An Unusual and Simple One-Pot Synthesis of Thiazolo[5,4-d]-thiazoles

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The reaction between ethyl isocyanoacetate and dichlorodisulfane in the presence of triethylamine afforded diethyl thiazolo[5,4-d]thiazole-2,5-dicarboxylate. This reaction provides a useful method for the synthesis of the above ring system.

In a previous paper4 we reported the synthesis of 2-arylthio-5-alkoxyoxazoles by cyclization of S-aryl N-(alkoxycarbonylmethyl)carbonimidochloridothioates, which were easily prepared from alkyl isocyanoacetates 1, arylsulfenyl chlorides, and triethylamine.

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\begin{align*}
\text{ArCl}_2 + \underset{\text{Ref. 1}}{\text{N}} & \underset{\text{OR}}{\text{O}} \quad \rightarrow \\
\text{1a} & \quad R = \text{C}_2\text{H}_5 \\
\text{b} & \quad R = \text{CH}_3
\end{align*}
\]

Analogously, employing dichlorosulfane, 5,5′-dialkoxy-2,2′-bis(oxazolyl) sulfides were obtained.5

\[
\begin{align*}
\text{SCl}_2 + 2 \underset{\text{Ref. 2}}{\text{N}} & \underset{\text{OR}}{\text{O}} \quad \rightarrow \\
\text{1a, b}
\end{align*}
\]

Continuing our studies on the reactivity of alkyl isocyanoacetates 1 toward compounds having S-Cl groups, we attempted the synthesis of 5-diethoxy-2,2′-bis(oxazolyl) disulfide (2) starting from ethyl isocyanoacetate (1a) and dichlorodisulfane.

Although attempts to obtain 2 were unsuccessful, we noted an interesting behavior of ethyl isocyanoacetate (1a) toward dichlorodisulfane. In fact, the reaction between dichlorodisulfane and 1a in the presence of triethylamine afforded an unexpected product which was found to be diethyl thiazolo[5,4-d]thiazole-2,5-dicarboxylate (3). A possible reaction pathway is outlined below.
The formation of intermediate 4 appears to be reasonable because of the high reactivity of S-Cl groups toward isocy- 
 cyanides. The presence of ethoxy carbonylmethyl isothiocya- 
 nate (6) in the reaction mixture accounts for the formation of the intermediate 5. The isolation of product 3 explains the formation of the intermediate 10 and, consequently, that of 9 which can be formed by a 1,3-dipolar cycloaddition of 8 on the C=S bond of 7. A similar reactivity has been described. Compound 3 was also obtained by reacting dichlorosulfane and isocyanide 1a in a 1:1 mole ratio; this represents a further confirmation of the formation of the intermediate 5.

Since we considered the analytical and spectral data of the reaction product as unsuitable to determine its structure, we carried out an X-ray analysis.

The synthesis of 3 has previously been accomplished following a tedious multi-step procedure starting from furfural and dithiooxamide. Therefore, our method provides a convenient synthetic route to the thiazolo[5,4-d]thiazole ring system.

Physical constants and spectra were determined using the following instrumentation. Melting points (uncorrected): Büchi 510; MS: Hewlett Packard 5790 A GC; IR: Perkin-Elmer 283; 1H-NMR.: Perkin-Elmer R-32; 13C-NMR: Varian FT-80 A.

**Diethyl Thiazolo[5,4-d]thiazole-2,5-dicarboxylate (3):**

A solution of dichlorosulfane (2.98 g, 22.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) is added to a solution of ethyl isocyanate (5 g, 44.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) maintaining the temperature at ~50°C. The resulting mixture is allowed to stand, without removing the cooling bath, until the temperature has risen to 10°C, and is then cooled again to ~50°C. Dry triethylamine (4.47 g, 44.2 mmol) is added dropwise and the mixture is stirred, without removing the cooling bath, until the temperature has risen to 10°C, and then filtered. Evaporation of the filtrate leaves a residue which is stirred with a little EtOH to give 3, yield: 1.61 g (52%); colorless needles, m.p. 140–141°C (EtOH) (Lit. 140–141°C).

C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> calc. C 41.95 H 3.52 N 9.78 (286.3) found 41.82 3.40 9.84

MW (osmometric): 281.

MS (70 eV): m/e = 142 (M<sup>+</sup>– 2 CO<sub>2</sub>H<sub>2</sub> + 2 H, 15); 214 (M<sup>+</sup>– CO<sub>2</sub>H<sub>2</sub> + H, 100); 241 (M<sup>+</sup>– OC<sub>2</sub>H<sub>5</sub>, 18); 286 (M<sup>+</sup>, 64).

IR (KBr): ν = 1735; 1450; 1005 cm<sup>-1</sup>.

1H-NMR. (DMSO-d<sub>6</sub>): # = 1.30–1.46 (t, 6 H, CH<sub>3</sub> + CH<sub>3</sub>; 4.34–4.58 (q, 4 H, CH<sub>3</sub> + CH<sub>3</sub>);

13C-NMR (CDCl<sub>3</sub>): δ = 14.00 (C-5 + C-5); 63.25 (C-4 + C-4); 154.19 (C-1 + C-1); 159.37 (C-2 + C-2); 162.03 (C-3 + C-3).

Compound 3 is also obtained by reacting S<sub>2</sub>Cl<sub>2</sub> and 1a in a molar ratio of 1:1 under the same conditions; yield: 40%.

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**Figure 1.** Molecular structure of diethyl thiazolo[5,4-d]thiazole-2,5-dicarboxylate (3) according to X-ray analysis; C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>. In the crystalline state, 3 is centrosymmetric, i.e., the fused heterocycle is planar. Monoclinic, space group P2<sub>1</sub>/a, = 10.889 (1), b = 13.780(1), c = 4.098(1). θ = 90.4°, v = 614.89 Å<sup>3</sup>. Z = 2, D<sub>x</sub> = 1.546 g cm<sup>-3</sup>, μ = 3.82 cm<sup>-1</sup>. 1481 Unique reflections were measured at 189 K on a Philips PW 1100 four-circle diffractometer using Mo Kα monochromatized radiation (λ = 0.7107 Å). θ/2θ scan mode to θ = 25°. 1235 Reflections were considered observed with 1 > 3.5 σ (I). The structure was solved by direct methods (MULTAN). Block-diagonal least-squares (unit weight) were used for the refinement, anisotropic for all the non-hydrogen atoms. The hydrogen atoms were calculated and not refined. The final R value was 0.0456.

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