A New Strategy for the Synthesis of Biflavonoids via Arylboronic Acids.

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Abstract : Amentoflavone derivatives were prepared by catalytic coupling of 8-flavoneboronic acids with iodoflavones. 3-Arylflavones, as biflavonoid synthon, are accessible by the method.

The synthesis of amentoflavone (1, R^1 to R^6 = H) and derivatives, a biflavonoid family with a dissymetrical I-3', II-8 connection¹, has not been widely explored². Nakazawa³ has described the formation of dioonflavone la and ginkgetin le by Ullmann coupling of 3'-and 8-iodoflavones. However this methodology gave a mixture of isomers the separation of which proved to be difficult, while yields were not very attractive.

R ²	о _В 1	R ⁶ C				,R⁵) ≈0	,R ⁴
1	R ¹	R ²	R^3	R ⁴	к ⁵	R ⁶	
a	Me	Me	Me	Me	Me	Ме	
Ь	Me	Ме	iPr	iPr	iPr	iPr	
c [Н	Me	Н	н	н	Н	
d	Me	Ме	Ме	iPr	iPr	iPr	
e	Н	Me	Me	Н	Н	Н	
fl	Ме	Me	Me	iPr	iPr	Ме	
q	н	Me	Me	Н	н	Me	

More recently Susuki 4 and others 5 have recommended the use of arylboronic acids for aryl-aryl bond formation taking advantage of the following catalytic process :

 $Ar-B(OH)_2 + Ar'-J = \frac{Pd (TPP)4}{toluene, Na_2CO_3^{2M}} Ar-Ar'$



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We have applied this strategy to the synthesis of amentoflavone ethers and have explored two pathways :

- synthesis of 3'- or 8-flavoneboronic acids followed by their catalytic coupling with a suitable iodoflavone ;

 synthesis, using boronic acids methodology, of 3'-arylflavones and subsequent building of the second flavone ring.

The problem of access to flavoneboronic acids was in part resolved via lithiation (n-BuLi/THF, -78°) of 8-iodoflavones 2a and $2b^6$ followed by addition of trimethylborate. This procedure provided boronic acids 3 in high yields, as crystalline solids, very stable under anhydrous conditions⁷. A very low temperature was required during the lithiation procedure to avoid side reactions occurring on the heterocyclic portion of the flavone. Therefore, the iodoflavone 2c, only partially soluble at -78°, could not be lithiated. Application of this procedure to 3'-iodoflavones 4 also failed due to isomerisation of lithiated species.

The catalytic coupling reaction of boronic acids **3** with 3'-iodoflavones **4** (refluxing dioxane, K_2CO_3 2M, Pd (TPP)4) is in competition with the protodeboronation of the boronic entity. Consequently an excess of boronic acid was necessary to achieve the complete reaction of the iodoflavone. Under these conditions, protected biflavones **1b**, **1d** and **1f** are obtained in nearly 90 % yields (based on iodoflavones). Selective deprotection at the 5-methoxy- or isopropoxy group and -4' or -7 position (for isopropoxy groups only) occurs under mild conditions and leads in excellent yields to sequoiaflavon **1b**, ginkgetin **1e** and sciadopytissin **1g**.

Aryl-aryl connection via boronic acids has also been tested in the second protocol : 2,4,6-trimethoxyphenylboronic acid 7, readily available from 1,3,5-trimethoxybenzene⁹ leads with high yield to the 3'-arylflavone 5^{10} . This compound can be acylated with p-methoxy-cinnamic acid employing BF₃ as catalyst. During this procedure a regio selective demethylation of the diorthosubstituted methoxy group¹⁰ occurs leading to the chalcone 6. Construction of the second flavone ring is achieved by oxidative cyclisation (I₂, H₂SO₄, DMSO) and gives the dioonflavone 1a.

The structures of boronic acids 3, intermediates 5, 6 and protected biflavones 1b, 1d and 1f have been established by elementary analysis and NMR spectroscopy. For the protected biflavones the non equivalence (NMR, 500 MHz) of the methyls of the isopropoxy groups in $4^{\circ}(R^3, R^6)$, $5(R^4)$ and $7(R^5)^{12}$ is noteworthy and indicates a restricted rotation around the aryl-aryl bond. The deprotected biflavones 1c, le and lf possess the same properties (UV, IR, NMR) as the natural products or synthetic material described in the literature. 13, 14, 15

These results indicate the utility of the boronic acid strategy in the synthesis of polysubstituted heterocyclic systems. Isopropyl protection is also very useful, as it improves the organic solubility of substrate and is easily introduced and removed.

Acknowledgements : We thank Ets Fournier, Dijon and C.N.R.S. for financial support, Dr .F. Bellamy and Prof. V. Snieckus for helpful discussions. 1) For the nomenclature of biflavonoids see B. Jackson, H.D. Locksley, F. Scheinmann and W.A. Wolstenhome, J. Chem. Soc (C), 1971, 3791.

M. Geiger and G. Quinn, The Flavonoids, J.B. Harborne, Ed. (Chapman and Hall, Ltd), 1988.
a) K. Nakazawa, Chem. Pharm. Bull. (Tokyo)), 1962, <u>10</u>, 1032; b) K. Nakazawa and K. Ito, ibid., 1963, <u>11</u>, 283.

4) N. Miyaura, T. Yanagi and A. Suzuki, Synth. Commun., 1981, 11, 513.

5) M.J. Sharp and V. Snieckus, Tetrahedron Lett., 1985, 26, 5997.

6) For the preparation of iodoflavones 2 and 4 sec ref. 3a and 5. Saxena, J.K. Makrandi and S.K. Grover, Synthesis, 1985, 697. MP.°C : 2a : 198-199; 2b : 177-178; 4b : 163.

7) Typical boronation procedure : to an anhydrous solution of 3,13 g (6 mmol) flavone 2a in 60 ml THF add 4.5 ml of 1.5 M n-BuLi in hexane (temp. < -70°) and after 10 min at the same temperature 1.5 ml (12 mmol) $B(OCH_3)_3$ with 2 ml THF. Stir 1 h at temps < -70° and then slowly return (3 h) to 20°. Add 10 ml H₂0 and dry ice. Dilute with 50 ml H₂0 and extract with CHCl₃. After distillation of solvent the residue is treated with iPr₂0. Dec °C(DSC), 3a : 166 ; 3b : 182.

8) Typical coupling procedure : 1,2 g (2.58 mmol) of flavone 4b, 2.85 g (6.45 mmol) of boronic acid 3a, 2.93 mg Pd (TPP)₄, 6.5 ml (2 éq./4b) of K_2CO_3 2M in water and 80 ml dioxane are heated (at reflux temperature) under argon stream 5 h. After cooling add 20 ml HCl 2N and 150 ml H₂O and extract with CHCl₃. Separation by flash chromatography (4AcOEt/4 $C_6H_{14}/1CH_3OH$) of deboronated flavone (1,3 g) and biflavone 1b (1,7 g, 91 %). MP°C, 1b : 127-130°, 1d : 140-142, 1f 154-157.

9) Synthesis from 1,3,5-trimethoxy benzene (n-BuLi/Et₂O/TMDA, -10°; B(DCH₃)₃, -60°; H₂O : 20°). Rdt : 70 %. MP°C : 109.¹H-RMN (CDCl₃) : 3.87 (s, 3H, CH₃O), 3.90 (s, 6H, CH₃O), 6.17 (s, 2H, H₃-H₅), 7.00 (2H exch. D₂O, OH).

10) Yield : 90 %/4a, MP°C : 250.

11) Yield : 76 %/5, MP°C : 244-245.

12) For 16, 8 doublets $(J - 6R_z)$ at (ppm) : 1.013 and 1.184 (R^3) , 1.265 and 1.283 (R^6) , 1.228 and 1.284 (R^5) , 1.511 and 1.518 (R^4) .

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