ORGANIC LETTERS

2004
Vol. 6, No. 20
3453−3456

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

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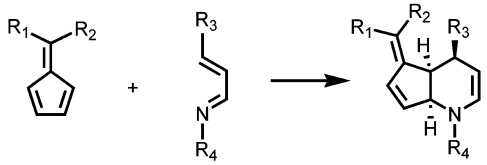
**Received June 29, 2004**

## ABSTRACT




$R_1$; $R_2$=H, Me, Et, Pr, Ph, *p*-$ClC_6H_4$, -$(CH_2)_5$-; $R_3$=$CO_2Et$, Ph; $R_4$=Ts, $SO_2Ph$

**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*-azirine[11] and *N*-alkylidene glycine esters[12] that yields [2]pyrindines. In conjunction with our continuing efforts in fulvene chemis-

(1) For recent reviews, see: (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (b) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (c) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149.

(2) For examples, see: (a) Boger, D. L.; Zhang, M. *J. Org. Chem.* **1992**, *57*, 3974. (b) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839. (c) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (d) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733. (e) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880.

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(7) (a) Gupta, Y. N.; Doa, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7336. (b) Yoshida, Z.-I.; Shibata, M.; Ogino, E.; Sugimoto, T. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 60.

(8) (a) For an example of an intermolecular [6 + 2] cycloaddition, see: Hong, B. C.; Shr, Y. J.; Wu, J. L.; Gupta, A. K.; Lin, K. J. *Org. Lett.* **2002**, *4*, 2249. (b) For an example of an intramolecular [6 + 2] cycloaddition, see: Suda, M.; Hafner, K. *Tetrahedron Lett.* **1977**, 2453. (c) Wu T. C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308.

(9) Barluenga, J.; Martinez, S.; Suárez-Sobrino, A. L.; Tomás, M. *J. Am. Chem. Soc.* **2001**, *123*, 11113.

(10) (a) Theoretically, the Diels−Alder reaction of isoxazole with alkenes should not proceed; see: Gonzãlez, J.; Taylor, E. C.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3753. (b) A low-yielding [4 + 2] cycloaddition of isoxazole has been reported; see: Nesi, R.; Giomi, D.; Papaleo, S.; Turchi, S. *J. Org. Chem.* **1992**, *57*, 3713. (c) A low-yielding [4 + 2] cycloaddition of triazine has been reported; see: Diaz-Ortiz, A.; Hoz, A.; Prieto, P.; Carrillo, J. R.; Moreno, A.; Neunhoeffer, H. *Synlett* **2001**, 236.

(11) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H. *Tetrahedron Lett.* **2004**, *45*, 1663.

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10.1021/ol048762c CCC: $27.50 
**Published on Web 08/31/2004**

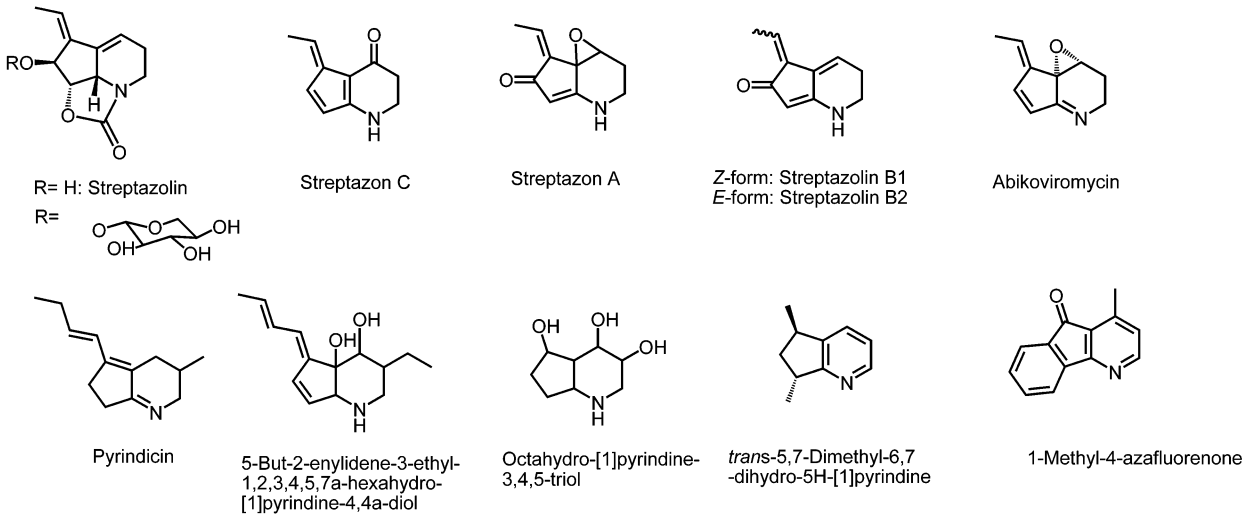



**Figure 1.** Examples of naturally occurring [1]pyrindine.

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 acitivity,[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 streptazone 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-butenoate[16] 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

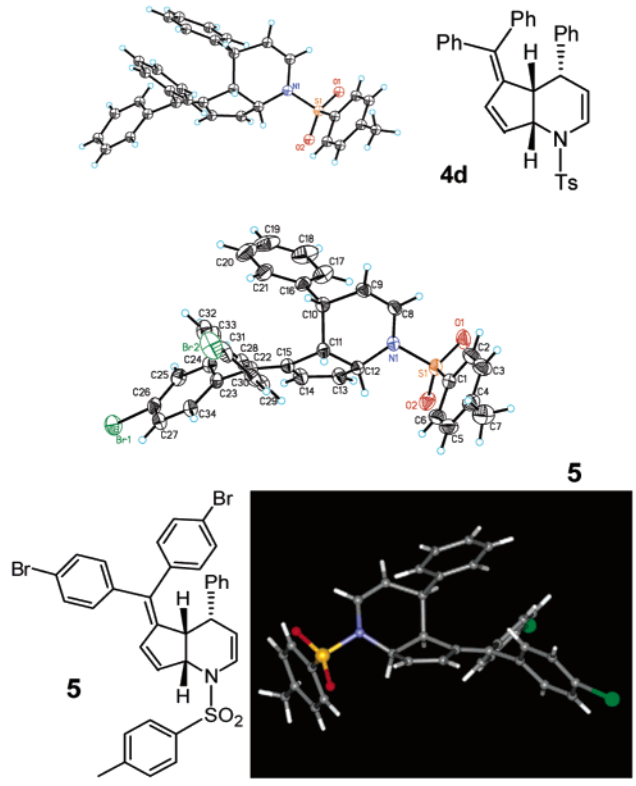



**Figure 2.** ORTEP plots for X-ray crystal structures of **4d** and **5**.

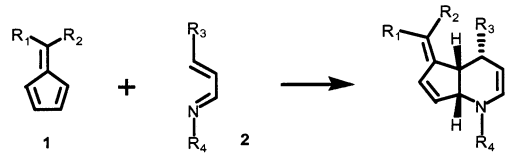
(13) For previous papers in this series, see: (a) Hong, B.-C.; Shr, Y.-J.; Wu, J.-L.; Gupta, A. K.; Lin, K.-J. *Org. Lett.* **2002**, *4*, 2249. (b) Hong, B.-C.; Shr, Y.-J.; Liao, J.-H. *Org. Lett.* **2002**, *4*, 663.

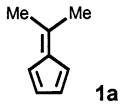
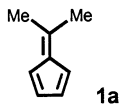
(14) (a) Streptazolin, streptazon C, and streptazon A were isolated from *Streptomyces FORM5*, Stain A1, *viridochromogenes* and *leteogriseus*. See: (i) Puder, C.; Krastel, P.; Zeeck, A. *J. Nat. Prod.* **2000**, *63*, 1258. (ii) Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *J. Nat. Prod.* **2001**, *64*, 42. (iii) Grabley, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem.* **1987**, *99*, 692. (b) Abikoviromycin was isolated from *Isolierung aus Streptomyces-Arten*. See: (i) Sakagami, Y.; Utahara, R.; Yagishita, K.; Umezawa, H. *J. Antibiot.* **1958**, *11*, 231. (ii) Gurevich, A. I.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V. *Tetrahedron Lett.* **1968**, *9*, 2209. (iii) Maruyama, H.; Okamoto, S.; Kubo, Y.; Tsuji, G.; Fujii, I.; Ebizuka, Y.; Furihata, K.; Hayakawa, Y.; Nagasawa, H.; Sakuda, S. *J. Antibiot.* **2003**, *56*, 801. (c) Pyrindicin was isolated from *Streptomyces sp. SCC 2313*. See: Hegde, V. R.; Dai, P.; Patel, M. G.; Troyanovich, J. J.; Das, P.; Puar, M. S. *J. Antibiot.* **1994**, *47*, 110. (d) *trans*-5,7-Dimethyl-6,7-dihydro-5*H*-[1]pyrindine was isolated from *aus Erdoel*. See: Monti, S. A.; Schmidt, R. R.; Shoulders, B. A.; Lochte, H. L. *J. Org. Chem.* **1972**, *37*, 3834. (e) Octahydro-[1]pyrindine-3,4,5-triol was Isolation from *Rhizoctonia leguminicola*. See: Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (f) 1-Methyl-4-azafluorenone was isolated from branches of *Porcelia macrocarpa (Warm.)*. See: Chaves, M. H.; Santos, L. de A.; Lago, J. H. G.; Roque, N. F. *J. Nat. Prod.* **2001**, *64*, 40.

(15) Several synthetic approaches to streptazolins have been reported. (a) For 8α-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**




| entry | fulvene | product | method | time (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **1a** | $R_1$=$R_2$=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 |  **1a** | $R_1$=$R_2$=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: $CH_2Cl_2$, 25 °C. Method B: $ClC_6H_5$, 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 TinyClave[18] at ca. 6 bar in toluene (3.5 h, 83% yield, method C). The structure of **3a** was assigned on the basis of IR, $^1$H, $^{13}$C NMR, COSY, DEPT, HMQC, MS, and HRMS analysis. The reaction also

**Scheme 1**

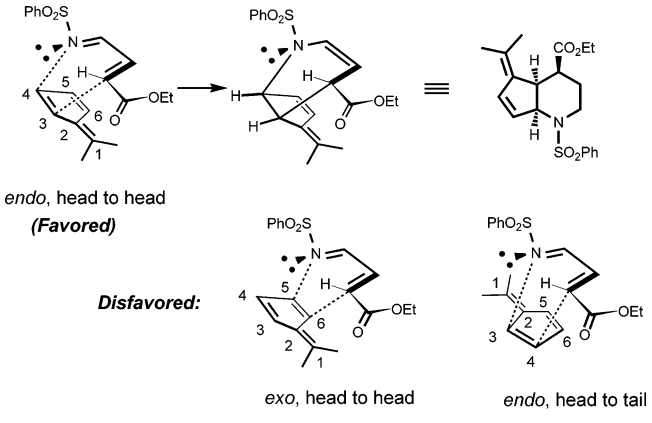
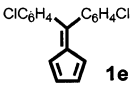



**Table 2.** Hetero Diels−Alder Reaction of 1-Aza-1,3-butadiene with Fulvenes

| entry | fulvene | product | method | time (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **1b** | $R_1$=$R_2$=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 |  **1c** | $R_1$=$R_2$=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 |  **1d** | $R_1$=$R_2$=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 |  **1e** | $R_1$=$R_2$=*p*-$ClC_6H_4$, $R_3$=$CO_2$Et, $R_4$=$SO_2$Ph; **3e** | A | 45 | 82 |
| | | | B | 0.67 | 89 |
| | | $R_1$=$R_2$= *p*-$ClC_6H_4$, $R_3$=Ph, $R_4$=Ts; **4e** | B | 8 | 70 |
| | | | C | 60 | 67 |
| 5 |  **1f** | $R_1$=$R_2$= -$(CH_2)_4$-, $R_3$=$CO_2$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 |  **1g** | $R_1$=$R_2$= -$(CH_2)_5$-, $R_3$=$CO_2$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 |  **1h** | $R_1$=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 |  **1i** | $R_1$=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 diastereoselectivity 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 $C_5$−$C_6$ double bond of fulvene and (2) the interaction between the ester carbonyl group and the $C_1$−$C_2$ double bond of fulvenes. The first feature is noticeably absent in the corresponding *exo*-head-to-head transition state, while the second interaction

(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-butenoate with electron-rich alkenes is well documented, yet there is only one example of the corresponding reaction of zimtaldehydiminotosylate.[20] In our hands, zimtaldehydiminotosylate[21] (**2b**) reacted with fulvene (**1a**) in $CH_2Cl_2$ 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 $ClC_6H_5$ 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.

(20) Croce, P.; Ferraccioli, R.; Rosa, C. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2499.

(21) Prepared from toluene-4-sulfonamide and 3-phenyl-propenal ($TiCl_4$, $NEt_3$, $CH_2Cl_2$, 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, $^{13}C$ 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**: $C_{34}H_{29}NO_2S$, $M = 515.64$, monoclinic, space group $P2_1$, $T = 298$ K, $a = 9.8136(10)$, $b = 37.446(4)$, $c = 15.0320(16)$ Å, $\beta = 90.095(2)°$, $V = 5523.9(10)$ Å$^3$, $Z = 8$, $D = 1.240$ g/cm$^3$, $\lambda$ (Mo K$\alpha$) = *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 $F^2 > 2\sigma(F^2)$].

(24) Compound **5** was prepared from di-*p*-bromophenylfulvene with **2b**, method B; 85% yield. Crystallographic data for **5**: $C_{34}H_{27}Br_2NO_2S$, $M = 673.45$, monoclinic, space group $P2_1/n$, $T = 298$ K, $a = 17.5841(15)$, $b = 9.7852(8)$, $c = 18.2955(15)$ Å, $\beta = 110.9240(10)°$, $V = 2940.4(4)$ Å$^3$, $Z = 4$, $D = 1.521$ g/cm$^3$, $\lambda$ (Mo K$\alpha$) = *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 $F^2 > 2\sigma(F^2)$].