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DERIVATIVES OF CONDENSED THIENO[2,3-*d*]PYRIMIDINES. 15*. SYNTHESIS OF 2-SUBSTITUTED 3-AMINO-6,6-DIMETHYL-5,6-DIHYDRO-8H-PYRANO[4',3':4,5]-THIENO[2,3-*d*]PYRIMIDIN-4-ONES

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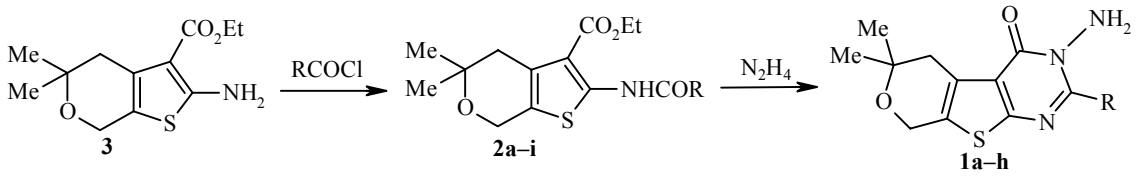
A method has been developed for the preparation of 2-R-substituted 3-amino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-d]pyrimidin-4-ones based on 2-R-amino-3-ethoxycarbonylpyrano-[2,3-c]thiophenes. It has been established that their cyclization with hydrazine hydrate requires vigorous conditions.

Keywords: pyranone, pyranothienopyrimidine, pyranothiophene, thienopyrimidine, thiophene.

The readily obtainable 2-acylamino-3-ethoxycarbonylthiophenes [2,3] are frequently used as starting materials for the synthesis of condensed thieno[2,3-*d*]pyrimidin-4-ones.

This paper reports a suitable method for the synthesis of new 2-R-3-aminothieno[2,3-*d*]pyrimidin-4-ones **1a-h** from 2-R-amido-3-ethoxycarbonylthiophenes **2a-i**. We developed this method to prepare 2-alkyl-substituted 3-aminothienopyrimidin-4-ones [4].

Compounds **2a-i** were synthesized by acylation of 2-amino-3-ethoxycarbonylthiophene with the corresponding acid chloride. The amido esters **2a-h** were converted into the thieno[2,3-*d*]pyrimidines **1a-i** by treatment with hydrazine hydrate. Compounds **2** appeared to be less reactive than the corresponding 2-alkyl-substituted compounds [4].



1, **2 a** R = Ph; **b** R = CH_2Ph; **c** R = C_6H_4OMe-4; **d** R = C_6H_4OBu-4; **e** R = C_6H_4Cl-2; **f** R = γ-pyridyl; **g** R = $C_6H_3(OMe)_2$-3,4; **h** R = C_6H_4OMe-3; **i** R = $CHPh_2$

* For paper 14, see [1].

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TABLE 1. Characteristics of 2-R-Amido-3-ethoxycarbonylthiophenes **2a-1** and 2-R-3-Aminothieno[2,3-*d*]pyrimidin-4-ones **1a-h**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm, coupling constant (*J*), Hz	Yield, %
		N	S				
1	2	3	4	5	6	7	8
2a	$C_{19}H_{21}NO_4S$	3.93 / 3.88	8.99 / 8.92	156-157	1680 (NCO); 1700 (COO); 3280 (NH)	12.61 (1H, s, NH); 8.96-7.46 (5H, m, H_{Ph}); 4.70 (2H, s, 7,7-H_2); 4.42 (2H, q, *J* = 7.0, CH_2); 3.48 (2H, s, 4,4-H_2); 1.33 (3H, t, *J* = 7, $CH_2\underline{CH_3}$); 1.20 (6H, s, 5,5-$(CH_3)_2$)	73.5
2b	$C_{20}H_{23}NO_4S$	3.76 / 3.72	8.65 / 8.58	98-99	1678 (NCO); 1705 (COO); 3282 (NH)	12.46 (1H, s, NH); 7.35 (5H, s, H_{Ph}); 4.65 (2H, s, 7,7-H_2); 4.25 (2H, q, *J* = 7.1, OCH_2); 3.80 (2H, s, $\underline{CH_2}Ph$); 2.70 (2H, s, 4,4-H_2); 1.41 (3H, t, *J* = 7.1, $CH_2\underline{CH_3}$); 1.30 (6H, s, 5,5-$(CH_3)_2$)	80.5
2c	$C_{20}H_{23}NO_5S$	3.60 / 3.59	8.52 / 8.48	160-161	1683 (NCO); 1700 (COO); 3279 (NH)	12.25 (1H, s, NH); 8.00 (2H, d, *J* = 6.0, H_{Ar}); 7.01 (2H, d, *J* = 6.0, H_{Ar}); 4.80 (2H, s, 7,7-H_2); 4.40 (2H, t, *J* = 6.0, $O\underline{CH_2}$); 3.90 (3H, s, OCH_3); 3.10 (2H, s, 4,4-H_2); 1.41 (3H, t, *J* = 6.0, $CH_2\underline{CH_3}$); 1.35 (6H, s, 5,5-$(CH_3)_2$)	78.0
2d	$C_{23}H_{29}NO_5S$	3.32 / 3.24	7.33 / 7.42	128-130	1678 (NCO); 1700 (COO); 3275 (NH)	12.20 (1H, s, NH); 8.00 (2H, d, *J* = 7.5, H_{Ar}); 7.01 (2H, d, *J* = 7.5, H_{Ar}); 4.78 (2H, s, 7,7-H_2); 4.40 (2H, q, *J* = 7.5, OCH_2); 4.10 (2H, t, *J* = 7.5, O-$\underline{CH_2}CH_3$); 2.80 (2H, s, 4,4-H_2); 1.81 (2H, t, *J* = 7.5, $OCH_2\underline{CH_2}$); 1.62-1.42 (2H, m, $\underline{CH_2}CH_3$); 1.41 (3H, t, *J* = 7.5, OCH_2CH_3); 1.26 (6H, s, 5,5-$(CH_3)_2$); 1.00 (3H, t, *J* = 7.5, $\underline{CH_3}$)	65.1
2e	$C_{19}H_{20}ClNO_4S$	3.87 / 3.90	8.86 / 8.94	139-140	1680 (NCO); 1710 (COO); 3275 (NH)	12.20 (1H, s, NH); 7.60–7.40 (4H, m, H_{Ar}); 4.82 (2H, s, 7,7-H_2); 4.65 (2H, q, *J* = 7.2, $O\underline{CH_2}$); 3.10 (2H, s, 4,4-H_2); 1.45 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$); 1.40 (6H, s, 5,5-$(CH_3)_2$)	61.0
2f	$C_{18}H_{20}N_2O_4S$	7.80 / 7.77	8.75 / 8.89	170-171	1685 (NCO); 1715 (COO); 3283 (NH)	12.45 (1H, s, NH); 8.85 (2H, d, *J* = 6.1, H_{Ar}); 7.85 (2H, d, *J* = 6.1, H_{Ar}); 4.80 (2H, s, 7,7-H_2); 4.40 (2H, q, *J* = 7, $O\underline{CH_2}$); 2.80 (2H, s, 4,4-H_2); 1.41 (3H, t, *J* = 7, $CH_2\underline{CH_3}$); 1.30 (6H, s, 5,5-$(CH_3)_2$)	52.0
2g	$C_{21}H_{25}NO_6S$	3.12 / 3.33	7.75 / 7.62	142-144	1680 (NCO); 1710 (COO); 3275 (NH)	12.30 (1H, s, NH); 7.90 (1H, d, *J* = 8.5, H_{Ar}); 7.79 (1H, s, H_{Ar}); 6.99 (1H, d, *J* = 8.5, H_{Ar}); 4.81 (2H, s, 7,7-H_2); 4.25 (2H, q, *J* = 7.1, $O\underline{CH_2}$); 4.00 (6H, s, 2-OCH_3); 2.95 (2H, s, 7,7-H_2); 1.40 (3H, t, OCH_2); 1.30 (6H, s, 5,5-$(CH_3)_2$)	76.5
2h	$C_{20}H_{23}NO_5S$	3.64 / 3.50	8.13 / 8.02	134-136	1670 (NCO); 1715 (COO); 3275 (NH)	12.20 (1H, s, NH); 7.61(2H, s, *J* = 7.8, H_{Ar}); 7.41 (1H, t, *J* = 7.8, H_{Ar}); 7.18 (1H, d, *J* = 7.8, H_{Ar}); 4.78 (2H, s, 7,7-H_2); 4.40 (2H, t, *J* = 7.26, OCH_2); 3.90 (3H, s, OCH_3); 2.80 (2H, s, 4,4-H_2); 1.41 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$); 1.38 (6H, s, 5,5-$(CH_3)_2$)	78.9

TABLE 1 (continued)

1	2	3	4	5	6	7	8
2i	$C_{26}H_{27}NO_4S$	$\frac{3.20}{3.11}$	$\frac{7.09}{7.13}$	118-119	1675 (NCO); 1705 (COO); 3276 (NH)	11.30 (1H, s, NH); 7.35 (10H, s, H_{Ph}); 5.19 (1H, s, CH); 4.70 (2H, s, 7,7-H_2); 4.20 (2H, q, J = 7.1, OCH_2); 2.70 (2H, s, 4,4-H_2); 1.36 (3H, t, J = 7.1, CH_2-$\underline{CH_3}$); 1.30 (6H, s, 5,5-$(CH_3)_2$)	53.2
1a	$C_{17}H_{17}N_3O_2S$	$\frac{12.76}{12.83}$	$\frac{9.71}{9.79}$	224-225	1665-1670 (CO); 3180-3250 (NH_2)	7.80-7.50 (5H, m, H_{Ph}); 5.10 (2H, s, NH_2); 4.82 (2H, s, 8,8-H_2); 3.08 (2H, s, 5,5-H_2); 1.28 (6H, s, 6,6-$(CH_3)_2$)	51.0
1b	$C_{18}H_{19}N_3O_2S$	$\frac{12.36}{12.30}$	$\frac{9.44}{9.39}$	212-214	1665-1675 (CO); 3185-3300 (NH_2)	7.30 (5H, br. s, H_{Ar}); 5.70 (2H, s, NH_2); 4.70 (2H, s, 8,8-H_2); 4.30 (2H, s, CH_2Ph); 2.85 (2H, s, 5,5-H_2); 1.25 (6H, s, 6,6-$(CH_3)_2$)	47.05
1c	$C_{18}H_{19}N_3O_2S$	$\frac{11.82}{11.75}$	$\frac{9.03}{8.96}$	230-232	1660-1675 (CO); 3190-3310 (NH_2)	7.85 (2H, d, J = 6,H_{Ar}); 7.00 (2H, d, J = 6,H_{Ar}); 5.10 (2H, s, NH_2); 4.85 (2H, s, 8,8-H_2); 3.90 (3H, s, OCH_3); 3.06 (2H, s, 5,5-H_2); 1.38 (6H, s, 6,6-$(CH_3)_2$)	50.0
1d	$C_{21}H_{25}N_3O_3S$	$\frac{10.58}{10.51}$	$\frac{8.12}{8.02}$	198-200	1665-1670 (CO); 3150-3300 (NH_2)	7.85 (2H, d, J = 6, H_{Ar}); 6.91 (2H, d, J = 6, H_{Ar}); 5.60 (2H, s, NH_2); 4.72 (2H, s, 8,8-H_2); 4.05 (2H, t, J = 6.05, OCH_2); 2.92 (2H, s, 5,5-H_2); 1.75-1.81 (2H, m, $C\underline{H_2}CH_3$); 1.45-1.60 (2H, m, $OCH_2\underline{CH_2}$); 1.32 (6H, s, 6,6-$(CH_3)_2$); 1.00 (3H, t, J = 6,$\underline{CH_3}$)	45.4
1e	$C_{17}H_{16}ClN_3O_2S$	$\frac{11.65}{11.59}$	$\frac{8.93}{8.84}$	212-214	1670-1675 (CO); 3185-3320 (NH_2)	7.50 (4H, m, H_{Ar}); 5.00 (2H, s, NH_2); 4.85 (2H, s, 8,8-H_2); 3.10 (2H, s, 5,5-H_2); 1.40 (6H, s, 6,6-$(CH_3)_2$)	61.1
1f	$C_{16}H_{16}N_4O_2S$	$\frac{17.21}{17.11}$	$\frac{9.68}{9.76}$	217-218	1660-1675 (CO); 3180-3335 (NH_2)	8.80 (2H, d, J = 6.3, H_{Het}); 7.75 (2H, d, J = 6.3, H_{Het}); 4.95 (2H, s, NH_2); 4.82 (2H, s, 8,8-H_2); 3.10 (2H, s, 5,5-H_2); 1.40 (6H, s, 6,6-$(CH_3)_2$)	48.5
1g	$C_{19}H_{21}N_3O_4S$	$\frac{10.93}{10.84}$	$\frac{8.33}{8.27}$	176-177	1665-1670 (CO); 3150-3300 (NH_2)	7.90 (1H, d, J = 8.5, H_{Ar}); 7.78 (1H, s, H_{Ar}); 6.98 (1H, d, J = 8.5, H_{Ar}); 5.10 (2H, s, NH_2); 4.82 (2H, s, 8,8-H_2); 4.00 (6H, d, J = 8.5, OCH_3); 2.95 (2H, s, 5,5-H_2); 1.38 (6H, s, 6,6-$(CH_3)_2$)	50.0
1h	$C_{18}H_{19}N_3O_3S$	$\frac{11.62}{11.75}$	$\frac{8.88}{8.96}$	218-220	1665-1675 (CO); 3180-3335 (NH_2)	7.66 (2H, t, J = 7.9, H_{Ar}); 7.45 (1H, t, J = 7.8, H_{Ar}); 7.20 (1H, d, J = 7.8, H_{Ar}); 5.00 (2H, s, NH_2); 4.80 (2H, s, 8,8-H_2); 3.85 (3H, s, OCH_3); 2.80 (2H, s, 5,5-H_2); 1.30 (6H, s, 6,6-$(CH_3)_2$)	52.0

It was found by varying the reaction conditions (time, temperature, and medium) that to obtain the best yields the process should be carried out in boiling *n*-butanol for a long time (15-20 h). The decreased activity is probably explained by steric hindrance caused by the substituent R, consequently the diphenylmethylamide **2i** did not cyclize to the desired thienopyrimidine under these reaction conditions.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 spectrometer. ^{1}H NMR spectra were recorded with a Varian Mercury 300 spectrometer (working frequency 300 MHz) using US CRDF RESC 17-S programs. The solvents were $CDCl_3$ (compounds **1a,b,e,f,h, 2a-i**) and DMSO-d_6 (compounds **1b,d,g**). Purity of the compounds synthesized was monitored by TLC on Silufol UV-254 plates with the eluent chloroform–ethyl acetate–ether (0.5:1.0:0.5), and development with UV light.

2-N-Acylamino-3-ethoxycarbonyl-5,5-dimethyl-4,5-dihydro-7-thieno[2,3-*c*]pyrans (2a-i). Dry triethylamine (0.01 mol) was added to a solution of compound **3** (0.01 mol) in dry benzene (30 ml), and then the corresponding acid chloride (0.01 mol) was added dropwise. The mixture was boiled (4 h) and then cold water (30 ml) was added, and the benzene was evaporated. The precipitate was filtered off, washed with water and methanol, and recrystallized from ethanol to give compounds **2a-i**.

2-R-3-Amino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-ones (1a-h). Hydrazine hydrate (10 ml, 85%) was added to a suspension of an amido ester **2** (0.01 mol) in *n*-butanol (15 ml) and the mixture was boiled for 15-20 h. The crystals which formed on cooling were filtered off, washed with ethanol and water, dried at 50°C, and recrystallized from ethanol to give **1**.

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