J. Org. Chem. 1996, 61, 2247−2250 2247

Cyclization of Enediyne Radical Cations through Chemical, Photochemical, and Electrochemical Oxidation: The Role of State Symmetry

Dhruva Ramkumar,[†] Mahadevan Kalpana,[†]
Babu Varghese,[‡] and Sethuraman Sankararaman*,[†]

Department of Chemistry and Regional Sophisticated Instrumentation Centre, Indian Institute of Technology, Madras - 600 036, India

Mavinahalli N. Jagadeesh and
Jayaraman Chandrasekhar*

Department of Organic Chemistry, Indian Institute of Science, Bangalore - 560 012, India

Received August 17, 1995

Enediyne chemistry has gained prominence in recent years in view of the presence of the moiety in several naturally occurring antitumor antibiotics.[1] Thermally activated cycloaromatization to form 1,4-dehydrobenzene diradical (Bergman cyclization) is of special interest as the process has been implicated in the DNA-cleaving ability of many natural products and synthetic analogues.[2] Photoinduced dimerization,[3] cis−trans isomerization,[4] and cycloaromatization[5] as well as photochemically triggered cyclization of enediynes[6] have also been studied. Recently, 1,5-cyclizations have been reported in a cyclic, dimeric derivative of 1,2-diethynylbenzene[7] and in tetrabenzocyclyne,[8] induced by iodine and lithium, respectively. The former presumably proceeds through a radical cyclization pathway, while the latter involves a radical anion. We now report electron transfer-mediated cyclization of aromatic enediynes. Of the three possible modes of cyclization (Scheme 1), the radical cations of aryl derivatives generated through chemical, photochemical, and electrochemical oxidation are shown not to follow the Bergman cyclization mode. The observed 1,5-cyclization process has been interpreted in terms of the symmetry of electronic states of the species involved.

Results and Discussion

Photooxidation of enediynes **4a**,**b** in acetonitrile in the presence of oxygen using 2,4,6-triphenylpyrilium tetrafluoroborate ($TPP^+BF_4^-$) as the sensitizer[9] yielded the corresponding indenone derivatives **5a**,**b**, respectively (Scheme 2).

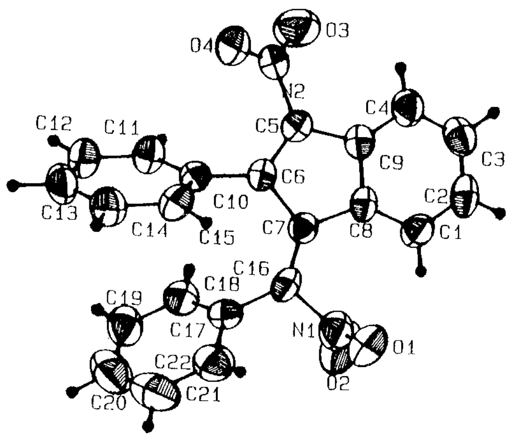
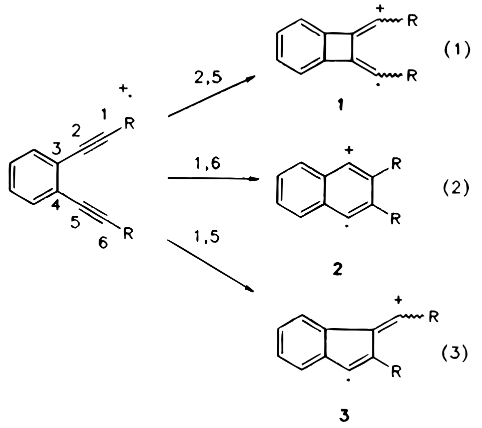
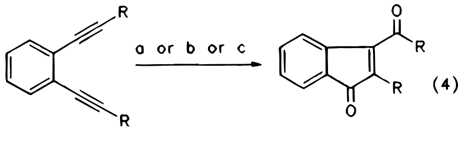


Figure 1. ORTEP diagram of the molecular structure of **6a** in the crystal.

Scheme 1



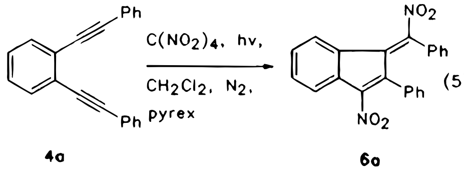
Scheme 2



4a R = C_6H_5 **5a**
4b R = 4-$MeOC_6H_4$ **5b**

a. $TPP^+BF_4^-$, CH_3CN, O_2, pyrex, hν;
b. 10 mole % $TBPA^+SbCl_6^-$, CH_2Cl_2, -78 °C, O_2
c. anodic oxidation, Pt, CH_3CN, O_2, TEAP

Scheme 3



4a **6a**

Photonitration of **4a** with tetranitromethane (TNM) in dichloromethane using a Pyrex filter yielded red orange crystals after column chromatographic purification of the crude material.[10] The product was identified as 3,8-dinitro-2,8-diphenylbenzofulvene (**6a**) from the X-ray crystal structure[19] shown in Figure 1 (Scheme 3). The

---

[†] Department of Chemistry.

[‡] Regional Sophisticated Instrumentation Centre.

(1) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497.

(2) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172. Nicolaou, K. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 7360. Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9276.

(3) Muller, E.; Zountsas, G. *Tetrahedron Lett.* **1970**, *52*, 4531.

(4) Konig, B.; Schofield, E.; Bubenitschek, P.; Jones, P. G. *J. Org. Chem.* **1994**, *59*, 7142.

(5) Turro, N. J.; Evenzahav, A.; Nicolaou, K. C. *Tetrahedron Lett.* **1994**, *35*, 8089.

(6) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867.

(7) Zhou, Q.; Carroll, P. J.; Swager, T. M. *J. Org. Chem.* **1994**, *59*, 1294.

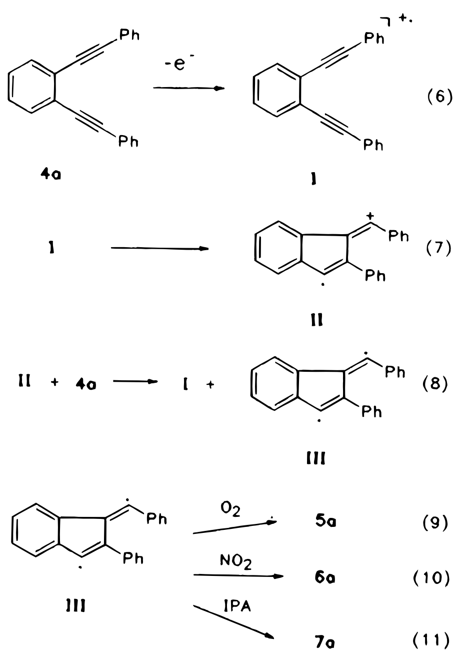
(8) Bradshaw, J. D.; Solooki, D.; Tessier, C. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1994**, *116*, 3177.

(9) For $TPP^+BF_4^-$: $E_{1/2}$ (red) = −0.29 V vs SCE in CH_3CN, E(S) = 2.8 eV, t(S) = 2.9 ns. Miranda, M. A.; Garcia, H. *Chem. Rev.* **1994**, *94*, 1063.

(10) For the mechanism of photonitration of arenes with TNM see Sankararaman, S.; Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1, 165 and references cited therein. Further details of the photochemistry of enediyne−TNM system will be published separately.

0022-3263/96/1961-2247$12.00/0

Scheme 4



crystal structure of **6a** unequivocally establishes that the product arises from the 1,5-cyclization mode to yield the benzofulvene structure.

Chemical oxidation of **4a**,**b**, by Barton's procedure,[11] using tris(*p*-bromophenyl)aminium hexachloroantimonate ($TBPA^+SbCl_6^-$) as the catalytic oxidizing agent in the presence of oxygen yielded **5a**,**b**, respectively (Scheme 2) in 60−70% isolated yields.

Electrochemical oxidation of **4a**,**b** was examined by cyclic voltammetry in acetonitrile which showed a single irreversible anodic peak at +1.49 V for **4a** and +1.31 V for **4b**, vs SCE, at 100 mV s^{-1} scan rate. The bulk electrolysis of **4a**,**b** at a constant potential corresponding to the anodic peak potential under oxygen atmosphere yielded **5a**,**b**, respectively, in good yields. Coulometric studies revealed that the reaction was a catalytic one-electron transfer process. Thus, for the electrolysis of 0.3 mmol of **4b**, only 4 C of current was consumed to yield 0.27 mmol of **5b**.

We propose a common pathway involving the enediyne radical cation in all the cases. Photoinduced electron transfer from **4a**,**b** to the singlet excited state of TPP^+ is feasible since the latter is a powerful oxidant.[9] This is further supported by the diffusion-controlled quenching of the fluorescence of TPP^+ by **4a**,**b** and also by the calculated ΔG_{et} values based on the redox potentials of the reactants.[12] The radical cation of the enediyne (I) cyclizes to the fulvenyl form (II) which further reacts with the neutral enediyne to yield the fulvenyl diradical (III) and the enediyne radical cation (I) (eqs 6−8, Scheme 4). Thus, the radical cation of the enediyne is the chain carrier. Such a mechanism is akin to the photoinduced electron transfer-mediated valence isomerization of hexamethyldewarbenzene radical cation.[13] Evidence for the formation of the fulvenyl diradical (III) comes from the isolation of *cis*- and *trans*-2,8-diphenylbenzofulvene (**7a**) from the photolysis of **4a** in the presence of $TPP^+BF_4^-$ when carried out in acetonitrile-isopropyl alcohol (IPA) mixture under nitrogen atmosphere (eq 12, Scheme 5). Formation of **7a** can only be explained by invoking the diradical III which undergoes hydrogen abstraction with IPA (eq 11). The lack of formation of products arising from the addition of IPA as a nucleophile to I and II suggests that the cyclization and the subsequent electron transfer processes (eqs 7 and 8) are very rapid. This also explains the absence of products arising from the addition of trinitromethide anion to I and II in the TNM reaction (eq 5), which is in sharp contrast to the previously reported photochemistry of arene−TNM complexes.[10] Furthermore, the ESR spectrum shown in Figure 2 arises from the trapping of a radical intermediate from the photolysis of **4a** with $TPP^+BF_4^-$ in CH_3CN under argon atmosphere, by *N*-*tert*-butyl-α-phenylnitrone as the spin trap. Even though the ESR spectrum does not provide any structural information on the radical intermediate, it clearly demonstrates the formation of such an intermediate from the enediyne in the photochemical reaction. A control experiment under identical conditions but without the enediyne **4a** did not show any ESR signal, thus clearly demonstrating that the observed ESR signal in the presence of **4a** is only due to a free radical intermediate formed by the oxidation of **4a** (Scheme 4, eq 8).

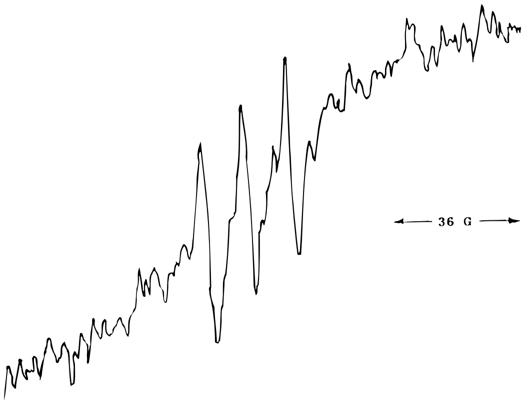
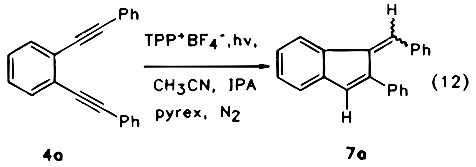


Figure 2. ESR spectrum of the adduct of the radical formed during photolysis of **4a** with *N*-*tert*-butyl-α-phenylnitrone in CH_3CN at rt.

Scheme 5



Similar steps (Scheme 4, eqs 6−9) are likely in the chemical and electrochemical oxidation reactions too after the initial generation of the enediyne radical cation. On the basis of these studies, we conclude that the radical cations of **4a**,**b**, irrespective of the mode of generation, show preponderant tendency to undergo 1,5-mode of cyclization, rather than Bergman cyclization.

The preferred 1,5-mode of cyclization of the radical cation is in sharp contrast to 1,6-Bergman cycloaroma-

---

(11) Barton, D. H. R.; Leclerc, G.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Chem. Commun.* **1972**, 447.

(12) For fluorescence quenching of TPP^+ by **4a** and **4b**, $k_q = 3.39 \times 10^{10}$ and 4.38×10^{10} M^{-1} s^{-1}, respectively. Since TPP^+ is used as the sensitizer, formation of singlet oxygen and superoxide anion radical as intermediates in the photooxygenation can be ruled out.[9]

(13) Jones, G. II; Becker, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 1276. Peacock, N. J.; Schuster G. B. *J. Am. Chem. Soc.* **1983**, *105*, 3632. Takahashi, Y; Sankararaman, S; Kochi, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2954.

tization found in neutral enediynes. Semiempirical (UHF/AM1)[14] and *ab initio* calculations (PMP2/6-31G* using 3-21G optimized geometries)[15,16] on $C_6H_4^{\bullet+}$ isomers suggest a deeper electronic origin. To ionize the enediyne, it is preferable to remove an electron from a π MO of the hexatriene moiety rather than from an in-plane π orbital of the triple bonds. Thus the ground electronic state is derived from a 5 π configuration. The radical cation of 1,4-dehydrobenzene prefers to retain an aromatic π sextet. The SOMO of the system is the antisymmetric combination of the hybrid orbitals at the 1- and 4- carbon centers. Hence cycloaromatization of the enediyne radical cation to 1,4-dehydrobenzene radical cation is an electronically forbidden process. On the other hand, formation of the 1,5-cyclization product, viz., 3,6-dehydrofulvene radical cation is predicted to be allowed. The ground state of the latter is computed to have 5 π electrons. An alternative 6 π state was computed to be consistently higher in energy at all theoretical levels used (ΔE AM1: 25.4, PUHF/6-31G*: 36.8, PMP2/6-31G*: 20.7 kcal/mol).[17] The reduced aromaticity in the 6 π form of fulvene as well as the possibility of reduced electron repulsion due to more effective Fermi correlation in the 5 π state probably contribute to the preferred electronic configuration. Consistent with the above electronic structures, attempts to locate a transition state for the 1,6-cyclization mode led to discontinuous surfaces and convergence difficulties, while a smooth energy surface with a productlike transition state could be located at both AM1 and 3-21G levels for the allowed 1,5-cyclization process.[17]

Conclusions

The radical cations of aryl-substituted enediynes **4a**,**b** generated by a variety of methods prefer to undergo 1,5-cyclization unlike their neutral counterparts. The 1,5-cyclization mode of the radical cation is suggested to be determined by electronic state symmetry.

Experimental Section

Photooxidation. A solution of **4a** (0.2 g, 0.72 mmol) and $TPP^+BF_4^-$ (0.028 g, 0.072 mmol) in CH_3CN (10 mL) was photolyzed in a Pyrex tube using the output from a 450 W Hanovia lamp with continuous bubbling of oxygen. During photolysis, the solution turned from yellow to dark red. After 30 h, solvent was evaporated and the crude was separated by column chromatography on silica gel (60−120 mesh). Elution with hexane yielded the unreacted **4a** (0.12 g, 0.43 mmol) followed by elution with hexane−ethyl acetate (95:5 v/v) gave **5a** (0.067 g, 0.22 mmol, 76% based on unrecovered **4a**). Photooxidation of **4b** was also carried out by the same procedure to yield **5b** in 78% yield.

Chemical Oxidation. A blue-colored solution of $TBPA^+SbCl_6^-$ (0.006 g, 7.4 × 10^{-6} mol) in dry CH_2Cl_2 (15 mL) was cooled to −78 °C, and then **4b** (0.025 g, 0.075 mmol) was added. The mixture was stirred at −78 °C with continuous bubbling of oxygen for 3 h to yield **5b** in 60% yield.

Electrochemical Oxidation. Cyclic voltammetry and bulk electrolysis of **4a**,**b** were studied on a BAS 100A Electrochemical Analyzer using platinum electrodes and SCE as reference electrode. In a divided cell a solution containing **4b** (0.1 g, 0.3 mmol) and tetraethylammonium perchlorate (TEAP) (0.7 g) in CH_3CN (30 mL) was electrolyzed with continuous bubbling of oxygen at a constant potential of +1.5 V vs SCE until the current dropped to a low constant value (1 h). During electrolysis, the yellow solution turned dark red. Usual workup followed by purification by preparative TLC on silica gel yielded **5b** (0.098 g, 0.26 mmol, 88%) as dark red gummy solid. From the coulometry the actual current consumed was found to be 4 C. Similarly, the oxidation of **4a** was carried out at a constant potential of +1.8 V vs SCE.

3-Benzoyl-2-phenylindenone (5a): IR (CCl_4) 1715, 1669 cm^{-1}; UV-vis ($CHCl_3$) $\lambda_{max}(\epsilon)$ = 435 (585), 330 (sh, 1800), 260 (31769), 235 nm (sh, 21660); ^1H NMR ($CDCl_3$) δ = 7.9 (m, 2H), 6.8−7.6 (m, 12H); ^{13}C NMR ($CDCl_3$) δ = 196 (s), 194.6 (s), 150.4 (s), 144.0 (s), 134.4 (d), 131.2 (d), 130.3 (s), 130.2 (d), 129.7 (s), 129.5 (s), 129.3 (d), 128.9 (d), 128.8 (d), 128.7 (s), 128.3 (d), 127.9 (d), 123.9 (d), 121.8 (d); MS (70 eV) *m/z* 310 (100) [$M^{\bullet+}$], 282 (56), 253 (24), 205 (72), 177 (65), 151 (45), 125 (38), 105 (63), 77 (61); HRMS calcd for $C_{22}H_{14}O_2$ 310.09938, found 310.09948.

3-(4-Methoxybenzoyl)-2-phenylindenone (5b): IR (CCl_4): 1712, 1654 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (ϵ) = 465 (1899), 270 (33636), 235 nm (15037); ^1H NMR ($CDCl_3$) δ = 7.92 (d, 2H, J = 9.3 Hz), 7.57 (d, 1H, J = 6.9 Hz), 7.43 (d, 2H, J = 9.0 Hz), 7.34 (apparent t, 1H, J = 8.0 Hz), 7.25 (apparent t, 1H, J = 7.3 Hz), 6.97 (d, 1H, J = 7.3 Hz), 6.83 (d, 2H, J = 9.3 Hz), 6.77 (d, 2H, J = 9.3 Hz), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 196.7 (s), 193.2 (s), 164.6 (s), 160.1 (s), 149.1 (s), 144.6 (s), 134.4 (d), 133.4 (s), 131.9 (d), 130.8 (d), 129.5 (s), 128.9 (d), 128.2 (s), 123.7 (d), 122.4 (s), 121.4 (d), 114.2 (d), 113.9 (d), 55.5 (q), 55.2 (q); MS (70 eV) *m/z* 370 (6.5) [$M^{\bullet+}$], 194 (16), 163 (100), 149 (24), 135 (15), 85 (18), 83 (29), 77 (16); HRMS calcd for $C_{24}H_{18}O_4$ 370.12054, found 370.11976.

Photoreduction of 4a to 2,8-Diphenylbenzofulvene (7a). A mixture of **4a** (0.2 g, 0.72 mmol) and $TPP^+BF_4^-$ (0.02 g, 0.05 mmol) in CH_3CN (10 mL) and isopropyl alcohol (5 mL) was photolyzed in a Pyrex tube for 26 h under N_2 atmosphere. During the photolysis, the solution turned dark yellow. After removal of the solvent, the crude product was purified by column chromatography on silica gel using hexane as the eluant to yield unreacted **4a** (0.075 g), *cis*-2,8-diphenylbenzofulvene (*cis*-**7a**) (0.02 g) as a yellow solid [mp 129 °C (lit.[18] 129−131 °C)] and *trans*-2,8-diphenylbenzofulvene (*trans*-**7a**) (0.04 g) as a yellow liquid. The products were characterized by the comparison of the IR, UV, ^1H-NMR spectral data with the literature[18] and also by mass spectral data.

Spin Trapping Experiment. A solution of **4a** (0.01 g, 0.035 mmol), $TPP^+BF_4^-$ (1 mg, 0.0026 mmol), and *N*-*tert*-butyl-α-phenylnitrone (0.05 g, 0.28 mmol) in CH_3CN (5 mL) was photolyzed for 1 h in a Pyrex tube under Ar atmosphere, and the ESR spectrum of the photolysate was recorded at rt. From the ESR spectrum of the radical adduct (Figure 2) the g value and a_N were calculated as 2.00416 and 12.0 G, respectively. A control experiment was carried out under identical conditions as above but without the enediyne **4a**. The photolysate under this condition did not show the ESR spectrum.

Acknowledgment. Financial support from DST, New Delhi, is gratefully acknowledged. We thank

---

[14] Stewart, J. J. P. *J. Comput. Aided Des.* **1990**, *4*, 1.

[15] Spin-projected Moller-Plesset theory is known to be more reliable in estimating energetics of species with varying degrees of contamination; see, Schlegel, H. B. *J. Phys. Chem.* **1988**, *92*, 3075. Sosa, C.; Schlegel, H. B. *J. Am. Chem. Soc.* **1987**, *109*, 4193.

[16] Calculations were carried out using the Gaussian 92 series of programs (Revision E.3): Frisch, M. J.; Trucks, G. W.; Head-Gordon, M; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J, J. P.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1992.

[17] The computed AM1 heats of formation (kcal/mol) and *ab initio* total energies (UHF/3-21G, PUHF/6-31G*, and PMP2/6-31G* in hartree) of radical cations, respectively, are the following: enediyne, 320.2, (227.82730, 229.12994, 229.80966); 1,4-dehydrobenzene, 341.5, (227.81961, 229.07806, 229.82352); 3,6-dehydrofulvene (5π), 363.1, (227.79831, 229.15994, 229.77390); 3,6-dehydrofulvene (6π), 388.5, (227.77629, 229.10135, 229.74095); transition state between enediyne and 3,6-dehydrofulvene (5π), 377.9, (227.74429, 229.02437, 229.74796).

[18] Whitlock, H. W. Jr; Sandvick, P. E; Overman, L. E; Reichardt, P. B. *J. Org. Chem.* **1969**, *34*, 879.

[19] The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Regional Sophisticated Instrumentation Centre, IIT, Madras for spectroscopic and X-ray crystallographic data. We gratefully acknowledge help from Dr. P. Ramamurthy, Department of Inorganic Chemistry, University of Madras, with the ESR experiments.

Supporting Information Available: The UHF/AM1 and UHF/3-21G optimized geometries and energies of radical cations of enediyne, 1,4-dehydrobenzene, 3,6-dehydrofulvene (5π and 6π configurations) and transition state between enediyne and 3,6-dehydrofulvene (4 pages). This material is contained in libraries on microfiche, immediately follows this article in this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951524Y

Additions and Corrections

Vol. 60, 1995

Carlos Alvarez-Ibarra,* Aurelio G. Csákÿ, Mercedes Maroto, and M. Luz Quiroga. Diastereoselective Synthesis of Substituted Glutamic Acid Derivatives *via* Michael Additions of *N*-[Bis(methylthio)methylene]glycinates under Solid−Liquid Phase Transfer Catalysis.

Page 6700. We failed to include the work of Hoppe and co-workers on the first utilizations of *N*-[bis(methylthio)methylene]glycine ester enolate for glycine anion reagents. They reported the deprotonation of **1a** by means of KO^{t}Bu, its (±)-mono- and (±)-dialkylation, and, as well, a deprotection procedure (HCO_2H/H_2O_2). The representative articles are as follows: (1) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 426. (2) Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.

JO9649611

Carlos Alvarez-Ibarra,* Aurelio G. Csákÿ, Raquel Maroto, and M. Luz Quiroga. Asymmetric Alkylation of 8-Phenylmenthyl *N*-[Bis(methylthio)methylene]glycinate Enolates. Synthesis of D- and L-α-Amino Acids from a Single Chiral Precursor.

Page 7934. We failed to include the work of Hoppe and co-workers on the first utilizations of *N*-[bis(methylthio)methylene]glycine ester enolate for glycine anion reagents. They reported the deprotonation of **1a** by means of KO^{t}Bu, its (±)-mono- and (±)-dialkylation, and, as well, a deprotection procedure (HCO_2H/H_2O_2). The representative articles are as follows: (1) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 426. (2) Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.

JO954034E