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Synthesis of novel 2*H*-spiro[1-benzofuran-3,4′-piperidin]ol scaffolds

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ABSTRACT

With the aim to enrich our 'privileged structure'-based library, novel 2*H*-spiro[1-benzofuran-3,4′-piperidin]ol scaffolds were prepared. The method involved a key intramolecular Heck cyclization which was successfully applied for three series of compounds. The desired scaffolds were obtained in overall yields of 42–53%.

The generalization of high-throughput screening (HTS) in drug discovery has been of significant interest for the design of chemical libraries with the goal of identifying new lead compounds. Initial HTS campaigns with random compound libraries—so-called blind screenings—have resulted in disappointingly low hit rates. Thus, compound synthesis for merely expanding proprietary compound stock, without taking any design or filtering criteria into account, is now considered an inefficient strategy.[1] As a consequence, a clear trend to optimize chemical libraries in terms of size[2] and diversity[3] has emerged. Nowadays the design of smaller and focused libraries is considered a highly promising strategy for hit-finding in drug discovery.[4–6] Concerning the generation of focused libraries, one of the widely used approaches is to create compound collections based on 'privileged structures'.[7] Libraries prepared according to this concept, are considered to provide an ideal source of new leads.[8,9] Scaffolds containing spiropiperidine motifs have been classified as 'privileged structures' owing to their rigid framework and ability to direct functional groups in a well defined space.[10,11] However, when considering the literature, it was found that the spiro scaffold 2*H*-spiro[1-benzofuran-3,4′-piperidin]ol **1** has received no attention (Fig. 1). With our aim to develop libraries based on 'privileged structures', spirocycle **1** appeared to be an attractive scaffold for combinatorial chemistry. With two distinct reactive functionalities for selective substitutions, this scaffold may easily provide a number of compounds with the high diversity needed for the development of new, selective compounds.

In this Letter, we report our preliminary results on the synthesis of 2*H*-spiro[1-benzofuran-3,4′-piperidin]ol scaffold **1** via a synthetic approach involving an intramolecular Heck reaction for the formation of the spiro core.

While the preparation of 2*H*-spiro[1-benzofuran-3,4′-piperidines] is well documented, the construction of this spirocycle structure, specifically with a hydroxy or an alkoxy moiety on the aryl ring, is comparatively less studied. Four potential strategies are described in the literature (Scheme 1). For both the nucleophilic aromatic substitution (S_NAr)[12] and dehydration[13,14] strategies, the major hurdle appeared to be the design of a straightforward method which could provide the required key intermediates **3** and **4**, respectively. Two other synthetic approaches, both based on key intermediate **5**, were studied by Cheng[15,16] for the synthesis of a morphine fragment. In view of a potential active pharmaceutical ingredient (API) preparation and to avoid purification issues due to the use of toxic Sn reagents in the radical cyclization strategy, we decided to explore the Heck cyclization-based approach[16] for the preparation of **2** (Scheme 1).

In accordance with our strategy, the synthesis of the desired spiro[benzofuran-piperidin]ols **1a–d** required the preparation of

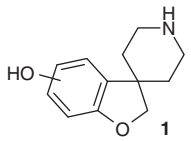

Figure 1. 2*H*-Spiro[1-benzofuran-3,4′-piperidin]ol scaffold **1**.

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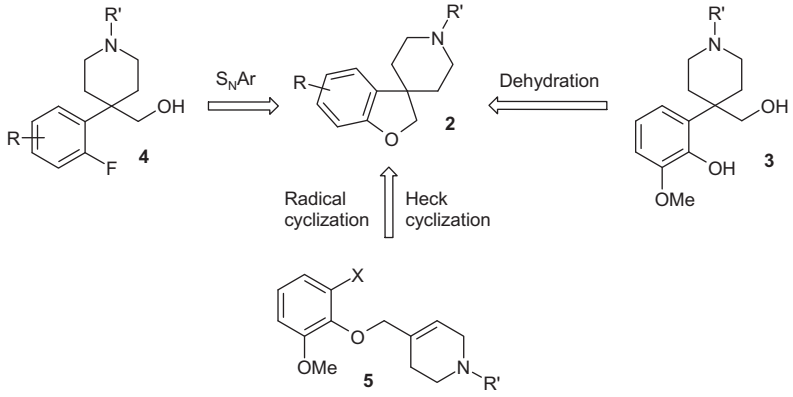
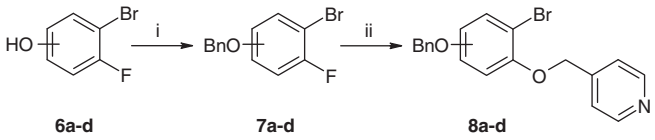


Scheme 1. Retrosynthetic approaches based on the literature.

Table 1
Benzylation and S_NAr reactions



6a-d **7a-d** **8a-d**

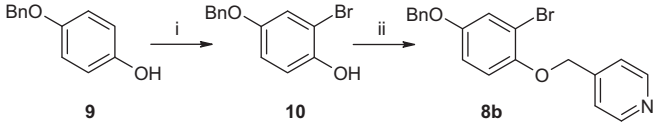
Entry	**6a–d**	Product	Yield[a] (%)	Product	Yield[a] (%)
1	2-Bromo-3-fluorophenol	**7a**	98	**8a**	71
2	3-Bromo-4-fluorophenol	**7b**	95	**8b**	12
3	4-Bromo-3-fluorophenol	**7c**	—[b]	**8c**	83
4	3-Bromo-2-fluorophenol	**7d**	97	**8d**	77

Reagents and conditions: (i) BnBr, K_2CO_3, acetone, reflux 4 h; (ii) pyridine-4-methanol, NaH, NMP, 100 °C, 2 h.
[a] Isolated yields after column chromatography.
[b] Compound **7c** is commercially available.

the corresponding pyridine intermediates **8a–d** (Table 1). Recently, several articles have described a straightforward method for the preparation of aromatic ethers and desymmetrized resorcinol derivatives via a S_NAr reaction of substituted aryl fluorides by metal alkoxides.[17–21] This methodology was applied for the preparation of **8a–d**, starting from commercially available bromofluorophenols **6a–d**. The benzyl protected phenols **7a–d** were then reacted with the sodium alkoxide of pyridine-4-methanol. After two hours at 100 °C in NMP,[19] complete conversion of **7a,c,d** had occurred and products **8a,c,d** were isolated in good yields (Table 1). The low isolated yield (12%) obtained for the formation of **8b** (entry 2, Table 1) is in agreement with previous observations in which this reaction proceeds poorly with *para*-substituted compounds.[18,19] Even with the addition of two extra equivalents of the sodium alkoxide, higher temperatures (until reflux)[19] or in a toluene/DMPU solvent system,[18] the reaction never reached completion.

An alternative two-step methodology was envisaged for the preparation of **8b**. First, 4-benzyloxyphenol **9** was brominated following the procedure of Dodsworth[22,23] and the intermediate **10** was converted into **8b** by reaction with 4-picolyl chloride (Scheme 2).

Intermediate pyridinium salts **11a–d** were easily prepared in 90–99% yields (Table 2) by N-benzylation of the corresponding pyridine derivatives **8a–d**. The subsequent reduction step was achieved with $NaBH_4$ to give regioselectively 1,2,3,6-tetrahydropyridines **12a–d** in excellent yields. No other reduction products were found. However, when the temperature was not carefully



9 **10** **8b**

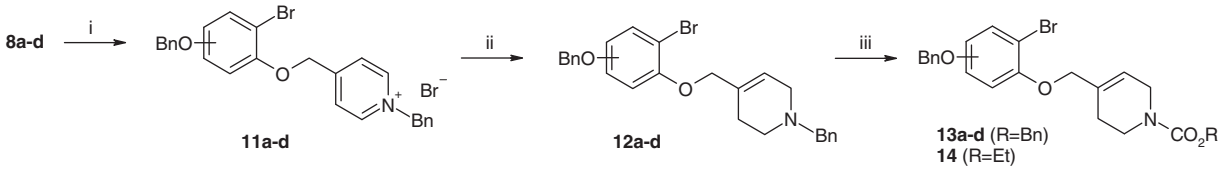
Scheme 2. Alternative pathway for the synthesis of **8b**. Reagents and conditions: (i) Br_2, $CHCl_3$, rt, 2 h, 72%; (ii) 4-picolyl chloride hydrochloride, K_2CO_3, CH_3CN, reflux, 18 h, 81%.

controlled (higher than 0 °C) during the addition of the reducing agent, small amounts of by-products could be detected due to a decoupling reaction.[24] Finally, compounds **12a–d** were converted into the corresponding benzyl carbamates **13a–d** using benzyl chloroformate in excess (4.5 equiv were required for total conversion),[25] or into **14** using ethyl chloroformate (Table 2).

For the intramolecular Heck reaction, we first used the conditions described by Cheng for the morphine fragment synthesis.[16] When a solution of **12c** in THF was heated in a sealed vessel to 120 °C in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (40 mol %), and Ag_2CO_3 (2 equiv), only unidentifiable products were obtained. However, with the neutral carbamate **13c** the expected product was obtained with 75% conversion (Table 3, entry 1). Considering this initial promising result, we next focused our efforts on finding the conditions that provided improved conversions with catalytic reagents requiring smaller quantities, to minimize purification issues. Despite the use of other ligands, solvents, or higher temperatures, the reactions did not exceed 75% conversion (entries 2–5). We attributed the incomplete conversions to catalyst decomposition and the formation of inert palladium black.[26] To circumvent this problem the Herrmann–Beller palladacycle was used as a catalyst which is described as a highly effective source of Pd(0), even at high temperatures.[27] Its reactivity has been attributed to the slow release of Pd(0) into the reaction medium, thus maintaining a constant level of the active catalytic species.[28] We were pleased to observe that the use of this catalyst in conjunction with Ag_2CO_3 led to complete conversion and with a good isolated yield (entry 9). Moreover, the amounts of catalyst and base used could be reduced to 4 mol % and 1.05 equiv, respectively, giving the same yield (entry 11).

The optimized conditions were then applied to the other substrates (Table 4) and similar results were obtained, except for the formation of **15a**. When applied to **13a**, the reaction conditions appeared to be totally inefficient, the starting material was recovered in 75% yield and product **15a** could not be detected (entry 1). This disappointing result appeared to be in accordance with the well known sensitivity of the Heck reaction to both steric hindrance and electron donating aryl group effects.[29] Removal of the benzyl and Cbz groups in conjunction with the double bond reduction

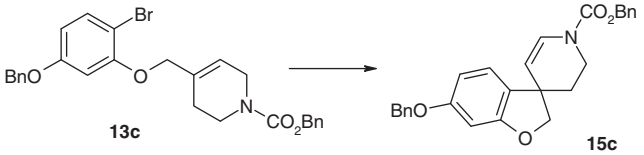
Table 2
Pyridium salt formation, partial reduction and carbamate preparation



Entry	Reactant	Product	Yield[a] (%)	Product	Yield[a] (%)	Product	Yield[a] (%)
1	**8a**	**11a**	90	**12a**	98	**13a**	86
2	**8b**	**11b**	97	**12b**	94	**13b**	98
3	**8c**	**11c**	99	**12c**	90	**13c**	94
4	**8d**	**11d**	97	**12d**	98	**13d**	85
5						**14**[b]	97

Reagents and conditions: (i) BnBr, acetone, reflux, 18 h; (ii) $NaBH_4$, MeOH, −5 °C, 2 h; (iii) For the preparation of **13a–d**: benzyl chloroformate, $KHCO_3$, CH_2Cl_2, rt, 18 h; for the preparation of **14**: ethyl chloroformate, $KHCO_3$, DCE, reflux, 2 h.
[a] Isolated yield after column chromatography.
[b] Prepared from **12d**.

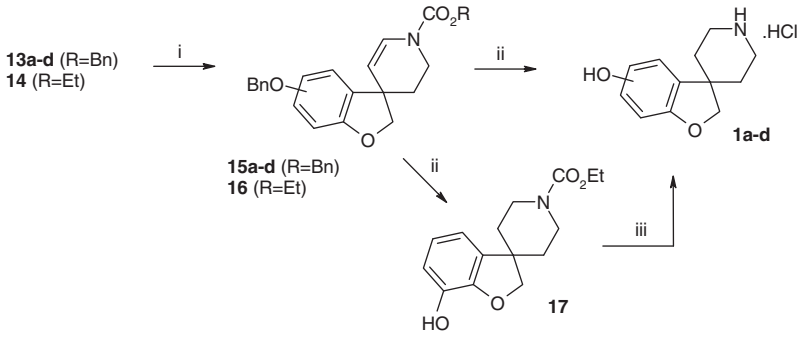
Table 3
Intramolecular Heck cyclization reaction starting from **13c** under various conditions



Entry	Catalyst (mol %)	Ligand (mol %)	Base (equiv)	Solvent	T (°C)	Conversion[a] (%)	Yield[b] (%)
1	$Pd(OAc)_2$ (10)	PPh_3 (40)	Ag_2CO_3 (2)	THF	120	75	nd[c]
2	$Pd(OAc)_2$ (5)	PPh_3 (15)	Ag_2CO_3 (2)	DMF	120	25	nd
3	$Pd(OAc)_2$ (5)	PPh_3 (15)	Ag_2CO_3 (2)	DMF	140	55	nd
4	$Pd(OAc)_2$ (5)	PCy_3 (15)	Ag_2CO_3 (2)	DMF	140	72	nd
5	$Pd(OAc)_2$ (5)	PCy_3 (15)	Ag_2CO_3 (2)	NMP	140	75	54
6	Herrmann–Beller (5)	—	*n*-BuNOAc (2)	NMP	140	63	nd
7	Herrmann–Beller (5)	—	$MeNCy_2$ (4)	NMP	140	44	nd
8	Herrmann–Beller (5)	—	K_2CO_3 (2)	NMP	140	100	0[d]
9	Herrmann–Beller (5)	—	Ag_2CO_3 (1.25)	NMP	140	100	87
10	Herrmann–Beller (2.5)	—	Ag_2CO_3 (1.05)	NMP	140	76	nd
11	Herrmann–Beller (4)	—	Ag_2CO_3 (1.05)	NMP	140	100	86

[a] Conversion was determined by LC–MS, using an internal standard after reaction for 18 h.
[b] Isolated yield.
[c] Not determined.
[d] Complete conversion observed, but only a mixture of unidentifiable products was obtained.

Table 4
Heck cyclization and protecting group cleavage



Entry	Reactant	Product	Yield[a] (%)	Product	Yield[a] (%)
1	**13a**	**15a**	0[b]	**1a**	—
2	**13b**	**15b**	86	**1b**	98
3	**13c**	**15c**	83	**1c**	91
4	**13d**	**15d**	81	**1d**	0
5	**14**	**16**	81	**1d**	92[c]

Reagents and conditions: (i) Herrmann–Beller catalyst (4 mol %), Ag_2CO_3 (1.05 equiv), NMP, 140 °C, 18 h; (ii) H_2, 10% Pd/C, MeOH/EtOAc/HCl, rt, 18 h; (iii) AcOH/HCl 12 N, reflux, 18 h.
[a] Isolated yield after column chromatography.
[b] **13a** recovered in 75% yield.
[c] First step **16** to **17**: 94%; second step **17** to **1d**: 98%.

generated **1b–c** in excellent yields (entries 2 and 3). Surprisingly, when **15d** was hydrogenated, only unidentifiable products were obtained. This issue was overcome using a two-step procedure starting from the corresponding ethyl carbamate **16** (entry 5).

In conclusion, an efficient strategy has been developed for the preparation of novel 2*H*-spiro[1-benzofuran-3,4′-piperidin]-5-ol (7 steps, 42%), 6-ol (6 steps, 53%), and 7-ol (8 steps, 51%) **1b–d** from commercially available starting materials. The amounts of catalyst and base used during the spirocyclization reaction were reduced to very acceptable levels. Unfortunately, the Heck conditions could not be applied for the synthesis of **15a**. Work is still in progress to solve this issue. The scaffolds **1b–d** have been used in our 'privileged structure'-based libraries for combinatorial chemistry and biological results will be published soon.[30]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.03.005. These data include MOL files and InChiKeys of the most important compounds described in this article.

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