



The superiority of properly prepared lithium 1-*N,N*-dimethylaminonaphthalenide (LDMAN) over other aromatic radical-anions for the generation of organolithiums by reductive lithiation [☆]

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ABSTRACT

The use of lithium 1-*N,N*-dimethylaminonaphthalenide (LDMAN) is found to be considerably superior in yield, ease of operation, and cost to the far more widely used lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB) in reductive lithiations by aromatic radical-anions to produce organolithium compounds, provided that careful temperature control is maintained during the generation of LDMAN. The main reason for the superiority is the great ease of separation of the aromatic byproduct dimethylaminonaphthalene by a dilute acid wash.

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Two 1978 papers reported the important finding that readily prepared alkyl phenyl thioethers could be converted into alkyl lithium compounds by the aromatic radical-anion lithium naphthalenide (LN).¹ Since that time, such reductive lithiation has developed into one of the most versatile methods known for generating synthetically useful organolithiums.² Other leaving groups have also been used, but they have proven considerably less versatile than the phenylthio group.² In 1980, two more useful aromatic lithium radical-anions, lithium 1-*N,N*-dimethylaminonaphthalenide³ (LDMAN) **1**, and lithium *p,p'*-di-*tert*-butylbiphenylide⁴ (LDBB) **2**, were introduced (Fig. 1). The former, **1**, has the advantage over lithium naphthalenide that the byproduct of electron transfer, 1-dimethylaminonaphthalene, can be readily separated from the desired product in most cases by a dilute acid wash and of course it can be recycled; a subsidiary advantage is that LDMAN can be used in solvents other than THF, the solvent universally used in synthetic procedures involving aromatic lithium radical-anions.⁵ The latter, **2**, has the advantage that it is a more powerful reducing agent than LN and presumably less subject to attack by the intermediate radical generated in the process of reductive lithiation.

A disadvantage of LDMAN is that above -45 °C it decomposes to 1-lithionaphthalene. This often appeared to be only a minor disadvantage since most reductive lithiations are successful at -78 °C. Furthermore, for those reductive lithiations that require a higher temperature, a work-around was developed, referred to as the cat-

alytic method, consisting of using, instead of preformed LDMAN, lithium metal and 25% 1-*N,N*-dimethylaminonaphthalene (DMAN).³ The reasoning was that because the rate of reductive lithiation is greater than that of formation of the radical-anion, the concentration of radical-anion and especially of the dianion, suspected of being the precursor of 1-lithionaphthalene, would remain extremely low and thus production of the latter would be inhibited.^{2,6} Nevertheless, the use of the catalytic method is not a perfect solution to the problem of the decomposition of LDMAN at temperatures above -45 °C, because in many cases the use of preformed radical-anion gives superior results to the use of a catalytic amount of the aromatic species.²

The use of LDMAN is rather widespread,^{2,3,5,7,8} but considerably less so than the use of LDBB.^{6b,9} In the past in our own laboratory, LDBB has generally been chosen unless the product of electrophile capture of the generated organolithium is non-polar in which case the use of LDMAN is virtually mandatory in order to ease the separation of the aromatic byproduct from the desired product. The reason for the preference for LDBB is that except in cases in which there is a separation problem, LDBB generally gave somewhat superior yields than LDMAN.^{10,7a}

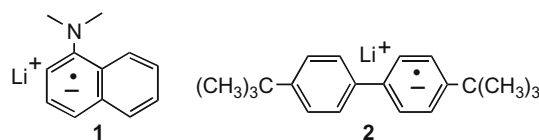


Figure 1. Radical-anion reductive lithiation reagents.

[☆] Taken in part from the Ph.D. thesis of Roman Ivanov, University of Pittsburgh, 2008.

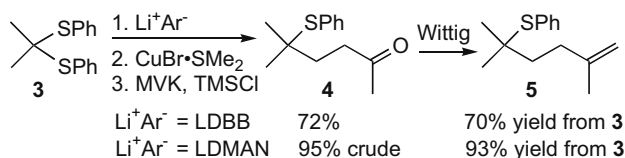
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A careful reexamination of the procedure¹¹ for the preparation of LDMAN has now revealed a previously unrecognized problem, the elimination of which makes LDMAN the reagent of choice in reductive lithiations. The problem is that the decomposition of LDMAN in THF actually commences at a noticeable rate even below $-45\text{ }^{\circ}\text{C}$ and that most if not all temperature controllers do not maintain a very constant temperature. For optimum yield, it is necessary to not allow the temperature to rise above $-52\text{ }^{\circ}\text{C}$.¹² We have found that this is best accomplished by maintaining a temperature of $-55 \pm 3\text{ }^{\circ}\text{C}$ by manual control.¹³ Under these conditions, the preparation takes about 5 h. At a lower temperature, the time that the control must be maintained becomes impractical. When this procedure¹⁴ is followed, every example that we have tested provides higher yields than the use of LDBB in preparative scale reductive lithiations. We also provide an example in which LDMAN gives a far better yield than that reported for the use of LN. In three of these comparisons, we repeated literature reductive lithiations but replaced the LN or LDBB with LDMAN whereas in the fourth, we tested LDBB against LDMAN for an unreported reductive lithiation and trapping.

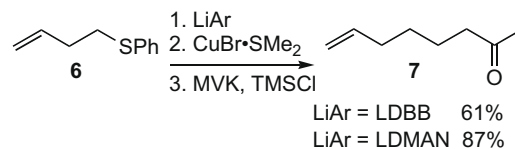
The reported^{7c} reductive lithiation of 2,2-bis(phenylthio)propane **3** with LDBB followed by capture of the product with methyl vinyl ketone (MVK) in the presence of cuprous bromide and TMSCl led to the formation of the corresponding ketone **4**, which could be separated from the aromatic byproduct DBB by using slow column chromatography (5% EtOAc/hexane, $R_f = 0.1$). Subsequent quantitative Wittig olefination afforded the 2,5-dimethyl-5-(phenylthio)hexene **5** in 70% yield over two steps (Scheme 1).^{7c} On the other hand, because DMAN can be completely removed with dilute aqueous HCl, the use of LDMAN instead of LDBB in the same synthetic routine leads to a 95% yield of the essentially pure ketone **4**, which can be submitted to Wittig olefination without the need of any further purification to afford the desired alkene **5** in 93% overall yield (Scheme 1).

In another example, 4-(phenylthio)-1-butene **6** was treated in separate experiments with LDBB and LDMAN and the reduction product was treated with methyl vinyl ketone (MVK) in the presence of cuprous bromide and TMSCl. In the case of LDBB, column separation of the large amount of DBB from the product **7** is inconvenient. Thus, vacuum distillation is performed to obtain the pure product **7** in only a moderate 61% yield (Scheme 2). However, in the case of LDMAN, carefully prepared at $-55\text{ }^{\circ}\text{C}$, it becomes possible again to remove the aromatic byproduct DMAN and then use fast column chromatography for product purification to afford 7-octene-2-one **7** in 87% yield (Scheme 2).

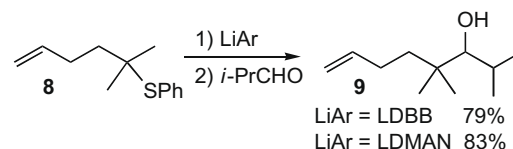
In the reductive lithiation of **8**,^{7c} although the improvement in the yield of purified product in going from LDBB to LDMAN was only minor, the improvement in ease of operation was great. In the case of reduction with LDBB, the reported separation of organic products required an extremely slow and time consuming column chromatography (3% EtOAc/hexane; $R_f = 0.1$) (Scheme 3). However, when LDMAN is used instead, the aromatic amine byproduct DMAN is completely removed with dilute HCl and fast and effective flash column chromatography (20% EtOAc/hexanes; $R_f = 0.7$) can thus be used (Scheme 3).



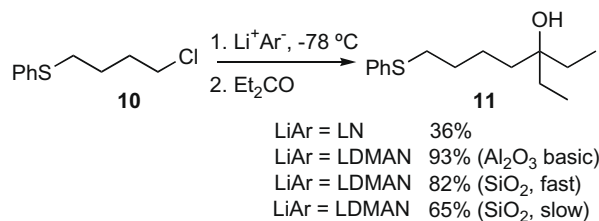
Scheme 1. Comparison of LDBB and LDMAN in the reductive lithiation of a thioacetal.



Scheme 2. Comparison of LDBB and LDMAN in the reductive lithiation of 4-(phenylthio)-1-butene.



Scheme 3. Comparison of LDBB and LDMAN in the production of a tertiary organolithium by reductive lithiation.



Scheme 4. Comparison of LN and LDMAN in the reductive lithiation of an alkyl chloride.

A dramatic example of the avoidance of separation problems by the use of LDMAN is a comparison of recently published data on the selective reductive lithiation of 1-chloro-4-(phenylthio)butane **10** with LN and capture of the resulting organolithium with diethyl ketone.¹⁵ When LN is used for selective lithiation (Scheme 4), only very slow column chromatography on silica gel (10% EtOAc/hexane; $R_f = 0.11$) can be used for effective separation to afford the desired tertiary alcohol **11** in only 36% yield.¹⁵ Because DMAN reacts extremely fast with a 3 M aqueous solution of HCl, a nearly stoichiometric amount of this acid can be used to wash out the DMAN completely with no harm to the tertiary alcohol **11**. Such chemically activated extraction allows one to obtain essentially pure product, which could be further purified by flash column chromatography using either basic alumina (93% yield) or even by using fast silica gel column with 20% ethyl acetate solution in hexane as eluant ($R_f = 0.6$) in 82% yield of purified product **11** (Scheme 4). Moreover, after being exposed to extremely slow silica gel column chromatography, the yield of the alcohol **11** decreased dramatically to 65%, undoubtedly because of dehydration.

In conclusion, LDMAN has been found to be superior to LDBB and LN, heretofore the most widely used reagents for the preparation of organolithium compounds by reductive lithiation using aromatic radical-anions. It was previously thought that LDMAN was only preferred when the product of capture of the resulting organolithium with an electrophile was very difficult to separate from the byproduct aromatic hydrocarbon since the aromatic byproduct in the case of LDMAN is a Lewis base and can be removed from the reaction mixture by an acid wash even if the reaction mixture contains a tertiary alcohol. Furthermore, it was believed that LDBB generally gave slightly higher yields of product than LDMAN. However, it has now been discovered that the decomposition of LDMAN commences at $-52\text{ }^{\circ}\text{C}$ rather than at $-45\text{ }^{\circ}\text{C}$, as previously thought, and that if care is taken to maintain a temperature of $-55 \pm 3\text{ }^{\circ}\text{C}$ during the generation of the LDMAN, the latter is far superior to

LDBB in reductive lithiations and it almost certainly should be the default choice. Another good reason for the choice of LDMAN is that the price of its precursor 1-*N,N*-dimethylaminonaphthalene is over three times less than that of *p,p'*-di-*tert*-butylbiphenyl and the former is easier to recover and recycle.

Acknowledgments

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References and notes

- (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064–1071; (b) Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, *19*, 4665–4668.
- Yang, A.; Butela, H.; Deng, K.; Doubleday, M. D.; Cohen, T. *Tetrahedron* **2006**, *62*, 6526–6535. and citations therein.
- Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311–317.
- Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.
- Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni, V. *J. Am. Chem. Soc.* **2001**, *123*, 3478–3483.
- In the earliest reports of the reductive lithiation of phenyl thioethers, there were several examples in which a sub-stoichiometric quantity of naphthalene was used along with a stoichiometric quantity of lithium metal: see Ref. 1a and (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713–719. More recently, Yus's group has extensively utilized a form of the catalytic method in which a large excess of lithium is used along with a catalytic amount of the aromatic, usually naphthalene or *p,p'*-di-*tert*-butylbiphenyl: (b) Yus, M., In *The Chemistry of Organolithium Compounds*, Rappoport, Z. Marek, I., Ed.; Wiley: Chichester, 2004; Part 2, Chapter 11; (c) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237.
- (a) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360–2372; Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106–12107; (b) Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* **2001**, *123*, 30–34; Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291–3304; Kulkarni, V.; Cohen, T. *Tetrahedron* **1997**, *53*, 12089–12100; Shook, C. A.; Romberger, M. L.; Jung, S.-H.; Xiao, M.; Sherbine, J. P.; Zhang, B.; Lin, F.-T.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 10754–10773; Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855–3865; Cabral, J. A.; Cohen, T.; Doubleday, W. W.; Duchelle, E. F.; Fraenkel, G.; Guo, B.-S.; Yü, S. H. *J. Org. Chem.* **1992**, *57*, 3680–3684; McCullough, D. W.; Bhupathy, M.; Piccolino, E.; Cohen, T. *Tetrahedron* **1991**, *47*, 9727–9736; Cohen, T.; Jung, S.-H.; Romberger, M. L.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 25–26; Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710–4711; Cohen, T.; Guo, B.-S. *Tetrahedron* **1986**, *42*, 2803–2808; Cohen, T.; Sherbine, J. P.; Mendelson, S. A.; Myers, M. *Tetrahedron Lett.* **1985**, *26*, 2965–2968; Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245–3252; Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131; Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520–525; Cohen, T.; Ouellette, D.; Senaratne, K. P. A.; Yu, L.-C. *Tetrahedron Lett.* **1981**, *22*, 3377–3380; Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6902; (c) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1994**, *50*, 12793–12810.
- (a) Streiff, S.; Ribeiro, N.; Desaubry, L. *J. Org. Chem.* **2004**, *69*, 7592–7598; (b) Giannini, A.; Coquerel, Y.; Greene, A. E.; Deprés, J. P. *Tetrahedron Lett.* **2004**, *45*, 6749–6751; Tsai, T. Y.; Shia, K.-S.; Liu, H.-J. *Synlett* **2003**, 97–101; Perales, J. B.; Makino, N. F.; Van Vranken, D. L. *J. Org. Chem.* **2002**, *67*, 6711–6717; Shimizu, M.; Hiyama, T.; Matsubara, T.; Yamabe, T. *J. Organomet. Chem.* **2000**, *611*, 12–19; Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **2000**, *122*, 12806–12812; Nowak, A.; Schaumann, E. *Synthesis* **1998**, 899–904; Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361–12378; Tamao, K.; Kawachi, A. *Organometallics* **1995**, *14*, 3108–3111; Block, E.; Guo, C.; Thiruvazhi, M.; Toscano, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 9403–9404; Block, E.; Schwan, A.; Dixon, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 3492–3499; Tanaka, K.; Minami, K.; Funaki, I.; Suzuki, H. *Tetrahedron Lett.* **1990**, *31*, 2727–2730; McDougal, P. G.; Condon, B. D. *Tetrahedron Lett.* **1989**, *30*, 789–790; Keys, B. A.; Eliel, E. L.; Juaristi, E. *Israel J. Chem.* **1989**, *29*, 171–186; Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Selim, M. R. *Tetrahedron Lett.* **1987**, *28*, 693–696; Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915–916; Barluenga, J.; Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183–194; Yus, M.; Concellón, J. M.; Bernad, P.; Alvarez, F. J. *Chem. Res. (S)* **1985**, 128–129; Lyle, T. A.; Mereyala, H. B.; Pascual, A.; Frei, B. *Helv. Chim. Acta* **1984**, *67*, 774–778; Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3019–3026; Kuwajima, I.; Takeda, R. *Tetrahedron Lett.* **1981**, *22*, 2381–2384.
- Recent reviews: (a) Strohmman, C.; Schildbach, D. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley: New York, 2004. Chapter 15; Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: London, 2002. Chapter 4; recent papers reporting the use of LDBB: Refs. 2, 7a and 8a and (b) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144–1161; Chen, W.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett.* **2006**, *8*, 2087–2090; Morin, M. D.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 2051–2053; La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873–1875; de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853–1856; Cooksey, J.; Gunn, A.; Kocienski, P. J.; Kuhl, A.; Uppal, S.; Christopher, J. A.; Bell, R. *Org. Biomol. Chem.* **2004**, *2*, 1719–1731; Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569–572.
- In some cases this was due to the sensitivity of the product of electrophile capture to the acid that was used to remove the dimethylaminonaphthalene byproduct: Brockunier, L. L., MS Thesis, University of Pittsburgh, 1988, p 21. However, even when the product is not acid-sensitive, some preliminary trials had indicated that LDBB gave superior results.
- Cohen, T.; Sherbine, J. P.; Hutchins, R. R.; Lin, M. T. *Organomet. Synth.* **1986**, *3*, 361–368.
- For 17 years after our introduction of LDMAN, members of our group have prepared this aromatic radical-anion in such a way as to maintain a temperature at least as low as -45°C as suggested in our published procedure.^{3,11} However, occasional irreproducibility and poor yields (for one literature example, see: Paquette, L. A.; Wells, G. J. *Tetrahedron Lett.* **1982**, *23*, 259–262) led to speculation that lower temperatures may lead to better results and starting in 1999, the temperature of -55°C was generally aimed for during the generation of LDMAN, although careful temperature control was not generally sought; apparently the first example was the lower temperature to prepare LDMAN only for the synthesis of **24** in: Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291–3304. However, most other groups that have reported the use of LDMAN are still using the original recipe.
- There may be automatic temperature controllers that can maintain the required narrow range, but we are unaware of any at this time.
- General procedure for the reductive lithiation with LDMAN: To a three-neck round bottomed flask, equipped with a magnetic stirrer, argon inlet and a rubber septum was added 40 mL of dry THF. The flask was cooled to -55°C . Lithium ribbon was prepared by scraping the dark oxide coating off of the surface while it was immersed in fresh mineral oil. The shiny metal was dipped into dry hexane in order to remove the oil and then weighed (0.1852 g, 0.0268 mol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexane prior to the addition to the flask. Then DMAN (4.9 mL, 0.030 mol) was added quickly via syringe at -55°C . A green color appeared in less than two minutes and became deep green in less than 5 min. The reaction mixture was stirred for 5 h at $-55 \pm 3^{\circ}\text{C}$, and the resulting LDMAN solution was suitable for reductive lithiation of 0.0127 mol of substrate.
- Abou, A.; Foubelo, R.; Yus, M. *Arkivoc* **2007**, v, 191–201.