

## Nitration of Organolithiums and Grignards with Dinitrogen Tetroxide: Success at Melting Interfaces

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Recently we reported that the sodium salts of 1,3,5,7-tetranitrocubane and 1,2,3,5,7-pentanitrocubane can be nitrated successfully with dinitrogen tetroxide in THF at low temperature.<sup>1</sup> These reactions apparently<sup>1</sup> proceed by N<sub>2</sub>O<sub>4</sub> oxidation of the anion to the radical and its combination with NO<sub>2</sub> (or N<sub>2</sub>O<sub>4</sub>). As far as we can find, these nitrations are the first successful examples of nitration of localized<sup>2</sup> group IA organometallics reported in the literature. As the common assumption is that nitration of a carbanion is not a useful reaction, we looked to see if the cubane cases above were special or if we had found conditions for anion nitration that were broadly useful. Indeed, as we now report, the latter pertains. We have a new method to effect nitration of common organometallics with N<sub>2</sub>O<sub>4</sub>. Our results should provide important clues for others who might need or want to develop this reaction further.

The literature reports only that dialkylhydroxylamines are formed from reaction of a Grignard with a dilute ethereal solution of nitrogen dioxide.<sup>3</sup> We find that direct N<sub>2</sub>O<sub>4</sub> nitration of primary and even secondary alkyl Grignards can be done with some success (Table 1), but this depends critically on methodology (*vide infra*).<sup>4</sup> It is noteworthy that both *n*-BuNO<sub>2</sub> (71% isolated yield) and *sec*-BuNO<sub>2</sub> (29%) were obtained pure even after a workup consisting of nothing more than simple extraction and evaporation. We suppose that much of the "missing" mass is in the butanes formed by radical abstraction of hydrogen atom from THF by the intermediate *n*-butyl or *sec*-butyl radicals. Both *t*-BuMgCl and *t*-BuLi gave only trace amounts of *t*-BuNO<sub>2</sub>. This might be due to further oxidation, *i.e.* the radical to *tert*-butyl cation. Cubyllithium, another tertiary example, could not be successfully nitrated. Only cubane (13%) and bicubyl (20%) were identifiable products. Both can form by way of the cubyl radical. We are not sure what blocks reaction of this radical with N<sub>2</sub>O<sub>4</sub>.

Although Grignards gave better yields than organolithiums in the aliphatic series, the reverse was true with phenyl Grignard versus phenyllithium. N<sub>2</sub>O<sub>4</sub> nitration of phenyllithium<sup>5</sup> and its

**Table 1.** Reaction of Aliphatic Organolithiums or Grignards with N<sub>2</sub>O<sub>4</sub>

| organometallic <sup>a</sup> | yield, <sup>b</sup> % |          | product                       |
|-----------------------------|-----------------------|----------|-------------------------------|
|                             | M = Li                | M = MgCl |                               |
| <i>n</i> -BuM               | 19                    | 71       | <i>n</i> -BuNO <sub>2</sub>   |
| <i>sec</i> -BuM             | 4                     | 29       | <i>sec</i> -BuNO <sub>2</sub> |
| <i>t</i> -BuM               | trace                 | trace    | <i>t</i> -BuNO <sub>2</sub>   |

<sup>a</sup> Organolithiums in alkane and Grignards in THF or Et<sub>2</sub>O were purchased from Aldrich Chemical. <sup>b</sup> Based on <sup>1</sup>H NMR integrations against an internal standard.

derivatives with electron-donating (e.g., methyl) or electron-withdrawing groups (e.g., diisopropylcarboxamido) afforded the corresponding nitro compounds in high yield (Table 2). A significant amount (15%) of *N,N*-diisopropylbenzamide was also isolated from 4-(*N,N*-diisopropylbenzamido)lithium, again suggesting that N<sub>2</sub>O<sub>4</sub> oxidizes the organometallic to a radical which can abstract hydrogen from the solvent or react with N<sub>2</sub>O<sub>4</sub>.

Our nitration procedure is also useful for preparing heteroaromatic nitro compounds (Table 2). Some of the necessary organolithiums, e.g., 4-pyridyllithium and 3-thienyllithium, were obtained by simple halogen–metal exchanges between the commercially available bromo compounds and *n*-BuLi. In other cases, direct lithiation was used; 2-thienyllithium and 2-(*N,N*-diisopropylbenzamido)lithium were prepared in this manner. Each of these organolithiums was successfully nitrated in good to very good yield *specifically at the position of lithiation*. Of course, some of these nitro compounds are available by other straightforward methods, but there are cases for which our method is now the one of choice. For example, 3-nitrothiophene can now be obtained in 70% overall yield from commercial 3-bromothiophene; this is far superior to the older literature procedure (20% from thiophene).<sup>6</sup>

**Table 2.** Nitration of Aryllithiums with N<sub>2</sub>O<sub>4</sub>

| Ar–Li  | product (isolated yields)                                    |
|--|--|
| phenyllithium  | nitrobenzene (87%)   |
| <i>p</i> -tolyllithium <sup>a</sup>                        | <i>p</i> -nitrotoluene (86%)                                 |
| 4-( <i>N,N</i> -diisopropylbenzamido)-lithium <sup>b</sup> | 4-nitro- <i>N,N</i> -diisopropylbenzamide <sup>c</sup> (81%) |
| 4-pyridyllithium <sup>c</sup>                              | 4-nitropyridine <sup>b</sup> (57%)                           |
| 3-thienyllithium <sup>d</sup>                              | 3-nitrothiophene <sup>f</sup> (70%)                          |
| 2-thienyllithium <sup>e</sup>                              | 2-nitrothiophene (76%)                                       |
| 2-( <i>N,N</i> -diisopropylbenzamido)-lithium <sup>f</sup> | 2-nitro- <i>N,N</i> -diisopropylbenzamide <sup>g</sup> (57%) |

<sup>a</sup> Reference 7a. <sup>b</sup> 4-(*N,N*-Diisopropylbenzamido)lithium was prepared from 4-bromo-*N,N*-diisopropylbenzamide and *n*-BuLi (1.1 equiv) in THF at –102 °C. <sup>c</sup> Reference 7b. <sup>d</sup> Reference 7c. <sup>e</sup> Reference 7d. <sup>f</sup> Reference 7e. <sup>g</sup> Reference 7f. <sup>h</sup> Reference 7g. <sup>i</sup> Reference 7h. <sup>j</sup> Reference 7i.

Such results lead us to believe that low-temperature N<sub>2</sub>O<sub>4</sub> nitration of organometallics is certainly worth considering as a simple and potentially quite efficient and effective approach to

(1) Lukin, K.; Li, J.; Gilardi, R.; Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 864.

(2) For nitration of delocalized anions, see: (a) Thiele, J. *Chem. Ber.* **1900**, *33*, 666. (b) Feuer, H. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives, Supplement F*; Patai, S., Ed.; John Wiley and Sons: New York, 1982; pp 805–848.

(3) (a) Wieland, H. *Chem. Ber.* **1903**, *36*, 2315. (b) Troyan, J. E. *J. Am. Chem. Soc.* **1942**, *64*, 3056.

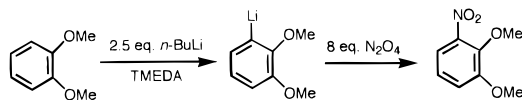
(4) CAUTION: N<sub>2</sub>O<sub>4</sub> is dangerous; use of an efficient hood and protecting shield is essential. Typical reaction conditions were as follows: In one flask a solution of the organometallic (0.50 mmol) in THF (2 mL) was frozen solid (THF: mp –108 °C) using an external liquid nitrogen bath (ca. –190 °C). Separately, gaseous dinitrogen tetroxide (N<sub>2</sub>O<sub>4</sub> ⇌ 2NO<sub>2</sub>) from a commercial cylinder was condensed into another weighed flask; 6–12 equiv was collected. This was evaporated (warm water bath), and the gas led through a cannula and deposited (mp –11 °C) onto the frozen organometallic/THF glass in the first flask. Once all the N<sub>2</sub>O<sub>4</sub> had been added, the flask was transferred from the liquid nitrogen bath to a room temperature methanol bath and shaken vigorously as it warmed to room temperature. The reaction appeared to start as soon as the frozen mixture began liquefying at the interface; it was over quickly and finished (no further color change) well before the mixture was fully liquid. Excess N<sub>2</sub>O<sub>4</sub> and solvent were removed (house vacuum, water bath <40 °C). The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water, and dried over anhydrous MgSO<sub>4</sub>. The crude product was examined by NMR. When appropriate, the major product was isolated by silica gel column chromatography. Usually THF and diethyl ether gave the same results, but in the latter case sometimes small amounts of nitrite and nitrate esters were formed.

(5) Cf.: Bunce, N. J.; Stephenson, K. L. *Can. J. Chem.* **1989**, *67*, 220.

(6) Blatt, A. H.; Bach, S.; Kresch, L. W. *J. Org. Chem.* **1957**, *22*, 1693.

(7) (a) DesEnfants, R. E., II; Gavney, J. A.; Hayashi, R. K.; Rae, A. D.; Dahl, L. F. *J. Organomet. Chem.* **1990**, *383*, 543. (b) Phillips, J. E.; Herber, R. H. *J. Organomet. Chem.* **1984**, *268*, 39. (c) Strekowski, L.; Harden, D. B.; Grubb, W. B., III; Patterson, S. E.; Czarny, A.; Mokrosz, M. J.; Cegla, M. T.; Wydra, R. L. *J. Heterocycl. Chem.* **1990**, *27*, 1393. (d) Furber, M.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 683. (e) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (f) Fong, C. W.; Grant, H. G. *Aust. J. Chem.* **1981**, *34*, 1205. (g) Kaneko, C.; Yamamoto, A.; Gomi, M. *Heterocycles* **1979**, *12*, 227. (h) Maag, H.; Manukian, B. K. *Helv. Chim. Acta* **1973**, *56*, 1787. (i) 2-Nitro-*N,N*-diisopropylbenzamide: mp 112.5–113.5 °C (light yellow plates from EtOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.11 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.62 (d, *J* = 6.8 Hz, 3H), 3.50–3.62 (m, 2H), 7.33 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.50–7.54 (m, 1H), 7.66–7.70 (m, 1H), 8.18 ppm (dd, *J* = 1.2, 8.0 Hz, 1H).

otherwise difficultly available nitro compounds. 3-Nitroveratrole is a cogent example. This compound cannot be made usefully by classical electrophilic nitrations of veratrole.<sup>8</sup> It was once considered "inaccessible" and only roundabout routes to it were available.<sup>5,8</sup> It can now be obtained using our method in 67% isolated yield (85% conversion) by direct ortho-lithiation of 1,2-dimethoxybenzene<sup>9</sup> followed by low-temperature N<sub>2</sub>O<sub>4</sub> nitration.<sup>10</sup>



Why are these nitrations successful? We first examined the effect of temperature. Experiments in which N<sub>2</sub>O<sub>4</sub> was introduced into unfrozen THF solutions of phenyllithium at -35, -75, or -105 °C gave very complex mixtures of products but little nitrobenzene. No reaction (as judged by color change) was seen when N<sub>2</sub>O<sub>4</sub> was deposited onto frozen THF at -120 °C, but at approximately -115 °C, at which point melting started at the THF/N<sub>2</sub>O<sub>4</sub> interface, reaction was immediate and

(8) 4-Nitroveratrole is obtained instead: (a) Takakis, I. M.; Hadjimihalakis, P. M. *J. Heterocycl. Chem.* **1991**, 28, 625. (b) Thompson, M. J.; Zeegers, P. J. *Tetrahedron* **1990**, 46, 2661.

(9) The procedure of McMurry et al. [McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers, D. R.; Shenvi, A. *J. Org. Chem.* **1984**, 49, 3803] for 2,3-dimethoxyphenyllithium was followed except 2.5 equiv of *n*-BuLi was used to complete ortho-lithiation. It is essential that all the veratrole be lithiated.

(10) 3-Nitroveratrole: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.93 (s, 3H), 3.99 (s, 3H), 7.09–7.16 (m, 2H), 7.33 (dd, *J* = 2.4, 7.6 Hz, 1H). The literature data<sup>5</sup> for the methoxy protons appear to be in error by 1 ppm downfield.

afforded nitrobenzene in good yield.<sup>11</sup> The striking difference in product distribution between reactions run in liquid THF at -105 °C and those taking place at the melting point of ca. -115 °C cannot be explained reasonably by the 10 °C difference in temperature. We suspect that the phase change itself is all important. We speculate that the reaction occurring at the melting interface is being controlled by the rate of delivery of one reactant to the other, dictated in some way by the melting process. And/or perhaps the latent heat of melting is providing critically for the moderation of temperature at an intimate microscopic level.

Although we cannot prove one or another such interpretation of our observations, we can offer additional evidence that it is the dynamics of interfacial melting rather than gross temperature that is significant. When N<sub>2</sub>O<sub>4</sub> was added to a fluid solution of phenyllithium in 1,2-dimethoxyethane (DME) at about -70 °C and the mixture brought to room temperature only a complex mixture of products containing just a trace of nitrobenzene was formed. When instead N<sub>2</sub>O<sub>4</sub> was deposited onto the surface of the same concentration solution of phenyllithium in DME frozen solid at about -80 °C and then the mixture melted (ca. -75 °C) and warmed to room temperature, the reaction was much cleaner and a 26% yield (by NMR) of nitrobenzene was obtained.

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(11) The yield (65–80%) was slightly lower than when (Table 2) N<sub>2</sub>O<sub>4</sub> was introduced at much lower temperature (cf. ref 4).