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The Preparation of Hindered Biphenyls Via the Suzuki Reaction

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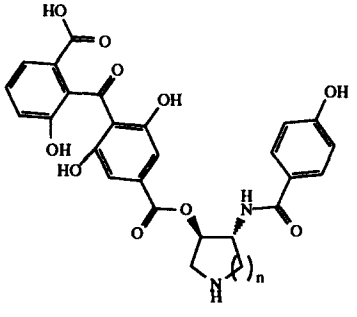
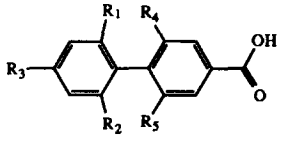
Abstract: The preparation of a number of hindered biphenyls is presented in which the arylboronate suffers from both steric crowding and electron withdrawing group deactivation.

In the course of our studies on the structure activity relationships of the potent protein kinase C (PKC) inhibitor Balanol (**1**)[1] and its equipotent analog (**2**)[2], we considered the replacement of the benzophenone portion of the molecule with suitably substituted biphenyls (**3**). Molecular modeling studies of the benzophenone led us to believe that the biphenyl, by virtue of its restricted rotation, could mimic the conformation adopted by the benzophenone and thereby open a new series of analogs for evaluation in our PKC program.



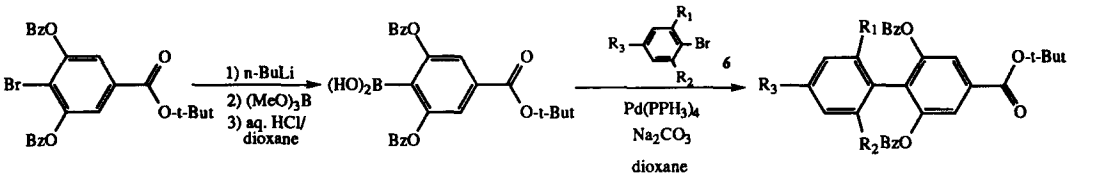
1 n=3
2 n=1



3

We initially considered several routes to the desired biphenyls. Ullman coupling[3], Gomberg chemistry[4], and radical coupling with reagents such as lead tetraacetate and AIBN were uniformly unsuccessful as either inter or intramolecular variations (Pschorr reaction[5]). We eventually investigated the Suzuki reaction, and, despite reports in the literature of poor yields when steric hindrance or electron withdrawing groups[6] were contained in the arylboronate, we were generally successful in the preparation of the desired biphenyl compounds.

The scheme below shows the general route used for the preparation of the title compounds.



4 5

3a R_1=R_3=H, R_2=OBz
3b R_1=CO_2Bz, R_3=R_2=H
3c R_1=CO_2Bz, R_2=OBz, R_3=H
3d R_1=R_3=CO_2Bz, R_2=H

Preparation of the borate (**5**) proceeded from the bromide (**4**)[7] with no evidence of butyl lithium attack at the ester carbonyl. Coupling of the borate with aryl bromides (**6**) under standard Suzuki conditions[8] gave good yields of **3a**, **b**, and **d**, but low yields of **c** (12%). Modifications suggested by Suzuki[6d] (eg. NaOH, K_3PO_4) did not improve the yield of **c**, nor did use of the aryl iodide.

To our knowledge these are the first examples of a Suzuki type coupling in which the presence of both steric hindrance and electron withdrawing group factors in both components were overcome. We can only speculate that the two vicinal benzyloxy groups provide stabilization of the boronate, reducing the deboronation side reaction and allowing for successful conversion to the desired products. A number of other biphenyl derivatives have been prepared by this route. Our studies on their conversion to balanol analogs and the biological activities of those analogs will be presented in due course.

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