New Insights on the Reaction of 2-Aminothiazole with Ethyl Bromopyruvate for the Synthesis of 6-Ethoxycarbonylimidazothiazole. Crystal Structure of 5-Acetyl-6-ethoxycarbonylimidazo-[2,1-*b*]thiazole and 2-Ethoxycarbonyl-2-hydroxy-7-oxo-thiazole[2,3-*b*]pyrimido[2,3-*d*]furan

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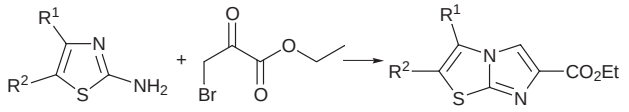
The reaction of 2-aminothiazole **1c** with ethylbromopyruvate yields two by-products **4** and **5**.

2-Aminothiazoles **1** differently substituted at C-4 and C-5 react with ethyl bromopyruvate **2** yielding 6-ethoxycarbonylimidazo[2,1-*b*]thiazoles **3**, which have pharmacological activity (Scheme 1).[1] Here, we describe the reaction of 2-aminothiazole **1c** with ethyl bromopyruvate in chloroform or ethanol under reflux, from which besides the main compound **3c**, already described previously,[2] we also obtained two by-products (**4** and **5**) which were isolated with similar yields and identified. The yields of the isolated products are not significantly affected by the solvent used and were reproducible in all the experiments. For all experiments 40–50% of starting aminothiazole was recovered.

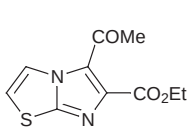


1 **2** **3**

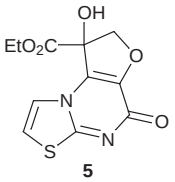
a: R^1 = Me, R^2 = H; **b**: R^1 = H, R^2 = Br; **c**: R^1 = R^2 = H

Scheme 1

The formation of compound **3c** (yield 10%) may be explained by the commonly accepted mechanism, which involves the nucleophilic attack of the endocyclic nitrogen of 2-aminothiazole **1c** on the bromomethylene carbon of the pyruvate and subsequent cyclisation by condensation of the α-ketone of the pyruvate moiety with the amino group of **1c**.[3]



4

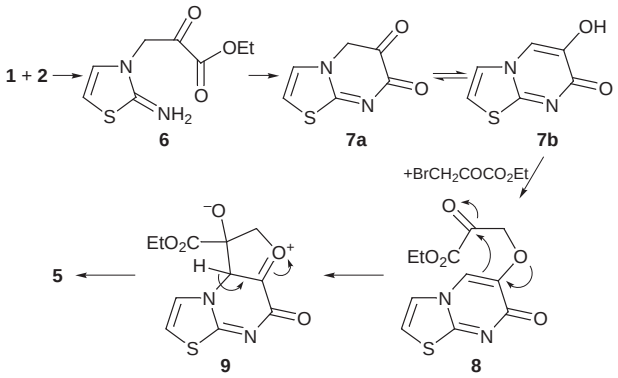


5

The formation of compound **4** (yield 9%) could arise from the reaction of imidazothiazole **3c** with ketene which could be formed from ethyl bromopyruvate in the reaction mixture. At this regard, two experiments were performed by reacting **3c** with ethyl bromopyruvate and ketene, adequately prepared, respectively; in neither case was compound **4** observed. Although we have no experimental evidence, we think that this type of acetylation may be easily explained by invoking the presence of ketene in the reaction mixture.

The structure of compound **4** was determined by X-ray analysis and its spectroscopic data were in accord with the structure found: the IR spectrum shows two absorptions at 1690 and 1630 cm^{-1} which, in comparison with the IR spectrum of **3c**, are due to the EtOC=O and MeC=O groups; the ^{1}H NMR spectrum, excluding the hydrogen at C-5, is similar to that of compound **3c**.

Although compound **5** shows a very simple ^{1}H NMR spectrum, it possesses a very complex structure which was elucidated by X-ray analysis. The spectroscopic data are in agreement with the structure found: the ^{1}H NMR shows a singlet at δ 7.45 for the hydroxy proton at C-2 and two doublets of the protons at C-1 which occur at δ4.98 and 4.50: the non-magnetic equivalence of these protons is due to the adjacent stereogenic center. The IR spectrum shows two intense absorptions at 1740 and 1640 cm^{-1} due to the CO_2Et and N−C=O groups respectively. The formation of **5** (yield 6%) can be easily explained by the reaction steps shown in Scheme 2.



Scheme 2

The intermediate **6**, which is the same as that affording compound **3c**, instead of cyclizing at the α-ketone of the pyruvate moiety, probably condensates at the carbonyl of the carbethoxy group leading to intermediate **7**, which exists in two tautomeric forms **a** and **b**. The enolic tautomeric form **7b** of this intermediate could react with another molecule of ethyl bromopyruvate leading to the final product

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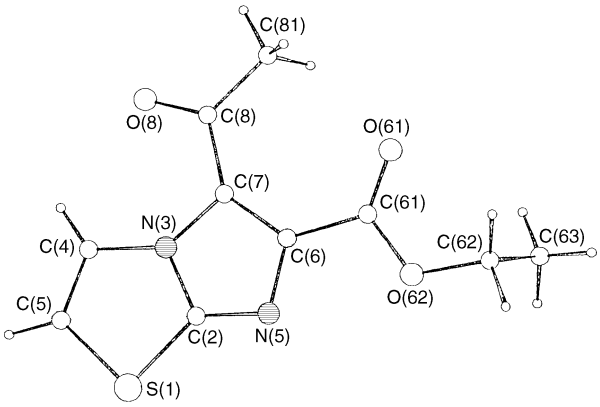

Fig. 1 Perspective view of 5-acetyl-6-ethoxycarbonyl-[2,1-*b*]thiazole **4**

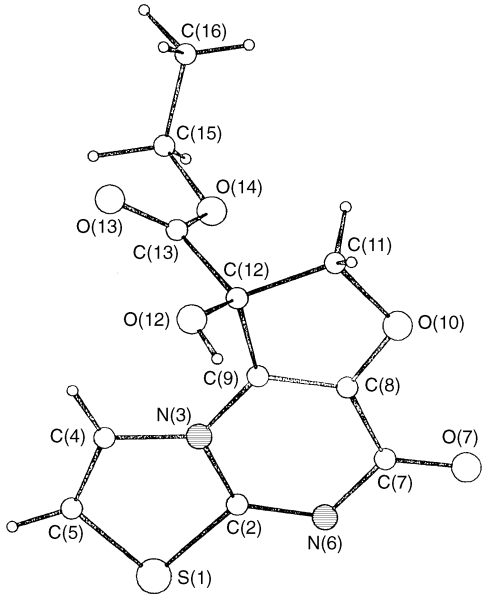

Fig. 2 Perspective view of 2-ethoxycarbonyl-2-hydroxy-7-oxothiazole[2,3-*b*]pyrimido[2,3-*d*]furan **5**

5 *via* intermediates **8** and **9**. The condensation of enol ethers with activated ketones is a well documented process.[5] The reaction was repeated several times in an attempt to isolate, even in small amounts, the key compound **7** not observed previously, but the experiments were unsuccessful.

Molecular Geometry of 5-*Acetyl*-6-*ethoxycarbonylimidazo*-[2,1-b]*thiazole* **4** *and* 2-*Ethoxycarbonyl*-2-*hydroxy*-7-*oxo*-*thiazole*[2,3-b]*pyrimido*[2,3-d]*furan* **5**. Selected bond distances and angles are given in Table 1 (see full text) and perspective views with the arbitrary numbering scheme used in the crystal analysis are shown in Figs 1 and 2 for compounds **4** and **5**, respectively.

The intramolecular bond lengths and angles, in line with the hybridization expected for the atoms involved, compare well with those of analogous compounds reported in literature.[6] Although there are different skeletons for the two molecules, the thiazole ring is very similar in both compounds: the S–C bonds have the same values [1.733(4), 1.733(5) Å in **4**; 1.735(2) and 1.723(4) Å in **5**] intermediate between those expected for a single (1.808 Å) and double bond (1.556 Å), proving that the S lone pair participates in the electronic bonding scheme; moreover even the N–C bonds [1.366(5), 1.398(6) Å in **4**; 1.359(4) and 1.407(3) Å in **5**] are indicative of a high degree of π-delocalized-bonding, being intermediate between a single (1.47 Å) and double (1.29 Å) bond. The bond angles at sulfur [89.7(2) in **4** and 90.9(1)° in **5**] are typical for the thiazole ring as is the C(4)–C(5) bond [1.338(6) and 1.333(5) Å in **4** and **5**, respectively] and the adjacent C–N bond [C(2)–N(5) 1.311(5) and C(2)–N(6) 1.315(3) Å] which have values characteristic for a degree of double bonding.

Analysis of the planarity indicates that only the thiazole ring in **4** is strictly planar while in that of **5** shows significant deviations from planarity: the Cremer and Pople parameters[7,8] indicate that this ring is close to a twist conformation with a *pseudo*-two-fold axis passing through C(4).

Techniques used: ^{1}H NMR, mass spectrometry, IR, crystallography

Table 1: Selected bond distances (Å) and angles (°) with esd's in parentheses for compounds **4** and **5**

Table 2: Experimental data for the X-ray diffraction studies on crystalline compounds **4** and **5**

Experimental: Spectroscopic data of the isolated products; crystal structure of compounds **4** and **5**

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