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THE POSSIBLE SYNTHESIS OF (3-ALKOXYCARBONYL-METHYL-4-OXO-3,4-DIHYDRO-2-PYRIMIDINYLSULFANYL) ACETATE ESTERS

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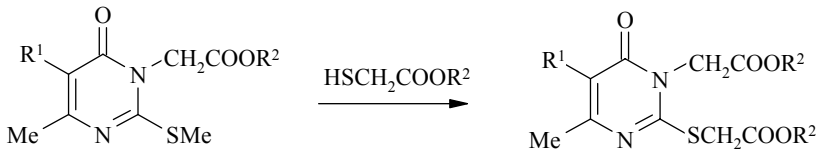
Compounds with alkoxycarbonylmethyl groups in adjacent positions in a pyrimidine ring can be used as synthons in the preparation of polycyclic heterosystems. Our previous attempt [1] to synthesize pyrimidine derivatives having S- and N-alkoxycarbonylmethyl groups respectively in positions 2 and 3 of the ring by alkylation of the corresponding 4-hydroxy-2-mercaptopyrimidine or methyl 4-hydroxy-2-methoxycarbonyl-methylsulfanylacetate with methyl bromoacetate were unsuccessful since only the S- or N-dialkylation product was formed. Continuing our work in this area we have found that compounds **2a,b** can be prepared by treating the corresponding 2-methylsulfanyl derivatives **1a,b** with methyl or ethyl mercaptoacetate in the presence of base:



1a,b **2a,b**

1,2 a R^1 = Br, R^2 = Me; **b** R^1 = NO_2, R^2 = Et

It should be noted that compound **2a** was obtained by refluxing compound **1a** in *tert*-butanol with methyl mercaptoacetate in the presence of potassium *tert*-butylate whereas treatment of compound **1b** with ethyl mercaptoacetate under the same conditions gave a complex mixture of products, from which pure compounds could not be separated. Compound **2b** was prepared with the use of triethylamine as base.

IR spectra were obtained on a Perkin-Elmer BX FT-IR spectrometer for KBr tablets. ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Unity Inova instrument (300 and 75 MHz respectively) using $CDCl_3$ relative to TMS.

Compound **1a** was prepared as described before [2].

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Ethyl 6-methyl-2-methylsulfanyl-5-nitro-4-oxo-3,4-dihydro-3-pyrimidinylacetate (1b). HNO_3 (d = 1.45, 0.88 g, 14 mmol) was added dropwise at room temperature to a solution of ethyl 6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinylacetate [3] (2.42 g, 10 mmol) in conc. H_2SO_4 (10 ml). The product was stirred for 0.5 h and poured onto ice. The precipitate formed was filtered off, washed with water, and recrystallized from methanol to give the product (1.95 g, 68%) with mp 140-141°C. IR spectrum, ν, cm^{-1}: 1688, 1743 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.33 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); 2.48 (3H, s, CH_3); 2.69 (3H, s, SCH_3); 4.3 (2H, q, J = 7.1, $C\underline{H}_2CH_3$); 4.87 (2H, s, NCH_2). ^{13}C NMR spectrum, δ, ppm: 14.3, 15.6, 21.7, 45.6, 62.8, 134.7, 154.4, 158.0, 164.5, 165.7. Found, %: C 41.97; H 4.48; N 14.81. $C_{10}H_{13}N_3O_5S$. Calculated, %: C 41.81; H 4.56; N 14.63.

Methyl 5-bromo-3-methoxycarbonylmethyl-6-methyl-4-oxo-3,4-dihydro-2-pyrimidinylsulfanylacetate (2a). A solution of compound **1a** (1.54 g, 5 mmol) in absolute *tert*-butanol (15 ml) was refluxed under a nitrogen atmosphere for 15 min. A solution prepared from methyl mercaptoacetate (0.53 g, 5 mmol), potassium (0.2 g, 5 mmol), and absolute *tert*-butanol (10 ml) was then added dropwise. The reaction mixture was refluxed for 2 h with stirring, cooled to room temperature, and several drops of water were added. The precipitate formed was filtered off, dried, and recrystallized from benzene to give the product (1.03 g, 56%) with mp 134-135°C. IR spectrum, ν, cm^{-1}: 1688, 1740 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.45 (3H, s, CH_3); 3.81 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.99 (2H, s, SCH_2); 4.88 (2H, s, NCH_2). ^{13}C NMR spectrum, δ, ppm: 24.9, 34.7, 46.2, 53.2, 53.3, 108.1, 157.7, 158.4, 161.2, 166.7, 168.4. Found, %: C 35.92; H 3.58; N 7.43. $C_{11}H_{13}BrN_2O_5S$. Calculated, %: C 36.18; H 3.59; N 7.67.

Ethyl 3-ethoxycarbonylmethyl-6-methyl-5-nitro-4-oxo-3,4-dihydro-2-pyrimidinylsulfanylacetate (2b). A solution of compound **1b** (1.44 g, 5 mmol) in absolute *tert*-butanol (45 ml) was stirred at 70°C under a nitrogen atmosphere for 15 min. A solution prepared from ethyl mercaptoacetate (0.6 g, 5 mmol) , triethylamine (0.51 g, 5 mmol), and absolute *tert*-butanol (10 ml) was added dropwise. The reaction mixture was stirred for 4.5 h at 70°, evaporated to one third volume, cooled to room temperature, and water (3 ml) was added. A mixture of compounds was obtained (1.26 g) and this was dissolved in a mixture of chloroform and ethyl acetate (20 : 1) and then separated on a Kieselgel silica gel chromatographic column (Kieselgel 60, 0.063-0.200 mm) to give the starting compound **1b** (0.44 g, 31%) with R_f 0.47 and compound **2b** (0.64 g, 36%) with R_f 0.4 (Alugram SIL G/UV_{254}, chloroform-ethyl acetate, 20: 1). Mp 102-104°C. IR spectrum, ν, cm^{-1}: 1695, 1739, 1753 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.30-1.37 (6H, m, 2 $CH_2C\underline{H}_3$); 2.44 (2H, s, SCH_2); 4.26-4.32 (4H, m, 2 $C\underline{H}_2CH_3$); 4.88 (2H, s, NCH_2). ^{13}C NMR spectrum δ, ppm: 14.3, 14.4, 21.5, 35.0, 45.8, 62.6, 62.9, 148.0, 154.2, 157.7, 162.6, 165.4, 167.3. Found, %: C 43.38; H 4.92; N 11.65. $C_{13}H_{17}N_3O_7S$. Calculated, %: C 43.45; H 4.77; N 11.69.

REFERENCES

1. V. Syadyaryavichyute and P. Vainilavicius, *Chemija (Vilnius)*, 70 (1993).
2. P. Vainilavichyus, V. Syadyaryavichiute, and S. Mocishkite, *Khim. Geterotsikl. Soedin.*, 1655 (1992). [*Chem. Heterocycl. Comp.*, **28**, 1420 (1992)].
3. V. Jakubkiene, M. M. Burbuliene, E. Udrenaite, V. Garaliene, and P. Vainilavichyus (Vainilavicius), *Pharmazie*, **57**, 610 (2002).