Acta Chemica Scandinavica B 32 (1978) 303—305

Phosphoramides. VII.* Phenyl *N,N'*-Dimethylphosphorodiamidate as a Reagent for Synthesis of 3-Methylthieno[2,3-*d*]-pyrimidin-4(3*H*)-ones

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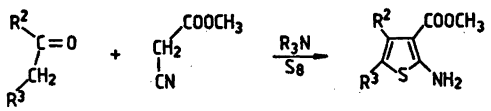
3-Methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones *4* were obtained in an exothermic reaction by heating phenyl *N,N'*-dimethylphosphorodiamidate *1* and methyl 2-acylamino-3-thiophenecarboxylates *3* to 250 °C. From *3* where $R^1 \equiv C_6H_5$, $R^2 \equiv H$, and $R^3 \equiv CH_3$ the expected *4* in 40 % yield was obtained, but 6-methyl-2-phenyl-4-methylaminothieno[2,3-*d*]pyrimidine *5* was also isolated in 45 % yield.

Recently we have shown that 3-methyl-4(3*H*)-quinazolinones with interesting biological and pharmacological activities can be prepared by heating methyl 2-acylaminobenzoates with equimolar amounts of phenyl *N,N'*-dimethylphosphorodiamidate *1* at 250 °C.[1] It was therefore of interest to find out whether this synthesis could be extended to heterocyclic carboxylic esters like methyl 2-acylamino-3-thiophenecarboxylates. It was known that these thiophene compounds undergo a quite different type of reaction with hexamethylphosphoric triamide (HMPT), forming 4,6-bis(dimethylamino)thieno[2,3-*b*]pyridines.[2]



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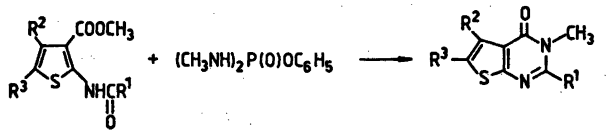
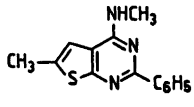
Methyl 2-amino-3-thiophenecarboxylates *2* were easily obtained (eqn. 1) by reaction of an appropriate carbonyl compound and methyl cyanoacetate with sulfur.[3] The starting materials *3*, which were needed for our reaction with the phosphorodiamidate *1*, were then obtained from *2* by acylation using standard methods.

It was found that heating of methyl 2-acylamino-3-thiophenecarboxylates *3* with *N,N'*-dimethylphosphorodiamidate *1* at 250 °C leads to the formation in an exothermic reaction of 3-methylthieno[2,3-*d*]pyrimidin-4(3H)-ones *4* in 20 – 48 % yield. If less than equimolar amounts of the phosphorodiamidate *1* were used, the starting material *3* was partly recovered. In the synthesis of the thienopyrimidine *4* ($R^1 = C_6H_5$, $R^2 = H$, and $R^3 = CH_3$), which was obtained in 40 % yield, 6-methyl-4-methylamino-2-phenylthieno[2,3-*d*]pyrimidine *5* was isolated in 45 % yield. *5* may be formed from demethylated *4* as it is known that phosphoramides can



3 *1* *4*

* Part VI: Pedersen, E. B. and Carlsen, D. *Synthesis* (1977) 890.



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substitute the potential hydroxygroup of quinazolinones with an amino-group.[4]

Table 1. 3-Methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones (*4*) prepared.

Product	R^1	R^2	R^3	Yield (%)
4a	H	H	H	27
4b	CH_3	H	CH_3	39
4c	CH_3	H	CH_2CH_3	27
4d	CH_3	H	C_6H_5	48
4e	CH_3	C_6H_5	H	20
4f	C_6H_5	H	CH_3	40[a]

[a] *5* was also isolated in 45 % yield.

EXPERIMENTAL

Methyl 2-amino-5-ethyl-3-thiophenecarboxylate m.p. 62 °C (H_2O-EtOH), *methyl 2-amino-4-phenyl-3-thiophene-carboxylate* m.p. 137–139 °C, (H_2O–EtOH), *methyl 2-amino-5-phenyl-3-thiophenecarboxylate* m.p. 182–185 °C (butanol) were prepared as described by Gewald *et al.*,[3] except that methyl cyanoacetate was used instead of ethyl cyanoacetate.

Methyl 2-acetylamino-5-methyl-3-thiophenecarboxylate m.p. 94–95 °C (EtOH–H_2O), *methyl 2-acetylamino-5-ethyl-3-thiophenecarboxylate* m.p. 58 °C (EtOH–H_2O), *methyl 2-acetylamino-4-phenyl-3-thiophenecarboxylate* m.p. 124–127 °C (EtOH–H_2O), and *methyl 2-acetylamino-5-phenyl-3-thiophenecarboxylate* m.p. 136–137 °C (butanol) were prepared by heating the corresponding amine in acetic anhydride and acetic acid. *Methyl 2-benzoylamino-5-methyl-3-thiophenecarboxylate* m.p. 170 °C (butanol) was prepared in the usual way by treating the corresponding amine with benzoylchloride in the presence of triethylamine.

Methyl 2-formylamino-3-thiophenecarboxylate. Methyl 2-amino-3-thiophenecarboxylate [5] (22 g) and formic acid (9 g) were refluxed for 6 h. The reaction mixture was distilled, b.p. 150–180 °C/0.2 mmHg to give 7 g (27 %) of the title compound, m.p. 118–120 °C (EtOH).

*Preparation of 3-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones* 4. *General procedure.* A mixture of the methyl 2-acylamino-3-thiophenecarboxylate (*3*) and phenyl *N,N'*-dimethylphosphorodiamidate (*1*) was heated in an oil bath at 250 °C. The temperature of the reaction mixture increased to 260–290 °C within 4–10 min. Heating was then continued for 15 min. The hot reaction mixture was poured directly onto ice (~200 g) in a separating funnel, and 2 M NaOH (100 ml) was added. The mixture was extracted with dichloromethane (50 ml portions) until all solid material had dissolved. The organic extract was evaporated and the residue (if nothing else is stated) was recrystallized from the solvent given.

*3-Methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one,* 4a, was prepared from methyl 2-formylamino-3-thiophenecarboxylate (5 g) and *1* (10 g). Yield 1.2 g (27 %); m.p. 160 °C (xylene with addition of decolorizing carbon), lit. m.p. 165 °C;[6] NMR ($CDCl_3$): δ 3.62 (s, 3 H), 7.35 (d, J = 5.8 Hz, 1 H), 7.50 (d, J = 5.8, 1 H), 8.02 (s, 1 H). MS: *m/e* (%), 166~M^+ (100); IR (KBr): 1680 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 214 nm (4.29), 253 nm (3.60), 262 nm (3.67), 293 nm (3.82).

*2,3,6-Trimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one,* 4b, was prepared from methyl 2-acetylamino-5-methyl-3-thiophenecarboxylate (10.7 g) and *1* (12.0 g). Yield 3.82 g (39 %); m.p. 104 °C (benzin 80–100 °C; NMR ($CDCl_3$): δ 2.52 (q, J = 1.1 Hz, 3 H), 2.56 (s, 3 H), 3.60 (s, 3 H), 7.07 (d, J = 1.1 Hz, 1 H); MS: *m/e* (%), 194~M^+ (100); IR (KBr): 1660 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 217 nm (4.60), 265 nm (3.76), 301 nm (3.89). Found: C 55.55; H 5.18; N 14.50; S 16.49. Calc. for $C_9H_{10}N_2OS$: C 55.66; H 5.19; N 14.43; S 16.48.

*2,3-Dimethyl-6-ethylthieno[2,3-*d*]pyrimidin-4-(3*H*)-one,* 4c, was prepared from methyl 2-acetylamino-5-ethyl-3-thiophenecarboxylate 9.0 g and *1* (10 g). The residue obtained according to the general procedure was an oil, which was distilled 155–180 °C/0.2 mmHg. This fraction was subjected to silica gel preparative TLC using ether – CH_2Cl_2 (1:1) for elution and 2.3 g (27 %) of the title compound was obtained. M.p. 49–51 °C; NMR ($CDCl_3$): δ 1.33 (t, J = 7.1 Hz, 3 H), 2.60 (s, 3 H), 2.77 (q, J = 7.1 Hz, 2 H), 3.60 (s, 3 H), 7.12 (s, 1 H); MS: *m/e* (%), 208 ~M^+ (62), 193 (100); IR (KBr): 1676 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 216 nm (4.37), 266 nm (3.92), 300 nm (4.00). Found: C 57.15; H 5.67; N 13.71; S 15.05. Calc. for $C_{10}H_{12}N_2OS$: C 57.68; H 5.81; N 13.46; S 15.37.

*2,3-Dimethyl-6-phenyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one,* 4d, was prepared from methyl 2-acetylamino-5-phenyl-3-thiophenecarboxylate (10 g) and *1* (12 g). Yield 4.5 g (48 %); m.p. 225 °C (xylene); NMR ($CDCl_3$): δ 2.62 (s, 3H), 3.62 (s, 3H), 7.28–7.78 (m, 6H); MS: *m/e* (%), 256~M^+ (100); IR (KBr): 1680 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 204 nm (4.36), 219 nm (4.48), 328 nm (4.32). Found: C 65.35; H 4.58; N 10.96; S 12.34. Calc. for $C_{14}H_{12}N_2OS$: C 65.62; H 4.72; N 10.93; S 12.49.

*2,3-Dimethyl-5-phenyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one,* 4e, was prepared from methyl 2-acetylamino-4-phenyl-3-thiophenecarboxylate

(13.7 g) and *1* (12 g). Yield 2.5 g (20 %); m.p. 197 °C (xylene); NMR ($CDCl_3$): δ 2.60 (s, 3 H), 3.50 (s, 3 H), 6.35 (s, 1 H), 7.26–7.60 (m, 5H); MS *m/e* (%), 256 ~M^+ (100); IR (KBr): 1675 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 222 nm (4.27), 242 nm (4.17), 302 nm (3.89). Found: C 65.50; H 4.71; N 10.91; S 12.47. Calc. for $C_{14}H_{12}N_2OS$: C 65.62; H 4.72; N 10.93; S 12.49.

*3,6-Dimethyl-2-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one*, 4f, and *6-methyl-4-methylamino-2-phenyl-thieno[2,3-d]pyrimidine* 5, were prepared from methyl 2-benzoylamino-5-methyl-3-thiophenecarboxylate (15 g) and *1* (16 g). The mixture was poured onto ice, without heating 15 min after the maximum temperature had been obtained. The residue obtined according to the general procedure was distilled 210–225 °C/0.8 mmHg. Preparative silica gel TLC using CH_2Cl_2 for elution yielded (i): 5.0 g (36 %) *4f*, m.p. 134–136 °C (benzin 80–100 °C); NMR ($CDCl_3$): δ 2.56 (d, J=1.2 Hz, 3 H), 3.53 (s, 3 H), 7.18 (q, J=1.2 Hz, 1 H), 7.56 (s, 5 H); MS: *m/e* (%), 256 ~ M^+ (94), 255 (100); IR (KBr): 1690 cm^{-1} (C=O); UV, λ_{max} (96 % EtOH) (log ε): 217 nm (4.72), 269 nm (3.75), 311 nm (4.47). Found: C 65.50; H 4.65; N 10.87; S 12.36. Calc. for $C_{14}H_{12}N_2OS$: C 65.62; H 4.72; N 10.93; S 12.49. (ii): 6.2 g (45 %) *5* m.p. 128–130 °C (benzin 80–100 °C); NMR ($CDCl_3$): δ 2.51 (d, J=1.2 Hz, 3 H), 3.19 (d, J=4.8 Hz, 3 H), 5.17 (NH, 1 H), 6.69 (q, J=1.2 Hz, 1 H), 7.4–7.5 (m, 2 H), 8.4–8.6 (m, 3 H). (By treatment with D_2O the signal at 5.17 ppm disappears and that at 3.19 ppm turns into a singlet); MS: *m/e* (%), 255 ~ M^+ (100); IR (KBr): 3325 cm^{-1} (NH); UV, λ_{max} (96 % EtOH) (log ε): 204 nm (4.43), 220 nm (4.44), 248 nm (4.44), 277 nm (3.98), 284 nm (3.99), 294 nm (3.99), 325 nm (4.12). Found: C, 65.50; H 5.10; N 16.23; S 12.50. Calc. for $C_{14}H_{13}N_3S$: C 65.87; H 5.13; N 16.46; S 12.54.

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Received November 30, 1977.