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One-Pot Claisen Rearrangement/*O*-Methylation/Alkene Isomerization in the Synthesis of *Ortho*-Methoxylated Phenylisopropylamines

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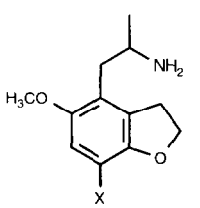
Abstract: An improved synthesis of a potent serotonin agonist **1a** and its novel derivative **1b** is described, making use of a Claisen rearrangement whose unstable phenolic product is methylated and isomerized *in situ*. This method may be of general use in the synthesis of *o*-methoxylated phenethylamine derivatives. The synthesis also includes an unusual, one pot demethylation/primary alcohol bromination with boron tribromide. Copyright © 1996 Elsevier Science Ltd

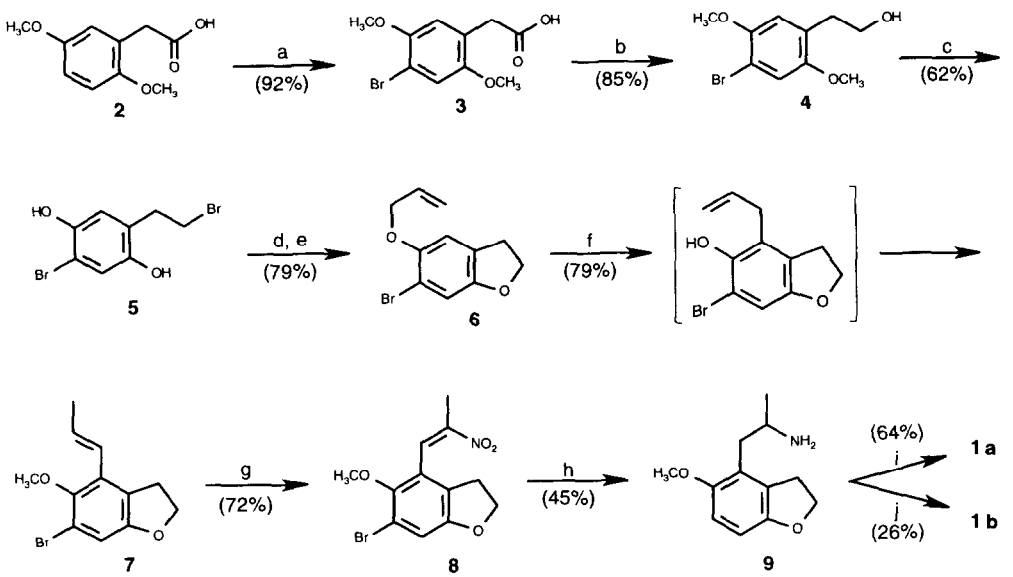
Working to improve the synthesis of **1a** (a potent 5-HT_2 agonist which had been synthesized previously in our laboratory[1]), we have found a reaction that may be of general use in the synthesis of *o*-methoxylated amphetamines, many of which are known to have agonist activity at central 5-$HT_{2A/2C}$ receptors.[2] This approach successfully yielded **1a,** as well as **1b**, a novel iodo derivative.



1a, X = Br
1b, X = I

In the original sequence, rearrangement of the nonbrominated congener of **6** had given a predominance of the undesired 6-allyl product.[1] It was our intention to modify this original synthesis only slightly, introducing a bromine atom in order to force regiospecificity onto the Claisen rearrangement of **6** (Scheme). An eventual $LiAlH_4$ reduction would remove the bromine atom as a matter of course without necessitating an extra deprotection step. Unfortunately, our attempts to carry out the Claisen rearrangement to give the phenol directly yielded an unstable product mixture that proved extremely difficult to handle. Thus, a method for trapping the intermediate phenol as its methyl ether was required.

Scheme[a]



[a]Reagents and conditions: (a) Br_2/HOAc, 25 °C, 2h; (b) BH_3/THF, 0 °C to 25 °C, 8h; (c) BBr_3/CH_2Cl_2, -78 °C to 25 °C, 22.5h; (d) K_2CO_3, acetone, reflux, 18h; (e) allyl bromide, 10.5h; (f) phenyltrimethylammonium methosulfate, K_2CO_3, DMF, reflux, 36h; (g) $AgNO_2$, I_2, pyridine, THF, 8.5h; (h) $LiAlH_4$/THF, reflux, 16h, then H_2O; (i) Br_2/HOAc, 25 °C, 21h; (j) Ag_2SO_4, I_2, EtOH, 25 °C, 15.5h

Unstable phenolic products of Claisen rearrangements have been trapped by simultaneous acylation with reagents such as butyric or acetic anhydride.[3] However, we could find no examples where such phenols were trapped by *alkylation*, as our synthesis required. Several methods were attempted until we discovered a simple, reproducible procedure for accomplishing the desired transformation of **6** to **7** in good yield (Scheme). Under the basic conditions chosen, the allylarene product resulting from the Claisen rearrangement also undergoes isomerization *in situ* to form the 1-propenylarene **7**, a fortuitous result in the context of our desired phenylisopropylamine synthesis.

Bromination of **2** gave **3** without difficulty, and the acid **3** was reduced with BH_3/THF. Alcohol **4** was then treated with excess boron tribromide. Although a recent study reported that primary alcohols are unaffected by treatment with boron tribromide,[4] this was not the case for the phenethylalcohol **4**. Surprisingly, we found that **4** was both demethylated and brominated smoothly by excess boron tribromide to give **5** in good yield (see Note 9). We have subsequently found that other 2-phenethylalcohols with one or more *o*-methoxy groups readily undergo this demethylation/bromination reaction upon treatment with excess BBr_3.[5] This finding suggests, perhaps, that the complexed primary alcohol may be attacked by the adjacent *ortho*-oxygen atom,

leading to the intermediacy of a dihydrofuran species that is subsequently cleaved by BBr_3 to generate the primary bromide product.

Reflux of **5** in acetone with potassium carbonate, followed later by introduction of allyl bromide into the refluxing mixture provided the allyl ether **6**. The rearranged, *O*-methylated, and isomerized material **7** was obtained after holding a mixture of **6**, phenyltrimethylammonium methosulfate, and potassium carbonate in dry DMF at reflux for 36 hours (see Note 10). Nitration of **7** with nitryl iodide, generated *in situ* from iodine and silver nitrite,[6] to give **8**, followed by $LiAlH_4$ reduction-reductive debromination afforded the parent phenylisopropylamine analog **9**. Direct bromination of **9** gave **1a**, as previously reported.[1] Finally, iodination of **9** with iodine and silver sulfate in ethanol[7] gave the novel iodo derivative **1b**.

In summary, we have found a novel synthetic approach that may be of general use in the synthesis of *o*-methoxylated phenylisopropylamines. A full report on the synthesis and structure-activity relationships of a large series of dihydrobenzofuran amphetamine analogs will be published in due course.[8]

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REFERENCES AND NOTES

1. Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Johnson, M. P.; Huang, X. *J. Med. Chem.* **1991**, *34*, 276-281.

2. Titeler, M.; Lyon R. A.,; Glennon, R. A. *Psychopharmacology* **1988**, *94*, 213-216; Sanders-Bush, E.; Burris, K. D.; Knoth, K. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 924-928; Seggal, M. R., Yousif, M. Y.; Lyon, R. A.; Titeler, M.; Roth, B. L.; Suba, E. A.; Glennon, R. A. *J. Med. Chem.* **1990**, *33*, 1032-1036; Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitler, M.; Leonhardt, S. *J. Med. Chem.* **1992**, *35*, 734-740.

3. See, for example Murray, R. D. H., and Ballantyne, M. M. *Tetrahedron* **1970**, *26*, 4667-4671.

4. Pelletier, J. D. and Poirer, D. *Tetrahedron Lett.*, **1994**, *35*, 1051-1054.

5 Monte, A. P. *Structure-Activity Relationships of Hallucinogens: Design, Synthesis, and Pharmacological Evaluation of a Series of Conformationally Restricted Phenethylamines*, Ph.D. thesis, 214 pp, Purdue University, 1995.

6. Sy, W. and By, A. W. *Tetrahedron Lett.* **1985**, *26*, 1193-1196.

7. Sy, W. *Tetrahedron Lett.* **1993**, *34*, 6223-6224.

8. Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1996**, in press; A. Monte, *et al.*, manuscripts in preparation.

9. Preparation of **2,5-dihydroxy-4-bromophenethylbromide (5)**: A solution of 11.32 g (43.5 mmol) of 2,5-dimethoxy-4-bromophenethylalcohol in 140 mL of methylene chloride was cooled to -78 °C in a dry ice/acetone bath. Boron tribomide (14 mL, 148 mmol) was slowly added to the stirred solution. The dry ice was allowed to melt, and the reaction vessel warmed to room temperature. After 22.5 hours, the reaction was again cooled to -78 °C, and was quenched

by the cautious addition of 300 mL of water, provoking a solid precipitate. Collection of this material by filtration, followed by recrystallization from ethyl acetate/hexane, yielded 8 g (62%) of pure **5**. Melting point: 142 - 145 °C. CIMS *m/z* 294, 296, 298 $[M]^+$, 295, 297, 299 $[M + H]^+$; ^1H NMR ($CDCl_3$) δ 3.0 (t, 2, $ArCH_2CH_2Br$), 3.6 (t, 2, $ArCH_2CH_2Br$), 6.6 (s, 1, Ar*H*), 6.9 (s, 1, Ar*H*).

10. Preparation of ***trans*-6-bromo-5-methoxy-4-(1-propenyl)-2,3-dihydrobenzofuran (7)**: A mixture of 2,3-dihydro-5-allyloxy-6-bromobenzofuran **6** (1.0 g, 3.9 mmol), phenyltrimethylammonium methosulfate (2.94 g, 11.9 mmol), and finely ground potassium carbonate (2.72 g, 19.7 mmol) was dried for several hours under high vacuum. The flask was then outfitted with a condenser and maintained under a dry nitrogen atmosphere. Dry DMF (50 mL) was added, and the stirred mixture was held at reflux for 36 hours. The reaction mixture was then cooled and filtered through Celite, and the filter cake was rinsed with 150 mL of ether. The filtrate was washed extensively with 1N hydrochloric acid (16 x 100 mL), water (2 x 100 mL), 2N sodium hydroxide (2 x 100 mL), and brine (2 x 100 mL). The organic phase was dried over magnesium sulfate, filtered, and the solvent was removed to afford a dark oil. The crude product was dissolved in hexane, leaving a dark solid impurity which was removed by filtration. Evaporation of the filtrate, followed by Kugelrohr distillation, gave 826 mg (79%) of **7** as a light yellow oil. CIMS *m/z* 268, 270 $[M]^+$, 269, 271 $[M + H]^+$; ^1H NMR ($CDCl_3$) δ 1.9 (d, 3, $CH_3CH=CH_2$), 3.2 (t, 2, $ArCH_2CH_2O$), 3.7 (s, 3, CH_3O), 4.5 (t, 2, $ArCH_2CH_2O$), 6.2 (m, 1, $ArCH=CHCH_3$), 6.5 (d, 1, $ArCH=CHCH_3$, J = 16 Hz), 6.8 (s, 1, Ar*H*).

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