Synthetic Methods

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Intramolecular Fischer Indole Synthesis and its Combination with an Aromatic [3,3]-Sigmatropic Rearrangement for the Preparation of Tricyclic Benzo[*cd*]indoles**

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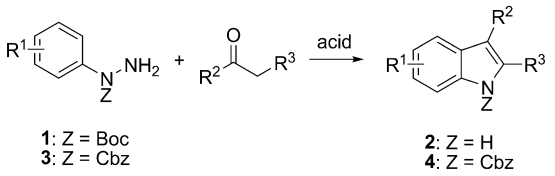
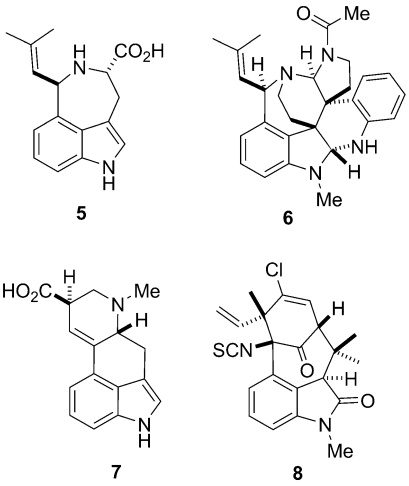
Indoles are arguably the most privileged molecular scaffolds that are present in nature.[1] A wide variety of important biological activities that are exhibited by many indole-based natural products has made them attractive synthetic targets over the years.[2] Accordingly, many elegant methods and strategies have been devised and used for their synthesis. The venerable Fischer indole synthesis, which was reported over 100 years ago, still remains of considerable value for its operational simplicity, despite the limited availability of the starting aryl hydrazines.[3] A few years ago, we reported that aryl hydrazide **1** is an effective surrogate for aryl hydrazines as it readily undergoes a Fischer indolization process to give the corresponding indole **2** (Scheme 1).[4] It was reported more



Scheme 1. Fischer indolization of aryl hydrazides.

recently that the Fischer indolization reaction of aryl hydrazide **3**, which contains the less acid-labile carboxybenzyl (Cbz) group, can proceed with the Cbz group remaining intact to give *N*-Cbz indole **4**.[5] The starting aryl hydrazides **1** and **3** in both cases are readily accessed from aryl halides by Pd^0- or Cu^I-catalyzed coupling reactions with the corresponding carbazate,[6] which expands the substrate scope of the conventional Fischer indole synthesis.[7]

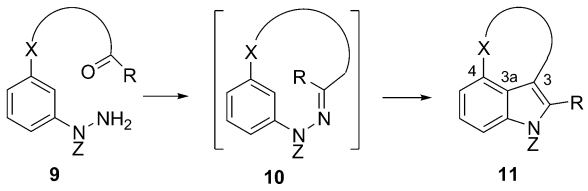
Indole-based natural products that contain tricyclic benzo[*cd*]indole cores[8] have emerged as a target of interest[9] for their intriguing biological activities and molecular architectures, as exemplified by clavicipitic acid (**5**),[10] communesin F (**6**),[11] lysergic acid (**7**),[12] and welwitindolinone C (**8**)[13] (Scheme 2). In spite of recent advances, the synthesis of such natural products is often complicated by the lack of



Scheme 2. Selected examples of benzo[*cd*]indole alkaloids.

adequate synthetic methods for producing the tricyclic benzo[*cd*]indole cores.

Our continuing interest in exploring the synthetic application of aryl hydrazides led us to envisage that an intramolecular Fischer indole synthesis could provide expedient access to tricyclic benzo[*cd*]indole systems. As depicted in Scheme 3, aryl hydrazide **9** with the carbonyl group attached to the *meta* position may cyclize into tricyclic benzo[*cd*]indole **11** after the hydrazone intermediate **10** is formed.[4a,5,14]



Scheme 3. Intramolecular Fischer indolization.

To probe the feasibility of this concept, we prepared aryl hydrazide **12a** and subjected it to the typical Fischer indole synthesis conditions by heating it in EtOH that contained a few drops of aqueous HCl (Scheme 4). However, the reaction stopped at hydrazone **10a**, with no evidence of the Fischer indolization reaction proceeding. Elongation of the tether gave no improvement (**12b** and **12c**). All of the attempts to push the reaction forward by increasing the harshness of the reaction conditions were in vain and mostly

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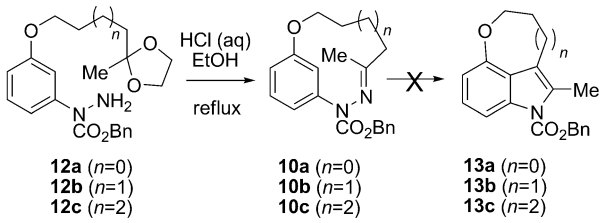
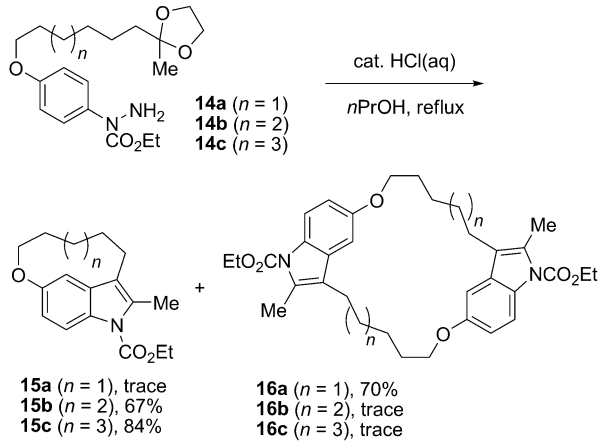


Scheme 4. Intramolecular Fischer indolization with compounds tethered at the C3 position. Bn = benzyl.

resulted in the formation of a complex mixture of unidentifiable decomposition products. The corresponding transition states for the desired products would have too much strain, as suggested by a simple molecular modeling study.[15]

We then examined the reactions of aryl hydrazides **14a–c**, in which the latent carbonyl group is tethered to the *para* position of the aromatic ring (Scheme 5). Surprisingly, aryl hydrazides **14b** and **14c** did undergo the intramolecular

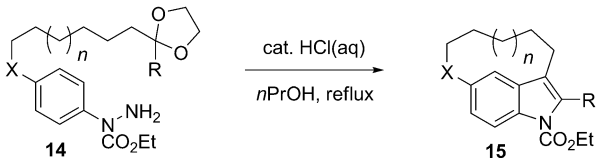


Scheme 5. Intramolecular Fischer indolization with compounds tethered at the C4 position.

Fischer indolization reaction to afford indolophanes **16b** and **16c**. In the case of the aryl hydrazide with the shorter tether (**14a**), intermolecular Fischer indolization prevailed to give dimeric indole **16a**. Evidently, the tether is not long enough in this case for the carbonyl group to wrap around and meet the amine group. The reaction was optimized by varying the reaction parameters, which include solvent, acid catalyst, reaction temperature, and the concentration of the reagents. Running the reaction in *n*-PrOH at reflux and at a concentration of 5 mM of the starting material gave the best rate of reaction and yield of isolated product (**15b** = 67%; **15c** = 84%). In this set of experiments, the *N*-Cbz group was replaced by ethyl carbamate to increase the solubility of the product for easier handling.

Enthused by these initial results, we next aimed to explore the substrate scope of the reaction by using two sets of aryl hydrazides that contain an acetal group (R = H) as well as an *N*-tosyl (*N*-Ts) linker (Table 1). Similar to **14a**, aryl hydrazide **14d**, which contains a latent aldehyde group, did not give the corresponding indolophane **15d**, but instead gave dimer **16d**

Table 1: Intramolecular Fischer indolization of aryl hydrazides **14**.

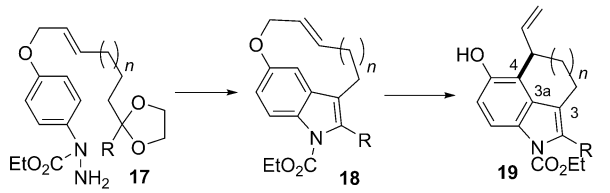


Entry	*n*	14	15	Yield [%]
1	1	**14d** (X = O, R = H)	**15d** (X = O, R = H)	trace[a]
2	2	**14e** (X = O, R = H)	**15e** (X = O, R = H)	50
3	3	**14f** (X = O, R = H)	**15f** (X = O, R = H)	52
4	1	**14g** (X = NTs, R = Me)	**15g** (X = NTs, R = Me)	50
5	2	**14h** (X = NTs, R = Me)	**15h** (X = NTs, R = Me)	50
6	3	**14i** (X = NTs, R = Me)	**15i** (X = NTs, R = Me)	80

[a] Dimeric indole **16d** (*n* = 1) was produced in 68% yield.

in 68% yield (Table 1, entry 1). However, aryl hydrazides **14e** and **14f**, which contain a longer tether, did undergo the Fischer indolization to afford the expected indoles **15e** and **15f** in good yield (50% and 52%, respectively, Table 1, entries 2 and 3). Compounds **14e** and **14f** pertain to the rare cases of the Fischer indolization reaction that can be conducted effectively with aldehydes. Aryl hydrazides that contain the *N*-Ts bridge **14g–14i** also undergo the Fischer indolization reaction to give **15g–15i**. In all series, those compounds that have longer tethers gave higher yields of products.

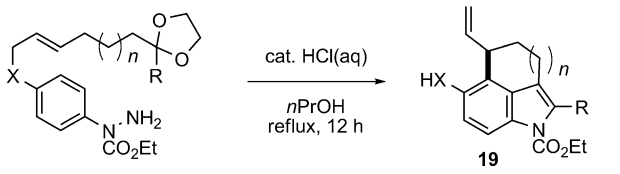
In further pursuit of a way of providing access to tricyclic benzo[*cd*]indole systems, we decided to incorporate a C–C double bond within the tether. We hypothesized that indole **18** would undergo an aromatic [3,3] sigmatropic rearrangement in a tandem fashion to construct the pivotal C–C bond at the C4-position (Scheme 6).



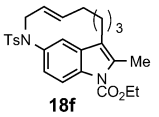
Scheme 6. Intramolecular Fischer indolization/aromatic Claisen rearrangement cascade.

To this end, aryl hydrazides **17a–17c** were prepared and subjected to the Fischer indolization conditions. Aryl hydrazides **17a** and **17b** underwent the aforementioned tandem process to give the corresponding tricyclic benzo[*cd*]indoles **19a** and **19b** in good overall yields (Table 2, entries 1 and 2). However, adding one extra methylene group to tether of the aryl hydrazide gave a complex product mixture (Table 2, entry 3). Reactions with aryl hydrazides **17d** and **17e** that contain the *N*-Ts bridge also afforded the expected tricyclic benzo[*cd*]indoles **19d** and **19e** (Table 2, entries 4 and 5). Analogous to **17c**, the reaction with aryl hydrazide **17f**, which contains a longer tether, did not give the tandem reaction

Table 2: Tandem intramolecular Fischer indole synthesis/aromatic [3,3]-sigmatropic rearrangement.



Entry	*n*	17	19	Yield [%]
1	1	**17a** (X = O, R = Me)	**19a**	56
2	2	**17b** (X = O, R = Me)	**19b**	63
3	3	**17c** (X = O, R = Me)	**19c**	trace
4	1	**17d** (X = NTs, R = Me)	**19d**	62
5	2	**17e** (X = NTs, R = Me)	**19e**	63
6	3	**17f** (X = NTs, R = Me)	**19f**	trace
7	2	**17g** (X = O, R = H)	**19g**	42



product, but instead gave indolophane **18f** in 70% yield (Table 2, entry 6). The formation of **18f** in such a high yield strongly implies that the Fischer indolization takes place before the aromatic aza-Cope rearrangement in this tandem process (Scheme 5). A simple molecular modeling study with **18f** suggests that the extra carbon unit on the tether may act as a hinge to force the olefin out and away from the aryl group, which prevents the ensuing sigmatropic rearrangement reaction. This tandem process is also effective with compounds that contain an acetal group. When subjected to the identical reaction conditions, aryl hydrazide **17g** was converted into the expected tricyclic indole **19g**, albeit in slightly lower yield (42%, Table 2, entry 7).

In summary, aryl hydrazides that contain a latent carbonyl group that is tethered to the *para* position of the aromatic ring undergo the Fischer indolization reaction in an intramolecular fashion. Strategic insertion of a C–C double bond in the tether enabled the indole product to form tricyclic benzo[*cd*]indoles in good overall yield by an aromatic [3,3] sigmatropic rearrangement reaction. This intramolecular Fischer indole synthesis may find further applications in the areas of related natural product syntheses, as well as pharmaceutical and materials sciences.

Experimental Section

Representative procedure for indolophanes **15**. Synthesis of **15b**: A solution of **14b** (0.1 mmol, 5 mM) in *n*PrOH (20 mL) was added slowly over 1 h to a solution of *n*PrOH (20 mL) that contained conc. HCl (three drops by Pasteur pipette) at 100 °C. The resulting mixture was heated for 12 h, before cooling to room temperature. The reaction mixture was then concentrated in vacuo, diluted with CH_2Cl_2 (20 mL), and neutralized by adding saturated aq $NaHCO_3$. The separated organic solution was washed with water, dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography on a silica gel column (100% CH_2Cl_2) to give **15b** (20 mg, 67%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.6$ Hz, 1H), 7.20 (d, $J = 2.4$ Hz, 1H), 6.76 (dd, $J = 8.6$ Hz, 2.4 Hz, 1H), 4.48–4.43 (m, 4H), 2.78 (t, $J = 5.9$ Hz, 2H), 2.51 (s, 3H), 1.62–1.49 (m, 6H), 1.47 (t, $J = 7.0$ Hz, 3H), 1.36–1.24 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.8$, 152.5, 133.3, 133.1, 129.4, 120.4, 116.7, 113.7, 106.9, 70.6, 62.7, 30.2, 29.0, 28.9, 28.8, 22.1, 14.6, 13.6 ppm; FT-IR (CH_2Cl_2): $\tilde{\nu} = 2928$, 1730, 1482, 1377, 1330, 1129 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{18}H_{23}NO_3$: 301.1678 [M^+]; found: 301.1678.

Representative procedure for tricyclic benzo[*cd*]indoles **19**. Synthesis of **19a**. A solution of **17a** (0.1 mmol, 5 mM) in *n*PrOH (20 mL) was added slowly over 1 h to a solution of *n*PrOH (20 mL) that contained conc. HCl (three drops by Pasteur pipette) at 100 °C. The resulting mixture was heated for 12 h, before cooling to room temperature. The reaction mixture was then concentrated in vacuo, diluted with CH_2Cl_2 (20 mL), and neutralized by adding saturated aq. $NaHCO_3$. The separated organic solution was washed with water, dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography on a silica gel column (100% CH_2Cl_2) to give **19a** (16 mg, 56%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$ (d, $J = 8.6$ Hz, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.05 (ddd, $J = 16.8$ Hz, 10.2 Hz, 7.0 Hz, 1H), 5.22 (d, $J = 10.2$ Hz, 1H), 5.07 (s, 1H, OH), 5.06 (d, $J = 16.8$ Hz, 1H), 4.46 (q, $J = 7.0$ Hz, 2H), 3.77 (dt, $J = 7.0$ Hz, 5.4 Hz, 1H), 2.63 (t, $J = 5.4$ Hz, 2H), 2.50 (s, 3H), 2.04–2.00 (m, 2H), 1.47 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.6$, 148.7, 140.5, 131.1, 129.4, 129.0, 116.9, 115.8, 114.9, 114.6, 112.7, 62.7, 37.7, 30.0, 18.0, 14.6, 14.1 ppm; FT-IR (CH_2Cl_2) $\tilde{\nu} = 3428$, 2976, 2926, 2854, 1730, 1701, 1405, 1339, 1148 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{17}H_{19}NO_3$: 285.1365 [M^+]; found: 285.1393.

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