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Synthesis of Substituted Thieno[2,3-*b*]pyrroles

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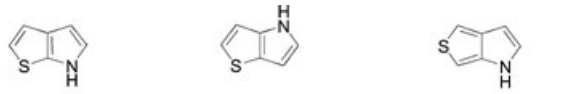
ABSTRACT: *Thieno[2,3-b]pyrroles can be synthesized through three steps: Gewald synthesis, alkylation, and Thorpe–Ziegler cyclization. Diethyl 3,6-bis((ethoxycarbonyl)methyl)-4-amino-6H-thieno-[2,3-b]pyrrole-2,5-dicarboxylate (***13***) has been obtained by one-pot method in DMF in good yield and high quality.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:236–238, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20290

INTRODUCTION

Thienopyrroles have been introduced into a range of biologically active compounds [1]. These include protein tyrosine phosphatases and CCK antagonists, as well as inhibitors of glycogen phosphorylase, cyclooxygenase, lipoxygenase, and MCP-1. In addition, the thienopyrrole ring system has been incorporated into bioisosteric analogs of the serotonin agonist *N,N*-dimethyltryptamine, and has been utilized as an isosteric replacement for tryptophan in physicochemical profiling of modified peptides.

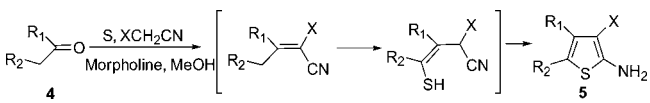
Thienopyrroles, especially the three different isomers **1, 2** and **3** fused onto the ***b*** junction of the pyrrole ring, are of interest because of their relationship to indoles [2]. Research in this field has mainly been centered on the preparation of analogues of naturally occurring indole derivatives.



1 6*H*-Thieno[2,3-*b*]pyrrole **2** 4*H*-Thieno[3,2-*b*]pyrrole **3** 1*H*- Thieno[3,4-*b*]pyrrole

RESULTS AND DISCUSSION

Thieno[2,3-*b*]pyrroles can easily be synthesized according to the Gewald reaction and the Thorpe–Ziegler cyclization. Gewald synthesis (Scheme 1) is probably the most versatile and important reaction for the preparation of biologically active compounds and intermediates containing a thiophene moiety **5** [5]. The reaction is a one-pot procedure involving the condensation of ketones (**4**) with active nitriles such as cyanoacetic esters and sulphur in the presence of an aliphatic amine such as morpholine. Thorpe–Ziegler cyclization (Scheme 2) is one of the most convenient methods for the synthesis of functionalized amino hetrocycles, especially five-membered heteroaromatics (**9**) [6]. A nitrile (**6**) undergoes ring closure by intramolecular addition of a deprotonated methylene group (EWG represents an



SCHEME 1 Gewald reaction of 2-aminothiophene

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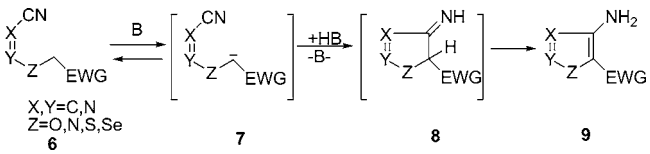
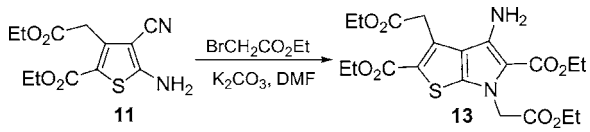


SCHEME 2 Thorpe-Ziegler cyclization

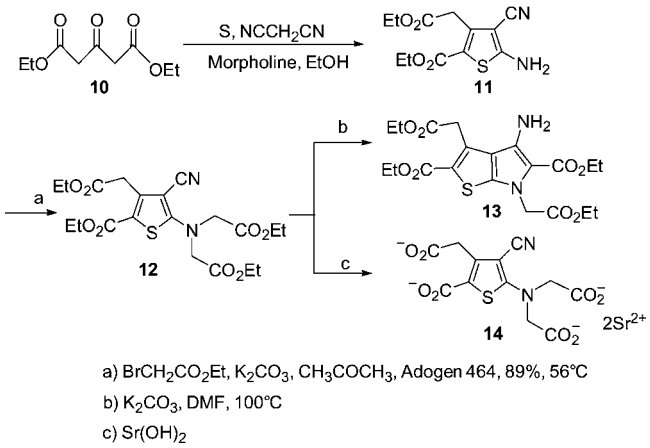


SCHEME 4

electron-withdrawing group) onto the cyano group, followed by a 1,3-H shift in the intermediate **8**. Thorpe–Ziegler cyclizations are mostly catalyzed by bases, although acid catalysis has also been used.

In this paper, we have utilized the above-mentioned reactions to prepare a novel substituted thieno[2,3-*b*]pyrrole, diethyl 3,6-bis((ethoxycarbonyl)methyl)-4-amino-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylate (**13**), which has not been found in the literature (Scheme 3). This compound may be selected as a ligand for preparing the strontium salt, and the present study intends to provide a strategy for preparing the substituted thieno[2,3-*b*]pyrroles.

Ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl) thiophene-2-carboxylate (**11**) was synthesized by the reaction of 3-oxo-glutarate (**10**) with malononitrile and sulphur via Gewald reaction [7]. Compound **11** in acetone was alkylated with ethyl bromoacetate in the presence of potassium carbonate and catalyst such as Adogen 464 at reflux for 4 h to give ethyl 3-((ethoxycarbonyl)methyl)-5-(bis((ethoxycarbonyl)methyl)amino)-4-cyano-thiophene-2-carboxylate (**12**), which is an intermediate of strontium ranelate (**14**), a medicine for the treatment of osteoporosis [7–9]. By making compound **12** undergo Thorpe–Ziegler cyclization, in the presence of potassium carbonate, using DMF as solvent, and refluxing at 150°C [10], the expected thieno[2,3-*b*]pyrrole (**13**) was prepared.



SCHEME 3

However, we found that diethyl 3,6-bis((ethoxycarbonyl)methyl)-4-amino-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylate (**13**) can also be obtained directly from compound **11** by a one-pot method (Scheme 4).

Compound **11** in DMF reacted with ethyl bromoacetate in the presence of potassium carbonate at 150°C for 7 h, undergoing alkylation and Thorpe–Ziegler cyclization at the same time, and 6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylate (**13**) was synthesized in good yield and high quality.

In conclusion, we report here two synthetic strategies for diethyl 3,6-bis((ethoxycarbonyl)methyl)-4-amino-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylate (**13**). More important, we found a convenient one-pot synthetic method for compound **13**.

We also report the structure comfirmation data and melting points of compounds **11** and **12** for the first time, even though they were known compounds.

EXPERIMENTAL

General Procedure

Melting points were determined on an RY-1 hot-stage microscope, and the thermometer was uncorrected.IR spectra were recorded on a Nicolet Impact 410 instrument as KBr disks.^{1}H NMR spectra were recorded on a Bruker Avance DPX-300/500 MHz instrument in $CDCl_3$, chemical shifts (δ) were reported in parts per million (ppm) relative to TMS as an internal standard. Mass spectra were recorded on Aglient 1100 LC-MS. Elementary analyses were performed on Elementar Vario ELIII instrument. All reactions were monitored by TLC on silica gel 60F-254 glass plates (E.Merk).

*Ethyl 5-Amino-4-cyano-3-(2-ethoxy-2-oxoethyl) thiophene-2-carboxylate (***11***) [7].* Morpholine (4.52 g) was added to diethyl 3-oxo-glutarate (**10**) (10.31 g, 0.051 mol) and malononitrile (3.37 g, 0.051 mol) in ethanol (20 mL). The reaction mixture was stirred for 1 h, while maintaining the temperature of the mixture below 30°C. Sulphur (1.72 g, 0.054 mol) was added into the above mixture and the reaction mixture was brought to reflux. After refluxing for 2 h, water was added into the mixture

until precipitation occurred. The precipitate was filtered, washed with water, and dried. The crude product was dissolved in ethanol, decolored with active charcoal, and recrystallized to obtain the title product in a yield of 90%.

mp: 128–129°C; IR (KBr): υ 3432, 3334, 2981, 2211, 1724, 1677, 1621, 1554, 1496, 1370, 1338, 1276, 1192, 1097, 1019, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.2–1.34 (m, 6H, $2 \times CH_3$), 4.00 (s, 2H, CH_2), 4.01–4.30(m, 4H, $2 \times OCH_2$), 5.48 (s, br, 2H, NH_2); MS *m/z* 281.0 $(M-1)^+$, 283.0 $(M+1)^+$, 306.1 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92. Found: C, 51.09; H, 4.92; N, 9.80.

*5-(Bis(2-ethoxy-2-oxoethyl)amino)-4-cyano-3-(2-ethoxy-2-oxoethyl)thiophene-2-carboxylate (***12***) [8].* Potassium carbonate (4.78 g, 0.035 mol) was added to a solution of **11** (5.00 g, 0.018 mol), ethyl bromoacetate (5.78 g, 0.036 mol) and Adogen 464 (0.16 g) in acetone (30 mL). The reaction mixture was brought to reflux. After refluxing for 5 h, the mixture was cooled and then filtered. The filtrate was concentrated and methanol (50 mL) was added into the concentrated mixture. The mixture was cooled, filtered, washed with water, and dried. The crude product was dissolved in ethanol, decolored with active charcoal, and recrystallized to obtain the title product in a yield of 89%.

mp: 105–106°C; IR (KBr): υ 2982, 2216, 1739, 1691, 1563, 1517, 1415, 1367, 1275, 1208, 1185, 1113, 1016, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3, $J = 7.00$ Hz), 1.30–1.33 (m, 9H, $3 \times CH_3$), 4.03 (s, 2H, CH_2), 4.18 (q, 2H, OCH_2, $J = 7.00$ Hz), 4.24–4.29 (m, 6H, $3 \times OCH_2$), 4.27 (s, 4H, $2 \times NCH_2$); MS: *m/z* 453.1 $(M-1)^+$, 455.1 $(M+1)^+$, 477.1 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{26}N_2O_8S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.90; H, 5.62; N, 6.04.

*Diethyl 3,6-Bis((ethoxycarbonyl)methyl)-4-amino-6H-thieno[2,3-b]pyrrole-2,5-dicarboxylate (***13***).* Method 1: Potassium carbonate (2.07 g, 0.015 mol) was added to a solution of **12** (4.54 g, 0.01 mol) in DMF (10 mL) and the reaction mixture was stirred at 150°C for 5 h. The mixture was poured into ice-cold water, solidified, filtered, and washed with water. The crude product was dissolved in chloroform, decolored with active charcoal, and then the solvent was removed in vacuo to yield the title product in a yield of 87%. Method 2: Ethyl bromoacetate (3.32 g, 0.02 mol) was added to a solution of **11** (2.82 g, 0.01 mol) and K_2CO_3 (4.14 g, 0.05 mol) in DMF (10 mL), and the reaction mixture was stirred at 150°C for 7 h. The mixture was handled and purification by the above method to give the title product in a yield of 92%.

mp: 198–200°C; IR (KBr): υ 3451, 3360, 2981, 2931, 1743, 1733, 1690, 1671, 1623, 1546, 1528, 1470, 1392, 1377, 1341, 1286, 1259, 1243, 1223, 1138, 1110, 1027, 670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.25–1.28 (m, 6H, $2 \times CH_3$), 1.34–1.38 (m, 6H, $2CH_3$), 4.17–4.24 (m, 4H, $2 \times OCH_2$), 4.29–4.39 (m, 4H, $2 \times OCH_2$), 4.35 (s, 2H, CH_2), 4.85 (s, 2H, NCH_2), 5.50 (s, br, 2H, NH_2); MS *m/z* 455 $(M+1)^+$, 477$(M+Na)^+$. Anal. Calcd for $C_{20}H_{26}N_2O_8S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.55; H, 5.58; N, 6.04.

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