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A CONVERGENT SYNTHESIS OF 4-(2-BENZOTHIAZOYL)PIPERIDINES WITH ANTIHISTAMINIC ACTIVITY

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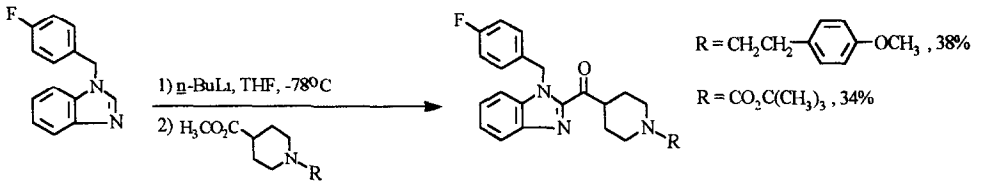
Abstract: The synthesis of 4-(*N*-methoxy-*N*-methylcarboxamido)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (**5**) is described Reaction of this intermediate with 2-lithiobenzothiazole followed by deprotection and N-alkylation yields a series of 4-(2-benzothiazoyl)piperidines with potent antihistaminic activity.

4-Aroylpiperidines and their corresponding alcohol reduction products possess a number of interesting biological activities including antagonism of H_1, D_2, and 5-HT_2 receptors.[1] In many instances, these compounds can be efficiently synthesized by Friedel-Crafts acylation using isonipecotoyl chloride hydrochloride. This approach fails, however, when applied to the acylation of basic, nitrogen-containing heterocycles, e.g. pyridines, and electron deficient aromatics. In addition, when successful, varying mixtures of regioisomers are often observed. In order to gain access to this class of compounds, we have recently developed a carbanion-mediated process for attaching the aromatic moiety to isonipecotic acid derivatives.[2] Thus, lithiation of **1** and subsequent acylation with appropriately N-substituted derivatives of ester **2** afforded the desired benzimidazoylpiperidines **3** in 34 to 38% yield (Scheme **I**). While this approach was successful in these

Scheme I

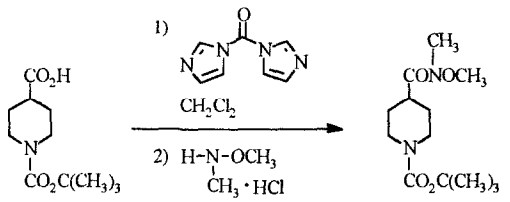


1 **2** **3**

instances, the reaction of **2** with other carbanions was often dominated by the formation of bis-addition products. For example, the reaction of **2** (R=4-$CH_3OC_6H_4CH_2CH_2$) and 2-lithiobenzothiophene resulted in the formation of the corresponding tertiary carbinol in 43% yield. As a solution to this problem, we now report the synthesis of 4-(*N*-methoxy-*N*-methylcarboxamido)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester[3] (**5**) and its use in the synthesis of a series of 4-(2-benzothiazoyl)piperidines with antihistaminic activity.

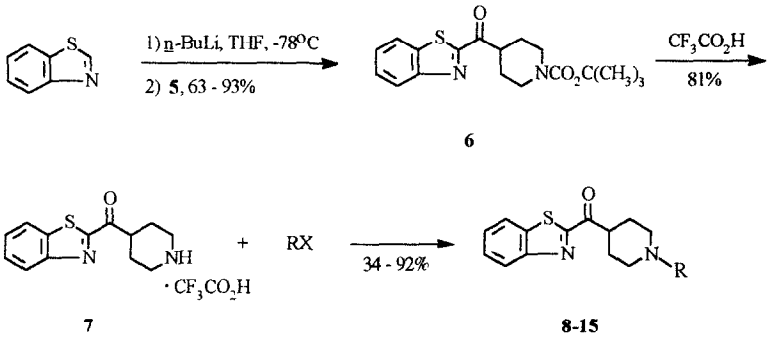
As outlined in Scheme **II**, amide[4] **5** was conveniently prepared from N-*t*-Boc-isonipecotic acid **4** by treatment with 1,1-carbonyldiimidazole[5] in dichloromethane at room temperature for 2 h followed by addition of N,O-dimethylhydroxylamine hydrochloride Compound **5**, initially isolated as a viscous oil after bulb-to-bulb distillation, crystallized on standing to give a colorless solid (mp 63-64 °C).

Scheme II



Treatment of **5** with one equivalent of 2-lithiobenzothiazole in THF at -78° for 2.5 h followed by warming to ambient temperature cleanly produced 4-(2-benzothiazoyl)piperidine **6** in 63-93% yield depending on the exact experimental procedure and purification technique used. Cleavage of the *t*-Boc protecting group using trifluoroacetic acid at 0 °C afforded the trifluoroacetate salt **7** in 81% yield after precipitation with cold ether and recrystallization from ethanol. N-alkylation of **7** with various alkyl halides using the conditions listed in Table **I** gave the 1-alkyl-4-(2-benzothiazoyl)piperidines **8-15** in 34-92% yield (Scheme **III**)

Scheme III



As reported in Table **I**, compounds **8-15** all act to antagonize the histamine induced contractile response of Guinea pig ileum. Compound **8**, possessing the 4-methoxyphenethyl N-substituent, displays the greatest activity with a pA_2 value of 9 3 (8.77-10.49, 95% confidence interval). At a concentration of 10^{-7} M, compound **8** had no effect on acetylcholine induced contraction or against calcium chloride induced contraction in K^+ (40 mM)

depolarized tissue. With the exception of compound **15**, each of the 1-alkyl-4-(2-benzothiazoyl)piperidines listed in Table **I** had an LD_{50} of >400 mg/kg in mice.

Table I

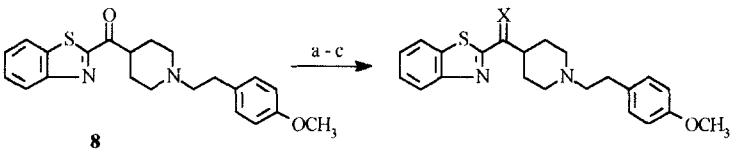
Product	RX	Alkylation Conditions	% Yield	pA_2*
8	4-$MeOC_6H_4CH_2CH_2Br$	K_2CO_3, DMF, 90 °C	59	9.3
9	4-$FC_6H_4CH_2CH_2Br$	NaOH, $(Et_3NCH_2Ph)^+Br^-$ CH_2Cl_2/H_2O, Δ	74	8.4
10	$C_6H_5CH_2CH_2Br$	K_2CO_3, $(Et_3NCH_2Ph)^+Br^-$ CH_2Cl_2/H_2O, Δ	34	7.8
11	4-$MeOC_6H_4OCH_2CH_2CH_2Cl$	$NaHCO_3$, NaI THF/H_2O, Δ	74	8.3
12	4-$MeO_2CC_6H_4OCH_2CH_2CH_2I$	$NaHCO_3$, THF/H_2O, Δ	76	8.6
13	4-$MeCONHC_6H_4OCH_2CH_2CH_2Cl$	$NaHCO_3$, NaI THF/H_2O, Δ	60	8.1
14**	MeO_2CCH_2Br	$NaHCO_3$ THF/H_2O, Δ	77	~7
15	3-$MeOC_6H_4CH_2Br$	K_2CO_3, THF/H_2O, Δ	92	7.3

*The method of Van Rossum[6] was used to determine pA_2 values for all compounds. The pA_2 value for compound **8** was refined by Schild plot[7] analysis The antihistaminic activity was determined on the histamine H_1 receptor. ** Isolated as the HCl salt.

The 4-(2-benzothiazoyl)piperidines are structurally interesting in that they lack the bis-aryl motif common to most previously reported classes of antihistamines.[8] In order to more closely approximate this structural feature, we reacted 4-benzothiazoylpiperidine **8** with phenyllithium affording tertiary carbinol **16** in 80% yield (Scheme **IV**). Other modifications of the 4-position carbonyl included sodium borohydride reduction giving secondary carbinol **17** in 45% yield and Wittig olefination providing **18** in 15% yield.

Interestingly, the phenyllithium addition product **16**, which is more structurally similar to classical antihistamines such as terfenadine[9] than is ketone **8** suffered a substantial decrease in antihistaminic potency. The secondary carbinol **17**, which maintains a heteroatom proximate to the 4-postition but changes the geometry at that position, also gave a significant loss of activity. Olefin **18**, which mimics the sp^2 geometry of the 4-position carbonyl but eliminates the possibility of a heteroatom-mediated interaction with the receptor at that position, also displayed diminished antihistaminic activity

Scheme IV



8

16, X = Ph, OH; pA_2 7 4
17, X = H, OH, pA_2 8 2
18, X = CH_2; pA_2 8 8

a PhLi, THF, -78 °C (**16**, 80%), b $NaBH_4$, CH_3OH, 0 °C (**17**, 45%), c $Ph_3P{=}CH_2$, THF, -10 °C (**18**, 15%)

In conclusion, we have developed an efficient carbanion-mediated synthesis of 4-aroylpiperidines from **5** and applied this methodology to the preparation of a novel class of antihistamines Recently, the utility of intermediate **5** was also demonstrated in the preparation of piperidine-based 5-HT_2 antagonists [10] Our continuing research with 4-(2-benzothiazoyl)piperidine antihistamines and related classes of molecules will be the subject of future reports

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