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Biphenyls as Surrogates of the Steroidal Backbone. Part 1: Synthesis and Estrogen Receptor Affinity of an Original Series of Polysubstituted Biphenyls

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Abstract—In the course of a programme aimed at discovering new ligands of the estrogen receptor, we explored a series of substituted biphenyls. Their synthesis and binding affinity are described.

Introduction

We have been actively involved during the past few years in the search for new compounds with estrogenic or antiestrogenic activities.[1] Today, the main classes of synthetic estrogens and antiestrogens are related to di[2]- and tri[3]-aryl-methanes, -ethanes and ethylenes[4] (e.g., DES[5] and Tamoxifen[6]). The other well represented class of nonsteroidal estrogen receptor ligands are the phenolic indoles,[7] indenes,[8] thiophenes (e.g., Raloxifen[9]) and pyrazoles.[10] Because of the parallelism between 4-hydroxy-4′-hydroxymethyl-biphenyl and estradiol (Fig. 1) and stimulated by Korach's report on estrogenic activities in several hydroxybiphenyls,[11] we became interested in exploring a little more thoroughly this potential new class of nonsteroidal estrogens.

The object of the present paper is to disclose the results we have obtained with a series of these compounds and their estrogen receptor binding affinities.

Chemistry

Most of the biphenyls described in this paper were obtained by aryl–aryl coupling reactions (Scheme 1, Table 1). Whenever substitution allowed for it, we made use of the *Suzuki coupling* (Table 1, conditions 1–5) of substituted phenylboronic acids[12] with arylhalides or triflates (entries 1–16). Even for 2,6-disubstituted aryl triflates or bromides acceptable yields were obtained (entries 3–8, 10, 11, 13–15). In the case of the coupling of the 2,6-dimethyl 4-methoxy boronic acid only the conditions described by Suzuki[13] for the coupling of hindered boronates with aryl iodides gave the product in modest yield (entry 12). The absence of reactivity of arylchlorides with boronic acids in the presence of tetrakis triphenylphopshine palladium has been reported by Mitchell.[14] All 2,6-disubstituted monochlorinated aryl triflates or bromides gave reasonable yields of coupling with boronic acids (entries 2, 6–8, 16). In the case of 2,6-dichlorosubstituted aryl triflates (entry 3), about 30% chlorine monoreduction also occurred. This problem was eliminated when the iodides were used in place of the triflates (entries 4, 14, 15), but the yields remained modest especially when the arylboronic acids bore electron-withdrawing substituents. On the other hand, in

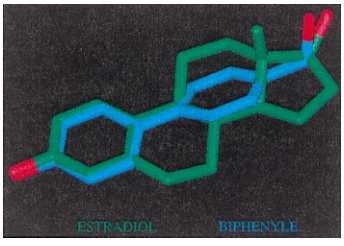

Figure 1.

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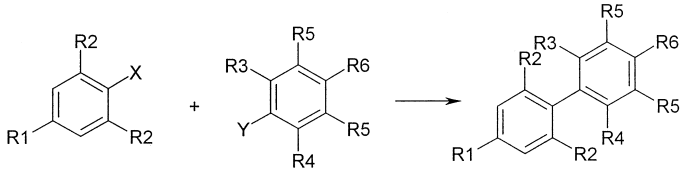
spite of the reported triflate versus bromide selective coupling of a vinylstannane with an aryltriflate,[15] in the case of 2,6-dibromotriflate only low yields of expected coupled product could be obtained (entry 5). We therefore had to devise a better way to obtain these 2,6-dibromobiphenyls. For this, we made use of the reported *selective Ullmann coupling reaction* (Table 1, conditions 6) for aryl halides having very different electronic properties.[16] The 2,6-dinitrochloro aromatic compounds could be coupled smoothly with iodoaryl derivatives (entries 17, 18). We also explored the synthesis of these 2,6-dihalosubstituted biphenyls by a *coupling reaction using arylzinc reagents in the presence of palladium*[17] (Table 1, condition 7). Kumada[18] and Tilley[19] have reported monocoupling reactions of arylzinc reagents with dibromoaromatics. Encouraged by a recent report by Grega[20] describing biphenyl coupling of a 2,6-difluoroaryl zinc with halopyridines, we first turned to the synthesis of the fluorinated analogues of our compounds using this method. 1,3-Difluoro-5-tetrahydropyranyloxymethylbenzene was orthometallated using BuLi and the lithium was exchanged with zinc from a freshly prepared zinc chloride tetrahydrofuran solution. The resulting arylzinc reagent was reacted with 4-benzyloxyphenylbromide at 50 °C in the presence of Pd(0) to give the desired compound (entry 19). Encouraged by the success of this reaction, we applied it to the synthesis of the 2,6-dichlorobiphenyls. Orthometallation of 1,3-dichlorobenzene has been reported by Kress;[21] the author reports that above 50 °C the lithium anion is unstable and gives rise to self-coupling by substitution of the chlorine atoms. We proceeded in the same way as for the difluorinated aromatics and were able to obtain the expected 2,6-dichlorobiphenyls (entries 20, 21). In the case of entry 21, the coupling reaction was achieved selectively by displacement of the bromo substituent of a bromochloroaromatic.[22]

The 2,6-dinitro biphenyls were further elaborated by sequential reduction of the nitro groups using cyclohexene



Scheme 1.

Table 1. Synthesis of the functionalized biphenyl compounds[fjk]

Entry	Compd	R1	R2	X	Y	R3	R4	R5	R6	Yield	Conditions[a]
1	**1**	OMe	—	B(OH)2	OTf	—	—	—	CHO	100	1
2	**2**	OBn	—	B(OH)2	OTf	Cl	—	—	COOMe	55	3
3	**4**	OSi*t*BuPh$_2$	—	B(OH)2	OTf	Cl	Cl	—	CHO	43[d]	3
4	**5**	OBn	—	B(OH)2	I	Cl	Cl	—	CH$_2$(OCH$_2$CH$_2$O)	25[g]	1
5	**6**	OMe	—	B(OH)2	OTf	Br	Br	—	CHO	6–10[e]	1
6	**7**	OBn	—	B(OH)2	OTf	Cl	OMe	—	CHO	23	3
7	**8**	OBn	—	B(OH)2	OTf	Cl	iPr	—	CHO	26	5
8	**9**	OBn	—	B(OH)2	OTf	Cl	CF$_3$	—	CHO	85/23	3
9	**10**	OBn	—	B(OH)2	Br	CF$_3$	—	—	CHO	85	2
10	**11**	OBn	—	B(OH)2	Br	OMe	OMe	—	CHO	39	2
11	**12**	OSi*t*BuPh$_2$	—	B(OH)2	OTf	Me	Me	—	CHO	29–40[c]	4
12	**14**	OMe	Me	B(OH)2	OTf	—	—	—	CHO	25	5
13	**15**	CHO	—	B(OH)2	Br	Me	Me	—	OBn	23	5
14	**16**	OBn	—	B(OH)2	I	Cl	Cl	Cl		65	2
15	**17**	CHO	—	B(OH)2	I	Cl	Cl	Cl	OBn	13[h]	2
16	**18**	CHO	—	B(OH)2	Br	Cl	—	—	OSi*t*BuMe$_2$	59[b]	2
17	**22**	OSi*t*BuMe$_2$	—	I	Cl	NO$_2$	NO$_2$	—	COOMe	72	6
18	**23**	OSi*t*BuMe$_2$	—	I	Cl	NO$_2$	NO$_2$	—	CH$_2$O Si*t*BuMe$_2$	39	6
19	**19**	OBn	—	Br	ZnCl	F	F	—	CH$_2$OTHP	58[i]	7
20	**20**	COOMe	—	Br	ZnCl	Cl	Cl	—	OSi*t*BuMe$_2$	27[c]	7
21	**21**	OSi*t*BuMe$_2$	Cl, H	Br	ZnCl	Cl	Cl		CH(OCH$_2$CH$_2$O)	17[g]	7

[a]Conditions: (1): Na_2CO_3 2 M/LiCl/$Pd(PPh_3)_4$/EtOH/Tol/Δ[23]; (2) $Pd(PPh_3)_4/K_3PO_4$/Dioxane/85 °C;[24] (3) $Pd(PPh_3)_4/K_3PO_4$ /KBr/Dioxane/85 °C; (4) $Pd(PPh_3)_4$/LiCl/Dioxane;[14] (5) $PdCl_2(PPh_3)_2/Ba(OH)_2$/DME aq;[13] (6) *n*BuLi/−78 °C; $ZnCl_2$/−78 °C–rt; $Pd(PPh_3)_4$/THD/Δ[25] (7) Cu/120 °C/DMF.[15]

[b]Desilylated compound along with 16% of protected analogue.

[c]After silyl deprotection (TBAF/THF).

[d]Containing ca. 30% of monochlorinated analogue.

[e]Along with 21% of compound resulting from coupling on the bromine atom and 10% of compound from double coupling on the bromine and the triflate.

[f]Mixture resulting mainly from double coupling on the bromine atoms.

[g]Yield of three consecutive steps: iodination of 3,5-dichloro-1-dioxolano-benzene (BuLi/THF, NIS), coupling and acetal deprotection (HCl 1 N/THF).

[h]Yield of three consecutive steps: iodination of tetrachlorobenzyloxybenzene (BuLi/THF, NIS), coupling and aldehyde reduction ($NaBH_4$/MeOH).

[i]After THP deprotection (HCl 2 N/MeOH).

[j]As a mixture of methyl and butyl esters.

[k]After LAH reduction of the ester.

in the presence of palladium followed by transformation of the resulting amine **25** into bromide,[26] iodide,[27] thioalkyl[28] or pyrrole compounds **24**–**30** (Scheme 2). The bromine and iodine atoms of these biphenyls could be replaced by further coupling with propargylamines as exemplified by the synthesis of **27**.

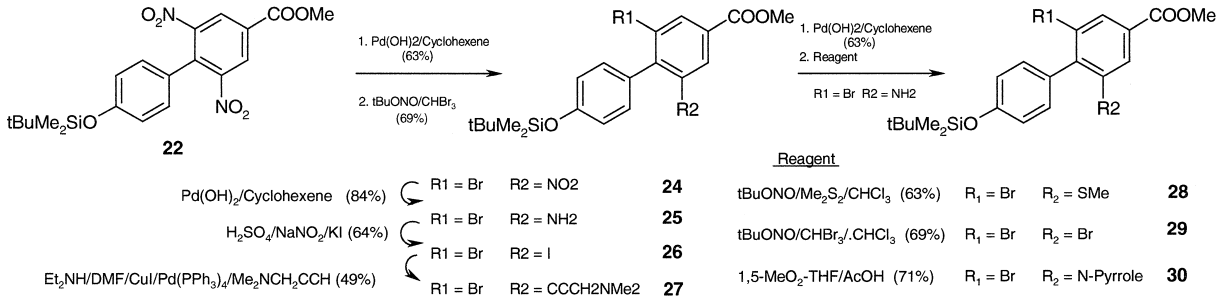
All these biphenyls were then further elaborated into final compounds **30**–**59** (Table 2) possessing a free phenol in the 4-position and a hydroxymethyl group in the 4′-position using standard chemistry.

Biology

Receptor binding affinities (RBAs) for human recombinant estrogen receptor alpha[29] were determined according to decribed procedures. Results were expressed as percent of the affinity of estradiol.

In view of the aforementioned report that estrogenic activities of several biphenyls were improved by conformational restriction brought about by one or two *ortho* chlorines, we wanted to study polysubstituted analogues of **30** with a special emphasis on halogen dervivatives. Of all sites for substitution on the biphenyl ring, the 2′,6′-position was best able to bring about positive changes (Table 2). A detectable change of affinity could be seen with the addition of a first chlorine in the 2′-position (**31**). Dramatic improvement of the affinity was then gained with the addition of a second halogen atom with the 2′,6′-dibromo- and dichlorobiphenyl **33** and **34** displaying, respectively, 425 and 104% of the receptor binding affinity of estradiol (100%). This effect was partially lost when one of the bromines was replaced by an iodine atom (**35**) and totally abolished when both halogens were fluorines (**32**). This first observation could be the result of steric hindrance or of the reported slightly wider torsion angle between the two aromatic rings when going from bromine and chlorine to iodine.[27] On the other hand, the 2′,6′-difluorobiphenyl has probably no more rotational constraints than the unsubstituted biphenyl. The 2′,6′-dinitro compound **49** still displayed about 25% of the estradiol affinity, which was totally lost upon reduction of one of the nitro groups to give the amine (**50**). This observation is in line with previous reports in the literature that polar substituents are generally poorly tolerated in the centre of the ligand binding pocket of estrogen receptor alpha, at least in some nonsteroidal ligands systems.[30] Similarly, when one of the bromines was replaced by a *N*-pyrrol-1-yl (**44**), the affinity was also lost.

Obviously, conformational constraint was not the only important factor for the estrogen receptor affinity since replacement of the halogens by methoxy or methyl groups resulted in total loss of affinity (**47** and **48**). Only the trifluoromethyl group was capable of retaining some affinity for the receptor (**38** and **39**). This effect of



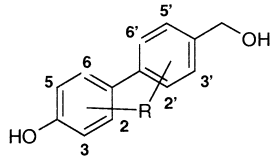
Scheme 2.

Table 2. Estrogen receptor binding affinity of substituted biphenyls

R	Compd	REH[a] RBA (%)	R	Compd	REH[a] RBA (%)
—	**30**	<	2′,6′-Br,CCNMe$_2$	**45**	0.2
2′-Cl	**31**	2	2′,6′-Br,SMe	**46**	4.5
2′,6′-F$_2$	**32**	0.93	2′,6′-OMe$_2$	**47**	0.24
2′,6′-Cl$_2$	**33**	34 (104[b])	2′,6′-Me$_2$	**48**	0.8
2′,6′-Br$_2$	**34**	106 (425 [b])	2′,6′-(NO$_2$) $_2$	**49**	24[b] 5
2′,6′-Br,I	**35**	41	2′,6′-NO$_2$, NH$_2$	**50**	0.03
2′,6′-Cl, Ome	**36**	2.5	3,5-Br$_2$	**51**	0
2′,6′-Cl, iPr	**37**	22	3,5-Me$_2$	**52**	0
2′,6′-Cl,CF$_3$	**38**	50	2,6-Me$_2$	**53**	0.06
2′-CF$_3$	**39**	9.5 (33[b])	2′,3′,5′,6′-Cl$_4$	**54**	5,4
2′,6′-[Cl,(4-HOPh)]	**40**	1	2,3,5,6-Cl$_4$	**55**	0
2′-(4-HOPh)	**41**	1	2,6-Cl$_2$	**56**	0.4
2′,6′-Br,NO$_2$	**42**	34	2-Cl-2′,6′-Cl$_2$	**57**	21
2′,6′-Br,NH$_2$	**43**	0.03	2-Cl	**58**	0.03
2′,6′-Br,N-pyrrole	**44**	2	3- CH$_2$Ph-2′,6′-Cl$_2$[32]	**59**	0.07

[a]REH = Recombinant human estrogen receptor, 24 h/0 °C.
[b]REH, 3 h/0 °C.

trifluoromethyl groups has been described in the diethylstilbestrol family.[31]



Other positions were explored on the biphenyl scaffold but no further improvement of the estrogen receptor affinity could be obtained. Addition of more chlorine atoms to **33** always resulted in diminished affinities (**54** and **57**). In this latter case, this had been observed also by Korach in his series and was interpreted as a result of the pK_a difference between the tetra- and disusbtituted aromatic compounds.

In addition, lipophilicity was not a very important parameter since positioning of the two chlorine atoms in the 2,6-positions of the first aromatic ring also resulted in a total loss of affinity (**56**). Halogen substitution on the first phenyl ring always gave very low affinities (**51**, **55**, **58**) as was the case for any substitution on this ring (**52** and **53**). A bulky benzyl group in the 3-position resulted in a total loss of affinity (cf. **59** with **33**).

Conclusion

Some simple scaffolds demonstrating excellent binding affinities for the estrogen receptor were discovered. The implications of these findings for future prospects in estrogen or antiestrogen treatment are under investigation.

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