Base-Catalyzed Condensation of Thioglycolic Ester with β-Chloropyrrolecarbaldehyde: One-Pot Approach to Substituted Thieno[2,3-*b*]pyrroles

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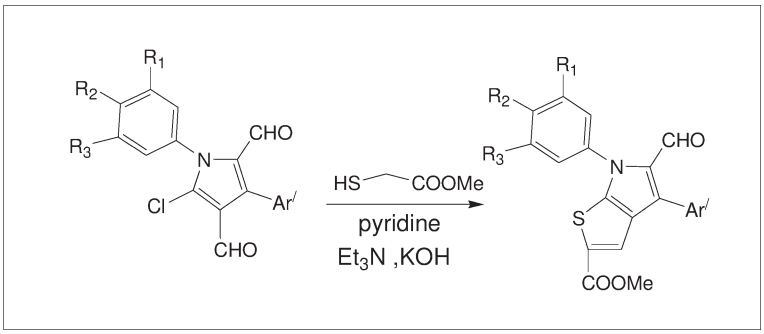

A simple methodology has been developed for the synthesis of thieno[2,3-*b*]pyrroles from *N*-aryl-diformylated-pyrroles by base catalyzed condensation with thioglycolic ester.

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INTRODUCTION

Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. The concept of bioisosterism is often considered to be qualitative and intuitive [1]. With the structure–activity relationships around the indole core evaluated, bioisosteric replacement of the indole arene ring with thiophene afforded a series of analogous thienopyrroles [2].

Blair *et al*. [3a] have shown that thiophene replacement of the annulated benzene ring in derivatives of piroxicam, amphetamine, had no effect on activity. Many thieno-fused bicyclic compounds such as thienopyridines, thienopyrimidines, and thienopyrroles have been recently prepared and tested for their biological properties. Among them, thienopyrroles are important from both theoretical and synthetic points of view, as they are isosteric with indole with their six π electrons. They are biologically active as PLA2 inhibitors, MCP-1 inhibitors, glycogen phosphorylase inhibitors, gonadotropin-releasing hormone antagonists, and antiviral agents [3b]. Moreover, the variable position of the heteroatom in thienopyrrole derivative increases the chance of suitable binding in a biological system.

RESULTS AND DISCUSSION

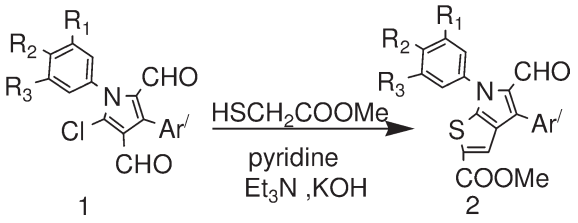
The synthesis of thienopyrroles has attracted much attention from organic chemists mainly because they are of pharmacological importance. However, the existing methods for the synthesis of thienopyrroles are laborious and have a number of limitations.

Whittamore *et al*. [4], Venable *et al*. [5], and Krayushkin *et al*. [6] have synthesized thienopyrroles by the condensation of the corresponding thiophenaldehydes with esters. Paulmier and coworkers [7] have synthesized thieno[3,2-*b*]pyrrole derivatives via palladium-catalyzed cyclization.

Herein, we use the *N*-phenyl-chloropyrroledicarboxaldehydes as starting materials, which are prepared from γ-lactam carboxylic acid derivatives [8]. The *N*-aryl-diformylated-pyrroles have a range of electrophilic center and a range of sterically encumbered heteroaryl pyrroles that can be synthesized from their reaction with nucleophiles. Clemens *et al*. [9] and Owton *et al*. [10] have used methyl thioglycolate for the construction of thiophene rings. Olesen *et al*. [11] have synthesized thieno[2,3-*b*]indole from methyl 1-benzylthieno[2,3-*b*]indole-carboxylate via debenzylation with aluminium trichloride in toluene and followed by decarboxylation. Herein, we wish to synthesize thienopyrroles by reaction with methyl thioglycolate with *N*-aryl-diformylated-pyrroles.

The heteroarylpyrroles are less stable than their simple pyrrole counterparts and, in general, classical methods are not applicable to their synthesis so their preparation was of very challenging to us. The condensation of thioglycolic ester with β-chloropyrrolecarbaldehyde in basic medium makes our methodology different from other previous literature methodology.

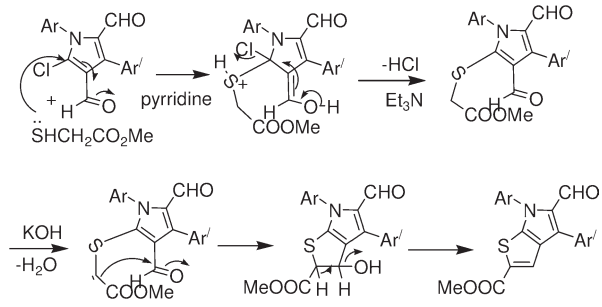
Scheme 1



The *N*-aryl-5-chloro-3-aryl/heteroaryl-pyrrole-2,4-dicarbaldehyde derivatives on treatment with thioglycolic ester and triethylamine in dry pyridine solution generates the head-to-head thienopyrrole derivatives in good yield (Scheme 1; Table 1).

However, the mechanism of the reaction is uncertain, and we were unable to isolate any intermediates, although a plausible mechanism may be written as depicted in Scheme 2 [12].

Scheme 2



CONCLUSIONS

In conclusion, we say that we have developed a new preparation method based on the use of active methylene thiol compounds and pyrrole-chloroaldehyde. The experimental simplicity of the reaction opens up new opportunities for the use of this reaction in synthetic and industrial processes.

EXPERIMENTAL

^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a BRUKER-AC 200 and 400 MHz spectrometer. Chemical shifts are reported in ppm. Data are reported as follows: chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet), and coupling constant (Hz).

^{13}C-NMR (50 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a BRUKER-AC 200 and 400 MHz spectrometer with complete proton decoupling. IR spectra were recorded on a Perkin-Elmer 883 and Shimadzu FTIR-8300 infrared spectrometers. EIMS (70 ev) spectra were taken using a VG Auto spec M mass spectrometer and ESI-MS spectra were taken using Waters LCT mass spectrometer. All reagents and solvents are obtained from commercial suppliers.

Chromatographic purification was done with either 60–120 or 100–200 mesh silica gels (SRL). Petroleum ether refers to the fraction boiling in the range 60–80°C. Tetrahydrofuran was freshly distilled over sodium–bezophenone.

General procedure for the synthesis of thieno[2,3-*b*]pyrrole derivatives (2). To a flask containing *N*-aryl-diformylated-pyrrole **1** (1 mmol) and methyl thioglycolate (2 mmol) in dry pyridine (3–5 mL) at O°C, triethylamine (2 mmol) was added dropwise. The reaction mixture was gradually allowed to attain the room temperature (25–30°C) and then stirred for additional 30 min at 45–50°C. Then, it was cooled to 10–15°C and 6 mL of 50% KOH (aq.) solution was added to it and stirred at that temperature for 20 min. The reaction mixture was then poured into ice cold water and extracted with CH_2Cl_2. The combined organic layer was repeatedly washed with 10% HCl solution and brine. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The product thus obtained was purified by silica gel (60–120 mesh) column chromatography [petroleum ether (60–80°C)–ethylacetate 20:1)].

Methyl-6-(3,4-dichloro-phenyl)-5-formyl-4-phenyl-6H-thieno [2,3-b]pyrrole-2-carboxylate (2a). Light yellow viscous semi-solid; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H), 7.51–7.63 (m, 7H), 7.93 (s, 1H), 8.10 (s, 1H), 9.7 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.40, 114.34, 125.60, 126.72 (2C), 128.84, 129.01 (2C), 129.70 (2C), 129.84, 130.12 (2C), 131.47, 131.99, 132.72, 133.89, 135.62, 136.48, 162.89, 179.95. ESI-MS Cal for $C_{21}H_{13}NO_3Cl_2S$ [M], [M + H^+] = 431.104 found 430.0994 (^{35}Cl, ^{35}Cl), 432.0977 (^{37}Cl, ^{35}Cl). Anal. Calcd. for $C_{21}H_{13}NO_3C_{l2}S$: C, 58.62; H, 3.05; N, 3.26%; Found: C, 58.46; H, 3.13; N, 3.41%.

Table 1

Synthesis of *N*-aryl-thienopyrrole derivatives (**2**) from *N*-aryl-diformylated-pyrroles (**1**).

Substrate		Ar	Products	Yield (%)
N-aryl-diformylated-pyrrole			*N*-aryl-thienopyrrole	
1a	$R_1 = H, R_3 = R_2 = Cl$	Phenyl	**2a**	61
1b	$R_1 = R_3 = H, R_2 = Br$	Phenyl	**2b**	60
1c	$R_1 = H, R_3 = R_2 = F$	Phenyl	**2c**	52
1d	$R_1 = Cl, R_2 = F, R_3 = H$	2-Thienyl	**2d**	58
1e	$R_1 = R_3 = R_2 = H$	Phenyl	**2e**	90
1f	$R_1 = R_3 = H, R_2 = Cl$	Phenyl	**2f**	87

Methyl-6-(4-bromo-phenyl)-5-formyl-4-phenyl-6H-thieno [2,3-b]pyrrole-2-carboxylate (2b). Light yellow viscous dense liquid; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.89 (s, 3H), 7.37 (dd, J = 1.5, 6.6 Hz, 2H), 7.50–7.53 (m, 3H), 7.58–7.68 (m, 4H), 7.93 (s,1H), 9.71 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 52.36, 122.34, 125.53, 126.90 (2C), 128.78, 128.94 (2C), 129.44, 129.54, 129.67, 130.04 (2C), 131.00, 131.34, 132.56 (2C), 133.92, 137.61, 162.86, 179.91. Anal. Calcd. for $C_{21}H_{14}BrNO_3S$: C, 57.28; H, 3.20; N, 3.18%; Found: C, 57.54; H, 3.63; N, 3.47%.

Methyl-6-(3,4-difluoro-phenyl)-5-formyl-4-phenyl-6H-thieno [2,3-b]pyrrole-2-carboxylate (2c). Light yellow viscous semi-solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.93 (s, 3H), 7.29–7.37 (m, 2H), 7.47–7.55 (m, 4H), 7.60 (d, J = 6.8 Hz, 2H) 7.93 (s, 1H), 9.7 (s, 1H). ^{13}C-NMR (CDC_{l3}, 100 MHz) δ: 52.41, 115.45, 115.65, 117.78, 117.96, 121.80, 121.83, 125.54, 128.78, 128.87, 128.99 (2C), 129.49, 129.59, 130.02 (2C), 130.83, 131.18, 132.65, 133.96, 162.80, 179.87. Anal. Calcd. for $C_{21}H_{13}F_2NO_3S$: C, 63.47; H, 3.30; N, 3.52%; Found: C, 63.66; H, 3.57; N, 3.28%.

Methyl-6-(3-chloro-4-fluoro-phenyl)-5-formyl-4-thiophene-2-yl-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (2d). Light yellow viscous semisolid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.90 (s, 3H), 7.20–7.32 (m, 2H), 7.35–7.39 (m, 2H), 7.53–7.56 (m, 2H), 8.03 (s, 1H), 9.92 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 52.46, 117.18, 117.41, 125.45, 125.53, 125.80, 127.93 (2C), 128.18, 128.78, 128.87, 129.20, 129.68, 130.83, 132.36, 132.64, 156.64, 159.14, 162.72, 179.36. ESI-MS Cal for $C_{19}H_{11}NO_3ClFS_2$ [M], [M + H^+] = 420.588 found 419.9525 (^{35}Cl), 421.9925 (^{37}Cl). Anal. Calcd. for $C_{19}H_{11}NO_3ClFS_2$: C, 54.35; H, 2.64; N, 3.34%; Found: C, 54.44; H, 2.81; N, 3.77%.

Methyl-5-formyl-4,6-diphenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (2e). Light yellow viscous dense liquid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.88 (s, 3H), 7.47–7.54 (m, 8H), 7.63 (d, J = 6.8 Hz, 2H), 7.94 (s, 1H), 9.73 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz, tertiary carbon not appeared) δ: 52.30, 125.27 (2C), 125.55, 128.59, 128.86 (2C), 129.43 (2C), 130.07 (2C), 152.54, 179.94. Anal. Calcd. for $C_{21}H_{15}NO_3S$: C, 69.79; H, 4.14; N, 3.88%; Found: C, 69.46; H, 3.83; N, 4.27%.

Methyl-6-(4-chloro-phenyl)-5-formyl-4-phenyl-6H-thieno [2,3-b]pyrrole-2-carboxylate (2f). Light yellow viscous dense liquid; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.86 (s, 3H), 6.97 (d, J = 8.6 Hz, 1H), 7.42–7.50 (m, 8H), 7.81 (d, J = 8.8 Hz, 1H), 9.67 (s, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.54, 122.64, 124.53, 126.89 (2C), 128.72, 128.94 (2C), 129.44, 129.54, 129.67, 130.04 (2C), 131.00, 131.34, 132.88 (2C), 133.92, 137.71, 162.86, 179.89. Anal. Calcd. for $C_{21}H_{14}ClNO_3S$: C, 63.72; H, 3.56; N, 3.54%; Found: C, 63.54; H, 3.83; N, 3.77%.

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