An Unusual Labilization of a 4-(Trifluoromethyl)thiazole

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Received February 21, 1991

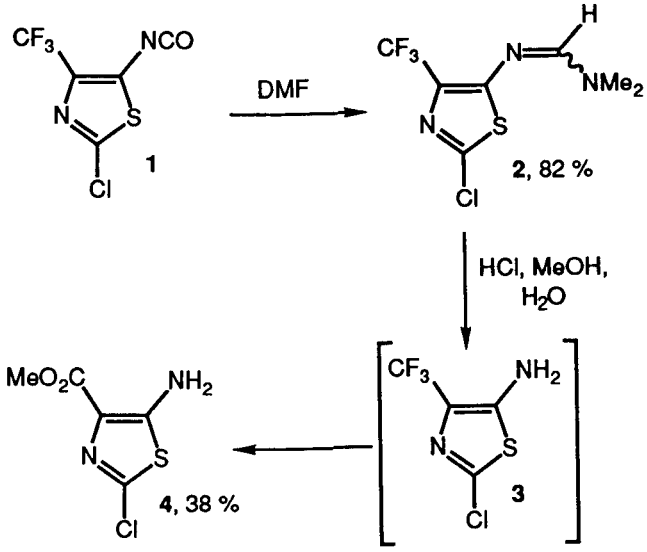
N-2-Chloro-4-(trifluoromethyl)-5-thiazolyl-*N'*,*N'*-diethylurea **5** has been found to undergo a facile labilization of the trifluoromethyl group under mild conditions. The reaction relies on the assistance of the nitrogen substitution at the 4-position of the thiazole ring. Treatment of **5** with triethylamine and either methanol or methanethiol replaced the trifluoromethyl group with a methyl ester or a trimethylorthothio ester respectively at room temperature. Combination of **5** with diethylamine led to an unusual thiazolidine with two exocyclic double bonds, **8**.

J. Heterocyclic Chem., **28**, 1013 (1991).

A wide variety of thiazole heterocycles are known for their unique biological activity [1]. We have an interest in 4-trifluoromethyl substituted thiazoles since they are useful as safeners (herbicide antidotes) for the acetanilide class of herbicides [2-4]. Previously we reported the synthesis of 2-chloro-4-(trifluoromethyl)-5-isocyanatothiazole **1** [5] and subsequently we found that derivatives of this highly reactive isocyanate can undergo a facile labilization of the trifluoromethyl group under very mild conditions.

We were able to show that when isocyanate **1** (Scheme I) was treated with *N,N*-dimethylformamide an exothermic reaction occurred to give the amidine **2** in 82% yield [5]. It

Scheme I

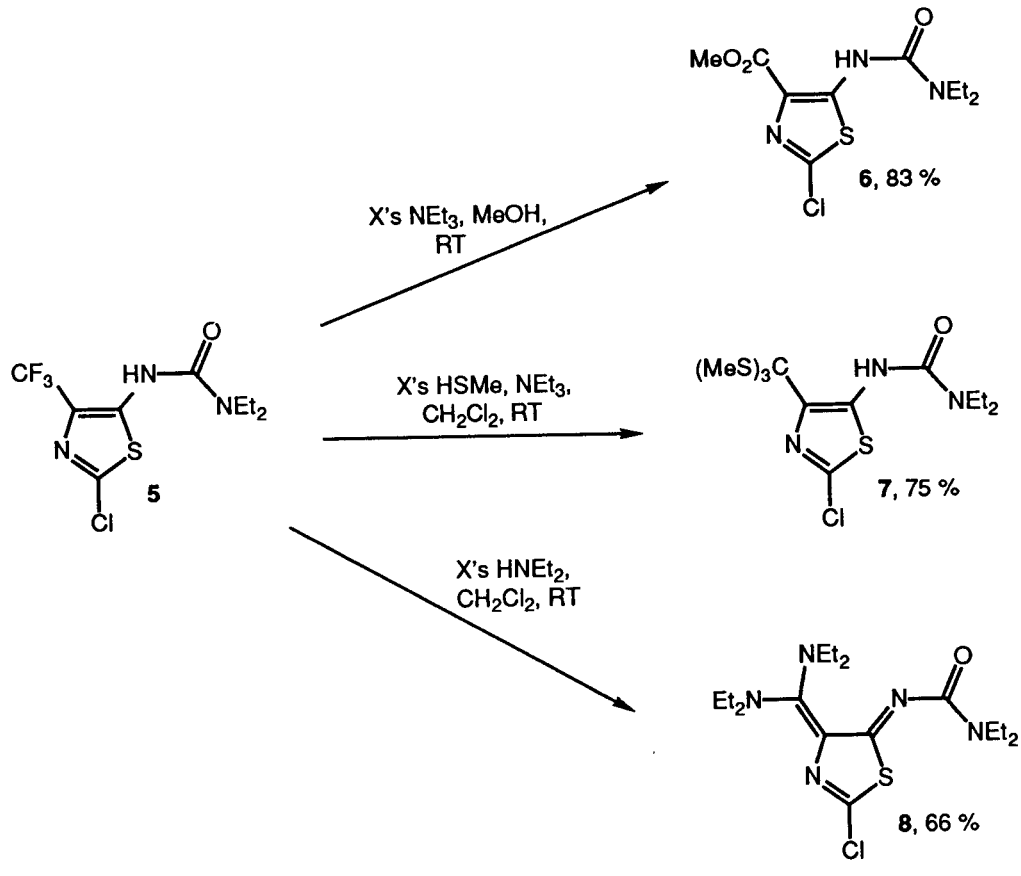


was surprising to find that when **2** was treated with hydrochloric acid in methanol and water the amine **3** was not isolated. Instead, the trifluoromethyl group on the thiazole was converted to the ester **4** in 38% yield. Apparently the amine **3** must have been formed as an intermediate which reacted further to give **4**. Alternatively, the trifluoromethyl group could have been labilized with the amidine intact followed by hydrolysis to the amine **4**. Normally 4-trifluoromethyl substituted thiazoles without nitrogen substitution at the 5-position have been found to be stable to acid and base under a variety of conditions [2-5]. It seemed that the presence of a nitrogen substitution *alpha* to the trifluoromethyl group was assisting in this labilization reaction. Burger has also proposed [6-7] that the nitrogen of a 5-amino-4-trifluoromethylthiazole participates in the reduction of the trifluoromethyl group to a methyl group using lithium aluminum hydride, but no further study of this reaction has appeared. Therefore we decided to study this interesting lability in more detail.

A convenient source of a 4-trifluoromethyl-5-nitrogen substituted thiazole for further study was found *via* the reaction of **1** (see the previous paper in this journal) with one equivalent of diethylamine at −30° in methylene chloride which gave urea **5** in 76% yield [5]. Treatment of **5**, Scheme II, with excess base and a nucleophile produced products analogous to what was observed under acidic conditions above where the fluorine atoms of the trifluoromethyl group were replaced by the nucleophile present in the reaction mixture. Combination of **5** with excess triethylamine in methanol at room temperature followed by a water work up gave the 4-thiazole methyl ester **6** in 83% yield. Treatment of **5** with excess triethylamine and methanethiol gave the orthothio ester **7** in 75% yield. When **5** was treated with excess diethylamine at room temperature an unusual thiazolidine **8** with two exocyclic double bonds was formed. Structure **8** was confirmed by an X-ray diffraction study, Figure 1. The above results suggest that the labilization of the 4-trifluoromethyl group in 5-nitrogen substituted thiazoles was a general reaction for a variety of nucleophiles taking place under very mild conditions.

A mechanism that explains the products observed in Scheme II is shown below in Scheme III. The first step in the nitrogen assisted labilization of the trifluoromethyl group may involve attack of the base on the urea proton of **5** with subsequent loss of hydrofluoric acid to give **9**, a highly reactive intermediate. Reaction of **9** with a nucleophile would give **10**. Loss of another fluoride would give rise to **11** followed by attack of another nucleophile would

Scheme II



produce **12**. Loss of the last fluoride would give structure **13** which has two exocyclic double bonds. When the nucleophile is a secondary amine (as in the case of **8** Scheme II) the reaction may stop at this point since the carbon that bears the two amines is either too hindered or not electrophilic enough to accept a third nucleophile. This is not the case when the nucleophile is methanol or methanethiol and reaction with a third nucleophile would give the ortho ester structure **14** (see **7** Scheme II). The ortho ester is probably not stable to water when the nucleophile is methanol and would give **15** during the work up (this corresponds to **6** Scheme II).

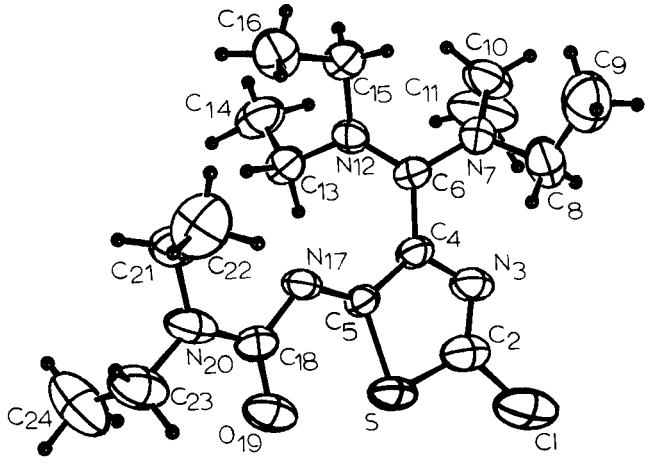
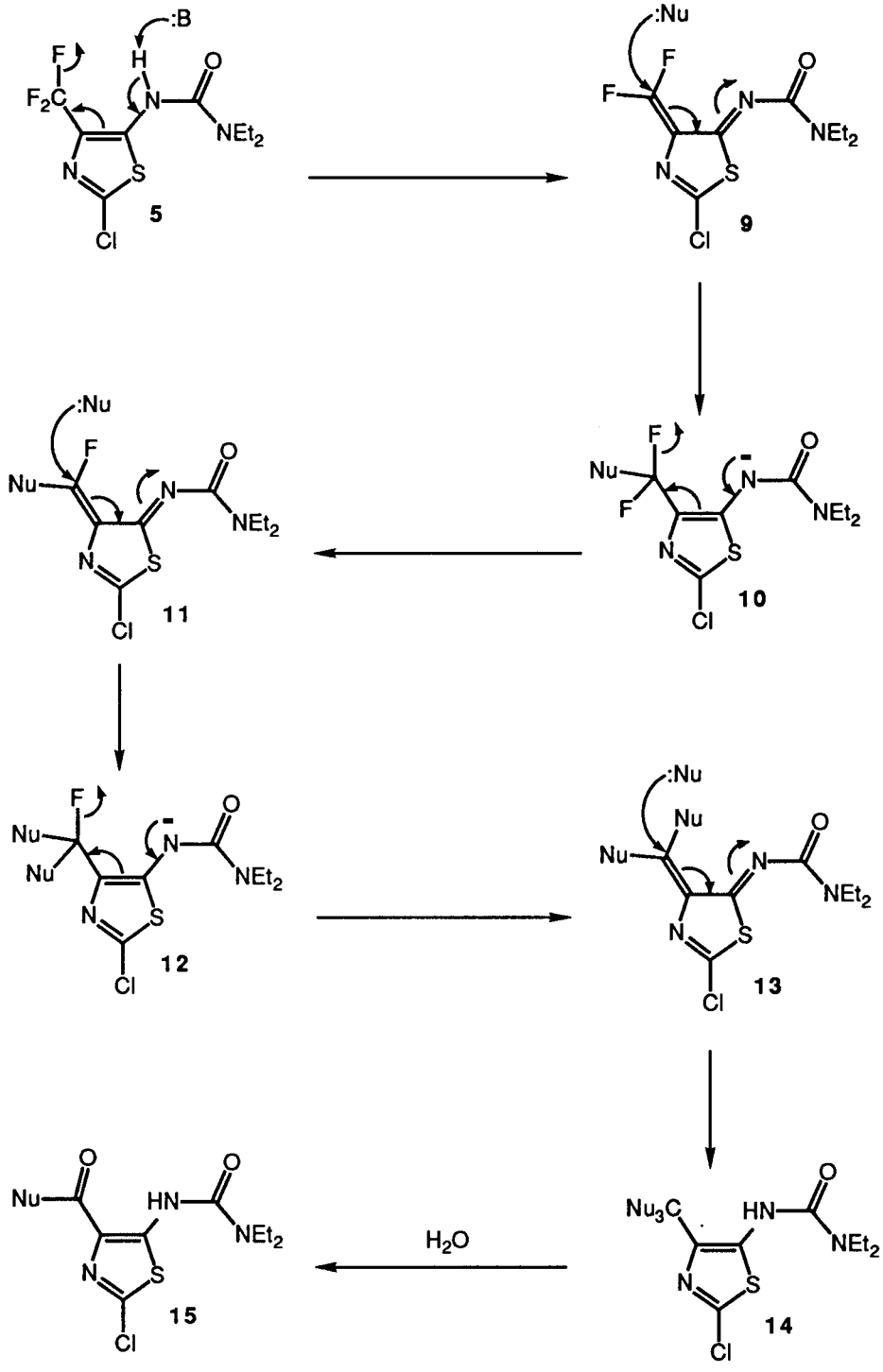


Figure 1

In summary, the 4-trifluoromethyl group of thiazole **5** underwent an unusual labilization that was assisted by the nitrogen substitution at the 5-position of the thiazole. This labilization *via* higly reactive intermediates led to products where the trifluromethyl group was replaced by the nucleophile present in the reaction mixture. The reaction was general for oxygen, sulfur, and nitrogen nucleophiles. We have developed other interesting chemistry around the 4-(trifluoromethyl)thiazole nucleus that will be reported at a future date. Also see the previous [5] and the following paper [8] in this journal.

Scheme III



EXPERIMENTAL

General Methods.

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The 60 MHz ^{1}H nmr were obtained on a Varian EM-360 at 1.4 tesla. The ^{13}C nmr and 360 MHz ^{1}H nmr were obtained on a Bruker WM-360 at 8.4 tesla. Absorptions are expressed in parts per million (δ) with tetramethylsilane or the deuterated solvent as internal reference. Infrared spectra were recorded on a Perkin-Elmer 781 spectrometer, and absorptions are reported in wavenumbers (cm^{-1}). Low-resolution electron impact mass spectra and chemical ionization mass spectra were ob-

tained on a Finnegan MAT CH7A instrument by a direct probe insertion at 70 eV. All mass spectra are electron impact unless noted otherwise. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Preparative separations were effected using a Waters Prep-500 instrument (refractive index detection) or a Harrison Research Chromatotron (uv visualization). All solvents were reagent grade and were obtained from Fisher Scientific. The solvents were used without further drying or purification. All commercially available chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI.

Methyl 2-Chloro-5-amino-4-thiazolecarboxylate (**4**).

Crude **2** (42.3 g, 164 mmoles) and 600 ml of 4:1, 3 *N* hydrochloric acid/methanol were added to a 1 l round-bottomed flask. The mixture was refluxed for 2 hours while monitoring the loss of starting material by tlc. The mixture was then made basic with concentrated ammonium hydroxide and extracted 3 x 400 ml with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvents were removed *in vacuo* and the crude product was recrystallized from ethyl acetate to give 12 g of **4** (38% yield), mp 196-197°; ir (chloroform): cm^{-1} 3460, 3325, 2980, 1675, 1582, 1500, 1445, 1390, 1280, 1135, 1030; ^1H nmr (60 MHz, dimethyl sulfoxide-d_6): δ 7.4 (bs, 2-H), 3.65 (s, 3-H); ms: m/z (relative intensity) 194 (M^+ + 2, 20.19), 192 (M^+, 53.07), 160 (100), 132 (17.95), 124 (11.08), 79 (18.41).

Anal. Calcd. for $C_5H_5ClN_2O_2S$: C, 31.18; H, 2.62; N, 14.54. Found: C, 31.28; H, 2.66; N, 14.51.

Methyl-*N*-2-chloro-4-thiazolecarboxylate-5-*N'*,*N'*-diethylurea (**6**).

Compound **5** (2.0 g, 6.63 mmoles), triethylamine (2.68 g, 26.51 mmoles), and methanol (50 ml) were added to a 100 ml round-bottomed flask. The mixture was stirred a room temperature under nitrogen for 2 hours. The solvent was removed *in vacuo* and the residue was dissolved in ether and filtered. The solvent was removed and the crude compound was chromatographed on the chromatotron using ethyl acetate/cyclohexane mixtures. After this procedure there were two spots present by tlc. This was probably a mixture of the ester and the ortho ester. The mixture was then treated with 50 ml of 1:1 tetrahydrofuran/1.2 *N* hydrochloric acid at room temperature for 30 minutes. The mixture was then partitioned between ether/water. The organic layer was dried (magnesium sulfate), filtered, and the solvents were removed *in vacuo* to give 1.6 g of **6** (83% yield), mp 106-107° from ethyl acetate/cyclohexane; ir (chloroform): cm^{-1} 3300, 3000, 1665, 1545, 1490, 1475, 1445, 1260, 1220; ^1H nmr (360 MHz, deuteriochloroform): δ 10.35 (s, 1-H), 3.80 (s, 3-H), 3.28 (q, J = 7.2 Hz, 4-H), 1.12 (t, = 7.2 Hz, 6-H); ^{13}C nmr (90 MHz, deuteriochloroform): δ 165.08, 152.41, 149.88, 143.08, 122.26, 52.48, 42.26, 13.75; ms: m/z (relative intensity), 293 (M^+ + 2, 7.33), 291 (M^+, 19.66), 187 (6.35), 100 (100), 72 (37.90).

Anal. Calcd. for $C_{10}H_{14}ClN_3O_3S$: C, 41.17; H, 4.84; N, 14.40. Found: C, 41.23; H, 4.87; N, 14.38.

N-2-Chloro-4-[(tris-thiomethyl)methyl]-5-thiazolyl-*N'*,*N'*-diethylurea (**7**).

Compound **5** (2.4 g, 7.95 mmoles), methanethiol (1.91 g, 39.75 mmoles), triethylamine (3.22 g, 31.8 mmoles), and 50 ml of methylene chloride were added to a 100 ml round-bottomed flask. The mixture was stirred under nitrogen at 0° for 30 minutes and then allowed to warm to room temperature and stir for 24 hours. The mixture was partitioned between ether and 1.2 *N* hydrochloric acid. The organic layer was dried (magnesium sulfate), filtered, and the solvents were removed *in vacuo*. The product was recrystallized from ether to give 2.1 g (75% yield) of **7** as a white solid, mp 122-124°; ir (chloroform): cm^{-1} 3320, 3000, 1650, 1535, 1478, 1263; ^1H nmr (360 MHz, deuteriochloroform): δ 8.78 (bs, 1-H), 3.32 (q, J = 8.1 Hz, 4-H), 1.93 (s, 9-H), 1.20 (t, J = 8.1 Hz, 6-H); ^{13}C nmr (90 MHz, deuteriochloroform): δ 152.52, 140.54, 133.20, 130.16, 72.26, 42.21, 14.21, 13.69; ms: m/z (relative intensity, chemical ionization) 388 (M^+ + 2, 7.27), 386 (M^+, 19.48), 338 (100), 292 (29.65).

Anal. Calcd. for $C_{12}H_{20}ClN_3OS_4$: C, 37.34; H, 5.23; N, 10.89. Found: C, 37.43; H, 5.26; N, 10.86.

N-2-Chloro-4-bis-diethylaminomethylene-4,5-dihydro-5-thiazolidene-*N'*,*N'*-diethylurea (**8**).

Compound **5** (2.0 g, 6.63 mmoles), diethylamine (1.45 g, 19.89 mmoles), and methylene chloride (50 ml) were added to a 100 ml round-bottomed flask. The reactants were stirred at room temperature under nitrogen for 3 hours. The organic layer was extracted 3 x 50 ml with water, dried (magnesium sulfate), filtered, and the solvents were removed *in vacuo*. The residue was recrystallized from ether/petroleum ether to give 1.7 g of **8** (66% yield) as a yellow solid, mp 96-97°. An X-ray structure determination was completed for **8**; ir (methylene chloride): cm^{-1} 3050, 2980, 2930, 1575, 1530, 1510, 1440, 1385, 1265; ^1H nmr (360 MHz, deuteriochloroform): δ 3.32 (bq, J = 7.2 Hz, 12-H), 1.0-1.3 (m, 18-H); ^{13}C nmr (90 MHz, deuteriochloroform): δ 166.58, 162.83, 162.75, 138.86, 117.51, 45.39, 40.24, 14.00, 13.56, 13.22; ms: m/z (relative intensity) 389 (M^+ + 2, 2.47), 387 (M^+, 6.46), 352 (13.72), 315 (29.30), 214 (6.64), 186 (9.11), 84 (64.44), 72 (15.73), 56 (70.70); X-ray crystal structure for **8** $C_{17}H_{30}ClN_5OS$, monoclinic, space group $Pca2_1$, (No. 29), with a = 19.445 (7)A, b = 9.254 (2)A, c = 11.718 (5)A, V = 2108.58 (2.11)A^3, Z = 4, and D(Calcd.) = 1.178 g/cm^3. Intensity data were collected in the standard $\theta/2\theta$ scan mode at −130° using graphite monochromatic $Mo_{k\alpha}$ radiation. Final convergence was reached at R_1 = 0.049 and R_w = 0.051 for 1152 reflections with an error in an observation of unit-weight of 1.712.

Anal. Calcd. for $C_{17}H_{30}ClN_5OS$: C, 52.63; H, 7.79; N, 18.05. Found: C, 52.52; H, 7.83; N, 18.05.

Acknowledgements.

Drs. M. Thompson and J. Ogilvie are responsible for the X-ray crystallography results reported here.

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