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Intramolecular Fischer Indole Synthesis for the Direct Synthesis of 3,4-Fused Tricyclic Indole and Application to the Total Synthesis of (−)-Aurantioclavine

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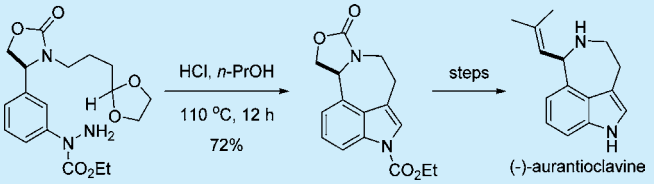
Supporting Information

ABSTRACT: Aryl hydrazides with a ketone or aldehyde containing side chains linked to the *meta*-position of the aromatic ring undergo acid-promoted intramolecular Fischer indole synthesis to generate 3,4-fused tricyclic indoles. The preparative utility of this conceptually new synthetic approach, which does not require prefunctionalization of the indole ring, was demonstrated by its application to a concise total synthesis of (−)-aurantioclavine.



Recently, tricyclic indole alkaloids bearing 3,4-fused rings have attracted much attention because of their interesting molecular architectures and important biological activities. This interest is witnessed by the large number of efforts targeted at the total syntheses of communesin F[1] and welwitindolinone C isothiocyanate[2] and related indole alkaloids (Figure 1). A

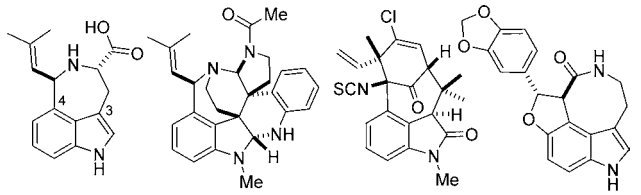
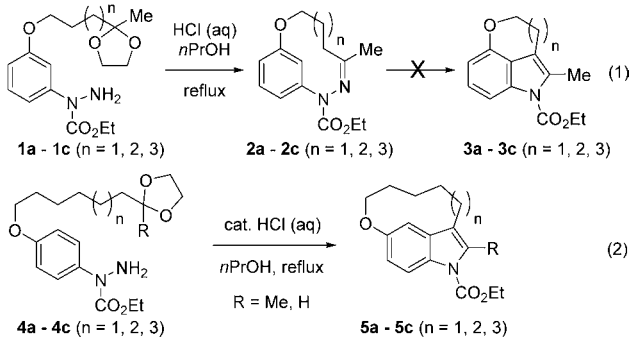


Figure 1. Selected 3,4-fused tricyclic indole alkaloids.

continuous influx of new synthetic methods and strategies has facilitated the synthesis of these complex polycyclic indole alkaloids.[3] Nonetheless, formidable synthetic challenges in this area still exist primarily because of difficulties with the construction of medium-sized ring bridges between the C3 and C4 indole positions.

In a previous study, we explored a new approach to the synthesis of 3,4-fused tricyclic indoles (**3a**−**3c**, eq 1, Scheme 1). The process involves intramolecular Fischer indole synthesis (IMFIS) of aryl hydrazides **1a**−**1c**, which bear a carbonyl group containing a side chain linked to the *meta*-position of the aromatic ring.[4] In contrast to expectation, we observed that aq HCl promoted reactions of these substrates, regardless of their side chain lengths, and all produced the corresponding cyclic hydrazones. Attempts to drive these processes to completion did not result in formation of the target indoles. On the contrary, aryl hydrazides **4a**−**4c**, with the carbonyl containing side chains

Scheme 1. Intramolecular Fischer Indole Synthesis



linked to the *para*-position, underwent intramolecular Fischer indolization reaction to form 3,5-fused tricyclic indoles **5a**−**5c**. This was a surprising result due to the expectation that the latter process would encounter larger enthalpic and entropic barriers (eq 2, Scheme 1).

The failure of the IMFIS of the *meta*-tethered aryl hydrazides **1a**−**1c** was initially attributed to the high strain energy barrier for conversion of the hydrazone intermediates to the indoles. However, the results of a simple molecular modeling study and comparisons to other intramolecular indole-forming reactions indicated that the ring strain was likely not the cause of the failure. Observations made in control experiments showed that the problem with these processes is actually a consequence of the instability of the tricyclic indole products **3a**−**3c** under the reaction conditions and not of strain of the transition state. To explore this strategy further, we conducted studies with other aryl hydrazides with a carbonyl group containing side chains linked to

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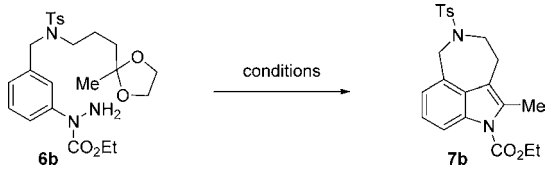
the *meta*-position of the aromatic ring. The results of this effort show that, as originally anticipated, several substrates in this group undergo IMFIS to form the corresponding 3,4-fused tricyclic indoles efficiently. Herein, we report the details of the IMFIS of *meta*-tethered aryl hydrazides and the application to the total synthesis of (−)-aurantioclavine.

Aryl hydrazide **6b**, having a *N*-Ts benzylamine containing *meta*-side chain, was chosen as the first substrate for this re-investigation. Interestingly, when treated with aq HCl in *n*PrOH at 100 °C, **6b** underwent IMFIS to form the corresponding 3,4-fused tricyclic indole **7b** in 71% yield (entry 1, Table 1). Reaction

Table 1. IMFIS of 6b under Various Conditions

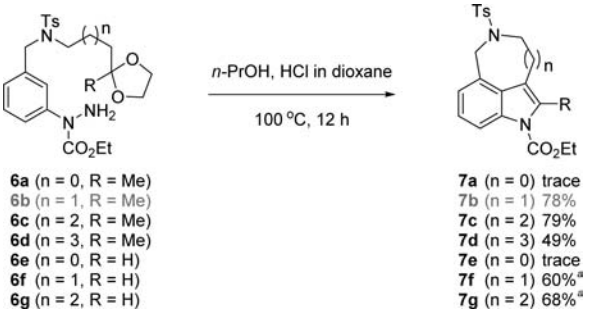


entry	conditions	results
1	*n*-PrOH, HCl (aq), 100 °C, 12 h	71%
2	EtOH, HCl (aq), 80 °C, 12 h	73%
3	EtOH, *p*-TsOH·H_2O (8.6 equiv), 80 °C, 12 h	53%
4	EtOH, *p*-TsOH·H_2O (0.1 equiv), 80 °C, 60 h	trace
5	*n*-PrOH, 4 M HCl in dioxane, 100 °C, 12 h	78%
6	PhMe, *p*-TsOH·H_2O (8.6 equiv), 100 °C, 12 h	trace
7	AcOH, 100 °C, 24 h	trace
8	*t*-amyl alcohol, AcCl, 100 °C, 24 h	55%
9	CF_3CH_2OH, AcCl, 80 °C, 12 h	trace

of **6b** in EtOH under reflux gave a slightly higher yield (entry 2), while replacement of aq HCl by *p*-TsOH resulted in no beneficial effect (entries 3 and 4). In addition, variations of the acid, solvent, and temperature did not lead to higher yields (entries 6−9). Finally, a maximum yield of 78% was obtained when the reaction was conducted in *n*PrOH at 100 °C, premixed with a solution of anhydrous HCl in 1,4-dioxane (entry 5).

Encouraged by these observations, we explored IMFIS of aryl hydrazides **6a**, **6c**, and **6d** with different chain lengths to see if tricyclic indoles with other 3,4-fused ring sizes could be generated (Scheme 2). Reaction of the one carbon shortened (n = 0) substrate was not found to produce even a trace of the IMFIS product **7a**. However, aryl hydrazide **6c** with a one carbon longer tether (n = 2) reacted efficiently to form the corresponding tricyclic indole **7c** containing an eight-membered ring fusing the C3 and C4 positions. IMFIS of **6d** with a one carbon extended tether (n = 3) was less efficient, affording **7d** in

Scheme 2. IMFIS of Aryl Hydrazides 6a−6g



6a (n = 0, R = Me)
6b (n = 1, R = Me)
6c (n = 2, R = Me)
6d (n = 3, R = Me)
6e (n = 0, R = H)
6f (n = 1, R = H)
6g (n = 2, R = H)

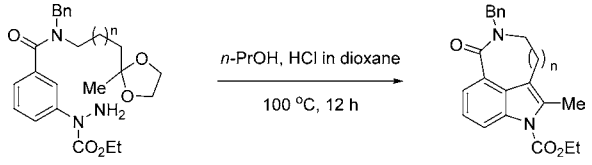
7a (n = 0) trace
7b (n = 1) 78%
7c (n = 2) 79%
7d (n = 3) 49%
7e (n = 0) trace
7f (n = 1) 60%[a]
7g (n = 2) 68%[a]

[a]The yield is for the reaction conducted at 100 °C in a sealed tube.

49% yield. Furthermore, the aryl hydrazides **6f** and **6g**, with aldehyde acetal containing *meta*-side chains, reacted under the optimized conditions to produce the respective indoles **7f** (15%) and **7g** (26%). Interestingly, the same products are generated in much higher yields (60 and 68%, respectively) when reactions of **6f** and **6g** were conducted at 110 °C.

Next, IMFIS of aryl hydrazides **8a−8d**, with benzamide containing tethers, was investigated as a prelude to potential applications to the syntheses of the naturally occurring 3,4-fused tricyclic indole alkaloids (Scheme 3). When subjected to the

Scheme 3. IMFIS of Aryl Hydrazides 8a−8d



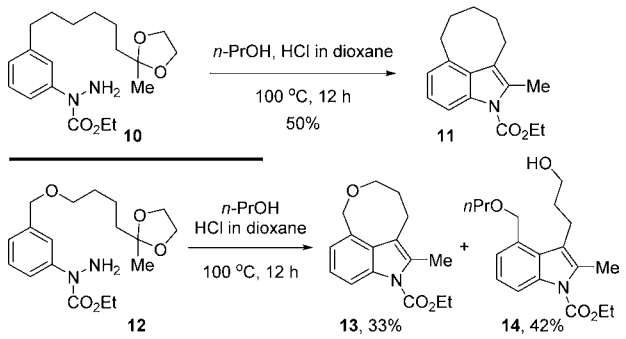
8a (n = 0)
8b (n = 1)
8c (n = 2)
8d (n = 3)

9a (n = 0), trace
9b (n = 1), 53%
9c (n = 2), 78%
9d (n = 3), 39%

optimized conditions, **8b** and **8c** reacted to form the corresponding tricyclic indoles **9b** and **9c** in 53 and 78% isolated yields, respectively. In a manner that is similar to that of **6d**, IMFIS of **8d** (n = 3) is much less efficient at forming **9d** in a 39% yield. Again, **8a** (n = 0) does not undergo IMFIS.

In an effort to further probe the substrate scope, aryl hydrazides **10** and **12** were subjected to IMFIS (Scheme 4).

Scheme 4. IMFIS of Aryl Hydrazides 10 and 12



Under the optimized conditions, aryl hydrazide **10** reacted to produce the corresponding 3,4-fused tricyclic indole **11** in 50% yield. The aryl hydrazide **12** with a benzyl ether tether also underwent IMFIS to give indole **13** in 33% yield, along with the ring-opened product **14** in 42% yield. The latter substance is likely formed by acid-mediated *trans*-etherification of **13**. When heated in toluene with catalytic *p*-TsOH, **14** underwent cyclization to generate **13** in 65% yield (see Supporting Information for details).

To demonstrate the preparative utility of the new IMFIS strategy, it was applied to the synthesis of (−)-aurantioclavine,[5] an ergot alkaloid isolated from *Penicillium aurantiovirens*. This small 3,4-fused tricyclic indole natural product could serve as a key synthetic intermediate in routes to members of the highly complex polycyclic communesin family of alkaloids.[6] Despite its small size, (−)-aurantioclavine is a deceptively elusive target because of the sensitive nature of its benzylic and allylic C−N bond. In our first attempt at the synthesis of this target, the fully decorated IMFIS precursor **15** was prepared and subjected to the

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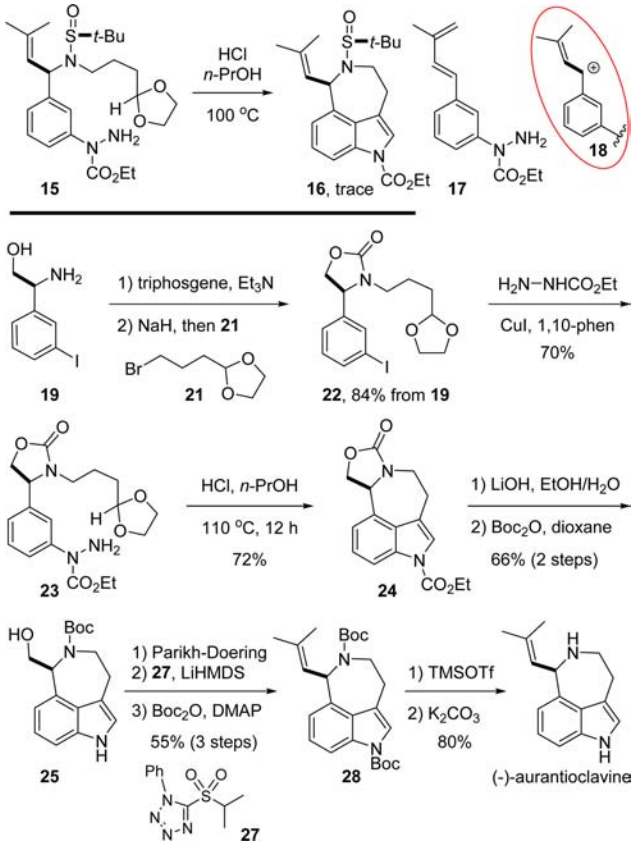
standard IMFIS conditions. However, the reaction did not form the anticipated tricyclic indole **16**, but rather diene **17** was generated presumably by proton loss from the stable intermediate carbocation **18** (Scheme 5). To circumvent the

Scheme 5. Synthesis of (−)-Aurantioclavine



formation of this carbocation, the synthetic route was revised to delay installation of the vinyl group in the target until after IMFIS. The new route was initiated by conversion of commercially available (*S*)-*β*-amino-3-iodo-benzeneethanol **19**[7] (see Supporting Information) to the corresponding oxazolidinone **22** by reaction with bromide **21** (84%, two steps). Cu(I)-catalyzed coupling reaction of **22** with ethyl carbazate proceeded uneventfully to form aryl hydrazide **23** in 70% yield. When subjected to the standard IMFIS conditions, to our delight, **23** reacted to form the desired IMFIS product **24** in 72% yield. Hydrolysis of **24** liberated the free hydroxyl group needed for installation of the dimethylvinyl side chain. After Boc protection of the ring nitrogen, the alcohol was oxidized to form the corresponding aldehyde using Parikh−Doering conditions.[8] Julia−Kocienski olefination[5a] with the resulting aldehyde **26** (not shown; see Supporting Information) followed by indole nitrogen Boc protection and the sequential removal of the two *N*-Boc groups culminated in the total synthesis of (−)-aurantioclavine. Unmasking the *N*-Boc group without protection of indolic nitrogen results in substantial yield reduction.

In conclusion, aryl hydrazides with ketone or aldehyde containing side chains at the *meta*-position of the aromatic ring were observed to undergo acid-mediated intramolecular Fischer indole synthesis to generate the corresponding 3,4-fused tricyclic indoles. This IMFIS strategy does not require cumbersome prefunctionalization, and as a result, it may serve to simplify the synthesis of polycyclic indole alkaloids. This proposal has been demonstrated by the application of the approach to a concise synthesis of (−)-aurantioclavine. Further applications of this method to structurally complex polycyclic indole natural products with a 3,4-fused tricyclic indole core are now being studied.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02541.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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