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Use of the Thiomethyl Group for Activation in the Synthesis of 8-Hydroxy-1-(spiro-1'-indan)benzazepines.

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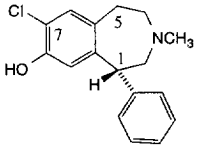
Abstract: The utilization of the thiomethyl group to activate an aromatic ring system for closure to form the corresponding conformationally restrained 8-methoxy-7-(methylthio)-3-methyl-1-(spiro-1'-indan)2,3,4,5-tetrahydro-1H-3-benzazepine is described. Subsequent removal of the thiomethyl group with Raney nickel followed by electrophilic substitution allows for the synthesis of other benzazepines that have electron withdrawing groups that normally would be inaccessible.

Binding studies conducted on conformationally restrained analogs of receptor ligands provide a means to probe the intricacies of molecular recognition.[1] Along these lines it was our desire to study the substituent effects at position 7 while controlling the role of the pendent phenyl group of the prototypical dopamine D_1 antagonist SCH-23390, **1**.[2] By synthesizing the 8-hydroxy-3-methyl-1-(spiro-1'-indan)2,3,4,5-tetrahydro-1H-3-benzazepines, **2**, we felt that we could fix the orientation of the pendent phenyl group in its proposed orthogonal bioactive conformation[3] while changing the electronic environment of the parent benzazepine by altering the substituents at position 7.



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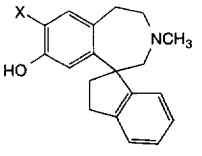
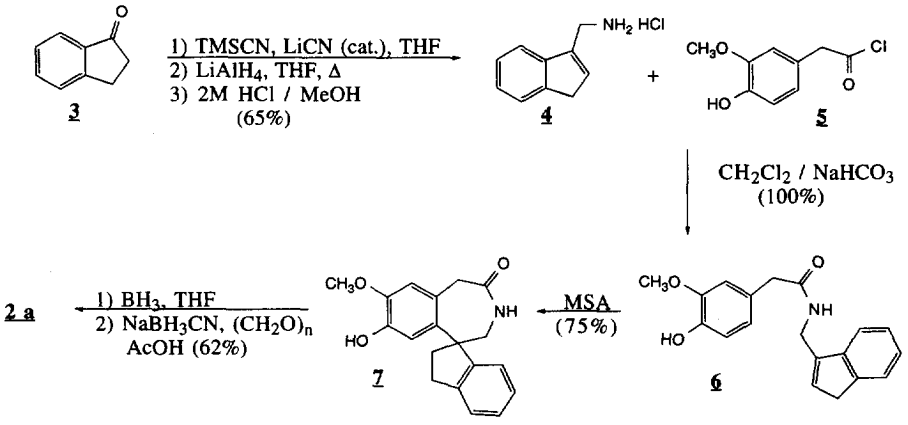


2a) X = OCH_3
b) X = H
c) X = Cl
d) X = Br
e) X = NO_2

Our initial investigation into the spirobenzazepine series resulted in the synthesis of **2a**. To that end, 1-indanone (**3**) was treated with TMSCN and a catalytic amount of LiCN at room temperature in THF for 20h, (Scheme 1). Subsequent solvent evaporation provided the crude TMS cyanohydrin which was then reduced to the amino alcohol with $LiAlH_4$.[4,5] After quenching with $Na_2SO_4 \cdot 10H_2O$, the crude amino alcohol was treated with 2M HCl/ MeOH to provide crystalline **4** in 65% yield from **3**. The amine **4** was then coupled to the 4-hydroxy-3-methoxyphenyl acetic acid chloride[6] (**5**) under Schotten-Baumann[7] conditions, which furnished the amide **6**. On exposure to methanesulfonic acid for 6h, **6** underwent smooth electrophilic aromatic substitution to provide the key intermediate

spirobenzazepin-4-one[8] **7** in 75% yield from **5**. Reduction of the amide with BH_3 followed by N-methylation utilizing the Borch[9] procedure furnished the desired **2a**, in 62% yield from **7**.

SCHEME 1



The route developed for synthesizing **2a** did not allow for the preparation of **2b**. Upon exposure of **8** to MSA, none of the desired spirobenzazepin-4-one could be detected. Instead, the oxazine **9** was the sole product isolated in 57% yield (Scheme 2).

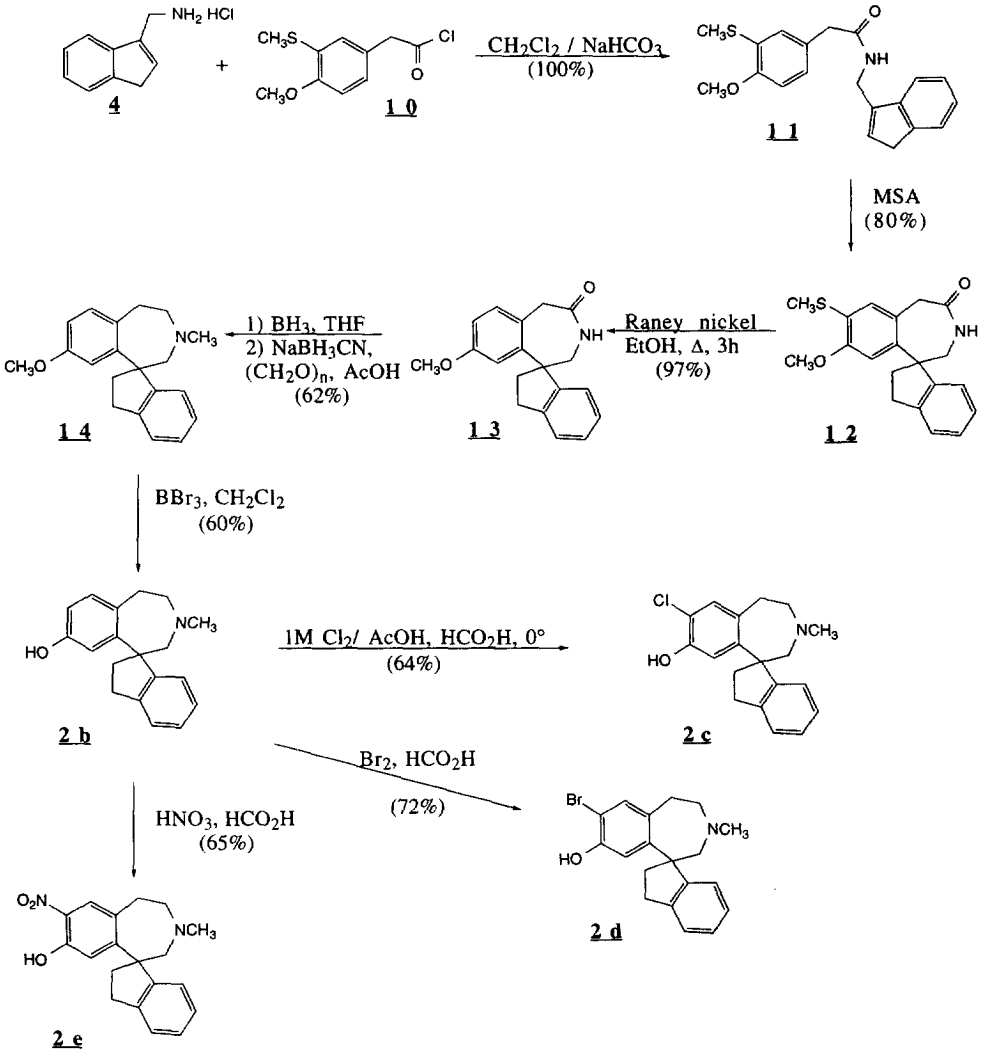
SCHEME 2

It appeared that the lack of an activating group ortho or para to the site of cyclization precluded ring closure. Further activation of the aryl group was expected to be neccessary in order to favor the desired cyclization. We specifically sought an aryl-activating group that could be removed at a later stage in the synthesis. The thiomethyl group was expected to meet these requirements as it has been shown that the thiomethyl group can activate and facilitate electrophilic aromatic substitution in the synthesis of tetrahydroisoquinolines and that it can be subsequently removed with nickel boride.[10]

3-Thiomethyl-4-methoxyphenylacetic acid, (**10**), was synthesized by the method of Burger,[11] and then coupled to the amine **4** via the acid chloride, to yield the amide **11**. The critical ring closure reaction of **11** proceeded smoothly and furnished compound **12** in 80% yield from **4**. The thiomethyl moiety was easily removed with Raney nickel to furnish the formerly inaccessible **13** in 97% yield. The reduction of the amide **13** to the amine and subsequent N-methylation provided **14** in 62% yield

(Scheme 3). Demethylation of **14** with BBr_3 produced **2b,** which served as an intermediate to furnish **2c - 2e** . Chlorination with Cl_2 / AcOH yielded **2c**. Likewise, bromination gave **2d** and nitration of **2b** then provided **2e**.

SCHEME 3



This work demonstrates the utility of the thiomethyl group for the activation of aryl groups to enable electrophilic aromatic substitution in good yield followed by its removal to allow for the

synthesis of spirobenzazepines **2b-e**. The *in vitro* and *in vivo* pharmacology of compounds **2a-d** has been evaluated and will be reported elsewhere.[12]

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