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An efficient one-pot synthesis of indanone fused heterocyclic compounds via $SeO_2/FeCl_3$ promoted intramolecular Friedel-Craft acylation reaction

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ABSTRACT

Indanones have been shown to exhibit a broad range of biological activities. An efficient and straightforward synthetic method for generating indanone fused heterocyclic compounds which contains a unique tetracyclic isoflavone moiety was developed. This unprecedented one-pot route utilizes a wide spread of substrates through three-step tandem Riley oxidation/Friedel-Crafts reaction/oxidation with $SeO_2/FeCl_3$ in moderate yield. Moreover, some of the synthesized heterocyclic compounds have shown moderate anticancer activities.

Introduction

In recent years, indanones and their structural analogues behave as key intermediates in medicine, agriculture and natural products synthesis, which display a broad spectrum of biological and pharmaceutical properties [1]. The extensive research on the biological activities of indanones has opened up more and more new application prospects (Fig. 1), such as anticancer [2], antibacterial [3], antiviral and antimicrobial agents [4], agents for Alzheimer's disease [5] and hepatitis C treatment [6]. In addition, indanone derivatives can be used as pesticides, fungicides and herbicides in agriculture [7]. In natural products synthesis, the indanone moieties are found in several natural compounds and also, can be used as intermediate in the synthesis of many different types of medicinally important molecules [8].Fig. 2

Consequently, the development of efficient methods for the synthesis of the indanone frameworks and the unique tetracyclic isoflavone derivatives is a topic of considerable importance. Known powerful and reliable syntheses for indanone formation include classical intramolecular Friedel-Crafts acylations [9], intramolecular [4 + 2] cycloaddition reactions of conjugated enynes [10], Grignard reactions [11], transition metal-catalyzed annulation of arylalkynes [12], radical cyclization [13], and base-promoted cyclization of β-alkynyl ketones [14].

In our previous study, an unexpected indanone byproduct excited our interest [15]. Driven by the need for a more efficient synthetic route to indanone derivatives, we were particularly interested in exploring a one-pot intramolecular cyclization (Scheme 1). In this paper, we disclose a one-pot pathway through Scheme 2.

Riley oxidation/Friedel-Crafts reaction/oxidation promoted by $SeO_2/FeCl_3$ to provide an efficient and straightforward protocol for the preparation of indanone fused heterocyclic compounds.

In line with our hypothesis, the 2-methyl-thiochromones **1** [16] was prepared and converted to aldehyde following Riley selenium dioxide oxidation. Next acid promoted intramolecular Friedel-Crafts reaction to generate the tetracyclic core and then subsquent aromatization and oxidation of the resulting benzyl alcohol gave corresponding indanone. To demonstrate its utility, we also describe a short and efficient total synthesis of Wrightiadione which exhibits a broad range of biological and pharmaceutical activities, especially the cytotoxicity against leukemia cell lines [17].

Based on the one-pot strategy, we studied the feasibility of the process to determine the most compatible conditions. For the fundamental study, our efforts began by exploring possible conditions using methyl thiochromone as model substrate. Oxidation/F-C reaction was conducted in the presence of SeO_2 with various Lewis

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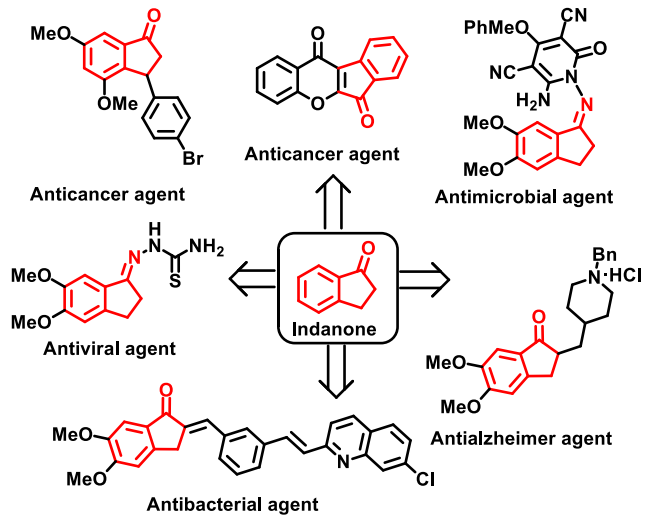


Fig. 1. Biologically active indanone derivatives.

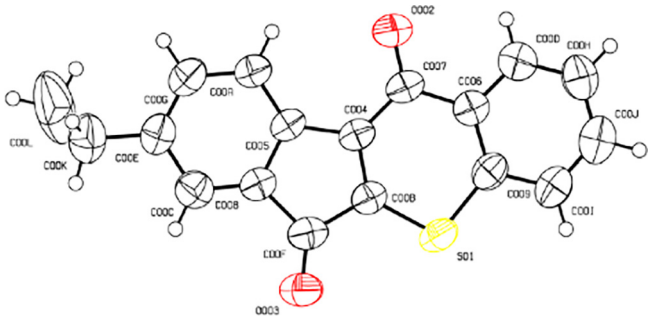
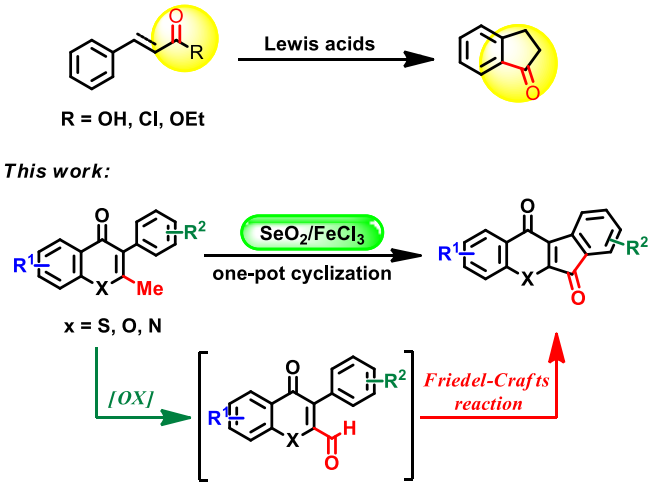


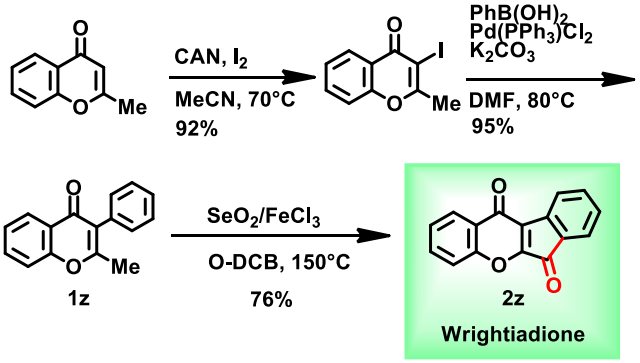
Fig. 2. X-ray crystal structure of **2g**.



Scheme 1. One-pot pathway to access indanone fused heterocyclic compounds.

acids in order to produce indanone fused heterocyclic compounds (Table 1).

In the initial attempt, As shown in entry1, in the presence of 2.4 equiv SeO_2 and 0.1 equiv $BF_3{\bullet}OEt_2$ in *o*-dichlorobenzene (*O*-DCB) the reaction proceeded at 150 °C within 12 h to give desired indanone **2a** as a sole product (34.7% yield, entry 1). $AlCl_3$ showed similar reactivity and gave similar result (41.0% yield, entry 2). Tin tetrachloride ($SnCl_4$) resulted in a much lower yield of 2a (17.2%



Scheme 2. Synthesis of Wrightiadione.

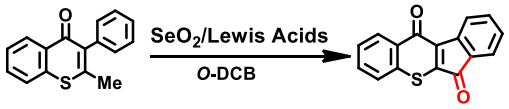
yield, entry 3) and $Sc(OTf)_3$ also gave unsatisfactory result (31.0% yield, entry 4). Further regulating the reaction conditions were achieved with $FeCl_3$, which worked to yield **2a** in moderate yield (entry 5). To our delight, when $FeCl_3$ reagent was increased to 0.5 equivalent, a dramatic improvement in the yield was achieved (87.7% yield, entry 6). Then, considering the impact of water, $FeCl_3$ (0.5 eq) was added separately after reaction time 8 h, the yield was no obvious improved (entry 7). It should be noted that, increasing equivalent of $FeCl_3$, prolonging reaction time and increasing reaction temperature did not improve the yield, but rather led to a decreased yield (entry 8, 9 and 10). Finally, the optimal condition was carried out in *O*-DCB with 2.4 eq. SeO_2 and 0.5 eq. $FeCl_3$ at 150 °C, after 12 h the desired transformation was successfully demonstrated.

With optimal conditions determined, our focus was directed toward studying the substrates in the presence of 2.4 eq. SeO_2 and 0.5 eq. $FeCl_3$. The substituents on R_1 and R_2 were investigated to see the substituent effect on the reactivity (Table 2). The tetracyclic scaffold could be easily equipped with an additional substituent at R_1 and R_2 by this one-pot process. It was noticed that even the present of aryl group bearing either electron-donating or withdrawing group at R_2, such as an alkyl (methyl and ethyl group), methoxy (**2f**, **2j**) and halogen (**2e**), the reactions were well-tolerated and generated the respective heteroindanones in moderate yields. The molecular structure of compound **2g** was independently confirmed by X-ray crystal structure analysis [18]. Evidently, the effect of the steric and electronic charactersof the substituent R_1 was not distinct on the course of the reaction (**2h**-**2u**). In addition, amenable to this protocol, nitrogen-containing derivatives were also investigated, and the expected products (**2v**-**2y**) were obtained in moderate yields (Table 2).

Specially, Wrightiadione which is an indanone derivative including a similar indanone fused heterocyclic structure, isolated from the bark of Wrightia tomentosa medicinally in Thailand. Based on the above studies, we envisioned that application of this one-pot approach reaction to produce the natural product starting from simple starting materials such as readily available 2-Methylchromone. In the synthetic route, iodination with CAN and I_2 was occurred firstly. Then, the Suzuki-Miyaura coupling of the resulting iodide with phenylboronic acid gave the desired compound in 90% overall yield. Satisfactorily, the desired product was produced smoothly via this one-pot procedure.

With these results, the reaction mechanism was shown in Scheme 3. Formation of the generated aldehyde (**a**) was carried out with the corresponding 2-methyl-thiochromones (**1**) following Riley selenium dioxide oxidation. The selenous acid generated from SeO_2 and H_2O, which was provided during Riley allylic oxidation. Next, under acid condition, promoted by $FeCl_3$ and selenous, the tetracyclic core (**b**) was generated by intramolecular

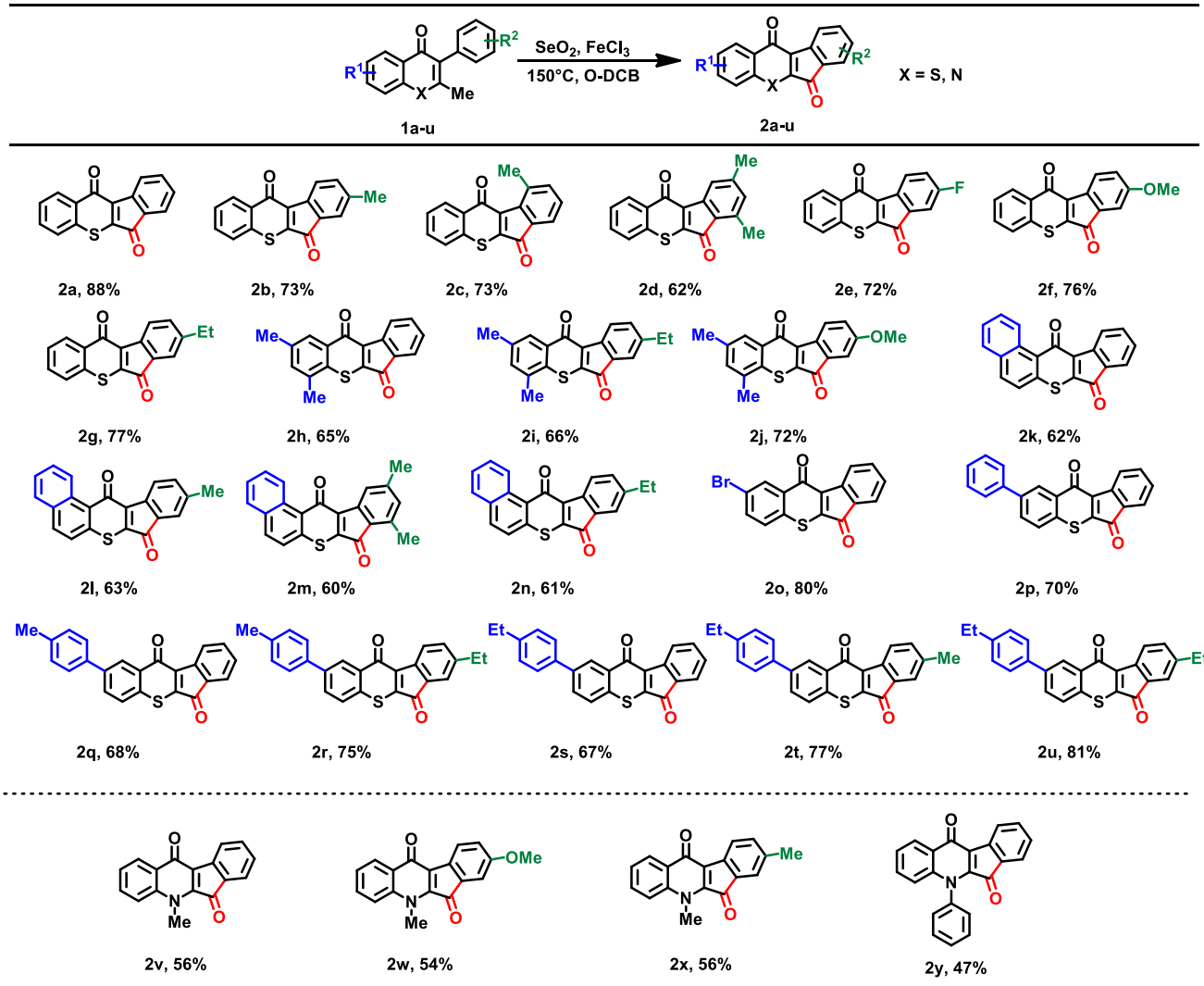
Table 1
Optimization of reaction conditions.



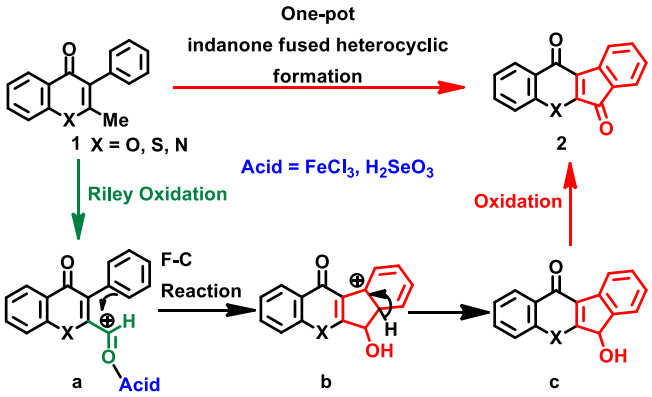
Entry	SeO_2 (eq)	Additive (eq)	Temp (°C)	Time (h)	Yield (%)[a]
1	2.4	$BF_3{\cdot}OEt_2$, 0.1	150	12	34.7
2	2.4	$AlCl_3$, 0.1	150	12	41.0
3	2.4	$SnCl_4$, 0.1	150	12	17.2
4	2.4	$Sc(OTf)_3$, 0.1	150	12	31.0
5	2.4	$FeCl_3$, 0.1	150	12	52.7
6	2.4	$FeCl_3$, 0.5	150	12	87.7
7	2.4	$FeCl_3$, 0.5	150	12	88.3[b]
8	2.4	$FeCl_3$, 1.0	150	12	82.1
9	2.4	$FeCl_3$, 0.5	150	48	87.1
10	2.4	$FeCl_3$, 0.5	180	12	84.3

[a] Reaction conditions unless specified otherwise: **1a** (0.3 mmol) and SeO_2 (2.4 eq) in dichlorobenzene (4.0 mL) Under an Ar atmosphere. The reaction was stirred at 150 °C under an Ar atmosphere for 12 h. Isolated yields.
[b] $FeCl_3$ was added separately, after reaction time 8 h.

Table 2
Scope of substituents leading to quaternary heteroindanones.[a,b]



[a] Reaction condition: 1 (0.3 mmol), SeO_2 (2.4 eq) and $FeCl_3$ (0.5 eq) in dichlorobenzene (4.0 mL) Under an Ar atmosphere. The reactionmixture was stirred at 150 °C for 12 h.
[b] Isolated yield.



Scheme 3. Proposed mechanistic pathways underlying the present one-pot reaction.

Friedel-Crafts reaction. Then indanones (**2**) were produced through subsequent aromatization and oxidation of the resulting benzyl alcohol (**c**).

In the midst of diverse known moieties, Wightiadione exhibit a broad range of biological activities including significant anticancer activity. Herein, all final quaternary heteroindanones **2a**-**2u** were screened for in vitro cytotoxic activity towards human lung cancer line (A549), human liver cancer line (SMMC-7721), human breast cancer line (MCF-7), and human cervical cancer line (Hela) (see the ESI†).

The results showed that quaternary heteroindanones with a nitro group or methoxyl group exhibits good inhibition activities. Compounds **2f**, **2g**, **2n**, and **2r** exhibited the best inhibition with IC_{50} of 23.15 ± 2.34, 24.58 ± 1.26, 22.15 ± 0.51, and 22.02 ± 3.54 μM against A549 cell line, respectively. Furthermore, **2f** (IC_{50} = 25.31 ± 0.78 μM), **2g** (IC_{50} = 17.54 ± 0.34 μM), **2 t** (IC_{50} = 21.15 ± 0.51 μM) and 2u (IC_{50} = 28.36 ± 0.28 μM) also showed the obvious growth inhibition activities against SMMC-7721 cell line. Compound **2j** (IC_{50} = 25.87 ± 0.34 μM) was found to be the most powerful cytotoxic agent against MCF-7 cell line. In addition, **2f** showed significant inhibitory effects on Hela cell line with IC_{50} of 18.54 ± 2.18 μM.

In conclusion, we have developed an efficient one-pot pathway for constructing the quaternary heteroindanones through Riley oxidation/Friedel-Crafts reaction/oxidation with SeO_2/$FeCl_3$ in moderate yields. Further studies broadened the synthetic application toward a short and efficient total synthesis of Wrightiadione. This reaction provides a new pathway for the preparation of biological precursor. Preliminary bioevaluation results of the newly synthesized compounds are shown that **2f**, **2g**, and **2j** exhibited moderate anticancer activities in vitro.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153070.

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[18] Crystallographic data of 2g has been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-2013442. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.