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2-FLUORO- AND 5-FLUORO-3,4-DIMETHYLPHENETHYLAMINE DERIVED FROM CLAISEN REARRANGEMENT PRODUCTS

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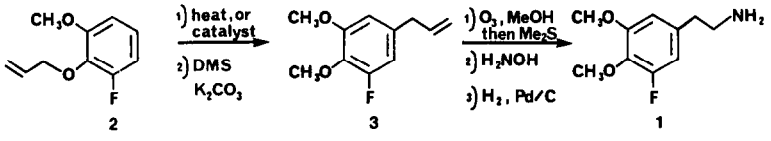
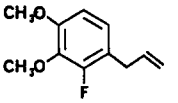
Abstract: The Claisen rearrangement of 2-allyloxy-3-fluoroanisole followed by methylation provided the para-rearranged product along with the unexpected 3-(3,4-dimethoxy-2-fluorophenyl)-1-propene.

A new method for the synthesis of 3,4-dimethoxy-5-fluorophenethylamine (1) was sought in order to obtain large quantities of it since a previously reported sequence provided an overall low yield of 1. In the previous sequence the low yielding step involved a photochemical-Schiemann reaction of 5-nitrovanillin and scale up of this previous scheme would likely be very difficult.[1] As a new alternative , the Claisen rearrangement and methylation of 2-allyloxy-3-fluoroanisole[2] (2) and subsequent ozonolysis, oxime formation and reduction was projected for the synthesis of 1 as illustrated below.



Various procedures for performing the Claisen rearrangement of 2 were examined. Thermal treatment of 2 did not provide the Claisen rearrangement product, however the rearrangement could be performed with a variety of Lewis acid catalysts, including $AlCl_3$. There are examples in the literature of catalysts being employed in Claisen rearragements, but few examples show the major product as being the para-substituted species.[3] The reaction proceeded by adding the $AlCl_3$ in one portion to a cold(-78°C) solution of 2 in CH_2Cl_2. The reaction was allowed to slowly warm to -20°C (about 2.5 h) at which time all the starting material had been consumed (as monitored by TLC, 5% EtOAc/hexanes). The mixture was poured onto crushed ice containing a small amount of conc. HCl. The layers were separated, the aqueous layer was extracted with CH_2Cl_2, the organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated to an oil which was vacuum

distilled to give an 80% yield of a mixture of two isomers. After methylation, closer examination, by the use of HPLC, indicated that the two isomers where present in a ratio of 3:2. The major product was identified as the Claisen product 3-(3,4-dimethoxy-5-fluorophenyl)-1-propene (3) while the other isomer was identified as 3-(3,4-dimethoxy-2-fluorophenyl)-1-propene (4).[4] The isolation of 4 , which resulted from methylation of a meta-propene substitued phenol, was unexpected since acid catalyzed Claisens have been reported to rearrange to ortho- and para-products.[5] Once 3 and 4 were separated they were transformed into the known phenethylamines 1 and 5 , respectively.[1,2]



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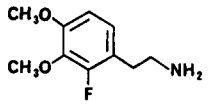

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This synthetic pathway proved to be unique in that two different phenethylamines 1 and 5 could be obtained from 2 , although it had originally been projected to be a selective method for the preparation of 1. It is interesting to note that Ladd, et al.[5] have reported that 2-allyloxy-3-fluorobenzene gave the expected ortho- and para-Claisen rearrangement products. The isolation of 4 provides a unique meta-product, in addition to 3 , after Claisen rearrangement and methylation of 2.

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References and notes

1) Kirk, K.L., Catacuzene, D., Collins, B., Chen, G.T., Nimit, Y., Creveling, C.R. J. Med. Chem. 1982 , 25 , 680.
2) Ladd, D.L., Weinstock, J. J. Org. Chem. 1981 , 46 , 203.
3) Rhoads, S.J. and Raulins, N.R. in " Organic Reactions, Vol. 22", Dauben, W.G., ed., John Wiley & Sons, Inc., New York, New York, pp 1-252.
4) Compounds 3 and 4 gave satifactory elemental analyses and spectral data. 270 MHz ^{1}H NMR spectral data are as follows.
3-(3,4-dimethoxy-5-fluorophenyl)-1-propene (3) δ6.57 (dxd, 1H, $J_{HH}m$ = 1.9 Hz, $J_{HF}o$ = 11.3), 6.51 (dxd, 1H, $J_{HH}m$ = 1.9 Hz, $J_{HF}p$ = 1.5 Hz), 6.00-5.85 (m, 1H), 5.14-5.06 (m, 2H), 3.89 (d, 3H, J_{HF} = 0.8 Hz), 3.86 (s, 3H), 3.32-3.29 (m, 2H); Anal. ($C_{11}H_{13}FO_2$) C, H.
3-(2-fluoro-3,4-dimethoxyphenyl)-1-propene (4) δ6.84 (dxd, 1H, $J_{HH}m$ = 8.7 Hz, $J_{HF}o$ = 8.3 Hz), 6.51 (dxd, 1H, $J_{HH}m$ = 8.7 Hz, $J_{HF}p$ = 1.6 Hz), 6.01-5.87 (m, 1H), 5.10-5.03 (m, 2H), 3.92 (d, 3H, J_{HF} = 0.8 Hz), 3.86 (s, 3H), 3.36-3.33 (m, 2H); Anal. ($C_{11}H_{13}FO_2$) C, H.
5) Bennett, B. G., Synthesis 1977, 589.
6) Ladd, D.L., Gaitanopoulas, D., Weinstock, J. Synth. Commun. 1985 , 15 , 61.

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