Bioscience for helpful discussions and his interest in our work.

JO0009447

(18) Rajasekharan, K. N.; Nair, K. P.; Jenardanan, G. C. *Synthesis* **1986**, 353.