JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Intramolecular [3 + 2] Cyclocondensations of Alkenes with Indolidenes and Indolidenium Cations

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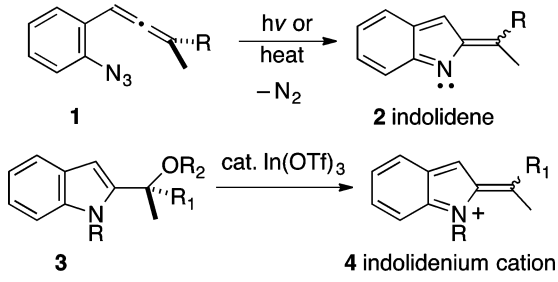
Supporting Information

ABSTRACT: C(2)−C(3) cyclopentannelated indole constructs are prepared by either (a) a cyclization cascade of an alkenyl sulfide tethered to a 2-azido-1-allenylbenzene core or (b) cationic cyclization of a tethered alkenyl sulfide with a putative 2-indolidenium cation. In both cases, issues of C−C versus C−N bond formation emerge, and the results indicate that the former is favored.

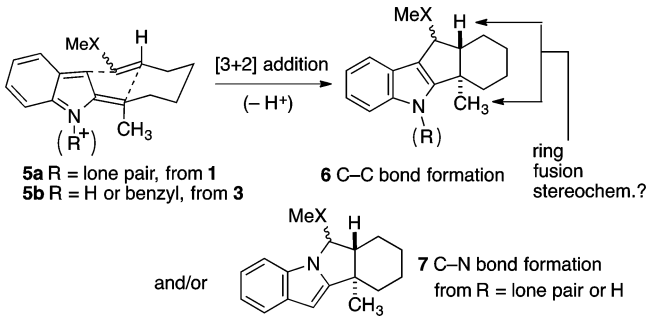
Indolidenes **2** and indolidenium cations **4** have been occasionally exploited in the service of C−C bond-forming reactions at the electrophilic C(2) alkylidene position.[1] These transformations have enabled the synthesis of complex molecular architectures from relatively simple precursors en route to several natural products.[1] We recently worked out a novel and general approach for the synthesis of indolidene intermediates via cyclization of 2-azido-1-allenylbenzenes (**1** → **2**),[2] and in addition, we have identified mild experimental conditions to generate putative indolidenium cations **4** from simple 2-(methylalcohol) derivatives **3**, as described in this report (Scheme 1).

Scheme 1. Indolidene and Indolidenium Electrophiles



With robust routes to these reactive intermediates in hand, we have begun exploring their chemical reactivity in C−C bond-forming processes. Herein we describe a new reaction of these indolidene and indolidenium cation intermediates: the [3 + 2] cyclocondensation with a tethered alkene **5a** or **5b** to generate cyclopentanylated indole products **6** featuring C−C bond formation at both the C(2) indolic position and C(3) of the indole nucleus (Scheme 2). Fundamental selectivity questions, such as the regiochemical bias for either C−C bond formation (to give **6**) or C−N bond formation (to give **7**) as a function of the nitrogen substituent R, and the stereochemical preference for either trans (e.g., **6**) or cis ring fusion, are explored below. Earlier work by Moody and co-workers hinted that this process

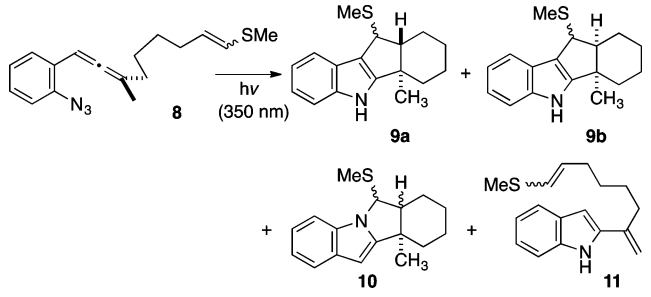
Scheme 2. [3 + 2] Cyclocondensation of Indolidene/Indolidenium Electrophiles with Pendant Alkenes



was feasible;[1h] we have identified an appropriate electronically matched alkene addend that proceeds in good yield with moderate diastereoselectivity. The product cyclopentanylated indole substructure can be found in a range of naturally occurring alkaloids, such as the fischerindoles[3] and the indolosesquiterpenes,[4] inter alia.

We have observed that when X = S in Scheme 2, both the indolidene- and indolidenium-mediated transformations proceed to the desired tetracyclic product. The indolidene chemistry is illustrated in Scheme 3, where irradiation of a CH_3CN solution

Scheme 3. Allenyl Azide Tricyclization via a Putative Indolidene Intermediate



of alkenyl sulfide substrate **8**[5] (as a 1.25:1 mixture of geometrical isomers) afforded a suite of products **9**−**11** that clearly demonstrated the feasibility of this [3 + 2] approach to indole C(2)−C(3) cyclopentanylation (Table 1, entry 1). The C−C-bonded products (major **9a** + minor **9b**) featured the formation of three new bonds in this cascade cyclization, including a new

Received: August 17, 2014
Published: October 16, 2014

   dx.doi.org/10.1021/ja508421e | J. Am. Chem. Soc. 2014, 136, 15138−15141

Table 1. Cascade Tricyclization of Allenyl Azide–Alkenyl Sulfide Substrate 8

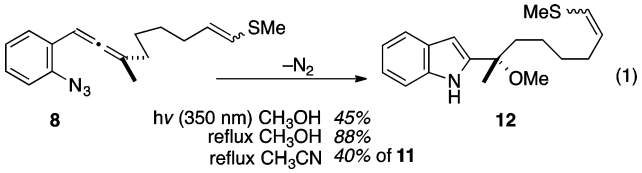
entry	solvent	9a[a]	9b[b]	10[a]	11[a]
1	CH_3CN	46	9	9	3
2	toluene	trace	–	–	20
3	CH_2Cl_2	trace	–	22	–

[a]Percent yields of isolated, pure products. [b]Percent yields determined by ^{1}H NMR integration of **9a**/**9b** mixtures.

C–C bond to C(3); only trace amounts of the C–N-bonded product (**10**) and the formal "ene"-type product **11** were isolated. Within the C–C-bonded product manifold, species **9a** with the trans ring junction was favored over the cis-fused diastereomer **9b** (~5:1). The stereochemical outcome at the MeS-bearing carbon was mixed, perhaps reflecting either the initial geometrical mixture of alkenyl sulfides or some mechanistically based preference during the tricyclization process. The relative stereochemical assignments of **9a** and **9b**, including tentative assignment at the MeS-bearing carbon, were based upon (1) comparison of the observed ^{1}H–^{1}H coupling between MeS–C*H* and the adjacent ring juncture proton to the predicted value for this coupling derived from energy-minimized structures (see the Supporting Information for calculational details and observed/predicted *J* values) and (2) the correlation of ^{1}H NMR spectral data of the products derived from H-for-SMe reduction (vide infra) with data reported for these species prepared by a different method.[1h]

This transformation clearly demonstrates a strong solvent effect (Table 1). Only by irradiation in the more polar solvent CH_3CN was the desired reaction course observed; irradiation of **8** in the less polar solvents toluene and CH_2Cl_2 did not lead to any more than a trace of cyclopentannelated indole products. Photochemical reaction in the preferred solvent CH_3CN at either (a) lower temperature (0 °C instead of 28 °C as in entry 1) or (b) at one-third the concentration of entry 1 (3 vs 10 mM) led to a suite of reaction products identical to those observed in entry 1. Inclusion of a catalytic amount of $In(OTf)_3$ (vide infra) or CuI[2b] under entry 1 conditions led to complete decomposition of the starting material, but no characterizable products formed.

Irradiation of **8** in CH_3OH led to only the methanol adduct **12** (eq 1). Apparently, the internal MeS-substituted alkene does not

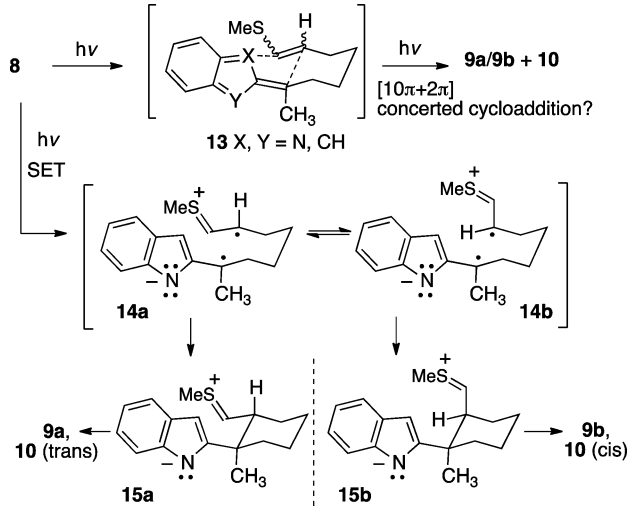


(1)

compete with methanol for the putative indolidene intermediate. The yield of **12** improved to 88% when **8** was heated to reflux in CH_3OH, but substrate **8** was converted largely to alkene **11** upon heating to reflux in CH_3CN.

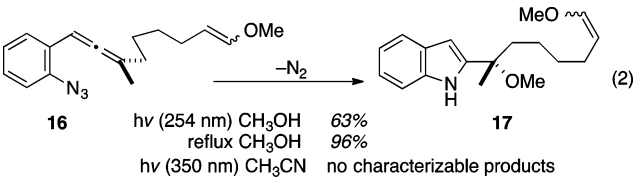
Mechanistic speculation can extend in two disparate directions in the absence of any differentiating data: (a) an unprecedented $[10\pi + 2\pi]$ photochemical concerted cycloaddition as per **13** or (b) a stepwise process perhaps promoted by photoinitiated single-electron transfer (SET) (**8** → **14a**) (Scheme 4). The intervention of dipolar intermediates such as **15a**/**b** in the latter pathway is reminiscent of the proposed sequence of steps by which alkenes combine with fulvenes in a formal [6 + 2] manner.[6]

Scheme 4. Mechanistic Speculation Governing the Formation of Cyclized Products



The observed regiochemical and stereochemical results can be accommodated through the SET process by invoking an energetically favorable chairlike transition-state geometry featuring a pseudoequatorial thioalkenyl appendage (e.g., **15a**) rather than the pseudoaxial alternative (e.g., **15b**).

We also examined allenyl azide enol ether **16**, the oxygen equivalent of substrate **8**, in both photochemical and thermal transformations (eq 2). In methanol, the methanol adduct

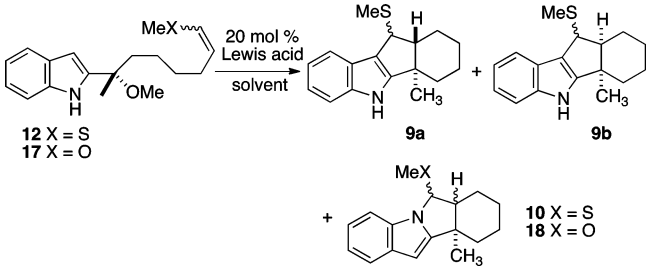


(2)

17, analogous to **12**, was formed in good yield under either irradiation or heat. On the other hand, irradiation in CH_3CN afforded complex mixtures from which no characterizable material could be isolated. Apparently there is a mismatch in reactivity between the putative indolidene intermediate and an enol ether nucleophile that is overcome by switching to the sulfur analogue.

The methanol adducts **12** and **17** provided an entry point into indolidenium chemistry (Scheme 5). Thus, treatment of either

Scheme 5. Lewis Acid-Mediated Bicyclizations via Putative Indolidenium Intermediates



the sulfur-containing substrate **12** (typically as a 1.3–1.7:1 mixture of alkene *E* and *Z* isomers[5]) or the enol ether analogue **17**

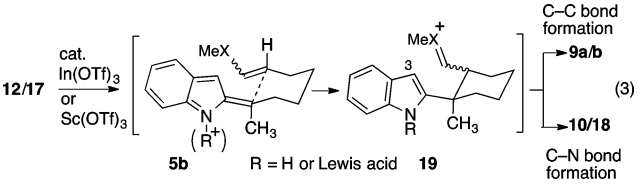
dx.doi.org/10.1021/ja508421e | J. Am. Chem. Soc. 2014, 136, 15138–15141

Table 2. Lewis Acid-Mediated Bicyclization of Indole Substrates 12 and 17

entry	substrate	conditions	9a[a]	9b[b]	10/18[a]
1	**12**	$In(OTf)_3$, toluene	52	–	38
2	**12**	$In(OTf)_3$, CH_2Cl_2	20	trace	decomp
3	**12**	$In(OTf)_3$, CH_3CN	38	13	decomp
4	**12**	$Sc(OTf)_3$, CH_3CN	42	13	decomp
5	**17**	$In(OTf)_3$, toluene	–	–	51

[a]Percent yields of isolated, pure products. [b]Percent yields determined by ^{1}H NMR integration of **9a**/**9b** mixtures.

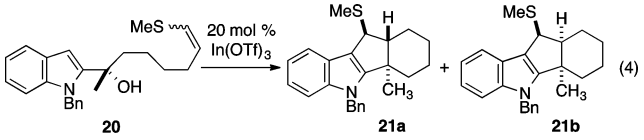
with 20 mol % $In(OTf)_3$ or $Sc(OTf)_3$ provided a suite of tetracyclic products that featured both C−C and C−N bond formation. The indium-mediated bicyclization of substrate **12** (Table 2, entries 1−3) most likely proceeds through indolidenium cation **5b** en route to highly electrophilic sulfur-stabilized carbocation **19** (eq 3). Once again, positing the



intervention of an intermediate like **19** leads to placement of the peripheral substituents in either equatorial or axial positions, and electrophilic capture of an equatorial indole unit by either a pseudoequatorially aligned S-stabilized carbocation or an axially oriented alternative rationalizes the results. In toluene, cyclization is split between C−C and C−N bond formation (Table 2, entry 1). Exploring this indium-mediated chemistry with substrate **12** in either CH_2Cl_2 or CH_3CN again led to the formation of the C−C-bonded products **9a**/**9b** (Table 2, entries 2 and 3), but in these solvents any C−N-bonded product **10** decomposed under the reaction conditions (control experiment). The ring juncture stereochemical outcome is completely selective for the trans configuration in toluene with $In(OTf)_3$ mediation, but there is some erosion of this selectivity in the other solvents examined. Overall, these stereochemical results are consistent with preferential initial C−C bond-forming cyclization through an intermediate of the type **5b** featuring a pseudoequatorial alkene unit. Substituting $Sc(OTf)_3$ for $In(OTf)_3$ led to essentially the same results (Table 2, entries 3 and 4).

The exclusive formation of C−N-bonded products **18** from indium-mediated bicyclization of the oxygen-bearing substrate **17** (Table 2, entry 5) is noteworthy in light of the strong (Table 1, entry 1) to moderate (Table 2, entry 1) preference for C−C bond formation when X = S. These disparate observations may speak to the intermediacy of species like **15a**/**b** (from **8** through the SET mechanistic path) or **19** (from **12**/**17**), where the "softer" sulfur-stabilized carbocation, compared with a "harder" oxygen-stabilized carbocation, might be a better reactivity match for the softer C(3) nucleophilic site of the indole unit within **15** and **19**. On this point, the ionization potential of methyl vinyl sulfide is significantly lower than the ionization potential of methyl vinyl ether,[7] an observation consistent with the hypothesis that thio-bearing substrate **8** might better participate in a (product-forming) SET process.

One obvious way to steer this system completely toward the C−C-bonded product is to remove the nitrogen as a nucleophilic option. The *N*-benzyl substrate **20**[5] accomplishes this goal (eq 4). The free alcohol in **20** results from the method used in its



synthesis.[5] Subjection of *N*-benzyl substrate **20** to the typical indium triflate-mediated bicyclization protocol in CH_3CN solvent delivered the expected C−C-cyclized products **21a** and **21b** exclusive of any C−N-bonded alternatives (Table 3). The

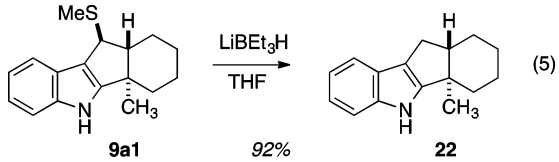
Table 3. Lewis Acid-Mediated Bicyclization of Indole Substrate 20

entry	solvent	21a[a]	21b[a]
1	CH_3CN	61	24
2	CH_2Cl_2	25	19
3	toluene	30	12

[a]Percent yields determined by integration of the ^{1}H NMR spectra of crude **21a**/**21b** mixtures.

exceptionally high yield in this series (85%; Table 3, entry 1) and the moderate preference for the trans ring fusion isomer **21a** is noteworthy. Switching to a less polar solvent (CH_2Cl_2 or toluene) led to inferior results (Table 3, entries 2 and 3). Once again, reaction through an indolidenium cation to give a highly electrophilic sulfur-stabilized carbocationic intermediate (e.g., **5b**, R = Bn, X = S) rationalizes the overall reaction outcome. In addition, the benzylated substrate **20** and the NH analogue **12** proceeded to tetracyclic products with similar trans/cis ring juncture stereochemical preferences in CH_3CN (~3:1 trans/cis).

Reductive removal of the thiomethyl ether unit from the major diastereomer of **9a** (labeled **9a1**) proceeded smoothly using Superhydride as the reductant (eq 5). The derived product



22 exhibited a ^{1}H NMR signal for the angular methyl protons at 1.02 ppm ($CDCl_3$). The cis-ring-fused diastereomer of **22** has been described; the ^{1}H NMR signal of its angular methyl was reported to appear at 1.29 ppm ($CDCl_3$).[1h] In that earlier report, a small amount of the trans-fused species **22** was isolated as a byproduct; the ^{1}H NMR signal of its angular methyl was given as 0.98 ppm ($CDCl_3$).[1h] Thus, in conjunction with the ^{1}H coupling constant analysis described above for **9a**/**9b**, these comparison data solidify the trans ring juncture assignment for **22** (and by implication, for **9a** as well).

In summary, we have identified a set of experimental conditions to conduct moderate-to-high-yielding bicyclizations and tricyclizations of either intermediate indolidenium cations or indolidenes, respectively, to form tetracyclic cyclopentannelated indole systems characteristic of the fischerindole and indolosesquiterpene families of natural products. These reactive intermediates are accessed via substrates derived from either allenyl azides (for indolidenes) or indole-2-alkanols (for indolidenium cations). The mechanistic course of the cyclization is an open question at present; experiments to probe this issue are ongoing, and the application of this chemistry in natural product synthesis is planned.

dx.doi.org/10.1021/ja508421e | J. Am. Chem. Soc. 2014, 136, 15138−15141

■ ASSOCIATED CONTENT

Supporting Information

Experimental descriptions of the synthesis of cyclization substrates **8**, **12**, **16**, **17**, and **20**; full experimental details for the cyclizations of these substrates and spectral characterization data for the cyclization products; copies of ^{1}H and ^{13}C NMR spectra for **8**, **9a1**, **10**−**12**, **16**−**18**, **20**, **21a**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Chemical Synthesis Division of the National Science Foundation for funding (CHE0956458).

■ REFERENCES

(1) (a) Kutney, J. P.; Beck, J.; Bylsma, F.; Cretney, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 4504. (b) Potier, P.; Langlois, Y.; Langlois, N.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670−671. (c) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639−649. (d) Tillequin, F.; Koch, M.; Pousset, J.-L.; Cavé, A. *J. Chem. Soc., Chem. Commun.* **1978**, 826−828. (e) Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3765−3786. (f) Bergman, J.; Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron* **1989**, *45*, 5549−5564. (g) Magnus, P.; Stamford, A.; Ladlow, M. *J. Am. Chem. Soc.* **1990**, *112*, 8210−8212. (h) Harrison, C.-A.; Leineweber, R.; Moody, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1127−1130. (i) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137−2139. (j) Ishikawa, H.; Colby, D. A.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 420−421. (k) Fu, T.-h.; Bonaparte, A.; Martin, S. F. *Tetrahedron Lett.* **2009**, *50*, 3253−3257. (l) Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 12984−12986.

(2) (a) Feldman, K. S.; Iyer, M. R.; Hester, D. K., II. *Org. Lett.* **2006**, *8*, 3113−3116. (b) Feldman, K. S.; Hester, D. K., II; López, C. S.; Faza, O. N. *Org. Lett.* **2008**, *10*, 1665−1668. (c) Feldman, K. S.; Hester, D. K., II; Iyer, M. R.; Munson, P. J.; López, C. S.; Faza, O. N. *J. Org. Chem.* **2009**, *74*, 4958−4974.

(3) (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257−3260. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935−9942. (c) Kim, H.; Krunic, A.; Lantvit, D.; Shen, Q.; Kroll, D. J.; Swanson, S. M.; Orjala, J. *Tetrahedron* **2012**, *68*, 3205−3209.

(4) Sings, H.; Singh, S. In *The Alkaloids: Chemistry and Biology*, Vol. *60*; Cordell, G. A., Ed.; Academic Press: San Diego, 2003; pp 51−163.

(5) Experimental details and full spectral data are provided in the Supporting Information.

(6) (a) Wu, T.-C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308−5309. (b) Hong, B.-C.; Shr, Y.-J.; Wu, J.-L.; Gupta, A. K.; Lin, K.-J. *Org. Lett.* **2002**, *4*, 2249−2252.

(7) The ionization potential of methyl vinyl ether is 8.93 eV. See: Mölder, U.; Pikver, R.; Koppel, I. I.; Burk, P.; Koppel, I. A. *J. Mol. Struct.: THEOCHEM* **2002**, *579*, 205−220. The ionization potential of methyl vinyl sulfide is 8.21 eV. See: Kao, J.; Eyermann, C.; Southwick, E.; Leister, D. *J. Am. Chem. Soc.* **1985**, *107*, 5323−5332.