STUDIES ON THE SYNTHESIS OF INDOTHIAZINONE AND ITS DERIVATIVES VIA DIRECT 3-ACYLATION OF INDOLE

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GRAPHICAL ABSTRACT

Abstract Indothiazinone is a natural 3-acylindole alkaloid, isolated from a culture of myxobacterial strain. It was found to possess antibacterial activity against yeast and filamentous fungi. Indothiazinone is also structurally related with a mammalian endogenous aryl hydrocarbon receptor ligand, (2-(1H-indole-3-carbonyl)thiazol-4-carboxylic acid methyl ester (ITE). In this article, the synthesis of indothiazinone has been disclosed for the first time. Key feature includes direct and selective 3-acylation of indole in the presence of Lewis acid. In addition, an efficient preparation of N-substituted indothiazinone derivatives has been demonstrated.

Keywords 3-Acylindole; AhR; indothiazinone; ITE

INTRODUCTION

Indole alkaloids are widely found in nature. Many of them have been known to possess various physiological activities.[1,2] In addition, the indole scaffold has been considered as one of privileged structures in pharmaceuticals and agrochemicals.[1] Among the indole alkaloids, especially 3-acylindole has attracted continuous
attention, possibly because it is found in nature and exhibits a variety of biological activities such as anticancer, antidiabetic, antinociceptive, and antibiotic.[3–6] Indothiazinone (1), a natural 3-acylindole alkaloid, was recently reported to be discovered in a culture of myxobacterial strain.[7] The structure was determined by mass spectrometry (MS) and NMR spectroscopic analysis to be an indolyl thiazolyl ketone, 1H-indol-3-yl(1,3-thiazol-2-yl)methanone (Fig. 1). This small natural product was found to possess antibiotic activity against yeast and filamentous fungi. Interestingly, it was also suggested that the microbial product is structurally related to the mammalian endogenous aryl hydrocarbon receptor (AhR) ligand ITE (2-(1H-indole-3'-carbonyl)thiazol-4-carboxylic acid methyl ester, 2), one of the strongest agonist recognized so far. AhR ligands are promising as modulators for the important cellular functions such as proliferation, migration, differentiation, development, and immunity.[8–12] Structurally related indole alkaloid 3 has also been isolated along with indothiazinone from a thermophilic bacterium, suggesting a bacterial endosymbiont might be responsible for producing ITE in a mammalian organ, which will likely lead to the identification of a novel metabolic pathway as well.[13] Searching for a “lead-like compound” from natural sources, we found indothiazinone (1), a novel indole alkaloid, to be a promising target. The structure of indothiazinone drew our attention because of the extraordinary scaffold, which is rarely found in nature. The suggested novel metabolic pathway also makes indothiazinone an attractive synthetic target. The synthesis of indothiazinone has never been achieved to our knowledge, and an efficient synthetic route for the preparation of indothiazinone and its derivatives is needed for further studies. Herewith, we report first synthesis of indothiazinone and preparation of its N-substituted derivatives.

RESULTS AND DISCUSSION

There have been significant approaches for the synthesis of 3-acylindoles via acylation including Friedel–Crafts or Vilsmeier–Haack[14] acylations and the use of Grignard reagents,[15] zinc salts,[16] metalated indoles,[17] and metal-catalyzed cross coupling.[18] Inarguably, direct acylation of indole at the 3-position in the presence of Lewis acid is one of the most efficient approaches for the synthesis of 3-acylindole alkaloids in terms of simplicity, straightforwardness, and atom-economy. Although indole is well known to undergo electrophilic substitution mainly at C-3, acylation of unprotected indole suffers from side reactions such as nonselective acylation or oligomerization. Thus, traditional approaches for the synthesis of 3-acylindoles via

![Figure 1. Structure of natural 2-(1'H-indole-3'-carbonyl)-thiazoles.](image_url)
regioselective acylation of indoles inevitably required tedious protection–
deprotection steps to avoid unwanted oligomerization as well as to deactivate the
indole system to overcome the concurrent nonselective acylation. The acylation of
indole salts is reported to provide 3-acylindoles in a reasonable yield,[15–17] but the
use of Grignard reagent or zinc reagent often limits its applicability in the presence
of labile functional groups. Recently, methods for the direct 3-acylation of indoles in
the presence of proper Lewis acids with activated carbonyl compounds have been
developed to overcome the challenges and has proven to be effective for the synthesis
of various 3-acylindoles.[19–22] Thus, indothiazinone was envisioned to be synthesized
via direct 3-acylation in the presence of an appropriate Lewis acid.

Our synthesis of indothiazinone commenced with an optimization of reaction
condition centered on exploring the selected Lewis acids. We tried SnCl₄,[20] TiCl₄,[23]
dialkylaluminium chloride,[19,22] and ZrCl₄,[21] which have been reported to play crucial
roles in the activation of acylating agents and to suppress undesirable side reactions in
direct acylation of indoles. The required activated carbonyl, thiazole-2-carbonyl chloride
(5), was prepared in situ in the presence of oxalyl chloride and a catalytic amount of
dimethylformamide (DMF) in dichloromethane (DCM), and was used as-is after moni-
toring the completion of reaction. It is noteworthy that we had difficulties in dissolution

Table 1. Synthesis of indothiazinone: Optimization

| Entry | 5° | Lewis acid (eq.°) | Solvent | Temperature | Time | Yield |
|-------|----|------------------|---------|-------------|------|-------|
| 1     | 1 eq. | SnCl₄ (1.2) | CH₂Cl₂ | 0°C to rt | 2 h | 44 |
| 2     | 1 eq. | SnCl₄ (1.2) | CH₂Cl₂ | 0°C to rt | 12 h | Trace |
| 3     | 1 eq. | TiCl₄ (1.2) | CH₂Cl₂ | 0°C to rt | 2 h | 42 |
| 4     | 1 eq. | TiCl₄ (1.2) | CH₂Cl₂ | 0°C to rt | 12 h | Trace |
| 5     | 0.7 eq. | Et₂AlCl (1.5) | CH₂Cl₂ | 0°C | 2 h | 29 |
| 6     | 1 eq. | Et₂AlCl (1.5) | CH₂Cl₂ | 0°C | 2 h | 48 |
| 7     | 2 eq. | Et₂AlCl (1.5) | CH₂Cl₂ | 0°C | 2 h | 63 |
| 8     | 2 eq. | Et₂AlCl (1.5) | CH₂Cl₂/CH₃NO₂ | 0°C | 2 h | 46 |
| 9     | 2 eq. | Et₂AlCl (1.5) | CH₂Cl₂ | 0°C | 12 h | Trace |
| 10    | 2 eq. | Et₂AlCl (1.5) | CH₂Cl₂ | –78°C | 2 h | 4.3 |
| 11    | 2 eq. | ZrCl₄ (1.5) | DCE | 0°C to rt | 3 h | 26 |
| 12    | 0.7 eq. | ZrCl₄ (1.5) | DCE | 0°C to rt | 3 h | 56 |
| 13    | 1 eq. | ZrCl₄ (1.5) | DCE | 0°C to rt | 3 h | 43 |
| 14    | 1.5 eq. | ZrCl₄ (1.5) | DCE | 0°C to rt | 12 h | 29 |

°Refers to the amount in molar equivalent.
°Refers to the period of time after the addition of 5.
°Isolated yield.
when the prepared solution of thiazole-2-carbonyl chloride (5) was dried and then dissolved in DCM again, possibly due to the salt formation or polymerization.

As shown in Table 1, indothiazinone (1) was successfully provided in the presence of various Lewis acids. Yields were poor to moderate, and the chemical yields significantly dropped in a prolonged period of reaction time regardless of Lewis acid. We also tried a cosolvent system because of the possible solvent effect, but the cosolvent system did not significantly improved chemical yield (entry 8). The structure of the synthesized indothiazinone was confirmed using \(^1H\) and \(^{13}C\) NMR and high-resolution mass spectrometry (HRMS). Spectral data of both \(^1H\) and \(^{13}C\) NMR were identical to those of the reported natural indothiazinone except for the broad singlet of the exchangeable proton of the indole moiety. Briefly, the appearance of typical chemical shifts of \(^1H\) NMR, including a down-field-shifted doublet, four aromatic peaks, and a broad singlet, comes from the exchangeable proton of the indole moiety, which supports the presence of an indole ring. The downfield carbon signal of \(^{13}C\) NMR correlates with the presence of 3-acyl carbon and quaternary carbon of thiazole.

With the optimized condition for the synthesis of indothiazinone in hand, we turned our attention to the synthesis of indothiazinone derivatives. As shown in

**Scheme 1.** Synthesis of N-substituted indothiazinone derivatives. Reagents and conditions: (a) Et\(_2\)AlCl, DCM, 0 °C, 63%; (b) DBU, iodomethane, CH\(_2\)Cl\(_2\), 80%; (c) DBU, allyl bromide, CH\(_2\)Cl\(_2\), 93%; (d) DBU, benzyl bromide, CH\(_2\)Cl\(_2\), 76% for 8a, 75% for 8b, 40% for 8c, 42% for 8d; (e) NaH, Ac\(_2\)O, DMF, 0 °C, 65%; and (f) DBU, benzoyl chloride, CH\(_2\)Cl\(_2\), 82%.
Scheme 1, various functional groups including alkyl, allyl, benzyl, acetyl, and benzoyl, have been successfully introduced in good yields to provide diverse N-substituted indothiazinone derivatives. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was our choice of base in these cases, because the use of strong bases such as NaH requires a strict control of anhydrous condition. The chemical yields using DBU were also greater in general, except for the acetylation to afford compound 9.

CONCLUSION

In summary, the synthesis of indothiazinone has been disclosed for the first time. Key features includes direct and selective 3-acylation of indole in the presence of Lewis acid. In addition, an efficient preparation of N-substituted indothiazinone derivatives has been successfully demonstrated. We believe our protocol for the synthesis of indothiazinone and its derivatives would provide a practical way to have them for further studies in the related fields. Studies on the biological activities of indothiazinone as well as the synthesized derivatives are currently in progress.

EXPERIMENTAL

Preparation of Thiazole-3-carbonyl Chloride (5) Solution in Dichloromethane

Thiazole-2-carboxylic acid was synthesized from 3-bromothiazole according to the reported procedure.[24] Oxalyl chloride (0.31 mL, 3.64 mmol) and a drop of N,N-dimethylamine were added to a stirred solution of thiazole-3-carboxylic acid (546.6 mg, 4 mmol) in dichloromethane (20 mL) at 0 °C. After 30 min, the reaction temperature was elevated to rt. After completion of reaction, which was monitored with a generation of methyl ester in methanol by thin-layer chromatography (TLC), the resulting solution was used for direct 3-acylation of indole. For the synthesis of indothiazinone in the presence of ZrCl₄, dichloroethane was used as solvent instead of dichloromethane (Table 1, entries 11–14).

Synthesis of Indothiazinone (1)

A solution of diethylaluminium chloride (25 w/v% in dichloromethane, 1.5 mL, 3 mmol) was added to a stirred solution of indole (234.3 mg, 2 mmol) in dichloromethane (10 mL) at 0 °C. After stirring for 30 min, a solution of thiazole-3-carbonyl chloride (5) (0.2 M in dichloromethane, 20 mL, 4 mmol) was added and stirred for 2 h at 0 °C. The resulting mixture was quenched with water, extracted with dichloromethane, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford indothiazinone (1, 288 mg, 63%) as yellow solid. 1: ¹H NMR (500 MHz, CDCl₃) δ 9.16 (d, 1H, J = 3.15 Hz), 8.78 (s, 1H), 8.56 (d, 1H, J = 7.25 Hz), 8.02 (d, 1H, J = 3.05 Hz), 7.64 (d, 1H, J = 3.05 Hz), 7.46 (m, 1H), 7.35 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 178.31, 170.28, 144.14, 136.48, 135.88, 126.80, 124.77, 124.08, 123.19, 122.72, 114.48, 111.43; HR-MS (EI+) calcd. for C₁₂H₈N₂OS [M]+ 228.0357; found 228.0355.
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SUPPLEMENTAL MATERIAL

Supplemental data (full experimental details including $^1$H and $^{13}$C NMR spectra) for this article can be accessed on the publisher’s website.

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