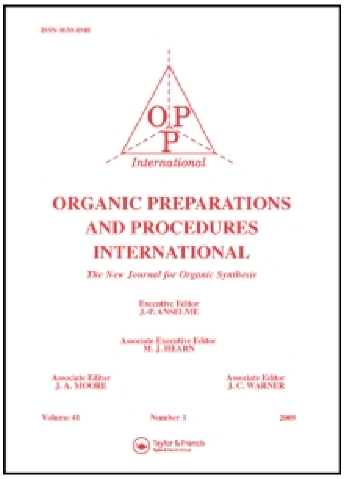


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF TWO PHOTOLABILE BENZYL MANGANESE DERIVATIVES INCORPORATING A GEOMETRICALLY INACCESSIBLE RADICAL TRAP

John F. W. Keana[a]; Sovitj Pou[a]
[a] Department of Chemistry, University of Oregon, Eugene, OR

To cite this Article Keana, John F. W. and Pou, Sovitj(1989) 'SYNTHESIS OF TWO PHOTOLABILE BENZYL MANGANESE DERIVATIVES INCORPORATING A GEOMETRICALLY INACCESSIBLE RADICAL TRAP', Organic Preparations and Procedures International, 21: 3, 303 — 308

To link to this Article: DOI: 10.1080/00304948909356383

URL: http://dx.doi.org/10.1080/00304948909356383

ORGANIC PREPARATIONS AND PROCEDURES INT. 21(3), 303-308 (1989)

SYNTHESIS OF TWO PHOTOLABILE BENZYL MANGANESE DERIVATIVES INCORPORATING A GEOMETRICALLY INACCESSIBLE RADICAL TRAP

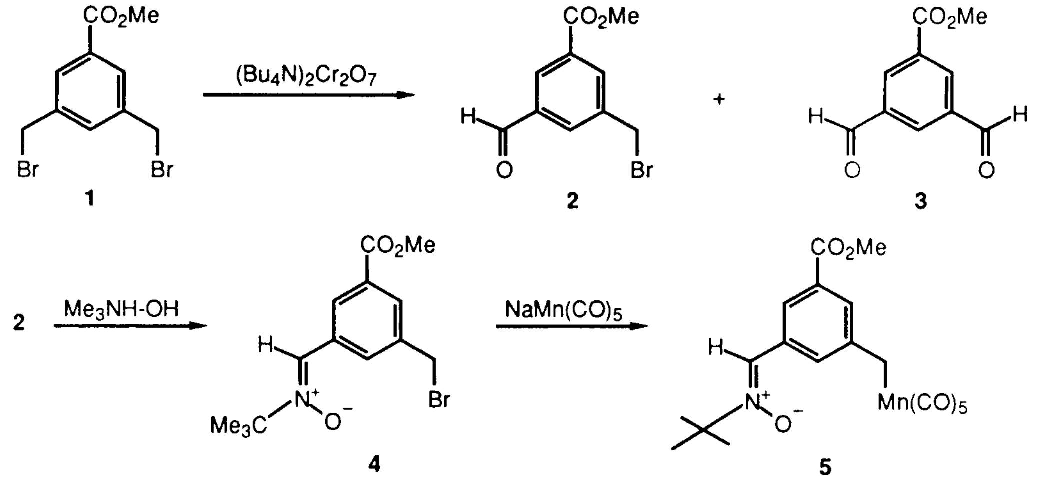
John F. W. Keana* and Sovitj Pou

Department of Chemistry,
University of Oregon, Eugene, OR 97403

With an eye toward the development of a new series of free radical-based photolabels,[1] we required molecules which contained a photolabile bond as the free radical source and a geometrically inaccessible radical trap. Herein we report the synthesis of two prototype molecules. The relatively low bond dissociation energy (DE < 40 Kcal/mole) for carbon-manganese homolysis,[2] and the ease of synthesis of benzyl manganese pentacarbonyl itself led us to select this unit as the photolabile component of both molecules. For one of the prototypes, a nitrone[3] was chosen as the spin trap,[4] while a stable nitroxide free radical[5] served this function in the other molecule.

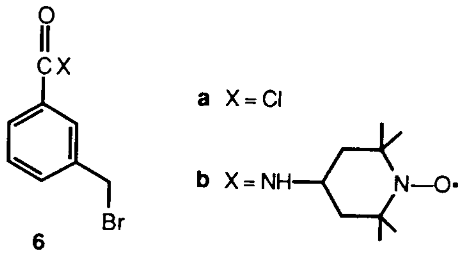
Our first target was benzyl manganese pentacarbonyl nitrone ester 5. In an adaptation of the procedure of Landini and Rolla,[6] dibromo ester 1[7] was treated with bistetrabutylammonium dichromate in refluxing $CHCl_3$, giving the desired 1,3,5-trisubstituted benzene 2 (31%) along with dialdehyde 3 (14%). We note in passing that 1,3,5-substitution patterns involving three different groups on a benzene ring are relatively rare. Thus, ester 2 constitutes a versatile functionally differentiated precursor for other molecules in which reactive groups must be geometrically inaccessible to one another.

The reaction of 2 with one equivalent of the nucleophilic reagent *N-tert*-butylhydroxylamine[8] in the presence of a catalytic amount of *p*-toluenesulfonic acid under anhydrous conditions took place selectively at the aldehyde site, giving 4 (82%) as a colorless oil. Nucleophilic displacement of the bromine atom of 4 by $NaMn(CO)_5$[9] gave the desired man-

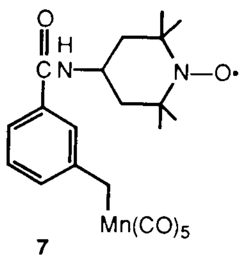


ganese pentacarbonyl nitrone 5 (70%) as white needles. Given that a variety of carbanions react readily with nitrones to give the corresponding α-alkylated *N*-hydroxy compounds,[5] it is noteworthy that the reaction of 4 with $:Mn(CO)_5^-$ occurred with clean displacement of the benzylic bromine atom. The IR spectrum of 5 displayed strong characteristic absorptions at 2108 cm^{-1} and 2017 cm^{-1} corresponding to CO bound to manganese.[10] The ^{1}H NMR spectrum of 5 included a two-proton singlet at 2.42 ppm for the $ArCH_2$-Mn protons.[10]

The synthesis of nitroxide benzyl manganese pentacarbonyl 7 was accomplished as follows. Treatment of acyl chloride 6a[11] with two equivalents of 4-amino-2,2,6,6-tetramethyl-1-piperidinoxy gave amide 6b in 96% yield as a red solid. Nitroxide 6b was next allowed to react with $NaMn(CO)_5$ (drybox) to give manganese pentacarbonyl nitroxide 7 in 59% yield as red-orange star-like crystals. Oxidation of the readily oxidized $:Mn(CO)_5^-$ anion by the nitroxide group of 6b was not an important side reaction, in contrast to that of a nitroxide group toward certain carbanions.[12] The IR spectrum of 7 exhibited absorptions at 2110, 2075, and 2000 cm^{-1} characteristic of CO bound to manganese.[10]



6



7

EXPERIMENTAL SECTION

Melting points were determined in a Thomas-Hoover oil bath apparatus and are uncorrected. ^1H NMR spectra were obtained in $CDCl_3$ using a Varian XL-100 or a General Electric QE-300 NMR spectrometer. Chemical shifts reported in δ units with Me_4Si as an internal standard. IR spectra were recorded either on a Beckman IR-10, a Sargent Welch 3-200, or a 5DxB FT-IR infrared spectrometer. X-Band ESR spectra were recorded on a Varian E-line line spectrometer. Mass spectra were recorded on a CEC 21-110B mass spectrometer. Elemental analysis were obtained from Desert Analytics, Tuscon, AZ. Analytical tlc ulitized Merck 60F-254 precoated silica gel plates; spots were visualized under ultraviolet light or by I_2. Preparative tlc ulitized Analtech 1000 μ silica gel plates. Flash chromatography utilized Davasil silica gel grade 633, 200-425 mesh, 60 A (Aldrich). Column chromatography utilized Baker (60-200 mesh) silica gel. $MgSO_4$ was used as the drying agent for organic solutions. Reactions were routinely run under an inert atmosphere of N_2. Reactions involving air-sensitive materials were performed inside an inert-atmosphere (N_2), double-length drybox (Vacuum Atmospheres Company). The O_2 level was maintained at < 1 ppm as indicated by an oxygen analyzer. Air-free transfers were effected by Hamilton gas-tight syringes or needlestock (stainless steel cannula) transfers. When working with light sensitive compounds, all reaction flasks were wrapped with aluminum foil and manipulations were done in subdued light.

Methyl 3-Formyl-5-bromomethylbenzoate (2).-The procedure of Landini and Rolla[6] was adapted. A solution of bromoester 1[7] (1.207 g, 3.75 mmol) and $[(n\text{-}C_4H_9)_4N]_2Cr_2O_7$ (1.747 g, 2.50 mmol) in $CHCl_3$ (10 mL) was refluxed for 1 hr. The resulting heterogeneous black mixture was filtered through a short silica gel column (10 g) using diethyl ether (100 mL) as eluent. The eluent was evaporated to dryness to give 831 mg of crude product as a brown oily solid. This was purified by flash chromatography. Elution first with 1:1 $CHCl_3$-hexanes gave 304 mg of starting 1. Continued elution with 4:1 $CHCl_3$-hexanes gave 300 mg (31%) of 2 as a white solid: ^1H NMR: δ 3.98 (s, 3), 4.56 (s, 2), 8.11 (s, 1), 8.32 (s, 1), 8.46 (s, 1), 10.08 (s, 1); IR ($CHCl_3$) 1722, 1702 cm^{-1}. Two recrystallizations from ether-$CHCl_3$ gave the analytical sample of 2 as long white needles, mp. 95-96°.

Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.70; H, 3.53. Found: C, 46.58; H, 3.49.

Continued elution with $CHCl_3$ gave 101 mg of 3 (14%) as a white solid: mp. 100-101°; ^1H NMR: δ 4.62 (s, 3), 8.56 (s, 1), 8.79 (s, 2), 10.17 (s, 2); IR ($CHCl_3$) 1735, 1705 cm^{-1}; MS, *m/e* (relative intensity) 192(48) (M^+, calcd for $C_{10}H_8O_4$, 192), 161(100), 147(25), 133(61), 75(50), 51(40).

Methyl [3-(*N-tert*-Butylformimidoyl)-5-bromomethyl]benzoate N-oxide (4).-The procedure of Cummins and Coates[13] was adapted. A mixture of bromo aldehyde 2 (129 mg, 0.502 mmol), *N-tert*-butylhydroxylamine[8] (49 mg, 0.55 mmol) *p*-toluenesulfonic acid monohydrate

(2 mg) and $MgSO_4$ (200 mg) in $CHCl_3$ (0.5 mL) was stirred at 25° for 24 hr. The mixture was filtered and the filtrate was evaporated to give 188 mg of oily solid which was purified by preparative tlc (4:1 $CHCl_3$-EtOH, $R_f = 0.4$) to give 33 mg of starting 2 and 100 mg (61%; 82% when adjusted for recovered 2) of 4 as thick oil. This material was of sufficient purity (NMR) for use in the next step: ^1H NMR: δ 1.62 (s, 9), 3.93 (s, 3), 4.53 (s, 2), 7.64 (s, 1), 8.10 (s, 1), 8.52 (s, 1), 8.94 (s, 1).

Pentacarbonylmanganese Sodium.-The procedure of Smith[9] was used. A suspension of $Mn_2(CO)_{10}$ (1.456 g, 3.730 mmol, Stern Co.) and pressed sodium (2.0 g, 87 mmol) in THF (25 mL) was stirred in the drybox for 12 hr. The gray-green solution of $NaMn(CO)_5$ was decanted from the excess of Na into a 40 mL centrifuge tube, which was then septum capped, removed from the drybox, and centrifuged to settle the sodium dispersion. The green solution was transferred via needlestock into a N_2-filled 100 mL flask. The flask was transferred into the drybox, and the solution was concentrated to dryness under vacuum over 24 hr to afford 1.60 g (100%) of a greenish white powder. Care must be taken to avoid O_2 during manipulations outside the drybox.

[3-(*N*-*tert*-Butylformimidoyl)-5-carboxy]-benzylpentacarbonylmanganio Methyl Ester *N*-Oxide (5).-To a solution of $NaMn(CO)_5$ (greenish white powder) (70 mg, 0.32 mmol) in THF (2 mL) in the drybox was added a solution of 4 (89 mg, 0.27 mmol) in THF (2 mL). The solution immediately changed from green to yellow and a white precipitate was formed. The mixture was stirred in the drybox for 15 min, and then it was brought out into the atmosphere and filtered. The filtrate was evaporated and dried under vacuum for 12 hr to give 137 mg of brown oil which was purified by preparative tlc (4:1 ether-pentane, $R_f = 0.4$) to give 83 mg (70%) of 5 as a white solid: ^1H NMR: δ 1.61 (s, 9), 2.42 (s, 2), 3.34 (s, 3), 7.52 (s, 1), 7.83 (s, 1), 8.42 (s, 2); IR ($CDCl_3$) 2108, 2017, 1712 cm^{-1}. Recrystallization from ether-pentane gave the analytical sample of 5 as white needles, mp. 120-121° (turned brown at 115°).

Anal. Calcd for $C_{19}H_{18}MnNO_8$: C, 51.48; H, 4.09; N, 3.16. Found: C, 51.72; H, 4.20; N, 3.12.

(3-Bromomethyl)-benzoyl Chloride (6a).-To a suspension of 3-(bromomethyl)-benzoic acid[14] (1.00 g, 4.70 mmol) in benzene (10 mL) was added distilled thionyl chloride (1.7 mL, 23 mmol). After a 3 hr reflux period, the benzene was evaporated and the oily residue was distilled (102-105°/0.5 mmHg) to give 0.90 g (82%) of 6a as white needles: mp. 33-35°; ^{1}H NMR: δ 4.37 (s, 2), 7.30-8.20 (m, 4); IR ($CDCl_3$) 1745, 1775 cm^{-1}. Acid chloride 6a has been used by other investigators.[11]

2,2,6,6-Tetramethyl-4-[3-(bromomethyl)benzoyl]amino-1-piperidinyloxy (6b).-A modification of the procedure of Brown and Tsukamoto[15] was used. To a solution of acid chloride 6a (198 mg, 0.85 mmol) in dry ether (7 mL) at 0° was added dropwise over 25 min a solution of distilled 2,2,6,6-tetramethyl-4-amino-1-piperidinyloxy (291 mg, 1.70 mmol, Aldrich Co.) in dry ether (10 mL). During the addition a red precipitate was formed. After stirring at 0° for 1 hr the mixture was filtered and the precipitate was washed with cold ether (10 mL) then with chilled water until the wash water was colorless (10-15 mL). The red precipitate was dissolved in $CHCl_3$ (20 mL) and dried. The solution was concentrated to dryness giving 301 mg (96% based on 6a) of 6b as a red solid. The excess starting nitroxide could be recovered by base extraction of the aqueous layer. Crystallization from ether-CH_2Cl_2 afforded the analytical sample of 6b as red stars: mp. 168-169° (dec); IR ($CHCl_3$) 3440, 1660 cm^{-1}; ESR ($CHCl_3$) three lines a_N = 16.0 G.

Anal. Calcd for $C_{17}H_{24}BrN_2O_2$: C, 55.44; H, 6.57; N, 7.60. Found: C, 55.14; H, 6.53; N, 7.34.

2,2,6,6-Tetramethyl-4-[[3-(pentacarbonylmanganio)methyl]-benzoyl]amino-1-piperidinyloxy (7).-To a solution of $NaMn(CO)_5$ (100 mg, 0.46 mmol) in THF (3 mL) in the drybox was added a solution of 6b (124 mg, 0.339 mmol) in THF (3 mL). The solution immediately changed from green to orange and a white precipitate was formed. The mixture was stirred in the drybox for 15 min and then it was brought out into the atmosphere and filtered. The filtrate was concentrated to dryness giving 203 mg of an orange solid. This was purified by flash chromatography ($CHCl_3$) to give 97 mg (59%) of 7 as an orange solid. Crystallization from ether-pentane afforded the analytical sample of 7 as small orange red stars: mp. 120-

130° (dec); ESR ($CHCl_3$) three lines a_N = 16.0 G; IR ($CHCl_3$) 3440, 2110, 2075, 2010, 2000, 1650 cm^{-1}.

Anal. Calcd for $C_{22}H_{23}MnN_2O_7$: C, 54.66; H, 5.00; N, 5.79. Found: C, 54.91; H, 5.11; N, 5.55.

Acknowledgement.- This research was supported by PHS research grant GM 27137.

REFERENCES

1. For a review on photoaffinity labelling, see H. Bayley "Laboratory Techniques in Biochemistry and Molecular Biology," Vol. 12, T. S. Work, R. H. Burdon, Eds, Elsevier, New York, 1983.
2. J. A. Connor, M. T. Zafarani-Moattar, J. Bickerton, N. I. El Saied, S. Suradi, R. Carson, G. Altakhin, and H. A. Skinner, *Organomet.*, 1, 1166 (1982).
3. B. E. Britigan, M. S. Cohen, and G. M. Rosen, *J. Leukocyte Biol.*, 41, 349 (1987).
4. For a series of papers dealing with different aspects of spin-trapping see *Can. J. Chem.*, 60, 1379-1636 (1982).
5. For a review on stable nitroxide free radical chemistry, see J. F. W. Keana, "Spin Labeling in Pharmacology" p. 1, J. L. Holtzman, Ed., Academic Press, New York, 1984.
6. D. Landini and F. Rolla, *Chem. Ind. (London)*, 213 (1979).
7. H. A. Staab and R. G. H. Kirostetter, *Ann.*, 886 (1979).
8. A. Calder, A. R. Forrester, and S. P. Hepburn, *Org. Synth. Coll. Vol. VI*, 803 (1988).
9. B. L. Smith, Ph.D. Thesis, University of Oregon, 1982.
10. The benzylic protons of benzylmanganese pentacarbonyl appear at δ 2.36 in CCl_4: K. Noack, U. Schaerer, and F. Calderazzo, *J. Organometal. Chem.*, 8, 517 (1967).
11. R. Young and C. K. Chang, *J. Am. Chem. Soc.*, 107, 898 (1985).
12. G. M. Whitesides and T. L. Newirth, *J. Org. Chem.*, 40, 3448 (1975).
13. C. H. Cummins and R. M. Coates, *Ibid.*, 48, 2070 (1983).
14. R. Subramanyam and A. G. Pinkus, *Org. Prep. Prod. Int.*, 14, 200 (1982).
15. H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, 83, 2016 (1961).

(Received August 8, 1988; in revised form January 23, 1989)