Formation of 4-Hydroxy-4-Substituted Sydno[3,4-a][4H]indoles via Dilithiation of 3-(2-Bromophenyl)syndone

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Novel fused-ring sydnoindoles (cf. 5) have been prepared, generally in excellent yield, by dilithiation of 3-(2-bromophenyl)syndone (3) and subsequent reaction with esters.

For some years we have been interested in the preparation of fused-ring syndones (cf. 1) wherein the effect of the fusion between the aryl and syndone rings is to permit delocalization from the latter (cf. 1a → 1b) with attendant modifications of the chemical and biological properties of these unique mesoionic systems. More recently, we discovered that a hitherto unknown type of fusion, viz. a one carbon bridge (as in 5, R² = Me) resulted from treatment of 3-(2-acetylphenyl)syndone (2) with bases. Such compounds are of interest on the basis that they may be dehydrated to vinyl species which should suffer delocalization as in 1a → 1b. However, further study of the generality of this transformation (to 5) and the nature of such products has been hampered by the difficult accessibility of the starting acyl compounds; one common intermediate, preferably a syndone, was clearly desirable. Since the syndone ring proton (at C-4) has a considerable acidity (pKₐ ~ 20), and abstraction with BuLi and subsequent reaction with ketones and aldehydes has been reported, it seemed likely that, double lithiation of 3-(2-bromophenyl)syndone (3) [readily available from 2-bromoaniline9] to form 4 and subsequent treatment with esters should lead to the desired sydnoindoles 5.

We now wish to report that this premise has been realized and treatment of 3 with two equivalents of butyllithium at -78 °C in THF under high dilution, followed by addition of various esters, yields the corresponding sydnoindoles 5, in good to excellent yield (see Table). Somewhat surprisingly, the best results were obtained with the most hindered esters [viz. methyl 2-methylpropanoate (entry 4) and methyl 2,2-dimethylpropanoate (entry 5)] and this may reflect the steric encumbrance of the initially formed ortho-ketone to intermolecular reaction, favoring intramolecular attack from the syndone ring. Consistent with this rationale is the finding that ethyl formate provides the most complex reaction mixture and the expected fused ring syndone 5a was not obtained.

The identities of the fused syndone products 5 were ascertained from their satisfactory spectral (IR, ¹H and ¹³C NMR, mass) and microanalytical data. The main features of their IR spectra were the characteristic carboxyl absorption at ca. 1750 cm⁻¹ for the syndone C=O stretch, strong OH stretch at ~3300 cm⁻¹ and the absence of the singular syndone ring C-H stretch at ~3150 cm⁻¹. The proton NMR spectra for the ethyl 5e, isopropyl 5d and benzyl 5f analogues displayed splitting patterns in line with the diastereotropic nature of the attached atoms or groups.

Table. Reactions of 3-(2-Bromophenyl)syndone (3) with BuLi/ R¹CO₂Bu²

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%) of 5</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Et</td>
<td>~8</td>
<td>98–100°</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Et</td>
<td>71</td>
<td>180–181°</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>Et</td>
<td>76</td>
<td>152–153°</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>Me</td>
<td>93</td>
<td>178–179°</td>
</tr>
<tr>
<td>5</td>
<td>i-Bu</td>
<td>Me</td>
<td>95</td>
<td>168–169°</td>
</tr>
<tr>
<td>6</td>
<td>PhCH₂</td>
<td>Et</td>
<td>80</td>
<td>153–154°</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Et</td>
<td>86</td>
<td>158–160°</td>
</tr>
</tbody>
</table>

a The major product was not the fused ring syndone 5a but an, as yet, unidentified syndone product of formula C₁₄H₁₆N₂O₄.

b Lit.² mp 184–187°C.

4-Hydroxy-4-Substituted Sydno[3,4-a][4H]indole 5; General Procedure

To a stirred solution of 3-(2-bromophenyl)syndone (3) [0.20 g, 0.83 mmol] in anhyd THF (50 mL) at -78 °C was added butyllithium (2.0 M in pentane, 0.91 mL, 1.8 mmol) dropwise under an atmosphere of dry N₂. After 0.5 h, the appropriate ester (1.00 mmol) was added and, after an additional 1 h, the mixture was allowed to warm to r.t. whereupon it was quenched with saturated brine (100 mL) then extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (MgSO₄) and evaporated in vacuo to yield oils which were purified by column chromatography (silica gel, CH₂Cl₂ : EtOAc (1 : 10) as eluant).

4-Hydroxy-4-methylsydno[3,4-a][4H]indole (5b)

This compound was prepared in 71% yield using the general procedure and EtOAc (0.097 mL) and was identical (TLC, mp, IR, NMR) to an authentic sample.²
4-Hydroxy-4-ethyldynaph[3,4-a]/4H/indole (5c): This compound was prepared in 76% yield using the general procedure and ethyl propaanoate (0.114 mL); mp 152-2°C (dec).

IR (KBr): ν_max = 3326 (OH), 2978 (alkyl CH), 1729 (C=O), 1485, 980, 774 cm⁻¹.

1H NMR (DMSO-d₆): δ = 7.98 (d, 1 H_arom), 7.72 (m, 3 H_arom), 6.31 (s, 1 H, OH); 2.21 (q, 1 H, J = 7 Hz); 1.94 (q, 1 H, J = 7 Hz); 0.94 (t, 3 H, J = 7 Hz).

13C NMR (DMSO-d₆): δ = 163.4 (C=O), 145.2, 133.2 (C_arom), 132.4, 130.0, 125.2, 114.2 (CH_arom), 111.2 (sydnone C-4), 76.8 (COH), 30.4 (CH₂), 8.9 (CH₃).

C₁₉H₁₅N₂O₃ calc. C 60.55 H 4.62 N 12.84 (218.21) found 60.39 4.57 12.69

4-Hydroxy-4-isopropylidencyclo[3.4-a]/4H/indole (5d): This compound was prepared in 93% yield using the general procedure and methyl 2-methylpropaanoate (0.114 mL); mp 178-9°C (dec).

IR (KBr): ν_max = 3347 (OH), 2973 (alkyl CH), 1733 (C=O), 1485, 1052, 775 cm⁻¹.

1H NMR (DMSO-d₆): δ = 8.00 (d, 1 H_arom), 7.73 (m, 3 H_arom), 6.33 (s, 1 H, OH), 2.47 (septet, 1 H, J = 7 Hz), 1.21 (d, 3 H, J = 7 Hz), 0.59 (d, 3 H, J = 7 Hz).

13C NMR (DMSO-d₆): δ = 163.7 (C=O), 145.0, 133.4 (C_arom), 132.5, 130.1, 125.2, 114.1 (CH_arom), 110.2 (sydnone C-4), 80.4 (C_OH), 35.3 (CH), 18.0 (CH₂), 17.0 (CH₃).

C₁₇H₁₄N₂O₃ calc. C 62.06 H 5.21 N 12.06 (232.24) found 62.29 5.11 12.09

4-Hydroxy-4-tert-butyldynaph[3,4-a]/4H/indole (5e): This compound was prepared in 95% yield using the general procedure and methyl 2,2-dimethylpropaanoate (0.113 mL); mp 168-9°C (dec).

IR (KBr): ν_max = 3327 (OH), 2964 (alkyl CH), 1729 (C=O), 1485, 1022, 773 cm⁻¹.

1H NMR (DMSO-d₆): δ = 8.00 (d, 1 H_arom), 7.70 (m, 3 H_arom), 6.33 (s, 1 H, OH), 1.05 (s, 9 H).

13C NMR (DMSO-d₆): δ = 163.7 (C=O), 144.1, 133.5 (C_arom), 131.8, 130.0, 126.6, 114.0 (CH_arom), 111.7 (sydnone C-4), 82.9 (C_OH), 39.1 (C_Me₃), 25.4 (CH₂).

C₁₉H₁₅N₂O₃ calc. C 63.41 H 5.73 N 11.38 (246.27) found 63.55 5.69 11.28

4-Hydroxy-4-benzylidencyclo[3,4-a]/4H/indole (5f): This compound was prepared in 80% yield using the general procedure and ethyl phenylacetate (0.159 mL); mp 153-4°C (dec).

IR (KBr): ν_max = 3336 (OH), 3065 (aromatic CH), 1739 (C=O), 1490, 733 cm⁻¹.

1H NMR (DMSO-d₆): δ = 7.88 (d, 1 H_arom), 7.75 (t, 2 H_arom), 7.60 (d, 1 H_arom), 7.07 (s, 3 H_arom), 6.89 (s, 2 H_arom), 6.66 (s, 1 H, OH), 3.56 (d, 1 H, J = 12.5 Hz), 3.44 (d, 1 H, J = 12.5 Hz).

13C NMR (DMSO-d₆): δ = 163.3 (C=O), 143.9, 134.4, 133.2 (C_arom), 132.1, 130.2, 129.6, 127.7, 126.8, 126.1, 113.8 (CH_arom), 110.5 (sydnone C-4), 76.7 (COH), 42.5 (CH₂).

C₁₆H₁₄N₂O₃ calc. C 68.47 H 4.32 N 9.99 (280.29) found 68.09 4.17 9.73

4-Hydroxy-4-phenylidencyclo[3,4-a]/4H/indole (5g): This compound was prepared in 86% yield using the general procedure and ethyl benzoate (0.142 mL); mp 158-9°C (dec).

IR (KBr): ν_max = 3346 (OH str.), 3065 (aromatic CH str.), 1750 (C=O str.), 1483, 1050, 769 cm⁻¹.

1H NMR (DMSO-d₆): δ = 8.05 (m, 1 H_arom), 7.54 (m, 8 H_arom), 7.05 (s, 1 H, OH).

13C NMR (DMSO-d₆): δ = 162.6 (C=O), 145.9, 138.8, 133.0 (C_arom), 132.7, 130.2, 128.5, 128.3, 126.8, 126.1, 125.5, 114.6 (CH_arom), 111.7 (sydnone C-4), 76.6 (COH).

C₁₅H₁₃N₂O₃ calc. C 67.67 H 3.79 N 10.52 (266.26) found 67.54 3.87 10.31


(3) Synthesis of such species starts from the appropriate o-substituted aniline (not always commercially available) & involves at least 4 steps. In one case, viz. o-aminobenzenophenone, preparation of the corresponding glycine, en route to the sydnone, could not be achieved.


(5) Greco, C.V.; O’Reilly, B.P.J. Heterocycl. Chem. 1972, 9, 207.
