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Graphical Abstract

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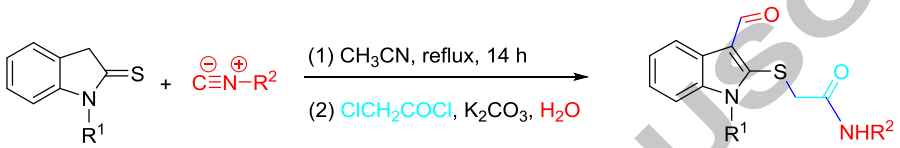

A Convenient Synthesis of 3-Formyl-2-thioacetamide-indole Derivatives via the One-Pot Reaction of Indolin-2-thiones, Isocyanides and Chloroacetylchloride

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Abstract

An efficient method has been developed to construct 3-formyl-2-thioacetamide-indoles *via* a one-pot, two-step procedure involving condensation of isocyanides with indolin-2-thiones to give a 3-aminomethylene-indolin-2-thione intermediate, followed by regioselective reaction with chloroacetylchloride and subsequent hydrolysis.

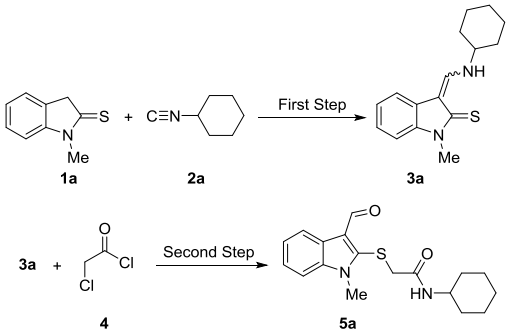
Keyword: Indolin-2-thiones, Isocyanide, Methylene-indolin-2-thiones, Indole derivatives

Introduction

Indole is a very important heterocycle that forms a main skeletal framework of a large number of biological and pharmacological molecules.[1] The importance of indole and its derivatives is evident from the growing volume of literature in the fields of pharmaceuticals,[2] natural products,[3] agrochemicals, [4] and synthesis.[5] Owing to their high importance, the development of efficient syntheses of indole derivative continues to attract significant attention.[6] Among the various derivatives, indole-based sulfides and sulfoxides are of particular interest because of their medicinal properties.[7-12] Biological activities such as antiviral,[7] HIV-1 reverse transcriptase inhibition,[8] protein tyrosine kinase inhibition,[9] antitumor,[10] antihyperlipidemic[11] and antiulcer activity[12] have been reported.

The utility of isocyanides as an electrophile is well established and this type of reactivity has been observed in the case of strong nucleophiles. [13] Although several Lewis acid promoted additions of weak nucleophiles, specifically, electron-rich aromatic compounds, onto isocyanides have been reported to date,[14] surprisingly such species have rarely been exploited in organic synthesis.[15] Previously we have reported the electrophilic reaction of cyclohexyl isocyanide with indoline-2-thiones to obtain cyclohexylaminomethylene-indolin-2-thiones, which, upon reaction with α-halocarbonyl compounds, produced a natural product-like thieno[2,3-*b*]indole framework. [16] In the context of

our continued interest in the application of indolin-2-thiones as substrates for the synthesis of natural product-like indole derivatives,[17] and broadening the synthetic utility of isocyanides as electrophiles in organic synthesis, we herein introduce a new and efficient synthesis of 3-formyl-2-thioacetamide-indole derivatives **5** via the one-pot two-step reaction of indolin-2-thiones **1**, isocyanides **2** and chloroacetylchloride **4** (Scheme 1). This reaction is based on the condensation of isocyanides with indolin-2-thiones to give 3-aminomethylene-indolin-2-thiones **3**, followed by regioselective reaction with chloroacetylchloride and subsequent hydrolysis to give 3-formyl-2-thioacetamide-indoles **5**. To the best of our knowledge, the present report is the first example of the use of an isocyanide in which it splits into two parts which are both incorporated in the final product.



Scheme 1. One-pot two step synthesis of 3-formyl-2-thioacetamide-indole **5a**.

Results and discussion

As a model reaction, indolin-2-thione derivative **1a** and cyclohexyl isocyanide **2a** were stirred in water for 6 hours at 60-65 °C. The condensation reaction proceeded well and the desired cyclohexylaminomethylene-indolin-2-thione **3a** was produced in good yield. To our surprise, the subsequent reaction of **3a** and chloroacetylchloride **4** with K_2CO_3 at room temperature was very sluggish and the desired product **5a** was only formed in 14% yield (Table 1, entry 1). We then examined the effect of base and solvent in the above reaction (Table 1). CH_3CN gave the most satisfactory result in comparison with other solvents (Entry 5). Varying the base (NaOH and $NaHCO_3$) and its absence significantly reduced the yield (Table 1, entries 7-9). When the first step of the reaction was performed at room temperature or H_2O was omitted in the second step, the desired product was not formed (Table 1, entry 6 and 11). Increasing the temperature reduced both steps reactions time (Table 1, entry 10 and 13). The best result was obtained using two equivalents of base and chloroacetylchloride **4**, to give the product in 85% yield (Table 1, entry 15).

Table 1. Effect of solvent, temperature and base on the two step synthesis of 3-formyl-2-thioacetamide-indole **5a**

	First step			Second step				
Entry	**Solvent**	**Temp. (°C)**	**Time (h)**	**Second solvent**	**Base**	**Temp. (°C)**	**Time (h)**	**Yield[a] (%)**
1	H_2O (7 mL)	60-65	6	CH_3CN (2 mL)	K_2CO_3 (1 equiv.)	rt	5	14
2	CH_3OH (7 mL)	60-65	22	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	8
3	$C_6H_5CH_3$ (7 mL)	60-65	22	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	20

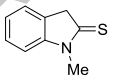
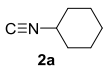
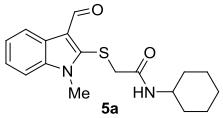
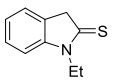
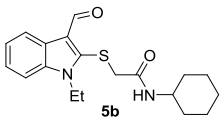
4	DMF (7 mL)	60-65	22	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	5
5	CH_3CN (7 mL)	60-65	22	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	58
6	CH_3CN (7 mL)	rt	22	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	0
7	CH_3CN (7 mL)	60-65	22	H_2O (1 mL)	NaOH (1 equiv.)	rt	5	17
8	CH_3CN (7 mL)	60-65	22	H_2O (1 mL)	$NaHCO_3$ (1 equiv.)	rt	5	30
9	CH_3CN (7 mL)	60-65	22	H_2O (1 mL)	-	rt	5	10
10	CH_3CN (7 mL)	reflux	14	H_2O (1 mL)	K_2CO_3 (1 equiv.)	rt	5	58
11	CH_3CN (7 mL)	reflux	14	-	K_2CO_3 (1 equiv.)	rt	5	0
12	CH_3CN (7 mL)	reflux	14	H_2O (1 mL)	K_2CO_3 (2 equiv.)	rt	5	63
13	CH_3CN (7 mL)	reflux	14	H_2O (1 mL)	K_2CO_3 (2 equiv.)	50-55	2	65
14	CH_3CN (7 mL)	reflux	14	H_2O (1 mL)	K_2CO_3 (2 equiv.)	reflux	2	48
15[b]	**CH_3CN (7 mL)**	**reflux**	**14**	**H_2O (1 mL)**	**K_2CO_3 (2 equiv.)**	**50-55**	**2**	**85**

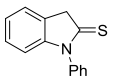
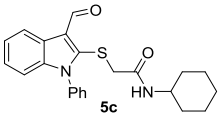
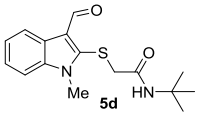
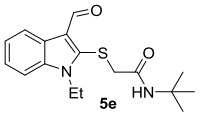
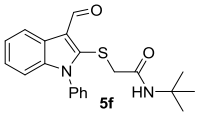
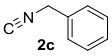
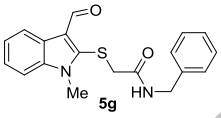
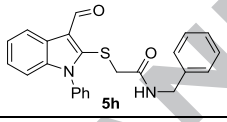
a) Yield of isolated product.
b) Two equivalents of chloroacetylchloride **4** were used.

Under the optimized reaction condition,[18] a series of 3-formyl-2-thioacetamide-indole derivatives **5** were synthesized using a various indolin-2-thiones **1** and isocyanide derivatives **2** (Table 2). The two step reaction sequences proceeded smoothly and the desired compounds were isolated by silica gel column chromatography.

The structures of the products were established from their NMR spectroscopic data (^{1}H NMR, ^{13}C NMR, DEPT) and IR as well as elemental analyses.[18] The characteristic signals for **5a–h** in the ^{1}H NMR spectra were a singlet for the $–SCH_2CO$ group between 3.03 and 3.59 ppm, a broad singlet for the CONH group between 5.91–6.12 ppm in $CDCl_3$ and 8.39–8.42 ppm in DMSO-d_6, and another singlet for the CHO group between 10.11–10.42 ppm. The corresponding signals of the $–SCH_2$, –CONH and –CHO groups in the ^{13}C NMR spectra appeared between 39.6–42.2 ppm, 165.7–167.8 ppm and 186.3–187.2 ppm, respectively.

Table 2. Synthesis of 3-formyl-2-thioacetamide-indole derivatives **5a-h**.[a]

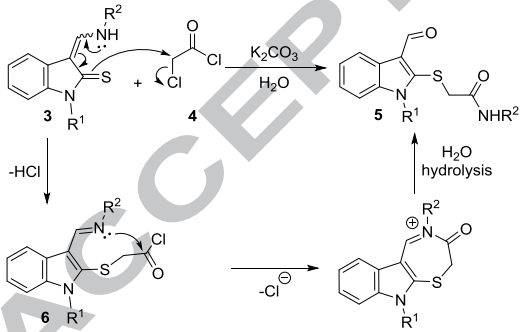
Indolin-2-thiones	Isocyanides	Product	Yield[b] (%)
 **1a**	 **2a**	 **5a**	85
 **1b**	**2a**	 **5b**	80

 **1c**	**2a**	 **5c**	88
1a	 **2b**	 **5d**	76
1b	**2b**	 **5e**	72
1c	**2b**	 **5f**	78
1a	 **2c**	 **5g**	87
1c	**2c**	 **5h**	90

a) Reagents and conditions: First step; CH_3CN (7 mL), reflux, 14 h. Second step; $ClCH_2COCl$ (2 equiv.), K_2CO_3 (2 equiv.), H_2O (1 mL), 50-55 ^oC, 2 h.

b) Yield of isolated product.

A plausible mechanism for the first step of the reaction involving the synthesis of compound **3** has previously been reported by our group.[16] The formation of 3-formyl-2-thioacetamide-indole derivatives **5** can be rationalized by the initial *S*-alkylation of compound **3** with chloroacetylchloride **4**, affording intermediate imine **6**, followed by *N*-acylation and hydrolysis to afford the desired products **5a-h** (Scheme 2).



Scheme 2. Proposed mechanism for the synthesis of 3-formyl-2-thioacetamide-indole derivatives **5a-h**.

Conclusion

In summary, we have reported a new and efficient one-pot, two step synthesis of 3-formyl-2-thioacetamide-indoles from various indoline-2-thiones, isocyanides and chloroacetylchloride. The present procedure has the

advantages of high yield and mild reaction conditions. Further studies to extend the scope and synthetic utility of 3-formyl-2-thioacetamide-indole for the conversion into thieno[2,3-*b*]indoles are currently in progress.

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18. To a stirred suspension of indolin-2-thiones **1a–c** (0.5 mmol) in CH_3CN (7 mL) were added isocyanide derivative **2a–c** (0.5 mmol). The reaction mixture was stirred at reflux for 14 h and the progress of the reaction monitored by TLC. After reaction completion, chloroacetylchloride **4** (2 mmol), K_2CO_3 (2 mmol) and H_2O (1 mL) were added to the mixture. The reaction was stirred at 50-55 °C for 2 h. After reaction completion, the solvents were evaporated and the residue subjected to SiO_2 column chromatography (EtOAc–hexane, 1:3) to obtain pure products **5a-h**. *N*-Cyclohexyl-2-((3-formyl-1-methyl-1H-indol-2-yl)thio)acetamide (**5a**): yellow powder, mp: 164–166 ^oC, yield; 85%. IR (KBr): 3299, 3072, 2923, 2849, 1664, 1630, 1538, 1457, 1369, 1130, 744 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97–1.30 (5H, m, CH_2), 1.54–1.73 (5H, m, CH_2), 3.48 (2H, s, SCH_2C=O), 3.59–3.65 (1H, m, CONH*CH*), 3.93 (3H, s, NCH_3), 6.05 (1H, bs, –NHC=O), 7.30–7.37 (3H, m, Ar–H), 8.27 (1H, d, *J* = 7.9 Hz, Ar–H), 10.32 (1H, s, CH=O). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1 (CH_2), 25.7 (CH_2), 31.1 (NCH_3), 33.1 (CH_2), 41.6 (SCH_2), 49.3 (CH), 110.6 (CH), 120.4 (C), 121.7 (CH), 123.9 (CH), 125.3 (CH), 125.7 (C), 138.5 (C), 140.6 (C), 166.3 (CONH), 186.6 (CHO). Anal.Calcd for $C_{18}H_{22}N_2O_2S$: C, 65.42; H, 6.71; N, 8.48%. Found: C, 65.55; H, 6.78; N, 8.40%.

Highlight bullet points

New way to synthesis of the 1,2,3-three substituted indole-based sulfides.

A new and efficient one-pot, two step synthesis of 3-formyl-2-thioacetamide-indoles.

Isocyanide splits into two parts and both are incorporated in the final products.

Regioselective reaction of aminomethylene-indolin-2-thione with chloroacetylchloride.