Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3059–3062

TETRAHEDRON LETTERS

2,3-Dihydroisoindolones by cyclisation and rearomatisation of lithiated benzamides

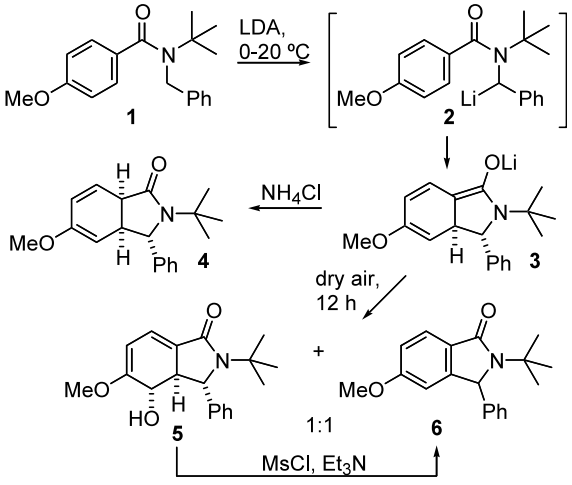
Jonathan Clayden* and Christel J. Menet

Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Received 14 February 2003; revised 24 February 2003; accepted 24 February 2003

Abstract—Lithiation of tertiary aromatic *N*-benzyl amides generates [α]-amido benzyllithiums which cyclise with dearomatisation to cyclic extended enolates. Rearomatisation by oxidation, or, in the case of methoxy-substituted enolates, elimination, yields 2,3-dihydroisoindoles. Enantiomerically enriched products may be formed either by using a chiral base to lithiate the starting material or by using a chiral starting material.

The isoindolone ring system is not the commonest of the 6,5-fused heterocycles[1,2] but can be found in a number of valuable compounds, including alkaloids such as nuevamine,[3] lennoxamine,[3,4] chilenine,[5,6] staurosporine,[7] aristoyagonine[8] and fumaridine,[9] and drugs such as indoprofen[9] and DN 2327.[10] In this paper, we describe a modification of our dearomatising cyclisation reaction of aromatic amides[11–14] in which the products are rearomatised[15] to 2,3-dihydroisoindolones. 2,3-Dihydroisoindolones may bear a stereogenic centre at C-3, and we describe methods for controlling its absolute stereochemistry.



We have previously reported that tertiary benzamides bearing *N*-benzyl groups such as **1** may be lithiated α to nitrogen, and that the benzyllithiums **2** undergo cyclisation to a bicyclic, dearomatised enolate **3**.[12–14] This enolate may be protonated or alkylated to yield dearomatised products **4**, and we have used such reactions in the synthesis for example of some kainoid amino acids.[16–18] We found that LDA is the most versatile base for the reaction,[14] but if the diisopropylamine is not rigorously distilled and degassed prior to use, or if reaction times are extended beyond 2 h, by-products arising from oxidation of the enolate may be observed. For example, when the cyclistion of **1** was carried out with LDA at –40°C for 24 h, the product **4** was contaminated with a mixture of **5** and **6**.

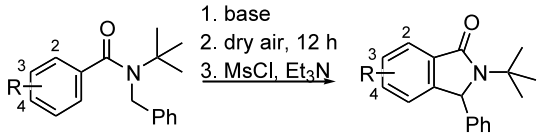
Yields of the oxidised products may be maximised if the reaction is warmed to 20°C for a minimum of 2 h to ensure complete cyclisation, and then opened to dry air (nitrogen line replaced with a drying tube) and stirred for 12 h. For example, **1**, was treated with LDA at 0°C, allowed to warm to 25°C over 2 h, then opened to dry air overnight. A single diastereoisomer of the alcohol **5** and the rearomatised 2,3-dihydroisoindolone **6** were now the sole products, isolated in a 1:1 ratio.[19] Compound **5**, in common with other partially saturated isoindolones, is remarkably stable—for example, no conversion to **6** by elimination of water was observed even on treatment with acid. However, **5** could be converted to the dihydroisoindolone **6** by treatment with methanesulfonyl chloride and triethylamine.

Application of optimised conditions[20] for cyclisation and rearomatisation of amides to 2,3-dihydroisoindolones are summarised in Table 1. The amides **1** and **7**–**10** were each lithiated and cyclised by treatment with

* Corresponding author. Fax: +44 161 275 4939; e-mail: j.p.clayden@man.ac.uk

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00545-8

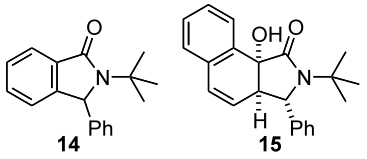
Table 1. Cyclisation–rearomatisation



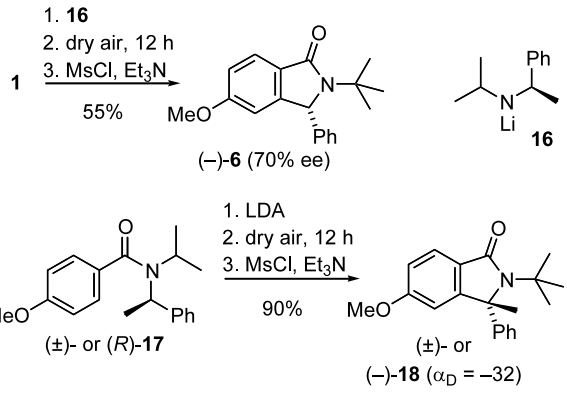
Entry	S.M.	R =	Product	Yield (%)	Notes
1	**1**	4-MeO	**6**	60	
2	**7**	2-MeO	**11**	50	[a]
3	**8**	4-CN	**12**	71	
4	**9**	4-Br	**13**	40	[b]
5	**10**	2,3-Benzo	–	–	[c]

[a] Plus 28% non-rearomatised and 12% **14**.
[b] Plus 39% **14**.
[c] 30% non-rearomatised plus 33% hydroxylated **15**.

LDA at 0°C, warming to 20°C over 2 h, and oxidised by exposure to dry air for 12 h. Treatment of the crude reaction mixture with MsCl–Et_3N promoted elimination and allowed us to isolate the dihydroisoindoles **6** and **11**–**13** in moderate to good yields. The main by-products were due to aromatic substitution (see below) or incomplete oxidation or elimination.



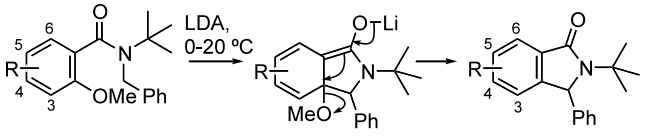
An important feature of the dearomatising cyclisation leading to **4** is the possibility of introducing asymmetry by forming the benzyllithium **2** enantioselectively. We have previously formed similar chiral benzyllithiums in two ways: by using a chiral lithium amide base to effect asymmetric deprotonation[21] or by using a chiral starting material, which undergoes deprotonation stereospecifically.[22] Cyclisation–oxidation reactions were carried out by both methods, using **1** and **17** as starting materials. Treatment of **1** with 1.1 equiv. the chiral base (*R*)-**16** and oxidation–elimination gave (–)-**6** in 70% ee, slightly lower than the comparable dearomatising cyclisation,[21] probably because of partial racemisation of the product.[23] Cyclisation–rearomatisation of both (±)- and (*R*)-**17** gave the 2,3-dihydroisoindolone **18** in excellent yield, and the product (–)-**18** from (*R*)-**17** was optically active, but unfortunately we were unable to quantify its enantiomeric excess. The comparable dearomatisation proceeds to yield a product with >99% ee.[22] There are few alternatives available for the asymmetric synthesis of 2,3-dihydroisoindolones.[24]



During this work, the anionic cyclisation of a phosphinyl amide was reported which led to a dihydroisoindole product by nucleophilic aromatic substitution.[25] Methoxy groups are well known to be good leaving groups in nucleophilic aromatic substitutions,[26–28] and we made a collection of amides **19**–**22** bearing ortho-methoxy groups for attempted cyclisation to isoindoles. Table 1 shows that 2-methoxy amide **7** cyclises with traces of substitution products, but we found that amides **19**–**21** which had no choice but to cyclise to positions carrying methoxy groups underwent nucleophilic aromatic substitution to give isoindoles **11**, **23**, **24** in good to excellent yield (Table 2). Amide **22** also undergoes cyclisation with rearomatisation to give **25**.

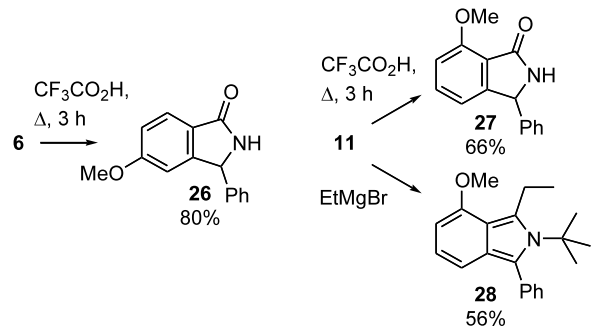
In order to use the isoindolone products in synthesis, it is necessary to remove the *N*-*t*-Bu substituent, a reaction which in dearomatised compounds **4** posed problems and led to our use of the *N*-cumyl protecting group.[14,29] However, treatment of **6** and **11** with trifluoroacetic acid resulted in clean de-*t*-butylation, giving the *N*-unsubstituted dihydroisoindolones **26** and **27**

Table 2. Cyclisation–substitution



Entry	S.M.	R =	Isoindolone product	Yield (%)
1	**19**	6-MeO	**11**	85
2	**20**	5,6-Benzo	**23**	80
3	**21**	3,4-Benzo	**24**	66
4	**22**	3-MeO	**25**	81

in yields of 80% and 66%, respectively. In a further demonstration of the potential of the isoindolones in synthesis, it was also possible to transform isoindolone **11** into the fully unsaturated isoindole **28** by treatment with a Grignard reagent.[30]



Acknowledgements

We are grateful to Aventis (C.J.M.) for support, and to Dr. Darren Mansfield for helpful discussions.

References

1. Donohoe, T. J. *Sci. Synthesis* **2001**, *10*, 653.
2. *Houben Weyl*; Herd, K. J.; Kreher, R., Eds.; Thieme: Stuttgart, 1995; Vol. E6a, pp. 451.
3. Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett*. **1984**, *25*, 599.
4. Fuchs, J. R.; Funk, R. L. *Org. Lett*. **2001**, *3*, 3923.
5. Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett*. **1982**, *23*, 39.
6. Danishefsky, S. J.; Fang, F. G. *Tetrahedron Lett*. **1989**, *30*, 2747.
7. Wood, J. L.; Stoltz, B. M.; Goodman, P. N. *J. Am. Chem. Soc*. **1996**, *118*, 10656.
8. Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C.; Rys, V. *Tetrahedron Lett*. **2002**, *43*, 2207.
9. Lawrence, N. J.; Liddle, J.; Bushell, S. M.; Page, M. I.; Slawin, A. M. Z. *J. Org. Chem*. **2002**, *67*, 457.
10. Linder, M.; Hadler, D.; Hofmann, S. *Human Psychopharm*. **1997**, *12*, 445.
11. Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun*. **1998**, 297.
12. Ahmed, A.; Clayden, J.; Yasin, S. A. *Chem. Commun*. **1999**, 231.
13. Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett* **2001**, 302.
14. Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett*. **2000**, *2*, 4229.
15. Some nucleophilic additions to aromatic rings unavoidably yield aromatic products by rearomatisation (see Clayden, J.; Kenworthy, M. N. *Org. Lett*. **2002**, *4*, 787 and references cited therein). By contrast we have found the partially saturated products of our dearomatising cyclisations to be surprisingly resistant to rearomatisation (Ref. 14).
16. Clayden, J.; Tchabanenko, K. *Chem. Commun*. **2000**, 317.
17. Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett*. **2001**, *42*, 3407.
18. Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727.
19. We speculate that the single diastereoisomer of **5** arises from non-diastereoselective oxidation followed by stereoelectronically favoured elimination from one diastereoisomer only. Assignment of stereochemistry to **5** is speculatively based on the possibility that the diastereoisomer with H and OH *syn* eliminates more slowly.
20. General procedure for cyclisation–rearomatisation: The amide **1** (0.43 g, 2.52 mmol) in dry THF (30 ml) was added to a solution of freshly prepared LDA (2.75 mmol) in THF (10 ml) at 0°C under nitrogen. After 2 h at 20°C, the nitrogen line was replaced with a drying tube and stirring was continued for 12 h. The mixture was concentrated and CH_2Cl_2 (30 ml) was added. The solution was cooled to 0°C, and triethylamine (6.3 mmol) and methanesulfonyl chloride (3.04 mmol) were added. After 1 h at 0°C water was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and concentrated to yield the crude product. Purification by flash chromatography, eluting with 7:3 petrol–EtOAc, afforded the dihydroisoindolone **6** as a white solid (0.23 g, 60%). Mp = 140–141°C. Found: M+H$^+$ 296.1654; $C_{19}H_{22}NO_2$ requires *M*, 296.1650; *m*/*z* (EI) 296 (M+H$^+$, 100%); δ_H (300 MHz, $CDCl_3$) 7.75 (1H, d, *J* 8.5, H7), 7.4–7.2 (5H, m, ArH), 6.93 (1H, dd, *J* 8.5, 2, H6), 6.52 (1H, d, *J* 2, H4), 5.65 (1H, s, H3), 3.77 (3H, s, CH_3O), 1.48 (9H, s, *tert*-butyl); δ_C (75 MHz, $CDCl_3$) 169.8, 162.6, 148.7, 141.1, 128.9, 127.7, 126.1, 124.7, 124.4, 114.5, 107.2, 64.6, 55.7, 55.4, 28.6; ν_{max} (film)/cm^{-1} 1677 (C=O).
Data for **11**: Mp = 178–179°C; Found: M$^+$ 295.1581; $C_{19}H_{21}NO_2$ requires *M*, 295.1572 (Found: C 76.94%, H 7.26%, N 4.74%; calc. C 77.26%, H 7.17%, N 4.74%); *m*/*z* (CI) 296 (M+H$^+$, 100%), 295 (M$^+$, 40%), 280 (M$^+$–CH_3, 40%); δ_H (300 MHz, $CDCl_3$) 7.4–7.2 (6H, m, ArH), 6.82 (1H, d, *J* 8, ArH), 6.62 (1H, d, *J* 7.5, ArH), 5.62 (1H, s, CH), 3.99 (3H, s, CH_3O), 1.47 (9H, s, *tert*-butyl); δ_C (75 MHz, $CDCl_3$) 172.2, 156.8, 149.3, 132.9, 128.9, 128.0, 127.7, 126.4, 126.1, 114.6, 109.5, 103.8, 64.2, 55.8, 55.7, 28.4; ν_{max}(film)/cm^{-1} 1683 (C=O).
Data for (–)-**18**: $[\alpha]_D^{22} = -32$ (*c* = 1.38 in $CHCl_3$). Mp = 143–145°C. Found: M$^+$ 295.1570; $C_{19}H_{21}NO_2$ requires *M*, 295.1571; *m*/*z* (EI) 295 (M$^+$, 80%), 280 (M–Me, 100%), 237 (50%); δ_H (300 MHz, $CDCl_3$) 7.78 (1H, d, *J* 8.5, H7), 7.3 (5H, m, PhH), 6.95 (1H, dd, *J* 8.5, 2, H6), 6.51 (1H, d, *J* 2.5, H4), 3.78 (3H, s, MeO), 3.35 (1H, sept, *J* 7, C**H**$(CH_3)_2$), 1.92 (3H, s, CH_3), 1.50 (3H, d, *J* 7, C**H**$_3$CH), 1.28 (3H, d, *J* 7, C**H**$_3$CH); δ_C (75 MHz, $CDCl_3$) 167.8, 162.8, 154.1, 140.2, 128.3, 127.8, 126.8, 124.6, 124.5, 114.3, 106.5, 67.7, 55.4, 45.5, 23.1, 20.7, 19.7; ν_{max}(film)/cm^{-1} 1678 (C=O), 1609 (Ar).
Data for **23**: Found: M$^+$ 315.1624; $C_{22}H_{21}NO$ requires *M*, 315.1623; *m*/*z* (CI) 316 (M+H$^+$, 100%), 315 (M$^+$, 60%); δ_H (300 MHz, $CDCl_3$) 8.67 (1H, d, *J* 8.5, ArH), 7.83 (1H, d, *J* 9, ArH), 7.63 (1H, d, *J* 8, ArH), 7.5–7.4 (2H, m, ArH), 7.4–7.1 (6H, m, ArH), 4.75 (1H, s, CH), 1.42 (9H, s, *tert*-butyl); δ_C (75 MHz, $CDCl_3$) 197.8, 164.0, 138.1, 138.0, 131.1, 129.7, 128.9, 127.9, 127.6, 126.9, 126.2, 123.6, 122.7, 114.5, 71.5, 56.3, 29.6; ν_{max}(film)/cm^{-1} 1677 (C=O).

Data for **24**: Found: M^+ 315.1622; $C_{22}H_{21}NO$ requires *M*, 315.1623; *m*/*z* (CI) 316 (M+H$^+$, 100%), 315 (M^+, 60%); δ_H (300 MHz, $CDCl_3$) 8.0–7.8 (4H, m, ArH), 7.5–7.2 (7H, m, ArH), 6.11 (1H, s, CH), 1.52 (9H, s, *tert*-butyl); δ_C (75 MHz, $CDCl_3$) 169.9, 144.0, 139.9, 135.3, 130.1, 129.4, 129.1, 128.7, 127.9, 127.0, 126.7, 126.1, 123.2, 119.5, 64.5, 56.0, 28.6; ν_{max}(film)/cm^{-1} 1679 (C=O).

Data for **25**: Found: M^+ 295.1581; $C_{19}H_{21}NO_2$ requires *M*, 295.1572; *m*/*z* (CI) 296 (M+H$^+$, 100%), 295 (M^+, 40%), 280 (M^+–CH_3, 40%); δ_H (300 MHz, $CDCl_3$) 7.5–7.2 (7H, m, ArH), 6.88 (1H, d, *J* 8, ArH), 5.75 (1H, s, CH), 3.66 (3H, s, CH_3O), 1.46 (9H, s, Boc); δ_C (75 MHz, $CDCl_3$) 169.8, 153.7, 139.3, 134.4, 133.9, 129.7, 128.0, 127.4, 127.3, 115.1, 113.3, 63.0, 55.8, 55.3, 28.3; ν_{max}(film)/cm^{-1} 1678 (C=O), 1608 (Ar).

Data for **26**: Mp = 200–202°C. Found: M^+ 239.0944; $C_{15}H_{13}NO_2$ requires *M*, 239.0946; *m*/*z* (CI) 240 (M+H$^+$, 100%); δ_H (300 MHz, $CDCl_3$) 7.82 (1H, d, *J* 7.5, H7), 7.18 (5H, m, PhH), 7.05 (1H, b, NH), 7.0 (1H, d, *J* 7.5, H6), 6.72 (1H, s, H4), 5.60 (1H, s, H3), 3.81 (3H, s, MeO); δ_C (75 MHz, $CDCl_3$) 171.3, 163.6, 150.7, 138.9, 129.3, 128.8, 127.1, 125.4, 123.7, 115.3, 108.2, 60.9, 55.9; ν_{max}(film)/cm^{-1} 3200 (NH), 1688 (C=O), 1610 (Ar).

Data for **27**: Mp = 179–181°C; Found: M^+ 239.0947; $C_{15}H_{13}NO_2$ requires *M*, 239.0946; *m*/*z* (CI) 240 (M+H$^+$, 100%); δ_H (300 MHz, $CDCl_3$) 7.5–7.2 (6H, m, ArH), 6.93 (1H, d, *J* 8, ArH), 6.81 (1H, d, *J* 7.5, ArH), 6.62 (1H, b, NH), 5.59 (1H, s, CH_2), 4.03 (3H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 170.1, 157.9, 151.8, 138.6, 134.0, 128.9, 128.4, 126.7, 115.3, 110.1, 60.1, 55.9; ν_{max}(film)/cm^{-1} 3200 (NH), 1690 (C=O).

21. Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun*. **2002**, 38.
22. Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett*., in press.
23. Using 2 equiv. of **16** further reduced the ee of (–)-**6** to only 50%.
24. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z.; Smith, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, *41*, 2219.
25. Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491.
26. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
27. Koshiishi, E.; Hattori, T.; Ichihara, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 377.
28. Kojima, T.; Ohishi, T.; Yamamoto, I.; Matsuoka, T.; Kotsuki, H. *Tetrahedron Lett*. **2001**, *42*, 1709.
29. Metallinos, C. *Synlett* **2002**, 1556.
30. Anderson, P. S.; Christy, M. E.; Colton, C. D.; Halczenko, W.; Ponticello, G. S.; Shepard, K. L. *J. Org. Chem*. **1979**, *44*, 1519.