

In the presence of boron trifluoride etherate, aryl and alkylthioamides react with ethyl diazopyruvate to give high yields of corresponding thiazoles.

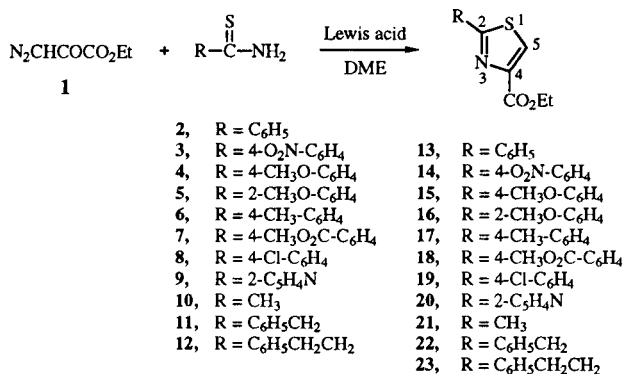
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Several methods [1] for the synthesis of thiazole derivatives have been known and developed during the last two decades because of their biologically and pharmaceutically important properties in thiazole-containing natural products such as leinamycin [2], nosiheptide [3], and bleomycin [4].

In the course of our research on the use of α -diazocarbonyl compounds for the synthesis of heterocycles such as β -furoic acid [5], γ -pyrone [6], and oxazole [7], we attempted the synthesis of thiazole derivatives *via* Lewis acid promoted reactions of diazopyruvate with thioamides. In this report, we will describe a new method for the synthesis of thiazole derivatives.

The thioamides **2-12** were prepared by treatment of amides with Lawesson's reagent and the amides were purchased or prepared from nitriles or carboxylic acids by literature methods [8]. Ethyl diazopyruvate **1** was prepared as reported [9]. Thiazole derivatives **13-23** were synthesized by treatment of thioamides **2-12** with ethyl diazopyruvate in the presence of common Lewis acids such as boron trifluoride etherate, aluminum chloride, or ferric chloride (Scheme 1).

Scheme 1



The reaction of ethyl diazopyruvate **1** with thiobenzamide **2** in the presence of two equivalents Lewis acid (*e.g.*, boron trifluoride etherate, aluminum chloride, ferric chloride) at 80°, after aqueous work up, resulted in 2-phenyl-4-carbomethoxythiazole **13**. The best result was obtained with boron trifluoride etherate. The yield of 2-phenyl-4-carbomethoxythiazole **13** from the aluminum chloride promoted reaction of ethyl diazopyruvate **1** with thiobenzamide **2** was less than that obtained with boron trifluoride etherate.

Table 1

Results of the Lewis Acid Promoted Reactions of Diazopyruvate **1** with Thioamides

Thioamide	R	Lewis acid	Product	Yield %	mp (°C)
2	C ₆ H ₅	BF ₃ •Et ₂ O	13	82	48-49
2	C ₆ H ₅	AlCl ₃	13	79	48-49
2	C ₆ H ₅	FeCl ₃	13	20	48-49
3	4-O ₂ N-C ₆ H ₄	BF ₃ •Et ₂ O	14	72	152-154
4	4-CH ₃ O-C ₆ H ₄	BF ₃ •Et ₂ O	15	89	97-98
5	2-CH ₃ O-C ₆ H ₄	BF ₃ •Et ₂ O	16	87	86-87
6	4-CH ₃ -C ₆ H ₄	BF ₃ •Et ₂ O	17	97	44.5-45
7	4-CH ₃ O ₂ C-C ₆ H ₄	BF ₃ •Et ₂ O	18	51	121.5-122
8	4-Cl-C ₆ H ₄	BF ₃ •Et ₂ O	19	68	100-100.5
9	2-C ₃ H ₄ N	BF ₃ •Et ₂ O	20	41	70.5-71
10	CH ₃	BF ₃ •Et ₂ O	21	57	57-57.5
11	C ₆ H ₅ CH ₂	BF ₃ •Et ₂ O	22	49	77-78
12	C ₆ H ₅ CH ₂ CH ₂	BF ₃ •Et ₂ O	23	75	51

[a] Isolated yields.

A similar low yield of thiazole was observed in the ferric chloride promoted reaction. Common solvents (*e.g.*, THF, DME, diethyl ether, 1,2-dichloroethane) can be used. However, DME as the solvent gave the best results. The representative results of the reaction between ethyl diazopyruvate **1** and various thioamides **2-12** are shown in Table 1. The relative yields of the thiazoles **13-23** were found to be influenced by the nature of the R groups attached to the thioamides. Aromatic thioamides gave higher yields than their aliphatic counterparts. Substitution on the *para* position of thiobenzamide by an electron-withdrawing group diminishes the yields of thiazoles.

Further investigation on the synthesis of thiazole derivatives which have an amino moiety in the alkyl side chain are presently being carried out.

EXPERIMENTAL

Melting points were measured using a Thomas-Hoover melting point apparatus, and are not corrected. The ir spectra were obtained on a Matton GL-6030E spectrophotometer on potassium bromide pellets. The ¹H and ¹³C nmr were recorded on a Bruker AM-300 or Varian Unity Plus-300. The chemical shifts of the ¹H nmr spectra (300.1 MHz) are given in ppm downfield from tetramethylsilane and ¹³C nmr spectra (75.5 MHz) were

referenced to deuteriochloroform at 77.0 ppm. Mass spectra were recorded on a Shimadzu QP-1000 spectrometer with electron energy of 20 eV or 70 eV with direct sample introduction. Elemental analyses were performed on a Carlo Erba 1106 instrument. Analyses (tlc) were carried out on precoated 0.2 mm Merk Kieselgel 60F₂₅₄ plates, visualizing with a 254-nm uv lamp. For routine column chromatography, Merck silica gel (70-230 mesh) was used as the adsorbent. All reactions were carried out under an atmosphere of argon.

Compound **1** has been prepared following a reported procedure [9]. The structure of **1** was confirmed by ir, ¹H nmr, and mass spectral data which are similar to those reported.

General Procedure for the Synthesis of Thiazoles 13-23.

To a stirred solution of thioamide **2-12** (1 mmole), boron trifluoride etherate (0.25 ml, 2 mmoles) in dry DME (5 ml) was added a solution of ethyl diazopyruvate **1** (142 mg, 1 mmole) in dry DME (3 ml) for 2 hours at room temperature and then the mixture was refluxed for 3 hours. The mixture was cooled to room temperature and then poured into water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate:hexane 1:4) to give 2-substituted-4-carbethoxythiazole.

2-Phenyl-4-carbethoxythiazole (13).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 82% yield, mp 48-49°; ir (potassium bromide): 3130, 2979, 1729, 1466, 1339, 1212, 1096, 1023, 772 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (t, J = 7.1 Hz, 3H, CH₂CH₃), 4.45 (q, J = 7.1 Hz, 2H, O-CH₂CH₃), 8.01-7.45 (m, 5H, H of Ph), 8.15 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.3 (CH₂CH₃), 61.4 (OCH₂CH₃), 126.9 (3', 5'-C of Ph and 5-C), 128.9 (2', 6'-C of Ph), 130.6 (4'-C of Ph), 132.8 (1'-C of Ph), 148.1 (4-C), 161.4 (2-C), 168.8 (C=O); ms: m/z 233 (M⁺, 18), 188 (M-OCH₂CH₃, 27), 160 (M-CO₂CH₂CH₃, 13), 121 (33), 77 (100).

Anal. Calcd. for C₁₂H₁₁NO₂S: C, 61.78; H, 4.76; N, 6.01. Found: C, 61.68; H, 4.72; N, 5.76.

2-(4'-Nitrophenyl)-4-carbethoxythiazole (14).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 72% yield, mp 152-154°; ir (potassium bromide): 3137, 2980, 1729, 1601, 1520, 1343, 1204, 1096 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.44 (t, J = 7.1 Hz, 3H, CH₂CH₃), 4.47 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 8.19 (m, 2H, 2', 6'-H of Ph), 8.28 (s, 1H, 5-H), 8.31 (m, 2H, 3', 5'-H of Ph); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 61.8 (OCH₂CH₃), 123.3 (5-C), 124.4 (3', 5-C of Ph), 127.7 (2', 6'-C of Ph), 128.5 (4'-C of Ph), 138.2 (1'-C of Ph), 149.0 (4-C), 161.1 (2-C), 165.8 (C=O); ms: m/z 278 (M⁺, 31), 233 (M-OCH₂CH₃, 32), 206 (M-CO₂CH₂CH₃ + H, 100), 205 (M-CO₂CH₂CH₃, 98), 166 (20).

Anal. Calcd. for C₁₂H₁₀N₂O₄S: C, 51.79; H, 3.62; N, 10.07. Found: C, 51.39; H, 3.51; N, 9.89.

2-(4'-Methoxyphenyl)-4-carbethoxythiazole (15).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 89% yield, mp 97-98°; ir (potassium bromide): 3137, 2971, 1729, 1466, 1258, 1208, 1095, 1026, 837 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.42 (t, J = 7.1

Hz, 3H, CH₂CH₃), 3.86 (s, 3H, OCH₃), 4.44 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 6.95 (m, 2H, 3', 5'-H of Ph), 7.95 (m, 2H, 2', 6'-H of Ph), 8.07 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 55.5 (OCH₃), 61.4 (OCH₂CH₃), 114.3 (3', 5'-C of Ph), 125.9 (1'-C of Ph), 126.2 (5-C), 128.6 (2', 6'-C of Ph), 147.9 (4-C), 161.6 (2-C), 161.7 (4'-C of Ph), 168.8 (C=O); ms: m/z 263 (M⁺, 100), 218 (M-OCH₂CH₃, 42), 191 (M-CO₂CH₂CH₃ + H, 100), 190 (M-CO₂CH₂CH₃, 23), 151 (100).

Anal. Calcd. for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.64; H, 5.14; N, 5.69.

2-(2'-Methoxyphenyl)-4-carbethoxythiazole (16).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 87% yield, mp 86-87°; ir (potassium bromide): 3122, 2983, 1725, 1593, 1497, 1470, 1439, 1297, 1208, 1096, 1015, 760 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (t, J = 7.2 Hz, 3H, CH₂CH₃), 4.02 (s, 3H, OCH₃), 4.44 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 7.02 (d, J = 8.5 Hz, 1H, 3'-H of Ph), 7.09 (m, 1H, 5'-H of Ph), 7.40 (m, 1H, 4'-H of Ph), 8.19 (s, 1H, 5-H), 8.51 (dd, J = 7.9, 1.5 Hz, 1H, 6'-H of Ph); ¹³C nmr (deuteriochloroform): δ 14.3 (CH₂CH₃), 55.5 (OCH₃), 61.2 (OCH₂CH₃), 111.2 (3'-C of Ph), 121.1 (5-C), 121.6 (1'-C of Ph), 127.7 (5'-C of Ph), 129.1 (4'-C of Ph), 131.2 (6'-C of Ph), 146.1 (4-C), 161.9 (2-C), 156.5 (2'-C of Ph), 163.0 (C=O); ms: m/z 264 (M⁺ + H, 53), 263 (M⁺, 40), 234 (M-CH₂CH₃, 100), 218 (M-OCH₂CH₃, 26).

Anal. Calcd. for C₁₃H₁₃NO₃S: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.47; H, 5.01; N, 5.44.

2-(4'-Methylphenyl)-4-carbethoxythiazole (17).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 97% yield, mp 44.5-45°; ir (potassium bromide): 3137, 2987, 1721, 1462, 1331, 1196, 1088, 1023, 803 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (t, J = 7.0 Hz, 3H, CH₂CH₃), 2.39 (s, 3H, CH₃), 4.44 (q, J = 7.0 Hz, 2H, OCH₂CH₃), 7.25 (d, J = 8.1 Hz, 2H, 2', 6'-H of Ph), 7.9 (d, J = 7.0 Hz, 2H, 3', 5'-H of Ph), 8.11 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 21.5 (CH₃), 61.5 (OCH₂CH₃), 126.8 (5-C), 127.0 (2', 6'-C of Ph), 129.7 (3', 5'-C of Ph), 130.3 (4'-C of Ph), 141.1 (1'-C of Ph), 148.0 (4-C), 161.5 (2-C), 169.1 (C=O); ms: m/z 247 (M⁺, 41), 202 (M-OCH₂CH₃, 19), 175 (M-CO₂CH₂CH₃ + H, 100), 174 (M-CO₂CH₂CH₃, 77), 135 (39), 91 (tropylium, 21).

Anal. Calcd. for C₁₃H₁₃NO₂S: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.47; H, 5.55; N, 5.38.

2-(4'-Carbomethoxyphenyl)-4-carbethoxythiazole (18).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 51% yield, mp 121.5-122°; ir (potassium bromide): 3130, 2987, 1725, 1281, 1261, 1104, 1026, 772 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.44 (t, J = 7.1 Hz, 3H, CH₂CH₃), 3.95 (s, 3H, CO₂CH₃), 4.46 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 8.07-8.14 (m, 4H, H of Ph), 8.21 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.3 (CH₂CH₃), 52.3 (OCH₃), 61.6 (OCH₂CH₃), 126.7 (5-C), 127.8 (2', 6'-C of Ph), 130.3 (3', 5'-C of Ph), 131.9 (1'-C of Ph), 136.6 (4'-C of Ph), 148.6 (4-C), 161.4 (2-C), 166.3 (CO₂CH₂CH₃), 167.5 (CO₂CH₃); ms: m/z 291 (M⁺, 37), 260 (M-OCH₃, 11), 246 (M-OCH₂CH₃, 15), 232 (M-CO₂CH₃, 8), 218 (M-CO₂CH₂CH₃, 11).

Anal. Calcd. for C₁₄H₁₃NO₄S: C, 57.72; H, 4.50; N, 4.81.

Found: C, 58.01; H, 4.57; N, 5.16.

2-(4'-Chlorophenyl)-4-carbethoxythiazole (19).

This compound was obtained as a bright red powder (dichloromethane-hexane) in 68% yield, mp 100-100.5°; ir (potassium bromide): 3133, 2994, 2951, 1729, 1459, 1208, 1030, 996, 830, 756 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (t, J = 7.1 Hz, CH₂CH₃), 4.45 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 7.42 (m, 2H, 2', 6'-H of Ph), 7.94 (m, 2H, 3', 5'-H of Ph), 8.15 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 61.6 (OCH₂CH₃), 127.1 (5-C), 128.2 (3', 5'-C of Ph), 129.3 (2', 6'-C of Ph), 131.4 (4'-C of Ph), 136.8 (1'-C of Ph), 148.4 (4-C), 161.3 (2-C), 167.5 (C=O); ms: m/z 267 (M⁺, 51), 222 (M-OCH₂CH₃, 38), 195 (M-CO₂CH₂CH₃ +H, 100), 194 (M-CO₂CH₂CH₃, 26), 155 (31).

Anal. Calcd. for C₁₂H₁₀ClNO₂S: C, 53.83; H, 3.76; N, 5.23. Found: C, 54.12; H, 3.53; N, 5.54.

2-(2'-Pyridyl)-4-carbethoxythiazole (20).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 41% yield, mp 70.5-71°; ir (potassium bromide): 3202, 2980, 1724, 1636, 1439, 1374, 1347, 1223, 1100, 1015 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.44 (t, J = 7.1 Hz, 3H, CH₂CH₃), 4.46 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 7.35 (qd, J = 7.8, 4.9 Hz, 1H, 5'-H of Py), 7.82 (td, J = 7.8, 1.4 Hz, 1H, 4'-H of Py), 8.25 (s, 1H, 5-H), 8.33 (d, J = 7.8 Hz, 1H, 3'-H of Py), 8.61 (dd, J = 4.9, 1.4 Hz, 1H, 6'-H of Py); ¹³C nmr (deuteriochloroform): δ 14.31 (CH₂CH₃), 61.4 (OCH₂CH₃), 120.3 (5'-C of Py), 125.1 (5-C), 129.4 (3'-C of Py), 137.1 (4'-C of Py), 148.3 (4-C), 149.4 (6'-C of Py), 150.5 (2'-C of Py), 161.4 (2-C), 169.9 (C=O); ms: m/z 234 (M⁺, 27), 189 (M-OCH₂CH₃, 38), 162 (M-CO₂CH₂CH₃ +H, 100), 161 (M-CO₂CH₂CH₃, 23), 122 (21).

Anal. Calcd. for C₁₁H₁₀N₂O₂S: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.56; H, 4.45; N, 11.98.

2-Methyl-4-carbethoxythiazole (21).

This compound was obtained as a colorless powder (dichloromethane-hexane) in 57% yield, mp 57-57.5°; ir (potassium bromide): 3092, 2982, 1714, 1485, 1335, 1219, 1179, 1107, 1028, 777 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.40 (t, J = 7.1 Hz, 3H, CH₂CH₃), 2.77 (s, 3H, CH₃), 4.42 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 8.04 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 19.4 (CH₃), 61.4 (OCH₂CH₃), 127.2 (5-C), 146.9 (4-C), 161.4 (2-C), 166.8 (C=O); ms: m/z 171 (M⁺, 26), 126 (M-OCH₂CH₃, 80), 99 (M-CO₂CH₂CH₃ +H, 100), 98 (M-CO₂CH₂CH₃, 80), 84 (14).

Anal. Calcd. for C₇H₉NO₂S: C, 49.11; H, 5.30; N, 8.18. Found: C, 49.09; H, 5.41; N, 8.45.

2-Benzyl-4-carbethoxythiazole (22).

This compound was obtained as yellow needles (dichloromethane-hexane) in 49% yield, mp 77-78°; ir (potassium bromide): 3095, 2963, 1713, 1482, 1219, 1100, 1026, 702 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7.1 Hz, CH₂CH₃),

4.39 (s, 2H, PhCH₂), 4.42 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 7.26-7.37 (m, 5H, H of Ph), 8.05 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.3 (CH₂CH₃), 40 (PhCH₂), 61.3 (OCH₂CH₃), 127.4 (5-C), 127.7 (4'-C of Ph), 128.9 (2', 6'-C of Ph), 129.0 (3', 5'-C of Ph), 137.2 (1'-C of Ph), 146.8 (4-C), 161.4 (2-C), 171.7 (C=O); ms: m/z 247 (M⁺, 83), 202 (M-OCH₂CH₃, 27), 173 (M-CO₂CH₂CH₃, 100), 91 (tropylium, 71).

Anal. Calcd. for C₁₃H₁₃NO₂S: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.46; H, 5.42; N, 5.87.

2-(2'-Phenylethyl)-4-carbethoxythiazole (23).

This compound was obtained as colorless needles (dichloromethane-hexane) in 75% yield, mp 51°; ir (potassium bromide): 3091, 2987, 2921, 1713, 1482, 1331, 1216, 1100, 1026, 779 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.40 (t, J = 7.2 Hz, 3H, CH₂CH₃), 3.13 (m, 2H, PhCH₂CH₂), 3.38 (m, 2H, PhCH₂), 4.43 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 7.21 (m, 3H, 3', 4', 5'-H of Ph), 7.29 (m, 2H, 2', 6'-H of Ph), 8.01 (s, 1H, 5-H); ¹³C nmr (deuteriochloroform): δ 14.4 (CH₂CH₃), 35.2 (PhCH₂CH₂), 35.9 (PhCH₂), 61.3 (OCH₂CH₃), 126.5 (5-C), 126.8 (4'-C of Ph), 128.4 (2', 6'-C of Ph), 128.6 (3', 5'-C of Ph), 140.0 (1'-C of Ph), 147.0 (4-C), 161.4 (2-C), 170.8 (C=O); ms: m/z 261 (M⁺, 81), 232 (M-CH₂CH₃, 7), 216 (M-OCH₂CH₃, 20), 215 (M-OCH₂CH₃ -H, 32), 188 (M-CO₂CH₂CH₃, 9), 91 (tropylium, 100).

Anal. Calcd. for C₁₄H₁₅NO₂S: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.21; H, 5.82; N, 5.55.

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