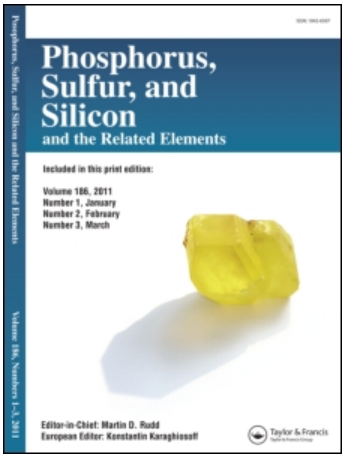

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A CONVENIENT SYNTHESIS OF NEW PYRIDOTHIENOPYRIMIDIN-4 (3H) ONES AND PYRIDOTHIENOPYRIMIDIN-2, 4(1H, 3H) DIONES

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Online publication date: 16 August 2010

Phosphorus, Sulfur, and Silicon, 179:1153–1157, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490459759

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(Received August 5, 2003; accepted October 14, 2003)

New derivatives of 2-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H) ones and 3-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) diones have been prepared by base catalyzed cyclocondensation of ethyl-3-aminothieno[3,2-b]pyridine-2-carboxylate with aryl nitriles and aryl- or alkyl isocyanates respectively.

Keywords: Base-catalyzed cyclization; cyclocondensation; isocyanates; nitriles; pyridothienopyrimidinone

Our interest in pyridothienopyrimidine synthesis emerges from few reports on their diverse biological activities.[1–3] The methods reported in the literature for the synthesis of these tricyclic compounds involve the ring transformation of thienopyridineoxazinone in the presence of different amines,[4–5] the cyclocondensation of pyridothiophene-2-aminocarboxamides with orthoesters[5] or with carbonyl compounds such as formamide,[7] acetic anhydride,[8] Vilsmeier reagen,[9] and dialkyl oxalate,[10] and also derivatization of pyridothienopyrimidines with suitable reagents.[11]

Synthesis from pyridothienoaminoester includes cyclisation with isothiocyanates in basic media[1] or with aliphatic nitriles in the presense of dry hydrogen chloride.[12–13] The latter has gained very little attention and there is also no report in the literature concerning the condensation of pyridothiophene aminoester with isocyanates. Prompted by these reports and in continuing our synthetic studies on bioactive heterocycles,[14] we wish to portray in this article a facile and convenient base catalyzed reaction of ethyl-3-aminothieno[2,3-b]pyrimidin-2-carboxylate 1 with aryl nitriles or aryl- and alkyl isocyanates

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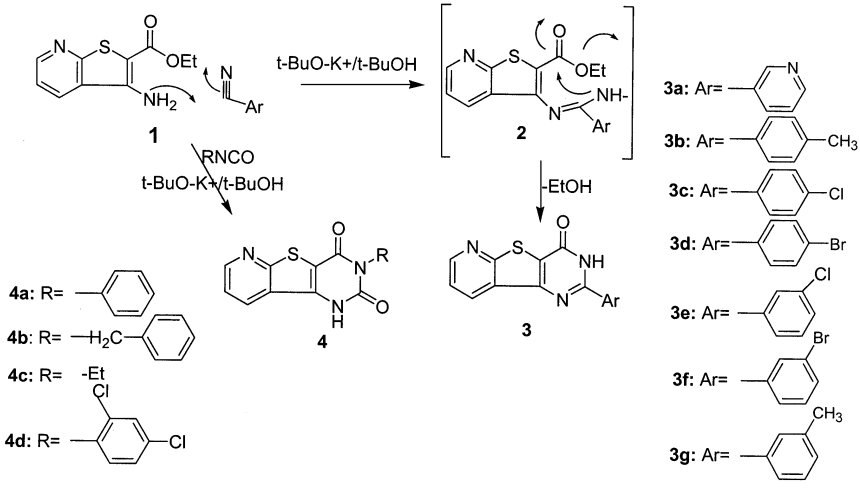
resulting in the formation of 2-substituted pyrido[3′,2′:4,5] thieno[3,2-d]pyrimidin-4(3H) ones and 3-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) diones.

RESULTS AND DISCUSSIONS

Treatment of ethyl-3-aminothieno[2,3-b]pyrimidin-2-carboxylate **1** with aromatic nitriles in the presence of potassium t-butoxide in t-butanol under reflux gave products identified as 2-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H) ones 3 (Scheme 1 and Table I). The structures of the products were deduced from their spectra data (Table I). For example, the ^{1}HNMR spectrum of **3b** in d_6-DMSO shows a singlet at δ 2.13 ppm (3H, Me), a multiplet at δ 7.43–7.75 ppm (7H, Ph and pyridine moiety) and a singlet at δ 13.1 ppm (1H, NH). The IR spectrum of this compound is devoid of the NH_2 and C=O (carboxyl) absorption bands of its precursor at 3330–3200 cm^{-1} and 1745 cm^{-1}, repectively, but instead shows two bands at 3250 cm^{-1} and 1690 cm^{-1} indicative of NH and C=O (amide) groups on the pyrimidine ring. The spectral data for compounds **3** are given in Table I.



SCHEME 1

When compounds **1** were reacted with isocyanates in the presence of potassium t-butoxide in t-butanol under reflux heterocyclisation occurred and gave the expected 3-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) diones **4**. Assignment of the structures

TABLE I Physical and Spectral Data of 2-Arylpyrido [3′,2′:4,5]thieno[3,2-d] pyrimidin-4(3H)ones **3 a–g**

Entry	Yield (%)	m.p. (°C)	Spectral data
3a	75	340	^{1}H-NMR: (DMSO-d_6)δ, IR (KBr disk): ν, m/z, 161; ^{1}H-NMR, 7.6 (m, 2H, Pyridin), 8.6 (m, 2H, Pyridine), 8.8 (m, 2H, Pyridin), 9.5 (s, 1H, Pyridine), 13.4 (broad, 1H, NH); IR, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$280.
3b	78	305	^{1}H-NMR, 2.13 (s, 3H, CH_3), 7.2 (d, 2H, C_6H_4), 7.6 (q, 1H, Pyridine), 8.1 (d, 2H, C_6H_4), 8.6 (m, 2H, Pyridine), 13.1 (broad, 1H, NH); IR, NH, 3100–3250 cm^{-1}, C═O, 1690 cm^{-1}; MS, M$^+$29
3c	51	315	^{1}H-NMR, 7.8 (d, 1H, C_6H_4), 7.8 (q, 1H, Pyridine), 8.4 (d, 2H, C_6H_4), 9.0 (m, 2H, Pyridine), 13.3 (broad, 1H, NH); IR, NH, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$313.
3d	67	280	^{1}H-NMR, 7.6 (q, 1H, Pyridine), 7.7 (d, 2H, C_6H_4), 8.1 (d, 2H, C_6H_4), 8.7 (m, 2H, Pyridine), 13.2 (broad, 1H, NH); IR, NH, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$357.
3e	65	332	^{1}H-NMR, 7.6 (m, 3H, C_6H_4), 8.2 (q, 1H, Pyridine), 8.3 (broad, 1H, C_6H_4, 8.7 (m, 2H, Pyridine), 13.3 (broad, 1H, NH); IR, NH, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$313.
3f	65	294–295	^{1}H-NMR, 7.6 (m, 3H, C_6H_4), 8.2 (q, 1H, Pyridine), 8.4 (broad, 1H, C_6H_4), 8.8 (m, 2H, Pyridine), 13.2 (broad, 1H, NH); IR, NH, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$357.
3g	72	302	^{1}H-NMR, 2.4 (s, 3H, CH_3), 7.4 (m, 3H, C_6H_4), 7.6 (q, 1H, Pyridine), 8.0 (broad, 1H, C_6H_4), 8.8 (m, 2H, Pyridin), 13.1 (broad, 1H, NH); IR, NH, 3100–3300 cm^{-1}, C═O, 1700 cm^{-1}; MS, M$^+$293.

4 was supported by their spectral data (Table II). The ^{1}H NMR of these compounds was devoid of the signal for the NH_2 group of the precursor at δ 5.93 ppm and showed a downfield signal at δ 12.7 ppm for NH group. Mass spectra showed the expected molecular ion peak and the fragmentation patern is according with the proposed structure.

In conclusion, we have developed a convenient method for one-pot conversion of ethyl-3-aminothieno[3,2-b]pyridine-2-carboxylate into2-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H) ones and 3-substituted pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) diones through base catalyzed cyclocondensation with nitriles and isocyanates respectively.

TABLE II Physical and Spectral Data of 3-Aryl and alkyl pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) diones **4 a–d**

Entry	Yield (%)	m.p (°C)	Spectral data
4a	72	342	^{1}HNMR: (DMSO-d_6) δ, IR (KBr disk): ν, m/z, 161, ^{1}H-NMR, 7.3 (m, 5H, Ph), 7.5 (q, 1H, Pyridine), 8.6 (m, 2H, Pyridin), 12.7 (broad, 1H, NH); IR, 3000–3200 cm^{-1}, C═O, 1710 cm^{-1}, C═O, 1650 cm^{-1}; MS, M$^+$295.
4b	78	328–329	^{1}H-NMR, 5.0 (s, 2H, CH_2), 7.25 (m, 5H, Ph), 7.5 (q, 1H, Pyridine), 8.6 (m, 2H, Pyridine), 12.6 (broad, 1H, NH); IR, NH, 3050–3200 cm^{-1}, C═O, 1700 cm^{-1}, C═O, 1650 cm^{-1}; MS, M$^+$309.
4c	82	294	^{1}H-NMR, 1.2 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 7.6 (q, 1H, Pyridine), 8.7 (m, 2H, Pyridine), 12.6 (broad, 1H, NH); IR, NH, 3000–3200 cm^{-1}, C═O, 1700 cm^{-1}, C═O, 1650 cm^{-1}; MS, M$^+$247.
4d	76	297–298	^{1}H-NMR, 7.6 (m, 3H, C_6H_3), 7.6 (q, 1H, Pyridine), 7.8 (broad, 1H, C_6H_3), 8.8 (m, 2H, Pyridine), 13.0 (broad, 1H, NH); IR, NH, 3000–3200 cm^{-1}, C═O, 1700 cm^{-1}, C═O, 1650 cm^{-1}; MS, M$^+$364.

EXPERIMENTAL SECTION

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on Bruker AC 100 Spectrometer in d_6.DMSO solution. Mass spectra were obtained from Varian CH-7 instrument at 70 eV.

General Procedure for the Preparation of 2-Aryl Pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H) Ones 3 a–g

A mixture of ethyl-3-aminothieno[2,3-b]pyrimidin-2-carboxylate **1** (4.5 mmol), the appropriate aryl nitrile (5.0 mmol) in DMF (4 ml) and potassium t-butoxide (4.8 mmol) in t-butanol (5 ml) was heated under reflux for 4.0 h. After the completion of the reaction, the solvent was evaporated in vacuo, the residue was dissolved in water (5 ml) and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from methanol to give compounds 3 in high yield (see Table I).

General Procedure for the Preparation of 3-Aryl and Alkyl Pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-2,4(1H,3H) Diones 4a–d

A mixture of ethyl-3-aminothieno[2,3-b]pyrimidin-2-carboxylate 1 (18 mmol), the appropriate isocyanate (20 mmol) in DMF (6 ml), and potassium t-butoxide (18 mmol) in t-butanol (4 ml) was heated under reflux for 4.0 h. After the completion of the reaction which was monitored by TLC, the solvent was evaporated in vacuo, the residue was dissolved in water (5 ml) and subsequently neutralized by 1N HCl. The crude product was collected, washed with hot chloroform and then recrystallized from methanol to give compounds 4 in high yield (see Table II).

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