De Novo Synthesis of Benzannelated Heterocycles

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Dedicated to Professor Dr. Herbert Mayr on the occasion of his 70th birthday

Abstract: Benzannelated heterocycles such as indoles and indazoles are prominent structural motifs found in natural products, pharmaceuticals and agrochemicals. For their synthesis, chemists traditionally either functionalize commercially available heterocycles or resort to transformations that make use of benzene derived building blocks. Here, we report a powerful cascade reaction that enables the *de novo* construction of variously substituted indoles, indazoles, benzofurans and benzothiophenes from readily available bicyclo[3.1.0]hexan-2-ones. The transformation can be conducted under mild, non-anhydrous conditions. For the synthesis of indoles, mechanistic studies revealed that the electrocyclic ring-opening of the bicyclic ring-system and aromatization precedes the 3,3-sigmatropic rearrangement.

Introduction

Five-membered benzannelated heterocycles are ubiquitous in biologically active molecules and are precious building blocks for the chemical industry (Figure 1).^[1] Conventional methods for the synthesis of substituted indoles and indazoles typically make use of either pre-functionalized heterocycles or rely on benzene-derived building blocks. Protocols that enable the *de novo* synthesis of these heterocycles are rare and often are associated with unsatisfactory functional group tolerance, efficiency, or practicability (e.g. use of stannanes, high temperatures, expensive transition metals).^[2] Examples (Figure 2a) include the Kanematsu indole synthesis, which involves a multistep sequence to access the allene precursor, requires high temperatures, and only tolerates alkyl and phenyl groups,^[3] and the Pagenkopf indole synthesis, in which the indole core is constructed via a nitrile/donor-acceptor cyclopropane [3+2] cyclization.^[4] The Funk group also reported a 6 π -electrocyclization/condensation approach to construct the indole structural motif of the natural product welwistatin.^[5]

Figure 1. Selected examples of biologically active molecules featuring an C6-functionalized indole or indazole structural motif.

Figure 2. a) Selected methods for the synthesis of indoles and indazoles from non-aromatic precursors. b) *De novo* synthesis of benzannelated heterocycles from bicyclo[3.1.0]hexan-2-ones.

Another rare example for the synthesis of an indazole from a non-aromatic precursor was described by Ainsworth^[6] and involves the condensation of hydrazine with a β -hydroxyketone. A drawback of these strategies is the need for toxic oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or the use of palladium in the final aromatization step.^[7]

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In recent work we demonstrated that bicyclic ring-systems can be efficiently converted to polyfunctionalized 3-hydroxybenzoates^[8] and orthogonally functionalized, chlorinated naphthoates.^[9] Initial efforts to incorporate heteroatoms in the ring-opening precursor were largely unsuccessful and only trace amounts of the desired heterocycles could be obtained. Here, we report a solution to this problem and show its general applicability to the efficient syntheses of indoles, indazoles, benzofurans and benzothiophenes.

Results and Discussion

We began our investigations with *O*-vinyl oxime **1**, which was prepared in two steps from readily available methyl bicyclo[3.1.0]hexan-2-ones (see Supplementary Information for details).^[10] To identify the optimal conditions for the synthesis of indole **2**, *O*-vinyl oxime **1** was subjected to an extensive screen of reaction conditions (Table 1). We found that conducting the reaction in sulfolane (0.2–0.5 M) at 190 °C (entry 1), afforded **2** in only 6% yield. Following this result, the effect of varying reaction temperatures was investigated (70–170 °C, entry 2 and Supplementary Information). While temperatures significantly above 170 °C or below 70 °C only led to trace amounts of **2**, maintaining the reaction temperature at 100 °C improved the yield of **2** to 37%. The presence of zinc chloride or acetic acid (entries 3 and 4), which are common additives in the related Fischer-indole synthesis, was not beneficial.

Table 1: Conversion of **1** to **2** under varying reaction conditions.

Entry	Solvent	Additive	T [°C]	t [h]	Yield [%] ^[a]
1	sulfolane	None	190	0.5	6
2	sulfolane	None	100	2	37
3	sulfolane	ZnCl ₂	100	3	traces
4	sulfolane	AcOH	100	5	39
5	HFIP	None	100	3	n.c.
6	Toluene	None	100	3	n.c.
7	toluene	PPh ₃ AuCl/AgBF ₄	100	48	traces
8	sulfolane	Amberlyst® 15	100	1.5	63
9	sulfolane	ClCOOEt	100	3	65
10	sulfolane	TFA ^[b]	100	1.5	65

[a] Yield of the isolated product. [b] 1.0 equiv TFA. TFA = trifluoroacetic acid, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

A survey of solvents revealed that hexafluoroisopropanol (HFIP) and toluene were ineffective, with only starting material being recovered (entries 5 and 6). In 2010, the Camp group reported a gold(I) catalyzed rearrangement of *O*-vinyl oximes to give substituted pyrroles.^[11] Unexpectedly, when **1** was subjected to these conditions, indole **2** was only produced in trace amounts (entry 7). However, significantly improved yields were achieved by employing Amberlyst® 15 as a proton source (63% yield, entry 8). In an attempt to combine the indole formation with an *in situ* *N*-protection, we heated a mixture of **1** and ethyl chloroformate in dry sulfolane at 100 °C (entry 9). Surprisingly, only formation of unprotected **2** (65%) was observed in this case. An identical yield was obtained when ethyl chloroformate was replaced with trifluoroacetic acid (entry 10). Although the exact role of the acid (or chloroformate) additive is unclear at this point, we believe that it simply increases the rate of imine to enamine tautomerization and thus facilitates initiation of the cascade reaction.

With the optimized conditions in hand, we applied our methodology to a variety of *O*-vinyl oximes, which were prepared in three steps from readily available cyclopenten-2-ones (Figure 3). The reactions could be conducted in an open-flask, with generally short reaction times (< 3 h), and the presence of one equivalent of trifluoroacetic acid was found to be optimal in all cases.

Figure 3. Synthesis of indoles and variation of the substitution pattern at C4–C7.

As demonstrated for **3** and **4**, substituents at the C4 and C5 position of the indole are well tolerated. We could further show that a variety of C7-substituted indoles (**5–10**) are accessible and that the transformation is not limited to aryl substituents (**5**). While indoles bearing a *para*-substituted C7-aryl group (compounds **7a–7e**) were produced in yields up to 83%, indoles bearing an *ortho*-substituted C7-aryl group (**8a** and **8b**) were isolated in excellent yields up to 97%. The method also worked well for naphthyl-substituted indole **9** and with heteroaromatic substituents such as 2-furyl (**10a**) and 2-thienyl (**10b**). To further vary the substitution pattern of the C6-position of the indole core, we also investigated the *gem*-dichloro cyclopropane derivative of *O*-vinyl oxime **1**. With this substrate, we obtained the 6-chloro indole **11** in 67% yield.

Mechanistically, we envisioned that the enamine tautomer **1'**^[11] would follow one of the two pathways illustrated in Scheme 1 to give indole **2**. In pathway A, a [3,3]-rearrangement produces the pyrrol intermediate **12**, which is then converted to **2** via a thermally induced 2 π -disrotatory ring-opening-aromatization sequence. In pathway B, the strain-releasing, ring-opening-aromatization reaction takes place first to give the aryl *O*-vinyl oxime **13** which undergoes a sequential [3,3]-rearrangement and condensation to deliver indole **2**.

Based on literature precedent,^[11,12a] it seemed reasonable that either of the two pathways could be operational, but it was unclear whether any of the proposed intermediates could be detected by NMR spectroscopy. Interestingly, when a solution of **1** and trifluoroacetic acid (1 equiv) in sulfolane was monitored by ¹H NMR spectroscopy and was gradually heated from 30 °C to 100 °C, we observed neither intermediate **12** nor intermediate **13**. After 1 h, heating was discontinued and indole **2** could be isolated as the sole product in 65% yield.

Scheme 1. Mechanistic hypotheses for the indole formation.

Since monitoring of the reaction by ¹H NMR spectroscopy did not allow us to differentiate between the two pathways, we next focused our attention on the synthesis of the modified components **14** and **17** (Scheme 2). First, we prepared unsubstituted cyclopropane fragment **14**, lacking the crucial chloride-leaving group for the ring-expansion reaction. Surprisingly, exposure of this substrate to trifluoroacetic acid in sulfolane at 30 °C for 14 h did not afford pyrrole **15**, but left the starting material unreacted. At elevated temperatures (100 °C), complete decomposition of the substrate occurred within 3 h.

Next, we attempted to synthesize the aryl *O*-vinyl oxime **17** via 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed 1,4-addition of *N*-aryl hydroxylamine **16** to methyl propiolate at –10 °C. However, using DABCO in the 1,4-addition step, did not afford **17** but rather directly gave rise to the corresponding indole **18**.^[12b] Based on these results, we concluded that the mechanism of the indole formation most likely proceeds via pathway B.

Scheme 2. Mechanistic probes for the indole formation. DABCO = 1,4-diazabicyclo[2.2.2]octane.

Having established a versatile platform for the synthesis of indoles, we turned our attention to the preparation of substituted indazoles. After intensive screening of reaction conditions, we were pleased to find that the condensation reaction of diketone **19** with hydrazine monohydrochloride in a sealed tube directly afforded **20**. Simple variation of diketone **19** gave access to a variety of C3-substituted indazoles, which are depicted in Figure 4. Indazoles bearing an aliphatic (**21** and **22**), phenyl (**23**) or methoxymethyl (**24**) group were obtained in yields up to 77%. Electron-deficient substituents, such as methyl ester (**25a** and **25b**) or trifluoromethyl (**26**) groups, and heteroaromatic substituents, such as 2-pyridinyl (**27**), 2-furyl (**28**) or 2-thienyl (**29**) were also well tolerated. In sharp contrast to the indole synthesis, formation of the related indazoles could also be conducted in a stepwise manner to first form a pyrazole at 23 °C. Upon heating to 100 °C, full conversion to the indazole was observed.

Having developed an efficient strategy for the synthesis of C6-substituted indazoles, we set out to further extend our *de novo* platform for the construction of other benzannulated five-membered heterocycles. Exposure of 1,4-diketone **30** and **32**^[13] to trifluoroacetic acid at 190 °C initiated the ring-

expansion/aromatization cascade reaction to provide in good yields benzofurans **31** and **33**, respectively. Alternatively, the use of Lawesson's reagent **36** in the cyclization reaction gave access to benzothiophenes **34** and **35**, respectively.

Figure 4. One-Pot Synthesis of substituted indazoles from bicyclo[3.1.0]hexan-2-ones. [a] Yield over two steps after chromatographic purification.

Conclusions

In conclusion, we have developed a protocol for the *de novo* construction of polysubstituted indoles, indazoles, benzofurans and benzothiophenes from non-aromatic precursors. The reaction can be conducted in an open-flask, is operationally simple and does not require expensive reagents or catalysts. Many of the presented heterocycles feature a unique substitution pattern and have never been synthesized before. A broad application of the developed strategy for the synthesis of highly substituted benzannulated heterocycles and its implementation in complex molecule syntheses are currently underway in our laboratory.

Experimental Section

Experimental details and compound characterization data and copies of ^1H and ^{13}C NMR spectra, are available in the Supporting Information.

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Keywords indoles • indazoles • benzofuran • cyclopropanes • ring-expansion

Scheme 3. Synthesis of benzofurans and benzothiophenes.

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