ON THE METALATION OF PHENOLIC COMPOUNDS: READY ACCESS TO HIGHLY SUBSTITUTED PHENOLS.

Antonio Costa and José M. Saá*

Departament de Química. Universitat de les Illes Balears E-07071. Palma de Mallorca. Spain.

Abstract: The direct metalation of several p-hydroxybenzylmethyl ethers has been studied. Those substrates possessing an electron-withdrawing group in a 1,3 relationship with the coordinating (-CH_OMe) group underwent regioselective metalation by the action of n-BuLi7THF. Highly substituted phenols can thus be readly prepared.

Very recently Posner and coworkers¹ demonstrated that phenol can be efficiently deprotonated to its dianion, though only by using the t-BuLi/THP system. Most interesting, metalation was proved to take place at a site ortho to the lithium phenolate group. The regioselectivity found -consistent with the idea of phenol dianion being an ion triplet- was interpreted as a consequence of the weak coordinating ability of the lithium phenolate for the incoming tert-butyl lithium (kinetic effect) and/or the stabilization of the carbon-lithium bond by the adjacent oxygen atom (thermodynamic effect)¹.

This finding, which has come to light thirty five years later than Gilman's pioneering work² in this field, obviously called for carrying out a thorough study on the direct metalation of phenols.

This communication highlights (vide infra) what we feel should be an advance in the field, namely that phenols having both a coordinating group and



Scheme 1

an electron-withdrawing group appropriately disposed in a 1,3 relationship, are amenable to direct metalation^{3,4} by n-BuLi, thus making this a powerful tactic for the preparation of the otherwise difficult-to-synthesize sterically congested phenolic compounds.

Soon it was learned that simple p-hydroxybenzylmethyl ethers^{5,6} 1, or the easily available analogs 2 and 3, both having extended "arms" for facilitating coordination of the incoming organolithium base, would not undergo ring metalation by the action of n-BuLi under a variety of conditions. Thus, the treatment⁷ of these compounds with n-BuLi (1.5 M, in hexanes, 1.5 eq.) followed by quenching of the resulting brownish solutions with Me_2S_2 or D_2O , led to almost total recovery of the corresponding starting material in the case of 1, though an important loss of material was observed when working with 2 or 3. On the other hand, Wittig rearrangement⁸ products were detected in c.a. 5-10 % yield (¹H-NMR) in the crude reaction product only when much longer reaction times were employed.

However, much to our delight, metalation of $\underline{4}^{5,6}$ under our set of standard conditions⁷, followed by treatment with Me₂S₂, D₂O, CO₂, DMF, MeI, (CH₃)₂C=CH-CH₂Cl, yielded the corresponding 2,3,4-trisubstituted phenolic compounds 5, 6, 7, 8, 9 and 10 in high isolated yields (60-90%), as evidenced by the presence of a clean AB system in the aromatic region of their ¹H-NMR spectra. Similarly, 11^{5,6} was easily converted into 12 and 13⁶, using CO₂ and Me₂S₂ as electrophiles, respectively. Under these conditions, only small amounts (0-5%) of the Wittig rearrangement product was detected (¹H-NMR)⁸.

Moreover, further metalation of <u>13</u> was efficiently achieved under the usual set of conditions⁷. Trapping of the resulting brownish solution of the dianion with solid CO₂ produced the highly substituted phenol <u>14</u>⁶, in a moderate isolated yield (65%). In striking contrast with this, attempted metalation of <u>5</u> as above, yielded only -after quenching with Me₂S₂- unchanged starting material.

In an effort to further delineate the wide applicability of this methodology for the preparation of highly substituted phenols, we have carried out several straightforward transformations as illustrated in Scheme 2. Among them, the preparation of the unusual phenolic phthalides <u>15</u>, <u>16</u> and <u>17</u>⁹ (obtained by treatment of <u>7</u>, <u>12</u> and <u>14</u> with trifluoroacetic anhydride in CH_3CN) in high isolated yield (60-80%) is worthy of note since it compares quite advantageously with the reported synthesis of <u>16</u>¹⁰ in 8 steps!. Also worthy of note is the simple preparation of deuterated vanillin <u>18</u>¹¹ (obtained in 90% yield by DDQ oxidation¹² of <u>6</u>) and 2,3,4-trisubstituted phenols <u>19</u>⁹ (obtained by treatment of <u>9</u> with KCN¹³, in 65% yield) and <u>20</u>⁹ (obtained by catalytic hydrogenation of <u>9</u> in 95% yield). Interestingly, direct deprotonation¹⁴ of phenolic phthalide <u>16</u> with LDA (THF, 0°C), followed by treatment with 3,4-dihydroisoquinolinium iodide, furnished the unnatural phenolic phthalideisoquinoline¹⁵ <u>21</u>, though in a low isolated yield (c.a. 5%)¹⁶.

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(a) DDQ/CH₂Cl₂-H₂O 18:1 (v:v); (b) (CF₃CO)₂O/CH₃CN; (c) KCN/DMF, 110-140°C, 6 h. ; (d) H₂ (10% Pd-C)/EtOH.

Scheme 2

Although it is somewhat premature to advance a general rule accounting for the direct metalation of phenols, the above results give support to the view that both a coordinating and an electron-withdrawing group are required¹⁷ for the efficient metalation of phenols by n-BuLi. Further work in progress will hopefully provide definitive experimental support to fully substantiate this concept.

Acknowledgments: We are pleased to acknowledge financial support by the CAICYT (Project nº 1073/84).

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- 5.- These compounds were straightforwardly prepared by stirring a solution of the p-hydroxybenzyl alcohol in methanol, ethyleneglycol monomethyl ether or diethyleneglycol monomethylether, in the presence of TsOH (cat.). This method was found to be superior to the uncatalyzed version of J. De Jonge, B.H. Bibo, Rec. Trav. Chim. Pays Bas, 74, 1448 (1955).
- 6.- All compounds gave correct analytical and spectroscopic data.
- 7.- Typical procedure: To a solution of phenolic substrate (2 mmol) in anhydrous THF (10 ml) at room temperature, a commercial solution of n-BuLi in hexanes (1.5 M, 4 ml, 6 mmol) was added dropwise (5 min). The resulting yellow solution slowly turned brownish on further stirring at room temperature for an additional 4 h. time. A solution of the apropriate electrophile (3 mmol) in THF (c.a. 5 ml) was the added to the above dianion solution previously cooled to -40°C. Stirring was continued for 30 min (-40°C) and then for an additional 2 h. (-40°C --> r.t.). Standard workup usually gave a crude product which was purified by column chromatography on silica gel, and eventually crystallized or distilled on a Kugelrhör apparatus.
- 8.- Alkylbenzyl ethers are generally considered unsuitable as ortho directors in lithiation reactions due to their propensity to undergo Wittig rearrangement. See ref. 4 and references therein.
- 9.- 200 MHz ¹H-NMR (CDCl₃) δ; 15: 4.24 (s,3H), 5.22 (d,2H, J=0.8 Hz), 6.10 (bs,1H), 7.03 (dt, 1H, J=8 and 0.8 Hz), 7.27 (d,1H, J=8 Hz). 16: 3.95 (s,3H), 4.16(s,3H), 5.14 (d,2H, J=0.9 Hz), 5.78 (bs,1H), 6.63 (t,1H, J=0.9 Hz). 80 MHz ¹H-NMR (CDCl₃) δ; 18: 3.94 (s,3H), 6.89 (bs,1H), 7.03 (d,1H, J=8.1 Hz), 9.82 (s,1H) 7.42 (D,1H, J=8.1 Hz). 19: 2.18 (s,6H), 3.75 (s,3H), 5.48 (bs,1H), 6.68 (d,1H, J=8 Hz), 6.81 (d,1H, J=8 Hz). 20: 2.26 (s,3H), 3.57 (s,2H), 3.76 (s,3H), 6.78 (d,1H, J=8.8 Hz), 6.98 (d,1H, J= 8.8 Hz).
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(Received in UK 9 September 1987)