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A Ring Expansion–Annulation Strategy for the Synthesis of Substituted Azulenes. Preparation and Suzuki Coupling Reactions of 1-Azulenyl Triflates

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ABSTRACT

A new strategy for the synthesis of substituted azulenes is reported, based on the reaction of β′-bromo-α-diazo ketones with rhodium carboxylates. The key transformation involves intramolecular addition of a rhodium carbenoid to an arene π-bond, electrocyclic ring opening, β-elimination, tautomerization, and trapping to produce 1-hydroxyazulene derivatives. The synthetic utility of the method is enhanced by the ability of the triflate derivatives to participate in Suzuki coupling reactions, as illustrated in a synthesis of the antiulcer drug egualen sodium (KT1-32).

The azulenes constitute the best known class of polycyclic nonbenzenoid aromatic compounds and have long fascinated chemists with their remarkable colors and unusual electronic properties.[1] Early approaches to the synthesis of azulenes involved low-yield dehydrogenation steps and were limited to the preparation of relatively simple systems. More recently, however, powerful annulation strategies have been developed that provide access to azulenes of more complex structure. Particularly useful annulation methods include the Ziegler−Hafner synthesis,[2] annulation methods based on 2*H*-cyclohepta[*b*]furan-2-ones,[3] [6 + 4] cycloadditions,[4] and [3 + 2] annulations involving the reaction of tropylium cation with allenylsilanes.[5] Unfortunately, while these methods provide efficient access to azulenes substituted on the five-membered ring and to azulene itself, they have limited utility for the synthesis of derivatives bearing substituents on the *seven-membered ring*.

The goal of our research has been the design of a general strategy for the synthesis of azulenes substituted on both the five- *and* seven-membered rings. Since a wide variety of substituted benzene derivatives are easily prepared or are commercially available, we have focused our attention on approaches that might employ these readily obtained compounds as starting materials. Most attractive to us in this regard have been "ring expansion−annulation strategies": cascade ("tandem") processes[6] in which the benzene ring is

(1) For reviews, see: (a) Zeller, K.-P. In *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, H., Ed.; Georg Thieme Verlag: Stuttgart, 1985; Vol. V/2c, p 127. (b) Lloyd, D. *Nonbenzenoid Conjugated Carbocyclic Compounds*; Elsevier: Amsterdam, 1984; pp 352−377. (c) Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*; John Wiley and Sons: Chichester, 1989; Chapter 13.

(2) (a) Hafner, K.; Meinhardt, K.-P. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 15. (b) Reviewed in Jutz, J. C. *Topp. Curr. Chem.* **1978**, *73*, 125.

(3) (a) Yang, P.-W.; Yasunami, M.; Takase, K. *Tetrahedron Lett.* **1971**, 4275. (b) Wakabayashi, H.; Yang, P.-W.; Wu, C.-P.; Shindo, K.; Ishikawa, S.; Nozoe, T. *Heterocycles* **1992**, *34*, 429 and references therein.

(4) Mukherjee, D.; Dunn, L. C.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 251 and references therein.

(5) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389.

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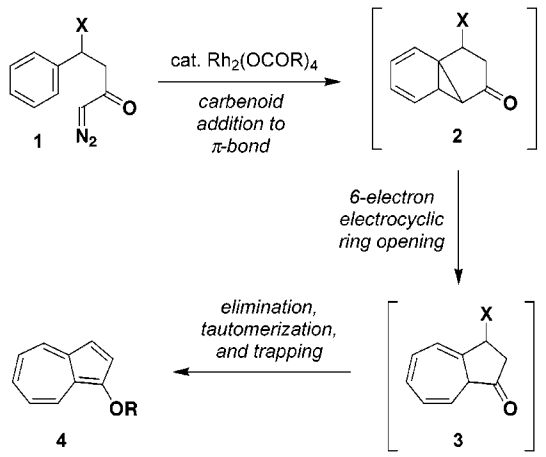
expanded to seven carbon atoms concomitant with the creation of the five-membered ring. As outlined in Scheme 1, the ring expansion−annulation strategy we report herein

Scheme 1



employs an intramolecular variant of the Büchner cycloheptatriene synthesis, which has previously been applied to the synthesis of *hydro*azulenes by Julia, Scott, and McKervey,[7] among others. Particularly relevant to our studies is the work of Scott,[8,9] who has previously employed the Büchner reaction in a synthesis of hydroazulenone **3** (X = H). Although exposure of **3** to alumina and then P_2O_5 in methanesulfonic acid at 60 °C effects its transformation to azulene, this process proceeds in only 30−50% yield, and attempts to apply a similar strategy to the synthesis of *substituted* azulenes gave the desired compounds in very low yield.[8]

The aim of our studies has been to devise a new variant of the intramolecular Büchner strategy that would deliver azulene derivatives directly and without the need for elevated temperatures or harsh reagents to effect elimination and/or dehydrogenation. Among the wide range of strategies we have examined,[10] the most effective has proven to be that outlined in Scheme 1 in which the intramolecular Büchner reaction is carried out using a substrate bearing a suitable leaving group "X". An attractive feature of this strategy is that it provides azulenes functionalized with hydroxy derivatives at the C-1 position, potentially including sulfonates that could be elaborated via transition-metal-catalyzed coupling reactions to form a wide variety of functionalized and substituted azulenes.

At the outset we recognized that for this approach to be successful it would be necessary to identify a leaving group that would be stable to the conditions of the carbenoid addition step, that would not undergo premature elimination at the stage of **1** or intermediate **2**, and whose elimination from **3** would take place more rapidly than the isomerization of the β,γ-double bond.[7] After considerable experimentation, we ultimately found that halogens, especially bromine, function as the best leaving groups for the desired transformation. The feasibility of the proposed strategy was first demonstrated using the known diazo ketone **5**.[11] Initial studies revealed that the desired ring expansion−annulation is best effected using rhodium carboxylate catalysts, among which rhodium(II) pivalate is particularly effective. Exposure of the resulting bromo ketone (**3**, X = Br) to tertiary amine bases then brings about elimination to form the expected 1-hydroxyazulene **4** (R = H). As a result of the known instability of the hydroxyazulene,[12] we chose to isolate it as the corresponding acetate by trapping with acetic anhydride. As outlined in eq 1, the entire multistage transformation can be conveniently accomplished as a simple "one-flask" operation.

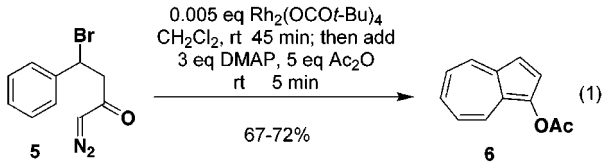


Table 1 delineates the scope of this ring expansion−annulation approach to the synthesis of substituted azulenes. Two alternate methods were employed for the preparation of the requisite β'-bromo-α-diazo ketones. Method A exploits the commercial availability of a variety of substituted cinnamic acids and involves addition of HBr to the alkene double bond followed by elaboration of the carboxylic acids to diazo ketones by employing standard Arndt−Eistert conditions. Attempts to add either HCl or HBr to cinnamic acid (**7**) initially were not fruitful, but success was finally achieved by using HBr/SiO_2 according to the general method of Kropp.[13] In the case of cinnamic acids substituted with electron-withdrawing groups, this procedure was not effective. For these cases, benzylic bromination of the corresponding hydrocinnamic acids provided access to the requisite β-bromo carboxylic acids (Method B).

Transformation of the β'-bromo-α-diazo ketone intermediates to the desired azulenes was effected in each case using the ring expansion−annulation conditions outlined in eq 1. Notably, the reaction tolerates incorporation of both electron-donating and electron-withdrawing substituents on the aromatic ring, as well as substitution at the carbon that becomes C-2 in the azulene five-membered ring. The success of the

(6) Reviews: (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Bunce, R. A.; *Tetrahedron* **1995**, *51*, 13103.

(7) For a review, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998; pp 289−324.

(8) Scott, L. T.; Minton, M. A.; Kirms, M. A. *J. Am. Chem. Soc.* **1980**, *110*, 6311.

(9) Scott, L. T.; Sumpter, C. A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 196.

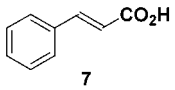
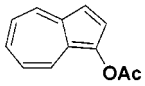
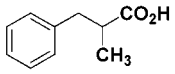
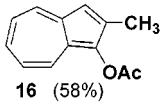
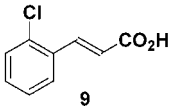
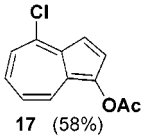
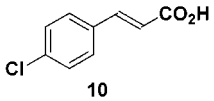
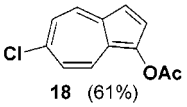
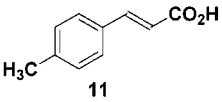
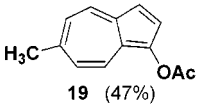
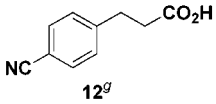
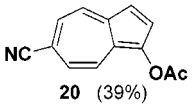
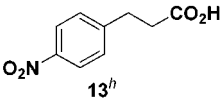
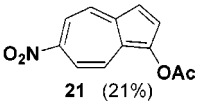
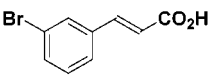
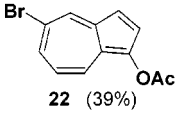
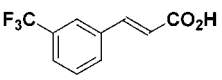
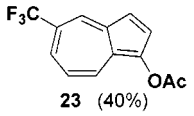
(10) Details will be reported in a full paper.

(11) Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.* **1976**, *41*, 3326.

(12) (a) Asao, T.; Ito, S.; Morita, N. *Tetrahedron Lett.* **1989**, *30*, 6693. (b) Asao, T. *Pure Appl. Chem.* **1990**, *62*, 507.

(13) Previously this procedure has only been applied to the reaction of HX with simple alkenes and alkynes; see: (a) Kropp, P. J.; Daus, K. A.; Crawford, S. D.; Tubergen, M. W.; Kepler, K. D.; Craig, S. L.; Wilson, V. P. *J. Am. Chem. Soc.* **1990**, *112*, 7433. (b) Kropp, P. J.; Daus, K. A.; Tubergen, M. W.; Kepler, K. D.; Wilson, V. P.; Craig, S. L.; Baillargeon, M. M.; Breton, G. W. *J. Am. Chem. Soc.* **1993**, *115*, 3071.

Table 1. Synthesis of Substituted Azulenes

starting material	diazo ketone intermediate[a] method,[b] yield (%)[c]	azulene product (% yield[c])
 **7**	A 69[d]	 **6**[e] (67-72%)
 **8**[f]	B 60	 **16** (58%)
 **9**	A 51	 **17** (58%)
 **10**	A 51	 **18** (61%)
 **11**	A 47	 **19** (47%)
 **12**[g]	B 41	 **20** (39%)
 **13**[h]	B 28	 **21** (21%)
 **14**	A 55	 **22** (39%)
 **15**	A 30	 **23** (40%)

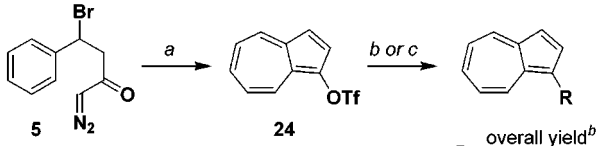
[a] ArCH(Br)CHRCOCHN$_2$; R = CH$_3$ in second entry and R = H in all other cases. [b] Method for preparation of intermediate diazo ketones. Method A: (1) HBr/SiO$_2$, CH$_2$Cl$_2$, rt, 24−360 h; (2) 1.2 equiv (COCl)$_2$, benzene, 65 °C, 15 h; (3) 4.0 equiv CH$_2$N$_2$, Et$_2$O, 0 °C → rt, 1−3 h. Method B: (1) 1.2 equiv NBS, cat. AIBN, CCl$_4$, 80 °C, sunlamp, 1−2 h; then reaction with (COCl)$_2$ and CH$_2$N$_2$ as in Method A. [c] Isolated yields of products purified by chromatography on silica gel. IR, UV, ^{1}H NMR, ^{13}C NMR, and mass spectral data were fully consistent with the assigned structures. Elemental analysis and/or high-resolution mass spectra were obtained for all new compounds. [d] Ref 11. [e] Ref 12a. [f] Prepared from ethyl propionate by (1) LDA, THF, PhCH$_2$Br; (2) KOH, H$_2$O (52% overall). [g] Prepared from CH$_3$CO$_2$*t*-Bu by (1) LDA, THF, α-iodo-*p*-tolunitrile; (2) TMSCl, NaI, CH$_3$CN, 45 °C, 45 min (77% overall). [h] Prepared by nitration of hydrocinnamic acid (HNO$_3$, H$_2$SO$_4$, 0 °C).

ring expansion−annulation in the case of halogenated substrates stands in contrast with earlier reports that halobenzenes do not participate in related reactions in good yield.[9] Also noteworthy is the regioselectivity of the process; in the case of *ortho* (**9**) and *meta* (**14**, **15**) substituted substrates, carbenoid addition occurs away from the substituent to afford predominantly one azulene regioisomer.[14]

We next turned our attention to the critical problem of effecting transition-metal-catalyzed coupling reactions[15,16] at the C-1 position of the ring expansion−annulation products. Initial efforts to achieve this key objective met with dismal failure. Although trapping the 1-hydroxyazulene annulation product with PhNTf$_2$ proceeded smoothly to generate the desired triflate **24**,[17] attempts to utilize this compound in efficient coupling reactions with various organotin, boron, zinc, aluminum, copper, and magnesium reagents were not successful. Remarkably, conditions that lead to efficient coupling reactions with the triflate derivative of 1-naphthol result only in the formation of uncharacterizable polymeric products in the case of azulene triflate **24**. This triflate appears exceptionally sensitive to cleavage, leading to the formation of 1-hydroxyazulene, which rapidly decomposes under the conditions of the reaction.

Successful coupling was ultimately realized by exploiting recent advances in the development of highly active catalysts for palladium-mediated cross-coupling and aromatic amination reactions. Most significantly, we have found that Suzuki coupling reactions[18] of **24** to afford 1-alkyl and 1-arylazulenes can be achieved in high yield by using Buchwald's *o*-(dicyclohexylphosphino)biphenyl ligand.[19] As outlined in Scheme 2, best results are obtained by employing triflate **24** in the Suzuki coupling reaction without prior purification. Alkylboranes are superior to boronic acid and ester deriva-

Scheme 2[a]



5 **24**

	R	overall yield[b] from **5**
25	Et	56%
26	Ph	60%

[a] Key: (a) 0.01 equiv Rh$_2$(OCO*t*-Bu)$_4$, CH$_2$Cl$_2$, rt, 45 min; then add 1.0 equiv PhNTf$_2$, 3.0 equiv DMAP, rt, 5 min. (b) 5 equiv *B*-ethyl-9-BBN, 0.05 equiv Pd(OAc)$_2$, 0.075 equiv (*o*-biphenyl)PCy$_2$, 3.0 equiv Cs$_2$CO$_3$, THF, rt, 2 h. (c) As in (b), but with 1.4 equiv *B*-Ph-9-BBN, 0.10 equiv (*o*-biphenyl)PCy$_2$, reflux, 15 min. [b]Isolated yields for products purified by chromatography on silica gel. Elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR data were fully consistent with the assigned structures.

(14) In the reactions of **14** and **15**, trace (<1%) amounts of byproducts were obtained, tentatively identified as the regioisomeric (1,7-substituted) azulene products.

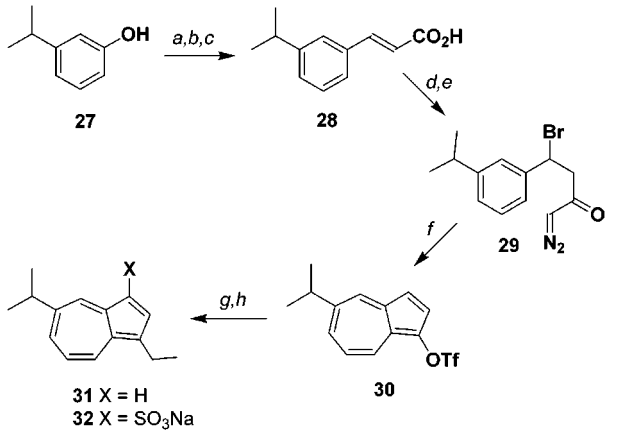
(15) For reviews, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Brandsma, L. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: New York, 1998. (c) *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Kidlington, 1995; Vol. 12.

(16) For examples of coupling reactions involving haloazulenes, see: (a) Morita, T.; Takase, K. *Bull. Chem. Soc. Jpn.* **1982,** *55*, 1144. (b) Iyoda, M.; Sato, K.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 3829. (c) Horino, H.; Asao, T.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 183.

tives for this coupling, and complete reaction takes place in THF under the indicated conditions either at room temperature for several hours or at reflux for several minutes. Overall yields for the sequence involving ring expansion annulation, sulfonylation with $PhNTf_2$, and Suzuki cross-coupling range from 56% to 60%.

The ability of this ring expansion−annulation strategy to streamline the preparation of substituted azulenes is illustrated by its application in the synthesis of the antiulcer drug egualen sodium (KT1-32).[20] As outlined in Scheme 3,

Scheme 3[a,b]



[a] Key: (a) 1.25 equiv Tf_2O, 1.4 equiv DMAP, CH_2Cl_2, −20 °C → rt, 2 h. (b) 5.0 equiv methyl acrylate, 0.1 equiv $Pd(OAc)_2$, 0.1 equiv dppp, DMSO, 120 °C, 16 h. (c) 7.5 equiv LiOH-H_2O, MeOH, 0 °C, 72 h. (d) HBr/SiO_2, CH_2Cl_2, rt, 20 h. (e) 1.4 equiv $(COCl)_2$, benzene, 65 °C, 15 h; then 4.0 equiv CH_2N_2, Et_2O, 0 °C → rt, 1 h; 51% overall from **27**. (f) 0.01 equiv $Rh_2(OCOt\text{-}Bu)_4$, Et_2O, rt, 45 min, then add 1.0 equiv $PhNTf_2$, 3.0 equiv DMAP, rt, 5 min. (g) 1.4 equiv Et_3B, 0.05 equiv $Pd(OAc)_2$, 0.075 equiv (*o*-biphenyl)PCy_2, 3.0 equiv KF, THF, reflux, 10−20 min, 25−42% overall from **29**. (h) SO_3/pyridine, benzene, 80 °C, 6 h; then NaOH, 90%; see ref 20a. [b]Isolated yields of products purified by chromatography on silica gel. IR, ^1H NMR, and ^{13}C NMR data were fully consistent with the assigned structures.

this synthesis delivers KT1-32 (**32**) in eight steps beginning with commercially available *m*-isopropylphenol, a considerable improvement over the prior route. Thus, Heck coupling of the triflate derivative of **27** with methyl acrylate furnished the expected cinnamic ester, which was saponified and elaborated to **29** by employing our standard protocol. The conversion of phenol **27** to the *β*′-bromo-α-diazo ketone **29** can be carried out without purification of any intermediates and proceeds in 51% overall yield. Surprisingly, ring expansion−annulation of **29** did not take place in good yield under our previous conditions but proceeded smoothly when diethyl ether was employed in place of dichloromethane as the reaction solvent. Suzuki coupling with triethylborane followed by sulfonylation with SO_3/pyridine then furnished KT1-32 with spectroscopic characteristics in full accord with those previously reported for this compound.

In summary, we have developed a ring expansion−annulation strategy that begins with readily available benzene derivatives and provides access to a variety of azulenes substituted on both the five- and seven-membered rings. The utility of the 1-hydroxyazulene annulation products is enhanced by the ability of their triflate derivatives to participate in Suzuki coupling reactions, as illustrated with the application of this methodology in an efficient synthesis of the antiulcer drug egualen sodium. Further studies on the synthesis of substituted and functionalized azulenes are in progress and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 28273), Kotobuki Seiyaku Co., Ltd., Pharmacia, and Merck Research Laboratories for generous financial support.

Supporting Information Available: Representative experimental procedures for key reactions and characterization data for all azulene products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Formed in 91% yield as estimated by ^1H NMR analysis. This compound is stable to storage in solution (e.g., diethyl ether or dichloromethane) at 0 °C but decomposes upon concentration.

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