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Synthesis of Spiro[Quinoline-2,4'-Piperidines]
Heck Versus Radical Reaction

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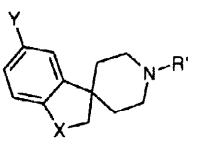
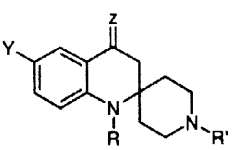
Abstract: **The synthesis of spiro[quinoline-2,4'-piperidines] by using a radical or a Heck reaction, as the key step, is described.** © 1998 Elsevier Science Ltd. All rights reserved.

Spiropiperidinyl compounds of type **A** are attractive derivatives which were evaluated in a number of different pharmacological classes such as growth hormone secretagogues[1,2], modulators of cholinergic function[3], antagonists of serotonergic transmission[4] or σ ligands[5]. Most of them are indane[1-3], indoline[2,6] or dihydrobenzofuran[2] derivatives and were obtained through a number of different chemical routes related to carbanionic reactions[5], free radical cyclisation[2], and more recently to Fischer indole reaction on solid phase[6]. Up to now, little attention has been payed to other heteroaromatic systems such as spiro[quinoline-2,4'-piperidines] of type **B** where the spiranic center is located on the carbon adjacent to the phenylamine nitrogen.

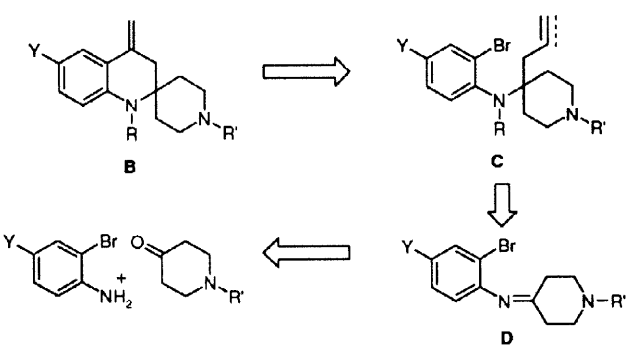


A (X = CH_2, NR, O)



B (Z = O, CH_2)

Here, we report the preparation of compounds of type **B** according to the following retrosynthetic Scheme. Depending on the degree of insaturation of the three carbon chain unit, intermediate **C** might be transformed into **B** via a radical cyclization or a Heck reaction.



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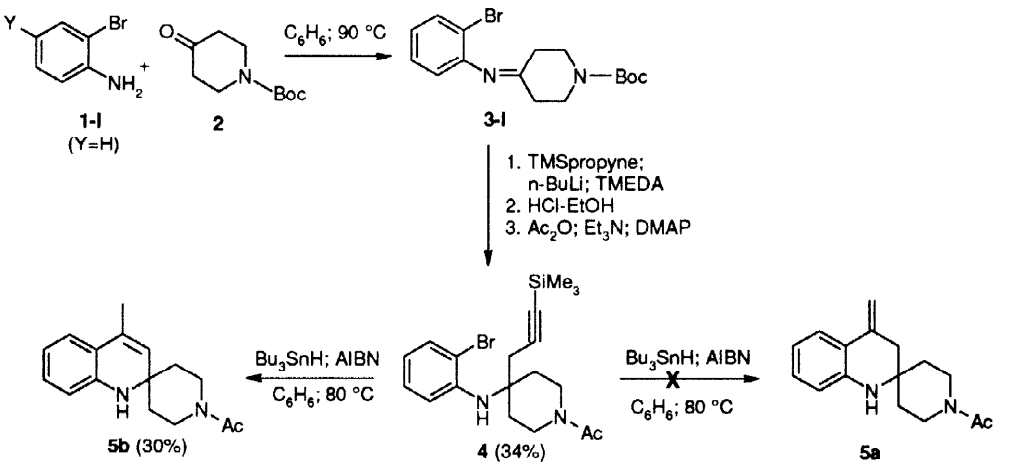
Although the generation of aryl radicals by tin hydride method is less common than that of alkyl radicals, these extremely reactive intermediates provide practical routes in organic synthesis. Our radical approach to spiro compounds of type **B** (Y = H) is outlined in the following Scheme.

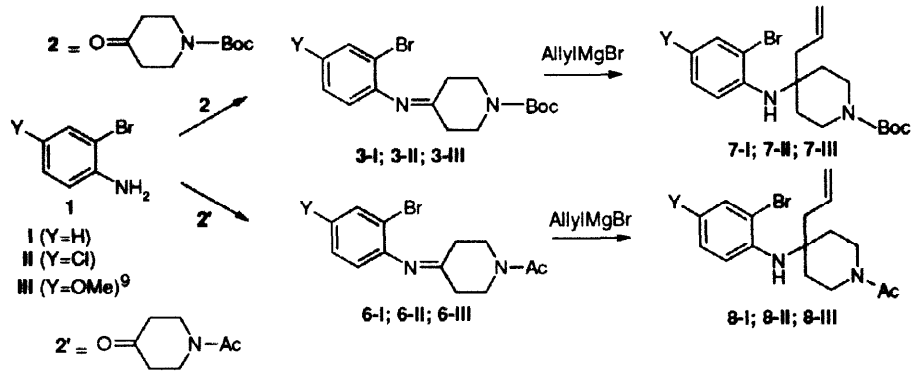
The condensation of the commercially available *N*-Boc protected piperidone **2** with *o*-bromoaniline **1-I** (Y=H) was achieved in boiling benzene with azeotropic removal of water. Imine **3-I** (Y=H) was obtained (90%) and the addition of lithio trimethylsilylpropyne in the presence of TMEDA (1.5 equiv.) afforded after 8 days the *N*-protected piperidine **4**. Under standard conditions (catalytic AIBN, boiling benzene), the addition of tin hydride (2.0 equiv.) to **4** led exclusively, after usual work-up, to the desilylated compound **5b** which was the result of a 6-*exo*-dig cyclisation process. None of the 7-*endo*-dig product was isolated or detected in the crude reaction mixture by ^{1}H-NMR analysis or GC/MS. A tentative to obtain **5a** from **5b** has proven yet to be unsuccessful probably due to the greater stability of the *endo* derivative **5b**.



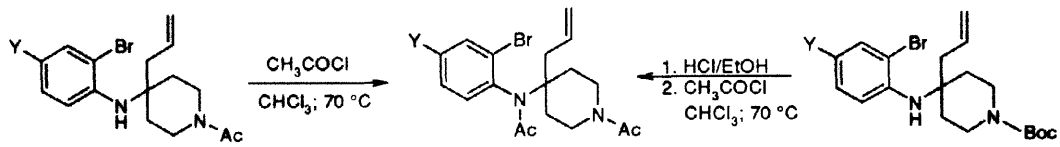
We next focused our efforts on palladium catalyzed intramolecular cyclization of allylic compounds of type **C**. The Heck reaction is a very simple technical reaction and very tolerant to a wide variety of functional groups[7]. Early research work demonstrated the considerable versatility of intramolecular Heck reaction for the construction of bridged rings, spirocycles and tetrasubstitued carbon centers. This reaction was applied to amine of type **C** in the aim of obtaining the desired spiro[quinoline-2,4'-piperidines] of type **B**.

The allylamine of type **C** (**7-I**, Y=H) was prepared by addition of allylmagnesium bromide at room temperature to a mixture of crude imine **3-I** and 18-crown-6 ether, in ether[8] (40% yield). Significative improvement of the yield resulted in using toluene instead of ether without crown ether (yield of **7-I** = 80%). We have to point out that the use of ether without crown ether did not give the desired product **7-I**.

This reaction was generalized and allylamines **7-II** (Y=Cl), **7-III** (Y=OMe), and **8-I** (Y=H), **8-II** (Y=Cl), **8-III** (Y=OMe) were obtained by addition of allylmagnesium bromide to the appropriate imines **3-II** (Y=Cl), **3-III** (Y=OMe), **6-I** (Y=H), **6-II** (Y=Cl), and **6-III** (Y=OMe) (yield: 65%-75% from **1**).



The obtained allylamino compounds **8** were transformed to the corresponding *N,N'*-diacetylated diamines **9-I**, **9-II**, and **9-III** by acetylation of **8-I**, **8-II**, and **8-III** or by treating **7-I**, **7-II** and **7-III** by HCl in EtOH followed by the addition of acetyl chloride (15 equiv.) in refluxing chloroform.



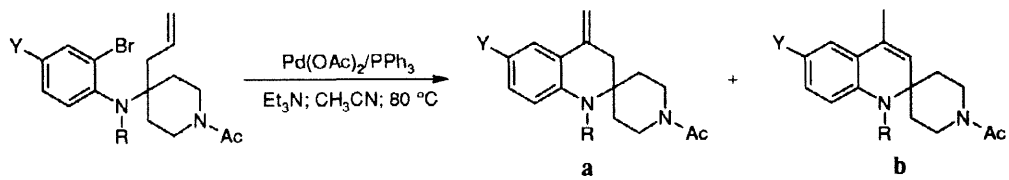
8-I (Y = H)
8-II (Y = Cl)
8-III (Y =OMe)

9-I (Y = H)
9-II (Y = Cl)
9-III (Y =OMe)

7-I (Y = H)
7-II (Y = Cl)
7-III (Y=OMe)

The allylamino substrates **8-I**, **9-I**, **9-II**, and **9-III** were subsequently treated under the standard Heck conditions. In these conditions two inseparable regioisomers **a** and **b** were obtained. The arylation, according to the Heck reaction, led to the expected spiranic skeleton according to the 6-*exo*-trig process. No product coming from the 7-*endo*-trig process have been detected (^{1}H-NMR or GC/MS). The results are reported in Table I.

Table I: Synthesis of spiro[quinoline-2,4'-piperidines] by using the Heck reaction.



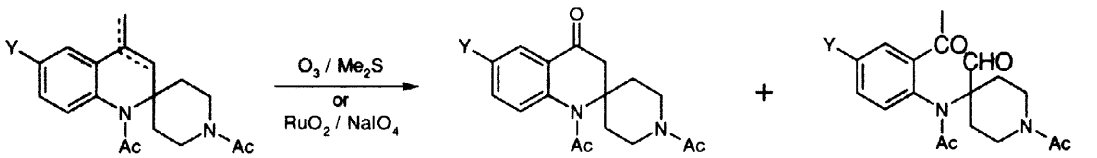
a **b**

Entry	Starting material	Ratio	Yield
1	**8-I**	**5a/5b** : 10/90	77%
2	**9-I**	**10a/10b**: 75/25	75%
3	**9-II**	**11a/11b**: 70/30	52%
4	**9-III**	**12a/12b**: 70/30	72%

The ratio of **a** and **b** depends on the substrate. When the phenylamine nitrogen was not protected the isomer **b** was preponderant (entry 1). On the contrary when the two amino groups were protected the isomer **a** was the major product (entries 2, 3, 4).

Attempts to prepare compounds of type **B** (Z=O), from the mixture of compounds **a** and **b**, were carried out by using two different oxidative cleavages. First of all, an ethanolic solution of diamides **10a/b**, **11a/b**, and **12a/b** was treated with O_3 at -78 °C. After decomposition of the ozonide by Me_2S the desired ketones **13**, **14**, and **15** were formed (Table II). Ketoaldehydes **16**, **17**, and **18** were also isolated in poor yield (< 10%). In a second attempt, oxidation by $RuO_2/NaIO_4$[10] led to the desired ketones in similar yield, but ketoaldehydes were not detected.

Table II: Oxidative cleavage of **10**, **11** and **12**.



Starting material	Ketone (Yield %)	Ketoaldehyde (Yield %)
10a/b (Y = H)	**13** (47)	**16** (10)
11a/b (Y = Cl)	**14** (50)	**17** (<10)
12a/b (Y =OMe)	**15** (39)	**18** (<10)

Although radical cyclisation and Heck reaction gave both access to the spiro[quinoline-2,4'-piperidine] skeleton, none of these reactions allowed the formation of compound of type **B** in pure form when Z = CH_2. However, oxidative transformation of the mixture of regioisomers **a** and **b** obtained from the Heck reaction allowed the formation of compounds of type **B** such as **13**, **14**, and **15**, with an overall yield of 7-10%.

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References and Notes

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