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SYNTHESIS AND REACTIONS OF (6-METHYL-2-METHYLSULFANYL-4-OXO-3,4-DIHYDRO-3-PYRIMIDINYL)ACETYL AZIDE

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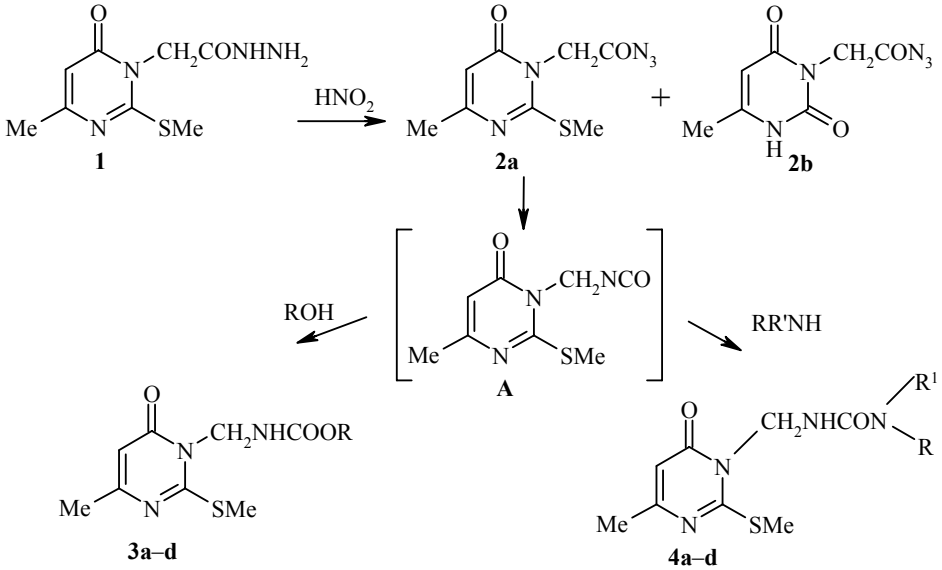
Nitrosation of (6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)acetic acid hydrazide using sodium nitrite in acid medium gave the corresponding azide. Reaction of the latter with alcohols or phenols gave carbamates and with amines gave carbamides.

Keywords: acyl azides, hydrazides, carbamates, carbamides, pyrimidines.

We have previously prepared the (6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)acetic acid hydrazide (**1**) [1] and studied its intramolecular cyclization [2] and reaction with C-electrophiles [3,4] in order to synthesize compounds which show cardiotonic [3] and anti-inflammatory [4] activity. However, this investigation has far from exhausted the synthetic potential of the given compound. Since the nitrosation of acylhydrazines using sodium or potassium nitrite in acid medium is one method for preparing acyl azides [5-10] (which are of interest as reactive intermediates in the synthesis of various compounds) we considered this method suitable for the synthesis of (6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)acetyl azide (**2a**) and the study of some of its reactions.



3 a R = Me, **b** R = Et, **c** R = Ph, **d** R = C_6H_4Cl-4, **4a** R = Bu, R^1 = H;
b R = Bz, R^1 = H; **c** R = R^1 = Pr; **d** R + R^1 = $(CH_2)_4O$

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Azide **2a** was prepared by the nitrosation of the hydrazide **1** using sodium nitrite at 0-5°C in 50% acetic acid (method A) or in dilute hydrochloric acid (method B). The use of hydrochloric acid in method B led to a small amount of the azide **2b** in addition to the target compound **2a**. In this case the greater strength of the hydrochloric compared with acetic acid can evidently cause fission of the C–S bond, as noted by us before [1].

A Curtius rearrangement was carried out by refluxing the azide **2a** in absolute benzene. However the isocyanate **A** could not be isolated in the pure state, apparently due to its tendency to polymerize. The Curtius rearrangement of the azide **2a** was used to prepare the carbamate **3** and carbamide **4** derivatives of the isocyanate **A**.

Refluxing the azide **2a** with absolute methanol or ethanol gave the carbamates **3a,b** and phenol and 4-chlorophenol in absolute benzene the carbamates **3c,d**. The carbamides **4a-d** were separated after refluxing the azide **2a** for 4 h in absolute benzene and the addition of the corresponding amine to the solution of the isocyanate **A** formed *in situ*. It should be noted that, in reverse order to their nucleophilicity, butyl- and benzylamine form the carbamides **4a,b** straight after addition of the amine but dipropylamine and morpholine form the carbamides **4c,d** after refluxing the reaction mixture for 2 h.

The IR spectrum of azide **2b** contains bands for the lactam $C_{(4)}$=O group at 1634 cm^{-1} and $C_{(2)}$=O at 1741 cm^{-1} which is typical of uracils [11, 12] and the IR spectra of compounds **2a, 3** and **4** show a band for the lactam $C_{(4)}$=O group at 1625-1678 cm^{-1} which is characteristic of $N_{(3)}$-substituted 2-alkylthiopyrimidin-4-ones [13, 14]. In the IR spectra of the azides **2a,b** the absorption band of the azide group is found at 2150-2154 cm^{-1} and the acetyl C=O group in the region of 1716 cm^{-1}. For the carbamates **3** and carbamides **4**, the IR absorption bands of the C=O groups are in the region 1720-1747 and 1685-1695 cm^{-1} and for the NH groups at 3205-3299 and 3323-3364 cm^{-1} respectively.

The ^{1}H NMR spectra of the carbamates **3** and carbamides **4** show, along with the signals for the remaining protons, the presence of doublets for the protons of the NCH_2 groups at 5.38-5.51 ppm and multiplets for the NH group protons at 5.80-6.83 ppm.

A study of the anti-inflammatory activity by E. Udrenaite (Medical Faculty, Vilnius University) has shown that the carbamides **4** suppress the anti-inflammatory process to a similar degree as acetylsalicylic acid.

TABLE 1. Characteristics for the Synthesized Compound **3, 4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_9H_{13}N_3O_3S$	44.62 / 44.43	5.26 / 5.35	17.25 / 17.27	124-126	69
3b	$C_{10}H_{15}N_3O_3S$	50.01 / 49.72	5.97 / 6.26	17.57 / 17.41	96-97	55
3c	$C_{14}H_{15}N_3O_3S$	55.35 / 55.07	4.67 / 4.95	13.87 / 13.76	132-134	84
3d	$C_{14}H_{14}ClN_3O_3S$	49.74 / 49.49	3.86 / 4.15	12.51 / 12.36	141-142	84
4a	$C_{12}H_{20}N_4O_2S$	50.86 / 50.68	6.74 / 7.09	19.78 / 19.73	154-157	52
4b	$C_{15}H_{18}N_4O_2S$	56.77 / 56.59	5.52 / 5.70	17.61 / 17.60	161-163	49
4c	$C_{14}H_{24}N_4O_2S$	54.12 / 53.82	7.75 / 7.74	17.99 / 17.93	97-98	76
4d	$C_{12}H_{18}N_4O_3S$	48.10 / 48.31	6.28 / 6.08	18.86 / 18.78	190-192	44

TABLE 2. IR and ^{1}H NMR Spectroscopic Data for Compounds **3, 4**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum($CDCl_3$), δ, ppm (*J*, Hz)
3a	3284 (NH); 1733 (C=O); 1678 ($C_{(4)}$=O)	2.23 (3H, s, CH_3); 2.58 (3H, s, SCH_3); 3.71 (3H, s, OCH_3); 5.40 (2H, d, *J* = 7, NCH_2); 6.03 (1H, s, CH); 5.94-6.28 (1H, m, NH)*
3b	3299 (NH); 1720 (C=O); 1649 ($C_{(4)}$=O)	1.24 (3H, t, *J* = 7, CH_3); 2.23 (3H, s, CH_3); 2.58 (3H, s, SCH_3); 4.15 (2H, q, *J* = 7, OCH_2); 5.38 (2H, d, *J* = 8, NCH_2); 6.05 (1H, s, CH); 5.92-6.23 (1H, m, NH)*
3c	3205 (NH); 1745 (C=O); 1657 ($C_{(4)}$=O)	2.25 (3H, s, CH_3); 2.57 (3H, s, SCH_3); 5.51 (2H, d, *J* = 8, NCH_2); 6.08 (1H, s, CH); 6.29-6.77 (1H, m, NH); 7.00-7.46 (5H, m, H_{arom})
3d	3267 (NH); 1747 (C=O); 1674 ($C_{(4)}$=O)	2.25 (3H, s, CH_3); 2.57 (3H, s, SCH_3); 5.49 (2H, d, *J* = 8, NCH_2); 6.07 (1H, s, CH); 6.44-6.77 (1H, m, NH); 7.08 (2H, d, *J* = 10, H_{arom}); 7.31 (2H, d, *J* = 10, H_{arom})
4a	3329 (NH); 1695 (C=O); 1627 ($C_{(4)}$=O)	0.77-1.06 (3H, m, CH_3); 1.15-1.67 (4H, m, CH_2); 2.22 (3H, s, CH_3); 2.57 (3H, s, SCH_3); 3.17 (2H, q, *J* = 7, $NH\underline{CH_2}$); 5.4 (2H, d, *J* = 8, NCH_2); 6.02 (1H, s, CH); 6.12-6.49 (2H, m, NH)
4b	3323 (NH); 1695 (C=O); 1625 ($C_{(4)}$=O)	2.14 (3H, s, CH_3); 2.56 (3H, s, SCH_3); 4.38 (2H, d, *J* = 7, $NH\underline{CH_2}$); 5.43 (2H, d, *J* = 8, NCH_2); 5.65 (1H, s, CH); 6.46-6.83 (2H, m, NH); 7.12-7.42 (5H, m, H_{arom})
4c	3364 (NH); 1687 (C=O); 1638 ($C_{(4)}$=O)	0.86 (6H, t, *J* = 8, CH_3); 1.50 (4H, q, *J* = 8, CH_2); 2.21 (3H, s, CH_3); 2.54 (3H, s, SCH_3); 3.13 (4H, q, *J* = 8, $NH\underline{CH_2}$); 5.45 (2H, d, *J* = 8, NCH_2); 6.01 (1H, s, CH); 5.80-6.17 (2H, m, NH)*
4d	1685 (C=O); 1645 ($C_{(4)}$=O)	2.23 (3H, s, CH_3); 2.58 (3H, s, SCH_3); 3.18-3.47 (4H, m, $N(CH_2)_2$); 3.53-3.78 (4H, m, $O(CH_2)_2$); 5.49 (2H, d, *J* = 8, NCH_2); 6.02 (1H, s, CH); 5.92-6.38 (1H, m, NH)*

* Signal obscured by the singlet for the CH group proton.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds was carried out on Silufol UV-254 plates. ^{1}H NMR spectra were recorded on a Tesla BS-587A instrument (80 MHz) using $CDCl_3$ solvent and TMS internal standard. IR spectra were taken on a Perkin-Elmer Bx FT-IR spectrometer in vaseline oil.

Basic characteristics for the compounds **3, 4** are given in Tables 1 and 2.

The synthesis of compound **1** has been reported in [1].

(6-Methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)- and (6-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)acetyl Azides (2a,b). A. A solution of the hydrazide **1** (1.14 g, 5 mmol) in 50% CH_3COOH (40 ml) was cooled to 0-5°C and a solution of $NaNO_2$ (0.4 g, 5.8 mmol) in water (1 ml) was added dropwise with vigorous stirring at such a rate that the reaction temperature did not exceed 5°C. The reaction mixture was stirred at the same temperature for 1.5 h, the precipitate was filtered off, and the filtrate was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and the solvent was evaporated to give compound **2a** (0.64 g, 53.6%); mp 83-84°C (hexane). IR spectrum (KBr), ν, cm^{-1}: 1690 ($C_{(4)}$=O), 1716 (C=O), 2154 (N_3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.25 (3H, s, CH_3); 2.58 (3H, s, SCH_3); 4.82 (2H, s, NCH_2); 6.09 (1H, s, CH). Found, %: C 40.43; H 3.64; N 29.12. $C_8H_9N_5O_2S$. Calculated, %: C 40.16; H 3.79; N 29.27.

B. Concentrated HCl (4 ml) was added to a suspension of the hydrazide **1** (1.14 g, 5 mmol) in water (15 ml) and a solution of $NaNO_2$ (1.04 g, 15 mmol) in water (1.3 ml) was added with vigorous stirring and at such a rate that the temperature of the reaction mixture did not exceed 5°C. The product was stirred at the same

temperature for 15 min and the precipitate formed was filtered off, washed with water, and dried in a vacuum desiccator over Na_2SO_4 to give compound **2a** (0.72 g, 60%). The filtrate was allowed to stand for 2 h at 5°C and the precipitate formed was filtered off, washed with water, and dried in a vacuum desiccator over Na_2SO_4 to give compound **2b** (0.05 g, 5%); mp 135-137°C. IR spectrum, ν, cm^{-1}: 1634 ($C_{(4)}$=O), 1716 (C=O), 1741 ($C_{(2)}$=O), 2150 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.18 (3H, s, CH_3); 4.65 (2H, s, NCH_2); 5.64 (1H, s, CH); 10.17 (1H, s, NH). Found, %: C 40.53; H 3.57; N 33.62. $C_7H_7N_5O_3$. Calculated, %: C 40.19; H 3.37; N 33.48.

Methyl and Ethyl (6-Methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)methylcarbamates (3a,b). A solution of the azide **2a** (1.2 g, 5 mmol) in absolute methanol (for **3a**) of ethanol (for **3b**) was refluxed for 7 h. Excess solvent was distilled off and the residue was recrystallized from water.

Phenyl and 4-Chlorophenyl (6-Methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)methyl-carbamates (3c,d). The corresponding phenol (5 mmol) was added to a solution of the azide **2a** (1.2 g, 5 mmol) in absolute benzene (10 ml) and refluxed for 5 h. Solvent was evaporated, the residue was triturated with octane, and the precipitate was filtered off and recrystallized from a mixture of octane and 2-propanol (5:1) (compound **3c**) or from octane (compound **3d**).

3-Butylamino- and 3-Benzylamino-1-(6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)-methylcarbamides (4a,b). A solution of the azide **2a** (1.2 g, 5 mmol) in absolute benzene (20 ml) was refluxed for 4 h and the corresponding amine (5.2 mmol) was added. A precipitate was formed immediately which, after the reaction mixture had been cooled, was filtered off and recrystallized from benzene.

3-Dipropylamino- and 3-Morpholinoamino-1-(6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinyl)methylcarbamides (4c,d). A solution of the azide **2a** (1.2 g, 5 mmol) in absolute benzene (20 ml) was refluxed for 4 h, the corresponding amine (5.2 mmol) was added, and refluxing was continued for a further 2 h. The solution was evaporated to half volume, cooled, and the precipitate formed was filtered off and recrystallized from hexane (compound **4c**) or methanol (compound **4d**).

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