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Transition-metal-free double C−S cross-coupling reaction by using Na_2S as a sulfurating reagent

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ABSTRACT

A highly efficient synthesis of N-substituted indolo[3',2':4,5]thieno[2,3-b]quinoxaline derivatives via double C−S cross-coupling reaction. The odorless and stable solid Na_2S was used as a suitable and environmentally friendly source of sulfur. The double C−S bonds have not previously have been achieved, which renders our observation more striking.

Keywords: Double C–S cross-coupling reactions, double heteroarylation, indolo[3',2':4,5] thieno[2,3-b]quinoxaline.

INTRODUCTION

Organosulfur compounds have gained attention because sulfur-containing building blocks are significant functions in general organic synthesis. Aryl sulfides and hetero aryl sulfides are valuable synthons in organic synthesis of biologically, pharmaceutically active molecules and natural products.[1] For example, thienodolin,[2] IK-1 and IK-2 etc.[3] Thienodolin was an alkaloid and it was isolated from the fermentation mixture of *Streptomyces albogriseolus* and it was characterized by Kanbe group.[4] The diversity of biological activities gave an impulse to the development of convenient synthetic routes for the synthesis of the indolo[3',2':4,5] thieno[2,3-b]quinoxaline derivatives.

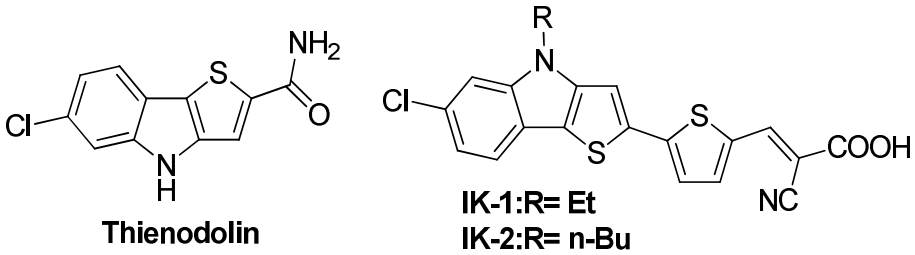


Fig. 1. Examples of natural and synthetic derivatives of thieno [2,3-*b*]indole skeleton

The most commonly employed methodologies are metal-catalyzed coupling of thiols.[5] However, these processes require either high temperature or high catalyst loading. The development of novel, efficient, and environmentally benign synthetic methodologies for the incorporation of sulfur into organic frameworks is a significant and challenging task. It was therefore necessary to develop a suitable and general synthetic route for double C–S cross-coupling reactions.

MATERIALS AND METHODS

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60-120mesh). Melting points were determined using an electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$, acetone, DMSO-*d6* (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer.

General Procedure for the Synthesis of indolo[3',2':4,5] thieno[2,3-b]quinoxaline derivatives: A mixture of dichloro compound **1** (1.0 mmol) and Na_2S (**2**, 1.1 mmol) was heated to 110±5°C till reaching to its molten state and then stirred at the same temperature under open air for the time mentioned in Table-1. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with cold water (10 mL). The mixture was stirred vigorously at room temperature for 10 min. The solid separated was filtered and washed thoroughly with cold water (3 x 5 mL). The solid obtained was dried under vacuum to gave the desired product **3**.

All new compounds gave satisfactory analytical and spectroscopic data.
7H-Indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3a): Pale yellow solid; yield: 91%; mp: 354-356 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.57 (s, br, 1H, NH), 8.21-8.11 (m, 3H, ArH), 7.88-7.68 (m, 3H, ArH), 7.37-7.33 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.29, 145.35, 144.72, 140.66, 140.21, 137.66, 129.36, 128.22, 128.07, 127.40, 122.96, 122.05, 121.46, 119.05, 112.65, 111.76; HRMS: m/z [M+1] calcd for $C_{16}H_{10}N_3S$ (M+H): 276.0595; found: 276.0603.

7-Methyl-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3b): Yellow solid; yield: 91.5%; mp: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.34 (m, 1H, ArH), 8.24 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.09 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.79-7.75 (m, 1H, ArH), 7.70-7.66 (m, 1H, ArH), 7.46-7.26 (m, 3H, ArH), 3.95 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.09, 146.98, 146.03, 141.29, 140.95, 138.09, 128.99, 128.61, 128.19, 127.09, 122.87, 122.79, 121.69, 120.39, 111.76, 109.36, 32.31; HRMS: m/z [M+1] calcd for $C_{17}H_{12}N_3S$ (M+H): 290.0752; found: 290.0751.

7-propyl-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3c): Yellow solid; yield: 92.0%; mp: 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39-8.36 (m, 1H, ArH), 8.24 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H, ArH), 8.09 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.79-7.74 (m, 1H, ArH), 7.69-7.65 (m, 1H, ArH), 7.48-7.39 (m, 1H, ArH), 7.38-7.26 (m, 2H, ArH), 4.29 (t, J = 7.2 Hz, 2H), 2.08-1.99 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.31, 146.54, 146.15, 141.06, 140.89, 138.25, 128.03, 128.68, 128.24, 127.14, 123.12, 122.79, 121.67, 120.54, 111.95, 109.79, 48.17, 22.64, 11.58; Mass: m/z [M+1] 318.20.

7-allyl-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3d): Yellow solid; yield: 92.0%; mp: 151-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, J_1 = 5.6 Hz, J_2 = 2.0 Hz, 1H, ArH), 8.25 (d, J = 7.6 Hz, 1H, ArH), 8.10 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.80-7.76 (m, 1H, ArH), 7.71-7.66 (m, 1H, ArH), 7.48-7.36 (m, 3H, ArH), 6.12-6.04 (m, 1H), 5.40-5.29 (m, 2H), 4.93 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.32, 146.38, 145.93, 141.00, 140.85, 138.28, 130.78, 129.03, 128.68, 128.26, 127.20, 123.06, 122.92, 121.83, 120.50, 119.47, 112.39, 109.85, 48.63; Mass: m/z [M+1] 316.20.

7-(but-3-en-1-yl)-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3e): Yellow solid; yield: 91.0%; mp: 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, J_1 = 6.8 Hz, J_2 = 3.6 Hz, 1H, ArH), 8.25 (d, J = 7.2 Hz, 1H, ArH), 8.11 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.80-7.76 (m, 1H, ArH), 7.71-7.66 (m, 1H, ArH), 7.50-7.48 (m, 1H, ArH), 7.40-7.38 (m, 2H, ArH), 5.86-5.82 (m, 1H), 5.14-5.07 (m, 2H), 4.41 (t, J = 7.0 Hz, 2H), 2.77 (q, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.31, 146.44, 146.15, 141.07, 140.75, 138.28, 133.50, 129.08, 128.69, 128.26, 127.22, 123.18, 122.87, 121.77, 120.59, 118.67, 112.11, 109.78, 46.16, 33.44; Mass: m/z [M+1] 330.20.

7-hexyl-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3f): Yellow solid; yield: 88.5%; mp: 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, J_1 = 7.6 Hz, J_2 = 3.6 Hz, 1H, ArH), 8.25 (d, J = 8.4 Hz, 1H, ArH), 8.10 (d, J = 8.4 Hz, 1H, ArH), 7.79-7.66 (m, 2H, ArH), 7.48-7.36 (m, 3H, ArH), 4.33 (t, J = 7.4 Hz, 2H), 2.03-1.96 (m, 2H), 1.46-1.19 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.29, 146.44, 146.10, 141.02, 140.80, 138.20, 129.01, 128.63, 128.22, 127.10, 123.09, 122.76, 121.64, 120.50, 111.89, 109.74, 46.56, 31.31, 29.15, 26.61, 25.85, 22.90, 22.44; Mass: m/z [M+1] 360.30.

7-benzyl-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3g): Yellow solid; yield: 89.0%; mp: 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 7.2 Hz, 1H, ArH), 8.25 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H, ArH), 8.08 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.79-7.75 (m, 1H, ArH), 7.70-7.65 (m, 1H, ArH), 7.49-7.26 (m, 8H, ArH), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.32, 146.58, 145.87, 141.06, 140.99, 138.30, 134.55, 129.13 (2C), 129.04, 128.67, 128.59, 128.26, 127.68 (2C), 127.22, 123.17, 123.04, 121.95, 120.52, 112.53, 109.99, 50.09; Mass: m/z [M+1] 366.20.

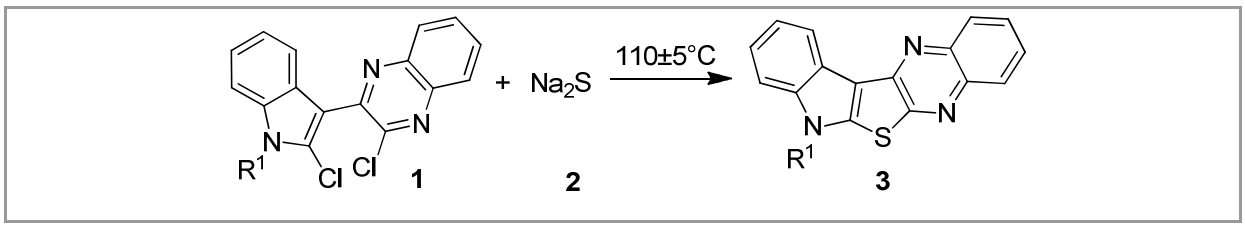
7-(4-methoxybenzyl)-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3h): Yellow solid; yield: 88.0%; mp: 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J = 8.4 Hz, 1H, ArH), 8.28 (d, J = 8.4 Hz, 1H, ArH), 8.07 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.79-7.75 (m, 1H, ArH), 7.69-7.65 (m, 1H, ArH), 7.54-7.49 (m, 1H, ArH), 7.42-7.26 (m, 4H, ArH), 6.96-6.87 (m, 2H, ArH), 5.42 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.90, 158.45, 146.63, 145.14, 140.93, 140.39, 138.10, 129.65, 129.39, 129.10, 128.60, 128.26, 128.19, 127.18, 125.95, 122.99, 121.94, 120.57, 114.44, 113.83, 112.22, 109.91, 55.26, 49.64; Mass: m/z [M+1] 396.2.

7-(2-chlorobenzyl)-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3i): Yellow solid; yield: 87.0%; mp: 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, J = 7.2 Hz, 1H, ArH), 8.26 (d, J = 8.4 Hz, 1H, ArH), 8.08 (d, J = 8.0 Hz, 1H, ArH), 7.80-7.66 (m, 2H, ArH), 7.49-7.26 (m, 5H, ArH), 7.19 (t, J = 7.4 Hz, 1H, ArH), 6.96 (d, J = 8.0 Hz, 1H, ArH), 5.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.24, 146.53, 145.82, 141.02, 138.35, 133.40, 132.09, 130.07, 130.00, 129.85, 129.15, 129.06, 128.81, 128.73, 128.26, 127.46, 127.28, 123.15, 123.12, 122.08, 112.76, 109.98, 47.68; Mass: m/z [M+1] 400.20.

7-(2-fluorobenzyl)-7H-indolo[3',2':4,5]thieno[2,3-b]quinoxaline (3j): Yellow solid; yield: 87.5%; mp: 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.25 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 8.09 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.79-7.75 (m, 1H, ArH), 7.70-7.66 (m, 1H, ArH), 7.52 (d, J = 7.6 Hz, 1H, ArH), 7.49-7.31 (m, 3H, ArH), 7.18-7.09 (m, 3H, ArH), 5.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.90, 159.44 (d, J = 125.3 Hz), 146.42, 145.80, 140.95 (d, J = 7.75 Hz), 138.28, 130.56 (d, J = 7.65 Hz), 129.58, 129.54, 129.06, 128.68 (2C), 128.23, 127.27, 124.74 (d, J = 3.83 Hz), 123.09, 122.00, 121.84 (d, J = 14.59 Hz), 120.50, 115.98 (d, J = 20.73 Hz), 112.60, 109.91, 43.80 (d, J = 5.34 Hz) ; Mass: m/z [M+1] 382.2.

RESULTS AND DISCUSSION

The synthesis of indole fused thieno [2,3-*b*]quinoxalines (**3**) is presented in scheme 1, these derivatives could be easily obtained by a reaction of dichloro compound **1** [6] with sodium sulfide **2**. The compound **3** was characterized by NMR, ^{13}C NMR and HRMS.



Scheme 1: Synthesis of *N*-substituted indolo[3',2':4,5]thieno[2,3-b]quinoxaline 3

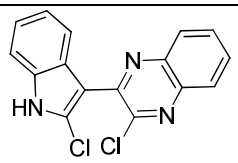
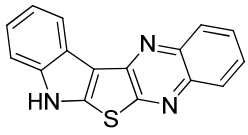
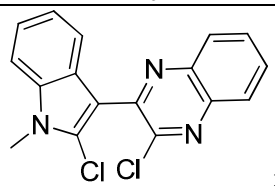
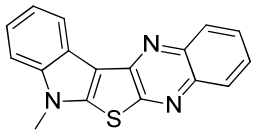
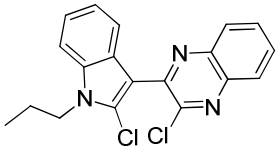
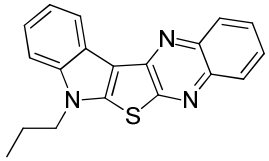
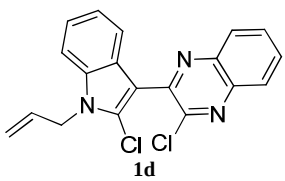
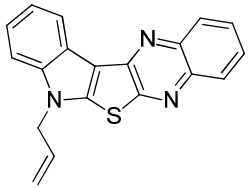
The compound **1** was reacted with Na_2S **2** under various conditions (Table 1). Initially, several combinations of solvents and sulfurating reagents were used for the C-S coupling of **1a** with **2** at 110-120°C depending on the solvents used e.g. DMF, toluene, DMSO and o-Xylene (entries 1–4, Table 1).

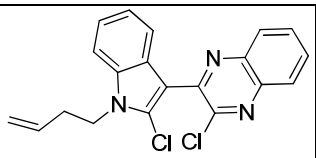
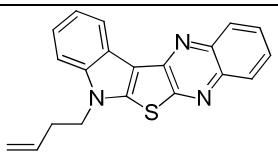
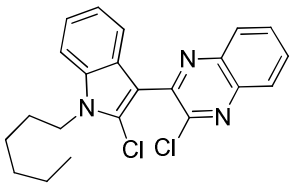
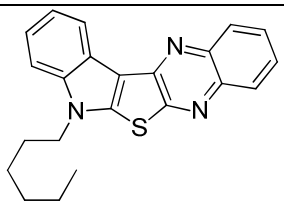
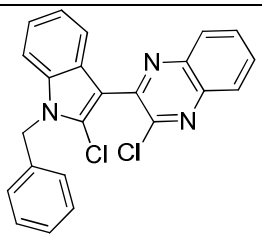
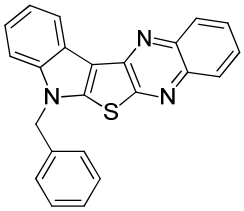
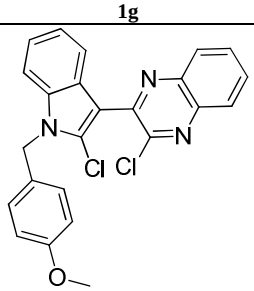
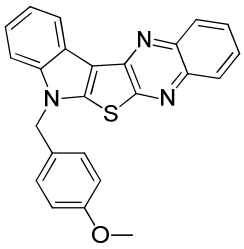
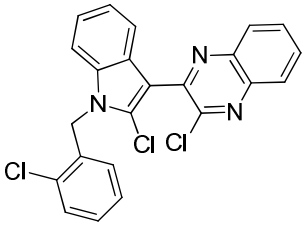
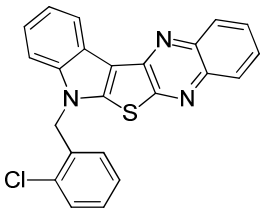
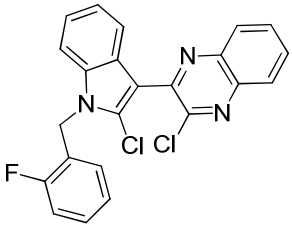
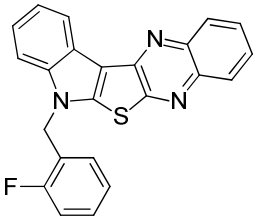
Table 1: Screening of solvents and sulfurating reagents

S.No.	Solvent	Reagent(2)	Time (hr)	Temperature (°C)	Product (%)
1	Toluene	$Na_2S_2O_3$	5	110	<5
2	DMSO	$Na_2S_2O_3$	5	120	10
3	DMF	$Na_2S_2O_3$	5	120	15
4	DMF	$Na_2S_2O_3/H^+$	5	120	70
5	o-Xylene	$Na_2S_2O_3/H^+$	5	120	40
6	Toluene	Na_2S	2	110	80
7	DMSO	Na_2S	1.5	120	75
8	DMF	Na_2S	1	120	85
9	o-Xylene	Na_2S	1	120	83
10	**-**	**Na_2S**	**1**	**110**	**91**

Reactions were carried out with other sulfurating agent like $Na_2S_2O_3$, but very poor yields observed (entries 1, 2 & 3, Table 1). However there was product formation observed in $Na_2S_2O_3/H^+$ condition with some extend (entries 4 & 5 Table 2). There were satisfactory results observed in DMF, toluene, DMSO and o-Xylene with Na_2S **2** (entries 6, 7, 8 & 9, Table 1). Interestingly, the product yield was continued to increase when the reaction was performed without any solvent (entries 10, Table 1). Indeed the reaction was completed within few minutes in these cases affording compound **3a** in 91% yield. As this approach not only avoids the environmental hazard but also reduce the cost. Moreover, the product **3a** was isolated in pure form without performing any chromatographic purification process. To explore the applicability of our reaction, we employed a variety of substituted dichloro compounds in the reaction to understand the scope and the generality of this methodology was presented in (Table-2)

Table-2.

Entry	Dichloro derivative (**1**)	Nucleophile (**2**)	Product (**3**)	Time (min)	Yield (%)
1	 **1a**	Na_2S **2**	 **3a**	60.0	91.0
2	 **1b**	**2**	 **3b**	30.0	91.5
3	 **1c**	**2**	 **3c**	45.0	92.0
4	 **1d**	**2**	 **3d**	45.0	92.0

5	 **1e**	**2**	 **3e**	50.0	91.0
6	 **1f**	**2**	 **3f**	90.0	88.5
7	 **1g**	**2**	 **3g**	65.0	89.0
8	 **1h**	**2**	 **3h**	65.0	89.0
9	 **1i**	**2**	 **3i**	70.0	87.0
10	 **1j**	**2**	 **3j**	70.0	87.5

CONCLUSION

In conclusion, we have developed a novel and simple strategy for the synthesis *N*-substituted indolo[3',2':4,5]thieno[2,3-b]quinoxaline derivatives *via* double C−S cross-coupling reaction. This operationally simple, solvent free and transition-metal free approach afforded a library fused indolo[3',2':4,5]thieno[2,3-b]quinoxaline derivatives. The double C−S bonds have not previously have been

achieved, which renders our observation more striking.

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