Pericyclic Reactions

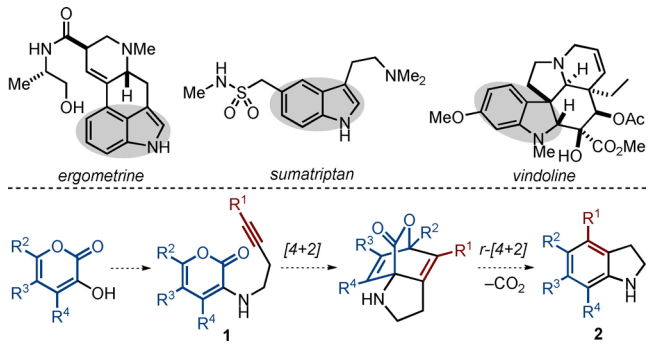
Regioselective Formation of Substituted Indoles: Formal Synthesis of Lysergic Acid

Gary L. Points, III, Kenneth T. Stout, and Christopher M. Beaudry*[a]

Abstract: A Diels–Alder reaction-based strategy for the synthesis of indoles and related heterocycles is reported. An intramolecular cycloaddition of alkyne-tethered 3-aminopyrones gives 4-substituted indolines in good yield and with complete regioselectivity. Additional substitution is readily tolerated in the transformation, allowing synthesis of complex and non-canonical substitution patterns. Oxidative conditions give the corresponding indoles. The strategy also allows the synthesis of carbazoles. The method was showcased in a formal synthesis of lysergic acid.

Aromatic heterocycles represent core architectures of natural products, pharmaceuticals, and biological polymers. The substitution pattern featured on the aromatic ring is directly related to molecular function and biological activity.[1] As a result, the preparation of heteroaromatics with control of substituent regiochemistry has been, and continues to be, an important longstanding theme in synthetic chemistry.

The substituted indole represents a common motif among molecules with potent activities toward G protein-coupled receptors.[2] As a result, substituted indoles are widely used pharmaceuticals (Scheme 1). Ergometrine features a C4-substituted indole, and it is used in obstetrics for postpartum bleeding. Sumatriptan is a migraine medicine that contains a C5-substituted indole (or tryptamine). Finally, vindoline is a precursor to the chemotherapeutic vinblastine, and it displays an indoline bearing a C6-methoxy group.



Scheme 1. Substituted indole derivatives: Structure and synthetic strategy.

The importance of such indole derivatives has inspired synthetic chemists over several decades to create methods for the synthesis of substituted indoles.[3] The synthesis of indoles with C4-substitution is notoriously challenging; however, substitution at the other benzenoid positions (C5, C6, and C7) is also far from trivial, particularly when multiple substituents are required.

Creative and elegant Diels–Alder reactions are known to prepare indoles, with substitution at C4 and the other benzenoid carbon atoms (Scheme 1).[4] For example, Wipf has demonstrated that aminofurans tethered with alkene dienophiles undergo Diels–Alder-elimination cascades to form indoles.[5] Boger has used alkyne- and allene-tethered diazines in Diels–Alder reaction-based sequences to prepare substituted indolines and indoles, respectively.[6] Other strategies featuring alkyne-tethered pyrones are also known, which use 6-aminopyrone architectures.[7] Snyder reported the cyclization of alkyne-tethered 4-chloro-6-amidopyrones to give *N*-acyl-6-chloroindolines.[8] Recently, Cui disclosed a reaction forming indolines from 6-sulfonamidopyrones bearing tethered alkynes.[9]

A flexible synthesis of indoles was sought that could not only deliver substitution at C4, but also create indoles with programmable substitution at other positions and avoid the use of activating or protecting groups on nitrogen. Our laboratory has been interested in using pericyclic reactions for the synthesis of substituted aromatic rings,[10] and we hypothesized that a Diels–Alder reaction-based strategy using 3-aminopyrones tethered with an alkyne dienophile (**1**) would deliver the 4-substituted indoles (**2**); however, this transformation is unknown in the literature.

We anticipated that the advantages of using 3-aminopyrones rather than either 6-aminopyrones or other heterodienes would be several fold. First, the key substrates **1** could be prepared using simple alkylations of 3-aminopyrones. Second, unlike with 6-aminopyrones, there would be no requirement that the nitrogen atom bears an electron withdrawing or protecting group (i.e., acyl or sulfonyl) for the synthesis or cyclization of **2**. Finally, all positions of the indoline product (i.e., R^1-R^4) could, at least in principle, be substituted with alkyl, heteroatom, or aromatic groups.

With these expectations in mind, our attempts to realize the 3-aminopyrone to indoline transformation began with the syn-

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thesis of alkyne-tethered 3-aminopyrones such as **1**. We surveyed several methods known for the synthesis of 3-aminopyrones;[7,8,11] however, we did not find a convenient and general synthesis of these compounds. Interestingly, the parent compound, 3-aminopyrone, was an unknown molecule.

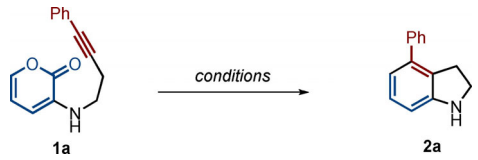
Eventually, we considered preparing 3-aminopyrones from the corresponding 3-hydroxypyrones. 3-Hydroxypyrone (**3a**) can be obtained commercially, or it can be prepared from inexpensive mucic acid.[12,13] 3-Hydroxypyrone (**3a**) was activated as the corresponding triflate, which was envisioned to undergo C–N bond formation to give 3-aminopyrone (**4a**).[14] However, this ostensibly benign C–N bond formation was complicated by the discovery that 3-triflato-2-pyrone immediately decomposed in the presence of bases commonly used for such couplings (e.g. NaO*t*Bu).[15] Additionally, the triflate was not stable to primary amines, precluding a direct coupling with butynylamines to give **1**. As a result, we investigated couplings with an ammonia-equivalent carbamate.

We found that Buchwald–Hartwig coupling of the triflate derived from **3a** with $BocNH_2$ followed by TFA removal gave 3-aminopyrone (**4a**).[16] Alkylation of **4a** with triflate **5a** gave our initial substrate (**1a**) to evaluate the pericyclic cascade. A benefit of this strategy for the synthesis of 3-aminopyrones is that the many known substituted 3-hydroxypyrones (**3**; Scheme 2, bottom) can be easily converted in to their substituted 3-amino congeners (**4**), and the corresponding alkynylated compounds (**1**, see the Supporting Information for details).

Simple heating of **1a** did induce conversion to the corresponding indoline **2a** in low yield (Table 1, entry 1); however, **2a** was accompanied by several decomposition products. Pyrones bearing acidic functional groups at C3 can be activated for cycloaddition by treatment of base.[17] We found that addition of DBU gave cycloaddition with fewer by products (entry 2); however, the reaction was still quite sluggish. We believe the base activates the amino pyrone through deprotonation to give a more electron-rich diene. Additionally, the added base may also eliminate adventitious acids that lead to decomposition of the starting material. Control experiments indicated that protic acids gave relatively fast decomposition of the starting material with no observable indoline (entry 3).[18]

More forcing conditions were also evaluated in order to increase the product yield. Increasing the temperature gave **2a** in 60%, albeit after a 7 d reaction time (entry 4). Increasing the equivalents of base did not noticeably improve the reaction yield or shorten the reaction time (entry 5).

Table 1. Optimization of reaction conditions.



1a **2a**

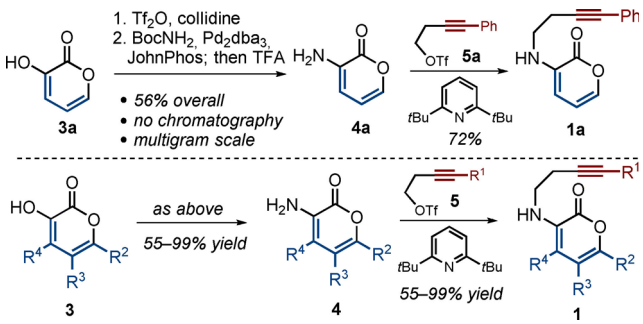
Entry	Conditions	*T* [C°]	*t*	Yield [%]
1	PhMe	120	30 d	17
2	DBU (0.2 equiv), PhMe	120	7 d	36
3	CSA (0.1 equiv), PhMe	100	31 h	0
4	DBU (0.2 equiv), PhMe	180	7 d	60
5	DBU (2 equiv), PhMe	180	7 d	46
6	DBU (0.2 equiv), BuCN	120	4 d	58
7	DBU (0.5 equiv), BuCN	200	22 h	99
8	K_2CO_3 (0.5 equiv), BuCN	200	22 h	91
9	CS_2CO_3 (0.5 equiv), BuCN	200	15 h	58
10	DBU (0.5 equiv), BuCN	200 (μW)	2 h	63
11	K_2CO_3 (0.3 equiv), BuCN	200 (μW)	2 h	99

The reaction rate did increase in more polar solvents, and we found butyronitrile (BuCN) to be an operationally convenient solvent with suitably high boiling point (entry 6). Increasing the amount of base, and the temperature (entry 7) gave **2a** in high chemical yield and with a tolerable reaction time. The reaction was sensitive to the choice of base, and use of potassium carbonate (entry 8) or other inorganic bases led to slightly decreased yields.

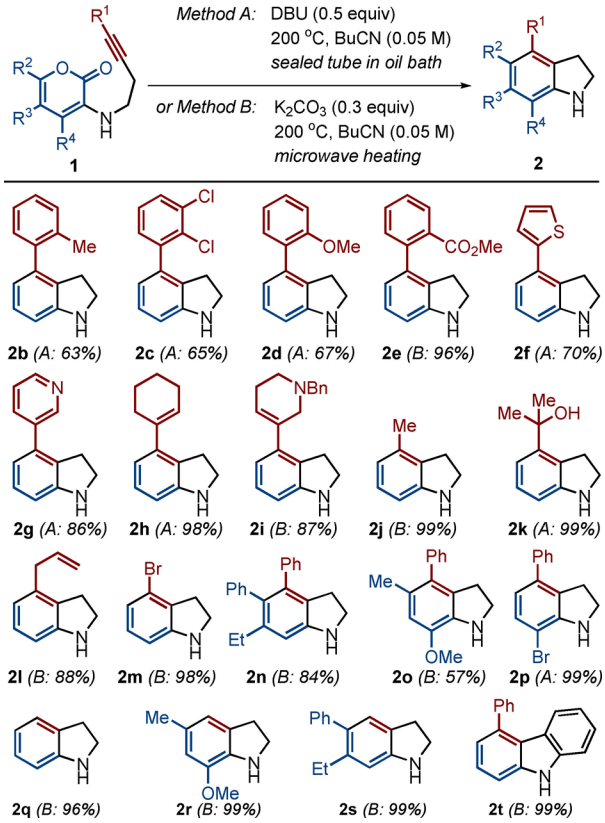
The reaction was also successful under microwave heating, and reaction times were significantly shorter (entry 10). A brief survey of bases revealed that K_2CO_3 gave higher yields than DBU with microwave heating (entry 11). Using these optimized conditions (entries 7 and 11) the yield of the pericyclic cascade was nearly quantitative.

The indoline synthesis was further evaluated with an expanded set of substrates (**1**→**2**, Scheme 3). A wide variety of substitution was possible on the alkyne. Substituted phenyl rings were tolerated giving **2b** and **2c**, which display branching adjacent to the biaryl bond. Indolines bearing phenyl rings with electron donating substituents (**2d**) and electron withdrawing substituents (**2e**) were formed in good yield. The rate of the reaction was not significantly different in these cases. Heteroaromatic rings were well tolerated; 4-(2-thiophenyl)-indoline (**2f**) and 4-(3-pyridinyl)-indoline (**2g**) were prepared. The alkyne substituent need not be aromatic, and cyclohexenyl-substituted indoline (**2h**) was prepared in high chemical yield. Enamine-containing product **2i** was also produced in good yield. Products bearing sp^3-hybridized carbon were also conveniently prepared, and indolines bearing a methyl (**2j**), tertiary carbinol (**2k**), and allyl groups (**2l**) at C4 were all formed in high yield. Finally, we found that bromoalkyne-tethered aminopyrone **1m** (R^1 = Br; R^2-R^4 = H) smoothly reacted to give **2m**.

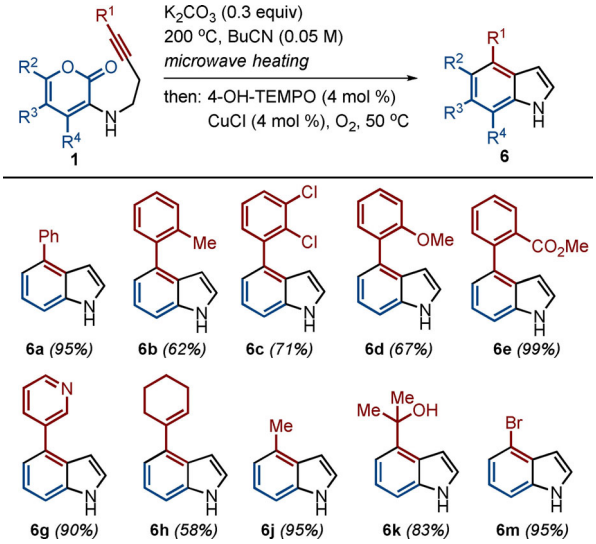
Synthesis of indolines with substitution at C4 is a classic challenge in organic chemistry; however, preparing indolines with additional substitution (i.e., 4,*x*-disubstituted or 4,*x*,*y*-tri-



Scheme 2. Synthesis of alkyne-tethered 3-aminopyrones.



Scheme 3. Synthesis of substituted indolines.



Scheme 4. Synthesis of substituted indoles.

substituted indolines) is also non-trivial. Gratifyingly, substitution was well tolerated on the pyrone ring. Substituted aminopyrones (**1**, R^2, R^3, or $R^4 \neq H$) were prepared from the corresponding substituted 3-hydroxypyrones following the conditions shown in Scheme 2 (see the Supporting Information). 4,5,6-Trisubstitited indoline **2n** was prepared in high yield. Heteroatom (**2o**) and halogen (**2p**) substituents were also tolerated in the reaction.

The reaction also produced indolines without substitution at C4 through use of terminal alkynes (**1**, $R^1 = H$). Indoline itself (**2q**) was produced in high yield. Additionally, 7-methoxy-5-methylindoline (**2r**) and 6-ethyl-5-phenylindoline (**2s**) were prepared. Finally, carbazole **2t** was prepared in high yield from the corresponding alkynyl-substituted diphenylaniline starting material.

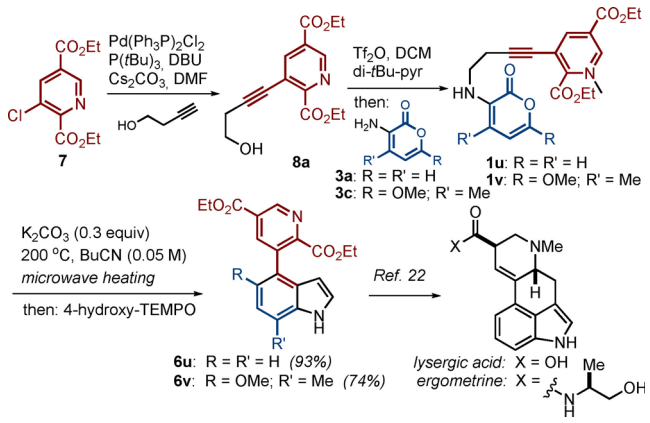
Our method was also extended to a one-pot indole synthesis (**1**→**6**, Scheme 4). Oxidations of indolines to indoles occurs under a variety of mild conditions.[3] We subjected standard substrate **1** to our optimized conditions for the pericyclic cascade (Method B). When the starting material was consumed (TLC check), we added an oxidant and observed formation of the corresponding indole. After a brief survey of oxidants, we found that the inexpensive 4-hydroxy-TEMPO gave clean conversion of the indoline to the corresponding indole.[19] The chemical yield on the one-pot indole formation was essentially identical to the yield of the indoline synthesis, and control experiments further confirmed that the oxidation of the indolines to indoles with 4-hydroxy-TEMPO was quantitative.

The one-step indole synthesis was evaluated using additional substrates (Scheme 4). Our standard substrate **1a** gave indole **6a** in high yield. 4-Arylindoles with substitution proximal to the biaryl bond were formed with no loss in yield compared with the indoline. Products bearing alkyl groups (**6b**), halogen substitution (**6c**), electron donating groups (**6d**), and electron withdrawing groups (**6e**) were all prepared in high yields. Pyridine (**6g**) substituents were also well tolerated in the reaction. Indoles bearing alkenyl groups (**6h**), a methyl group (**6j**), a tertiary carbinol (**6k**), and a C4-bromide (**6m**) were also prepared in high yield.

Among indole natural products that feature substitution at C4, the ergot alkaloids are perhaps the most well-known. This family of alkaloids is represented by several clinically-used pharmaceuticals (e.g. ergometrine), as well as notorious psychedelic drugs.[20] A common precursor to these ergot-derived molecules is lysergic acid. Many syntheses of lysergic acid are known,[21] and a central concern in the synthesis of this molecule is the method by which the C4-substituted indole is constructed.

Our approach to substituted indoles was applied in a formal synthesis of lysergic acid. Chloropyridine **7** was prepared following the method of Hendrickson,[22] and it was converted to **8a**. 3-Aminopyrone (**3a**) was alkylated with the triflate derived from **8a** to give pericyclic cascade substrate **1u**. Oxidative cyclization following our conditions gave indole **6u** in good chemical yield. Intermediate **6u** is a known precursor to lysergic acid (Scheme 5).[22]

Many previous synthetic approaches toward lysergic acid cannot be extended to analogs with increased substitution. However, our method was extended using 3-aminopyrone **3c**, which gave pyrone **1v**. Pericyclic cascade reaction under our conditions gave **6v**, which contains additional substitution on the ergot alkaloid A-ring. Such substitution may be used to probe the structure activity relationship between the A-ring and activity in dopamine and serotonin receptors. Efforts to



Scheme 5. Formal synthesis of lysergic acid and ergometrine.

advance this material to ergometrine derivatives are underway in our laboratory.

In summary, we have discovered a new pericyclic cascade approach to substituted indolines and indoles that allows for programmed substitution on the benzenoid ring of the heterocycle. Chemical yields are high, even when multiple substituents are present. Substituents at the indoline C4 position can be aryl, heteroaryl, alkenyl, alkyl, or halogen groups. Conducting the key transformation in the presence of 4-hydroxy-TEMPO results in the formation of the corresponding indole with very little decrease in chemical yield. Synthesis of indolines and indoles with substitution at the other benzenoid positions is possible, and 4,*x*-disubstituted or 4,*x*,*y*-trisubstituted indolines are readily prepared. We have showcased this reaction in a formal synthesis of lysergic acid. Finally, congeners such as **6v**, with additional substitution on the A-ring are also available using this transformation.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: indoles · indolines · lysergic acid · pericyclic reactions · total synthesis

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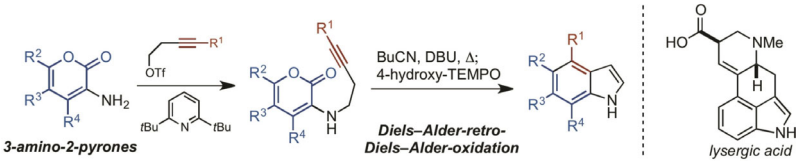

Pericyclic cascade of alkyne-tethered 3-aminopyrones gives indolines or indoles with substitution at C4. Additional substitution is readily tolerated to give 4,*x*-disubstituted or 4,*x*,*y*-trisubstituted indolines. The reaction was showcased in a formal synthesis of lysergic acid (see scheme).

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