N-Alkylation in the reactions of 5-imidazolylphenylthiourea with alkyl halides and chloroacetone

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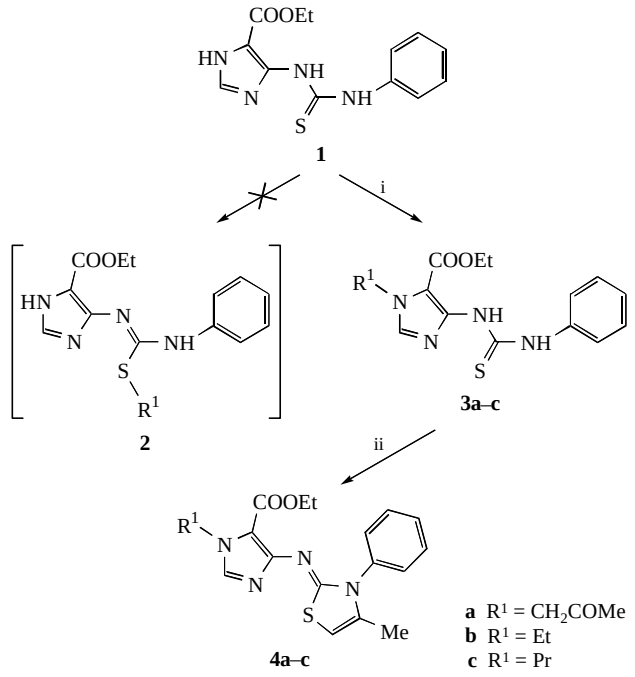
The title reaction resulted in *N*-alkyl imidazolyl derivatives 3 rather than isothiourea 2, and compounds 3 were transformed to imidazolylthiazoles 4 by the subsequent reaction with chloroacetone.

Azolyl-2-thiazoles are of great interest as biologically active compounds.[1,2] The reactions of thioamides and thioureas with -halogenoketones are a classical preparation method for thiazole derivatives.[3] We report here on the syntheses of substituted imidazolylthiazoles, which are structural analogues of antinociceptive antipiryliminothiazoline.[2]

It is well known that thioureas are alkylated at the sulfur atom to give isothioureas,[4] hence one could expect the formation of compound **2** as the product of alkylation of 5-imidazolylphenylthiourea **1** (Scheme 1). However, we found that the alkylation of compound **1** proceeds in a different way to form *N*-alkyl derivatives **3**. The formation of *N*-alkyl derivatives rather than S-alkylated products is confirmed by the ^{1}H NMR spectra, in which the resonance of protons belonging to the N–CH_2–R group was observed at δ 5.25 ppm. However, the presence of four nitrogen atoms in the starting molecule makes it impossible to determine the reaction site by spectroscopy. We performed the reactions of compound **1** with alkyl halides (ethyl iodide and propyl bromide) and chloroacetone and found that in all cases products **3a**–**c** were formed.† To determine their structure, we transformed primary alkylation products **3a**–**c** into bicyclic derivatives **4a**–**c**.‡

A study of compounds **4a**–**c** by NMR spectroscopy using 2D ^{1}H–^{1}H COSY, 2D ^{13}C–^{1}H COSY (*J* 195, 165, 135 and 10 Hz) demonstrated that all of the compounds belong to the same structural type with the same heterocyclic system. X-ray single crystal analysis of *N*-propyl derivative **4c** enabled us to determine its molecular structure§ (Figure 1). According to the X-ray data, the biheterocyclic system of compound **4c** is planar to within ±0.094(3) Å. The bond lengths in the thiazole ring are consistent with the published data for 3- and 4-aryl derivatives of 4-thiazolines.[6] The phenyl group and the thiazole ring are not conjugated, and the dihedral angle between the planes is 75.7(1)°. The ester moiety lies in the plane of the imidazole fragment [the dihedral angle N(4)–C(13)–C(14)–O(1) is 5.1(1)°] and is conjugated with the heterocycle, although the C(13)–C(14) bond [1.444(5) Å] is somewhat shorter than the average value 1.464(18) Å for the conjugated bonds (N)=C_{sp^2}–C_{sp^2}(=O) of the same type.[7]



Scheme 1 *Reagents and conditions*: i, DMF, Et_3N, AlkHal, 25 °C, 12 h; ii, DMF, Et_3N, $ClCH_2COMe$, 70 °C, 24 h.

Thus, we found that the successive treatment of 5-imidazolyl-

† An alkyl halide (0.76 mmol) was added to a solution of imidazolylthiourea **1** (0.2 g, 0.69 mmol, prepared according to the known method[5]) in a mixture of DMF (1.5 ml) and Et_3N (0.1 ml, 0.76 mmol), and the reaction mixture was stirred at room temperature for 12 h and then poured into ice-cold water (25 ml). White crystals were filtered off, washed with ethanol and dried to give compounds **3a**–**c** in 50–80% yields.[2]

3a: yield 50%, mp 108–109 °C. ^{1}H NMR (Bruker WM-250, 250 MHz, $CDCl_3$) δ: 12.29 (s, 1H, NH), 9.31 (s, 1H, NH), 7.93 (s, 1H, $H_{imid.}$), 7.69–7.21 (m, 5H, H_{Ar}), 5.25 (s, 2H, NCH_2), 4.30 (q, 2H, OCH_2, *J* 7.02 Hz), 2.22 (s, 3H, Me), 1.30 (t, 3H, Me, *J* 7.02 Hz). Found (%): C, 55.77; H, 5.00; N, 15.98; S, 9.07. Calc. for $C_{16}H_{18}N_4O_3S$ (%): C, 55.49; H, 5.20; N, 16.18; S 9.25.

3b: yield 80%, mp 118–119°C. Found (%): C, 56.37; H, 5.80; N, 17.42; S 9.87. Calc. for $C_{15}H_{18}N_4O_2S$ (%): C, 56.60; H, 5.66; N, 17.61; S, 10.06.

3c: yield 75%, mp 96–97 °C. Found (%): C, 58.03; H, 5.90; N, 17.08; S, 9.77. Calc. for $C_{16}H_{20}N_4O_3S$ (%): C, 57.83; H, 6.02; N, 16.87; S, 9.64.

‡ A mixture of compound **3** (0.66 mmol), Et_3N (0.79 mmol), chloroacetone (0.79 mmol) and DMF (1.5 ml) was heated at 70 °C for 24 h. The resulting mixture was poured into water, the precipitate was separated by filtration and purified by crystallization from 95% ethanol to afford compounds **4** in 35–39% yield.

4a: yield 36%, mp 173–174 °C. ^{1}H NMR (Bruker DRX-500, 500 MHz, $CDCl_3$) δ: 7.50–7.33 (m, 5H, H_{Ar}), 7.45 (s, 1H, $H_{imid.}$), 5.95 (br. s, 1H, $H_{thiaz.}$, *J* 1.2 Hz), 4.89 (s, 2H, NCH_2), 4.00 (q, 2H, OCH_2, *J* 7.02 Hz), 2.17 (s, 3H, Me), 1.90 (d, 3H, Me, *J* 1.2 Hz), 1.33 (t, 3H, Me, *J* 7.02 Hz), 0.94 (t, 3H, Me, *J* 7.02 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.78, 161.65, 161.53, 151.91, 138.40, 137.76, 133.87, 129.30, 128.83, 109.52, 128.40, 99.10, 59.67, 56.10, 26.76, 15.02, 13.88. Found (%): C, 59.57; H, 5.08; N, 14.33; S, 8.20. Calc. for $C_{19}H_{20}N_4O_3S$ (%): C, 59.37; H, 5.21; N, 14.58; S, 8.33.

4b: yield 35%, mp 163–164 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.54–7.33 (m, 5H, H_{Ar}), 7.45 (s, 1H, $H_{imid.}$), 5.93 (br. s, 1H, $H_{thiaz.}$, *J* 1.2 Hz), 4.29 (q, 2H, OCH_2, *J* 7.02 Hz), 4.04 (q, 2H, NCH_2, *J* 7.02 Hz), 1.88 (d, 3H, Me, *J* 1.2 Hz), 1.33 (t, 3H, Me, *J* 7.02 Hz), 0.94 (t, 3H, Me, *J* 7.02 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.48, 161.00, 152.08, 137.81, 136.80, 133.96, 136.80, 129.35, 128.91, 128.44, 99.00, 59.54, 42.73, 16.52, 15.19, 13.99. Found (%): C, 60.49; H, 5.81; N, 15.52; S, 9.17. Calc. for $C_{18}H_{20}N_4O_2S$ (%): C, 60.67; H, 5.62; N, 15.73; S, 8.99.

4c: yield 39%, mp 158–159 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.54–7.34 (m, 5H, H_{Ar}), 7.44 (s, 1H, $H_{imid.}$), 5.95 (br. s , 1H, $H_{thiaz.}$, *J* 1.2 Hz), 4.16 (t, 2H, NCH_2, *J* 7.03 Hz), 4.04 (q, 2H, OCH_2, *J* 7.02 Hz), 1.89 (d, 3H, Me, *J* 1.2 Hz), 1.73 (m, 2H, CH_2), 0.95 (t, 3H, Me, *J* 7.02 Hz), 0.85 (t, 3H, Me, *J* 7.02 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.37, 161.11, 152.37, 137.89, 137.53, 133.77, 129.82, 128.86, 128.32, 109.47, 98.77, 59.44, 49.32, 23.98, 15.20, 13.93, 10.73. Found (%): C, 61.80; H, 6.10; N, 15.08; S, 8.77. Calc. for $C_{19}H_{22}N_4O_2S$ (%): C, 61.62; H, 5.95; N, 15.14; S, 8.65.

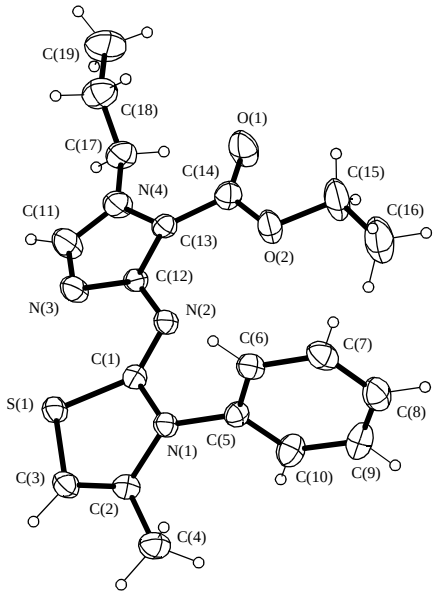


Figure 1 Molecular structure of ethyl 5-(4-methyl-3-phenyl-3*H*-thiazol-2-ylideneamino)-3-propyl-3*H*-imidazole-4-carboxylate **4c** according to X-ray single crystal analysis. Selected bond lengths (Å): S(1)–C(1) 1.761(3), C(1)–N(1) 1.382(4), N(1)–C(2) 1.409(4), C(2)–C(3) 1.326(4), S(1)–C(3) 1.735(3), C(1)–N(2) 1.288(4), N(2)–C (12) 1.382(4), C(12)–C(13) 1. 392(4), C(13)–N(4) 1.393(4), C(13)–C (14) 1.444(5), N(4)–C (11) 1.330(5), C(11)–N(3) 1.310(5), C(12)–N(3) 1.352(4); selected bond angles (°): C(1)–S(1)–C(3) 90.8(1), S(1)–C(1)–N (1) 108.3(2), C(1)–N(1)–C (2) 115.6(2), N(1)–C(2)–C(3) 111.4(3), S(1)–C(3)–C(2) 113.9(2), C(11)–N(3)–C(12) 105 .2(3), N(3)–C(12)–C(13) 110.0(3), C(12)–C(13)–N(4) 105.0(3), C(13)–N(4)–C (11) 105.8(3), N(3)–C(11)–N(4) 114.0(3).

§ 3561 independent reflections were measured on a Bruker P4 diffractometer with graphite monochromated MoK radiation using $\theta/2\theta$ scans with $\theta < 25°$. The crystal system of compound **4c** (Figure 1) is monoclinic, space group $P2_1/c$, a = 18.185(1), b = 10.5689(7), c = 10.0401(7) Å, β = = 92.216(6)°, V = 1928.3(2) Å^3, $C_{19}H_{22}N_4O_2S$, M = 370.47, Z = 4, d_{calc} = = 1.276 g cm^{-3}, μ = 0.188 mm^{-1}, $F(000)$ = 784, crystal size 0.16×0.42×0. 52 mm. The structure was solved by the Patterson method (SHELXS-97) and refined in the anisotropic–isotropic approximation using SHELXL-97 to wR_2 = 0.1790, S = 1.000 for all reflections (R = 0.0563 for 2384 $F > 4\sigma$). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/70.

phenylthiourea with alkyl halides and chloroacetone leads to substituted esters of 4-(4-methyl-3-phenyl-3*H*-thiazole-2-ylideneamino)-3*H*-imidazole-5-carboxylic acid.

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