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Free Radical Method for the Synthesis of Spiro-Piperidinyl Heterocycles

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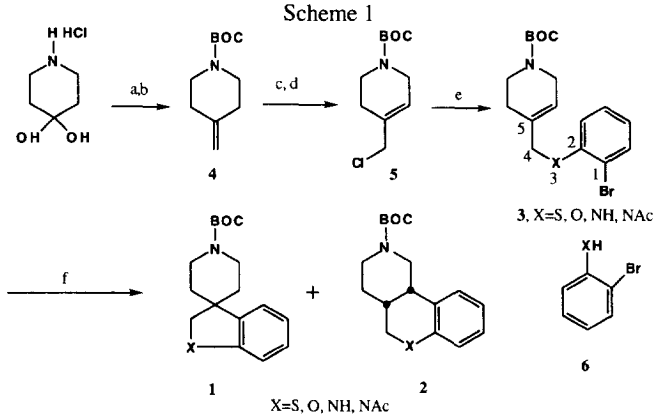
Abstract: *A general approach to spiro-piperidinyl heterocycles (1, X=S, O, NH, NAc) was obtained from the key intermediate 3 via an efficient radical reaction.* Copyright © 1996 Elsevier Science Ltd

As part of our medicinal chemistry program to generate growth hormone secretagogues, we synthesized derivatives of the spiroindanylpiperidine **1** (X=CH_2). It was subsequently discovered that incorporation of polar functionality into the benzylic position of the spiroindanylpiperidine (**1**, X=CHOH, CO) led to an increase in secretagogue potency.[1] However, facile investigation of spiro-piperidinyl heterocycles (**1**, X=$S(O)_n$, O, NR) as possible bioisosteres of spiro-indanylpiperidine **1** (X=CHOH, CO) was hampered by the lack of a general synthetic method for these types of structures. In this letter we present methodology to prepare spiro-piperidinyl heterocycles (**1**, X= $S(O)_n$, O, NR) from the key intermediate **3** via an efficient tin hydride cyclization reaction.[2] Although the use of aryl radicals[3] in the tin hydride method is less well known than that of alkyl radicals, these extremely reactive radical intermediates provide practical routes in organic synthesis.[4]

Scheme 1



Reagents and conditions: a) $(^tBOC)_2O$, NaOH/dioxane, RT, 3 h, 95%. b) Ph_3PCH_3I, BuLi, THF, 0°C, 2 h, 82%. c) 5% SeO_2/SiO_2, ^tBuOOH, RT, overnight, 52%. d) thionyl chloride, 2,6-lutidine, toluene, 35°C, 2 h, 98%. e) **6** (X=S and O): K_2CO_3, acetone, 60°C, overnight, X=S, 75%, X=O, 93%; **6** (X=NH): K_2CO_3, EtOH, 80°C, overnight, 52%; **6** (X=NAc): KOH (powder), DMSO, 60°C, overnight, 50%. f) Bu_3SnH (1.5 eq), AIBN (cat. amount), benzene (0.02N), 100°C, 12h see table 1 for isolated yields.

Our synthesis of spiro compounds **1** is outlined in Scheme 1. The amino group of 4-piperidone hydrate hydrochloride salt was protected with Boc group and the keto functionality was converted in a Wittig reaction to the exocyclic methylene **4**. Allylic oxidation[5] and chlorination gave the useful intermediate **5** which served as an electrophile to react with a variety of nucleophiles such as **6** (X=S, O and N) to generate the cyclization precursor **3**. Under standard tin hydride cyclization conditions,[6] the desired spiro-piperidinyl heterocycles (5-exo products) **1**[7] were isolated as the major products in moderate to good yields (Table 1). The cis benzo-fused heterocycles (6-endo products) **2**[8] were isolated as minor products in some cases (X=S, NH and NAc).

Table 1[a,c]

entry #	X	1	2
1	S	42%	19%
2	O	89%	--
3	NH	59%[b]	2%[b]
4	NAc	72%	7%

[a] Isolated yield; excess tin hydride and tin halide by-product were removed by DBU workup procedure.[9] [b] Isolated from chromatography without DBU workup procedure. [c] due to instability of BOC protecting group in GC analysis conditions, the 5-exo/6-endo ratio was not available.

Substitution at the 5- position is known to disfavor 5-exo vs. 6-endo cyclization. However, the oxygen or nitrogen present at the 3- position of the precursor (**3**, X=O, NH, NAc) powerfully accelerate the reaction rate to provide the 5-exo product **1**. This could be due to better overlap between radical orbital and vacant π orbital of the olefin in the 5-exo transition state.[2] We were glad to observe in this study that the radical reaction favored the 5-exo product **1** (entry 1) even with the sulfur containing precursor. This novel compound **1** (X=S) was synthesized in a moderate yield which was reproducible on a large scale (over 100 mmole) by the tin hydride method. Compound **1** (X=S) can be further oxidized to the corresponding sulfoxide and sulfone which may act as a bioisosteres of ketone (X=CO). None of the 6-endo product **2** (entry 2, X=O) was isolated or detected by TLC and crude NMR analysis in our reaction conditions (0.5M, 0.1M and 0.02M). The unprotected aniline derivative **3** (entry 3, X=NH) was also cyclized very effectively to give the desired product **1** (X=NH) which can further be modified to provide a variety of structurally diverse analogs. In summary, a general and straightforward method to synthesize spiro-piperidinyl heterocyclic compounds has been developed. Application of this methodology to other types of spiro compounds is under further investigation.

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6) Bu_3SnH, 1.5 eq; AIBN, cat. amount; 0.02N/benzene, 100°C; 12 h.

7) Spectral dada for **1** (X=S): ^{1}H-NMR (400 Mz, $CDCl_3$): 7.18 (d, 7 Hz, 1H), 7.12 (td, 7, 2 Hz, 1H), 7.04 (m, 2H), 4.10 (br s, 2H), 3.30 (s, 2H), 2.87 (m, 2H), 1.79 (br s, 4H), 1.46 (s, 9H).

8) Spectral dada for **2** (X=S):^{1}H-NMR (400 Mz, $CDCl_3$): 7.22 (m, 1H), 7.05 (m, 3H), 3.87 (m, 1H), 3.71 (dt, 14, 5 Hz, 1H), 3.39 (m, 1H), 3.27 (t, 12 Hz, 1H), 3.14 (br t, 14 Hz, 1H), 2.95 (dt, 10, 4 Hz, 1H), 2.75 (m, 1H), 2.43 (m, 1H), 1.88 (m, 1H), 1.70 (m, 1H), 1.46 (s, 9H). The cis stereochemistry was confirmed both by NOE observation and the coupling constant of the junction protons.

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