Synthesis of thieno[3,4-*d*]pyrimidines by the reactions of 3-amino-4-carbamoylthiophene derivatives with 1,3-dicarbonyl compounds

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The reactions of ethyl 3-amino-4-carbamoyl-5-methylthiophene-2-carboxylate with 1,3-dicarbonyl compounds were studied. During the reactions, the corresponding ketone is eliminated to give ethyl 5-methyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylates.

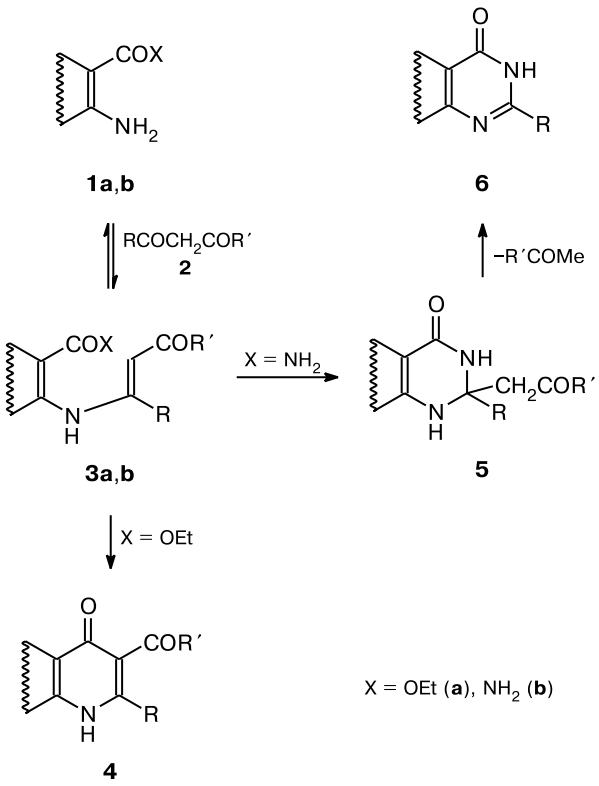
Key words: thiophenes, thieno[3,4-*d*]pyrimidines, 1,3-dicarbonyl compounds, cyclization, alkylation.

The present study is devoted to reactions of *ortho*-aminoarenecarboxylates and -carboxamides **1a**,**b** with 1,3-dicarbonyl compounds **2** (Scheme 1). These reactions begin with an acid-catalyzed condensation of the carbonyl group of compound **2** with the NH_2 group of derivatives **1**, giving the corresponding enamines **3**.[1,2] The condensation is reversible under these conditions since water is liberated and enamines are highly hydrolyzable.[2] Subsequent transformations of intermediate enamines **3a**,**b** depend on the character of *ortho*-substituents.

In the reactions of *o*-amino esters **1a** with β-dicarbonyl compounds **2** under acid catalysis conditions, intermediates **3a** undergo cyclization to give 1,4-dihydropyridin-4-one derivatives **4**.[3,4] The reactions of β-diketones **2** with *o*-amino carbamoyl derivatives **1b** such as anthranilamide or 4-amino-5-carbamoylthiazoles[5,6] afford enaminones **3b**, which are attacked by the carbamoyl NH_2 group at the α-position to form 2-acylmethyl-1,2,3,4-tetrahydropyrimidin-4-ones (**5**). Under the same conditions (heating and acid catalysis), ketone can be eliminated, yielding 3,4-dihydropyrimidin-4-one derivatives **6**.[7—10] The literature data for analogous reactions with compounds containing both functional groups ($CONH_2$ and CO_2Alk) are lacking.

In the present work, we studied the reactions of ethyl 3-amino-4-carbamoyl-5-methylthiophene-2-carboxylate (**7**)[11] with carbonyl compounds **2** (acetylacetone, benzoylacetone, ethyl acetoacetate, acetoacetamide, ethyl benzoylacetate, and α-cyanoacetophenone). The goal of this study was to specify cyclization products of intermediate enamine **8** between thieno[3,4-*d*]pyrimidines **9** and thieno[3,2-*b*]pyridines **10** (Scheme 2).

Scheme 1



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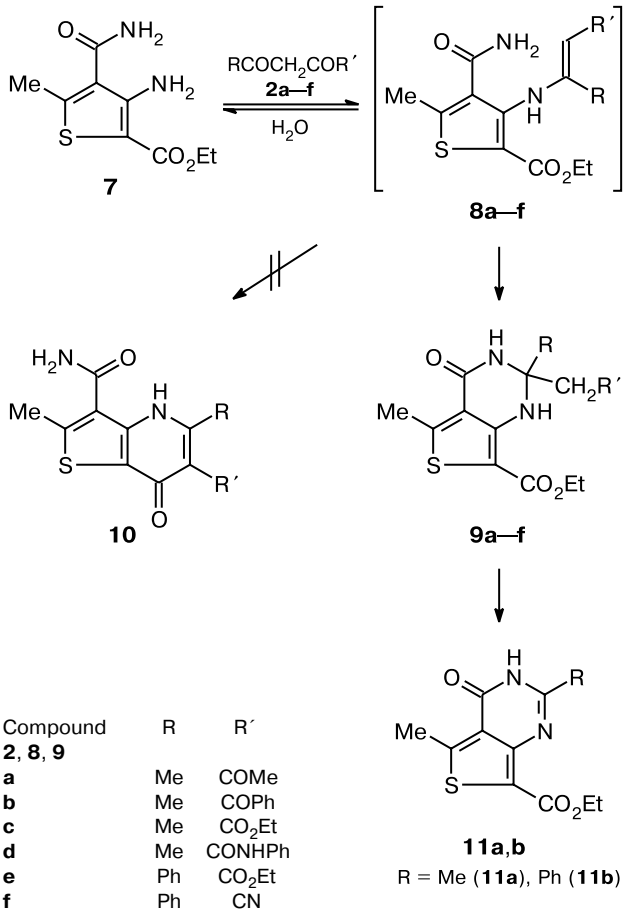
Scheme 2



Compound	R	R′
2, **8**, **9**		
a	Me	COMe
b	Me	COPh
c	Me	CO_2Et
d	Me	CONHPh
e	Ph	CO_2Et
f	Ph	CN

Results and Discussion

The reaction of compound **7** with acetylacetone (**2a**) (toluene, 110 °C, 6 h, TsOH) affords ethyl 2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylate (**11a**) in 86% yield; in this case, cyclization into a pyrimidine ring dominates clearly. Intermediate **9a** is stabilized by elimination of acetone (GLC). The structure of bicycle **11a** was unambiguously proved by ^1H and ^{13}C NMR, IR, and mass spectra, elemental analysis data (Tables 1—4), and by an independent synthesis from thiophene **7** and triethyl orthoacetate in the presence of Ac_2O (the yield of compound **11a** was 40%).

The reaction of compound **7** with $PhCOCH_2COMe$ (**2b**) follows the same scheme as described for acetylacetone (**2a**); however, prolonged heating is required for the process to be completed (32 h, TLC). According to the TLC data, the reaction mixture contains the starting reagents **7** and **2b**, thienopyrimidine **11a**, and the detached acetophenone only; *i.e.*, intermediate **9b** is rapidly transformed into compound **11a**. Hence, the rate-limiting step of the process is the cyclization into a pyrimidine ring. A second possible product **11b** was not detected either in the reaction mixture (^1H NMR data) or in a crude product (mass spectra). This indicates that the acetyl group is more reactive than the benzoyl one, in which the partial positive charge at the carbonyl C atom is compensated by conjugation with the aromatic ring.

The reactions of ethyl acetoacetate and acetoacetanilide **2c**,**d** with thiophene **7** occur in a different way; in these cases, hydrogenated pyrimidine derivatives **9c**,**d** can both be isolated in ~70% yield, which was impossible for the reactions of β-diketones **2a**,**b**. Subsequent prolonged heating of compounds **9c**,**d** under the same conditions (toluene, 110 °C, TsOH) results in elimination of ethyl acetate and MeCONHPh to give thienopyrimidinone **11a** in 60 and 40% yields, respectively. Analogously, intermediate **9e** was isolated in the reaction of compound **7** with $PhCOCH_2CO_2Et$ (**2e**); when heated, compound **9e** releases ethyl acetate to form ethyl 5-methyl-4-oxo-2-phenyl-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylate (**11b**).

The reaction of thiophene **7** with α-cyanoacetophenone (**2f**) yields a cyanomethyl derivative **9f**; under these conditions, the C—C bond is mostly retained and, consequently, MeCN is not eliminated.

The structures of hydrogenated derivatives **9** was studied by ^1H NMR (for **9c** and **9f**, see Table 1) and ^{13}C NMR spectroscopy (for **9c**). Compounds **9** contain an asymmetric C(2) atom, which makes the methylene protons of the CH_2R' fragment nonequivalent; as the result, two doublets with $^2J_{CH_2} = 14.7$ (**9c**) and 16.4 Hz (**9f**) appear in their ^1H NMR spectra. These spectra also show signals for two NH protons with a weak spin-spin coupling ($^4J_{NH,NH} = 1.2$ Hz). The ^{13}C NMR spectrum of compound **9c** contains a signal for the sp^3-hybridized C(2) atom at δ 70.0.

According to quantum-chemical calculations,[7] similar reactions (*e.g.*, the reaction of anthranilamide with acetylacetone, which gives ethyl 2-methyl-4-oxo-1,2,3,4-tetrahydroquinazol-2-ylacetate and subsequently 2-methyl-3,4-dihydroquinazolin-4-one), proceed with a significant gain in energy. However, data on mechanisms of cyclization and ketone elimination following carbon-carbon bond cleavage are lacking; in addition, it remains unclear how these processes depend on the structure of starting β-dicarbonyl compounds.

Hence, one can assume that the synthesis under study of thieno[3,4-*d*]pyrimidines includes (1) reversible condensation of thiophene **7** with ketones to give enamines of type **8**, (2) cyclization involving the enamine α-C atom and the amide NH_2 group, and (3) C—C bond cleavage with elimination of the carbonyl-containing molecule.

1. Reversible condensation of thiophene 7 with ketones into enamines of type 8. Enamines **8** were found[7] to be

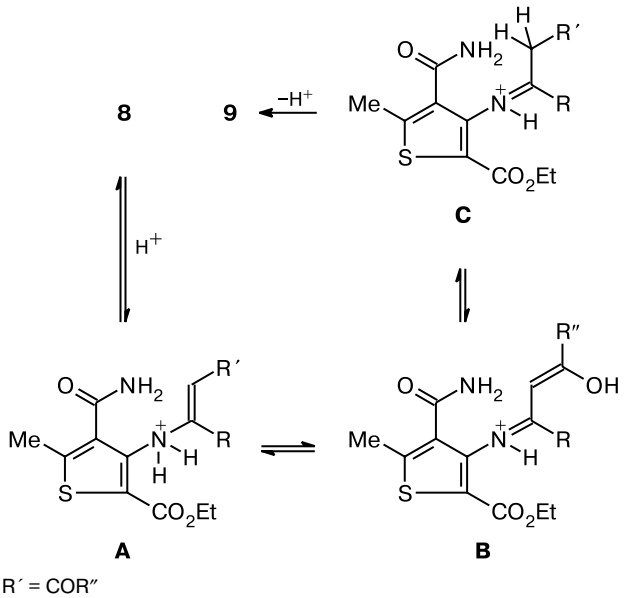
Table 1. ^{1}H NMR spectra of the compounds obtained (DMSO-d_6, δ)

Compound	$CH_2C\underline{H}_3$, t,	C(2)Me, s	C(5)Me, s	$C\underline{H}_2CH_3$, q	Other groups
9c	1.24	1.49	2.65	4.20 (^3J = 6.8)	1.13 (t, 3 H, $CH_2C\underline{H}_3$); 2.76 (q, 2 H, $C\underline{H}_2CO_2Et$, ^2J = 4.8); 3.98 (q, 2 H, $C\underline{H}_2CH_3$, ^3J = 5.2); 7.30 (br.d, 1 H, N(1)H); 8.26 (br.d, 1 H, N(3)H, $^4J_{NH,NH}$ = 1.2)
9f	1.27	—	2.59	4.29 (^3J = 6.8)	3.04 and 3.69 (both q, 2 H each, $C\underline{H}_2CN$; J = 16.4); 7.28—7.45 (m, 5 H, Ph); 8.07 (br.d, 1 H, N(1)H); 9.25 (br.d, 1 H, N(3)H, $^4J_{NH,NH}$ = 1.2)
11a	1.27	2.27	2.83	4.25 (^3J = 7.0)	11.84 (br.s, 1 H, NH)
12a	1.28	2.40	2.88	4.26 (^3J = 7.2)	5.25 (s, 2 H, $C\underline{H}_2Ph$); 7.20—7.38 (m, 5 H, Ph)
12b	1.29	2.50	2.86	4.28	1.22 (t, 3 H, $CH_2C\underline{H}_3$); 4.18 (q, 2 H, $C\underline{H}_2CH_3$, ^3J = 7.6); 4.82 (s, 2 H, $C\underline{H}_2CO_2Et$)
12c	1.27	2.56	2.85	4.25 (^3J = 7.2)	5.07 (s, 2 H, NCH_2)
12d	1.28	2.41	2.88	4.27 (^3J = 6.8)	5.24 (s, 2 H, NCH_2); 7.24, 7.39 (both d, 2 H each, ClC_6H_4)
12e	1.31	2.48	2.87	4.29 (^3J = 7.2)	2.25 (s, 3 H, $C\underline{H}_3C_6H_4$); 7.11, 7.45 (both d, 2 H each, $CH_3C_6\underline{H}_4$); 10.22 (br.s, 1 H, NH)
16b	—	2.62	2.87	—	4.05, 4.35 (both d, 2 H each, 2 $NHC\underline{H}_2$, $^3J_{CH,NH}$ = 5.2, $^3J_{CH,NH}$ = 6.0); 5.41 (s, 2 H, CH_2CO); 2 C_5H_5N: 7.32 (m, 2 H); 7.60 (d, 1 H); 7.67 (d, 1 H); 8.44 (d, 1 H); 8.50 (m, 2 H); 8.54 (d, 1 H); 8.62, 9.91 (both t, 1 H each, 2 $N\underline{H}CH_2$)

metastable systems, and some energy is required for their formation (ΔH = +11—19 kJ mol^{-1}).

2. Cyclization involving the enamine α-C atom and the amide NH_2 group. This process is favored by protonation of enamines (Scheme 3). Enamine protonation is known to occur at the N- and β-C atoms, while enaminones are protonated at the N, β-C, and O(C=O) atoms.[12] Under our conditions (nonpolar solvent, catalytic amount of an acid), the protonation of enamines has not been studied. However, a nucleophilic attack at the α-position of an enamine is known[13] to be hindered for an *N*-protonated form (**A**), be possible for an *O*-protonated form (**B**), and occur most easily for immonium cations (**C**). However, it is not always possible to determine, under reaction conditions, the ratio between protonated forms for a particular β-substituent in an enamine.

Scheme 3



3. C—C bond cleavage with elimination of a carbonyl-containing molecule. On the assumption that the transition state (TS) of this process for carbonyl-containing compounds **9a—e** in the presence of TsOH as an acid agent can be represented as shown in Scheme 4, the elimination of the enol fragment will be hindered by any group R′ capable of conjugating with the C=O$^+$H group; the stronger the conjugation the stronger this effect of R′

Scheme 4

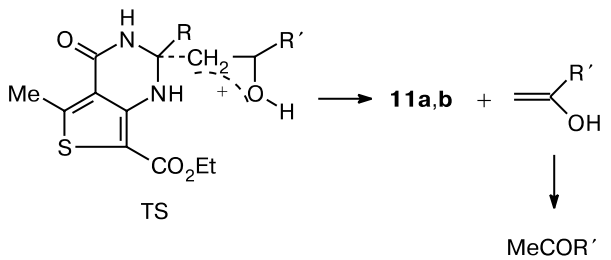


Table 2. Yields, properties, and elemental analysis data for the compounds obtained

Compound	Yield (%)	M.p./°C (solvent)	Molecular formula	Found / Calculated (%)			
				C	H	N	S
9c	70	131—133 (acetone—DMF)	$C_{15}H_{20}N_2O_5S$	52.87 / 52.93	6.00 / 5.92	8.36 / 8.23	9.27 / 9.42
9d	70	220—222 (acetone—DMF)	$C_{19}H_{21}N_3O_4S$	58.76 / 58.90	5.55 / 5.46	10.99 / 10.84	8.07 / 8.28
9e	50	175—176 (EtOH—DMF)	$C_{20}H_{22}N_2O_5S$	59.44 / 59.69	5.39 / 5.51	7.12 / 6.96	7.91 / 7.97
9f	55	>255 (aqueous DMF)	$C_{18}H_{17}N_3O_3S$	60.73 / 60.83	4.73 / 4.82	12.08 / 11.82	8.88 / 9.02
11a	86 (**A**)	276—278 (CH_3CN—DMF)	$C_{11}H_{12}N_2O_3S$	52.45 / 52.37	4.69 / 4.79	11.12 / 11.10	12.59 / 12.71
11b	20	>255 (DMF)	$C_{16}H_{14}N_2O_3S$	60.98 / 61.13	4.56 / 4.49	8.80 / 8.91	10.02 / 10.20
12a	65	137—139 (aqueous CH_3CN)	$C_{18}H_{18}N_2O_3S$	62.98 / 63.14	5.18 / 5.30	8.03 / 8.18	9.19 / 9.36
12b	71	133—135 C_2H_5OH	$C_{15}H_{18}N_2O_5S$	53.18 / 53.24	5.42 / 5.36	8.09 / 8.28	9.29 / 9.48
12c	64	73—74 (EtOH)	$C_{13}H_{13}N_3O_3S$	53.85 / 53.60	4.56 / 4.50	14.49 / 14.42	10.87 / 11.01
12d*	56	136—138 (acetone)	$C_{18}H_{17}ClN_2O_3S$	57.18 / 57.37	4.43 / 4.55	7.61 / 7.43	8.45 / 8.51
12e	61	>255 (Pr^iOH : DMF, 1 : 2)	$C_{20}H_{21}N_3O_4S$	60.01 / 60.14	5.23 / 5.30	10.68 / 10.52	7.87 / 8.03
15	63	133—134 (EtOH)	$C_{15}H_{22}N_2O_4$	61.39 / 61.21	7.45 / 7.53	9.38 / 9.52	—
16a	72	206—207 (acetone—DMF)	$C_{27}H_{28}N_4O_3S$	66.56 / 66.37	5.59 / 5.78	11.31 / 11.47	6.51 / 6.56
16b	69	224—225 (EtOH—DMF)	$C_{23}H_{22}N_6O_3S$	59.57 / 59.73	4.68 / 4.79	18.39 / 18.17	6.81 / 6.93

* Found (%): Cl, 9.27. Calculated (%): Cl, 9.41.

since its interaction with the charged carbonyl group is significantly more intense than with the C=C bond.

As a result, the conjugation energy is partially lost upon the bond cleavage, the TS energy increases, and the process decelerates. In the case of **9a** (R′ = Me), the TS

Table 3. Mass spectra (EI, 70 eV) of the compounds obtained

Compound	*m/z*
9c	340 $[M]^+$ (57), 325 $[M - NH]^+$ (46), 295 $[M - OEt]^+$ (29), 279 $[M + H - Me - OEt]^+$ (100), 253 $[M - Me - CO_2Et]^+$ (78)
11a	252 $[M]^+$ (43), 207 $[M - OEt]^+$ (69), 180 $[M + H - CO_2Et]^+$ (100)
12e	399 $[M]^+$ (7), 354 $[M - OEt]^+$ (4), 293 $[M - NH - C_6H_4 - CH_3 + H]^+$ (100), 265 $[M - NH - C_6H_4 - CH_3 + H - CO]^+$ (58)
15	310 $[M]^+$ (98), 295 $[M - Me]^+$ (10), 265 $[M - OEt]^+$ (43), 237 $[M - CO_2Et]^+$ (100)
16a	488 $[M]^+$ (45), 368 $[M - NHCH_2CH_2Ph]^+$ (37), 340 $[M - CONHCH_2CH_2Ph]^+$ (70), 311 $[M + H - NCH_2CONHCH_2CH_2Ph]^+$ (100)
16b	462 $[M]^+$ (18), 370 $[M - CH_2Py]^+$ (20), 327 $[M - NHCOCH_2Py]^+$ (13), 298 $[M + H - NCH_2NHCH_2CH_2Ph]^+$ (100)

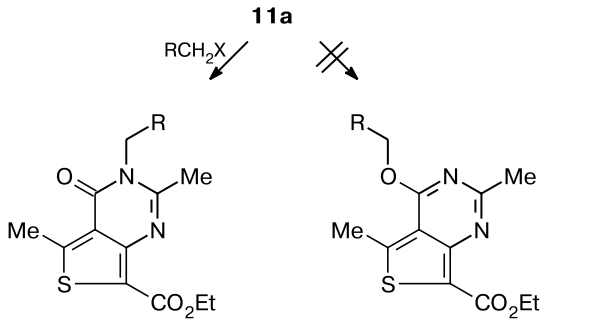
Table 4. IR spectra of the compounds obtained

Compound	ν/cm^{-1}
9c	3363, 3167 (NH), 1723, 1682, 1771 (CO), 1595 (C=C)
9d	3350, 3308, 3258, 3197, 3134 (NH), 1685, 1660, 1648 (CO)
9e	3341, 3167, 3060 (NH); 1734, 1682, 1660 (CO); 1600 (C=C)
9f	3284, 3305 (NH); 2247 (CN); 1658 (CO)
11a	3140 (NH); 1665 (CO); 1610 (C=C)
11b	3168 (NH), 1680 (CO)
12a	1714, 1672 (CO)
12b	1742, 1714 (CO); 1674 (C=C)
12c	2256 (CN), 1723, 1686 (CO), 1646 (C=C)
12e	3285 (NH); 1714, 1685 (CO), 1667 (C=C)
15	1710, 1725 (CO); 1655 (C=C)

energy increases insignificantly since the Me group weakly interacts with the double bonds. For R′ = Ph and especially electron-donating OEt and NHPh groups capable of conjugating with the C=O$^+$H group, the TS energy becomes substantially higher. For this reason, the reaction of thiophene **7** with acetylacetone (**2a**) proceeds most easily. Benzoylacetone (**2b**) reacts with more difficulty, although intermediate **9b** cannot be isolated in this case. In contrast, intermediates **9c—e** were isolated, and a corresponding carbonyl compound was eliminated only on prolonged heating. In the reaction of thiophene **7** with α–cyanoacetophenone (**2f**), no intermediate alleneimmonium TS was formed for thermodynamic reasons, and acetonitrile was not liberated. Hindrances to the elimination of ethyl acetate from derivative **9e** (heating for more than 100 h) are due to the presence of a bulky phenyl group in position 2 of the tetrahydropyrimidine ring, which causes the ethoxycarbonylmethyl group to deflect from the bicycle plane, thus increasing the TS energy. Although the mechanism proposed above explains the experimental data qualitatively and consistently, it is only tentative and calls for extensive kinetic investigation.

Thienopyrimidine **11a** obtained was a starting reagent for the synthesis of some derivatives of this system. Alkylation of **11a** smoothly proceeds in acetone or DMF in the presence of K_2CO_3 (Scheme 5).

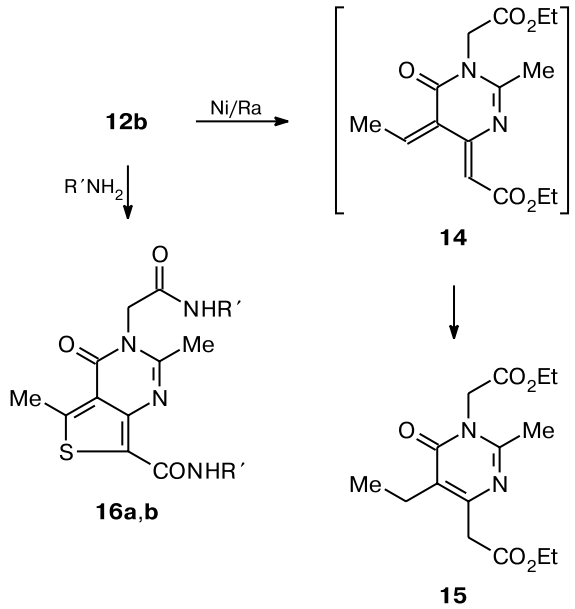
Scheme 5



Compound **12**	**a**	**b**	**c**	**d**	**e**
R	Ph	CO_2Et	CN	C_6H_4-Cl-*p*	$CONHC_6H_4Me$-*p*

The process can involve both the endocyclic N(3) atom to give derivatives **12a—e** and the exocyclic O atom to form compounds **13** (Scheme 5). Based on the ^{13}C NMR data, we assigned structure **12** to the products obtained. Thus, the ^{13}C NMR spectrum of compound **12a**, recorded without total but selective proton decoupling for C(2)C$\underline{H}_3$ (δ 2.40) and NHC$\underline{H}_2$Ph groups (δ 5.26), shows a multiplet at δ 151.7 ($^2J_{C(2),CH_3}$ = 6.6 Hz and $^3J_{C(2),NHCH_2}$ = 3.9 Hz) for the C(2) atom (in the case of *O*-alkylation, a signal for the C(2) atom would appear as a quartet because of a spin-spin coupling between C(2) and the CH_3 protons). Apparently, the reaction regioselectivity is ensured by the shielding effect of the C(5)-bound Me group on the amide CO group.[14—16]

Scheme 6



R′ = CH_2CH_2Ph (**a**), 2-$PyCH_2$ (**b**)

It was illustrated with compound **12b** that desulfurization is possible under the action of Raney nickel (Scheme 6). Intermediate **14** is subsequently reduced with the catalyst-absorbed hydrogen to give diethyl 5-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidine-1,4-diacetate (**15**); its structure was proved by ^1H and ^{13}C NMR spectra.

Compound **12b** smoothly reacts with amines to give bis(carbamoyl) derivatives (**16a**,**b**).

Experimental

^1H NMR spectra were recorded on a Varian Unity plus 400 MHz spectrometer in DMSO-d_6 with $SiMe_4$ as the internal standard. IR spectra were recorded on a Perkin-Elmer 457 spectrometer (Nujol). The course of the reactions were monitored and the purity of the products were checked by TLC on Kieselgel 60 F_{254} plates (Merck Co.). Melting points were determined on a Boetius hot stage at a heating rate of 2 to 3 K min^{-1}.

Characteristics of the compounds obtained are given in Tables 1—4.

Ethyl 2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylate (11a). ***A.*** Thiophene **7** (15.0 g, 66 mmol) and

TsOH (0.1 g) were added to a solution of acetylacetone (70 mL) in 80 mL of toluene. The reaction mixture was refluxed for 9 h. The precipitate that formed was filtered off and washed with EtOH. The yield of compound **11a** was 13.3 g (86%).

B. A mixture of thiophene **7** (1.02 g, 4.4 mmol), $MeC(OEt)_3$ (10 mL), and Ac_2O (10 mL) was refluxed for 20 h. The precipitate that formed was filtered off. The yield of compound **11a** was 0.44 g (40%).

C. A mixture of thiophene **7** (1.02 g, 4.4 mmol), benzoylacetone (2.0 g, 12.3 mmol), and TsOH (0.1 g) in 50 mL of toluene was refluxed for 32 h. The precipitate that formed was filtered off. The yield of product **11a** was 0.67 g (60%).

D. A mixture of tetrahydropyrimidine **9c** (1.02 g, 3 mmol) and TsOH (0.1 g) in 40.0 mL of toluene was refluxed for 48 h. The precipitate that formed was filtered off. The yield of product **11a** was 0.45 g (60%).

E. A mixture of thiophene **7** (1.02 g, 4.4 mmol), $MeCOCH_2CONHPh$ (23.4 g, 13.2 mmol), and TsOH (0.1 g) in 50 mL of toluene was refluxed for 20 h. The precipitate that formed was filtered off. The yield of compound **11a** was 0.44 g (40%). ^{13}C NMR, δ: 14.6 (q, $CH_2\underline{Me}$, $^1J_{CH}$ = 127.1 Hz); 16.1 (q, C(5)$\underline{Me}$, $^1J_{CH}$ = 131.2 Hz); 21.9 (q, C(2)$\underline{Me}$, $^1J_{CH}$ = 128.9 Hz); 60.5 (t, $\underline{C}H_2Me$, $^1J_{CH}$ = 148.0 Hz); 115.8 (br.s, C(7)); 122.0 (q, C(4a), $^3J_{CH}$ = 3.8 Hz); 151.4 (q, C(5), $^2J_{CH}$ = 7.6 Hz); 151.8 (br.s, C(7a)); 156.6 (q, C(2), $^2J_{CH}$ = 7.8 Hz); 159.3 (br.s, C(4)); 161.2 (t, C(7)$\underline{C}O$, $^3J_{CO,CH_2}$ = 3.9 Hz).

Ethyl 2-methyl-4-oxo-5-phenyl-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylate (11b). Thiophene **7** (1.02 g, 4.4 mmol) was added to a solution of $PhCOCH_2CO_2Et$ (30 mL) in 30 mL of toluene. The reaction mixture was refluxed for 105 h and then cooled. The precipitate that formed was filtered off and washed with EtOH to give product **11b** (0.28 g, 20%).

Ethyl 2-(ethoxycarbonylmethyl)-2,5-dimethyl-4-oxo-1,2,3,4-tetrahydrothieno[3,4-*d*]pyrimidine-7-carboxylate (9c). A mixture of thiophene **7** (8.0 g, 35 mmol), $MeCOCH_2CO_2Et$ (50 mL), and TsOH (0.1 g) in 60 mL of toluene was refluxed for 6 h and then cooled. The precipitate that formed was filtered off and washed with EtOH. The yield of compound **9c** was 8.3 g (70%). ^{13}C NMR, δ: 14.12 and 14.68 (2 $CH_2\underline{Me}$, $^1J_{CH}$ = 127.4 Hz and $^1J_{CH}$ = 127.7 Hz); 15.6 (C(5)$\underline{Me}$, $^1J_{CH_2}$ = 131.2 Hz); 28.6 (C(2)$\underline{Me}$, $^1J_{CH_2}$ = 127.4 Hz); 46.5 (CH_2, $^1J_{CH}$ = 131.2 Hz); 60.17 and 60.70 (2 $O\underline{C}H_2$, $^1J_{CH}$ = 148.0 Hz and $^1J_{CH}$ = 148.0 Hz); 70.0 (br.s, C(2)); 95.8 (br.s, C(7)); 117.6 (m, C(4a)); 150.7 (br.s, C(7a)); 153.0 (q, C(5), $^2J_{CH}$ = 7.4 Hz); 160.0 (br.s, C(4)); 162.9 (t, C(7)$\underline{C}O$, $^3J_{CH}$ = 3.6 Hz); 169.9 (m, C(2)$\underline{C}O$).

Ethyl 2,5-dimethyl-4-oxo-2-(*N*-phenylcarbamoylmethyl)-1,2,3,4-tetrahydrothieno[3,4-*d*]pyrimidine-7-carboxylate (9d). A mixture of thiophene **7** (1.6 g, 7 mmol), $MeCOCH_2CONHPh$ (4.9 g, 21 mmol), and TsOH (0.1 g) in 60 mL of toluene was refluxed for 4 h and then cooled. Compound **11a** (0.2 g, 10%) was filtered off. The mother liquor was concentrated *in vacuo*. The residue was recrystallized from acetone—DMF to give product **9d** (1.9 g, 70%).

Ethyl 2-(ethoxycarbonylmethyl)-5-methyl-4-oxo-2-phenyl-1,2,3,4-tetrahydrothieno[3,4-*d*]pyrimidine-7-carboxylate (9e). A mixture of thiophene **7** (1.6 g, 7 mmol), $PhCOCH_2CO_2Et$ (40.3 g, 21 mmol), and TsOH (0.1 g) in 40 mL of toluene was refluxed for 5 h and then cooled. The precipitate that formed was filtered off and washed with EtOH. The yield of compound **9e** was 1.4 g (50%).

Ethyl 2-cyanomethyl-5-methyl-4-oxo-2-phenyl-1,2,3,4-tetrahydrothieno[3,4-*d*]pyrimidine-7-carboxylate (9f). A mixture of thiophene **7** (1.6 g, 7 mmol), $NCCH_2COPh$ (3.05 g, 21 mmol), and TsOH (0.1 g) in 40 mL of toluene was refluxed for 48 h and then cooled. The precipitate that formed was filtered off and washed with EtOH. The yield of compound **9f** was 1.37 g (55%).

Ethyl 3-alkyl-2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylates (12a—e) (general procedure). A mixture of compound **11a** (0.45 g, 1.8 mmol), an alkyl halide (2.1 mmol), and K_2CO_3 (0.35 g, 2.5 mmol) in 30 mL of acetone was refluxed with stirring for 6 h (reaction conditions: DMF, 70 °C, 2 h (**12b**); DMF, 50 °C, 5 h (**12c**,**d**); and DMF, 100 °C, 1 h (**12e**)). The reaction mixture was poured into water, and the precipitate that formed was filtered off. Compound **12a**: ^{13}C NMR, δ: 14.5 ($CH_2\underline{Me}$, $^1J_{CH}$ = 126.7 Hz); 16.3 (q, C(5)$\underline{Me}$, $^1J_{CH2}$ = 132.0 Hz); 23.7 (q, C(2)$\underline{Me}$, $^1J_{CH}$ = 128.9 Hz); 45.7 (tt, N(3)$\underline{C}H_2$, $^1J_{CH}$ = 140.4 Hz); 60.7 ($O\underline{C}H_2$, $^1J_{CH}$ = 148.0 Hz); 115.9 (br.s, C(7)); 121.1 (q, C(4a), $^3J_{CH}$ = 3.8 Hz); signals for the aromatic carbon atoms, δ: 126.4 (2 C); 127.5 (1 C); 129.1 (2 C); 136.8 (m); 149.6 (br.s, C(7a)); 152.2 (q, C(5), $^2J_{CH}$ = 7.6 Hz); 157.1 (m, C(2), $^2J_{C(2),CH_3}$ = 6.6 Hz, $^3J_{C(2),NCH_2}$ = 3.9 Hz); 158.9 (t, C(4), $^3J_{C(4),CH_2}$ = 3.5 Hz); 160.5 (t, C(7)$\underline{C}O$, $^3J_{CO,CH_2}$ = 3.8 Hz).

Ethyl 4-(ethoxycarbonylmethyl)-5-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-1-ylacetate (15). A 50% suspension of Ni/Ra (7.5 g) was carefully added in portions to a boiling solution of compound **12b** (1.5 g, 4.4 mmol) in 40 mL of ethanol. The reaction mixture was refluxed for 4 h then filtered. The filtrate was concentrated *in vacuo*, and the residue was crystallized from EtOH. The yield of compound **15** was 0.86 g (63%). ^1H NMR, δ: 0.96 (t, 3 H, $CH_2C\underline{H}_3$); 1.17, 1.20 (both t, 3 H each, 2 $CH_2C\underline{H}_3$); 2.38 (m, 5 H, $C\underline{H}_2CH_3$ + C(2)Me); 3.61 (s, 2 H, $C\underline{H}_2C(4)$); 4.08 and 4.15 (both q, 2 H each, 2 $C\underline{H}_2CH_3$); 4.78 (s, 2 H, $C\underline{H}_2N(1)$). ^{13}C NMR, δ: 13.0 ($\underline{C}H_3CH_2$); 14.3 and 14.4 (2 $CO_2CH_2\underline{Me}$); 19.4 ($CH_3\underline{C}H_2$); 22.5 (C(2)Me); 40.3 (C(4)$\underline{C}H_2$); 46.0 (N(1)$\underline{C}H_2$); 60.8 and 61.7 (2 $CO_2\underline{C}H_2Me$); 124.4 (C(5)); 154.0 (C(4)); 161.8 (CO); 168.0 (CO); 169.0 (CO).

3-(*N*-Alkylcarbamoylmethyl)-2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxamides (16a,b) (general procedure). A mixture of compound **12b** (2.3 g, 7 mmol) and an amine (30 mmol) in 40 mL of anhydrous EtOH was refluxed for 9 h. The precipitate that formed on cooling was filtered off.

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