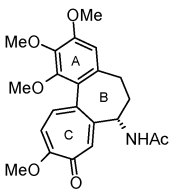
A facile synthesis of dibenzopyrroloazepinones as tetracyclic allocolchicinoids—an unusual 1,2-phenyl shift†

Liang Wu, Abil E. Aliev, Stephen Caddick, Richard J. Fitzmaurice, Derek A. Tocher and Frank D. King*

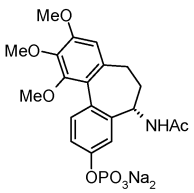
Received (in Cambridge, UK) 15th September 2009, Accepted 11th November 2009
First published as an Advance Article on the web 30th November 2009
DOI: 10.1039/b919114c

A facile synthesis of dibenzopyrroloazepinones *via* an electrophilic cyclisation of a biphenyl-acyliminium ion is described; an unusual 1,2-phenyl shift occurs when the C-1′ carbon is the more nucleophilic than the C-2′ carbon.

Inhibition of microtubulin assembly is a proven anti-cancer mechanism as exemplified by the marketed drugs vinblastine, vincristine, taxol and taxotere.[1] Colchicine **1** is an inhibitor of microtubulin assembly and the related allocolchicines, in which the tropinone ring of colchicine is replaced by a phenyl, as exemplified by ZD6126 **2**, retain the biological activity and are reported to be in clinical trials for cancer.[2,3]

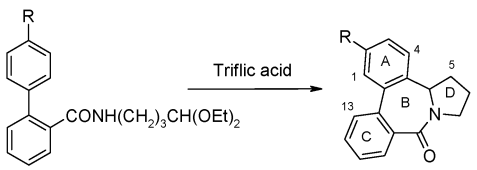


1 colchicine



2 ZD6126

We wished to use our recently reported triflic acid-mediated electrophilic cyclisation of acylpyrrolidinium ions[4] to generate dibenzopyrroloazepinones, which contain the allocolchicinoid biphenyl core structure. We initially investigated the cyclisation of the acyliminium ions derived from the commercially available 2-phenyl- and 2-*p*-tolyl-benzoic acids (Scheme 1). Heating the 2-phenyl amide **3a** in $CHCl_3$ with 10 equivalents of triflic acid gave the tetrahydro-dibenzopyrroloazepin-9-one **4a** in 68% yield. The structure of **4a** was assigned by ^{1}H- and ^{13}C-NMR, and MS.



3a R = H
3b R = Me

4a R = H
4b R = Me

Scheme 1 Synthesis of the dibenzopyrroloazepinones **4a** and **4b**.

Department of Chemistry, University College London, 20 Gordon Street, London, UK WC1H 0AJ. E-mail: f.d.king@ucl.ac.uk

† Electronic supplementary information (ESI) available: Experimental procedures and characterising data for all newly formed products and crystal structure details for **4b** and **6**. CCDC 748250 and 748251. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b919114c

The 2-*p*-tolyl amide **3b** also gave a tetracyclic product in 61% yield. However, after extensive characterisation, the product proved not to be the expected 3-methyl isomer, which would be formed by simple electrophilic addition to the C-2′ position, but the 2-methyl isomer **4b**. Specifically, nOe enhancements were observed between the C-4 proton and one of the C-5 protons, and between the C-1 and C-13 protons. The structure of **4b** was confirmed by X-ray structure analysis (Fig. 1).‡

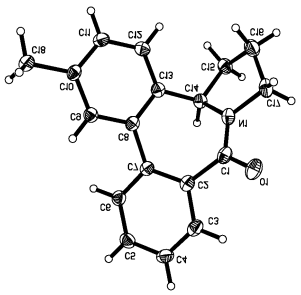


Fig. 1 X-Ray crystal structure of **4b**.

We believe that the formation of **4b** occurs because the methyl group activates the C-1′ carbon to electrophilic attack, forming a spiro intermediate which undergoes an unusual cation-mediated 1,2-phenyl shift (Fig. 2). Although cationic 1,2-aryl shifts on alkane frameworks have been well studied,[5] very few such rearrangements on the phenyl framework have been reported and have required extreme conditions (>400 °C) and/or the presence of bulky groups to impose a steric strain.[6] Thus it was surprising to observe this 1,2-phenyl shift under relatively mild conditions.

We then applied this triflic acid-mediated cyclisation to substrates including the appropriate functionality in the A and C rings consistent with providing potent microtubulin

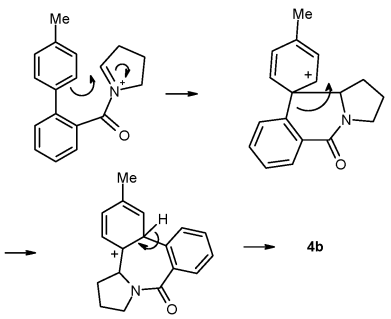
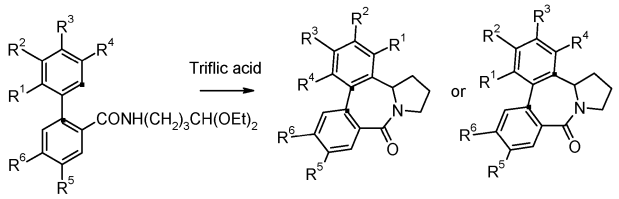


Fig. 2 Proposed mechanism for the cyclisation to give **4b**.

Table 1 Synthesis of the dibenzopyrroloazepinones **4c–g** and **5**



3c-h **4c-g** **5**

		Tetracyclic amide							
Amide	Lactam	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	Rearr.
3c	**4c**	OMe	H	H	H	H	H	62	Yes
3d	**4d**	OMe	H	H	H	OMe	OMe	75	Yes
3e	**4e**	OMe	H	H	OMe	OMe	OMe	51	—[a]
3f	**4f**	OMe	OMe	OMe	H	OMe	OMe	50	Yes
3g	**4g**	OMe	OMe	OMe	H	OMe	H	41	Yes
3h	**5**	OMe	OMe	H	H	OMe	OMe	20	No

[a] See text.

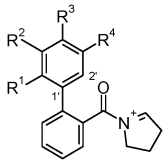
assembly inhibition. The required biphenyl acids were prepared in good overall yield (70–98%) by Suzuki coupling of the appropriately substituted 2-iodobenzoic acid methyl esters and the commercially available phenylboronic acids, followed by base hydrolysis. The acids were converted into amides *via* the acid chlorides. A previously reported attempt to form the acid chlorides of related 2′-methoxybiphenyl acids with thionyl chloride had resulted in the exclusive formation of benzo[*c*]chromen-6-ones.[7] Indeed, we found that our standard method of using oxalyl chloride with the addition of a small (1–2 drops) catalytic quantity of DMF gave up to 35% formation of the benzo[*c*]chromen-6-ones. However, it was found that the formation of this by-product could be minimised by more rapid formation of the acid chlorides using a larger quantity of DMF (5 drops) to give the amides **3c–h** in high yield (66–100%).

The results from the cyclisations of **3c–h** are shown in Table 1. For the majority of compounds, the unexpected regioisomeric products from the 1,2-aryl shift were obtained, confirmed by nOe enhancements. The good yields of **4c** and **4d** contrast with the failure of the equivalent phthalimido acyliminium ion cyclisation.[8] However, it was notable that the 2,3-dimethoxyamide **3h** gave the conventional cyclisation product **5** by cyclisation onto the C-2′ carbon. For the 2,5-dimethoxyamide **3e**, both mechanisms would give the same product **4e**.

Cyclisation of the 3,4,5-trimethoxyamide **3i** ($R^1 = R^6 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$) gave the same product **4g** as cyclisation *via* rearrangement of the 2,3,4-trimethoxyamide **3g** and in the same yield of 41%. The yield of **4g** was relatively low due to its instability under the reaction conditions. Thus heating **4g** under reflux in $CHCl_3$ with triflic acid for 4 h resulted in an 80% conversion to a mono-demethylated product. The lactam **4g** was reduced to the amine **6** with LAH and the product isolated as a hydrochloride salt. An X-ray structure confirmed the positions of the methoxy substituents (Fig. 3).§

In all cases, only one regioisomer was isolated and this is consistent with our hypothesis that the mode of cyclisation is determined by the relative nucleophilicity of the C-1′ and C-2′

Table 2 Estimated nucleophilicity of C-1′ and C-2′ based upon Hammett σ values



Entry	R^1	R^2	R^3	R^4	$\sum\sigma$ at C-1′[a]	$\sum\sigma$ at C-2′[a]	Posn of addition
1	H	H	Me	H	*−0.17*	−0.07	1′
2	OMe	H	H	H	*−0.18*	0.12	1′
3	OMe	OMe	H	H	−0.06	*−0.15*	2′
4	OMe	OMe	OMe	H	*−0.33*	−0.03	1′
5	H	OMe	OMe	OMe	−0.03	*−0.33*	2′

[a] Summation of the Hammett σ values for the substituents R^1–R^4, the italics denotes the more nucleophilic carbon.

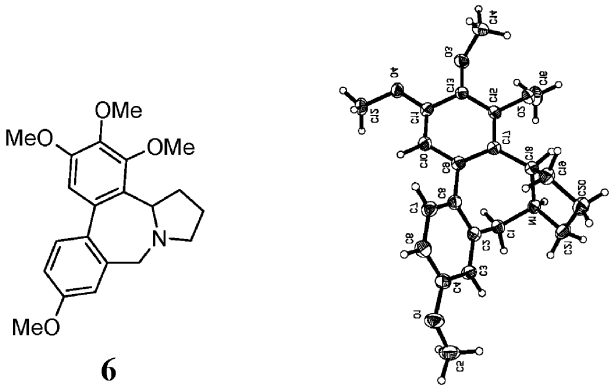


Fig. 3 X-Ray crystal structure of **6**.HCl.

carbons of the biphenyl group. The rate and position of electrophilic substitution normally correlates with the Hammett σ value. Recently it was proposed that the *ortho* σ value can be estimated as 0.65 of the *para* value.[9] Using this and the standard σ values,[10] and assuming the effect of the phenyl substituent is constant throughout, the relative substituent effects on the nucleophilicity of C-1′ and C-2′ can be estimated (Table 2). Thus, within this limited dataset it is possible to correlate the site of addition with the sum of the Hammett σ values and this may be useful to predict the outcome of future cyclisations with other substituents.

In conclusion, a facile synthesis of the dibenzopyrroloazepine ring system is described. Only one example of this ring system has been reported.[11] In contrast to previously reported cationic-mediated 1,2-phenyl shifts,[6] the present results demonstrate 1,2-phenyl shifts can occur with a simple biphenyl system under relatively mild conditions. This rearrangement is likely to occur in a wide range of electrophilic cyclisations of appropriately substituted biphenyls. The biological results of the dibenzopyrroloazepines will be reported elsewhere.

Notes and references

‡ Crystal data for **4b**: $C_{18}H_{17}NO$, M = 263.33, orthorhombic, a = 18.680(2), b = 7.2722(8), c = 19.090(2) Å, U = 2593.3(5) Å^3, T = 150(2) K, space group *Pbca*, Z = 8, 20 861 reflections measured,

3153 unique (R_{int} = 0.0598) which were used in all calculations. The final w$R(F_2)$ was 0.1339 (all data). CCDC no. 748250.

§ Crystal data for **6**: $C_{21}H_{26}ClNO_4$, M = 391.88, monoclinic, a = 14.9657(13), b = 12.7574(11), c = 10.6945(9) Å, β = 90.813(2)°, U = 2041.6(3) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, 17 052 reflections measured, 4848 unique (R_{int} = 0.0323) which were used in all calculations. The final w$R(F_2)$ was 0.2511 (all data). CCDC no. 748251.

1 B. Bhattacharyya, D. Panda, S. Gupta and M. Banerjee, *Med. Res. Rev*., 2008, **28**, 155.

2 (*a*) P. M. LoRusso, S. M. Gadgeel, A. Wozniak, A. J. Barge, H. K. Jones, Z. S. DelProposto, P. A. DeLuca, J. L. Evelhoch, S. A. Boerner and C. Wheeler, *Invest. New Drugs*, 2008, **26**, 159; (*b*) J. W. Lippert III, *Bioorg. Med. Chem*., 2007, **15**, 605.

3 V. Columbel and O. Baudoin, *J. Org. Chem*., 2009, **74**, 4329.

4 (*a*) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev*., 2004, **104**, 1431; (*b*) F. D. King, A. E. Aliev, S. Caddick, D. A. Tocher and D. Courtier-Murias, *Org. Biomol. Chem*., 2009, **7**, 167; (*c*) F. D. King, A. E. Aliev, S. Caddick and R. C. B. Copley, *Org. Biomol. Chem*., 2009, **7**, 3561.

5 *Rearrangements in Ground and Excited States*, ed. P. de Mayo, Academic Press, New York, 1980.

6 (*a*) J. L. Ormsby, T. D. Black, C. L. Hilton, A. Bharat and B. T. King, *Tetrahedron*, 2008, **64**, 11370; (*b*) R. G. Pritchard, M. Steele, M. Watkinson and A. Whiting, *Tetrahedron Lett*., 2000, **41**, 6915; (*c*) R. A. Friedel, M. Orchin and L. Reggel, *J. Am. Chem. Soc*., 1948, **70**, 199; (*d*) M. Orchin and L. Reggel, *J. Am. Chem. Soc*., 1948, **70**, 1245; (*e*) V. P. Senthilnathan and S. E. Stein, *J. Org. Chem*., 1988, **53**, 3000; (*f*) G. Perez and M. Raimondo, *Chemosphere*, 1996, **32**, 1301; (*g*) K. Y. Koltunov, I. B. Repinskaya, M. M. Shakirov and L. N. Shekegoleva, *Russ. J. Org. Chem. (Transl. of Zh. Org. Khim.)*, 1994, **30**, 88; (*h*) G. A. Olah and M. W. Meyer, *J. Org. Chem*., 1962, **27**, 3682.

7 J. W. Cook, G. T. Dickson, J. Jack, J. D. Loudon, J. McKeown, J. Macmillan and W. F. Williamson, *J. Chem. Soc*., 1950, 139.

8 G. Hilt, F. Galbiati and K. Harms, *Synthesis*, 2006, 3575.

9 A. Beteringhe, *Cent. Eur. J. Chem*., 2005, **3**, 585–591.

10 *Medicinal Chemistry: Principles and Practice*, ed. F. D. King, RSC, Cambridge, 1st edn, 1994, appendix 5.

11 Y. Kubo, T. Araki and K. Maruyama, *Bull. Chem. Soc. Jpn*., 1985, **58**, 2863.

