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Allenyl Azide Cycloaddition Chemistry. Synthesis of Annelated Indoles from 2-(Allenyl)phenyl Azide Substrates

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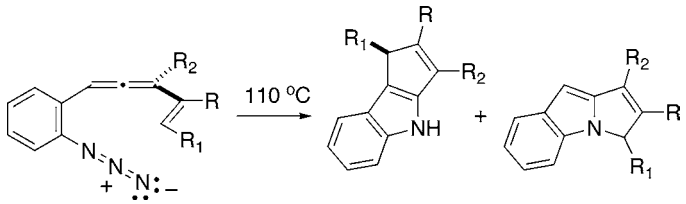
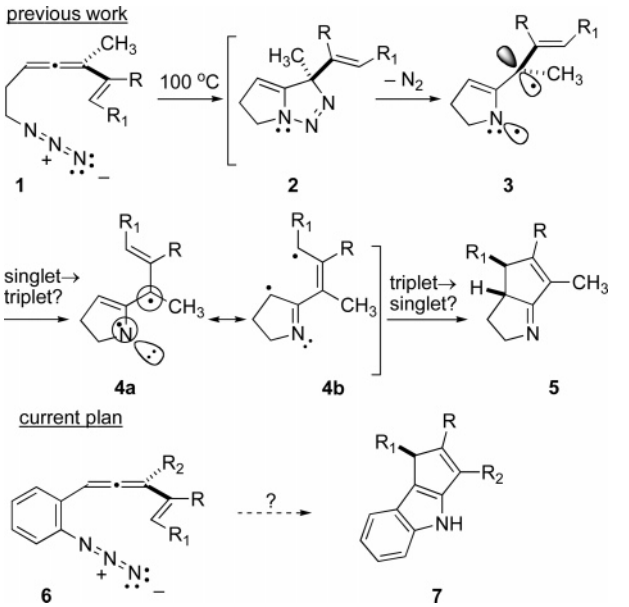
ABSTRACT



Thermolysis of 2-(allenyl)phenyl azides leads to a cascade cyclization sequence furnishing both C(2)–C(3) and N–C(2) cyclopentannelated indoles.

Organic synthesis via diyl cyclization has had an episodic history, with surges in activity quickly following the discovery of novel diradical generating reactions.[1] One of the more notable advances to emerge from this area of chemistry stemmed from the observation that N_2 extrusion from 4-methylene-1,2-diazenes led efficiently to triplet trimethylenemethane (TMM) diyls, species that have served a central role in numerous cyclization- and cycloaddition-based approaches to cyclopentanoid natural products.[2] One little-studied modification of the TMM diyl, azatrimethylenemethane (ATMM), can be constructed, at least in principle, by simply exchanging one methylene fragment for a nitrogen (cf. **4**, Scheme 1). By analogy with TMM chemistry, the ATMM variant might provide ready access to polycyclic cyclopentanoid alkaloid frameworks. The development of ATMM chemistry has lagged far behind its all-carbon cousin, but early studies that hinted at its existence[3] and more recent suggestions of its intermediacy in azide−allene cyclization cascades[4] (Scheme 1) may yet elevate this species to a position of prominence in alkaloid synthesis.

Scheme 1. Intramolecular Azide−Allene Cycloaddition Cascades for Nitrogen Heterocycle Synthesis



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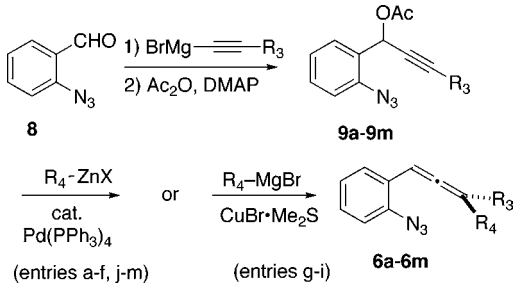
C(2)−C(3) annelated indoles represent one potential target class for this chemistry, and given the success of the **1**→**5** conversion, wherein only cyclization through the imine species **4b** was observed, it seemed plausible to expect that incorporation of an aryl residue in the allene−azide tether (cf. **6**) would lead by analogy to the C(2)−C(3) cyclopentannelated indole products **7**. As described in this report, this goal was achieved in practice. However, the unanticipated intervention of subtle electronic (?) effects, presumably as a consequence of the electronic connectivity supplied by the intervening aryl ring, served to divert some of the reactive intermediate(s) down alternative channels, leading to N−C(2) annelated products as well. A description of the scope of this process for cyclopentannelated indole synthesis with both alkenyl- and aryl-substituted 2-(allenyl)phenyl azides is detailed below.

The syntheses of suitable 2-(allenyl)phenyl azides of the type **6** were accomplished by straightforward chemistry using Konno's procedure for palladium-mediated aryl(alkenyl)zinc addition to propargylic acetates **9**[5] or the cuprate-based alternative procedure of Palenzuela[6] (Table 1). The azide

Table 1. 2-(Allenyl)phenyl Azide Cyclization Substrate Synthesis



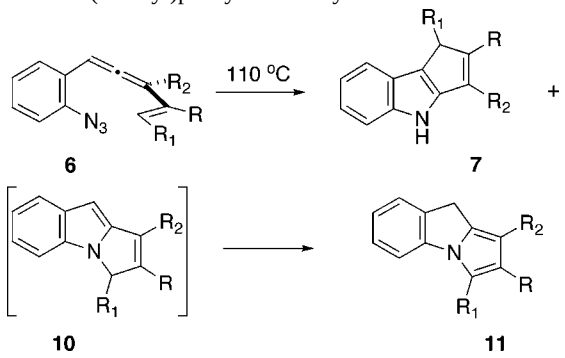
entry	R_3	R_4	yield **9** (%)[a]	yield **6** (%)[a]
a	CH_3	$H_2C{=}CH-$	48	58
b	CH_2OTBS	$H_2C{=}CH-$	91	55
c	CH_2CH_2OTBS	$H_2C{=}CH-$	73	57
d	*t*-Bu	$H_2C{=}CH-$	78	63
e	CH_3	$H_2C{=}C(Ph)-$	48	67
f	CH_3	$H_2C{=}C(CH_3)-$	48	59
g	$PhCH{=}CH-$	CH_3	47	34
h	1-cyclohexenyl	CH_3	31	37
i	1-cyclopentenyl	CH_3	49	30
j	CH_3	Ph	48	[b]
k	CH_3	*p*-$(CH_3O)C_6H_4$	48	[b]
l	CH_3	*m*-$(CH_3O)C_6H_4$	48	[b]
m	CH_3	*m*-FC_6H_4	48	[b]

[a] Yield for chromatographically pure, characterized material. [b] These allenes were too reactive to isolate and characterize, so they were carried into the thermolyses as crude materials.

function survived exposure to these organometallic reagents with no detectable decomposition, but attempts to add (Bu_3-Sn)CuSPh to **9a** met with concomitant azide reduction to furnish an amide product following *O*−*N* acetyl transfer. The (alkenyl)allenyl azides **6a**−**6i** were stable, isolable, and characterizable compounds, but the aryl-substituted analogues **6j**−**6m** were sensitive to chromatography and could not be isolated in pure form. Therefore, these species were routinely carried on to the thermolysis procedure as crude materials.

The thermolysis/cyclization studies commenced with the prototype substrate **6a** featuring unelaborated methyl and vinyl units at the allene terminus (Table 2). Heating a 0.1

Table 2. 2-(Allenyl)phenyl Azide Cyclization Results



entry	R	R_1	R_2	yield **7** (%)[a]	yield **11** (%)[a]	ratio **7**/**10**[b]
a	H	H	CH_3	40	56	1:1.2
b	H	H	CH_2OTBS	22	29	1.2:1
c	H	H	CH_2CH_2OTBS	52	43	1.5:1
d	H	H	*t*-Bu	57	20	2.7:1
e	Ph	H	CH_3	40	30	1:1.2
f	CH_3	H	CH_3	36	36	1:1.3
g	H	Ph	CH_3		35 (**10g**)	1:1.1
h	$-(CH_2)_4-$		CH_3	36	51	1:1.4
i	$-(CH_2)_3-$		CH_3		40 (**10i**)	1:1.5

[a] Yield for chromatographically pure, characterized material. [b] Ratio by ^1H NMR analysis of the crude thermolysate.

M solution of **6a** in toluene-d_8 led cleanly to the formation of two new species whose gross spectral data were suggestive of the presence of tricyclic ring systems in both cases. Chromatographic purification of the crude thermolysate furnished samples of both compounds, and their spectroscopic data were entirely consistent with those expected for the desired C(2)−C(3) annelated indole **7a** as well as the unanticipated pyrrole **11a**. The more slowly eluting compound **7a** exhibited the characteristic N−H resonance of an indole (δ 8.03 (s)) as well as signals for an alkene-bound

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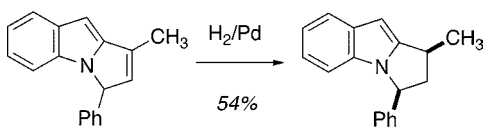
CH_3 (δ 2.22, d, J = 1.6 Hz) and for a single alkenyl proton (δ 6.22, m). The faster eluting species displayed spectral data that were strikingly similar to those reported for the characterized reference compound des methyl **11a**,[7] allowing ready assignment of **11a** as a pyrrole. X-ray crystallographic analysis of **11a** later confirmed the structural assignment (see Supporting Information). Examination of the crude reaction product by ^{1}H NMR prior to purification indicated the presence of only **7** and **10**; pyrrole **11** was not formed until exposure of the crude thermolysate to SiO_2. The ratio of isolated **7** to isolated **11** occasionally was at variance with the **7**/**10** ratio as it appeared in the ^{1}H NMR spectrum of the crude thermolysate, presumably as a consequence of differential chromatographic stability, and so the latter value is reported as well. In addition, ^{1}H NMR-based examination of the crude thermolysate immediately after reaction allowed identification of signals consistent with the indole species **10**, but these signals decayed over the course of a few hours as the spectroscopic signature for the pyrrole **11** grew in. In only a few cases (**6g**, **6i**) was this N−C(2) cyclopentannelated indole isolable, but even in those instances, isomerization into the pyrrole followed after a few more hours at room temperature. The next three examples (**6b**−**6d**) demonstrated that both silyl ethers (**6b**,**c**) and steric bulk (**6d**) at the R_2 position are tolerated in the transformation with little impact on yield. Interestingly, comparing entries a−d reveals that the ratio of C(3)/N cyclization is responsive to the size of the R_2 substituent, with the bulkiest entry (**6d**, R_2 = *t*-Bu) leading to the greatest selectivity for the desired C(2)−C(3) cyclization regioisomer **7**.

The next two entries (**6e**,**f**) test the effect of a substituent at the internal (R) position of the alkene. For both substrates, the reaction proceeds similarly to the simpler R = H cases to afford nearly equal mixtures of the indole **7e**/**7f** and pyrrole **11c**/**11f** products. The R substituent resides at a position that apparently exerts little steric or electronic influence on the course of the reaction, as both the R = CH_3 and R = Ph cases proceed to product(s) in very similar yields/selectivities. The Ph-bearing substrate **6g** introduces at the alkene terminus a group that might confer both electronically favorable (i.e., radical stabilizing; cf. **4**) and sterically unfavorable characteristics, and the tradeoff between these possibly opposing effects appears to favor the latter. For the first time, the C(2)−C(3) cyclized indole product did not survive attempted chromatographic purification, and the regioisomeric N−C(2) indole **10g** was the only identifiable species isolated. However, the indole **7g** was detected in the crude thermolysate admixed with **10g** (1:1.1 ratio, Table 2). Hydrogenation of **10g** (Scheme 2) furnished the cis-disposed indole product

Scheme 2. Formation of a Derivative Characterizable by X-ray Crystallography

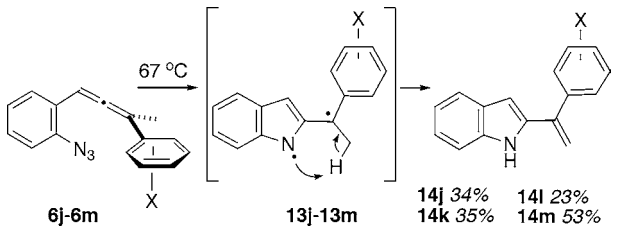


10g **12g** X-ray

12g whose structure was secured by single-crystal X-ray analysis (see Supporting Information). The final two entries, **6h** and **6i**, probed the capability of this cascade cyclization sequence to deliver tetracyclic material. The cyclohexenyl case **6h** proceeded uneventfully to deliver a slightly biased mixture of the pyrrole **11h** and the indole product **7h** in excellent overall yield. The cyclopentyl lower homologue **6i**, in contrast, yielded only a moderate amount of the N−C(2) cyclized indole product **10i** as the only tetracyclic material to survive chromatography. The corresponding C(3)-cyclized material **7i** was observed in the crude thermolysate's ^{1}H NMR spectrum, at the ratio reported in Table 2, but it decomposed upon attempted purification.

Thermolyses of the aryl-substituted 2-(allenyl)phenyl azides **6j**−**6m** did not provide tetracyclic material (Scheme 3). In each instance, the methylidene-containing products

Scheme 3. Thermolysis of Phenyl-Substituted 2-(Allenyl)phenyl Azides



6j-6m **13j-13m** **14j** *34%* **14k** *35%* **14l** *23%* **14m** *53%*

14j−**14m** were isolated in moderate yields. Presumably, a diyl intermediate represented by **13** underwent H-atom transfer, possibly via an intramolecular pathway as shown, to yield the product alkene. These results stand as another point of departure from the saturated tether series **1**, where pendant aryl rings (R⁀R_1 = aryl ring) did participate in diyl cyclizations to afford benzannelated products **5** (R⁀R_1 = aryl ring via alkene isomerization). The failure of the analogous species **13** to cyclize remains a mystery, but a rationale might be tied to the different nature of the diyl intermediate in the unsaturated series vis á vis the saturated series **1**, as discussed below.

Given the similarities and the differences between the reactions of the diyls derived from **1** and **6**, it is appropriate to consider the conceivable roles that the different candidate diradicals might play in product formation. Figure 1 details the plausible diyl (and related) options. Singlet σ/π orthogonal diyl **15a** is the likely first-formed species immediately following N_2 extrusion. This presumably short-lived diyl could cyclize via initial C−C bond rotation and then C−N closure to give products of the type **10**, or it could undergo singlet−triplet interconversion to give a new diyl that could not cyclize directly and therefore might have a long enough lifetime to realize other chemistry. As an alternative to direct cyclization, singlet or triplet **15a** could undergo an electronic reorganization that is tantamount to placing one electron from the nitrogen's π orbital into its half-occupied sp^2 orbital, giving the orthogonal π/π diyl **15b** (singlet or triplet).

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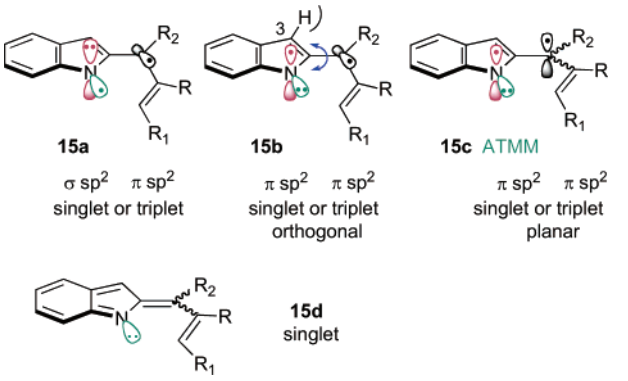

Figure 1. Possible intermediates along the cyclization pathway.

This species provides the means to access the C−C bonded product **7** via (singlet) diyl closure following bond rotation. In fact, this rotation (indicated by the blue arrow in **15b**) may hold the key to understanding the regiochemical divergence of diyl closure.[8] Rotation of singlet **15b** in the clockwise direction (observing down the C(2) → C(•) bond) would lead to the C−C bond formation product **7**, whereas the opposite direction of rotation would bring N(•) and C(•)-R_1 together to form **10**. To the extent that the C(3)−H/R_2 steric interaction shown in **15b** becomes energetically penalizing upon counterclockwise rotation, larger R_2 groups arguably should differentially favor the alternative clockwise motion, leading to a preference for C−C bond formation (→**7**). This expectation is borne out by the limited results with **6a**−**6d**.

Triplet **15b**, on the other hand, could participate in similar divergent rotations to furnish the planar (*E* or *Z*) ATMM intermediate **15c**. The *E*/*Z* preference could be tied to the same steric features (avoiding C(3)−H/R_2 steric interactions) discussed for singlet **15b**. Upon intersystem crossing, the now singlet **15c** could cyclize (electrocyclize?) with either C−C bond formation from the *E* species or C−N bond formation from the *Z* isomer. Finally, the singlet version of **15c** might best be represented as the closed-shell (*E*/*Z*) alkylidene indolinene **15d**, a species whose (electro)cyclization manifold is identical to singlet ATMM **15c**. At this point, it is not possible to sort between these options and provide a comprehensive description of this 2-(allenyl)phenyl azide cyclization cascade. Work in that direction will continue.

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Supporting Information Available: Experimental procedures and characterization data for **6a**−**6m**, **7a**−**7f**, **7h**, **10g**, **10i**, **11a**−**11f**, **11h**, and **14j**−**14m**. In addition, details for the X-ray crystal structure determination of **11a** and **12g** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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