Efficient Mono- and Dilithiation of 2-Bromo-1,1-diphenylethene with n-Butyllithium/Tetramethylethylenediamine

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Abstract: Lithiation of 2-bromo-1,1-diphenylethene (2) with n-butyllithium or tert-butyllithium/tetramethylethylenediamine (TMEDA) in pentane at –100 °C effects a halogen–lithium exchange to give 2-lithio-1,1-diphenylethene (3) exclusively, which reacts with electrophiles to provide 2-substituted-1,1-diphenylethenes 5–8 in high yields. Further lithiation of the monolithium derivative 3 with n-butyllithium/TMEDA results in the direct ortho-lithiation of the located phenyl ring to give dilithium derivative 9, which forms disubstituted ethenes 11–13 or heterocycles 15–17 on treatment with electrophiles. tert-Butyllithium/TMEDA is ineffective for the second lithiation step.

Key words: halides, lithiation, organometallic reagents, complexes, regioselectivity

Two different reaction pathways are known for the lithiation of 2-halo-1,1-diphenylethenes.2,3 The first path includes proton removal (Scheme 1, route a) under the action of a strong base with the formation of 1-halo-1-lithioethene A. In the case of the chloro derivative (X = Cl) this intermediate is sufficiently stable at low temperature (–100 to –85 °C) to react with electrophiles, like CO₂ or Br₂, resulting in the formation of 1-substituted 1-halo-2,2-diphenylethenes in moderate yields.4,6 At higher temperature or in the cases of bromo and iodo derivatives (X = Br, I), which are significantly more reactive, A readily rearranges into diarylacetylene B.3,9 This classical example of the anionic rearrangement was discovered in 189410 and recognised as a very suitable way for the synthesis of diarylacetylenes.7,8

The second possibility is halogen–metal exchange (Scheme 1, route b) to give the vinyllithium C.5,11,12 This way is more distinctive for bromo- and iodo-derivatives (X = Br, I) and provides a versatile synthetic tool for the preparation of 2-substituted 1,1-diarylethene D. Unfortunately, this halogen-metal exchange is accompanied usually by the formation of acetylenes that reduce the synthetic scope of the reaction.12,13

We wish to report here improved conditions for selective and efficient halogen–lithium exchange in 2-bromo-1,1-diphenylethene (2) in the presence of TMEDA, which result in the formation of 1,1-diphenylethylene derivatives on treatment of the intermediate vinyllithium compound 3 with electrophiles. Alternatively, the vinyllithium compound 3 can undergo further lithiation of the phenyl ring.

Lithiation of 2-bromo-1,1-diphenylethene (2) with 3 equivalents of n-BuLi or t-BuLi in pentane in the presence of 3 equivalents of TMEDA results in complete halogen-lithium exchange at –100 °C already within 20 minutes (Scheme 2). Product distribution at different temperatures were investigated by treatment of the reaction mixture with iodine (Table 1). At –100 °C the iodide 5 together with a small amount of ethene 1 were identified as the only products along with traces of the starting bromide 2 (<2%). When the reaction was allowed to warm to 0 °C during 1 h, further deactivation of the lithium derivative 3 to ethene 1 was observed. No rearranged tolane 4 was detected not only after instant warming up, but also on keeping the reaction mixture at 20 °C during 10 hours. TMEDA is of great importance for this reaction since only 5% of bromide 2 underwent Br–Li exchange to form lithium derivative 3 and 95% of the starting bromide 2 were recovered in the absence of TMEDA. On the one hand, TMEDA accelerates Br–Li exchange in bromoethene 2, and on the other hand it stabilises the intermediate vinyllithium compound 3 in a form of a complex up to room temperature and prevents its deactivation to ethene 1.

Since the yield of the lithium derivative 3 under original conditions was nearly quantitative, it was of interest to examine its reaction with various electrophiles. The lithium derivative 3 was readily converted into substituted ethenes 5–8 in high yields (93–96%) by treatment with iodine, methanol-d₄, deuterium oxide, dimethyl sulfate or chlorotrimethylsilane, respectively (Table 2). Products were identified by MS, NMR and IR spectra and by comparison with the data reported in the literature.
In principle, only 2 equivalents\(^{14}\) of \(n\)-BuLi are required for the successful Br–Li exchange under the same conditions, and only traces of the rearranged tolane \(4\) (<1\%) were detected in the reaction mixture by GC in this case. Diethyl ether increases deactivation of the lithium derivative \(3\) resulting in the formation of 5–10% of ethene \(1\) when used as a co-solvent to pentane (Table 1).

It is interesting, that further metalation of the lithium derivative \(3\) in the ortho-position of the \(Z\)-located phenyl ring took place at temperatures higher than 0 °C when 3 equivalents of \(n\)-BuLi/TMEDA were used. The reaction was monitored by treatment with iodine, as before (Scheme 3, Table 1). More than 90% of vinyllithium \(3\) turned to the dilithium derivative \(9\) after 4 hours stirring at 20 °C. Further keeping of the reaction mixture at this temperature or under reflux caused deactivation of \(9\) with the formation of the vinyllithium derivative \(3\) and ethene \(1\).

No rearranged tolane \(4\) was detected also in this case by GC and \(^{13}\)C NMR analysis.

Scheme 3  Reagents and conditions: a) \(n\)-BuLi (3 equiv) or \(t\)-BuLi (3 equiv), TMEDA (3 equiv), pentane, –100 °C, 20 min; b) electrophile, –90 °C.

Unexpectedly \(t\)-BuLi/TMEDA was ineffective for further metalation of \(3\) to \(9\), and formation of ethene \(1\) was the only process on stirring the reaction mixture at 20 °C over a 4 h period. Upon refluxing the reaction mixture for 2 h, the formation of rearranged tolane \(4\) became essential (11\%), and dilithium derivative \(9\) was formed only in traces (<3\%) together with the formation of vinyllithium \(3\) and ethene \(1\).

No rearranged tolane \(4\) was detected also in this case by GC and \(^{13}\)C NMR analysis.

Scheme 2  Reagents and conditions: a) \(n\)-BuLi (3 equiv) or \(t\)-BuLi (3 equiv), pentane, –100 °C, 20 min; b) electrophile, –90 °C.

**Table 1** Reaction Conditions and Products Distribution from the Lithiation of \(2\) Followed by \(I_2\)-Quench\(^{a}\)

<table>
<thead>
<tr>
<th>Base/Reaction Conditions</th>
<th>Products</th>
</tr>
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<tbody>
<tr>
<td><strong>(n)-BuLi</strong></td>
<td></td>
</tr>
<tr>
<td>–100 °C</td>
<td>&lt;2 (&lt;2) 89 (95) – (–) 11 (&lt;1) – (–)</td>
</tr>
<tr>
<td>–25 °C</td>
<td>– (–) 84 (95) 5 (–) 11 (4) – (–)</td>
</tr>
<tr>
<td>0 °C</td>
<td>– (–) 70 (95) 20 (–) 7 (3) (–)</td>
</tr>
<tr>
<td>20 °C, 0.5 h</td>
<td>– (–) 57 (17) 35 (78) 4 (&lt;1) (–)</td>
</tr>
<tr>
<td>20 °C, 4 h</td>
<td>– (–) 7 (6) 81 (90) &lt;1 (&lt;1) (–)</td>
</tr>
<tr>
<td>20 °C, 10 h</td>
<td>– (–) 12 (5) 70 (91) 6 (&lt;1) (–)</td>
</tr>
<tr>
<td>Reflux, 2 h</td>
<td>– (–) 25 (3) 20 (92) 34 (&lt;1) (&lt;1)</td>
</tr>
<tr>
<td>20 °C, 10 h</td>
<td>95(^{b}) 4 – (–) – (–)</td>
</tr>
<tr>
<td><strong>(t)-BuLi</strong></td>
<td></td>
</tr>
<tr>
<td>–100 °C</td>
<td>&lt;2 90 – 10 –</td>
</tr>
<tr>
<td>0 °C</td>
<td>– 57 – 39 –</td>
</tr>
<tr>
<td>20 °C, 0.5 h</td>
<td>– 51 – 43 –</td>
</tr>
<tr>
<td>20 °C, 4 h</td>
<td>– 38 – 55 –</td>
</tr>
<tr>
<td>20 °C, 10 h</td>
<td>– 16 – 73 –</td>
</tr>
<tr>
<td>Reflux, 2 h</td>
<td>5 3 60 11</td>
</tr>
</tbody>
</table>

\(^{a}\) Ratio \(n\)-BuLi or \(t\)-BuLi/TMEDA/2 = 3:3:1; solvent: pentane–Et\(_2\)O (1:1); in parenthesis for pentane only; reaction mixture was quenched with \(I_2\); analysis of the crude reaction mixture by \(^1\)H NMR and GC-MS; yields are determined by GC.

\(^{b}\) Reaction without TMEDA.
The most significant spectral evidence for the ortho-substitution in the aromatic ring was provided by the $^1$H NMR spectrum of diiodide 11 which showed 4 unequal multiplets from 4 protons in the ortho-substituted aromatic ring (experimental part). In order to confirm the lithiation of the Z-located phenyl ring in 3, compound 9 was treated with sulfur dichloride and dichlorodimethylsilane. Products with the correct spectral characteristics for benzothiophene 17 and silaindenone 15 were obtained in 84 and 88% yields, respectively. Similarly, treatment of 9 with dichlorodimethylstannane gave stannaindene 16 in 74% yield. It is interesting to note that, the treatment of dilitium derivative 9 with chlorotrimethylsilane results in the formation of cyclic silaindenones 15 together with some amount of mono-substituted ethene 8, and no disilylated ethene 14 was identified by NMR and GC-MS analysis in the reaction mixture. Nearly the same cyclization was reported earlier, when the reaction of 2,2'-bislithiobiphenyl with chlorotrimethylstannane afforded 5,5-dimethyldibenzostannane in 34% yield instead of the expected 2,2'-bis(trimethylstannyl)biphenyl.\(^{15}\)

In conclusion, TMEDA selectively accelerated Br–Li exchange in bromoethene 2 resulting in the formation of mono- and dilitium derivatives 3 and 9 in high yields. They serve as key intermediates for the facile and convenient preparation of 1-substituted-2,2-diphenylethenes 5–8 and disubstituted ethenes 11–13 and various heterocycles 15–17 in good yields.

All procedures were carried out under N$_2$. Pentane, Et$_2$O, THF and TMEDA were dried and distilled consecutively over sodium and NaH under N$_2$. Commercially available dimethyl sulfate (DMS), chlorotrimethylsilane (CTMS), dichlorodimethylsilane (DCDMS), dichlorodimethylstannane (DCDMS) and sulfur dichloride (SDC) were deoxygenated by a slow stream of N$_2$ for 10–15 min before use. Standard solutions of n-BuLi in hexane (1.6 M) and t-BuLi (1.6 M) in pentane were analysed before use by titration with anhyd MeOH using 2,2'-bipyridyl as indicator.\(^{16}\) Mixture of EtOH and liquid N$_2$ was used as a cooling bath (–100 to –105 °C).\(^{17}\) H,\(^{13}\)C NMR spectra were recorded on a Bruker ARX 400 instrument at 400.14, 61.42 and 100.62 MHz respectively, chemical shifts are given in $\delta$ (ppm). El mass spectra were determined at 70 eV by using a HP 5989B spectrometer. IR spectra were recorded on a Pye UNICAM SP3-200 spectrometer. Analytical TLC was performed on Kieselgel 60 F$_254$ and Al$_2$O$_3$ 60 F$_{254}$ neutral (Type E) plates (Merck). Al$_2$O$_3$ (Fluka) for chromatography (100–125 mesh, neutral) and silica gel 60 (Merck) for chromatography (63-200 mesh, neutral) were used as sorbents. Melting points are uncorrected.

2-Bromo-1,1-diphenylethen (2) was synthesised by the reaction of 1,1-diphenylethene (1) with bromine in CCl$_4$.\(^2\) The crude product was dissolved in CH$_2$Cl$_2$ was washed with 10% aq NaHCO$_3$ and purified by two consecutive distillations under N$_2$ in 80% yield as a solid with spectroscopic data identical to those reported in the literature (IR,\(^{17}\)1 H NMR,\(^{18}\)13 C NMR\(^{19}\)). Bp 100–104 °C/0.1 mbar; mp 40–41 °C (Lit.\(^2\) bp 124–140 °C/1.0 mbar; mp 40–41 °C).

\[ \text{Scheme 4} \quad \text{Reaction conditions: a) electrophile, } -100 \text{ °C.} \]

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2-Lithio-1,1-diphenylethen (3) A solution of n-BuLi in hexane (1.25 mL, 2 mmol) was added to a solution of TMEDA (0.3 mL, 2 mmol) in pentane (10 mL) at –100 °C (internal temp) during 1 min and the reaction mixture was stirred at –100 °C for 10 min. A solution of the bromide 1 (259 mg, 1 mmol) in pentane (5 mL) was added dropwise at –100 °C over a 3 min period and the mixture was allowed to warm to 0 °C over a 30 min period resulting in the formation of orange-yellow solution of 3. A solution was again cooled to –90 °C and thus generated suspension of 3 was used for further reactions.

2-Iodo-1,1-diphenylethen (5): General Procedure Excess of powdered I$_2$ (493 mg, 2 mmol) was added at –90 °C (internal temp) during 4 min to a stirred suspension of 3 prepared as above. The reaction was allowed to warm to 20 °C over a 1 h period.
and was stirred at this temperature for the next 3 h. The mixture was treated with 10% aq Na₂S₂O₃ to destroy the excess of I₂, the light yellow organic layer was separated, and the aqueous phase was extracted with Et₂O (3 × 5 mL). The combined organic phases were washed with H₂O, dried (Na₂SO₄), and the crude product was purified by column chromatography over silica gel (10 g) using hexane as eluent (200–500 mL); yield: 284 mg (93%); mp 39–40 °C (Lit.² 40–41 °C).

³¹C NMR (CDCl₃): δ = 152.7 (Ph₂Cn), 141.8, 141.1, 129.4, 128.3, 128.2, 128.0, 127.9, 79.0 (CH₃).

IR: ν= 3065, 3037, 3025, 2965, 2927, 1965, 1938, 1446, 1431, 1393, 1351, 1345, 1307, 1238, 1205, 1255, 1155, 1100 cm⁻¹.

MS: m/z (%) = 432 (8, M⁺), 306 (15), 305 (92), 179 (15), 178 (100), 159 (14), 158 (44), 157 (20).
\(1^1\text{H NMR (CDCl}_3\): } \delta = 7.59 (dd, 1 H, H-7, J = 6.6, 1.3, 1.0 Hz), 7.45–7.21 (m, 8 H, Ar), 6.16 (s, 1 H, =CHSi), 0.37 [s, 6 H, Si(CH}_3\)].

\(1^3\text{C NMR, IR and MS were in a good agreement to those partially reported.}\)

### 1.1-Dimethyl-3-phenyl-1-stannaindene (16)

A solution of DCDMST (439 mg, 2 mmol) in Et_2O (5 mL) was added dropwise to a suspension of 3 mmol of \(-\text{BuLi}\) (192 mg, 3 mmol), TMEDA (348 mg, 3 mmol) and bromide \(1\) in THF (15 mL) as an alternative to pentane starting from 3 mmol of \(n\text{-BuLi}\). The solution was removed at reduced pressure (50 mbar) and the residue was extracted with pentane (5 x 5 mL). The combined extracts were concentrated and yellow-orange oil was distilled in a Kugelrohr apparatus at 190–210 °C/0.1 mbar; yield: 483 mg (74%); colourless oil.

An attempt was made to use column chromatography on alumina for the purification of 10, but only ethene 1 in nearly quantitative yield was eluted with Et_2O.

### References

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15. One equivalent of n-BuLi is required for the metatlation of 2 to 3. The second equivalent reacts with butyl bromide formed to turn the metalation equilibrium to the side of products: 2 + BuLi ⇌ 3 + BuBr, BuLi + BuBr −→ Bu–Bu + LiBr.


