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Synthesis of constrained arylpiperidines using intramolecular Heck or radical reactions

Christophe Morice,[a] Mathias Domostoj,[a] Karin Briner,[b] André Mann,[a,*] Jean Suffert[a] and Camille-Georges Wermuth[a]

[a]*Laboratoire de Pharmacochimie de la Communication Cellulaire, Université Louis Pasteur, Faculté de Pharmacie, UMR 7081 du CNRS/ULP, 74, route du Rhin, BP 24, 67401 Illkirch Cedex, France*
[b]*Lilly Research Laboratories, Eli-Lilly and Company, Indianapolis, IN 46285, USA*

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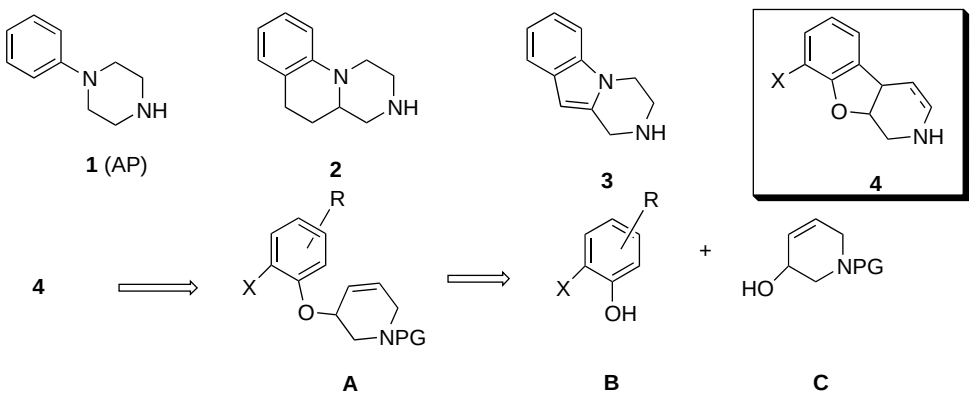
Abstract—Two intramolecular routes were experimented to reach the hexahydrobenzofuro[2,3-*c*]pyridine platform: a Heck and a radical reaction. The radical route was applicable to all substrates, whereas the Heck route was of limited use. The key adducts were obtained via a Mitsunobu condensation between halogenated phenols and an allylic alcohol, the 3-hydroxy-tetrahydropyridine.

The examination of medicinal chemistry reports revealed that the structures of a great deal of pharmacological tools and/or drugs are constituted of an arylpiperazine (AP) core **1**.[1] This is not really surprising if one considers that the AP moiety is isosteric to dopamine or serotonine which are among the most targeted endogenous neurotransmitters in medicinal chemistry. Furthermore conformational restriction is a powerful device for the identification of a bioactive conformation,[2] several constricted AP were designed such as **2** or **3**.[3,4] In our current work for the design of new selective agents acting in the central nervous system (CNS), we decided to prepare tricyclic adducts such as **4**, hexahydrobenzofuro[2,3-*c*]pyridines. The design of this platform was motivated by the following points (i) piperidines and AP have generally comparable bioactivity, therefore the less basic nitrogen was skipped; (ii) the oxygen atom link between the rings is a potential hydrogen bond acceptor;[5,6] (iii) the distance of the basic nitrogen and the phenyl ring is fixed by the *cis* junction of the structure; (iv) few operative methods for the preparation of **4** are available in the literature. With all these considerations, we embarked on the synthesis of **4**, in the quest of new leads for the CNS receptors (Scheme 1). The reported routes to **4** are linear, requiring tedious transformations and lacking



Scheme 1. Structures of some conformational restricted phenylpiperazines, and retrosynthesis analysis towards **4**.

Keywords: Heck reaction; radical reaction; benzofuropyridine; conformational restriction.
* Corresponding author. Tel.: +(33) 33 90 24 42 27; fax: +(33) 3 90 24 43 10; e-mail: andre.mann@pharma.u-strasbg.fr

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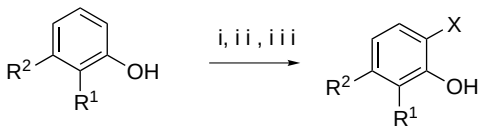
flexibility,[7] we designed a short and versatile synthesis of these compounds in order to reach diversity (Scheme 1). This paper describes our findings during the preparation of **4**.

Our retrosynthesis relies on a disconnection crossing the furano ring between the two six-membered cycles. In fact the phenolic ether link is rather easy to construct from phenols **B** and allylic alcohol **C**. If now an halide is attached *ortho* to the oxygen atom on the aromatic ring, an intramolecular Heck type coupling[8] or alternatively a radical drived process may produce the ring junction via the formation of a C–C bond, provided that an acceptor such as a double bond is properly set as it will be in the 3-OH-tetrahydropyridine **C**. With synthon **A**, where X stands for I or Br, we have identified the desired structure, which is accessible by coupling of fragments **B** (phenols) and **C** (piperidinol). Indeed several *ortho* halogenated phenols are commercially available, or accessible in few known steps, and the synthesis of tetrahydropyridinol **C** has been described. Such tricyclic constructions have already been made in the past but only in an all carbon version.[9,10] Here we have experimented the intramolecular cyclization with an heterocyclic partner.

The key intermediates **A** were obtained in the following way. The phenols **6a–c** are commercially available, whereas the phenols **6d–h** were prepared by *ortho*-metallation using a three-step sequence starting from the phenols **5d–h**: the phenolic oxygen was protected as a MOM ether (methoxymethylether), then the adjacent proton was abstracted with BuLi in Et_2O, and the subsequent stabilized anion, quenched with I_2 as solution in ether.[11] The non optimized yields were moderate to good over the three steps (Scheme 2).

The piperidinol fragment **C** was obtained uneventfully as reported from 4-oxopiperidine.[12] Then the halogenophenols **6a–e** were coupled to compound **C** under classical Mitsunobu conditions to reach the phenolic ethers **7a–e** in good yields.[13] The intramolecular Heck reaction was performed on **7a–h** using classical conditions reported by Negishi:[10] a catalytic amount of $Pd(PPh_3)_4$, triethylamine as base in a refluxing THF/CH_3CN mixture.[9,10] In our hands when performed on compounds **7c–e** the expected Heck adducts **8c–e** could be isolated in good to modest yields (75 and 30%). The cyclic carbopalladation was effective and furthermore, the dehydropalladation was regioselective, installing the double bond so as to produce an enamide function in **8c–e**. Interestingly this acyl-enamide function could be exploited for the introduction of various groups next to the nitrogen atom. Unfortunately the other substrates **7a–b** and **7f–h**, under the same conditions gave no trace of cyclization: the starting material disappeared, only phenol and dihydropyridine were recovered. We believe that in the case of the bromides **7a–b**, and the more sterically crowded iodide **7f–h** the oxidative palladium insertion did not occur. The reaction follows an other pathway: a π-allyl complex is formed and the phenol behaves as a leaving group. Owing to these disappointing results no other catalytic mixture was tried. We experimented directly the second alternative which makes use of a radical pathway. The ethers **7a–h** were submitted to the conditions recommended by Snieckus:[14] Bu_3SnH (2.5 equiv.) and a catalytic amount of AIBN. As expected the intramolecular 5-*exo* radical cyclization proceeds cleanly and, we were pleased to observe a complete consumption of the starting material, after 3 h refluxing in benzene.[15] The reaction was productive either with bromine (**7a–b**) or with iodine (**7c–h**), irrespective of the substituents present on the aromatic ring. To facilitate the work-up of these reactions we used the procedure of Curran.[16] The compounds were purified by column chromatography on silica gel and excellent yields of the tricyclic adducts **9a–h** were obtained (from 79 to 90%). As expected and confirmed by extensive NMR studies, the stereochemistry of the ring junction was *cis*. A single X-ray analysis performed on the corresponding *t*-Boc analogue **9a′** of **9a** confirmed the assigned structure.[17] Similarly catalytic hydrogenation of compounds **8c–d** provided also the adducts **9c–d**. Finally the carbamate protection on the nitrogen was cleaved under basic hydrolytic conditions to give rise to the expected final compounds **10a–h**, as crystalline hydrochlorides in satisfying yields (Scheme 3).



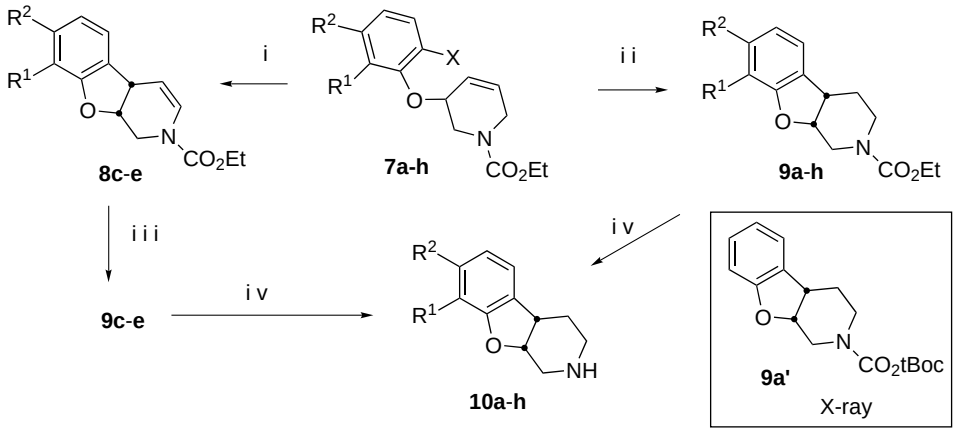
5a-h **6a-h**

			yield %**
a	R^1 = H; R^2 = H;	X = Br	*
b	R^1 = Br; R^2 = H;	X = Br	*
c	R^1 = H; R^2 = H;	X = I	*
d	R^1 = H; R^2 = Me;	X = I	70
e	R^1 = H; R^2 = OMe;	X = I	45
f	R^1 = H; R^2 = CF_3;	X = I	74
g	R^1 = H; R^2 = F;	X = I	79
h	R^1 = Me; R^2 = Me;	X = I	75

*The compounds are commercial

** Isolated overall yields

Scheme 2. *Reagents and conditions*: (i) NaH, $MeOCH_2Cl$, THF; (ii) BuLi, then I_2 as solution in ether; (iii) TMSCl, NaI, CH_3CN.



	R^1	R^2	X	**8**[a]	**9**[a]	**10**[a,b]
a	H	H	Br	0	86	88
b	Br	H	Br	0	80	80
c	H	H	I	75	81	90
d	H	Me	I	30	90	50
e	H	OMe	I	30	90	60
f	H	CF_3	I	0	87	44
g	H	F	I	—	79	58
h	Me	Me	I	—	79	53

a) yield in %; b) yield as the hydrochloride.

Scheme 3. *Reagents and conditions*: (i) $Pd(PPh_3)_4$, triethylamine, CH_3CN/THF, reflux 20 h (see Ref. 18); (ii) Bu_3SnH, AIBN, C_6H_6, reflux (see Ref. 19); (iii) H_2 $Pd(OH)_2$/C in methanol, 30 psi; (iv) KOH, EtOH, reflux, then HCl (gas) in Et_2O.

Finally we have prepared a series of benzofuropiperidines **10a–h** from rapidly accessible precursors using intramolecular pathways, either a Heck or a radical reaction, the last route being the most reliable from a preparative point of view. Compounds **10a–h** will be submitted to a biological trial, and the obtained results will be reported on another forum.

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18. Experimental for the preparation of **8c**: A solution of **7c** (950 mg, 2.6 mmol) in a mixture of CH_3CN/THF (30 ml/10 ml) under argon was treated with $Pd(PPh_3)_4$ (294 mg, 0.195 mmol), and Et_3N (530 μl, 3.8 mmol) and refluxed for 15 h. The solvent was removed in vacuo and the resulting residue was purified by flash chromatography on silica gel eluting with ether/hexane: 20/80. Compound **8c** was obtained as a colorless oil (475 mg, 75%). ^{1}H NMR (**8c** as a mixture of rotamers): ($CDCl_3$, 330 K, 200 MHz) δ (ppm): 1.29 (brs, 3H), 3.72 (dd, *J* 13.7 and 3.5 Hz, 1H), 3.91 (br d, *J* 4.4 Hz, 1H), 4.02 (m, 1H), 4.22 (m, 2H), 5.05 (m, 2H), 6.81 (d, *J* 7.8 Hz, 1H), 6.96 (br s, 1H), 7.14 (q, *J* 7.8 Hz, 1H), 7.17 (d, *J* 7.5 Hz, 1H).
19. Experimental for the preparation of **9h**: A 0.02 N degazed benzene solution (150 ml) of **7h** (1.17 g, 3 mmol) under argon was treated with Bu_3SnH (1.245 ml, 4.5 mmol), and AIBN (50 mg) and refluxed for 2 h. Solvents were removed in vacuo and the resulting residue was dissolved in ether (150 ml) and treated with DBU (670 μl, 4.5 mmol). Excess of DBU was neutralized with a 1 M Br_2 solution, the precipitate filtered and the solution concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with ether/hexane: 40/60. Compound **9h** was obtained as a colorless oil (711 mg, 90%). ^{1}H NMR: ($CDCl_3$, 200 MHz, 300 K) δ (ppm): 1.27 (br s, 3H), 1.86 (m, 1H), 2.10 (m, 1H), 2.21 (s, 1H), 3.25 (br m, 1H), 3.40 (m, 1H), 3.59 (dt, *J* 8.7 and 5.6 Hz, 1H), 3.67 (br d, *J* 12.9 Hz, 1H), 3.91 (dd, *J* 14.3 and 5 Hz), 4.15 (q, *J* 6.8 Hz, 2H), 4.90 (br s, 1H), 6.79 (t, *J* 7.2 Hz), 6.96 (d, *J* 7.5 Hz, 1H), 6.97 (d, *J* 7.2 Hz). ^{13}C NMR: ($CDCl_3$, 50 MHz, 300°K) δ (ppm): 14.6, 15.1, 26.2, 38.8, 39.9, 42.7, 61.2, 79.4, 119.8, 120.6, 121.4, 128.5, 129.7, 156.2, 157.8.