

Azadiene Diels–Alder Cycloaddition of Fulvenes: A Facile Approach to the [1]Pyrindine System

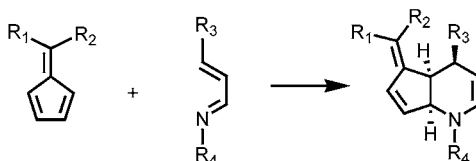
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Received June 29, 2004

ABSTRACT



R₁; R₂=H, Me, Et, Pr, Ph, *p*-ClC₆H₄, -(CH₂)₅; R₃=CO₂Et, Ph; R₄=Ts, SO₂Ph

Regioselective and stereoselective inverse-electron-demand Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadiene with fulvenes are described. The methodology provides an efficient and novel route to tetrahydro-[1]pyrindine systems.

Inverse-electron-demand Diels–Alder chemistry has attracted much attention over the past two decades,¹ and many natural products have been prepared in this manner from *N*-sulfonyl-1-aza-1,3-butadienes.² Cycloadditions of fulvenes (e.g., [4 + 3],³ [2 + 2],⁴ [4 + 2],⁵ [2 + 4],⁶ [6 + 4],⁷ [6 + 2],⁸ [6 +

3]⁹) provide versatile and powerful approaches to various polycyclic systems and natural products. However, to the best of our knowledge, preparation of tetrahydro-[1]pyrindine systems from azadienes and fulvene has never been reported.¹⁰

Recently, we reported a new type of reaction: a formal [6 + 3] cycloaddition of fulvenes and 2*H*-azirine¹¹ and *N*-alkylidene glycine esters¹² that yields [2]pyrindines. In conjunction with our continuing efforts in fulvene chemis-

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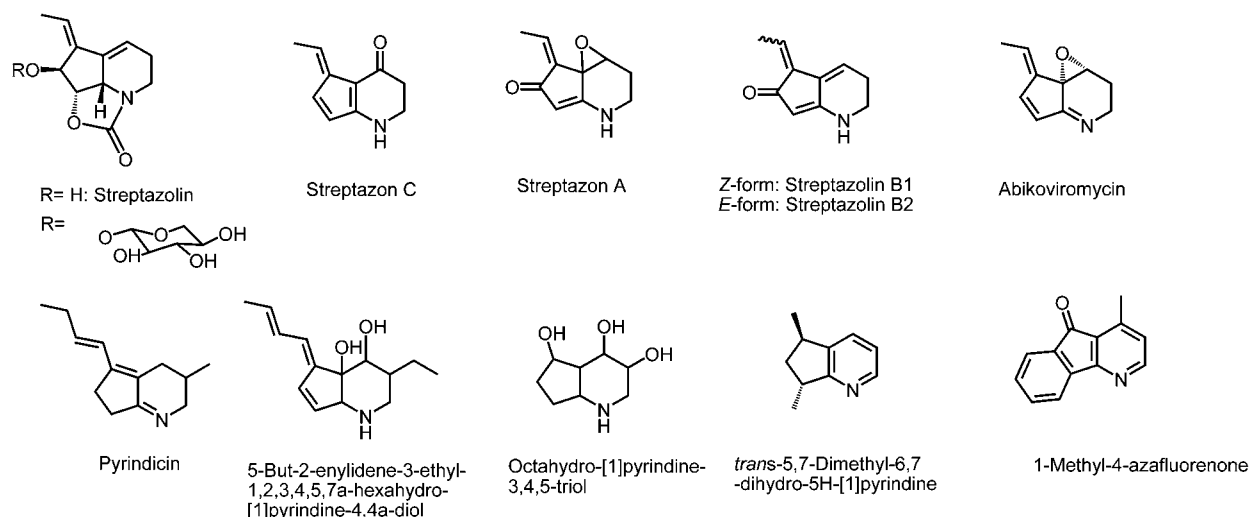


Figure 1. Examples of naturally occurring [1]pyrindine.

try,¹³ we have now developed an efficient and general hetero Diels–Alder cycloaddition of fulvenes with azadienes to give tetrahydro-[1]pyrindines.

Piperidine alkaloids are common constituents of plants and possess a wide range of biological activities. For example, streptazolin, a microbial metabolite, has antibiotic and antifungal activity,¹⁴ while 5-*O*-(β -D-xylopyranosyl)-streptazolin shows in vitro cytotoxic activity against certain human cancer cell lines, Figure 1. The unique structural features and promising bioactivity of streptazolins and specifically streptazon C prompted us to explore the synthesis of this natural product via a fulvene cycloaddition strategy.¹⁵ We initially envisioned that an electron-deficient azadiene such as ethyl (*E*)-4-[(phenylsulfonyl)imino]-2-butenolate¹⁶ and

fulvene would undergo an inverse-electron-demand Diels–Alder reaction to afford the hetero [4 + 2] cycloadduct.¹⁷ In a model study, dimethyl fulvene (**1a**) and azadiene (**2a**) were stirred in CH_2Cl_2 for 65 h to afford [1]pyrindine **3a** as the only isolable product (70% yield), Table 1, entry 1, method A. A higher yield and a faster reaction time were achieved under microwave conditions (30 min, 96% yield, method

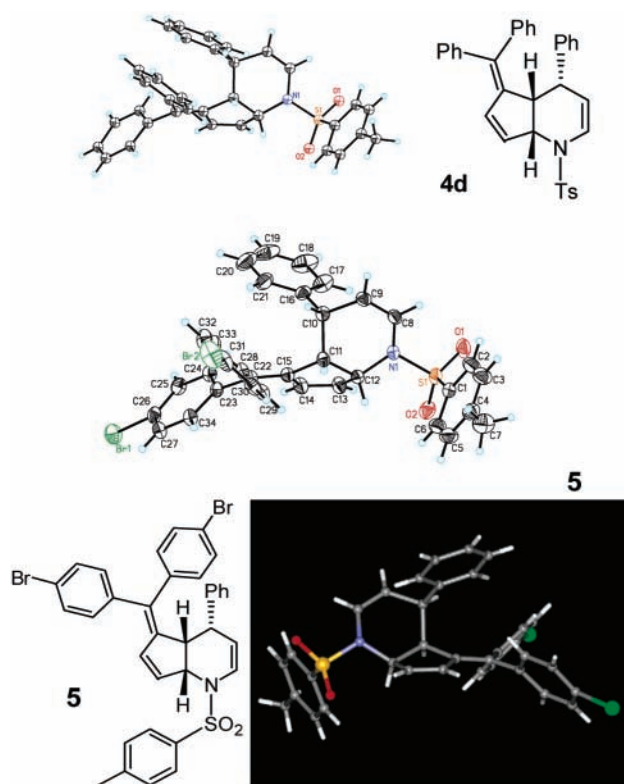


Figure 2. ORTEP plots for X-ray crystal structures of **4d** and **5**.

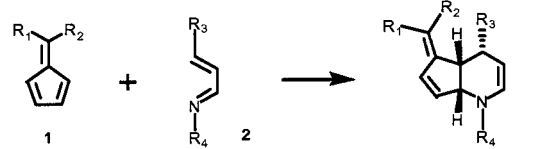
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(15) Several synthetic approaches to streptazolins have been reported. (a) For 8 α -hydroxystreptazolone, see: Izumi Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, 69, 1803. (b) For streptazolin, see: Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, 107, 1763.

(16) Prepared from the corresponding 4-oxo-crotonic acid ethyl ester and benzenesulfonamide (Et_3N , TiCl_4 , CH_2Cl_2 ; 60% yield), see: Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, 55, 5439 and ref 2c.

Table 1. Hetero Diels–Alder Reaction of 1-Aza-1,3-butadiene with Fulvene **1a**



2a: R₃ = CO₂Et; R₄ = Bs
2b: R₃ = Ph; R₄ = Ts

3: R₃ = CO₂Et; R₄ = Bs
4: R₃ = Ph; R₄ = Ts

entry	fulvene	product	metho d	time (h)	yield (%) ^a
1		R ₁ =R ₂ =Me, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3a	A	65	70
			B	0.48	96
			C	3.5	83
			D	5.5	76
			E	7	64
			F	3.5	67
			G	0.5	29 ^c
			H	0.83	68
			I	1.25	65
2		R ₁ =R ₂ =Me, R ₃ =Ph, R ₄ =Ts; 4a	A	240	27 ^b
			B	7	92
			C	65	80
			D	72	48 ^c
			E	72	46 ^c
			F	72	54 ^c
			G	5	36
			H	7	65
			I	7	48 ^c

^a Isolated yield based on starting azadiene. ^b Recovered most of the starting material. ^c Recovered some starting material and many complicated mixtures. Method A: CH₂Cl₂, 25 °C. Method B: ClC₆H₅, microwave, 125 °C. Method C: toluene, TinyClave, ~6 bar, 110 °C. Method D: EDC, reflux, 85 °C. Method E: benzene, reflux, 80 °C. Method F: toluene, reflux, 110 °C. Method G: DMF, microwave, 110 °C. Method H: toluene, microwave, 100 °C. Method I: 1,4-dioxane, microwave, 90 °C.

B). The reaction was also attempted in a TinyClave¹⁸ at ca. 6 bar in toluene (3.5 h, 83% yield, method C). The structure of **3a** was assigned on the basis of IR, ¹H, ¹³C NMR, COSY, DEPT, HMQC, MS, and HRMS analysis. The reaction also

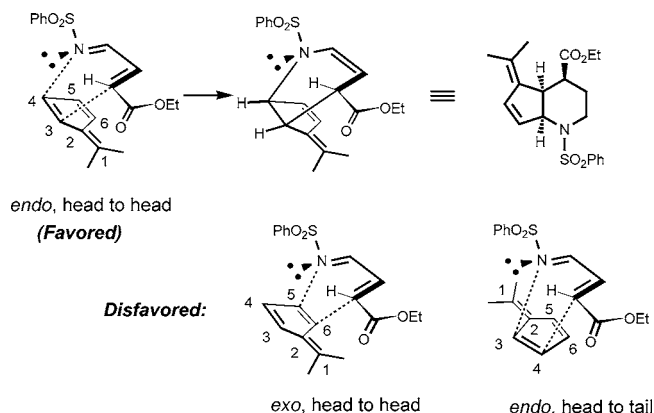
Table 2. Hetero Diels–Alder Reaction of 1-Aza-1,3-butadiene with Fulvenes

entry	fulvene	product	metho d	time (h)	yield (%) ^a
1		R ₁ =R ₂ =Et, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3b	A	68	64
			B	0.48	92
		R ₁ =R ₂ =Et, R ₃ =Ph, R ₄ =Ts; 4b	B	7	91
			C	72	75
2		R ₁ =R ₂ =Pr, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3c	A	68	63
			B	0.5	87
		R ₁ =R ₂ =Pr, R ₃ =Ph, R ₄ =Ts; 4c	B	7.5	82
			C	72	74
3		R ₁ =R ₂ =Ph, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3d	A	56	73
			B	0.58	86
		R ₁ =R ₂ =Ph, R ₃ =Ph, R ₄ =Ts; 4d	B	7.5	77
			C	65	68
4		R ₁ =R ₂ =p-ClC ₆ H ₄ , R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3e	A	45	82
			B	0.67	89
		R ₁ =R ₂ =p-ClC ₆ H ₄ , R ₃ =Ph, R ₄ =Ts; 4e	B	8	70
			C	60	67
5		R ₁ =R ₂ =-(CH ₂) ₄ -, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3f	A	78	63
			B	0.48	90
		R ₁ =R ₂ =-(CH ₂) ₄ -, R ₃ =Ph, R ₄ =Ts; 4f	B	7	85
			C	75	56
6		R ₁ =R ₂ =-(CH ₂) ₅ -, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3g	A	72	65
			B	0.5	87
		R ₁ =R ₂ =-(CH ₂) ₅ -, R ₃ =Ph, R ₄ =Ts; 4g	B	7.5	82
			C	75	57
7		R ₁ =Ph, R ₂ =H, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3h	A	56	73(3:4)
			B	0.33	74(3:4)
		R ₁ =Ph, R ₂ =H, R ₃ =Ph, R ₄ =Ts; 4h	B	6.7	73(1:4)
			C	62	71(1:4)
8		R ₁ =Me, R ₂ =H, R ₃ =CO ₂ Et, R ₄ =SO ₂ Ph; 3i	A	45	67(3:4)
			B	0.33	72(3:4)
		R ₁ =Me, R ₂ =H, R ₃ =Ph, R ₄ =Ts; 4i	B	6	70(1:1)
			C	54	65(1:1)

^a Isolated yield based on starting azadiene.

works in other solvents at reflux, albeit with lower yield (entry 1, methods D–I). The exclusive regio- and diastereo-selectivity of the reaction can be attributed to two mutually reinforcing occurrences that stabilize the *endo*-head-to-head transition state as depicted in Scheme 1: (1) secondary orbital interactions between the azadiene and the C₅–C₆ double bond of fulvene and (2) the interaction between the ester carbonyl group and the C₁–C₂ double bond of fulvenes. The first feature is noticeably absent in the corresponding *exo*-head-to-head transition state, while the second interaction

Scheme 1



(17) For other regioselective [2 + 4] cycloadditions of fulvenes to electron-deficient dienes, see: (a) Houk, K. N.; Luskus, L. J. *J. Org. Chem.* **1973**, *38*, 3836. (b) Bimanand, A. Z.; Gupta, Y. N.; Doa, M. J.; Eaton, T. A.; Houk, K. N. *J. Org. Chem.* **1983**, *48*, 403. (c) Lewis, N. J.; Collins, W. J.; Knight, D. B. *J. Med. Chem.* **1979**, *22*, 1505. (d) Nair, V.; Anilkumar, G.; Radhakrishnan, K. V.; Sheela, K. C.; Rath, N. P. *Tetrahedron* **1997**, *53*, 17361.

(18) TinyClave (Büchiglassuster) is a miniature laboratory autoclave for safe small-scale experiment under pressure. It allows one to run chemical reactions in organic media under pressure up to 10 bar and 150 °C.

provides the high regioselectivity of the product and is disfavored in the *endo*-head-to-tail approach.¹⁹

The hetero [4 + 2] cycloaddition of 4-[(phenylsulfonyl)-imino]-2-butenolate with electron-rich alkenes is well documented, yet there is only one example of the corresponding reaction of zimaldehydiminotosylate.²⁰ In our hands, zimaldehydiminotosylate²¹ (**2b**) reacted with fulvene (**1a**) in CH₂-Cl₂ at ambient temperature to yield a similar hetero Diels–Alder adduct (**4a**). However, this reaction was much slower and gave a lower yield when compared to **2a** (240 h, 27% yield, vs 65 h, 70% yield, entries 1 and 2, Method A). Various solvents and reaction conditions were screened, and the best yield (92%) was observed under microwave conditions in ClC₆H₅ at 125 °C.

A series of homologous fulvenes were then reacted with 1-aza-1,3-butadienes **2a** and **2b** to afford the corresponding [1]pyrindines (entries 1–8, Table 2).²²

The structure of **4d**²³ and the *p*-bromobenzoate derivative **5**²⁴ (prepared from the corresponding dibromophenylfulvene) were unambiguously assigned by single-crystal X-ray analysis, Figure 1. Interestingly, the olefinic isomers of the

monoalkylfulvenes **1h** and **1i** gave the two olefinic regioisomers in a nearly 1:1 ratio.

In summary, the above regioselective and stereoselective hetero [4 + 2] cycloadditions emphasize a new feature of the reactivity of fulvene and azadienes. This methodology represents an unprecedented approach to tetrahydra-[1]-pyrindine. Further applications of this methodology toward total synthesis of natural products are currently under active investigation in our laboratory, and the results will be published in due course.

Acknowledgment. We are grateful to Dr. Sepehr Sarshar for valuable discussions. Financial support from National Science Council and National Health Research Institute are gratefully acknowledged.

Supporting Information Available: Crystallographic information files (CIF) for **4d** and **5**. Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) Selectivity may also be explained by the LUMO (azadiene) and HOMO (fulvene) coefficients; see ref 2c.

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(21) Prepared from toluene-4-sulfonamide and 3-phenyl-propenal (TiCl₄, NEt₃, CH₂Cl₂, 78%); see: Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1942**, 7, 1729.

(22) All new compounds were fully characterized by ¹H NMR, ¹³C NMR, DEPT, IR, MS, and HRMS. In most cases, COSY and HMQC spectra were also obtained. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

(23) Four independent molecules in an asymmetric unit. Crystallographic data for **4d**: C₃₄H₂₉NO₂S, *M* = 515.64, monoclinic, space group *P*2₁, *T* = 298 K, *a* = 9.8136(10), *b* = 37.446(4), *c* = 15.0320(16) Å, β = 90.095(2)°, *V* = 5523.9(10) Å³, *Z* = 8, *D* = 1.240 g/cm³, λ (Mo Kα) = 0.71073 Å, 34 867 reflections collected, 20 465 unique reflections, 1374 parameters refined on *F*², *R* = 0.0852, w*R*₂[*F*²] = 0.1495 [13 042 data with *F*² > 2σ(*F*²)].

(24) Compound **5** was prepared from di-*p*-bromophenylfulvene with **2b**, method B; 85% yield. Crystallographic data for **5**: C₃₄H₂₇Br₂NO₂S, *M* = 673.45, monoclinic, space group *P*2₁/*n*, *T* = 298 K, *a* = 17.5841(15), *b* = 9.7852(8), *c* = 18.2955(15) Å, β = 110.9240(10)°, *V* = 2940.4(4) Å³, *Z* = 4, *D* = 1.521 g/cm³, λ (Mo Kα) = 0.71073 Å, 34 131 reflections collected, 7166 unique reflections, 362 parameters refined on *F*², *R* = 0.0457, w*R*₂[*F*²] = 0.1250 [5487 data with *F*² > 2σ(*F*²)].