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SYNTHESIS OF SUBSTITUTED 4-ARYLPIPERIDIN-2-ONES BY A 6-*EXO*-TRIG RADICAL CYCLIZATION

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This paper is dedicated with respect and admiration to Prof. Steven M. Weinreb on the occasion of his 65th birthday

Abstract – A series of 5-substituted-4-arylpiperidin-2-ones have been synthesized in a 4 step sequence involving a radical 6-*exo*-trig cyclization as the key step.

INTRODUCTION

4-Arylpiperidines have been investigated since early times in view of their interesting pharmacological activities, such as analgesic[1] and local anesthetic properties.[2] More recently 4-arylpiperidines have been found to act as monoamine receptor antagonists, monoamine transporter inhibitors, Na^+/Ca^{2+} channel blockers, renin inhibitors, opioid antagonists and γ-secretase inhibitors, which makes them promising candidates in a number of therapeutic areas such as cancer, depression, psychosis, hypertension, benign prostatic hyperplasia, ischemia, cocaine addiction, obesity and Alzheimer's disease.[3] Some 4-arylpiperidines are currently commercial drugs, such as the antidiarreic loperamide, the analgesic meperidine, the antidepressant paroxetine and the antipsychotic haloperidol (Figure 1).

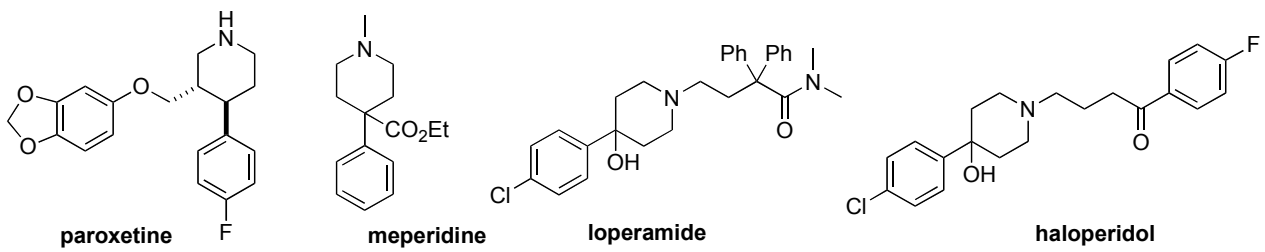


Figure 1. Drugs containing a 4-arylpiperidine motif.

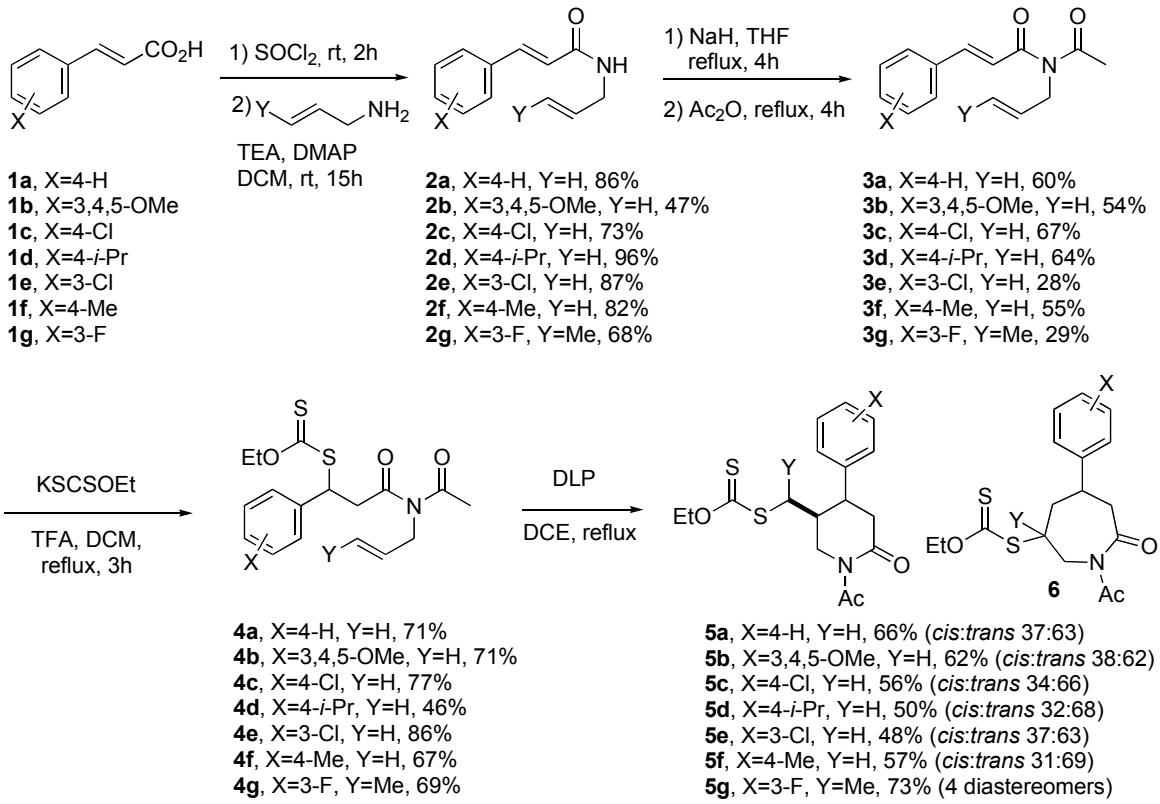
In contrast with this wide range of pharmacological activities, only three general methods for their synthesis have been reported to date.[4] These include the addition of an aryl Grignard to an *N*-protected piperidin-4-one, followed by elimination and reduction; copper catalysed coupling of aryl Grignards with *N*-acylpyridinium species followed by reduction of the resulting 1,4-dihydropyridine; and Suzuki or Negishi cross-coupling between the enol triflate of an *N*-protected piperidine-4-one with an arylboronic acid or an arylzinc iodide, followed by reduction of the resulting monounsaturated piperidine. Also, the reverse is possible, i.e. the coupling of an *N*-protected-4-piperidinylzinc iodide with an aryl halide. In this case no reduction step is required. These methods are limited to molecules possessing functional groups compatible with Grignard reagents and reductive conditions, and are often constrained by a lack of starting materials with the desired substituents.

Recently, Leśniak *et al*. reported a synthesis of substituted 4-arylpiperidin-2-ones by a radical 6-*endo*-trig cyclization of 3-phenylacryl enamides mediated by Bu_3SnH/AIBN.[5] In continuation of a previous work involving a radical synthesis of 2-aryl and 3-arylpiperidines,[6] we present a new straightforward synthesis of 4-arylpiperidin-2-ones obtained via a key step involving a 6-*exo*-trig cyclization of a benzyl type radical upon a non-activated olefin using tin-free conditions.

RESULTS AND DISCUSSION

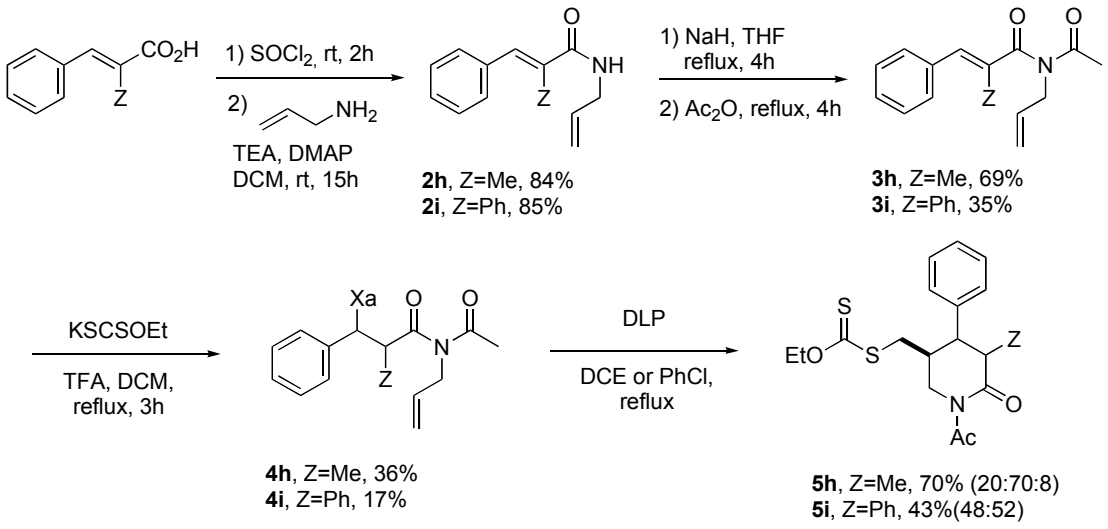
Our synthetic design, depicted in Scheme 1, relies on the rich chemistry of xanthates[7] and starts from commercially available cinnamic acids **(1a-g)**. Conversion into the acyl chlorides followed by addition to allylamine or butenylamine afforded secondary amides **(2a-g**). These were subsequently acetylated, by treating amides **(2)** with sodium hydride followed by acetic anhydride. The acetylation proceeded in moderate yield and, in all the cases, a small amount of starting material was recovered. With imides **(3)** in hand, 1,4-conjugate addition of potassium *O*-ethyl xanthate under acidic conditions yielded radical precursors **(4a-g)** in moderate to good yields. It is interesting to note that conjugate addition does not take place with amides **(2)**, and these have to be activated as the corresponding imides.[8] Finally, radical cyclization of xanthates **(4)** mediated by a small amount of lauroyl peroxide as radical initiator in 1,2-dichloroethane afforded the desired piperidones in moderate to good yields, and as a mixture of cis/trans diastereomers for compounds **(5a-f)**, which were separated by column chromatography, and as a mixture of 4 diastereomers for compound **(5g)**, which could not be separated. Lactams **(6)**, derived by a 7-*endo* cyclization, were also isolated in most of the cases, but in only 3-7% yield. It is important to point out that the cyclization involves a benzylic radical and occurs onto a non activated olefin. Cyclization of benzylic radicals is known to be difficult for other than 5-membered-ring formation, as they are stabilized and somewhat unreactive species.[9] The generation of a benzylic radical generally involves reduction of the corresponding halides (or chalcogenides) or a 1,5-H shift if possible,[9] and these methods do not

usually provide the radical with enough lifetime to undergo slow ring-closures such as a 6-*exo* addition on a non-activated olefin. Thus, despite their apparent simplicity, such ring-closures are not easy to accomplish with more traditional radical reactions.



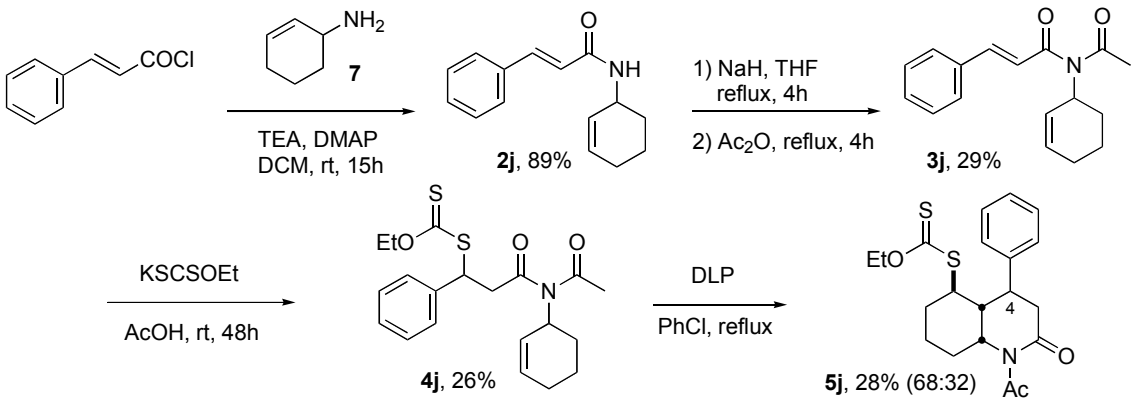
Scheme 1. Synthesis of 4-arylpiperidines.

Having demonstrated that the method was efficacious for the synthesis of the desired 4-arylpiperidones, we undertook a broader exploration of its scope. We thus examined the case of α-substituted cinnamic acids (Scheme 2). Treatment of commercially available α-methylcinnamic acid and α-phenylcinnamic acid (easily prepared from benzaldehyde and phenylacetic acid[10]) with allylamine afforded amides **(2h)** and **(2i)** in good yields. For amide **(2h)**, the acetylation proceeded in good yield to furnish imide **(3h)**, but the formation of the xanthate proceeded in a modest yield of 36%. Nevertheless, the radical cyclization furnished 3-methyl-4-phenylpiperidine **(5h)** in good yield and as a mixture of 3 diastereomers which could be separated by column chromatography and whose relative stereochemistry was established by NOESY experiments. Amide **(2i)** was transformed into the corresponding imide **(3i)** and xanthate **(4i)** respectively, albeit both reactions proceeded in a rather low yield. The reversibilty of the conjugate addition of the xanthate salt could account for the low yield observed. The radical cyclization occurred in a moderate yield of 43%, and chlorobenzene had to be used instead of 1,2-dichloroethane. In that case only 2 diastereomers were recovered in a ratio slightly different from the simpler piperidines **(5a-g)**, their relative stereochemistry being also established by NMR techniques.



Scheme 2. Synthesis of 3-substituted-4-arylpiperidines.

Finally, we tested the radical cyclization on a cyclic olefin, in order to prepare a phenyl substituted bicyclic heterocycles. Thus, radical precursor **(4j)** was prepared from cinnamoyl chloride by reaction with amine **(7)**, followed by acetylation and 1,4-addition. The conjugate addition under the same conditions described before (DCM/TFA, reflux) resulted, however, in the decomposition of the imide by breaking of the allylic N-C(cyclohexenyl) bond. TFA was therefore replaced with AcOH, and the reaction was performed at room temperature. In that case we obtained the desired product albeit in a low yield (26%), the remaining being starting material. Radical cyclisation of xanthate **(4j)** in chlorobenzene afforded the desired 4-phenylperhydroquinoline in 22% yield and as a mixture of 2 diastereomers, which could be separated by column chromatography. On the basis of previous experience, we assumed the ring fusion to be *cis*, and NOESY experiments showed that they were epimers at C-4. This was consistent with the obtention of two different compounds after reductive removal of the xanthate group in **(5j)** using tributylstannane.



Scheme 3. Synthesis of bicyclic arylpiperidines.

In conclusion, we have developed a simple and flexible synthesis of substituted 4-arylpiperidines starting from cheap and commercially available starting materials. The use of xanthates is not only tin-free, but also avoids high dilutions and is experimentally very easy to perform. The sequence can be modified to introduce a variety of substituent onto the piperidine ring. It is interesting to note that the xanthate group in the product is easily cleaved into the thiol, which can then be converted into numerous sulfur based functional groups. Such derivatives have recently been reported to have interesting biological activities.[11] Further studies aimed at improving some of the yields and at extending the scope are under way.

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