A New and Facile Synthesis of Thieno[2,3-*b*]indole Derivatives via Condensation of Isocyanide and Indolin-2-thiones

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Abstract: A new one-pot synthesis of thieno[2,3-*b*]indole ring systems is described. Condensation of cyclohexyl isocyanide with indolin-2-thiones yielded 3-cyclohexyaminomethylene-indolin-2-thiones, which upon reaction with α-halocarbonyl compounds produced the title compounds.

Key words: thieno[2,3-*b*]indole derivatives, isocyanide, thioamide

Thiophene derivatives are important chemical building blocks. A variety of molecules containing the thiophene ring display a wide range of biological activity and find applications as pharmaceuticals.[1] Heterocyclic-fused systems such as thieno-indoles have attracted a great deal of interest, due to their presence in natural products,[2] as novel conducting polymers[3] and antifungal agents.[4] Thieno[2,3-*b*]indole derivatives are useful for the treatment of epilepsy, neurological diseases such as senile dementia, Parkinson's disease, pain, and deficiencies of mental and motoric performance seen after conditions of brain ischemia (Figure 1).[5]

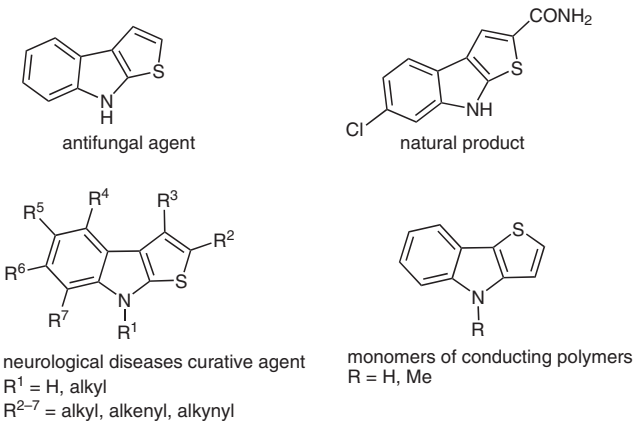
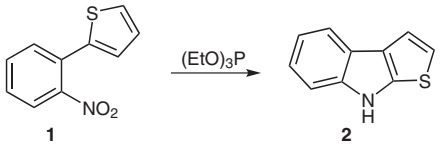


Figure 1

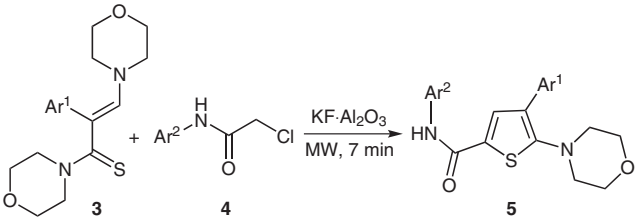
However, limited attention has been given to the synthesis of thieno[2,3-*b*]indole ring systems. To the best of our knowledge, there are few methods for synthesis of the thieno[2,3-*b*]indole skeleton in the literature. The deoxygenative cyclization of *o*-nitro arenes **1** in refluxing triethyl phosphate as solvent is the main method to synthesize framework **2** (Scheme 1).[6] This nitrene-mediated reductive cyclization procedure suffers from poor substituent tolerance, drastic reaction conditions, and long reaction times, although an improved Cadogan reductive cyclization has also been developed.[7]



Scheme 1

In 2004, Bergman et al. reported an efficient total synthetic pathway to the alkaloid thienodolin starting from 2-chloroindole-3-carbaldehyde.[8] Thienodolin was isolated from the culture broth of *Streptomyces albogriseolus* and was shown to have both growth promoting and inhibiting activities in rice seedlings.[2] Recently the Friedel–Crafts (FC) reaction has also been used for the preparation of thieno[2,3-*b*]indole derivatives;[9] wherein the authors reported their results on the electrophilic recyclization of isothiocyanates in the presence of anhydrous $AlCl_3$. Thieno[2,3-*b*]indoles can also be synthesized by tandem cyclization involving sequential sigmatropic rearrangements.[10]

It is evident that a novel and flexible protocol with wide substituent tolerance and mild reaction conditions is desirable in the preparation of thieno[2,3-*b*]indoles. Thioamides have been used as useful synthones in the substrates of heterocycles.[11] Previously we have reported an efficient synthesis of 5-acyl thiophenes **5** as anti-inflammatory agents using thioamides (Scheme 2).[12]



Scheme 2

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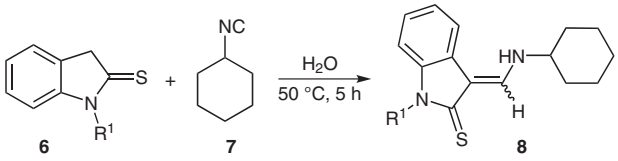
The starting thioamides **3** were obtained by the reaction of the corresponding thioacetomorpholides with morpholine and triethyl orthoformate. However, extention of this strategy to indoline-2-thiones failed. On the other hand, isocyanides are compounds with an extraordinary reactivity that have been investigated for over one and half centuries.[13] In the context of our general interest in the synthesis of thiophene derivatives using thioamides,[14] we were intrigued by the possibility of the reaction of cyclohexyl isocyanide with indoline-2-thiones to obtain cyclohexyaminomethylene-indolin-2-thiones, which, upon reaction with α-halocarbonyl compounds, could produce the desired thieno[2,3-*b*]indole framework.

Thus, when indolin-2-thiones **6** were treated with cyclohexyl isocyanide **7** in water and stirred for 5 hours at 50 °C, cyclohexyaminomethylene-indolin-2-thiones **8** were obtained in good yields (Scheme 3).



Scheme 3

The ^{1}H NMR and ^{13}C NMR spectra of the product clearly indicated the formation of **8**. The ^{1}H NMR spectrum of **8** (R^1 = Me) consisted of a broad line at δ = 12.08 ppm (exchangeable with D_2O) correlating with the NH, a doublet for the vinyl proton at δ = 8.05 ppm (J = 13.71 Hz), four lines for the aromatic protons at δ = 7.44-7.13 ppm, a sharp singlet for NCH_3 at δ = 3.77 ppm, a multiplet for the NCH cyclohexyl proton at δ = 3.50–3.49 ppm, and a multiplet for the cyclohexyl ring between δ = 1.37–2.11 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **8** showed 14 distinct resonances in agreement with the proposed structure.

The effect of the reaction temperature was studied by carrying out the model reaction at room temperature and 50 °C. It was observed that the yield was increased by raising the temperature. Low yields with long reaction time were observed in the organic solvents such as CH_2Cl_2 and MeCN.

Mechanistically, it is conceivable that the reaction involves the initial depronondation of an indolin-2-thione **6** by cyclohexyl isocyanide **7**. Then, the positively charged ion might be attacked by the anion of the indolin-2-thione **6** leading to **9**. Such an addition product may isomerize under the reaction conditions employed to produce **8** (Scheme 4).

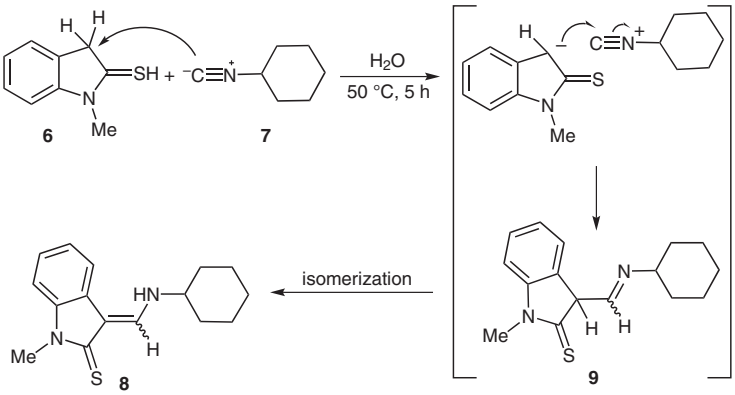
Reaction of **8** with α-halocarbonyl compounds **10** under basic conditions led to desired thieno[2,3-*b*]indole ring system **11** with high yield. To our knowledge, the thieno[2,3-*b*]indole ring system **11** is unprecedented. The reaction proceeded in aqueous acetonitrile (2:1) and was complete within 3 hours at room temperature. The structures of the products **11** were confirmed by analytical data, ^{1}H NMR and ^{13}C NMR spectra,[15] and by comparison with known data in the literature for **11e**.[9]

To generalize this method, we used a series of α-halocarbonyl compounds and indolin-2-thione derivatives to obtain their corresponding thieno[2,3-*b*]indoles (Table 1).

A plausible mechanism for the formation of the thieno[2,3-*b*]indoles is shown in Scheme 5. Component **8** undergoes *S*-alkylation with α-haloketone **10** affording the iminium ion **12**. Subsequently **12** can hydrolyze to corresponding aldehyde **13** or be transformed to **14**. Subsequent treatment with K_2CO_3 leads to formation of thieno[2,3-*b*]indole **11** with elimination of water and cyclohexylamine.

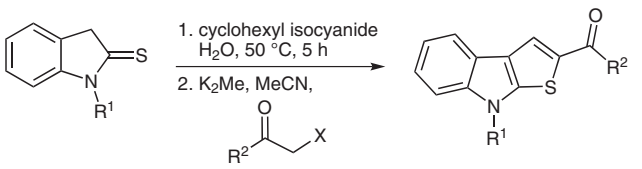
To confirm the proposed mechanism, the reaction of chloroacetonitrile **15** with **8** in H_2O was studied in order to trap **16** (Scheme 6). Indeed, in this case the iminium ion was hydrolyzed to **17**, which was isolated and its structure was confirmed.

In conclusion, we have reported a new and efficient one-pot synthesis of thieno[2,3-*b*]indoles from various indoline-2- thiones and α-halocarbonyl compounds. The present procedure has the advantages, not only of good functional-group tolerance and high yields, but also the reaction can be performed under mild conditions.



Scheme 4

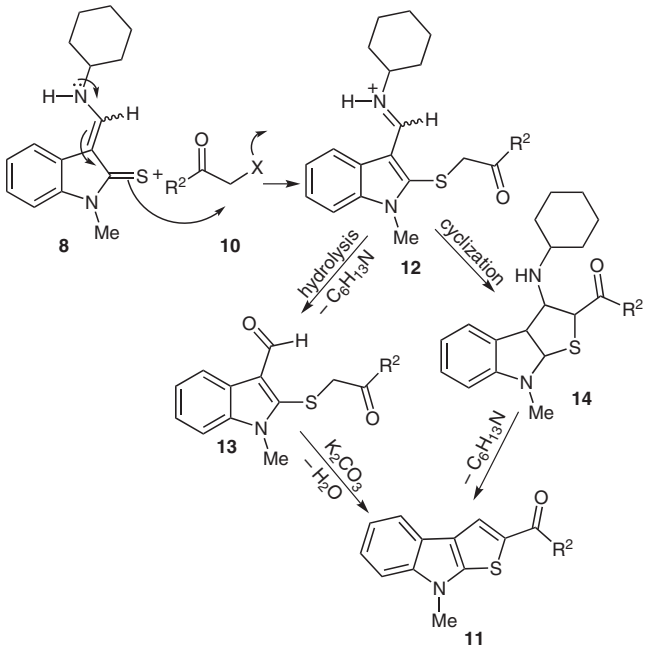
Table 1 Synthesis of Thieno[2,3-*b*]indoles



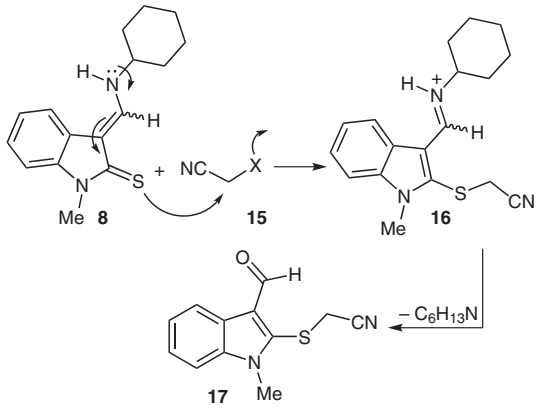
Entry	R^1	R^2	X	Product	Yield (%)
1	H	4-BrC_6H_4	Br	**11a**	87
2	H	4-ClC_6H_4	Br	**11b**	81
3	H	4-MeC_6H_4	Br	**11c**	74
4	H	4-PhC_6H_4	Br	**11d**	85
5	H	Me	Cl	**11e**	73
6	Me	Ph	Br	**11f**	83
7	Me	4-BrC_6H_4	Br	**11g**	85
8	Me	4-ClC_6H_4	Br	**11h**	83
9	Me	4-MeC_6H_4	Br	**11i**	79
10	Me	4-PhC_6H_4	Br	**11j**	84
11	Me	Me	Cl	**11k**	68
12	Et	Ph	Br	**11l**	80
13	Et	4-BrC_6H_4	Br	**11m**	77
14	Et	4-ClC_6H_4	Br	**11n**	71
15	Et	4-MeC_6H_4	Br	**11o**	75
16	Et	4-PhC_6H_4	Br	**11p**	78
17	Et	Me	Cl	**11q**	71
18	Ph	4-ClC_6H_4	Br	**11r**	75
19	Ph	4-PhC_6H_4	Br	**11s**	70
20	Ph	Me	Cl	**11t**	75

General Procedure for the One-Pot Synthesis of Thieno[2,3-*b*]indoles 11a–t

Indoline-2-thiones **6** and α-halocarbonyl compounds **10** were prepared according to previously reported procedures.[16] Cyclohexyl isocyanide **7** (1 mmol) was added to a stirred suspension of indoline-2-thione **6** (1 mmol) in H_2O (4 mL). The reaction mixture was stirred at 50 °C for 5 h. After completion of the reaction, α-halocarbonyl compound **10** (1 mmol) in MeCN (2 mL) and K_2CO_3 (1 mmol) were added to mixture. The reaction mixture was stirred at r.t. for 3 h, and the progress of the reaction was monitored by TLC. After completion of reaction, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and then evaporated. The residue was subjected to column chromatography (EtOAc–hexane, 1:5) on SiO_2 to obtain pure products.



Scheme 5



Scheme 6

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(15) **Representative Analytical Data**
Compound **8b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.08 (m, 1 H), 8.06 (d, J = 13.71 Hz, 1 H), 7.43 (d, J = 7.55 Hz, 1 H), 7.21 (t, J = 7.51 Hz, 1 H), 7.13–7.16 (m, 2 H), 3.77 (s, 3 H), 3.50–3.49 (m, 1 H), 2.11–2.07 (m, 2 H), 1.93–1.89 (m, 2 H), 1.69–1.59 (m, 3 H), 1.51–1.37 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.69 (C=S), 148.33 (CH), 139.86 (C), 127.68 (C), 123.16 (CH), 122.01 (CH), 114.61 (CH), 109.21 (CH), 106.58 (C), 58.76 (CH), 34.15 (CH_2), 29.75 (CH_3), 25.60 (CH_2), 24.62 (CH_2) ppm.
Compound **11a**: mp 285–287 °C. ^{1}H NMR (500 MHz, $CDCl_3$/DMSO): δ = 11.33 (s, 1 H), 7.48 (s, 1 H), 7.35–7.30 (m, 3 H), 7.26 (d, J = 8.30 Hz, 2 H), 7.03 (d, J = 8.17 Hz, 1 H), 6.83 (t, J = 7.67 Hz, 1 H), 6.73 (t, J = 7.51 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$/DMSO): δ = 187.19, 149.22, 143.10, 137.71, 135.26, 131.71, 130.50, 128.38, 126.04, 125.79, 123.71, 122.35, 120.55, 119.71, 112.16 ppm.
Compound **11b**: mp 280–282 °C. ^{1}H NMR (500 MHz, $CDCl_3$/DMSO): δ = 11.33 (s, 1 H), 7.49 (s, 1 H), 7.40 (d, J = 8.36 Hz, 2 H), 7.35 (d, J = 7.73 Hz, 1 H), 7.10 (d, J = 8.36 Hz, 2 H), 7.04 (d, J = 8.12 Hz, 1 H), 6.85 (t, J = 7.38 Hz, 1 H), 6.76 (t, J = 7.40 Hz, 1 H)ppm. ^{13}C NMR (125 MHz, $CDCl_3$/DMSO): δ = 187.11, 149.21, 143.11, 137.50, 137.29, 135.33, 130.35, 128.77, 128.33, 125.80, 123.72, 122.37, 120.55, 119.71, 112.17 ppm.
Compound **17**: mp 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.43 (s, 1 H), 8.38 (d, J = 7.95 Hz, 1 H), 7.48–7.47 (m, 2 H), 7.42–7.40 (m, 1 H), 4.07 (s, 3 H), 3.67 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.02, 138.82, 136.22, 125.96, 125.84, 124.18, 122.13, 121.48, 115.69, 110.87, 31.17, 23.33 ppm.
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