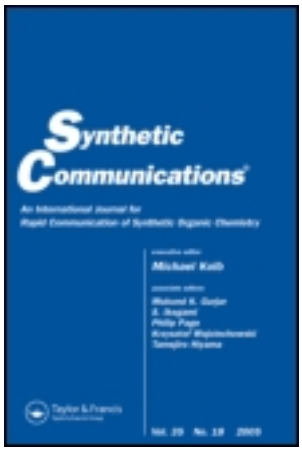

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Aug 2006.

To cite this article: Mohammad M. Mojtahedi , Mohammad R. Saidi , Jafar S. Shirzi & Mohammad Bolourtchian (2001) ULTRASOUND ACCELERATED REDUCTIVE COUPLING OF IMINE OR IMINIUM ION GENERATED IN 5 M LITHIUM PERCHLORATE SOLUTION BY LITHIUM METAL, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:23, 3587-3592, DOI: 10.1081/SCC-100107005

To link to this article: http://dx.doi.org/10.1081/SCC-100107005

SYNTHETIC COMMUNICATIONS, 31(23), 3587–3592 (2001)



# ULTRASOUND ACCELERATED REDUCTIVE COUPLING OF IMINE OR IMINIUM ION GENERATED IN 5 M LITHIUM PERCHLORATE SOLUTION BY LITHIUM METAL

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## ABSTRACT

A novel one-pot reductive coupling of imine or iminium ion generated in the concentrated ethereal lithium perchlorate solution was achieved in the presence of lithium metal. The yield of the reaction depends on the reactivity preformed imine or iminium ion. Diamines were formed with high diastereoselectivity in some cases in about 5 h. The reaction time was doubled without the use of ultrasound acceleration.

*Corresponding author.

Vicinal diamines occur frequently in natural products and medicinal compounds. The synthesis of aromatic vicinal diamines by various methods has been an active area of research for many years. As a result many methods are currently available in the literature.[1,2] The reductive coupling of imines can be used as a method for synthesis of these compounds. The reductive coupling of aldimines catalyzed by titanium tetrachloride,[2] chlorosilane and zinc metal,[3] samarium diiodide and nickel diiodide,[4] and a great variety of other reagents,[5] are well-documented chemistry with wide applications.

Imines and iminium salts are important intermediates in organic synthesis. These salts may be produced *in situ* by the reaction of lithium hexamethyldisilazane or (trimethylsilyl)dialkyl amines with various aromatic aldehydes, promoted by a 5 M solution of $LiClO_4$ in diethyl ether[6–8] (Scheme 1).

$$\underset{\mathbf{1}}{ArCHO} + (Me_3Si)_2NLi \xrightarrow[r\,t]{LiClO_4/\ ether} \underset{\mathbf{2}}{[Ar\text{-}CH = NSiMe_3]}$$

$$ArCHO + Me_3SiNR_2 \xrightarrow[r\,t]{LiClO_4/\ ether} \underset{\mathbf{3}}{[Ar\text{-}CH = N\,R^{+}_{2}]}$$

***Scheme 1.***

In continuation of our research studies on Mannich type reactions, we now report the one-pot reductive coupling of imine or iminium ion generated in 5 M lithium perchlorate solution by lithium metal. Aromatic aldehydes and lithium hexamethyldisilazane or (trimethylsilyl)dialkyl amines in the concentrated ethereal lithium perchlorate solution produce the imine or iminium salts very quickly as an intermediate at room temperature, which can be detected in the solution by $^{13}C$ NMR spectroscopy.[9,10] Upon addition of lithium metal to the preformed imine or iminium ion in 5 M ethereal $LiClO_4$ solution under sonocation, followed by aqueous work-up, the coupling product (diamine) was produced in about 5 h. By this method, variety of diamines **4** and **5** could be synthesized within 5 h in moderate to good yields with high diastereoselectivity in some cases (Scheme 2). From a series of experiments, we found that 2.5 equivalent of lithium metal was required for the maximum yields of aromatic diamines. Increasing the reaction time did not change the yield of the products. Without sonocation, the reaction time was more than 10 h. The vicinal diamines are obtained as a diastereomeric (*meso : dl*) mixture. The stereochemical assignment of the vicinal diamine





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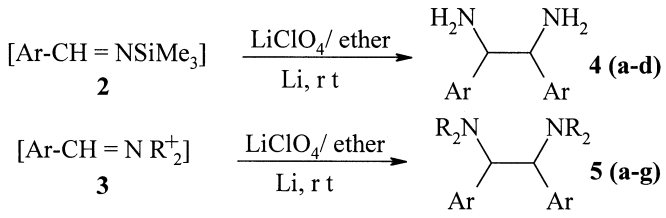



*Scheme 2.*

was made by comparison of the resonance of benzylic protons for the *meso* and *dl* isomers as reported in the literature.[11] The diastereomeric ratio was determined by NMR from the non-equivalent benzylic protons and carbon (in $^{1}H$ and $^{13}C$ NMR) with *meso*/*dl* ratio between 97 and 52. As indicated in Tables 1 and 2, the isolated yield of vicinal diamines varies from 36% to 87%. The low yield of the diamine **4d** is due to the low reactivity of imine **2**.

***Table 1.*** Reductive Dimerization of Imine by Li Metal

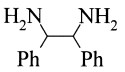
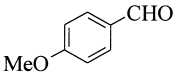
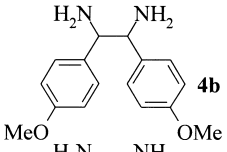
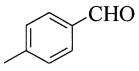
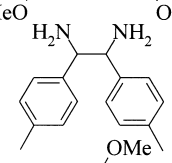
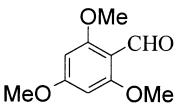
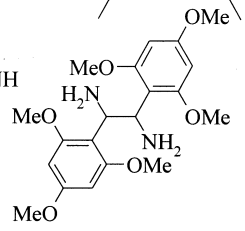
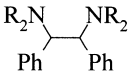
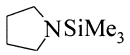
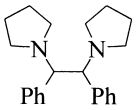
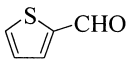
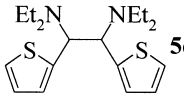
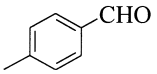
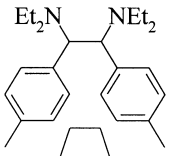
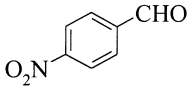
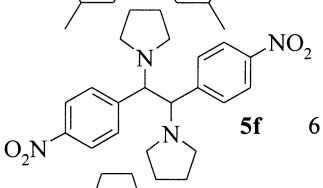
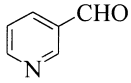
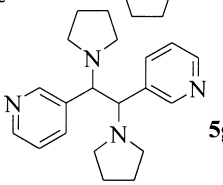
| Starting aldehyde | $Me_3SiNR_2$ | vicinal diamine | meso:dl ratio | %Yield |
|---|---|---|---|---|
| PhCHO | $(Me_3Si)_2NH$ |  **4a** | 76:24 | 42 |
|  | $(Me_3Si)_2NH$ |  **4b** | 95:5 | 44 |
|  | $(Me_3Si)_2NH$ |  **4c** | 97:3 | 54 |
|  | $(Me_3Si)_2NH$ |  **4d** | 74:26 | 36 |

***Table 2.*** Reductive Dimerization of Iminium Ion by Li Metal

| Starting aldehyde | $Me_3SiNR_2$ | vicinal diamine | meso:dl ratio | %Yield |
|---|---|---|---|---|
| PhCHO | $Me_3SiNMe_2$ |  **5a,** R=Me<br>**5b,** R=Et | 38:62<br>41:59 | 60<br>52 |
| PhCHO |  |  **5c** | 55:45 | 57 |
|  | $Me_3SiNEt_2$ |  **5d** | 46:54 | 56 |
|  | $Me_3SiNEt_2$ |  **5e** | 48:52 | 40 |
|  |  |  **5f** | 61:39 | 73 |
|  |  |  **5g** | 38:62 | 87 |

## EXPERIMENTAL

CAUTION: Although we did not have any accident using lithium perchlorate ($LiClO_4$), it is advisable to dry lithium perchlorate in a hood behind a lab-shield.

### General Procedure for the Preparation of Vicinal Diamine from an Aldehyde

Method A: The aldehyde (2 mmol) and 3 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon and stirred for 5 min.





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(Trimethylsilyl)dialkyl amines (3 mmol) was then added via syringe. After 10 min, lithium metal (5 mmol, 35 mg) was added and the mixture stirred for 5 h at room temperature under sonocation. Then, ether (30 mL) was added and excess lithium metal removed by filtration. About 30 mL of water was added to the filtrate and the organic phase was separated, dried over $MgSO_4$, and the solvent was removed by the means of rotary evaporator. The crude material was further purified by chromatography on basic alumina or aqueous acid extraction, if needed.

Method B: Hexamethyldisilazane (3.3 mmol, 0.54 g) was placed in two-necked flask fitted with a condenser, and a stirring bar under argon, and 3.5 mmol of sodium hydride (60–65%, after washing with light pet. ether) or 3.4 mmol of methyllithium in dry diethyl ether was added, and the mixture was stirred for about 5 min. Then 3 mL solution of 5 M lithium perchlorate in diethyl ether and 2 mmol of aldehyde were added via syringe. After stirring for 30 min, lithium metal (5 mmol, 35 mg) was added and the mixture stirred for 5 h at room temperature under sonocation. Then, ether (30 mL) was added and excess lithium metal removed by filtration. About 30 mL of water was added to the filtrate and the organic phase was separated, dried over $MgSO_4$, and the solvent was removed by the means of rotary evaporator. The crude material was further purified by chromatography on basic alumina or aqueous acid extraction, if needed.

In conclusion, we have described one-pot reductive coupling of aromatic imine or iminium ion derivatives generated in 5 M lithium perchlorate solution by lithium metal, with formation of 1,2-diarylethylendiamines or *N*,*N*,*N*′,*N*′-tetraalkyl-1,2-diarylethylendiamines which was accelerated by ultrasound. 1,2-Diarylethylendiamines were formed with high diastereoselectivity in some cases in about 5 h. The reaction time was doubled without the use of ultrasound acceleration.

## SELECTED SPECTROSCOPIC DATA

**5a** (dl isomer); IR (neat): $\nu = 2930$, 1630, 1453, 707 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 2.04$ (s, 12H), 4.25 (s, 2H), 7.10–7.30 (m, 10H). $^{13}C$ NMR ($CDCl_3$): $\delta = 40.4$ ($CH_3$), 67.5 (CH), 126.8 (CH), 128.1 (CH), 129.0 (CH), 132.5 (C). MS, *m*/*z*: 268 ($M^+$), 134 (base peak), 91 and 77.

**5d** (meso isomer); IR (neat): $\nu = 2953$, 2815, 1600, 1453, 1253, 1130, 846, 707 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 0.81$ (t, 12H, 7.1 Hz), 1.85–2.34 (m, 8H), 4.48 (s, 2H), 6.60–7.25 (m, 6H). $^{13}C$ NMR ($CDCl_3$): $\delta = 13.3$ ($CH_3$), 44.1 ($CH_2$), 61.9 (CH), 123.0 (CH), 125.1 (CH), 126.2 (CH), 140.9 (C). MS, *m*/*z*: 336 ($M^+$), 168 (base peak), 97, 85 and 56.





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**5e** (dl isomer); IR (neat): $\nu = 2969, 2807, 1615, 1515, 1453, 1384, 1115, 807\,cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 0.75$ (t, 12H, 6.8 Hz), 1.85–2.15 (m, 8H), 2.32 (s, 6H), 4.32 (s, 2H), 6.90–7.20 (m, 8H). $^{13}C$ NMR ($CDCl_3$): $\delta = 13.7$ ($CH_3$), 20.9 ($CH_3$), 43.4 ($CH_2$), 63.6 (CH), 127.5 (CH), 129.2 (CH), 134.7 (C), 135.3 (C). MS, *m*/*z*: 352 ($M^+$), 176 (base peak), and 105.

**4b** (meso isomer); $^1H$ NMR ($CDCl_3$): $\delta = 2.06$ (broad s, 4H), 3.72 (s, 6H), 4.51 (s, 2H), 6.79 (d, 4H, J = 8.8 Hz), 7.20 (d, 4H, 8.8 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta = 55.0$ ($CH_3$), 65.1 (CH), 123.7 (CH), 128.3 (CH), 130.2 (C), 134.8 (C). MS, *m*/*z*: 272 ($M^+$), 136, 121 (base peak), 97, 95 and 57.

## ACKNOWLEDGMENTS

We thank "Volkswagen-Stiftung, Federal Republic of Germany" for financial support towards the purchase chemicals. M. R. Saidi thanks Iranian National Research Council for partial financial support.

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Received in Japan November 7, 2000