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Chemoselective Debenzylation Involving Removal of a 2-Hydroxy-1-phenylethyl Group from Nitrogen

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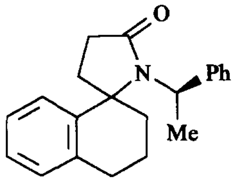
Abstract: In 2-(2-hydroxy-1-phenylethyl)-1-isoindolinone, selective removal of the 2-hydroxy-1-phenylethyl group is conveniently achieved *via* a 3-step sequence (mesylation, elimination, hydrolysis) without breaking an endocyclic benzylic nitrogen bond. © 1997 Elsevier Science Ltd.

Structures such as **1**, **2** and **4** contain two benzylic groups attached to nitrogen, and selective removal of the side chain is impossible by means of the usual reductive methods for debenzylation. Indeed, treatment of **1** with sodium and liquid ammonia resulted in cleavage of the wrong (*ie* endocyclic) benzylic bond between nitrogen and the spiro carbon atom.[1] This problem was addressed by Meyers[2] in the case of **2**, which was degraded in two steps *via* the phenylthio derivative **3** to (*S*)-2-phenylpyrrolidine in 51% overall yield. We wished to find an improved procedure for removal of the benzylic side chain from nitrogen applicable to the series of spiro lactams **4**[3] and to other heterocyclic products resulting from asymmetric synthesis using bicyclic lactams **5**[4] derived from phenylglycinol.



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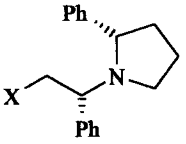
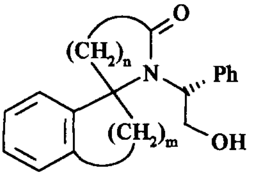


2 X = OH
3 X = PhS



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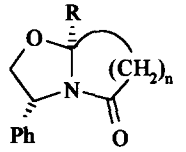
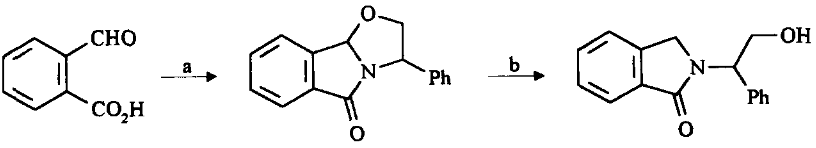


5

We chose the isoindolinone **7** as a model compound on which to test alternative procedures. Compounds similar to **7** have recently been prepared[5] by reaction of phthalaldehyde with α-amino alcohols. However, the same procedure using phenylglycinol was less than satisfactory. A better approach involved reduction of the tricyclic lactam **6**[6] with triethylsilane, whereby **7**[7] was obtained cleanly and in 59% overall yield in two steps from phenylglycinol (Scheme 1).

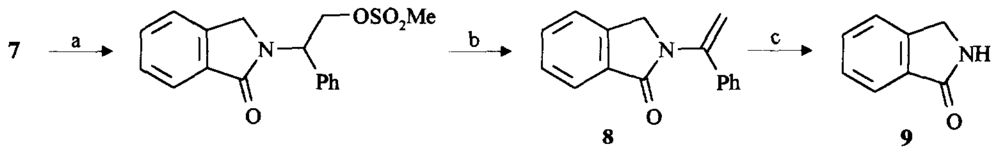


6 **7**

Scheme 1. Reagents: (a) $PhCH(NH_2)CH_2OH$; (b) $Et_3SiH/TiCl_4$

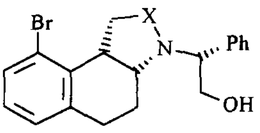
Interestingly, treatment of **7** with *N*-bromosuccinimide and AIBN in refluxing toluene gave back **6** in 40% yield. Apparently, bromination occurs selectively at the benzylic CH_2 position, leading to iminium ion formation and recyclisation to **6**.

For removal of the 2-hydroxy-1-phenylethyl group from nitrogen, it was our intention was to utilise the primary alcohol of the side chain of 7. Thus, alcohol 7 was converted to the mesylate and then to the enamide **8**[8] by treatment with sodium ethoxide in ethanol (Scheme 2). Hydrolysis of **8** with dilute hydrochloric acid afforded acetophenone and isoindolinone **9**, the latter identical with an authentic sample[9] obtained by reduction of phthalimide with tin and hydrochloric acid. The three steps can be conveniently completed within one day, without purification of the intermediates, to give **9** in 80–83% overall yield.



Scheme 2. Reagents: (a) $MeSO_2Cl/Et_3N$; (b) NaOEt/EtOH/r.t.; (c) 3M HCl/EtOH-H_2O/80 °C

This sequence is accomplished more quickly and in much milder conditions than a similar two-step elimination–hydrolysis procedure for debenzylation of lactam **10**,[10] in which the presence of bromine precluded use of the usual reductive methods. It represents a big improvement in yield and convenience over the method used for debenzylation of **2**,[2] and it should be applicable to other heterocyclic products obtained by routes starting from phenylglycinol.



10 X = CO
11 X = CH_2

Acknowledgement

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References and Notes

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7. 2-(2-Hydroxy-1-phenylethyl)-1-isoindolinone **7**: mp 142–143 °C; δ_H ($CDCl_3$) 3.99 (1H, s, OH), 4.19 and 4.44 (each 1H, d, *J* 17.2 Hz, NCH_2), 4.22–4.35 (2H, m, OCH_2), 5.34 (1H, dd, *J* 4.4 and 8.5 Hz, NCH), 7.26–7.51 (8H, m, ArH), and 7.81 (1H, d, *J* 7.3 Hz, H-7); δ_C 48.7 (NCH_2), 59.5 (NCH), 63.2 (OCH_2), 122.6, 127.9, 128.0, 128.9, and 131.5 (arom CH), 132.5, 137.5 and 141.5 (arom C), and 169.7 (C=O); Found MH^+ (CIMS) *m/z* 254.1187. Calc. for $C_{16}H_{16}NO_2$ 254.1181.
8. 2-(1-Phenylvinyl)-1-isoindolinone **8**: mp 81.5–83 °C; δ_H ($CDCl_3$) 4.54 (2H, s, NCH_2), 5.48 and 5.56 (each 1H, s, vinyl CH_2), 7.33–7.61 (8H, m, ArH) and 7.92 (1H, d, *J* 7.3 Hz, H-7); δ_C 51.8 (NCH_2), 109.6 (vinyl CH_2), 122.7, 124.3, 126.8, 128.3, 128.5 and 128.6 (arom CH), 132.5, 136.8, 140.8 and 143.1 (arom C), and 167.9 (C=O); Found M^+ (EIMS) *m/z* 235.0995. Calc. for $C_{16}H_{13}NO$ 235.0997.
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