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A Convenient Synthesis to *N*-Aryl-Substituted 4-Piperidones

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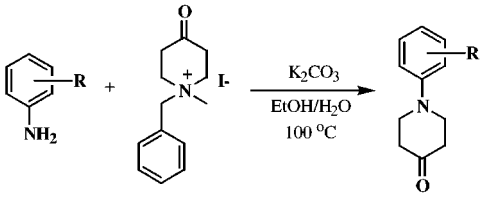
ABSTRACT



A general and efficient procedure for the synthesis of *N*-aryl-substituted 4-piperidones was developed. The general methodology was applied to the synthesis of several different *N*-aryl-4-piperidones utilizing an expedient two-step process.

The synthesis of *N*-aryl-substituted 4-piperidones has been a subject of continuing research because of its importance as a synthetic building block in medicinal chemistry. These heterocycles have been used as synthetic intermediates en route to a considerable number of pharmacologically active agents.[1] Most notably, this pharmacophore is predominant in many CNS agents such as antidepressants, anxiolytics, and antipsychotics.[2] The synthetic methodology leading to the preparation of aryl-4-piperidones is well documented.[3] All of these methods, however, have their shortcomings.

The most convenient approach has been reported by Bowden and Green[4] and then later optimized by Scherer et al.[1b] In this method, the piperidone was made in a two-step synthesis where the *N* substituent was introduced in the final step. Therein, the authors demonstrated that 1,5-dichloro-3-pentanone was capable of directly reacting with various anilines to yield *N*-aryl-4-piperidones. The drawback to this approach is the tedious synthesis of the 1,5-dichloro-3-pentanone. Kuehne[5] and co-workers have reported a convenient synthesis of *N*-alkyl-substituted 4-piperidones by the reaction of *N*-methyl-4-piperidone methiodide with tryptamine for the synthesis of complex alkaloids. Although the synthesis of *N*-alkyl piperidones has been reported using this methodology, the preparation of *N*-aryl-substituted 4-piperidones has not been addressed.

Herein we report a general and efficient method for the synthesis of *N*-aryl-substituted 4-piperidones. The aryl piperidones were synthesized in two steps utilizing a modified method[6] of Kuehne. In this process, the *N*-aryl-piperidones were prepared directly from the easily accessible *N*-methyl-*N*-benzyl-4-oxopiperidinium iodide (**2**). Construction of the *N*-aryl-substituted 4-piperidones was conveniently achieved

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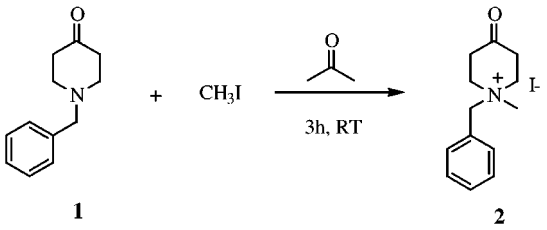
by the exchange reaction between *N*-methyl-*N*-benzyl-4-oxopiperidinium iodide (**2**) with the desired aniline. This iodide salt **2** was prepared by exposure of commercially available *N*-benzyl-4-piperidone (**1**) to methyl iodide in acetone (Scheme 1).[7] The aniline was then treated with

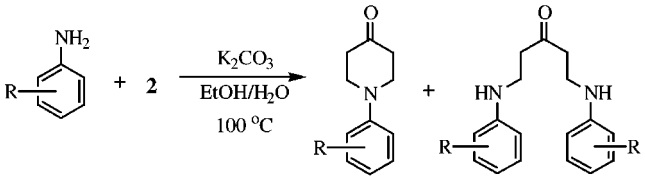
Scheme 1



1 **2**

N-methyl-*N*-benzyl-4-oxopiperidinium iodide (**2**) in the presence of K_2CO_3 in aqueous ethanol at 100 °C (Scheme 2).[8]

Scheme 2



3 **4**

Utilizing this methodology, *N*-aryl-substituted 4-piperidones (Table 1) were obtained conveniently and rapidly in fair to excellent yields from a wide variety of anilines. The anilines studied with this methodology varied in electronic and steric properties. As one might expect, reactions of the electron rich anilines gave the highest yields of product, while reaction of anilines which were electron deficient or sterically hindered gave lower yields.

Table 1: Examples of *N*-Aryl-Substituted 4-Piperidones Prepared

entry	R	% yield of **3**	% yield of **4**
1	3,4-OCH_2CH_2O	99	0
2	2-CH_3-5-OCH_3	71	0
3	3,4,5-OCH_3	80	0
4	3-Cl-4-OCH_3	73	0
5	3,4-N=CHS	51	0
6	3-CN	28	0
7	2,4-OCH_3-5-Cl	63	0
8	3-CN-4-F	23	0
9	3-Cl	29	0
10	2,4-F-3-CN	0	49
11	3-CN-4-Cl	8	44
12	2,3-NSN=	0	42
13	2,6-OCH_3−4-CH_3	34	0
14	2,6-OCH_2CH_3	30	0
15	2-OPh	20	30

We believe that the mechanism of the reaction presumably follows the process previously described by Rubiralta et al.[9] This process may be a β-elimination/intramolecular cyclization to form the *N*-aryl-substituted piperidones. In particular, *N*-methyl-*N*-benzyl-4-oxopiperidinium iodide (**2**) undergoes a base-catalyzed Hofmann elimination to form the transient Michael acceptor. The aniline nucleophile then adds in a Michael type fashion, and the resulting secondary amine may displace benzylmethylamine to give the desired product. We also observed that when the aniline is of an electron deficient nature or sterically hindered, cross-coupled side product **4** is observed along with the desired product (entries 11 and 15, Table 1). In some cases, this side product is all that is isolated (entries 10 and 12, Table 1). This cross-coupled side product may be obtained from the intermolecular displacement of benzylmethylamine by aniline.

In summary, we have demonstrated that *N*-aryl-4-piperidones can be conveniently prepared utilizing a simple two-step procedure. In most cases, the key cyclization step proceeds with a large variety of anilines, including those having electron-withdrawing and electron-donating groups. Overall yields are typically good, allowing for the easy and rapid synthesis of *N*-aryl-substituted 4-piperidones.

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(7) **Preparation of *N*-methyl-*N*-benzyl-4-oxopiperidinium iodide (2)**: Methyl iodide (11.3 mL, 181.5 mmol) was slowly added to a solution of *N*-benzylpiperidone (27.3 mL, 147.3 mmol) in acetone (150 mL) at room temperature. The mixture was stirred at room temperature for 3 h, and the product was collected by filtration and washed with acetone (4 × 50 mL). The product was dried in vacuo for 16 h to provide 47 g (96% yield): ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.55 (m, 4H), 3.12 (s, 3H), 3.70 (m, 4H), 4.72 (s, 2H), 7.54 (m, 5H).

(8) **General Procedure for *N*-Aryl-Substituted 4-Piperidone**: A slurry of iodide salt **2** (1.8 g, 5.4 mmol) in water (2.8 mL) was added over 30 min to a refluxing solution of 3,4,5-trimethoxyaniline (650 mg, 3.55 mmol) and potassium carbonate (70 mg, 0.50 mmol) in ethanol (6.5 mL). The reaction mixture was heated to reflux for an additional 45 min. Water (20 mL) was then added, and the product was extracted with dichloromethane (2 × 30 mL). The combined extracts were evaporated in vacuo, and the residue was chromatographed on silica gel (hexane:ethyl acetate = 4:2) to give 750 mg (80% yield) of the desired *N*-aryl-piperidone: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.56 (t, J = 6 Hz, 4H), 3.50 (t, J = 6 Hz, 4H), 3.78 (s, 3H), 3.86 (s, 6H), 6.19 (s, 2H). MS (E+) *m*/*z*: 266 (MH^+).

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