Substitution Reactions of Specifically Ortho-Metalated Piperonal Cyclohexylimine

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The specific ortho metalation of piperonal and 6-bromopiperonal cyclohexylimine is discussed. Typical reactions of the lithio and cuprous organometallics are explored.

Since the observations of Hauser2 concerning the stabilizing effect of a neighboring tertiary amine on the stability of ortho-lithiated aryls, this type of reaction has been applied to monosubstituted amides,3 oxazolines,4 and imines.5 Reiff has observed6 that when acetophenone cyclohexylimine is treated with n-butyllithium (n-BuLi) in ether at -78 °C, addition to the imine is the major reaction pathway with minor effect of a neighboring tertiary amine on the stability of the methyl group and the ortho position.

We have observed in the instance of piperonal cyclohexylimine (1a) that reaction with n-BuLi in tetrahydrofuran (THF) at 0 °C afforded products of imine addition. When the temperature was lowered to -78 °C, only lithiation at the 2 position (1b) was observed, since low-temperature deuteration provided 2-deuteriopiperonal cyclohexylimine (1d) with a characteristic ortho-coupling pattern in its NMR spectrum.6 When 6-bromopiperonal cyclohexylimine (2e) was lithiated at -78 °C, the NMR spectrum of the deuterium oxide quenched product indicated that deuteration had occurred exclusively at the 6 position (2d). However, when the 6-lithiated imine was allowed to warm to ambient temperature and then quenched with iodine at the same temperature or at -78 °C, only the 2-iodomine 1f was observed. Thus, the 2 position of imine 1a is the site of kinetic and thermodynamic lithiation due to the electron-withdrawing effect of the adjacent oxygen atom. In the latter case, metal–halogen exchange is the kinetic process rather than C-2 deprotonation.7 The equilibration is thought to be promoted by piperonal cyclohexylimine acting as a proton source. Although a sufficient excess of butyllithium was used in control runs to ensure the metal–halo exchange of all of the piperonalimine, exchange still occurred. This may imply a disproportionation in which 2 mol of 6-lithiated imine affords 2,6-dilithiated imine and piperonalimine, thereby generating the necessary exchange medium. Alternatively, decomposition (i.e., oxidation and hydrogen abstraction from THF) would also generate piperonalimine.

Both ortho-lithiated imines were subjected to alkylation with allyl bromide and methyl iodide. The data in Table 1 under entries A and B indicate that methylation is virtually

References and Notes

(1) W. Reinders and W. E. Ringer, Recl. Trav. Chim. Pays-Bas, 18, 326 (1899). A more recent, noteworthy, report is due to J. H. Gorvin (Chem. Ind. (London), 56, 1526 (1967)) who found that 4-nitrobenzenophenone readily undergoes replacement of the nitro group by methoxide ion in dipolar aprotic solvents. Still more recently the reaction of sodium phenoxide with 1,2-dihalo-1-nitroalkanes has been described [E. Radmann, W. Schmidt, and G. E. Nitsch, Makromol. Chem., 130, 45 (1969)]. The fact that certain nitrophenol imides undergo replacement of the nitro group by methoxide ion is also of interest [L. Caswell and T. Kao, J. Heterocyclic Chem., 3, 333 (1966)].


(3) Actually, the product of eq 2 is methyl 3-hydroxybenzo[d]thiophene-2-carboxylate which results upon cyclization of 2.


(6) Our thanks are due to Dr. C. S. Yeh and her associates for the microanalyses.


(9) N. Kornblum and A. Scott, to be published.


(11) We are indebted to E. L. DuPont de Nemours and Co. for a generous supply of HMPA.

(12) This compound when prepared from p-cyanocumyl chloride has mp 60–60.5 °C: R. T. Swiger, Ph.D. Thesis, Purdue University, 1970.

(13) H. Meyer, Ber., 38, 2492 (1905).


(15) J. Houwen and W. Fischer, Ber., 64, 240 (1931).

(16) Sadtler Reag. no. 26471; NMR no. 476.


(22) R. C. Kerker, Ph.D. Thesis, Purdue University, 1965.


(26) F. Meyer, Ber., 42, 3050 (1909).
Ortho-Metalated Piperonal Cyclohexylimine

**Table I**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>1h</th>
<th>2h</th>
<th>1i</th>
<th>2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>61 (0)</td>
<td>79 (1)</td>
<td>61 (12)</td>
<td>57 (31)</td>
</tr>
<tr>
<td>B</td>
<td>69 (9)</td>
<td>66 (2)</td>
<td>11 (59)</td>
<td>56 (18)</td>
</tr>
<tr>
<td>C</td>
<td>94 (4)</td>
<td>86 (8)</td>
<td>71 (11)</td>
<td>53 (1)</td>
</tr>
<tr>
<td>D</td>
<td>61 (15)</td>
<td>66 (9)</td>
<td>62 (3)</td>
<td>61 (3)</td>
</tr>
</tbody>
</table>

A: BuLi (−78 °C); RX (−78 °C, 3 h); warm to room temperature; H₂O; H₂O₂
B: BuLi (−78 °C); RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H₂O; H₂O₂
C: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); warm to room temperature; H₂O; H₂O₂
D: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H₂O; H₂O₂

*Yields are absolute and unless specified are determined by GLC and corrected for differences in thermal conductivity.*

**Table II**

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>From 1b</th>
<th>From 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₂O</td>
<td>100⁰⁶</td>
<td>100⁰⁶</td>
</tr>
<tr>
<td>Cl₂O</td>
<td>60⁰⁶</td>
<td>64⁰⁶</td>
</tr>
<tr>
<td>CO₂</td>
<td>54⁰⁶</td>
<td>43⁰⁶</td>
</tr>
<tr>
<td>CICO₂Me</td>
<td>68⁰⁶</td>
<td>66⁰⁶</td>
</tr>
</tbody>
</table>

*Electrophiles: D₂O, Cl₂O, CO₂, CICO₂Me.*

**Experimental Section**

Melting points (corrected) were determined on a Fisher-Johns apparatus. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. NMR spectra were determined on a JEOLO MININAR 100-II NMR or Perkin-Elmer R-39 90-MHz spectrometer, using Me₃Si (δ) as an internal standard. Gas chromatographic analyses were performed on a Varian 90-20 programmable (GC) using a 20 ft, 80/100 SE-20 on an Analarom 50/70 SD column. Tetrachloroethylene was distilled from sodium benzenophenoine ketyl. All glassware was flame dried prior to use.

**Preparation of Piperonal Cyclohexylimines**

The imines were prepared from the aldehydes (1.0 equiv) and cyclohexylamine (1.2 equiv) in the presence of copper. Although a change in mechanism for the imine formation was observed, the lithiated imine could be obtained in greater yield when the aldehyde was metalated in the absence of copper. The imines were obtained by metalation from methanol or distillation provided the imines in the reaction mixture were deuterated at C-2. In a similar fashion 2b provided 2d which showed no resonance at the C-2 position. In a similar fashion 2b provided 2d which showed no resonance at the C-2 position.
The 6-lithiated imine 2b afforded 459 mg (64%) of 2f as white needles. The combined organic extracts were washed with 5% NH₄OH, dried (MgSO₄), filtered, and concentrated. Hydrolysis afforded a solid.

Methyl 2-allylpiperonal (2i) was prepared as a crude oil: NMR (CDCl₃, FT) δ 6.02 (2 H, s), 6.71 (1 H, s), 7.31 (2 H, s), 7.29 (2 H, s), and 10.18 (1 H, s).

2-Formyl-5,5-methyleneoxybenzoic Acid (1j). To a 2 ml solution of 2f (1 mmol) in THF, 15 ml of 10% HCl and 15 ml of ether were added and the mixture was stirred at -78 °C. After warming to room temperature, 15 ml of 10% HCl and 15 ml of ether were added and the mixture stirred overnight. The organic layers were separated, extracted with 10% aqueous KCl, acidified with concentrated HCl, and concentrated, providing 211 mg (54%) of acid upon recrystallization from water: mp 105.5-106.5 °C (lit. 167 °C); ir (CHCl₃) 1763 cm⁻¹ (lactol); NMR (acetone-d₆) δ 3.8 (1 H, br s, lactol -OH, D₂O exchange), 6.22 (2 H, 7.1-7.3 (2 H, m, aryl). Methylation with CH₃₂O₃ provided ester 1k. mp 103.5-105.5 °C.

In a similar fashion, 2-formyl-4,5-methyleneoxybenzoic acid (2j) was prepared from 2b (45%): mp 105.5-106.5 °C (lit. 167 °C); ir (CHCl₃) 1775 cm⁻¹ (lactol); NMR (acetone-d₆) δ 2.9 (1 H, br s, lactol OH, D₂O exchange), 6.21 (2 H, 6.01 (1 H, br s, methine), and 7.19 (1 H, s, aryl).

Acknowledgments. We wish to thank the National Cancer Institute, National Institutes of Health (CA 18432-01), and Hoffmann-La Roche for generous support of this work.

Registry No.—la, 58343-42-3; lb, 58384-27-3; lc, 58384-28-4; ld, 58384-43-4; lf, 58343-44-5; lg, 58343-45-6; 1h, 58343-46-7; lh, 58343-47-8; li, 58343-48-9; lk, 58343-49-0; lb, 58343-50-2; le, 58343-51-4; ln, 58343-52-5; lr, 58343-53-6; ls, 58343-54-7; lt, 58343-55-8; lu, 51877-66-8; cyclohexylamine, 108-91-8; piperonal, 120-57-0; 6-bromopiperonal, 15903-53-7; m-methoxybenzaldehyde, 591-31-1; m-methoxybenzaldehyde cyclohexylamine, 58048-56-9; myristicinaldehyde, 5790-07-4; myristicinaldehyde cyclohexylamine, 58048-57-0; allyl bromide, 106-95-6; methyl chloroformate, 79-22-1.

References and Notes
(6) Although this metallation was complete in 15 min, the metallation of dimethyl piperonalamine occurred exclusively at the 2 position to the extent of 67% in 30 min at -78 °C.
(7) Lithium disopropylamide (THF, -78 °C) was capable of forming 1b from 1a to the extent of 75% (deuteration) in a stoichiometric reaction.
(8) Copper reagents derived from alkylidenebenzylamines have been investigated: G. van Koten and J. G. Noltes, Rec. Trav. Chim., 55, 129 (1936), and earlier papers cited in this series.