Reactions of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid and its esters with amines. The inverse of reactivity in a pyrimidine ring

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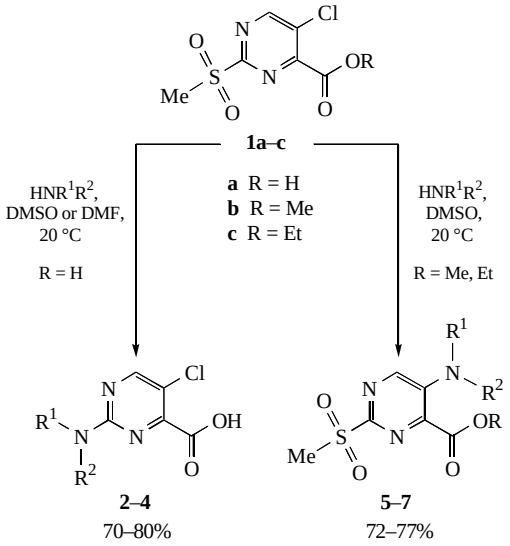
Reactions of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid with aliphatic amines afford 2-amino-5-chloro-4-pyrimidinecarboxylic acid, whereas 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylates form 5-amino-2-methylsulfonyl-4-pyrimidinecarboxylates under the same conditions.

As continuation of our work on the behaviour of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid derivatives towards nucleophiles,[1] we report here the reactions of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid **1a** and its esters **1b**,**c** with amines. Because of an electron-withdrawing effect of the aza group, the C-2, C-4 and C-6 positions of the pyrimidine ring show an enhanced activity towards nucleophilic reagents. It is well known that nucleophilic substitution for a halogen at the C-5 position of the pyrimidine ring is difficult to perform, unlike the C-4 and C-2 positions.[2] Therefore, in polysubstituted pyrimidines, a halogen at the 5-position is replaced last, and severe conditions are required to carry out this reaction.



Scheme 1

The reaction between acid **1a** and aliphatic amines *via* substitution for the methylsulfonyl group resulted in previously unknown[3] 2-amino-5-chloro-4-pyrimidinecarboxylic acids **2**–**4**.† The ^{1}H NMR spectra ([$^2H_6$]acetone) of compounds **2**–**4** show the presence of an amine moiety, along with a singlet at 8.42–8.48 ppm assigned to the C-6 proton of the pyrimidine ring. The IR spectra of **2**–**4** exhibit absorption bands at 1720–1700 cm^{-1}, which were ascribed to unionised carbonyl group stretching modes, and an absorption band of NH stretching modes around 3300 cm^{-1} for compound **4**. Thus, the betaine form was not observed for amino acids **2**–**4** in the solid state.

5-Chloro-2-methylsulfonyl-4-pyrimidinecarboxylates **1b**,**c** exhibited a different behaviour under the same conditions. In the reactions with amines, nucleophilic substitution at the C-5 position took place with the formation of esters of hitherto unknown 5-amino-2-methylsulfonyl-4-pyrimidinecarboxylic acids **5**–**7**.‡ The structures of these compounds were assigned on the basis of analytical and spectroscopic data. The above reaction is a rare example of the regioselective replacement of a halogen at the 5-position of a pyrimidine ring in the presence of another good leaving group.[4] The reaction was conducted in dimethyl sulfoxide at ambient temperature, and the reaction mixture spontaneously warmed up to 50–60 °C. The ease of substitution for a chlorine atom in compounds **1b**,**c** can be explained by the activation of the C-5 position of the pyrimidine ring by both methylsulfonyl (σ_p = 0.72)[5] and ester groups.

In the former case (R = OH), the anion of acid **1a** reacts, and only the methylsulfonyl group activates the C-5 position. Therefore, a nucleophilic attack takes place on the second position, as it was expected.

† *Preparation of 2-amino-5-chloro-4-pyrimidinecarboxylic acids* **2**–**4**. To a solution of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid **1a** (3 mmol) in 6 ml of DMSO or DMF a corresponding amine (3 mmol) and triethylamine (6 mmol) were added. The reaction mixture was allowed to stand at ambient temperature for 24 h; then, 25–30 ml of water was added, and the mixture was acidified with hydrochloric acid to pH 5–6. The solid precipitated for 2–8 h was isolated by filtration, dried and recrystallised from aqueous ethanol, if needed.

5-Chloro-2-pyrrolidino-4-pyrimidinecarboxylic acid **2**: yellow solid, yield 81%, mp 160–161 °C (decomp.). ^{1}H NMR (100 MHz, [$^2H_6$]acetone) δ: 8.45 (s, 1H, H-6), 3.64–3.47 (m, 4H, CH_2–N–CH_2), 2.1–1.92 (m, 4H, CH_2CH_2). IR (KBr, ν/cm^{-1}): 1710 (COOH). Found (%): C, 47.6; H, 4.3; N, 18.4. Calc. for $C_9H_{10}ClN_3O_2$ (%): C, 47.48; H, 4.43; N, 18.46.

5-Chloro-2-morpholino-4-pyrimidinecarboxylic acid **3**: yellow solid, yield 70%, mp 119.5–120.5 °C (decomp.). ^{1}H NMR (100 MHz, [$^2H_6$]-acetone) δ: 8.48 (s, 1H, H-6), 3.85–3.62 (m, 8H, morpholine CH_2). IR (KBr, ν/cm^{-1}): 1705 (COOH). Found (%): C, 44.3; H, 4.3; N, 17.4. Calc. for $C_9H_{10}ClN_3O_3$ (%): C, 44.37; H, 4.14; N, 17.25.

5-Chloro-2-phenethylamino-4-pyrimidinecarboxylic acid **4**: yellow solid, yield 75%, mp 171.5–172.5 °C (decomp.). ^{1}H NMR (100 MHz, [$^2H_6$]acetone) δ: 8.43 (s, 1H, H-6), 7.26 (m, 5H, H_{arom}), 6.88 (br. s, 1H, NH), 3.67 (m, 2H, CH_2CH_2NH), 2.95 (t, 2H, CH_2CH$_2$NH). IR (KBr, ν/cm^{-1}): 1710 (COOH), 3290 (NH). Found (%): C, 56.3; H, 4.5; N, 15.1. Calc. for $C_{13}H_{12}ClN_3O_2$ (%): C, 56.23; H, 4.36; N, 15.13.

‡ *Preparation of 5-amino-2-methylsulfonyl-4-pyrimidinecarboxylates* **5**–**7**. To a solution of the methyl or ethyl ester of 5-chloro-2-methylsulfonyl-4-pyrimidinecarboxylic acid **1b** or **1c** (3 mmol) in 5 ml of DMSO a corresponding amine (3 mmol) and triethylamine (3 mmol) were added. The reaction mixture was allowed to stand at ambient temperature for 5–10 h; then, 40 ml of water was added, and the mixture was acidified with hydrochloric acid to pH 6–7. The precipitate was filtered off, dried and recrystallised from ethanol.

Ethyl 2-methylsulfonyl-5-pyrrolidino-4-pyrimidinecarboxylate **5**: white solid, yield 74%, mp 134.5–135.5 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 8.78 (s, 1H, H-6), 4.47 (q, 2H, OCH_2Me), 3.64–3.47 (m, 4H, CH_2–N–CH_2), 3.20 (s, 3H, SO_2Me), 2.1–1.92 (m, 4H, CH_2CH_2), 1.41 (t, 3H, OCH$_2$*Me*). IR (KBr, ν/cm^{-1}): 1730 (CO), 1130, 1300 (SO_2). Found (%): C, 48.0; H, 5.8; N, 14.1. Calc. for $C_{12}H_{17}N_3O_4S$ (%): C, 48.15; H, 5.72; N, 14.04.

Methyl 2-methylsulfonyl-5-morpholino-4-pyrimidinecarboxylate **6**: white solid, yield 77%, mp 135–136 °C. ^{1}H NMR (100 MHz, [$^2H_6$]acetone) δ: 8.77 (s, 1H, H-6), 3.94 (s, 3H, OMe), 3.96–3.62 (m, 8H, morpholine CH_2), 3.24 (s, 3H, SO_2Me). IR (KBr, ν/cm^{-1}): 1730 (CO), 1130, 1300 (SO_2). Found (%): C, 43.8; H, 4.9; N, 13.9. Calc. for $C_{11}H_{15}N_3O_5S$ (%): C, 43.85; H, 5.02; N, 13.95.

Ethyl 2-methylsulfonyl-5-diethylamino-4-pyrimidinecarboxylate **7**: white solid, yield 72%, mp 103–104 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 8.74 (s, 1H, H-6), 4.43 (q, 2H, OCH_2Me), 3.66 (q, 4H, CH_2–N–CH_2), 3.19 (s, 3H, SO_2Me), 1.39 (t, 3H, OCH$_2$*Me*), 1.18 (t, 6H, NCH$_2$*Me*). IR (KBr, ν/cm^{-1}): 1730 (CO), 1130, 1300 (SO_2). Found (%): C, 47.9; H, 6.5; N, 14.0. Calc. for $C_{12}H_{19}N_3O_4S$ (%): C, 47.83; H, 6.35; N, 13.94.

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