



An interrupted Heyns rearrangement approach for the regioselective synthesis of acylindoles†

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An efficient and general method for the synthesis of 2- and 3-acylindoles has been achieved with high regioselectivity from *o*-acylanilines and α -hydroxycarbonyl or its equivalent. The strategy involves the intramolecular trapping of an *in situ* generated aminoenol intermediate and an interrupted Heyns rearrangement pathway, followed by aromatization or rearrangement/aromatization. Important features include excellent regiocontrol, good functional group tolerance, operational simplicity and application to gram-scale synthesis and the synthesis of an anti-tumor agent.

Indoles are some of the frequently encountered *N*-heterocycles in natural products, pharmaceuticals, and agrochemicals, as well as in materials science.¹ Among them, 2-acyl indoles and 3-acyl indoles are of particular importance because of their presence as core moieties in many drug molecules with diverse pharmacological effects (Fig. 1).² Due to their high importance, the synthesis of functionalized indoles has been of long-lasting interest in organic synthesis³ and a number of metal catalyzed synthetic methods for indoles⁴ have been developed in contemporary organic synthesis research. However, methods known for the construction of 2- or 3-acylindole are scarce.

The synthesis of 3-acylindole derivatives⁵ is relatively well studied compared to the synthesis of 2-acylindoles,⁶ possibly due to the inherent reactivity of the indole moiety. However, most of the known methods suffer from poor regioselectivity, harsh conditions, side reactions and the need for precious metal catalysts as well as the use of pre-functionalized indoles as precursors, which limit their synthetic applicability. Therefore, the development of a unified, regioselective, metal-free and complementary strategy to access both 2- and 3-acylindoles remains highly desirable.

The Heyns rearrangement is an important and renowned reaction in carbohydrate chemistry and the key reaction in the biosynthesis of D-glucosamine-6-phosphate from fructose and ammonia.⁷ This rearrangement involves the initial reaction of α -hydroxycarbonyls with amines to form aminoenol intermediates, which upon tautomerism afford α -aminocarbonyls, called Heyns adducts (Scheme 1). Although the Heyns rearrangement is well known in carbohydrate chemistry, its application in organic synthesis is rather limited.

The known transformations involve the one-pot functionalization of the formed Heyns adduct, derived from a nucleophile tethered amine derivative, for the synthesis of various nitrogen based heterocycles (Scheme 1).⁸ However, these methods are limited to the functionalization of the Heyns adduct and offer poor regioselectivity for the unsymmetrically substituted α -hydroxycarbonyls. Importantly, the *in situ* trapping of the aminoenol intermediate with a suitable electrophile, by way of interrupted Heyns rearrangement, is scarcely studied. The only known method has been demonstrated most recently by Ghorai *et al.* utilizing an enone as an electrophile and highly reactive α -hydroxycyclobutanone for the synthesis of azaspirocyclobutanones.⁹ Thus, the development of a general and efficient interrupted Heyns rearrangement is highly warranted. The successful development of this method would offer novel interrupted Heyns rearrangement and will open a new avenue for the functionalization of the Heyns intermediate. Thus, we herein disclose the regioselective interrupted Heyns rearrangement for the

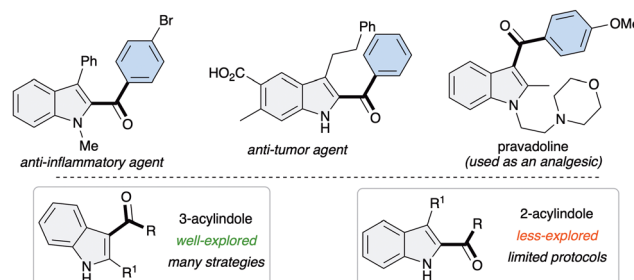
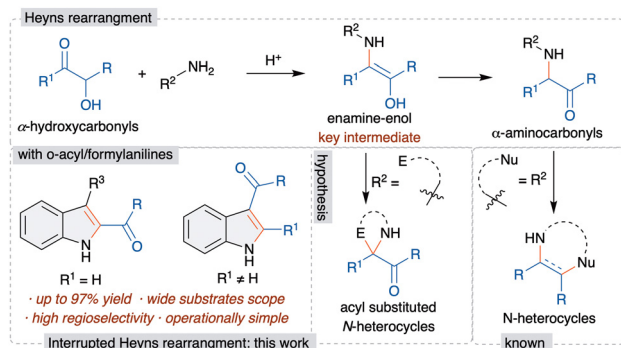


Fig. 1 Representative examples of bioactive 2 and 3-acylindoles.

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Scheme 1 Heyns and interrupted Heyns rearrangements.

unified synthesis of various substituted 2- and 3-acylindole derivatives (Scheme 1).

To test our hypothesis, α -hydroxydimethylacetal **1a**, an equivalent of α -hydroxyaldehyde, and *o*-aminoacetophenone **2a** were chosen as model substrates. Initially, **1a** and **2a** mixed at an equimolar ratio were treated with 1 N HCl in ethanol at room temperature. As postulated, the formation of 2-benzoylindole derivative **3a** was observed in 34% yield (Table 1, entry 1). The formation of **3a** proves the potential intramolecular trapping of amino-enol with the carbonyl motif, a successful interrupted Heyns rearrangement. Having identified the formation of **3a**, conditions were optimized to improve the yield of **3a**. Reaction in the absence of acid did not afford **3a**, which demonstrates the importance of acid for this reaction (Table 1, entry 2).

Subsequently, various acids were examined to understand their influence in the reaction. Most of the Brønsted acids examined showed inferior results (Table 1, entries 3–5). Next, using 1 N HCl as the promoter, critical parameters were varied to improve the yield of **3a**. Increasing the temperature to 60 °C improved the yield of **3a** to 50% (Table 1, entry 6). Further increasing the temperature to 80 and 90 °C furnished **3a** in

Table 1 Synthesis of 2-aryl indole and optimization

Entry	Acid	Temp (°C)	Solvent	Yield ^a (%)
1	1N HCl (2)	rt	EtOH	34
2	—	rt	EtOH	— ^b
3	0.5N H ₂ SO ₄ (2)	rt	EtOH	— ^c
4	AcOH (1)	rt	EtOH	— ^c
5	PTSA (1)	rt	EtOH	— ^c (60) ^d
6	1N HCl (2)	60	EtOH	50
7	1N HCl (2)	90	EtOH	84 (83) ^d
8	1N HCl (2)	90	Dioxane	90
9	1N HCl (2)	90	CH ₃ CN	87
10	1N HCl (2)	90	H ₂ O	66
11	1N HCl (2)	100	Dioxane	94 (93) ^e

Reaction conditions: **1a** (0.23 mmol, 1 equiv.), **2a** (0.23 mmol, 1 equiv.), acid (equiv.), solvent (3 mL for 0.23 mmol), temp, 18 h. ^a All are isolated yields. ^b **1a** and **2a** were recovered. ^c **1a** was decomposed and **2a** was recovered. ^d 80 °C. ^e 120 °C.

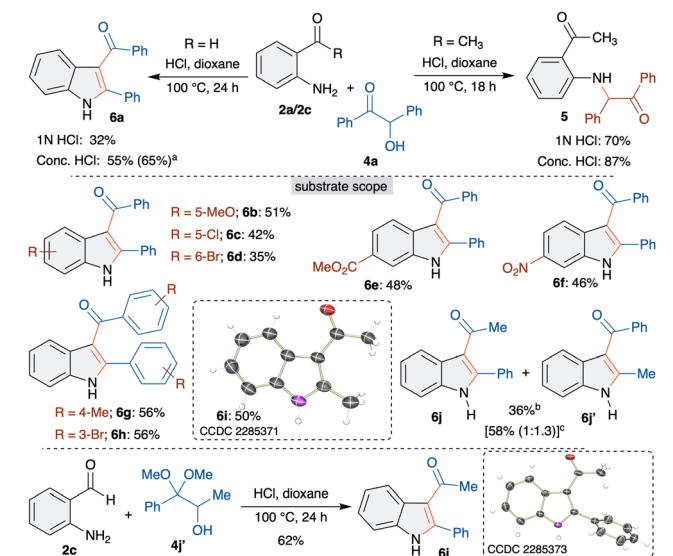
~83% yield (Table 1, entry 7). The use of dioxane and acetonitrile resulted in a slight improvement in the yield, but the reaction in water furnished **3a** in 66% yield (Table 1, entries 9 and 10). Finally, the use of dioxane at 100 °C gave **3a** in 94% yield (Table 1, entry 11). Thus, **1a** (1 equiv.), **2a** (1 equiv.), 1 N HCl, dioxane, and 100 °C for 18 h were chosen as the best optimized conditions for further studies.

Having the suitable optimized conditions in hand, we next moved on to study the scope and limitations with respect to *o*-acylaniline derivatives. Gratifyingly, all of the examined *o*-acylaniline derivatives led to the formation of 2-acylindole derivatives in good to excellent yield (Scheme 2). For instance, the reaction of alkylketone derived *o*-acylaniline furnished products **3a**, **3b** and **3d** in >85% yield. The synthesis of **3c** was achieved in 72% yield from *o*-aminobenzaldehyde.

Interestingly, vinyl ketone also gave 2-acylindoles **3e** in 71% yield. Substituted aryl and heteroaryl ketone derived *o*-acylanilines led to the formation of **3f–3h** in excellent yield. The formation and structure of **3g** was unambiguously confirmed by single crystal X-ray analysis. Next, methyl- and chloro-substituted *o*-acylanilines were treated with **1a** to afford **3i** and **3j** in 84 and 93% yields, respectively. Similarly, phenyl, and pyrenyl substituted 2-acylindoles **3k** and **3l** were achieved in good yields. Importantly, heteroaryl, pyridyl containing 2-acylindoles **3m** were synthesized in 80% yield. Besides, *N*-methyl and allyl substituted aniline derivatives were also successfully converted to indole derivatives **3n** and **3o**.

Consequently, diverse substituted α -hydroxydimethylacetal derivatives **1** were examined under optimized conditions with *o*-aminobenzophenone. α -Hydroxydimethylacetal derived from methoxy- and fluoro-substituted acetophenone afforded products **3p–3r** in excellent yields. Electron withdrawing CF₃- and

Scheme 2 Scope of *o*-acylaniline derivatives. ^a In CH₃CN at 90 °C.



Scheme 3 Synthesis of 3-acylindoles **6** and substrate scope. ^a At 120 °C. ^b Only **6j** was observed. ^c TFA (0.5 equiv.) at 130 °C, 12 h.

nitro-substituted 2-benzoylindoles **3s** and **3t** were achieved in 84% yield. The replacement of phenyl with furan, a heteroaryl moiety, also gave **3u** in 85% yield. Furthermore, α -hydroxydimethylacetal derived from an aliphatic aldehyde underwent a smooth reaction to furnish **3v** and **3w** in >85% yield.

Having successfully studied the α -hydroxyaldehyde equivalent, we next directed our attention to the study of α -hydroxyketones. In this context, we chose benzoin **4a** as a suitable substrate. The reaction of **2a** and **4a** under optimized conditions with 1 N HCl did not furnish the cyclized product. Instead, the formation of Heyns adduct **5** was observed in 70% yield (Scheme 3). To force the cyclization, conc. HCl was employed, which also gave **5** in 87% yield. In addition, all other attempts to obtain the trapped product was unsuccessful.

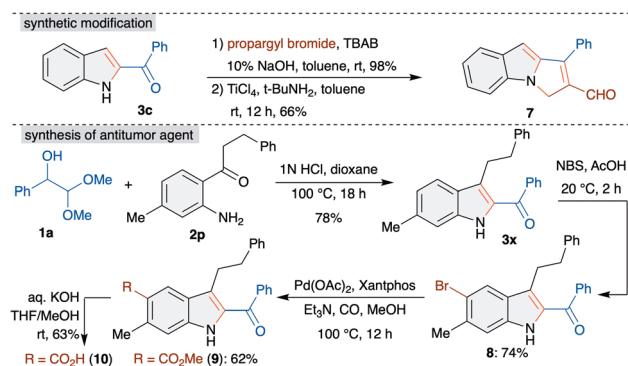
Based on this observation, we rationalized that developing steric crowd in the cyclization step possibly hinders the trapping. Hence, we envisaged to employ *o*-aminobenzaldehyde **2c** with benzoin **4a**. Interestingly, when benzoin **4a** was treated with **2c** in the presence of 1 N HCl, to our delight, the formation of the trapped product, 3-acylindole derivative **6a**, was observed in 32% yield (Scheme 3). It is important to mention that the formation of **6a** is accompanied by C–C bond cleavage and selective acyl migration. Having identified the unique reactivity, next, conditions were optimized to improve the yield of **6a** (see supporting information for more details). Interestingly, increasing the concentration of acid gave **6a** in 55% yield. The best yield of 65% was observed when **2c** and **4a** were treated with conc. HCl at 120 °C for 24 h.

After successfully optimizing the synthesis of 3-acylindoles **6**, scope and limitations were investigated. Initially, various substituted *o*-aminobenzaldehydes **2** were examined. 5-Methoxy, 5-chloro and 4-bromo substituted 2-aminobenzaldehydes gave 3-acylindoles **6b–6d** in moderate yields (Scheme 3). The reduction in the yields is due to the poor cyclization, which led to the isolation of the

corresponding Heyns adducts (~38% yield). Electron withdrawing methoxycarbonyl and nitro substituents were well tolerated under optimized conditions to afford 3-acylindoles **6e** and **6f** in good yields. Next, substituted benzoin derivatives were examined and all of them afforded 3-acylindoles **6g** and **6h** in 56% yield. Interestingly, use of acetoin also led to the formation of **6i** in 50% yield. The structure of **6i** was unambiguously confirmed by single crystal X-ray analysis. On the other hand, reaction of a mixed benzoin derivative, α -hydroxypropiophenone, with **2e** furnished **6j** in 36% yield. Attempts to increase the yield with TFA gave a regioisomeric mixture of **6j** and **6j'** in 58% yield in a 1:1.3 ratio. The formation of **6j'** could be explained through the *in situ* isomerization of α -hydroxypropiophenone to α -hydroxyphenylacetone followed by an interrupted Heyns rearrangement. Based on our earlier observation and to avoid regioselectivity issues, α -hydroxydimethylketal **4j'** was synthesized and treated with **2c**. The reaction afforded **6j** as the sole product in 62% yield, which was confirmed by X-ray analysis. This proves that α -hydroxydimethyl(ac)ketals are efficient equivalents for α -hydroxycarbonyls.

Consequently, we focused our attention on the synthetic applicability of the developed method. At first, to demonstrate the synthetic viability, a gram scale reaction was performed with **1a** and *o*-aminobenzophenone **2f**, which led to the formation of **3f** in comparable yield (see ESI† for more details). Subsequently, cyclopenta[*a*]indole **7**, a higher cyclic analogue, was achieved from **3c** in two steps. Propargylation of **3c** with propargyl bromide, TBAB and NaOH followed by reaction with TiCl₄ and *t*-BuNH₂ in toluene furnished **7** in 66% yield (Scheme 4).¹⁰

Furthermore, the development of a short synthesis of anti-tumor agent **10** was investigated.¹¹ The sequence started with the reaction of **1a** with **2p** under optimized conditions, which afforded the key intermediate **3x** in 78% yield. C5-bromination of **3x** to **8** followed by palladium catalyzed methoxycarbonylation with Pd(OAc)₂, Xantphos and Et₃N in methanol under a carbon monoxide atmosphere at 100 °C gave the methoxycarbonylated product **9** in 62% yield. The final hydrolysis of the ester in **9** with aq. KOH gave **10** in 62% yield. This represents the four step synthesis of anti-tumor agent **10**.



Scheme 4 Synthetic applications.



Scheme 5 Plausible mechanism.

We next proposed a possible mechanism for the synthesis of 2- and 3-acylindoles. As shown in Scheme 5, reaction of **1** with acid would generate oxonium species **A**, which upon reaction with **2** would generate an imine **B**. Imine-enamine tautomerism of **B** would give aminoenol intermediate **C**, a Heyns intermediate. The intramolecular trapping of **C** with carbonyl would afford **D**. Next, **D** can undergo acid promoted dehydration to give **E**, which can undergo aromatization *via* two pathways based on *R* and *R*². When *R* = H and *R*² ≠ H, aromatization with loss of proton would furnish **3**. On the other hand, when *R* ≠ H and *R*² = H, aromatization with selective acyl migration occurs to give **6**.

In conclusion, we have developed an acid promoted efficient and expedited synthesis of 2-acyl and 3-acylindole derivatives from *o*-acyl/formylanilines and the α -hydroxycarbonyl equivalent. This method involves an interrupted Heyns rearrangement and the *in situ* generation and intramolecular trapping of aminoenol with tethered carbonyl, followed by aromatization with or without 1,2-acyl migration. The developed method allows the synthesis of diverse substituted 2-acyl and 3-acylindoles in good to excellent yields. Importantly, the present method offers excellent regiocontrol, good functional group tolerance, and gram-scale synthesis and allows the synthesis of higher analogues of indoles and an anti-tumor agent.

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Conflicts of interest

There are no conflicts to declare.

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