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Indium/TFA-Catalyzed Synthesis of Tetracyclic [6,5,5,6] Indole Ring, via a Tandem Cycloannulation of *β*-Oxodithioester with Tryptamine

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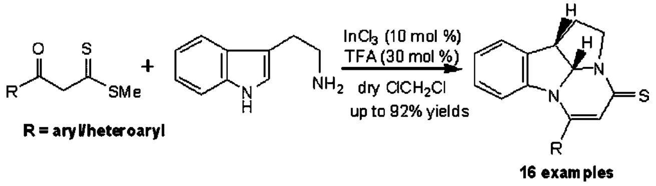
ABSTRACT



The cycloannulation of β-oxodithioesters and tryptamine in dichloromethane in the presence of a catalytic amount of $InCl_3$ and TFA gave the novel 5-aryl/heteroaryl 2a^1,9b-dihydro-1*H*-2a,5a-diaza-cyclopenta[*jk*]fluorene-3(2*H*)-thiones in moderate to good yields. The reaction was proposed to involve a tandem transformation of thioamide, protonation, and dehydrative cyclization. $KMnO_4$-oxidation of these newly prepared compounds yielded oxidative desulfurization products in good yields.

Indoles and their derivatives constitute an important class of biologically active natural products, which also have been used as synthons of complex molecules.[1] The development of a highly stereoselective domino reaction for the construction of indole polycyclic rings is still a challenge and remains difficult.[2] Among the indole derivatives, the tetrahydropyrrolo[2,3-*b*]indole skeleton is a key structural motif which is present in a growing class of bioactive alkaloids,[3] such as the potent vasodilator amauromine **1**,[4] the insecticidal okaramine C,[5] and the *Bacillus subtilis* pheromone ComX **2**[6] (Figure 1). On the other hand, the tetrahydroimidazo[1,2-*a*]indole is present in the cholecystokinin antagonist asperlicin **3**[7]and in the substance P antagonists fiscalins **4**.[8] The tetracyclic ring system **C** and **D** can be considered as a combination of tetrahydropyrrolo[2,3-*b*]indole **A** and tetrahydroimidazo [1,2-*a*]indole **B** (Scheme 1). Also, Chen et al.[9]reported the isolation of two alkaloids of tetracyclic [6,5,5,6] ring system **D** derivatives from the root of Chinese *Isatis indigotica*. Thus, the presence of these two tetracyclic ring systems **C** and **D** in a bioactive moiety and natural products led organic chemists to hunt for novel synthetic strategies.[10,11]

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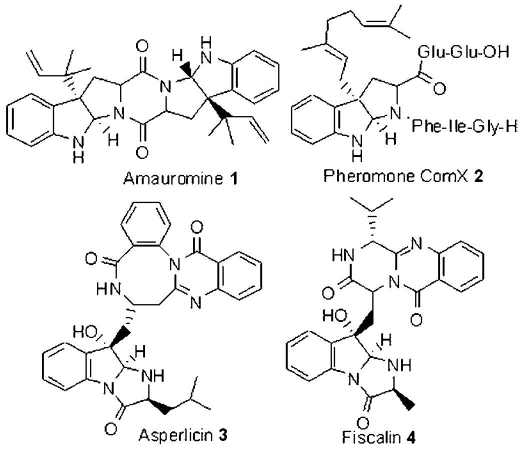
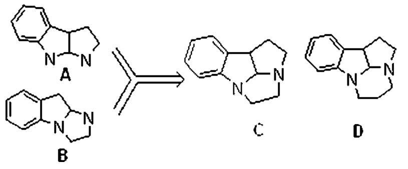


Figure 1. Structures of naturally occurring tetrahydropyrrolo[2,3-*b*]indole and tetrahydroimidazo[1,2-*a*]indole skeletons.

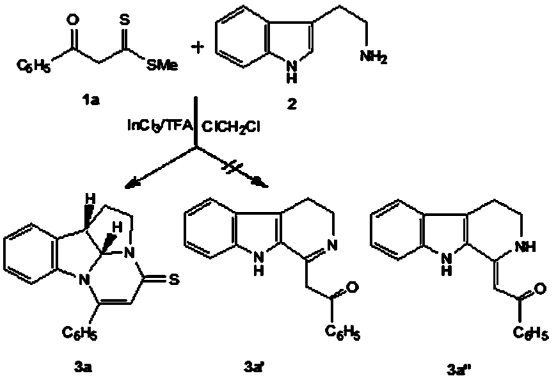
Scheme 1. Tetracyclic Ring Systems **C** and **D**



Reports on the synthesis of the tetracyclic [6,5,5,6] ring system **D** are extremely limited. Moreover, the earlier reported methods require toxic organic solvents, costly reagents, cumbersome experimental procedures, and multiple steps. Therefore, more general and convenient routes involving simple operations for the synthesis of [6,5,5,6] ring system **D** derivatives would be of great interest to both synthetic and medicinal chemists. Thus, we became intrigued in scouting the use of β-oxodithioesters to develop a more generalized synthetic strategy for the synthesis of functionalized indoles as a part of our ongoing research project for the synthesis of bioactive heterocycles using β-oxodithioesters and related synthons.[12] Herein, we report a synthesis of tetracyclic [6,5,5,6] ring systems by the one-pot tandem cycloannulation of β-oxodithioesters with tryptamine in ClCH$_2$Cl catalyzed by InCl$_3$ and TFA (Scheme 2).

Since ketene *N,S*-acetals and dithioesters having electron-withdrawing groups are known to produce 1,2,3,4-tetrahydro-β-carbolines on reaction with tryptamine through Bischler−Napieralski type cyclizations,[13] it was anticipated that the treatment of β-oxodithioesters with tryptamine under the present conditions would afford the 1,2,3,4-tetrahydro-β-carbolines in a single step (Scheme 2). The previous work involved two steps in which the β-carbolines were obtained from the corresponding thioamide by cyclization using TFA in ClCH$_2$Cl at rt. So, our main focus was finding an appropriate catalyst and cocatalyst which could perform the reaction in a one-pot system. However, to our surprise a series of unexpected products with the structure of tetracyclic [6,5,5,6] ring systems were found by using the InCl$_3$/TFA combination in ClCH$_2$Cl. The unambiguous structures of the newly synthesized compounds were confirmed by spectral, analytical, and single-crystal X-ray data (Figure 2).

Scheme 2. Synthesis of 5-Phenyl 2a^1,9b-Dihydro-1*H*-2a,5a-diaza-cyclopenta[*jk*]fluorene-3(2*H*)-thione



The reaction of methyl 3-oxo-3-phenylpropanedithioate (**1a**) with tryptamine (**2**) leading to 5-phenyl 2a^1,9b-dihydro-1*H*-2a,5a-diaza-cyclopenta[*jk*]fluorene-3(2*H*)-thione (**3a**) was used as the model to optimize the reaction conditions. We screened common solvents with InCl$_3$ as the metal halide. The results indicated that ethanol, methanol, and acetonitrile give the lowest yields, whereas dichloromethane gave a reasonable yield of 85% (Table 1). For other solvents such as THF, DMF, and toluene, the reaction did not proceed even after 24 h of reflux. It was also observed that no reaction occurred in the absence of solvent. The amount of TFA was also explored by using 20, 25, 30, and 35 mol %, and it was found that 30 mol % of TFA was sufficient for the cycloannulation reaction.

Further, it was observed that InBr$_3$ could also catalyze the corresponding 5-aryl/heteroaryl 2a^1,9b-dihydro-1*H*-2a,5a-diaza-cyclopenta[*jk*]fluorene-3(2*H*)-thiones in good yield (Table 2, entry 10). Thus, different metal halides were tested for the reaction in ClCH$_2$Cl in the presence of TFA. The results indicated that metal halides such as InCl$_3$, InBr$_3$, ZnCl$_2$, and ZnBr$_2$ could afford the tetracyclic [6,5,5,6] indole products. However, it was observed that the yields were higher in the case of chlorides except in the case of copper halides (Table 2, entries 7 and 10, entries 5 and 13, and entries 2 and 12). Further, the catalytic ratio of InCl$_3$ was tested in the range 5, 10, and 15 mol %, and

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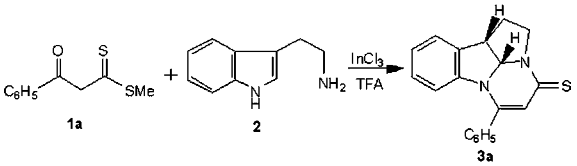
Table 1. Optimization of TFA-Mediated Cycloannulation Using $InCl_3$

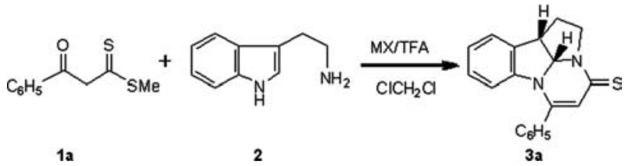


entry	solvent	time (h)[a]	yield (%)[b]
1	$ClCH_2Cl$	4	85
2	EtOH	20	45
3	MeCN	20	37
4	MeOH	18	55
5	THF	24	–
6	DMF	24	–
7	toluene	24	–
8	no solvent	24	–

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), and solvent (15 mL). [b] Isolated yields.

10 mol % was found to be the optimal amount for this reaction. However, this reaction did not proceed at rt even for longer reaction times (> 36 h). From the above experimental results, we found that the combination of a catalytic amount of $InCl_3$ (10 mol %) and TFA (30 mol %) was found to be the best among the tested catalysts and cocatalyst in 15 mL of $ClCH_2Cl$ under reflux for this tandem cyclocondensation.

Table 2. Synthesis of 5-Phenyl 2a[1],9b-Dihydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-3(2*H*)-thione by Using Different Metal Halides

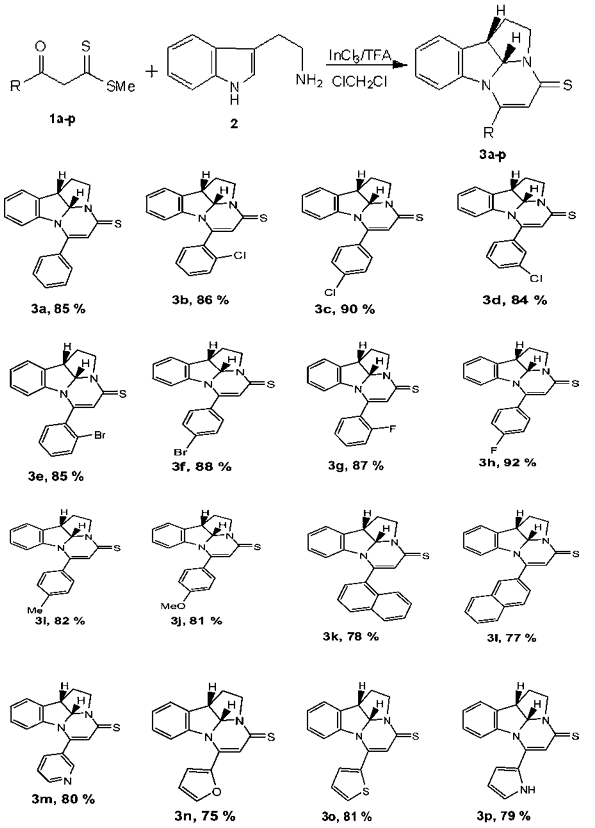


entry	metal halide	time (h)[a]	yield (%)[b]
1	$FeCl_3$	24	40
2	$CuCl_2$	14	53
3	$CoCl_2$	24	27
4	$CaCl_2$	24	35
5	$ZnCl_2$	15	58
6	$MgCl_2$	22	43
7	$InCl_3$	4	85
8	KCl	24	0
9	NaCl	24	0
10	$InBr_3$	6	75
11	$FeBr_3$	21	28
12	$CuBr_2$	24	57
13	$ZnBr_2$	24	54
14	$MgBr_2$	24	34
15	NaBr	24	0
16	KBr	24	0

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), and solvent (15 mL). [b] Isolated yields.

With the reaction conditions optimized, we next examined the substrate scope of the reaction (Scheme 3). A series of aryl/heteroaryl substituted *β*-oxodithioesters (**1b**–**p**) reacted with **2** smoothly under identical conditions to afford the corresponding products in moderate to good yields. Aromatic groups bearing electron-withdrawing groups in the *para*, *meta*, and *ortho* positions (**3b**–**3h**) or electron-donating groups (**3i** and **3j**) were well tolerated. However, higher yields were obtained for aromatic systems with electron-withdrawing substituents (**3h**). Naphthyl and heteroaryl (furan, thiophene, pyrrole, and pyridine) substituted *β*-oxodithioesters were also compatible with the reaction conditions, which broadens the scope for the generation of libraries of this class of tetrahydropyrroloindoles **3k**–**3p**.

Scheme 3. Synthesis of Tetracyclic [6,5,5,6] Indole Derivatives via Cycloannulation of *β*-Oxodithioesters and Tryptamine[a]



[a] Optimal reaction conditions: **1** (0.5 mmol) and **2** (0.5 mmol) using $InCl_3$ (10 mol %) and TFA (30 mol %) in $ClCH_2Cl$ (15 mL) in 4 h.

Further, we intended to perform experiments of oxidative dehydrogenation for compounds **3** using the inexpensive oxidizing agent $KMnO_4$.[14] Here again, we isolated unexpected oxidative desulphurization products instead of the expected dehydrogenated products. A quick literature survey revealed that $KMnO_4$ could be used for this oxidative desulfurization,[15] which holds true with our work.

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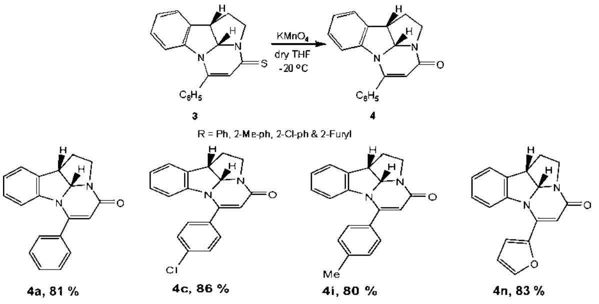
Scheme 4. Oxidative Desulfurization Using $KMnO_4$[a]



[a] Reaction conditions: **3** (0.2 mmol), dry THF (10 mL), and $KMnO_4$ (0.75g) at −20 °C, THF = tetrahydrofuran.

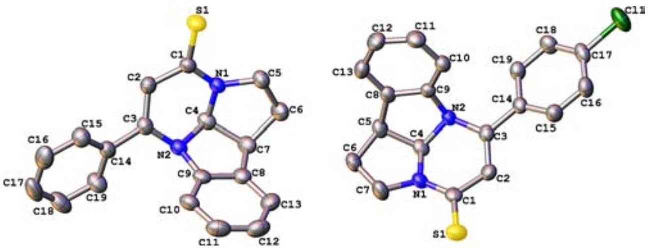
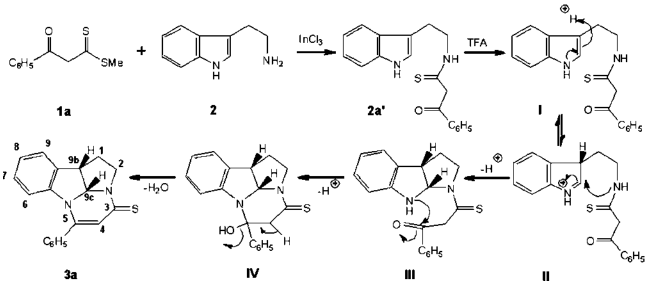


Figure 2. X-ray crystal structure of **3a** and **3c**.

Thus, **3a**, **3c**, **3i**, and **3n** were selected and successfully converted to the corresponding 5-aryl/heteroaryl 2a^1,9b-dihydro-1*H*-2a,5a-cyclopenta[*jk*]fluorene-3(2*H*)-ones **4a**, **4c**, **4i**, and **4n** on treatment with $KMnO_4$ in the presence of dry THF at −20 °C (Scheme 4). However, the conversion was not successful at rt. Further investigation on this oxidative desulfurization using different alkaloids is still ongoing in our laboratory.

In the ^1H NMR spectrum of **3a** a doublet at δ 5.5 (J 7.2 Hz) was observed, which could be assigned to the 9c-H, correlating well with other tetrahydropyrrolo-indoles.[10,11] In the ^{13}C NMR spectrum, the signals at δ 45.2 and 80.3 correspond to C-9b and C-9c, respectively, and the characteristic peak at δ 184.5 was assigned for C=S. From the IR, the C=S stretch of **3a** shows an absorption at 1130 cm^{-1}. The relative configuration of the product was determined based on single-crystal X-ray diffraction of **3a** and **3c** (see the Supporting Information). The compound **4a** shows a similar pattern of ^1H NMR spectrum as **3a**, but in the ^{13}C NMR spectrum, the peak at δ 162.4 correlates to C=O in place of C=S. Analytical and spectral data further support the structures of all the newly synthesized compounds.

Scheme 5. Proposed Mechanism of Indium(III) Mediated Tandem Cycloannulation



A possible mechanism is proposed in Scheme 5. The reaction of **1a** and tryptamine **2** is presumably initiated by the formation of thioamide **2a′** in an acidic solution, which underwent protonation to generate intermediates **I** and **II**. **II** is probably transformed to tetrahydropyrrolo[2,3-*b*]-indole system **III** by intramolecular nucleophilic attack at the C2 of the indole. Participation of the indolyl−NH in the intramolecular cyclization with a nucleophilic attack at the carbonyl group followed by elimination of H_2O leads to the tetracyclic [6,5,5,6] indole ring **3a**.

In summary, we have described the application of β-oxodithioesters **1** to synthesize 5-aryl/heteroaryl 2a^1,9b-dihydro-1*H*-2a,5a-diazacyclo-penta[*jk*]fluorene-3(2*H*)-thiones **3** in a tandem cycloannulation reaction with tryptamine. In these reactions, at least five different active sites are involved; three C−N bonds and two new rings are constructed with all reactants efficiently utilized in the chemical transformation. Further, oxidative desulfurization of the few products was successfully carried out using $KMnO_4$. To the best of our knowledge, no report on the use of β-oxodithioesters as starting materials for the synthesis of tetracyclic [6,5,5,6] ring systems is known. Undoubtedly, this tandem cycloannulation opens a new convenient and effective way to construct the tetracyclic [6,5,5,6] indole ring systems from readily available starting materials.

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Supporting Information Available. General procedure for synthesis, characterization data, and ^1H and ^{13}C NMR spectra of all compounds. X-ray crystal structure of **3a** (CCDC 921594) and **3c** (CCDC 921595). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.