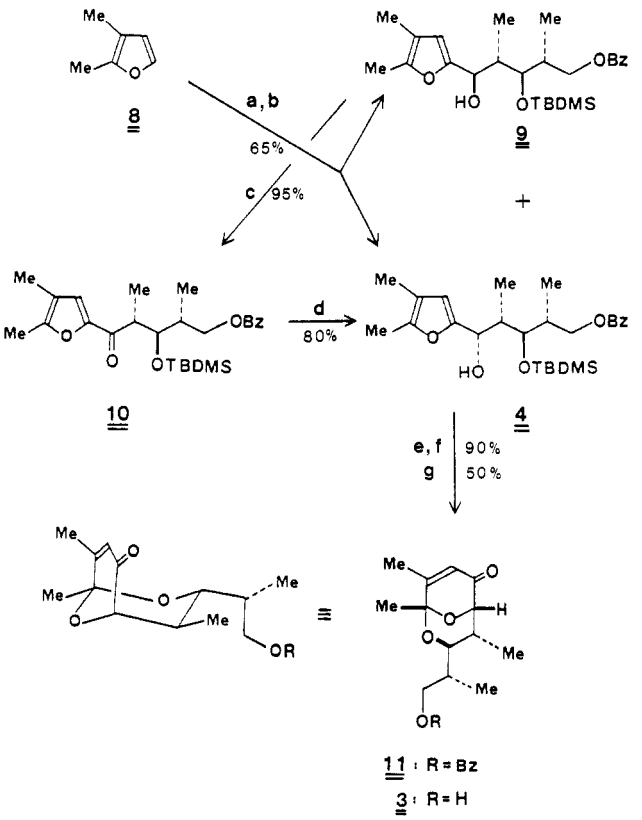
Scheme III[a]



[a] (a) *t*-BuLi, ether, 0 °C; (b) **5**, ether, −78 °C; (c) $BaMnO_4$, CH_2Cl_2, room temperature; (d) $Zn(BH_4)_2$, ether, room temperature; (e) mCPBA, CH_2Cl_2, 0 °C; (f) 5% aqueous HF, CH_3CN, room temperature; (g) Me_3SiCl, NaI, CH_3CN, room temperature.

damycin (Scheme I). In this strategy, the four contiguous asymmetric centers, C-5, C-4, C-3, and C-10, in **3** are established early in the sequence by utilizing aldehyde **5**[7] The key transformation in this strategy is the oxidation of furan–alcohol **4** to produce the bicyclic ring system found in **3**. We[5] and others[6,10] had earlier shown that oxidation of furan–alcohols could be used to prepare pyranones similar to **3**.

Synthesis of racemic **5** is outlined in Scheme II. Readily available homoallylic alcohol **7**[11] was converted to the TBDMS ether under standard conditions[14] and oxidized with ozone to give the unstable aldehyde **5** in 70% overall yield.

Metalation of 2,3-dimethylfuran (**8**)[15] followed by addition to aldehyde **5** gave a ~1:1 mixture of diastereomeric alcohols **4** and **9** (Scheme III).[16] The alcohols were separated by column chromatography, and **9** was oxidized to ketone **10** with $BaMnO_4$ (95%).[17] Reduction of **10** with $Zn(BH_4)_2$[18] resulted in selective formation of diastereomer **4** by "chelation-controlled" reduction.[19]

With **4** in hand, the critical step of the strategy could be investigated (vide supra). Oxidation of **4** with *m*-chloroperbenzoic acid[20] followed by cleavage of the silyl ether with HF in acetonitrile gave the bicyclic enone **11** in 90% yield.[21] Removal of the benzyl ether protecting group with MeSiI[22] gave **3** (50%), which was identical by IR and ^1H NMR with the Ireland alcohol. Alcohol **3** has been converted into tirandamycic acid (**2**) in four additional steps, and thus this synthesis constitutes a formal total synthesis of **2**.

The sequence outlined above for the synthesis of **3** is short (seven steps), stereospecific, and allows us to rapidly assemble the complex functionality of the bicyclic system of tirandamycin. We are currently attempting to employ this methodology for the total synthesis of tirandamycin and related antibiotics.

Acknowledgment. We acknowledge the Research Corp. for financial support. We acknowledge helpful discussions with Professors D. A. Evans and Y. Kishi concerning the preparation of **7**. We also thank Professor Ireland for IR and ^1H NMR spectra of **3**.

Registry No. (±)-**1**, 85880-71-3; (±)-**3**, 85880-72-4; (±)-**4**, 85828-13-3; (±)-**5**, 85828-12-2; (±)-**7**, 85880-73-5; **8**, 14920-89-9; (±)-**9**, 85880-74-6; (±)-**10**, 85828-14-4; (±)-**11**, 85828-15-5.

Supplementary Material Available: IR and NMR spectral data for compounds discussed and MS data for selected compounds (10 pages). Ordering information is given on any current masthead page.

(7) Aldehyde **5** is also a key synthon in the synthesis of the tirandamycin-related antibiotics streptolydigin[1,8] and nocamycin[9] since these compounds have the identical stereochemical relationship at the four asymmetric centers corresponding to C-5, C-4, C-3, C-10 in **1**.

(8) Rinehart, K. R., Jr.; Buk, J. R.; Bonders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4028.

(9) Horvath, G.; Brazhnikova, M. G.; Konstantinova, N. V.; Tolstykh, I. V.; Potapora, N. P. *J. Antibiot.* **1979**, *32*, 555. Nakagawa, S. Naito, Y.; Kawaguthi, H. *Heterocycles* **1979**, *12*, 477.

(10) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661. Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359.

(11) Racemic **7** was used in these experiments; however, both enantiomers of **7** can be prepared by either the "chiral auxiliary" methodology of Evans[12] or the Kishi methodology beginning from the "Roche alcohol".[13]

(12) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737 and references cited therein. D. A. Evans and R. Dow, unpublished results.

(13) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343 and references cited therein.

(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(15) Rice, K. C.; Dyer, J. R., Jr. *J. Heterocycl. Chem.* **1975**, *12*, 1325.

(16) Changing a variety of reaction parameters did not lead to a significant alteration in the ratio of diastereomers produced.

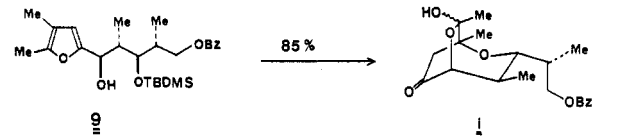
(17) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.

(18) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641 and references cited therein.

(19) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035 and references cited therein.

(20) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143.

(21) Oxidation (MCPBA) of the diastereomeric alcohol **9** followed by acid treatment did not give a bicyclo[3.3.1]nonane system in analogy with **4**. Instead **i** was produced by Michael-like addition of the alcohol to the enone moiety.



(22) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225 and references cited therein. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

Philip DeShong,* Subban Ramesh, Joseph J. Perez
Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802
Received March 14, 1983

Catalysis of Nitration of Naphthalene by Lower Oxides of Nitrogen[1]

Summary: Nitrous acid catalyzed nitration of naphthalene does not proceed through nitrosation, and the mechanism

(1) Part 4 of the series Studies in Aromatic Nitration. Part 3: Ross, D. S.; Malhotra, R.; Ogier, W. C. *J. Chem. Soc., Chem. Commun.* **1982**, 1353.

0022-3263/83/1948-2118$01.50/0

is best understood in terms of a chain reaction involving naphthalene radical cation.

Sir: Nitrous acid (NO^+, N(III)) can play contrasting roles in aromatic nitrations. It acts as an anticatalyst in the nitration of most aromatics in nitromethane/nitric acid mixtures and in nitric acid alone. On the other hand, in nitric acid/sulfuric acid mixtures it catalyzes the nitration of substrates such as phenol, aniline, and other aromatics activated toward electrophilic substitutions.[2] This catalytic effect has been classically explained through initial nitrosation, followed by oxidation to the corresponding nitroaromatic by nitric acid[3] (N(V)).

$$ArH + HONO \rightarrow H_2O + ArNO$$

$$ArNO + HNO_3 \rightarrow ArNO_2 + HONO$$

Recently Giffney and Ridd[4] reported a mechanism for nitrous acid catalyzed nitration of *N,N*-dimethylaniline in about 85% sulfuric acid not proceeding through C-nitrosation. A key step in the proposed mechanism involves the oxidation of the aromatic by NO^+ and the formation of *N,N*-dimethylaniline radical cation. Under conditions of lower acidities, however, these authors admit that the reaction could proceed by prior nitrosation. More recently Main, Moodie, and Schofield[5] have shown the reaction of 1,2,3-trimethoxy-5-nitrobenzene with nitric acid in 60–70% sulfuric acid to be also catalyzed by nitrous acid in a manner analogous to the nitration of *N,N*-dimethylaniline.

We have previously shown that nitrous acid catalyzes the nitration of phenol by a mechanism not involving prior nitrosation.[6] However, since phenol undergoes nitrosation, it was not possible to study the kinetics of N(III)-catalyzed nitration proceeding with no nitrosation as distinct from the component proceeding by nitrosation followed by oxidation. We required as a substrate an aromatic hydrocarbon that would be subject to special nitration but not undergo nitrosation. We report here the results of our study of the nitrous acid catalyzed nitration of naphthalene, which proceeds under conditions where naphthalene does not nitrosate.

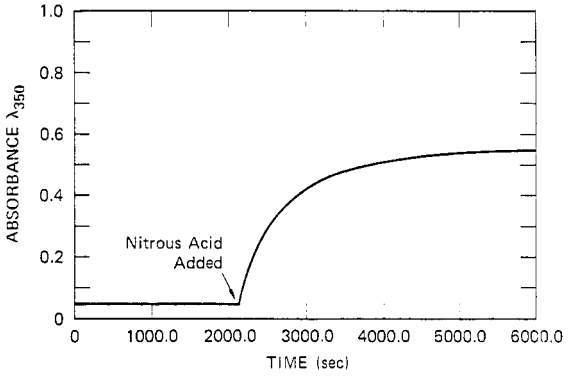


Figure 1. Effect of nitrous acid on the nitration of naphthalene in 55.9% H_2SO_4: naphthalene, 1.31×10^{-4} M; nitric acid, 1.30×10^{-2} M; nitrous acid, 6.56×10^{-5} M.

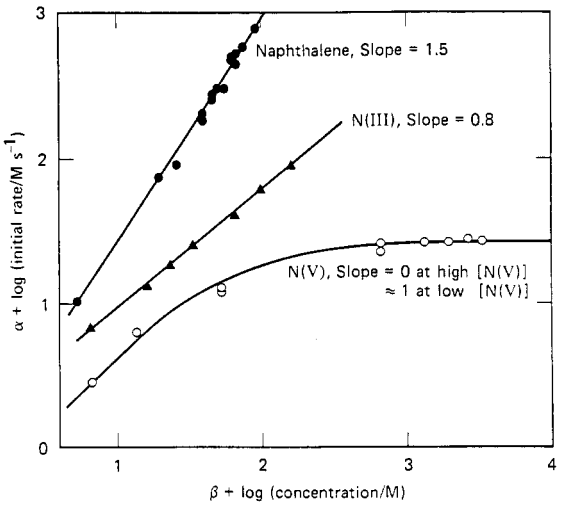
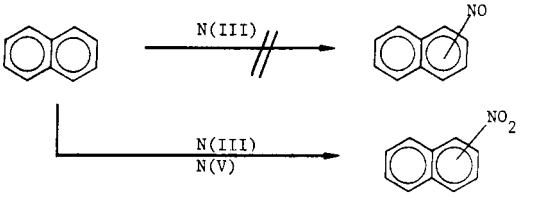


Figure 2. Variation of the initial rate of nitration of naphthalene in 60.4% H_2SO_4 at 25 °C with various reactants. (●) Naphthalene: $\alpha = 9.38$; $\beta = 5.74$; nitric acid, 1.30×10^{-2} M; nitrous acid, 3.30×10^{-5} M. (▲) N(III): $\alpha = 8.58$; $\beta = 6.00$; nitric acid, 1.30×10^{-2} M; naphthalene, 1.31×10^{-4} M. (○) N(V): $\alpha = 8.65$; $\beta = 4.98$; nitrous acid, 3.30×10^{-5} M; naphthalene, 1.31×10^{-4} M.

In all runs the additions of N(III) and N(V) were as aliquots of aqueous solutions of the respective sodium salts. Thus for the reactions with N(V), initially the solutions were free of lower oxide species. Below 60% sulfuric acid the nitration rate for naphthalene in such media is very slow, as is shown in Figure 1. However, as is also shown in the figure, the addition of a small quantity of nitrous acid dramatically brought about a very rapid nitration. The conversion is quantitative and the identity of the products was confirmed by GC and HPLC. The α/β isomer ratio was determined to be 25 ± 3. In contrast, if the same quantity of nitrous acid were added to a similar solution without N(V), the naphthalene was observed to be unchanged after 80 min. The rate of nitrosation is thus below 3%/h.

The promotion of nitration by N(III) is considered to be related to the change in product α/β ratio with the purposeful addition of N(III),[2] and as stated above the reaction route was considered to be prior nitrosation followed by oxidation of the nitrosoaromatic. However, our observations here suggest such a model to be incorrect; here we have a clear case of catalysis by N(III) not involving prior nitrosation.



To understand the mechanism of the catalysis, we investigated the kinetics of the reaction in 56.4% H_2SO_4. To assure that the results applied to a homogeneous condition, we first determined that the absorbances of naphthalene in the solutions prior to the addition of oxynitrogen species followed Beer's law (ϵ_{276} 5390 M^{-1} cm^{-1}). The fit was satisfactory up to the upper limit of the concentration range of the study, and the slight deviation at higher concentrations could well be due to some association of the dissolved hydrocarbon, although this factor was not confirmed. Several kinetic runs were conducted in which the concentrations of nitric and nitrous acids were held constant at 1.3×10^{-2} and 3.3×10^{-5} M, respectively, while the naphthalene concentration was varied between $9.7 \times$

(2) Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K., "Nitration and Aromatic Reactivity" Cambridge University Press: London, 1971.
(3) Bunton, C. A.; Hughes, E. D.; Ingold, C. K.; Jacobs, D. I. H.; Jones, T. H; Minkoff, G. J.; Reed, R. J. *J. Chem. Soc.* **1950**, 2628.
(4) (a) Giffney, J. C.; Ridd, J. H., *J. Chem. Soc. Perkin Trans. 2*, **1979**, 618. (b) Al-Omran, F.; Fujiwara, K.; Giffney, J. C.; Ridd, J. H.; Robinson, S. R. *Ibid.* **1981**, 518.
(5) Main, L.; Moodie, R. B.; Schofield, K., *J. Chem. Soc., Chem. Commun.* **1982**, 48.
(6) Ross, D. S.; Hum, G. P.; Blucher, W. G. *J. Chem. Soc., Chem. Commun.* **1980**, 532.

10^{-6} and 1.4×10^{-4} M. None of these runs gave good first-order or second-order plots, and we therefore obtained the order of the reaction in naphthalene by analyzing the initial rates (r_i) as shown in Figure 2. By this method the order in napthalene was determined to be 1.5. This surprising result was verified by reexamination of the full kinetic runs, which were found to fit plots for a reaction 1.5 order in naphthalene. These results are in contrast to those of Ridd and Co-workers,[4] who found N(III)-catalyzed nitration of *N,N*-dimethylaniline to be first order in the aromatic. This finding is moreover obviously not in accord with the prenitrosation scheme.

The order of nitration in nitrous acid was also determined by the method of initial slopes and found to be 0.8 for the range of nitrous acid concentrations between 6.7×10^{-6} and 1.7×10^{-4} M (Figure 2). The order with respect to nitric acid changed in the range of concentrations studied. The reaction was zero order in nitric acid when the concentration of nitric acid was above 6.3×10^{-3} M. Below 10^{-4} M nitric acid, the order was approximately 1. Variation of the log initial rate with log initial nitric acid concentration is also shown in Figure 2.

From these kinetic data we can draw some conclusions regarding the mechanism of the reaction. The order of 1.5 in naphthalene can be explained in terms of a chain mechanism in which both initiation and propagation steps are first order in naphthalene. The changing order in nitric acid indicates a change in the rate-limiting step with changing N(V) concentration. We stipulate that nitric acid is involved in a propagation step following the step in which naphthalene is consumed. Zero order in nitric acid for high concentrations is consistent with the electron-transfer oxidation scheme of Ridd and co-workers,[4] and recently Main, Moodie, and Schofiled[5] found evidence for such a limiting kinetic form in the case of nitrous acid catalyzed nitration of 1,2,3-trimethoxy-5-nitrobenzene.

Further support for electron transfer is provided by the results of electrochemical nitration of naphthalene. Eberson et al.[7] and Achord and Hussey[8] reported that controlled potential electrolysis of naphthalene at +1.3 V (vs. Ag/Ag^+) in the presence of N_2O_4 produces nitronaphthalenes with an α/β isomer ratio of 23 ± 3, a value we have been able to reproduce, but significantly different from that reported by Perrin.[9]

However, the order of 1.5 in naphthalene cannot be reconciled with a simple scheme involving oxidation by NO^+, followed by reaction with NO_2. We support the idea of electron transfer being an important step, but the overall scheme must include a chain. So far we have not been able to identify the NO_x species involved in the reaction, primarily because at the acidity we have worked, several of the NO_x species are present in a significant quantities, including NO, HONO, NO^+, NO_2, N_2O_4, NO_3^-, and HNO_3.[9] We are currently studying the acidity dependence of N(III)-catalyzed nitration of naphthalene, with the hope to establish the identity of the oxidant and develop a detailed mechanism. However, it is clear that the nitration of simple hydrocarbons can be complex and the role of the lower nitrogen oxides can be significant.

Acknowledgment. We acknowledge the generous support of the U.S. Army Research Office. We also thank Professor R. B. Moodie for helpful discussion.

(7) Eberson, L.; Jonsson, L.; Radner, F. *Acta Chem. Scand., Ser. B* **1978**, *B32*, 749.
(8) Achord, J. M.; Hussey, C. L. *J. Electrochem. Soc.* **1981**, *128*, 255–261.
(9) Perrin, C. L. *J. Am. Chem. Soc.* **1977**, *99*, 5516.
(10) Ross, D. S.; Gu, C. L., to be published.

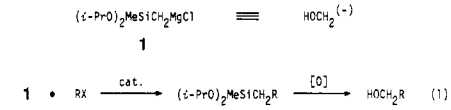
Registry No. Naphthalene, 91-20-3; nitrous acid, 7782-77-6.

David S. Ross,* Kelly D. Moran
Ripudaman Malhotra
Physical Organic Chemistry Department
SRI International
Menlo Park, California 94025
Received January 27, 1983

(Diisopropoxymethylsilyl)methyl Grignard Reagent: A New, Practically Useful Nucleophilic Hydroxymethylating Agent

Summary: The (diisopropoxymethylsilyl)methyl Grignard reagent serves as a new, versatile nucleophilic hydroxymethylating agent of organic halides via the metal-catalyzed cross-coupling and the subsequent oxidative cleavage of the silicon–carbon bond.

Sir: Despite its anticipated potent utility in synthetic organic chemistry,[1] nucleophilic hydroxymethylation has only been described in a few scattered papers.[2] The previous approaches have limited applicability, because of the limited availability of starting materials and low functional group tolerance. We have now developed the (diisopropoxymethylsilyl)methyl Grignard reagent (1) as a new nucleophilic hydroxymethylating agent that is readily available, convenient to handle, and of general applicability (eq 1).



The present methodology is based on our recent observation that an alkoxysilyl group is synthetically equivalent to the hydroxy group.[3,4] Thus, the carbon–silicon bond in organoalkoxysilanes is readily cleaved by 30% H_2O_2[3] as well as MCPBA[4] in the presence of fluoride ions to form the corresponding alcohol. Such a unique reactivity of silicon–functional organosilicon compounds suggests a variety of new synthetic possibilities that are not possible with the more common trimethylsilyl derivatives.[5]

Despite the possible reactivity due to the coexistence of a reactive primary alkyl Grignard reagent and a labile alkoxy group on silicon, the Grignard reagent 1 could be prepared in a normal manner from $(i\text{-PrO})_2MeSiCH_2Cl$ (2)[6] and magnesium activated with dibromoethane in THF.[7]

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(2) (a) $ArCO_2CH_2Li$/LAH: Beak, P.; McKinnie, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213. (b) R_2BCH_2Li/[O]: Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94*, 6854. (c) Ar_2BCH_2Li/[O]: Pelter, A. *Chem. Soc. Rev.* **1982**, *11*, 191. (d) Bu_3SnCH_2OH/2BuLi: Meyer, N.; Seebach, K. *Ber.* **1980**, *113*, 1290. See also: (e) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1929. (f) $(Me_3SiO)CH{=}C(OSiMe_3)_2$: Wissner, A. *Tetrahedron Lett.* **1978**, 2749.
(3) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M., manuscript in preparation.
(4) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. See also: Hosomi, A.; Iijima, S.; Sakurai, H. *Chem. Lett.* **1981**, 243.
(5) Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981.
(6) Andrianov, K. A.; Makorova, L. I.; Volkova, L. M.; Odinets, V. A. *Dokl. Acad. Nauk, SSSR* **1954**, *95*, 269; *Chem. Abstr.* **1955**, *49*, 3787.

0022-3263/83/1948-2120$01.50/0