hence (−)-albene must be 1*S*,7*R*! Only two of the four tricyclo[5.2.1.0^{2,6}]dec-3-ene isomers under consideration[2] could have given the results reported, one with exo methyl groups and one with endo methyls. The norcamphor unit in the keto nitrile degradation product which showed the negative Cotton effect limited the absolute stereochemical assignment for (−)-albene to I or 1; as soon as it became known that the methyls in (−)-albene are endo,[5] the absolute stereochemistry of (−)-albene might have been seen to be as shown in 1. If (−)-albene were the mirror image of 1, as proposed by Kreiser and co-workers,[10,18] the keto nitrile from the degradation of albanone would have been *ent*-**9**, which would have shown a positive Cotton effect, and the degradation findings of the Prague group would have been inexplicable. The absolute stereochemistry of (−)-albene one can deduce from the present reinterpretation of the 1972 degradative work[2] agrees with our chemical correlation[14] between a chiral synthetic precursor to both (+)-albene and (−)-β-santalene: (−)-albene is the 1*S*,2*S*,6*S*,7*R* isomer of 2-*endo*,6-*endo*-dimethyltricyclo-[5.2.1.0^{2,6}]dec-3-ene, structure 1.

Experimental Section

Analytical gas chromatographic analyses were done using a 0.2-mm i.d. 12.5-m cross-linked dimethyl silicone fused silica capillary column, a Hewlett-Packard (HP) 5790 instrument, and a HP 3390A reporting integrator; preparative separations were accomplished with a 0.63 cm × 1 m silicone QF-1 on Chromosorb W column and a Varian Aerograph A90-P3 instrument. The GC/MS data were secured with HP 5890, 5970B, and 9836 instruments and computer. Both ^{1}H and ^{13}C NMR spectra were obtained on a General Electric GN 500 MHz for ^{1}H (125.76 MHz for ^{13}C) spectrometer.

3-*exo*-(Cyanoethyl)-3-*endo*-methylbicyclo[2.2.1]heptan-2-one. To a stirred solution of 3-*endo*-methylbicyclo[2.2.1]heptan-2-one[16] (1.69 g, 14 mmol), morpholine (4.73 g, 54 mmol; dried over 4A molecular sieves) and *o*-xylene (50 mL; dried over sodium) at 0 °C was added dropwise over a 20-min period 1.29 g (6.8 mmol) of $TiCl_4$.[19,20] The stirred reaction mixture was allowed to warm to room temperature and, after 36 h, was filtered. Distillation at atmospheric pressure left a residue, which, upon Kugelrohr distillation at 16 torr and a bath temperature of 90–95 °C, gave 1.42 g of a clear yellow oil. This impure enamine, 20 mL of absolute ethanol, and 20 mL of freshly distilled acrylonitrile were combined and heated to reflux for 24 h.[20] The reaction mixture was diluted with 10 mL of water, heated to reflux 1 h, cooled, and extracted with ether. The ethereal extract was washed with 1 N hydrochloric acid, dried over magnesium sulfate, and filtered. Concentration and Kugelrohr distillation at 16 torr and a bath temperature of 140–150 °C gave 3-*exo*-(cyanoethyl)-3-*endo*-methylbicyclo[2.2.1]heptan-2-one (200 mg; 94% purity according to capillary GC analysis).

Preparative gas chromatography gave a colorless sample of ketone **9** estimated to be 99.8% pure; mass spectrum (70 eV), *m/e* (relative intensity) 177 (M$^+$, 13), 136 (8), 134 (9), 108 (51), 93 (20), 81 (29), 67 (100), 55 (22), 53 (20), 41 (56), 39 (44); ^{13}C NMR ($CDCl_3$) δ 220.17, 119.83, 50.03, 48.86, 43.99, 34.85, 31.09, 24.71, 23.11, 17.94, 12.53; ^{1}H NMR CH_3 singlet at δ 1.024; IR (CCl_4) 2250, 1740 cm^{-1}.

A sample of "keto nitrile IX"[2] sent from Prague, bp 120 °C (12 torr), had an identical vapor-phase chromatographic retention time (11.56 min, column helium flow 1 mL/m, temperature increase 7 °C/m from 80 to 250 °C): mass spectrum, *m/e* 177 (M$^+$, 4), 136 (6), 134 (7), 108 (53), 93 (22), 81 (31), 67 (100), 55 (23), 53 (21), 41 (57), 39 (45); ^{13}C NMR δ 220.19, 119.80, 50.04, 48.85, 44.03, 34.85, 31.09, 24.69, 23.10, 17.95, 12.53; ^{1}H NMR CH_3 singlet at 1.024; IR[2] 2249, 1741 cm^{-1}.

Acknowledgment. We thank Professor V. Herout of the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, Prague, for his supportive interest in the present work and for providing us with a sample of "keto nitrile IX".[2] We are indebted to the National Science Foundation for partial support of our work on (−)-albene.

Registry No. 1, 38451-64-8; **9**, 100759-23-7; (1*R*,4*R*)-3-*endo*-methylbicyclo[2.2.1]heptan-2-one, 100759-24-8; (1*R*,4*S*)-2-(*N*-morpholino)-3-methylbicyclo[2.2.1]hept-2-ene, 100606-56-2.

(18) Synthesis is not necessarily a final proof of structure or of absolute stereochemistry, indeed, neither is X-ray crystallography. For recent perspectives on these issues, see: Kelly, T. R.; Saha, J. K.; Whittle, R. R. *J. Org. Chem.* **1985**, *50*, 3679–3685. Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339–4341.

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Lanthanides in Organic Synthesis. 2. Reduction of α-Heterosubstituted Ketones

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Reduction of α-heterosubstituted ketones has long been recognized as a useful synthetic transformation. Several distinct classes of heterosubstituted ketones have been used in such transformations in organic synthesis, and many different reducing agents have been utilized to accomplish the desired reductions. For example, a number of reagents have been developed for reduction of α-halo ketones to the corresponding unsubstituted ketones.[1] Keto sulfides, sulfoxides, and sulfones have found considerable utility in organic synthesis, particularly in regioselective ketone alkylation reactions. Generally, these processes necessitate removal of the sulfur-containing functional groups subsequent to alkylation. Several methods have therefore been devised for this purpose.[2] Reduction of α-oxygenated ketones has also seen substantial use as a routine synthetic transformation.[3]

Current methods that achieve these reductions often require rather harsh reaction conditions. Among the more widely utilized methods are zinc metal[1h,i,3a,c,e] and chromous ion induced[1b,3f] reductions. Both of these methods involve

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0022-3263/86/1951-1135$01.50/0

Table I. Reduction of α-Oxygenated Ketones with Samarium Diiodide

$$C_5H_{11}C(=O)CHXC_5H_{11} \xrightarrow[\text{THF/MeOH}\ -78\ ^\circ C]{2SmI_2} C_5H_{11}C(=O)C_6H_{13}$$

entry	X	% GC yield
1	OAc	(75)[a]
2	$OSiMe_3$	98
3	$OCOCH_2Ph$	100
4	OTs	94
5	OH	29

[a] Isolated yield.

use of acidic media for extended reaction times, often at elevated temperatures. Only a limited array of functionality can be tolerated under such conditions. Other methods (e.g., dissolving metal reductions,[2b,c,3b] phosphorus-[4] or silicon-based[5] reducing agents, as well as many other reported methods[6]) either lack demonstrable chemoselectivity or have not been thoroughly investigated to ascertain the scope of their capabilities.

Our interest in applications of lanthanide derivatives in organic synthesis[7] led us to investigate the use of samarium diiodide (SmI_2) as a reductant for α-heterosubstituted ketones. Several features of SmI_2 reductions exhibited in previous studies[8] led us to conclude it would be an ideal reagent for these reductions. Samarium diiodide is soluble in tetrahydrofuran (THF) and therefore does not require use of aqueous media for effective reduction. Reductions take place under essentially neutral conditions. This, combined with the high chemoselectivity exhibited by SmI_2, assured us that a number of functional groups could be tolerated under the reaction conditions. In fact, we have discovered that reduction of a broad spectrum of α-heterosubstituted ketones takes place in high yield under extremely mild conditions with SmI_2, making it the reagent of choice in most cases for this type of transformation.

Results and Discussion

As shown in Table I, a wide range of α-oxygenated ketones undergoes reduction at −78 °C on addition of the substrate in THF/MeOH to a solution of SmI_2 in THF. As far as we are able to ascertain, reduction is instantaneous. Simple workup of the reaction mixture allows generation of ketones in yields approaching quantitative. Only α-hydroxy ketones provide disappointingly low yields (entry 5).[9] This problem can be alleviated to some extent by simply adding a solution of the α-hydroxy ketone and acetic anhydride in THF to SmI_2. Moderate yields of ketone can therefore be obtained without preparing and isolating the acetate (or another derivative) in a separate step.

$$C_2H_5C(=O)CH(OH)C_2H_5 \xrightarrow[\text{THF/}-78\ ^\circ C]{2SmI_2/Ac_2O} C_2H_5C(=O)C_3H_7$$
59%

In addition to the functional groups listed in Table I, α-alkoxy ketones are also readily reduced under the reaction conditions. Thus, benzoin methyl ether is converted to deoxybenzoin in quantitative yield under the same reaction conditions.

$$PhC(=O)CH(OMe)Ph \xrightarrow[\text{THF/MeOH}\ -78\ ^\circ C]{2SmI_2} PhC(=O)CH_2Ph$$
100% isolated yield

As expected, the reaction has proven to be exceedingly chemoselective. Primary iodides are readily accommodated under the reaction conditions. Remarkably, the reaction can be performed in the presence of isolated ketones. Reaction of a 1:1 mixture of 7-acetoxydodecan-6-one and cyclohexanone with 2 equiv of SmI_2 leads to nearly quantitative detection of both the desired product and cyclohexanone. No cyclohexanol could be detected by gas chromatographic analysis.

$$PhC(=O)CH(OAc)(CH_2)_3I \xrightarrow[\text{THF/MeOH}\ -78\ ^\circ C]{2SmI_2} PhC(=O)(CH_2)_4I$$
87% isolated yield

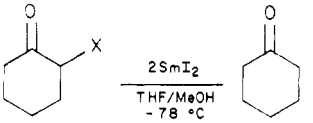
$$C_5H_{11}C(=O)CH(OAc)C_5H_{11}/c\text{-}C_6H_{10}O \xrightarrow[\text{THF/MeOH}\ -78\ ^\circ C]{2SmI_2} \underset{92\%}{C_5H_{11}C(=O)C_6H_{13}} + \underset{95\%}{c\text{-}C_6H_{10}O} + \underset{0\%}{c\text{-}C_6H_{11}OH}$$

We envision that the initial steps in the reaction mechanism closely resemble that of dissolving metal reductions of ketones.[8c,10] Thus, reaction of SmI_2 with the ketone generates a ketyl, which is rapidly protonated by methanol. Further reduction by the second equivalent of SmI_2 produces a carbanion, inducing a β-elimination. Tautomerization of the resulting enol provides the observed ketone.

In addition to α-oxygenated derivatives, a number of other α-substituted ketones are readily reduced. These include α-halosubstituted ketones and a variety of α-thiosubstituted ketones (Table II).

Curiously, it appears that only one of the diastereomeric sulfoxides reacts under standard conditions. The other

Table II. Reduction of α-Heterosubstituted Cyclohexanones with Samarium Diiodide



entry	X	% GC yield of cyclohexanone
1	Cl	100
2	SPh	76
3	S(O)Ph	64[a]
4	SO_2Ph	88
5	HgCl	94

[a] Starting material detected by GC analysis.

(4) (a) Borowitz, I. J.; Grossman, L. I. *Tetrahedron Lett.* **1962**, 471. (b) Borowitz, I. J.; Kirby, K. C., Jr.; Rusek, P. E.; Lord, E. *J. Org. Chem.* **1969**, *34*, 2687. (c) Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 1431. (d) Borowitz, I. J.; Virkhaus, R. *J. Am. Chem. Soc.* **1963**, *85*, 2183.

(5) (a) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531. (b) Ho, T.-L. *Synth. Commun.* **1981**, *11*, 101. (c) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

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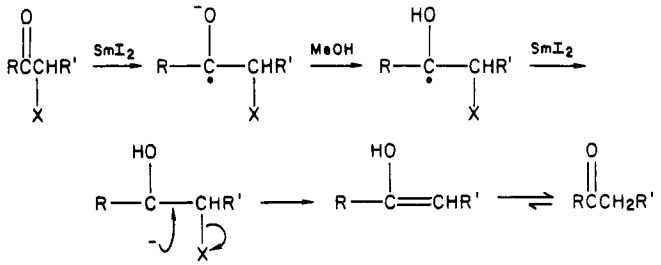
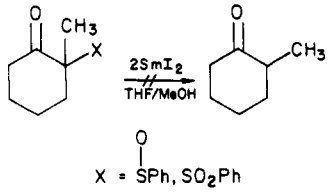
(9) (a) Cope, A. C.; Barthel, J. W.; Smith, R. D. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 218. (b) Ho, T.-L.; Wong, C. M. *Synthesis* **1975**, 161. (c) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 665.

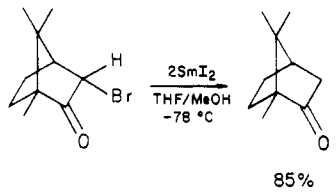
(10) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 399.



diastereomer is detected intact by gas chromatographic analysis (Table II, entry 3). Studies designed to determine whether or not enolization was competing with reduction in these instances led us to uncover one limitation of the reaction. Reduction of 2-methylcyclohexanone derivatives with SmI_2 led to complex product mixtures in which very little of the desired 2-methylcyclohexanone could be detected. Further studies in this area are in progress.



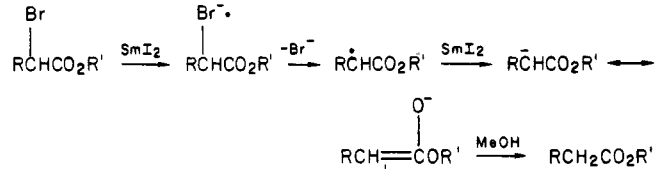
Otherwise, reduction is unaffected by steric crowding about the reaction center. Thus, even a ketone as highly hindered as 3-bromocamphor is reduced with ease under the standard reaction conditions. α-Halo esters can be



reduced under the same reaction conditions utilized for α-heterosubstituted ketones; however, α-acetoxy esters are inert. This implies a different mechanism for the reduction of α-haloesters than the corresponding α-heterosubstituted ketones. Since esters do not undergo reduction with SmI_2,[8b] the α-halo esters presumably react via direct reduction of the halide.

$$(CH_3)_2CBrCO_2Et \xrightarrow[\text{THF/MeOH}]{2SmI_2} (CH_3)_2CHCO_2Et$$
$$-78\ ^\circ C,\ 98\%$$

$$CH_3CH(OAc)CO_2Et \xrightarrow[\text{THF/MeOH/}-78\ ^\circ C]{2SmI_2} \text{no reaction}$$



Conclusions

Samarium diiodide has proven to be an exceptional reagent for the reduction of α-heterosubstituted ketones as well as α-halo esters. It is general in its scope, readily reducing a wide range of substrates in high yields. The reduction takes place with extreme ease under essentially neutral conditions and is therefore tolerant of a wide range of functional groups. As a consequence, SmI_2 appears to be the reagent of choice for the accomplishment of many such reductions.

Experimental Section

All boiling points and melting points are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer using $CDCl_3$ or CCl_4 as the solvent and $CHCl_3$ (δ 7.2) or Me_4Si (δ 0.00) as the internal standard. ^{13}C NMR spectra were recorded on a Magnachem A-200 spectrometer using $CDCl_3$ as both solvent and internal standard (δ 77.00). Gas–liquid chromatographic analyses were conducted on GLC columns (10 ft × $^1/_8$ in.) packed with Carbowax 20M (3% on AW-DMCS Chromosorb W) or SE-30 (5% on AW-DMCS Chromosorb W). Flash chromatography was carried out under standard procedures.[11] Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon immediately prior to use. Methanol was dried over 3-Å molecular sieves. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for the handling of air-sensitive materials.[12]

Reduction of α-Heterosubstituted Carbonyl Substrates with SmI_2. General Procedure. To a slurry of the Sm powder[13] (0.32 g, 2.1 mmol) in THF (2 mL) at room temperature was added a solution of 1,2-diiodoethane (0.56 g, 2.0 mmol) in THF (2 mL). The resultant olive-green slurry was stirred at ambient temperature for 1 h, after which time the resulting dark blue slurry of SmI_2 formed was cooled to −78 °C (dry ice/acetone) and treated with a solution of the α-heterosubstituted carbonyl substrate (1.0 mmol) in MeOH (1 mL) and THF (2 mL). The resultant brown mixture was stirred for 10 min at −78 °C, warmed to room temperature, and then poured into saturated aqueous K_2CO_3. The aqueous phase was extracted with Et_2O (5 × 10 mL) and the combined extracts were dried ($MgSO_4$).

Reduction of 7-Acetoxy-6-dodecanone. Using the general procedure described above, 7-acetoxy-6-dodecanone (0.24 g, 1.0 mmol) was reduced to provide 0.14 g (75%) of 6-dodecanone[14] after Kugelrohr distillation: bp 115 °C (8 mmHg); IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (t, J = 4.5 Hz, 4 H), 1.8–1.0 (m, 14 H), 0.8 (t, J = 6 Hz, 6 H); ^{13}C NMR δ 211.65, 42.78, 42.71, 31.59, 31.40, 28.90, 23.82, 23.53, 22.46 (2 C), 13.99, 13.89.

Reduction of 4-Hydroxy-3-hexanone. To a slurry of SmI_2 (2.0 mmol) in THF at −78 °C prepared as described above was added a solution of 4-hydroxy-3-hexanone (0.12 g, 1.0 mmol) and acetic anhydride (0.19 mL, 2.0 mmol) in THF (2 mL). The resultant blue-green mixture was warmed to room temperature, stirred for 30 min, poured into saturated aqueous K_2CO_3 (10 mL), and worked up as described above. GLC analysis (5% SE-30, 50 °C) revealed the presence of 0.59 mmol (59%) of 3-hexanone.

Reduction of Benzoin Methyl Ether. With the general procedure described above, benzoin methyl ether (0.24 g, 1.0 mmol) was reduced to provide 0.21 g (100%) of deoxybenzoin[15] after flash chromatography (elution with 1:1 hexanes/ethyl acetate): mp 56–57 °C; IR (CCl_4) 1700, 1610, 1590, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9 (d, J = 7.2 Hz, 2 H), 7.4–7.1 (m, 8 H), 4.1 (s, 2 H); ^{13}C NMR δ 197.40, 136.38, 134.20, 133.00, 129.30 (2 C), 128.48 (4 C), 126.71, 45.30.

Reduction of 2-Acetoxy-5-iodo-1-phenyl-1-pentanone. Using the general procedure described above, 2-acetoxy-5-iodo-1-phenyl-1-pentanone (0.35 g, 1.0 mmol) afforded 0.24 g (87%) of 5-iodo-1-phenyl-1-pentanone after recrystallization from Et_2O; mp 72–73 °C; IR 1690 cm^{-1}; ^1H NMR (CCl_4) δ 7.9 (m, 2 H), 7.4 (m, 3 H), 3.2 (t, J = 6 Hz, 2 H), 2.9 (t, J = 7.5 Hz, 2 H), 1.8 (m, 4 H); ^{13}C NMR δ 199.26, 136.63, 132.90, 128.21 (2 C), 127.84 (2 C), 37.09, 32.85, 24.92, 6.12; exact mass spectral analysis, calcd for $C_{11}H_{13}IO$ 288.0012, found 288.0011.

Competition Study. To a slurry of SmI_2 (2.0 mmol) in THF at −78 °C, prepared as described above, was added a solution of 7-acetoxy-6-dodecanone (0.24 g, 1.0 mmol) and cyclohexanone (0.10 g, 1.0 mmol) in MeOH (1 mL) and THF (2 mL). The resultant brown mixture was stirred for 10 min, warmed to room

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Brown, H. C. "Organic Syntheses via Boranes"; Wiley: New York, 1975.
(13) Samarium powder was obtained from Research Chemicals, Phoenix, AZ 85063.
(14) Literature: bp 88–90 °C (3 mmHg). Okamoto, Y.; Sakurai, H. *Kogyo Kagaku Zasshi* **1967**, *70*, 1178; *Chem. Abstr.* **1968**, *68*, 39725u.
(15) Literature: mp 55–56 °C. Allen, C. F. H.; Barker, W. E. In "Organic Syntheses"; Adams, R., Ed.; Wiley: New York, 1932; p 16.

temperature, and worked up as described above. GLC analysis (SE-30, 50–200 °C at 40 °C/min) revealed the presence of (0.92 mmol, 92%) 6-dodecanone and 0.95 mmol (95%) of cyclohexanone. No cyclohexanol could be detected.

Acknowledgment. We thank the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM 31013) for support of this work. An instrumentation grant from the National Institutes of Health (RR 01709) is also gratefully acknowledged.

Substituent Effects on Nitroxide Hyperfine Splitting Constants

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Substituent effects on the ESR hyperfine splitting constants (hfsc) in a variety of radicals containing substituted phenyl moieties have been investigated.[1-19] In theory, measurements of this type should accurately reflect the changes in electron density due to substituent variation and should, therefore, correlate with the Hammett σ constants;[1,20] in fact, however, only marginal correlations are observed. Since the substituted phenyl moiety was directly bound to a site of high spin density in nearly all of the radical systems studied, some of the deviations have been attributed, quite reasonably, to resonance effects.[1,3] The present report shows that an excellent correlation of nitrogen hfsc can be achieved by using Hammett σ parameters alone when a nitroxide radical center and substituted phenyl moiety are insulated from one another by a saturated carbon atom.

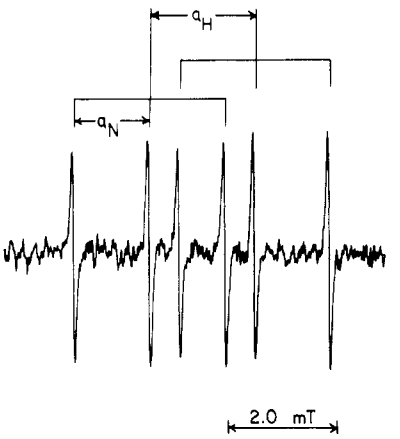


Figure 1. A typical spin adduct ESR spectrum showing the nitrogen and hydrogen hfsc. In this case, the spin adduct is that of the unsubstituted phenyl radical with DMPO. The instrument parameters are as follows: microwave power, 20 mW; modulation frequency, 100 kHz; modulation amplitude, 0.025 mT; gain, 1.25 $\times 10^5$; time constant, 20 ms; scan range, 7.0 mT; scan time, 50 s; number of scans, 3.

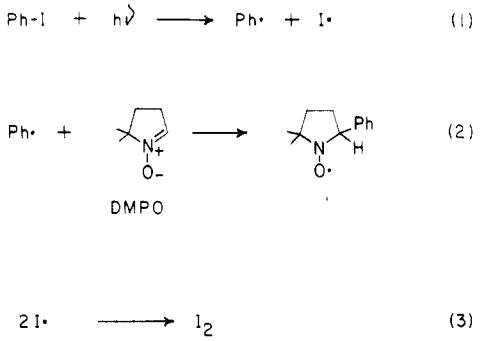
Table I. Hyperfine Splitting Constants of Substituted Phenyl Spin Adducts of DMPO in Benzene

substituent	σ^a	$a_N{}^b$	$a_H{}^b$
p-OCH_3	−0.27	1.393 ± 0.002	1.951 ± 0.003
p-CH_3	−0.17	1.391 ± 0.003	1.940 ± 0.002
m-CH_3	−0.07	1.388 ± 0.003	1.931 ± 0.003
H	0.00	1.382 ± 0.001	1.927 ± 0.002
m-OCH_3	0.12	1.383 ± 0.001	1.897 ± 0.002
p-Cl	0.23	1.382 ± 0.002	1.936 ± 0.001
m-Cl	0.37	1.379 ± 0.002	1.924 ± 0.002
m-CF_3	0.43	1.377 ± 0.002	1.945 ± 0.004
p-CN	0.66	1.375 ± 0.002	1.930 ± 0.002
m-NO_2	0.71	1.373 ± 0.002	1.956 ± 0.004
p-NO_2	0.78	1.370 ± 0.003	1.933 ± 0.007

[a] σ substituent constants from: Leffler, J. E.; Grunwald, E. In "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; p 173. [b] In units of mT; deviations expressed as 95% confidence limits, $(t_{0.05,1})$(standard deviation)$/n^{0.5}$.

Results and Discussion

When a benzene solution of phenyl iodide or one of its substituted derivatives and the spin trap 5,5-dimethyl-1-pyrroline N-oxide (DMPO) is photolyzed in the cavity of an ESR instrument, a six-line spectrum characteristic of a phenyl radical spin adduct of DMPO is immediately observable (see Figure 1 for a typical ESR spectrum). This result can be accounted for by the mechanism shown in eq 1–3. Photolysis causes the rupture of the phenyl–iodine



bond, giving a phenyl radical and atomic iodine (eq 1). The phenyl radicals are then rapidly scavenged by the spin trap (eq 2), while the iodine atoms combine (eq 3). Both the

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