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Thermal Cycloisomerization of Putative Allenylpyridines for the Synthesis of Isoquinoline Derivatives

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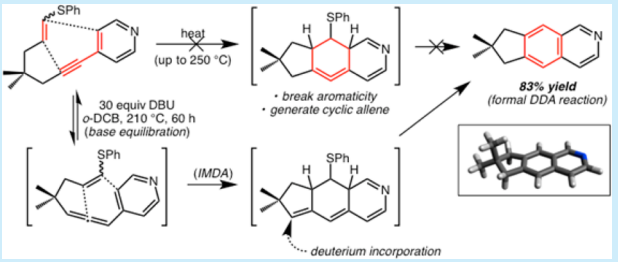
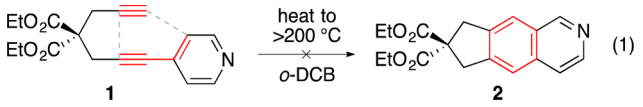
Supporting Information

ABSTRACT: A cascade (cyclo)isomerization/elimination process produces novel isoquinoline derivatives of potential interest for pharmaceutical, biomedical, and energy-related research. Mechanistic experiments support a putative allenylpyridine (reminiscent of the Garratt−Braverman cyclization) as a key intermediate in the cascade process.



One of the perpetual challenges in chemical synthesis is to identify and push outward the limits of reactivity. Cyclization of entropically biased (e.g., tethered) π-systems has been a powerful tool for addressing this challenge,[1] as it enables one to focus more specifically on enthalpy parameters. We have identified an aspirational transformation that lies beyond the limits of chemical reactivity (eq 1). Malonate-tethered diynylpyridine **1**[2] was heated at temperatures up to and exceeding 200 °C in an effort to produce isoquinoline **2**, but only unreacted starting material and/or unidentifiable decomposition products were observed.

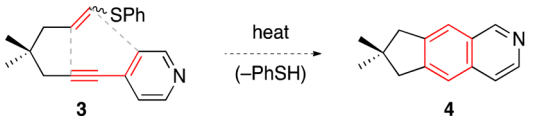


(1)

This hypothetical cycloaromatization[3] process could be described as a modified Garratt−Braverman cyclization[4] and/or a dehydro-Diels−Alder[5] reaction; such methodologies receive considerable attention for their favorable reaction thermodynamics, mechanistic nuances, and recognized synthetic utility. In this case, however, it seems that the kinetic barrier to thermal cycloaddition is too high, which results in competing decomposition of the substrate.

There are several reasons why the prospective isoquinoline synthesis shown in eq 1 may exceed the limits of reactivity. Most significantly, to produce the postulated cycloaddition intermediate (**1a**[6]) would require introduction of a strained cyclic allene[7] *and* disruption of pyridine aromaticity.[8,9] Secondary considerations include the unactivated alkyne dienophile[10] and malonate ester functionality, which provides the desired Thorpe−Ingold conformational bias[11] but may also introduce competing decomposition pathways.

Here we describe efforts to extend the reactivity limits of thermal pericyclic cycloadditions for the synthesis of novel isoquinolines (eq 2). The first strategic step was to address the aforementioned secondary considerations. We replaced the malonate functionality with a *gem*-dimethyl group, which is arguably the simplest and most innocuous structural feature that still provides Thorpe−Ingold effects. We also replaced the alkyne dienophile with a vinyl sulfide. Sulfides are good electron-donating groups for Diels−Alder-type reactions (e.g., with electron-deficient π-systems),[12] and vinyl sulfides are at the same oxidation level as alkynes. Late-stage extrusion of thiophenol was envisioned en route to the target isoquinolines.



(2)

We prepared alkynylpyridines **3** and **10** by tandem fragmentation and olefination of triflate **5**[13] followed by Sonogashira coupling of the resulting phenylthio-enynes (**7** and **8**)[14] with 4-iodopyridine (Scheme 1).[15] Initial attempts at tandem thermal cycloisomerization and elimination (**3** → **4**) focused on high-boiling, nonpolar solvents from which the desired isoquinoline could be separated easily. No desired product (**4**) was observed in the absence of base; excess DBU was selected (e.g., for base-mediated elimination of thiophenol) following a brief and qualitative screening of different bases. In the end, isoquinolines **4** and **11** were obtained in 81% and 73% yield, respectively, after heating the corresponding alkynylpyridines along with DBU (30 equiv) in *o*-dichlorobenzene (*o*-DCB) at 210 °C for 2.5 days, followed by direct chromatographic purification of the reaction mixture on silica gel. Shorter reaction times and less DBU resulted in lower yields and/or recovery of alkynylpyridine.

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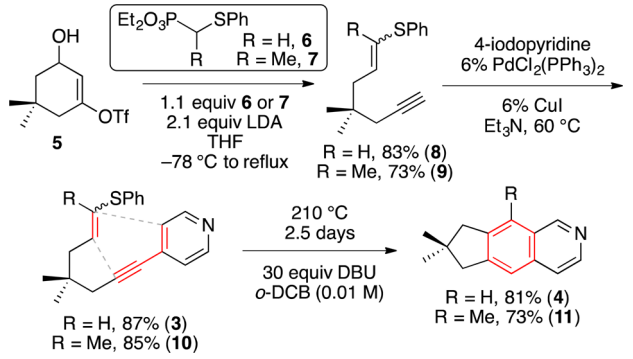
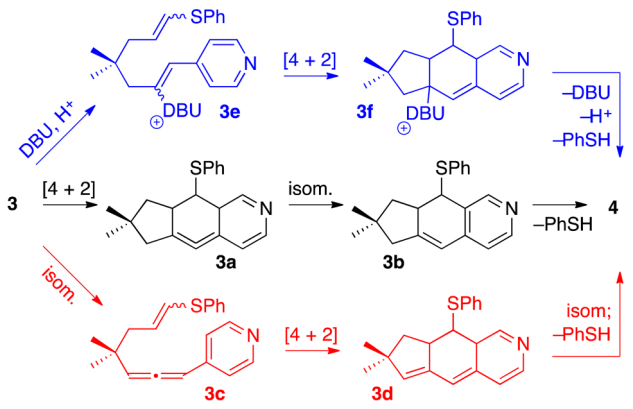
Scheme 1. Synthesis of Phenylthio-enyne Substrates and Tandem (Cyclo)Isomerization/Elimination



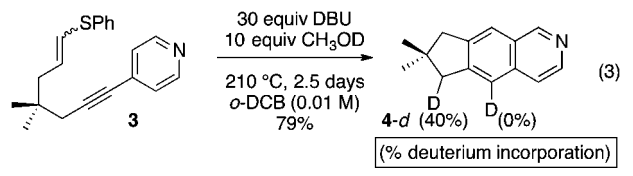
Based on the need for a large excess of DBU, we inferred that the role of DBU was not limited to base-mediated elimination of thiophenol. Three alternative mechanistic hypotheses are outlined in Scheme 2. The most conceptually straightforward

Scheme 2. Proposed Mechanistic Pathways



pathway is illustrated in black: thermal [4 + 2] cycloaddition of **3** to produce dearomatized cyclic allene **3a**, followed by isomerization to dihydroisoquinoline **3b** and elimination to **4**. The first alternative, depicted in red, bypasses cyclic allene **3a** en route to **4** via initial DBU-mediated isomerization of *alkynyl-* to *allenyl-*pyridine (**3** → **3c**), cycloaddition (**3c** → **3d**), and finally isomerization and elimination. A third possibility (illustrated in blue) is that DBU acts as a nucleophilic catalyst by adding to alkynylpyridine **3** (along with adventitious H^+) prior to cycloaddition (**3** → **3e** → **3f** → **4**), thereby also bypassing cyclic allene **3a** en route to **4**.

Important mechanistic insights came from a deuterium-labeling experiment involving methanol-d_1 (10 equiv, eq 3).



Surprisingly, we observed 0% deuterium incorporation on the benzene core, although we do not identify any concerted intramolecular mechanisms for delivering hydrogen to this position. We interpret this result as being consistent with a *stepwise* intramolecular isomerization event in which a proton or hydrogen atom is rapidly translocated across a molecular surface within the transient solvent cage. Such rapid-stepwise[16] "remove-and-return" isomerization events can be envisioned for **3a** → **3b** and also for **3** → **3c**. On the other hand, it is harder to rationalize 0% deuterium incorporation on the benzene ring for the reaction pathway that commences with DBU·H^+ addition to the alkynylpyridine (**3** → **3e**). Deuterium incorporation at the benzylic methylene position[17] is clearly most consistent with the intermediacy of **3d**, which we interpret as evidence in support of the initial isomerization of **3** to allenylpyridine **3c** (red pathway). Thus, we propose isomerization of the alkynyl- to allenyl-pyridine (**3** → **3c**) as the first and key step in this new isoquinoline synthesis.[18]

Isoquinolines are ubiquitous in synthetic and medicinal chemistry, and new isoquinolines are potentially attractive for pharmaceutical discovery.[19] The present benzannulation-centered isoquinoline synthesis strategically complements venerable reactions such as the Pictet–Spengler,[20] Bischler–Napieralski,[21] and Pomeranz–Fritsch[22] isoquinoline syntheses, as well as several more recent transition-metal catalyzed pathways,[23] the vast majority of which involve annulation of a pyridine ring onto a preformed benzene core. Novel methods for isoquinoline synthesis are needed to explore chemical structure space that cannot be conveniently accessed by these and related heterocyclization methods. Thus, in exploring the scope of this new benzannulation approach to isoquinolines, we focused on preparing previously unreported isoquinolines that pass *in silico* screening in the Eli Lilly Open Innovation Drug Discovery (OIDD) platform.[24,25]

Differential substitution on the heterocycle may best be accomplished by judicious choice of the pyridine partner, as examined in experiments recounted in Table 1. Sonogashira coupling of the terminal alkyne of phenylthio-enyne **8** with several commercially available halopyridines provided us with a small but diverse array of benzannulation precursors (Table 1) in good to excellent yields.[15] These test substrates comprise alkyl, halo, and fused arene substructures to probe the effect of substitution patterns on regioselectivity and yield. Regioselectivity was poor for the distally substituted (relative to the alkyne) pyridines (entries 4 and 5) and good for proximally substituted (entry 6) and/or electronically differentiated substrates (entries 7 and 8). Entries 5, 7, and 8 suggest that this methodology is similarly amenable to producing quinolines, phenanthridines, and probably other polycyclic (hetero)aromatics, as long as the substrate-associated regioselectivity biases are sufficient for the needs at hand.

The *gem*-dimethylcyclopentane motif, which differentiates these from previous synthetic isoquinolines, is ubiquitous in natural products (cf. hirsutene,[26] pentalenene,[27] and the isoquinoline illudinine[28]) but conspicuously absent from most synthetic pharmaceutical screening libraries. The rigid, hydrophobic topology of *gem*-dimethylcyclopentanes (cf. Figure 1) is expected to impart specific pharmacological perturbations that will be of interest to medicinal chemistry research.

Future efforts are planned for establishing and expanding the scope and potential impact of this methodology. For example, differential substitution of the isoquinoline benzene core can be achieved by choice of olefination partner in the initial phenylthio-enyne synthesis (cf **6** or **7**, Scheme 1), and/or by site-selective substitution of the derived isoquinolines. Along these lines, dibromination of **4** (→ **24**) and monobromination of **11** (→ **25**) proceeded smoothly using conditions described by Gouliaev (eq 4),[29] and dimethylisoquinoline **13** is amenable to site-selective metalation for further functionalization (cf. eq 5).

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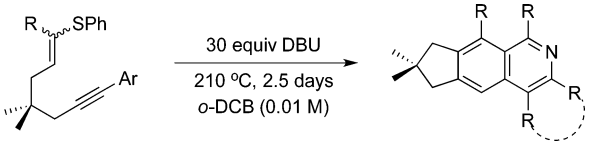
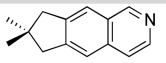
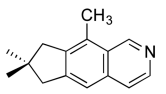
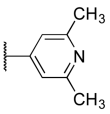
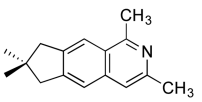
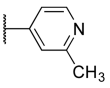
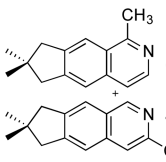
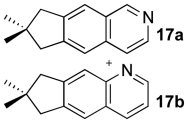
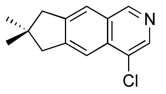
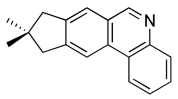
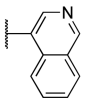
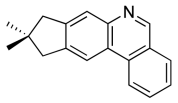
Table 1. Synthesis of Isoquinolines (and Quinolines) via DBU-Promoted Benzannulation



entry (#)	R	Ar	product	yield, % (#)
1 (**3**)	H			81 (**4**)
2 (**10**)	CH_3			73 (**11**)
3 (**12**)	H			84 (**13**)
4 (**14**)	H			91 (**15a** + **15b**)
5 (**16**)	H			80 (**17a** + **17b**)
6 (**18**)	H			71 (**19**)
7 (**20**)	H			86 (**21**)
8 (**22**)	H			>95 (**23**)

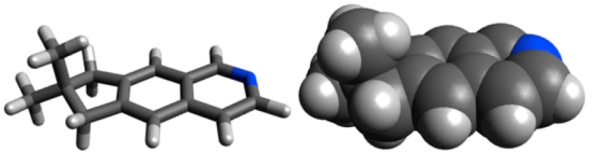
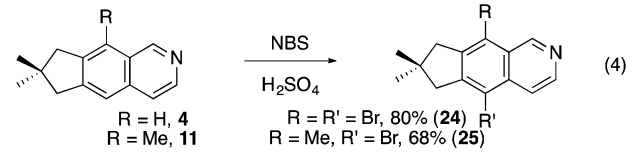
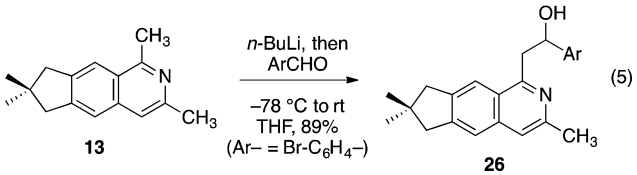


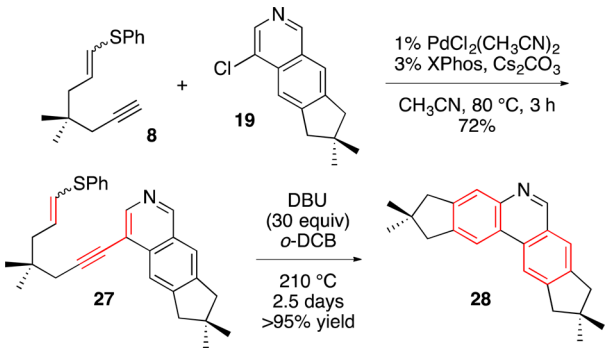
Figure 1. Three-dimensional representations of *gem*-dimethylcyclopentane-fused isoquinoline **4**.





Finally, we note that the solution- and/or solid-state molecular photophysics of new *gem*-dimethyl-cyclopentane derivatives may be of interest for bioimaging and/or light-harvesting applications. Chloroisoquinoline **19** can be recycled through our two-step process (Sonogashira and benzannulation) to produce pentacyclic phenanthridine **28** (Scheme 3). The solution-phase emission

Scheme 3. Synthesis of Pentacyclic Phenanthridine 28



spectrum for **28** is red-shifted relative to the parent phenanthridine,[15] and single-crystal X-ray analysis reveals that crystal packing of **28** (Figure 2, left) is quite distinct from that of the

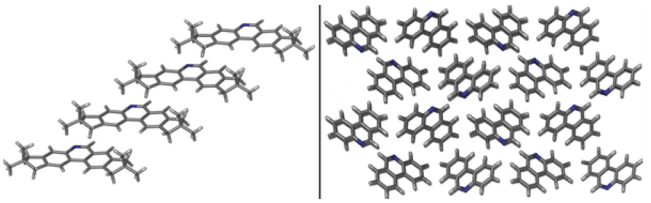


Figure 2. (Left) Crystal packing of phenanthridine **28**. (Right) Phenanthridine itself. Phenanthridine itself packs in a herringbone pattern, with edge-to-face interactions at a distance of 2.92 Å, whereas *gem*-dimethylcyclopentane-fused phenanthridine **28** packs in a loosely staggered arrangement.[15]

parent phenanthridine[30] (Figure 2, right). The potential utility of *gem*-dimethylcyclopentane derivatives of other fluorescent dye molecules is being explored.

In conclusion, we identified a DBU-mediated cascade of (cyclo)isomerizations and elimination to produce novel isoquinoline derivatives of potential interest for pharmaceutical, biomedical, and energy-related research. The cascade process is thought to involve an allenylpyridine intermediate as the 4π component in an intramolecular [4πs + 2πs] cycloaddition, thereby avoiding the intermediacy of the strained cyclic allene that would be produced by direct cycloisomerization of the alkynylpyridine substrate (cf. **3** → **3a**, Scheme 2). Electron-rich vinyl sulfides purportedly act as the 2π component of inverse-demand cycloadditions; the substrates are prepared by an important extension of our previous fragmentation/olefination methodology.[13] This new isoquinoline synthesis anneals a benzenoid structure onto a pre-existing pyridine, strategically complementing most established methods for isoquinoline synthesis. Future efforts to expand the scope and mechanistic understanding of the isoquinoline synthesis and harness unique physical and pharmacological properties of *gem*-dimethylcyclopentane-fused arenes will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02034.

Experimental procedures, spectroscopic characterization data, copies of ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **28** (CIF)

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Notes

The authors declare no competing financial interest.
The CIF for compound **28** file can be downloaded via the CCDC citing structure number 1486383.

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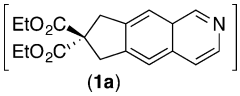
(6) Postulated cyclic allene intermediate:



(**1a**)

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(9) Certain reactions involving ynamides are postulated to proceed via dearomatized cyclic allenes under some conditions; see: (a) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213. (b) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Synthesis* **2004**, *2004*, 761.

(10) Alkyne π-bonds are stronger than alkene π-bonds, which can translate into larger activation barriers for reactions that break those π-bonds; see: Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1991**, *113*, 6750.

(11) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080. (b) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278.

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(13) Hoang, T. T.; Dudley, G. B. *Org. Lett.* **2013**, *15*, 4026.

(14) Production here of electron-rich alkenes represents an important conceptual expansion of our previously reported tandem fragmentation/olefination methodology (ref 12), which exclusively produced electron-deficient alkenes.

(15) See Supporting Information.

(16) We do not invoke any concerted intramolecular hydride shifts in our mechanistic hypotheses.

(17) The four benzylic methylene hydrogens in the ^{1}H NMR spectrum of **4** appear as a singlet that integrates to 4.0 hydrogens. The corresponding singlet in the ^{1}H NMR spectrum of **4**-*d* integrates to 3.6 hydrogens, which we interpret as 40% deuterium incorporation. Subjecting **4** to these same conditions results in no more than 10% deuterium incorporation. See Supporting Information.

(18) Having identified this auxiliary role for DBU as an isomerization catalyst as well as a thiophenol scavenger, we repeated the experiment outlined in eq 1 in the presence of DBU, but to no avail. For a previous example of a DBU-catalyzed cycloisomerization, see: Fang, Z.; Liu, Y.; Barry, B.-D.; Liao, P.; Bi, X. *Org. Lett.* **2015**, *17*, 782.

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