Tetrahedron Letters 51 (2010) 2457–2460

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2-hydroxy-3-indolinones and 3-hydroxy-2-indolinones by anionic cyclization, in situ oxidation and rearrangement

Iain Coldham *, Harry Adams, Neil J. Ashweek, Thomas A. Barker, Andrew T. Reeder, Melanie C. Skilbeck

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK

ARTICLE INFO

Article history:
Received 14 January 2010
Revised 11 February 2010
Accepted 26 February 2010
Available online 4 March 2010

ABSTRACT

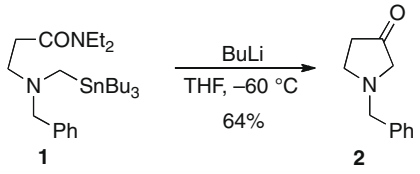
Lithiation with butyllithium of 2-(benzylamino)benzamides (*N*-benzyl anthranilamides) occurs at the benzylic position to give an α-amino-organolithium that cyclizes to the 3-indolinone (indoxyl) ring (similar to a Parham cyclization). Autoxidation in air gives 2-hydroxy-3-indolinones. In the absence of a proton source, rearrangement of the aryl group from C-2 to C-3 occurs to give the 3-hydroxy-2-indolinone (oxindole) ring.

The Parham-type cyclization of an organometallic species onto a carboxylic amide group has been used for the preparation of a variety of substituted cyclic ketones.[1] The chemistry is amenable to the presence of a heteroatom in the ring to provide a method to prepare heterocyclic ketones.[2–5] Our research group has a long-standing interest in the preparation of cyclic amines using an anionic cyclization (intramolecular carbometalation) strategy.[6] This chemistry involves the cyclization of an α-amino-organolithium onto an alkene, although we have previously reported one example of a cyclization onto a carboxylic amide (Scheme 1).[7] In this case, the organolithium derived from the stannane **1** undergoes cyclization to give the pyrrolidin-3-one **2** after aqueous work-up.

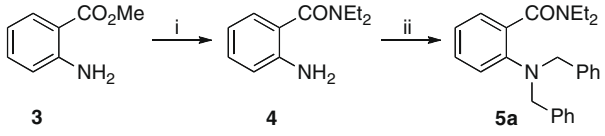
One of the problems with this chemistry is that it involves the use of potentially toxic organotin compounds. We therefore considered how to conduct such cyclizations by simple proton abstraction. This would require a relatively acidic molecule that could be deprotonated in preference to reaction of the base with the carboxylic amide (or other carbonyl group). We reasoned that benzylic organolithiums could be formed in this way and could be sufficiently reactive to cyclize onto the pendant carbonyl group.[4,5] We report here the successful demonstration of this approach and its application to the preparation of 2- or 3-indolinones (oxindoles or indoxyls).

To avoid complications with enolate formation, we selected the carboxylic amide **5a** for initial studies. Amide **5a** was prepared in two steps from methyl anthranilate (**3**) (Scheme 2). This was accomplished by reaction of methyl anthranilate with lithium diethylamide followed by double N-benzylation with excess benzyl bromide in acetonitrile and potassium carbonate.

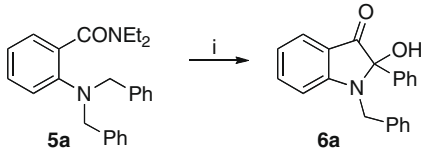
The key step in our sequence is the treatment of the benzylamine **5a** with a base. There are several protons that could be removed from compound **5a**, although we were hoping that one of the benzylic protons alpha to the nitrogen atom would be most acidic, possibly helped by a complex-induced proximity effect.[8] After screening several bases and conditions we found that *n*-BuLi in Et_2O provided a reasonable yield of a cyclization product arising from benzylic deprotonation (Scheme 3). Lower yields were



Scheme 1. Cyclization to the pyrrolidin-3-one **2**.[7]



Scheme 2. Preparation of the carboxylic amide **5a**. Reagents and conditions: (i) Et_2NH, BuLi, Et_2O, 0 °C then heat, 90 min, 55%; (ii) $PhCH_2Br$, MeCN, K_2CO_3, rt, then heat, 24 h, 80%.



Scheme 3. Cyclization to the 3-indolinone **6a**. Reagents and conditions: (i) 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, 4 h, then air, 30 min, then MeOH, 51%.

* Corresponding author. Tel.: +44 (0)114 222 9428; fax: +44 (0)114 222 9346.
E-mail address: i.coldham@sheffield.ac.uk (I. Coldham).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.159

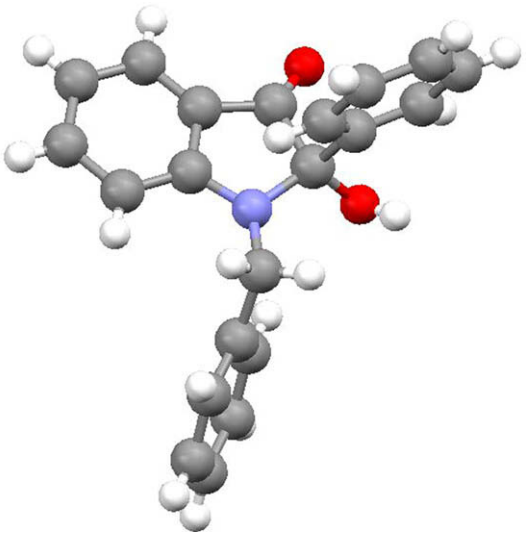


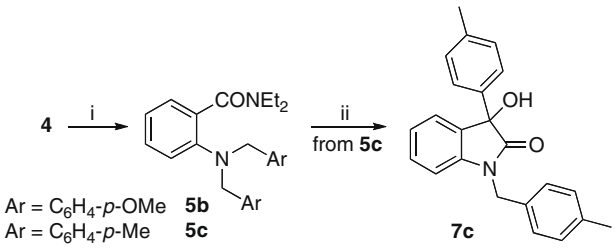
Figure 1. Single crystal X-ray structure of product **6a**.

obtained using different bases or solvents (e.g., *n*-BuLi in THF, PhMe or Et_2O/TMEDA). Spectroscopic analysis revealed that the product **6a** was not that from simple cyclization and loss of diethylamide, but contained a hydroxy group. This was confirmed by single crystal X-ray analysis (Fig. 1). From this we deduce that the product from initial cyclization undergoes oxidation in air, and indeed the yield of the product **6a** was slightly enhanced by allowing the mixture to stir in air after warming to room temperature. This methodology therefore allows a novel and unusual entry to a 2-phenyl-2-hydroxy-3-indolinone (a 2-hydroxyindoxyl).[9]

To explore the scope of this transformation, we prepared the carboxylic amides **5b** and **5c** by analogous chemistry, starting from the amine **4** (Scheme 4). Treatment of the amide **5b** with *n*-BuLi under the same conditions as used for compound **5a** gave none of the desired cyclic product. Quenching this reaction with D_2O gave recovered starting material **5b**, suggesting that no proton abstraction was occurring. By contrast, the *para*-methyl analogue **5c** did undergo the deprotonation–cyclization reaction, however the product was not the expected ketone, but the oxindole **7c**.

Evidence for the oxindole product **7c** came from ^{13}C NMR spectroscopic studies (in $CDCl_3$), in which the carbonyl carbon resonates at 179 ppm, whereas the ketone carbon in compound **6a** resonates at 198 ppm (in C_6D_6).

In addition, X-ray crystallographic analysis of **7c** showed the oxindole ring system (Fig. 2). The conversion of the amide **5c** into the oxindole **7c** presumably occurs through the ketone **6c** (formed by autoxidation of the intermediate indolin-3-one) followed by rearrangement (Scheme 5). This rearrangement has been proposed in related chemistry.[10,11]



Scheme 4. Formation of the substrates **5b** and **5c** and treatment with base. Reagents and conditions: (i) *p*-$MeOC_6H_4CH_2Cl$ or *p*-$MeC_6H_4CH_2Br$, MeCN, K_2CO_3, rt, then heat, 24 h, **5b** 47%, **5c** 79%; (ii) 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, 6 h, then air, 30 min, then MeOH, **7c** 47%.

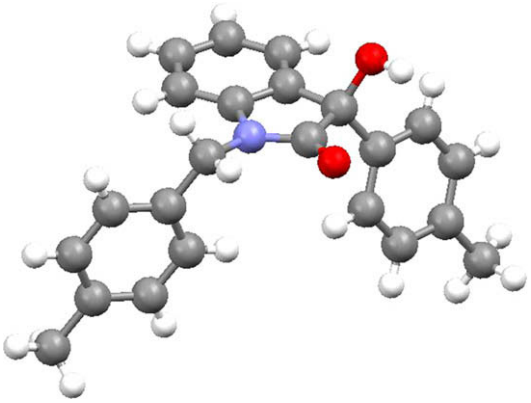
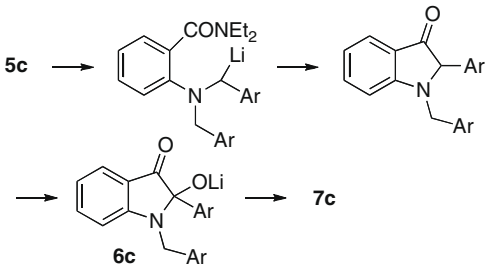


Figure 2. Single crystal X-ray structure of product **7c**.

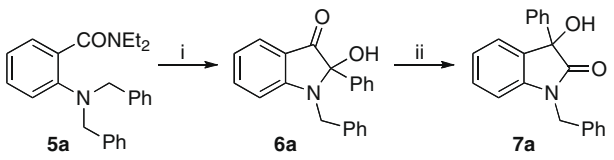


Scheme 5. Possible pathway for the formation of oxindole **7c**.

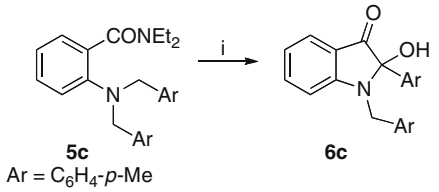
We therefore re-explored the lithiation of the amide **5a** with *n*-BuLi and found that, under what seemed to be identical conditions to those described in Scheme 3, the oxindole **7a** was now the major product, as judged by NMR spectroscopy (46% yield).[12] The formation of the oxindoles (**7a** and **7c**) seemed to depend on the amount of base that was added. A more reliable method to prepare the ketone **6a** was found, in which acetic acid was added at room temperature before exposing to air (Scheme 6). It was reasoned that this should promote protonation of any alkoxide and thereby disfavour rearrangement, and we were pleased to find that the ketone **6a** was formed under these conditions [38% yield, together with a small amount (<10% yield) of starting material **5a**, but no oxindole **7a**].[13] In addition, the ketone **6a** could be transformed in high yield into the oxindole **7a** by heating with KOH in ethanol.

The ability to prepare either the 3-indolinones **6** or the 2-indolinones **7** was confirmed by treating the amide **5c** with butyllithium followed by warming to room temperature, the addition of acetic acid then exposure to air. This gave the desired 3-indolinone **6c** (and none of the oxindole **7c**), (Scheme 7). This illustrates the ability to prepare either cyclization product (**6** or **7**) from the same amide substrate (**5**).

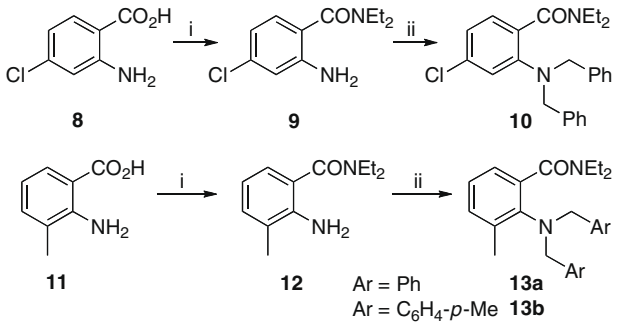
To investigate the possibility of carrying out the chemistry with substituents on the benzamide ring, we prepared compounds **10**, **13a** and **13b** (Scheme 8). Starting with the substituted anthranilic



Scheme 6. Cyclization to the ketone **6a** and conversion into the oxindole **7a**. Reagents and conditions: (i) 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, 6 h, then AcOH (4 equiv), air, 1 h, then MeOH **6a**, 38%; (ii) KOH, EtOH, heat, **7a**, 88%.



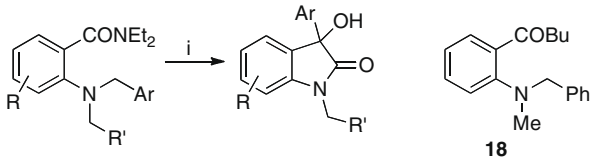
Scheme 7. Cyclization to the ketone **6c**. Reagents and conditions: (i) 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, 16 h, then AcOH, air, 1 h, then MeOH, 33%.



Scheme 8. Preparation of the carboxylic amides **10**, **13a** and **13b**. Reagents and conditions: (i) *N*-hydroxysuccinimide, DCC, dioxane, rt, 3 d, then isolation of the (crude) activated ester (from **8** 67%, from **11** 55%), then Et_2NH, 60 °C, 4 h, **9** 43%, **12** 56%; (ii) $ArCH_2Br$, MeCN, K_2CO_3, rt, then heat, 2 d, **10** 67%, **13a** 57%, **13b** 50%.

acids **8** and **11**, the carboxylic amides **9** and **12** were obtained via the activated esters of **8** and **11** (using *N*-hydroxysuccinimide plus dicyclohexylcarbodiimide followed by treatment with diethylamine). Benzylations then provided the substrates **10**, **13a** and **13b**. In addition to these substrates, we prepared the *N*-benzyl-*N*-methyl derivative **16** (see Scheme 9) from commercial methyl *N*-methyl anthranilate by amide formation (Et_2NLi) followed by N-benzylation.

Treatment of the substrates **10**, **13a** and **13b** with *n*-BuLi in Et_2O (no acetic acid quench) gave the oxindoles **14**, **15a** and **15b**, respectively, in moderate yields (Scheme 9). In each case IR and NMR spectroscopic data, together with high resolution mass spectrometry, confirmed the identity of the products. The substrate **16** gave mixed results, with the ketone **18** as the major product using *n*-BuLi. However, using *sec*-BuLi a reasonable yield of the cyclized product **17** was obtained (Scheme 9).



	R	R′	Ar	
10	4-Cl	Ph	Ph	**14** 35%
13a	3-Me	Ph	Ph	**15a** 53%
13b	3-Me	C_6H_4-*p*-Me	C_6H_4-*p*-Me	**15b** 39%
16	H	H	Ph	**17** 43%

Scheme 9. Cyclization to the oxindoles **14**, **15a**, **15b** and **17**. Reagents and conditions: (i) for **10**, **13a** and **13b**: 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, then air, 1 h, then MeOH; or, for **16**: 2 equiv *n*-BuLi, Et_2O, −78 °C to rt, 6 h, then air, 1 h, then MeOH, **17** <10%, **18** 78%; or 2 equiv *sec*-BuLi, Et_2O, −78 °C to rt, 17 h, then air, 1 h, then MeOH, **17** 43%, **18** <10%.

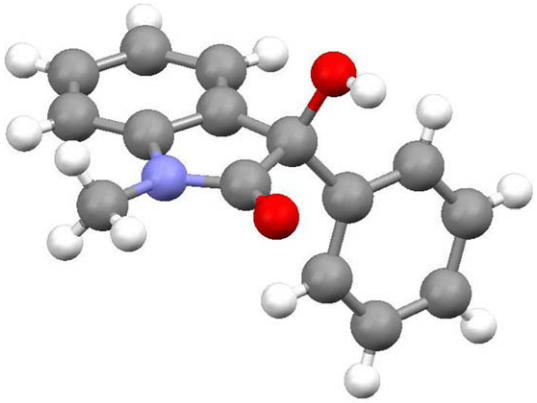


Figure 3. Single crystal X-ray structure of product **17**.

In line with the other oxindole products, the carbonyl carbon in compound **17** resonates at 180 ppm in the ^{13}C NMR spectrum (in $CDCl_3$). An authentic sample of the oxindole **17** was prepared from *N*-methylisatin and phenylmagnesium chloride and its spectroscopic data were identical to that from the product of deprotonation–cyclization of **16**. In addition, a single crystal X-ray structure of the oxindole **17** was obtained (Fig. 3). An attempt to carry out the cyclization with acetic acid quench gave only a very low yield of the 3-indolinone product.

In summary, we have demonstrated a simple method for the preparation of 2-aryl-2-hydroxy-3-indolinones and 3-aryl-3-hydroxy-oxindoles. This occurs by regioselective lithiation at the benzylic position of *N*-benzyl anthranilic acid amides followed by cyclization onto the carboxylic amide group. The 3-indolinone products were found to be the result of autoxidation in air and these rearrange under basic conditions to oxindole ring products.

Acknowledgements

We thank the University of Sheffield, the Nuffield Foundation (URB/34219) and Pfizer for support for undergraduate student bursaries. Mr. C. Lloyd is acknowledged for preliminary work. Professor C. J. Moody is thanked for helpful discussions. We are grateful to the EPSRC X-ray crystallography service for the structure of **6a** (CCDC 217920). We wish to acknowledge the use of the Chemical Database Service at Daresbury,[14] and the software ConQuest[15] and Mercury[16] for crystal structure searching and visualization. Compounds **7c** and **17** have been submitted to the Cambridge Crystallographic Data Centre: **7c** CCDC 754780, **17** CCDC 754779.

References and notes

1. (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300; (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon, 2002. p 282, Chapter 7.2; (c) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59; (d) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275.
2. (a) Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, 3188; (b) Ruiz, J.; Sotomayor, N.; Lete, E. *Tetrahedron* **2006**, *62*, 6182; (c) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311; (d) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115.
3. (a) Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385; (b) MacNeil, S. L.; Gray, M.; Briggs, L. E.; Snieckus, V. *Synlett* **1998**, 419; (c) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710.
4. (a) Sanz, R.; Miguel, D.; Martínez, A.; Pérez, A. *J. Org. Chem.* **2006**, *71*, 4024; (b) Pradhan, T. K.; De, A. *Tetrahedron Lett.* **2005**, *46*, 1493; (c) Linderman, R. J.; Viviani, F. G.; Kwochka, W. R. *Tetrahedron Lett.* **1992**, *33*, 3571.
5. For cyclizations onto nitriles or other carbonyl derivatives, see: (a) Seong, C. M.; Park, C. M.; Park, N. S. *Tetrahedron Lett.* **2009**, *50*, 1029; (b) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311; (c) Lötter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2007**, *63*, 2263; (d) Wang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2001**, *12*, 725; (e) Cartoon, M. E. K.; Cheeseman, G. W. H. *J. Organomet. Chem.* **1981**,

212, 1; For a recent cyclization onto an alkyne, see: (f) Kanazawa, C.; Goto, K.; Terada, M. *Chem. Commun.* **2009**, 5248.

6. (a) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111; (b) Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem. Eur. J.* **2002**, *8*, 195; (c) Coldham, I.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennall, G. P. *Synthesis* **2001**, 1523; (d) Coldham, I.; Vennall, G. P. *Chem. Commun.* **2000**, 1569; (e) Coldham, I.; Fernàndez, J.-C.; Price, K. N.; Snowden, D. J. *J. Org. Chem.* **2000**, *65*, 3788; (f) Coldham, I.; Fernàndez, J.-C.; Snowden, D. J. *Tetrahedron Lett.* **1999**, *40*, 1819; (g) Coldham, I.; Hufton, R.; Rathmell, R. E. *Tetrahedron Lett.* **1997**, *38*, 7617; (h) Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541; (i) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322; (j) Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157; Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275.
7. Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R. E.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621.
8. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
9. (a) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197; (b) Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236. The literature (Ref. 2) suggests that the *N*-methyl-*N*-methoxy (Weinreb) amide analogue of **5** should be a slightly better substrate for cyclization, although attempts to prepare this substrate from methyl *N*,*N*-dibenzylanthranilate or from the *N*-methyl-*N*-methoxy amide of anthranilic acid were unsuccessful.
10. Sukari, M. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2219; (b) Kafka, S.; Klasek, A.; Kosmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394; (c) Hewitt, M. C.; Shao, L. *Arkivoc* **2006**, *11*, 37.
11. For some recent references describing 3-hydroxy-2-indolinones, see: (a) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946; (b) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283; (c) Hillgren, J. M.; Marsden, S. P. *J. Org. Chem.* **2008**, *73*, 6459; (d) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413; (e) Ramachary, D. B.; Reddy, G. B.; Mondal, R. *Tetrahedron Lett.* **2007**, *48*, 7618; (f) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881; (g) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488; (h) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353; (i) Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040.
12. *Typical procedure for the formation of the oxindole* **7a**: *n*-BuLi (0.22 mL, 0.54 mmol, 2.5 M in hexanes) was added to the amide **5a** (0.1 g, 0.27 mmol) in dry Et_2O (5 mL) at −78 °C. The mixture was allowed to warm to room temperature over 4 h then air was blown over the surface for 30 min. MeOH (1 mL) was added, the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (3:1), to give **7a** (0.04 g, 46%) as a solid; mp 139–141 °C (lit.[10b] 144–145 °C); R_f [petrol–EtOAc (4:1)] 0.17; ν_{max} (cm^{-1}) 3360, 3060, 3025, 1700, 1615; δ_H (400 MHz, $CDCl_3$) 3.41 (1H, s), 4.86 (1H, d, *J* 15.5 Hz), 5.08 (1H, d, *J* 15.5 Hz), 6.80–6.82 (1H, m), 7.05–7.09 (1H, m), 7.23–7.45 (12H, m),[10b] found MH^+ (ES) 316.1338, $C_{21}H_{18}NO_2$ requires 316.1338.
13. *Typical procedure for the formation of the 3-indolinone* **6a**: *n*-BuLi (0.44 mL, 1.08 mmol, 2.45 M in hexanes) was added to the amide **5a** (0.2 g, 0.54 mmol) in dry Et_2O (10 mL) at −78 °C. The mixture was allowed to warm to room temperature over 6 h, then acetic acid (0.12 mL, 2.2 mmol) was added and the mixture was exposed to the atmosphere for 1 h. MeOH (1 mL) was added, the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), to give **6a** (0.065 g, 38%) as a solid; mp 78–80 °C; R_f [petrol–EtOAc (4:1)] 0.37; ν_{max} (cm^{-1}) 3390, 3060, 3030, 1690, 1615; δ_H (400 MHz, $CDCl_3$) 3.47 (1H, s), 4.43 (2H, s), 6.59–6.61 (1H, m), 6.78–6.82 (1H, m), 7.24–7.61 (12H, m); δ_C (100 MHz, $CDCl_3$) 47.2, 91.6, 109.0, 117.6, 118.6, 126.0, 126.1, 127.1, 127.3, 128.7, 128.9, 129.0, 136.5, 137.7, 138.8, 160.7, 199.7; found MH^+ (ES) 316.1331, $C_{21}H_{18}NO_2$ requires 316.1338.
14. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.
15. Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. *Acta Crystallogr., Sect B* **2002**, *58*, 389.
16. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453.