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SYNTHESIS OF DIARYLIC COMPOUNDS BY PALLADIUM CATALYZED REACTION OF AROMATIC TRIFLATES WITH BORONIC ACIDS

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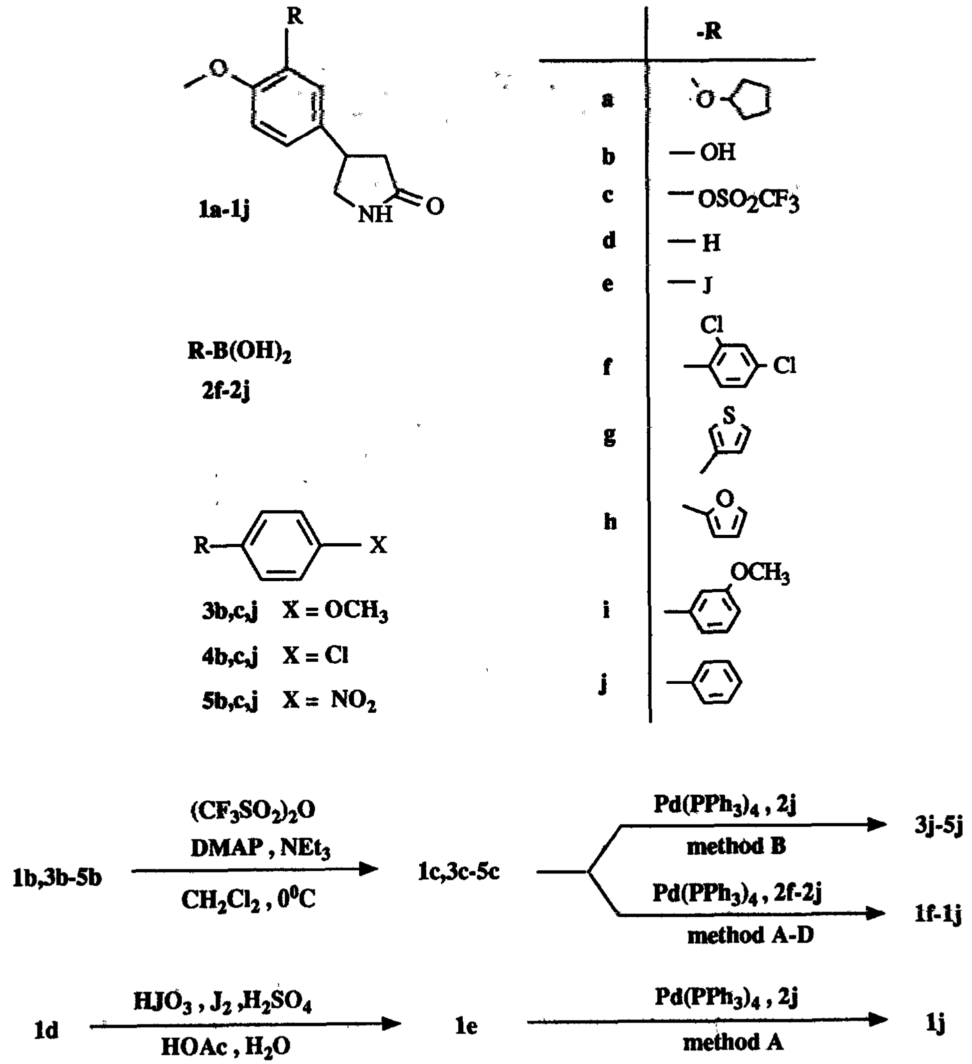
Abstract-The known triflates **3c**-**5c** react with the boronic acid **2j** to produce the known biarylic compounds **3j**-**5j**.An extension of this new procedure by reacting the novel triflate **1c** with the arylboronic acids **2f-j** affords the new correspondingly arylated compounds **1f-j**.

Rolipram (**1a**) is a clinically proven antidepressant with a novel mechanism of action$^{1)}$.In the course of modifications of this molecule we became interested in replacing the cyclopentyloxy moiety in **1a** by an aromatic ring.Within the last few years a number of palladium-catalyzed arylation techniques have been developed.In this respect the reactions of halo-aromatics with arylboronic acids$^{2,3)}$,arylstannanes$^{4,5)}$and arylzinc compounds$^{6)}$are already known.Trifluoromethanesulfonates (triflates) have been used instead of the halides to a certain extent.Thus the reaction of phenoltriflates with aryltin compounds$^{7)}$and (of enoltriflates) with arylzinc compounds $^{8)}$but -according to our knowlegde- not with boronic acids have been reported in the literature. In order to prepare **1f**-**1j** we decided to investigate this as yet unknown reaction of triflates with boronic acids **2**.The simple triflates **3c**$^{7)}$,**4c**$^{13)}$,**5c**$^{7)}$ were chosen as a model;they did not react with phenylboronic acid (**2j**) following the procedure of Suzuki$^{2)}$ (method A,table 1),but gave reasonable yields in the presence of 2 equivalents of lithium chloride (method B),which is known to be necessary in other reactions of triflates$^{9)}$.However the methoxy compound reacted sluggishly and incompletely.Surprisingly and despite its o-methoxy group the triflate of the easily accessible hydroxymethoxyphenylpyrrolidinone **1b**$^{10)}$ reacts smoothly with the boronic acids **2f**-**2j** to produce in acceptable yields the pyrrolidinones **1f**-**1j** even in the absence of lithium chloride (method A,table 1).The reaction could be further improved by the addition of lithium chloride (method B,table 1).Another procedure$^{3)}$using DMF as solvent and triethylamine as base (method C) gave no reliable results with **2j** and could not be improved by lithium chloride (Method D).Thus method B seems to be the best of the four tried procedures.The most important advantage compared to method A is the higher turnover rate,which allows a simple purification of the product by recrystallisation.

We were furthermore interested to compare the reactivity of the triflate **1c** with the corresponding iodide **1e**, easily prepared from 4-methoxyphenylpyrrolidinone (**1d**)$^{11)}$ by analogy to the method of Wirth$^{12)}$.Compound **1e** reacted in a similar manner (method A,table 1) with **2j**.Thus method B with lithium chloride in triflates works as well as method A in iodides.

In conclusion,the reaction of aromatic triflates of phenols with boronic acids is a valuable supplement to the already known arylation techniques,which mostly use aromatic halides as starting material.The described method - as those previously mentioned $^{7,8)}$- allows the replacement of an aromatic hydroxy group by an aromatic ring,but it avoids the known problems of working with tin or zinc compounds.



EXPERIMENTAL

Melting points were determined with a Büchi melting point apparatus(Dr.Tottoli)and are not corrected.Solvents of analytical grade were used after drying over a molecular sieve.Phenylboronic acid (**2b**) was obtained from Aldrich,2,4-dichlorophenylboronic acid (**2f**) from Alfa-Ventron.The other boronic acids were synthesized from the lithiumorganic (**2g** and **2h**) or from the Grignard reagent (**2i**) according to the literature[3].Column chromatographie was performed at medium pressure(up to 0.5 bar)over silica gel (63-200µm,Merck)with methylene chloride:ethanol=10:1,if not otherwise stated.Elemental analyses were carried out by our "Analytisches Kontrollabor" under the direction of Dr. Merz. HPLC was performed on Zorbax with CH_3CN:buffer=6:4; (buffer:1.58g NH_4HCO_3/ltr. H_2O).

Table 1

product	starting comp.	replaced group	method (yield [a];reaction time)			
			A[b]	B[c]	C[d]	D[e]
1f	**1c**	OTf	34%[f];4+2h[g]	53%[h];2h		
1g	**1c**	OTf	46%[f];4h	69%[h];2h		
1h	**1c**	OTf	59%[i];3+2h[g]	68%[h];2+3h[g]	54%[f];3+3h	
1i	**1c**	OTf	63%[f];2+5h[g]	77%[h];2h		
1j	**1c**	OTf	60%[k];7h	58%[h];5h	-[l];6h	-[l];10h
3j	**3c**	OTf	-[l];1h	50%[n];1h		
4j	**4c**	OTf	-[l];1h	49%[m];5h		
5j	**5c**	OTf	-[l];1h	51%[m];4h		
1j	**1e**	I	62%[f];4h			

a.)Isolated yields;^{1}H-NMR-Spectra are in accordance with the given structures.
b.)2M-Na_2CO_3;EtOH;toluene;Pd^{0};boronic acid.
c.)2M-Na_2CO_3;EtOH;toluene;Pd^{0};boronic acid;LiCl.
d.)NEt_3;DMF;Pd^{0};boronic acid.
e.)NET_3;DMF;Pd^{0};boronic acid;LiCl.
f.)Obtained by chrom. and recryst.
g.)Second addition of boronic acid and Pd^{0} and second boiling period necessary.
h.)Obtained by recrystallisation.
i.)Obtained by chromatographie.
k.)Calculated from HPLC;6:3 mixture of **1c** and **1j**.
l.)No product could be detected by TLC.
m.)Obtained by chrom.with ethyl acetate:cyclohexane=2:98 and recryst.
n.)Calculated yield,obtained by chrom.with ethyl acetate:cyclohexane=2:98 as 3:2 mixture with starting material.

4-(4-Methoxy-3-trifluormethanesulfonyloxyphenyl)-pyrrolidin-2-one (**1c**)
A solution of 14.9g(72 mmol) of 4-(3-hydroxy-4-methoxyphenyl)-pyrrolidin-2-one (**1b**)[10]and 29 g (0.23 mol)of dimethylaminopyridine (DMAP) in 700 ml methylene chloride was treated dropwise at 0^{0}C with a solution of 12.5 ml (75 mmol) of trifluoromethanesulfonic anhydride (triflic anhydride).After stirring at 0^{0}C for 1h another 4.1g (32 mmol)of DMAP and 1.25 ml (7.5 mmol)of triflic anhydride were added and again stirred for 1h.Then it was washed twice with 300ml of 1N-hydrochloric acid and once with 300ml of water. The organic layer was dried,filtered and evaporated.The residue was recrystallized from ethyl acetate/hexane to afford 37.5g (77%) of **1c**,m.p. 103^{0}C.Another 8.2g (16%) were obtained by chromatographie of the mother liquor.($C_{12}H_{12}F_3NO_5S$;339.29;requires:C,42.48;H,3.56;F,16.80;N,4.13; S,9.45;found:C,42.36; H,3.70;F,17.22;N,4.02;S,9.42%).
In an analogous manner the following triflates were obtained:
4-Methoxyphenoltriflate(**3c**)[7];yield:97 %;oil.
4-Chlorophenoltriflate(**4c**)[13];yield:98 %;oil.
4-Nitrophenoltriflate(**5c**)[7];yield:98 %;m.p.50-52^{0}C (lit[7]52-53^{0}C).

4-(3-Iodo-4-methoxyphenyl)pyrrolidin-2-one (**1e**)
A mixture of 19.1g(100 mmol) of 4-(4-methoxyphenyl)pyrrolidin-2-one (**1d**)[11] in 200 ml of glacial acetic acid with 4.8ml of water,1.2 ml of conc.sulfuric acid,3.4g (20 mmmol)of iodic acid (Fluka) and 8.8g (34.8 mmol)of iodine were stirred for 10h at 80^{0}C.After evaporation the residue was recrystallized from ethyl acetate to afford 15.2g (33%) of **1e** (m.p.155^{0}C).Another 10.5g (33%) were obtained by chromatographie of the mother liquor and recrystallisation from ethyl acetate (m.p.158^{0}C).($C_{11}H_{12}INO_2$+ 0.15 ethyl acetate; 325.54;requires:C,42.8;

H,4.09;I,38.98;N,4.30;found:C,42.63;H,4.35;I,38.36; N,4.67%).

Method A,B

0.5 mmol of **1c**,**3c**,**4c**,**5c** or **1e** were dissolved in 4.5ml of toluene.Then successively 19mg (0.016 mmol) of $Pd(PPh_3)_4$0.65ml of 2-M Na_2CO_3,2ml of ethanol,0.55mmol of the boronic acid and in method B 1 mmol of lithium chloride were added.Afterwards it was stirred for the specified time at 95^{0}C (table 1).In indicated cases it was necessary to add 0.15 mmol of the boronic acid and 0.005 mmol of $Pd(PPh_3)_4$ and to stirr at 95^{0}C for an additional period of time.Subsequently the mixture was treated with ethyl acetate and extracted first by 1-N NaOH and then by saturated NaCl. The organic layer was dried,filtered and evaporated.The residue was purified in the manner described in table 1.

Method C and D

0.5mmol of **1c** were dissolved in 10 ml of DMF. 19mg (0.016 mmol) of $Pd(PPh_3)_4$ and 4 ml of triethylamine (and 1 mmol of lithium chloride in method D) were added and the mixture heated at 95^{0}C under an atmosphere of argon for the time shown in table 1.After evaporation the residue was worked up as described in method A and B.

By method A-D the following compounds were obtained (yields see table 1):

1f(m.p.145-146^{0}C;ethanol,ethyl acetate,hexane)($C_{17}H_{15}Cl_2NO_2$;336.22;required: C,60.73;H,4.50;Cl,21.09; N,4.17;found:C,60.49;H,4.70;Cl,21.11;N,3.70%).

1g(m.p.132-133^{0}C;ethyl acetate,hexane)($C_{15}H_{15}NO_2S$ + 0.2 ethyl acetate;290.98;required:C,65.22;H,5.75; N,4.81;S,11.19;found:C,65.10; H,5.76;N,4.81;S,11.20%).

1h(m.p.152-153^{0}C;ethanol,hexane)($C_{15}H_{15}NO_3$ + 0.5 ethanol;279.2;required:C,68.68;H,6.30;N,5.01;found: C,68.66;H,6.32;N,4.86%).

1i(m.p. 137-139^{0}C,ethanol,ethyl acetate,hexane)($C_{18}H_{19}NO_3$;217.35;required:C,72.71;H,6.44;N,4.71;found: C,72.77;H,6.41;N,4.60%).

1j(m.p.150-151^{0}C,ethyl acetate,hexane)($C_{17}H_{17}NO_2$ + 0.4 ethyl acetate;302.57;required:C,73.84;H,6.73; N,4.63;found:C,73.61;H,6.33;N,4.97 %).

3j m.p.(lit$^{14)}$90^{0}C).

4j m.p.73-74^{0}C,(lit$^{15)}$76^{0}C).

5j m.p.109-111^{0}C,EtOH (lit$^{16)}$114-114.5^{0}C).

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