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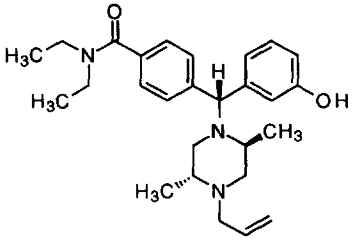
An Efficient Synthesis of the Benzhydrylpiperazine Delta Opioid Agonist (+)-BW373U86

Michael J. Bishop*, Robert W. McNutt

Division of Organic Chemistry, Burroughs Wellcome Co., Research Triangle Park, NC 27709

Abstract: A diastereoselective version of Katritzky's method for tertiary amine formation provides an efficient route to the highly selective, non-peptidal, delta opioid agonist (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-N,N-diethylbenzamide [(+)-BW373U86], **1**.

The ability of certain benzhydrylpiperazines to act as strong opioid agonists has recently been discovered.[1] For example, (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-N,N-diethylbenzamide, (+)-BW373U86, **1**, is a highly selective non-peptidal δ-receptor agonist, and has generated considerable interest due to its unique pharmacological profile.[2] Using a stereoselective version of Katritzky's powerful benzotriazole chemistry for the production of tertiary amines, we have developed an efficient synthesis of this compound.

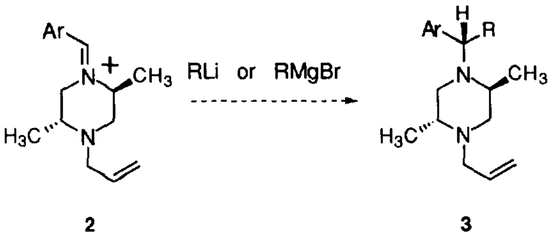


1

Previous approaches to benzhydrylpiperazine opioids have relied on forming a racemic benzhydryl alcohol, converting the alcohol to the corresponding benzhydryl chloride, then displacing the chloride with enantiopure 1-allyl-2,5-dimethylpiperazine.[3] This approach provides a 50:50 mixture of diastereomers, epimeric at the benzhydryl position, which presents a difficult separation by column chromatography.

As an alternative, we envisioned a stereoselective addition of an organometallic nucleophile to an iminium salt (Scheme **1**).

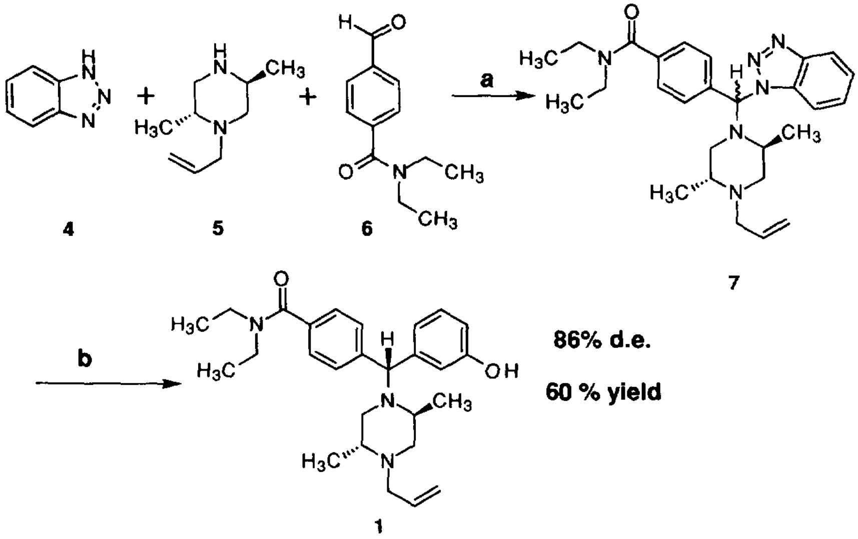
Scheme 1



The addition of organometallics to imines is a well-documented reaction,[4] which includes stereoselective versions.[5] While organometallics add more readily to iminium salts than to imines, there are fewer examples of stereoselectivity in these reactions.[6] This may be attributed to several factors, including the absence of the nitrogen lone pair that is useful for coordination, the increased reactivity of iminium ions, and the difficulties sometimes associated with forming and handling iminium salts.

In fact, our inability to isolate an iminium salt such as **2** prompted us to slightly alter our approach. "Masked iminiums", such as α-aminoethers, are often used to avoid the troubles associated with iminium salts.[6] We chose an α-benzotriazolylamine as our "masked iminium", due to its well-documented ability to undergo nucleophilic displacement of benzotriazole.[7] This adaptation of the Katritzky method for forming tertiary amines provided the desired diastereomer **1** with an 86% diastereomeric excess.

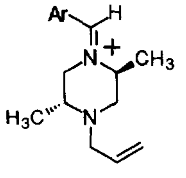
Scheme 2



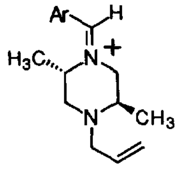
(a) toluene, 111 °C, (–H_2O); (b) 3-(t-butyldimethylsilyloxy)phenylmagnesium bromide, THF, 25 °C; 3N HCl.

(+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-N,N-diethylbenzamide, **1**, was synthesized from aldehyde **6**,[8] benzotriazole, and (2R, 5S)-1-allyl-2,5-dimethylpiperazine **5**[3] (Scheme **2**). These reagents were heated at reflux in toluene with a Dean-Stark trap attached to remove water. Adduct **7** was cooled to room temperature, and the entire solution in toluene was added directly, via a double-ended needle, to 3-(t-butyldimethylsilyloxy)phenylmagnesium bromide[9] in THF at room temperature. The reaction is exothermic, the solution warmed spontaneously and became cloudy as the reaction progressed. Subsequent acidic removal of the silyl protecting group provided product in 60% overall yield in a 93:7 ratio of diastereomers, in favor of the desired compound **1**.[10] The benzhydrylpiperazine can be partioned into aqueous acid, while benzotriazole can alternatively be recycled by mild aqueous base extraction, thus careful work-up with the appropriate washes can afford very clean compound from this reaction sequence.

Compound **7** can be considered a "masked iminium" salt, as the adduct exists in equilibrium with the iminium cation-benzotriazolyl anion pair.[11] The iminium ion is presumably the actual species that reacts with the Grignard reagent. In fact, a trial run of the reaction was unsuccessful at 0 °C, possibly due to very low levels of dissociation at this temperature. Assuming that the iminium ion is the reactive entity, the stereoselectivity appears to rely on two separate events: (1) Preferential formation of one of the two possible iminium ions (**2a** versus **2b**), and (2) facial selectivity of the nucleophilic attack on the iminium ion.



2a



2b

It is reasonable to assume that a greater proportion of adducts will dissociate to give the sterically less demanding iminium ion, **2a**, with the methyl-bearing carbon of the piperazine *trans* to the aromatic ring. Next, the nucleophile must approach **2a** from the *Si* face, away from the methyl group, to give the observed diastereoselectivity. The steric effect of the methyl group on the piperazine ring is apparently responsible for this substantial stereoselectivity.

These results indicate that on the appropriate substrate, Katritzky's tertiary amine formation can be used to achieve good diastereoselectivity. This highly convergent procedure is substantially higher yielding than previous approaches to opioid benzhydrylpiperazines. Thus, this provides an efficient, new route to the highly specific delta opioid receptor agonist (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-N,N-diethylbenzamide [(+)-BW373U86].

Acknowledgments

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References and Notes

1. Chang, K.-J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852-857.

2. (a) Childers, S. R.; Fleming, L. M.; Selley, D. E.; McNutt, R. W.; Chang, K.-J. *Molecular Pharmacology*, **1993**, *44*, 827-834. (b) Comer, S. D.; Hoenicke, E. M.; Sable, A. I.; McNutt, R. W.; Chang, K.-J.; De Costa, B. R.; Mosberg, H. I.; Woods, J. H. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 888-895, and references cited therein.

3. (a) Chang, K.-J.; Boswell, G. E.; Bubacz, D. G.; Collins, M. A.; Davis, A. O.; McNutt, R. W. International Patent Application WO 93/15062, Aug. 5, 1993. (b) Calderon, S. N.; Rothman, R. B.;

Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125-2128.

4. For some examples, see: Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp. 975-1006.

5. Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161-3162.

6. For a review of nucleophilic additions to imines and iminium salts, see: Volkmann, R. A. In *Comprehensive Organic Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp. 355-396.

7. (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 805-809. (b) Katritzky, A. R.; Najzarek, Z.; Dega-Szafran, Z. *Synthesis* **1988**, 66-69. (c) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 225-233.

8. This aldehyde was prepared by heating 4-carboxybenzaldehyde to reflux in neat thionyl chloride until complete dissolution, removing all volatiles, and treating the residue with excess diethylamine in dichloromethane at 0 °C. This procedure gives aldehyde **6** in 98 % yield without need for further purification.

9. Prepared from 3-bromophenol. The silyl protecting group was affixed using t-butyldimethylsilyl chloride with imidazole in DMF. Treatment with n-BuLi in THF at -78 °C, followed by addition to a stirring solution of magnesium bromide etherate in THF at 25 °C generated the 3-(t-butyldimethylsilyloxy)phenylmagnesium bromide.

10. The diastereomeric ratio was determined by HPLC on a μ-Bondapak C-18 column (125 Å, 3.9 x 300nm, Waters Chromatography Division, Milford, Massachusetts), in 70% methanol / 30% 0.1 M ammonium acetate solution, at a flow rate of 1 mL/min. Also checked using 300 MHz NMR by integration of the phenolic proton peaks in DMSO-d_6.

11. Katritzky, A. R.; Yannakopoulou, K. *Heterocycles* **1989**, *28*, 1121-1134.

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