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Mechanism-controlled regioselective synthesis of indolyl benzo[*b*]carbazoles

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Abstract

Benzo[*b*]carbazoles can be synthesised readily and in good yields from the combination of 2,3-unsubstituted indoles and *o*-phthaldialdehyde in the presence of acid catalysts. Use of phosphoryl chloride in chloroform gives rapid reactions and yields 11-(3-indolyl)benzo[*b*]carbazoles, whereas the use of *p*-toluenesulfonic acid in methanol gives slow reactions and yields the isomeric 6-(3-indolyl)benzo[*b*]carbazoles.

Keywords: polycyclic heterocyclic compounds; indoles; regioselectivity; antitumour compounds.

We wish to report the regioselective synthesis of indolyl-benzocarbazoles from acid-catalysed reactions of indoles with *o*-phthaldialdehyde. There are many reports of acid-catalysed reactions of indole with formaldehyde and acetone, and numerous products are formed.[1–7] There are further reports of reactions with 1,4-dicarbonyl compounds, typically in the synthesis of carbazoles.[8–12]

In an attempt to produce the triptycene analog **5**, indole **1** was combined with *o*-phthaldialdehyde **2** (in a 2:1 ratio) in anhydrous chloroform in the presence of phosphoryl chloride (Scheme 1). The reaction was complete after 1 hour and afforded the 11-(3-indolyl)benzo[*b*]carbazole **4** in 58% yield. The suggested mechanism involves formation of a 3,3-di-indolylmethane **3**, which undergoes cyclisation and aromatisation to give benzocarbazole **4**, rather than form a 2,2-di-indolylmethane link and give the triptycene **5**. The structure of the benzocarbazole **4** was confirmed by X-ray crystallography. The reasonable generality of this reaction is illustrated by the conversion of the indoles **6–8** into the indolyl-benzocarbazoles **9–11**, respectively, in 62–67% yields (Scheme 2).[13] Under the same conditions, the activated 4,6-dimethoxyindole **12** gave a complex mixture of products and the less reactive 1-aroyl derivative **13** gave no reaction. 1-Methyl-4,6-dimethoxyindole **14** gave a 19% yield of the benzocarbazole **15**.

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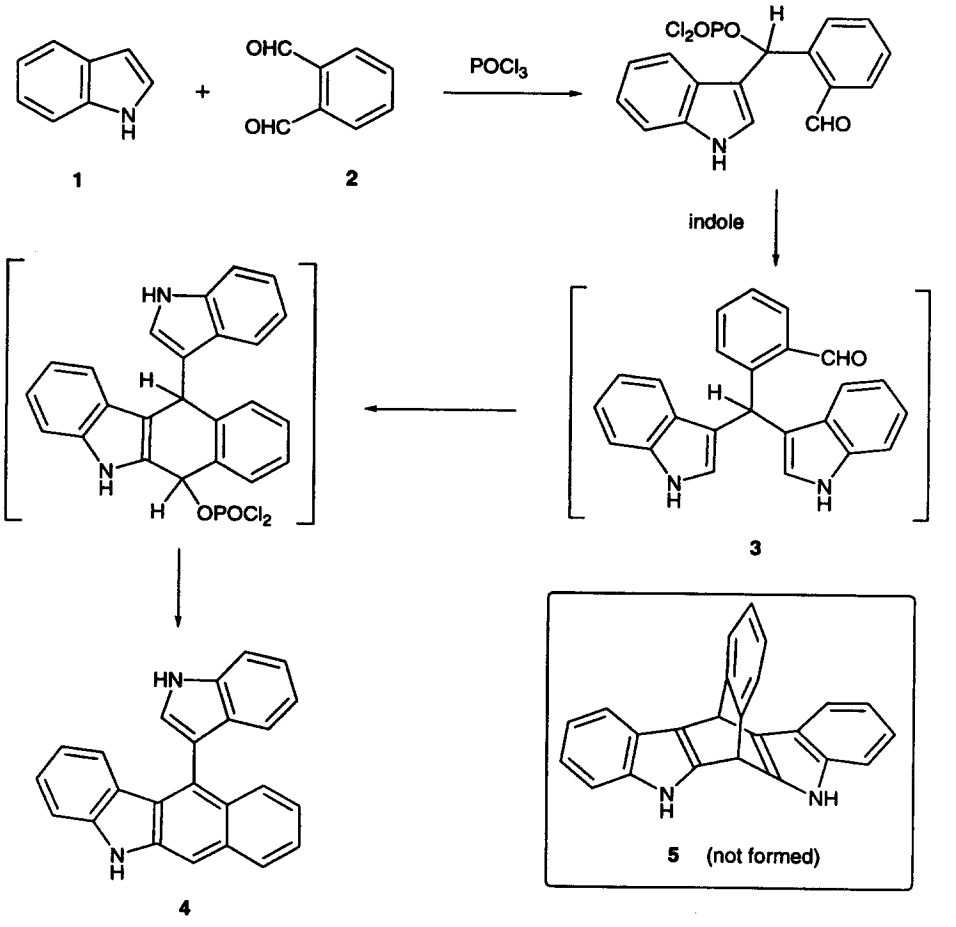
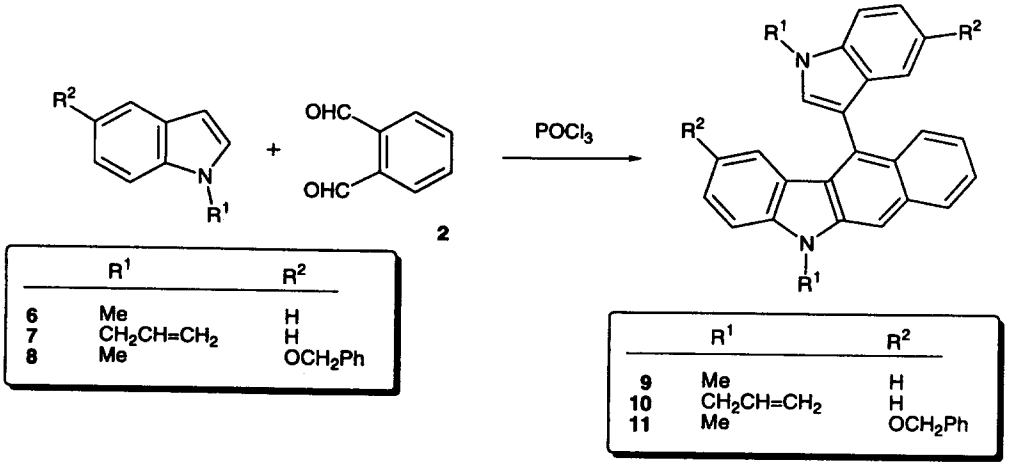
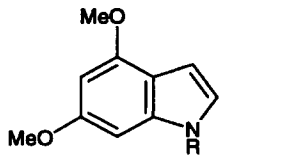


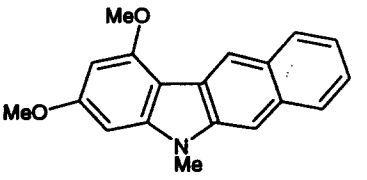
Scheme 1.



Scheme 2.



R	
12	H
13	CO(4-ClC$_6$H$_4$)
14	Me



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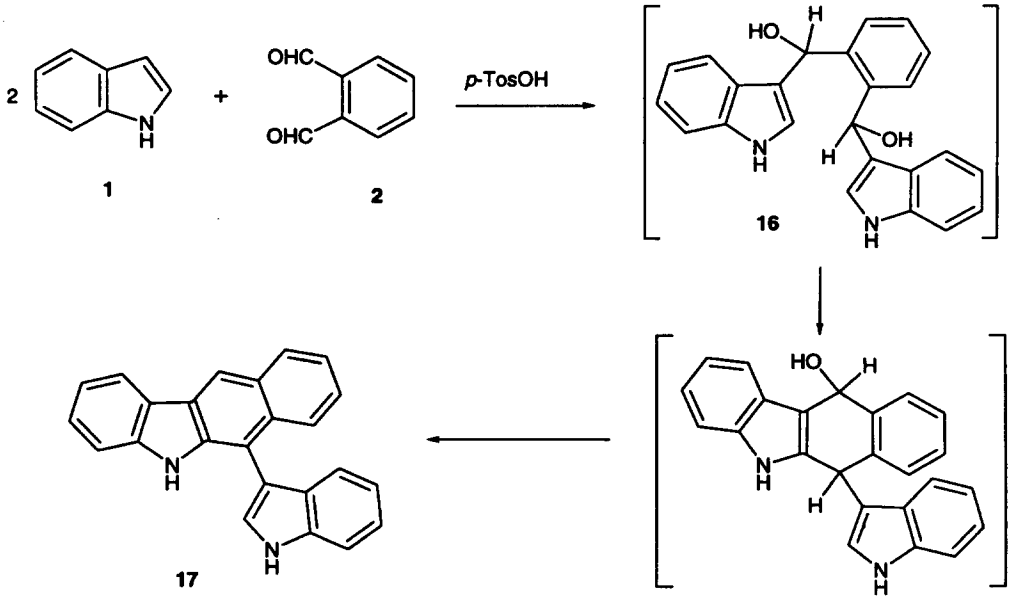
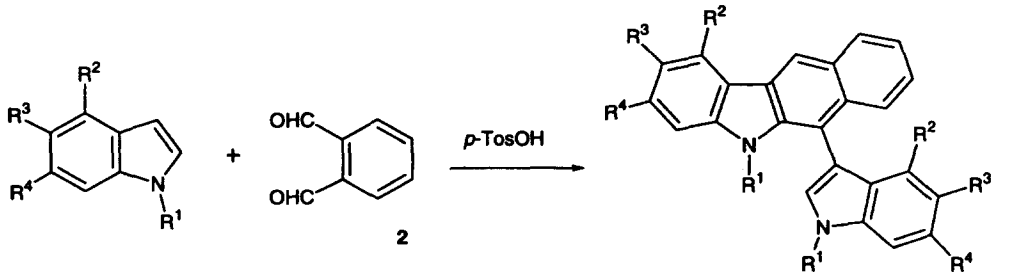
In view of these results, use of a milder acid catalyst was investigated. Reaction of indole **1** with *o*-phthaldialdehyde **2** (in a 2:1 ratio) in anhydrous methanol in the presence of *p*-toluenesulfonic acid gave after 4 hours the 6-(3-indolyl)benzo[*b*]carbazole **17** in 79% yield (Scheme 3). In this instance the mechanism presumably involves the attack of one indole at each aldehyde to give the dicarbinol **16**, which undergoes cyclisation and dehydration to benzocarbazole **17**. This reaction shows wider generality and although much slower (up to 6 days) gives higher yields than the previous one. The indoles **18–23**, which include activated examples, gave benzocarbazoles **24–29**, respectively, in 72–84% yield (Scheme 4).[13] The structures of benzocarbazoles **17** and **29** were also confirmed by X-ray crystallography.



Scheme 3.

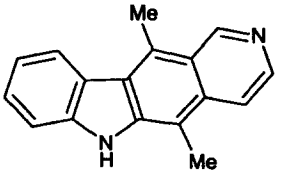
Benzo[*b*]carbazoles are of interest because of their relationship to the antitumour agent ellipticene **30**, and are therefore desirable synthetic targets as potential DNA intercalating agents.[14–16] Although there are various benzo[*b*]carbazole syntheses available, they deliver only a very narrow range of substituents, (methyl, phenyl and cyano) at the 6- and 11-positions.[17–20] The above simple reactions significantly enhance the synthetic access to new benzo[*b*]carbazoles.



	R^1	R^2	R^3	R^4
18	H	Br	H	H
19	H	H	Br	H
20	H	H	OCH_2Ph	H
21	Me	H	OCH_2Ph	H
22	Me	OMe	H	OMe
23	$CH_2CH{=}CH_2$	OMe	H	OMe

	R^1	R^2	R^3	R^4
24	H	Br	H	H
25	H	H	Br	H
26	H	H	OCH_2Ph	H
27	Me	H	OCH_2Ph	H
28	Me	OMe	H	OMe
29	$CH_2CH{=}CH_2$	OMe	H	OMe

Scheme 4.



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References

1. von Dobeneck, H.; Maas, I. *Chem. Ber.* **1954**, *87*, 455–463.
2. Noland, W. E.; Richards, C. G.; Desai, H. S.; Venkiteswaran, M. R. *J. Org. Chem.* **1961**, *26*, 4254–4262.
3. Noland, W. E.; Venkiteswaran, M. R. *J. Org. Chem.* **1961**, *26*, 4263–4269.
4. Chatterjee, A.; Manna, S.; Banerji, J.; Pascard, C.; Prangé, T.; Shoolery, J. N. *J. Chem. Soc., Perkin Trans. 1* **1980**, 553–555.
5. Bergman, J.; Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron* **1989**, *45*, 5549–5564.
6. Black, D. StC.; Ivory, A. J.; Kumar, N. *Tetrahedron* **1995**, *43*, 11801–11808.
7. Noland, W. E.; Konkel, M. J.; Konkel, L. M. C.; Pearce, B. C.; Barnes, C. L.; Schlemper, E. O. *J. Org. Chem.* **1996**, *61*, 451–454.
8. Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan. J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715–2727.
9. Jackson, A. H.; Jenkins, P. R.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1698–1704.
10. Lallemand, J.-Y.; Lemaitre, P.; Beeley, L.; Lesca, P.; Mansuy, D. *Tetrahedron Lett.* **1978**, *19*, 1261–1264.
11. Lancelot, J.-C.; Rault, S.; Robba, M.; Dung, N. H. *Chem. Pharm. Bull.* **1987**, *35*, 425–428.
12. Hall, R. J.; Jackson, A. H.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *Heterocycles* **1990**, *31*, 401–405.
13. All new compounds were characterised fully by spectroscopy and microanalysis e.g. compound **4**: m.p. 257–258°C; ν_{max} 3380 cm^{-1}; λ_{max} (MeOH) 226 nm (ε58,000), 272 (69,000), 282sh (58,000), 294 (34,000); ^1H NMR spectrum ($CDCl_3$): δ 6.81–8.65, 16H, ArH, NH; mass spectrum (EI): *m/z* 332 (M, 100%). Compound **17**: m.p. 130–131°C; ν_{max} 3400 cm^{-1}; λ_{max} (MeOH) 223 nm (ε105,000), 272 (122,000), 281sh (105,000), 293 (61,000); ^1H NMR spectrum ($CDCl_3$): δ 7.13–8.67, 16H, ArH, NH; mass spectrum (EI): *m/z* 332 (M, 100%).
14. Pindur, U.; Haber, M.; Erfanian-Abdoust, H. *Heterocycles* **1992**, *34*, 781–790.
15. Dräger, M.; Haber, M.; Erfanian-Abdoust, H.; Pindur, U.; Sattler, K. *Monatsh. Chem.* **1993**, *124*, 559–576.
16. Pindur, U.; Haber, M.; Sattler, K. *J. Chem. Educ.* **1993**, *70*, 263–272.
17. Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2505–2508.
18. Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215–5228.
19. Oishi, E.; Taido, N.; Iwamoto, K.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1990**, *38*, 3268–3272.
20. Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J. *Tetrahedron* **1994**, *50*, 4811–4828.