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SYNTHESIS OF FLUORINATED BIPHENYLS VIA ARYNE REACTION

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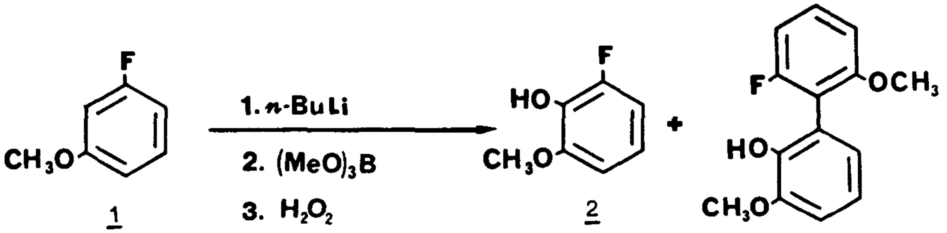
Abstract: Synthesis of fluorinated biphenyls via attack of a benzyne by an anion of *3-fluoroanisole*.

The reactions of fluoroanisole with phenyllithium at room temperature has been studied.[1] Synthesis of fluoroveratroles from fluoroanisole also has been described.[2] The latter study is important because it described a synthetic entry to many ring-fluorinated compounds such as the pharmacologically important phenethylamines.[2,3] This paper reports a side reaction observed in the synthesis of fluoroveratrole as shown by equation 1. This side reaction has been developed into a useful synthetic entry into fluorinated biphenyls.



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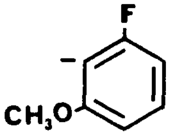

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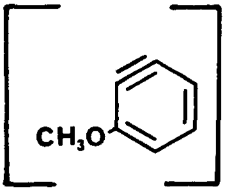

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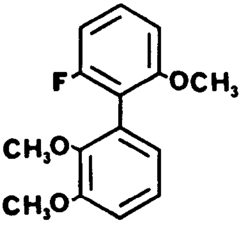

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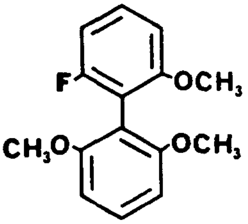

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When 3-fluoroanisole 1 is treated with an equimolar amount of n-butyllithium at low temperature (-75°C), it forms the anion 4. This anion can be trapped and developed into the phenol 2.[2] Once formed, another option available to the anion is collapse to form the benzyne 5. The benzyne can undergo several reactions including reaction with anion 4 to generate a biphenyl anion. The biphenyl anion resulting from attack at the position meta to the methoxy group of the benzyne is expected to be formed as a result of the stabilizing inductive effect of the benzyne methoxy group. Attack at the position ortho to the methoxy group is not favored since it will lead to the less stable biphenyl anion. In this study, the anion formed was trapped as the borate ester and oxidized to form the phenol 3.[2,4] The crude phenol in methylene chloride was passed over decolorizing carbon and purified by flash chromatography using 20% ethyl acetate in petroleum ether as the eluting solution. The light yellow viscous liquid phenol (36%) obtained upon removal of solvents under vacuum crystallized to give white crystalline material. Recrystallization was carried out in ether/hexane.

The time between generation of anion 4 and trapping it seems to be the major determining factor as to the ratio of phenols 2 and 3 formed. Trapping at 2h or less leads to high yield of phenol 2 whereas trapping at 5h leads to high yield of phenol 3. High dilution and low temperature are essential for formation of phenol 2 whereas these don't seem to be as critical in the formation of phenol 3. Methylation was used to confirm the structure of the biphenyl phenol 3. Biphenyl 7 would have been obtained on methylating the phenol resulting from ortho attack of anion 4 on the benzyne. In this case, two of the three methoxy groups should be equivalent. The three methoxy groups on biphenyl 6 would all be expected to be different. Methylation was done using dimethyl sulfate[2] (89% yield). Three different methyl resonances were observed on examining the ^{1}H NMR Spectrum of the product[5], confirming structure 6 as the product.

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References and Notes

1) Huisgen R., Rist, H. Justus Liebigs Ann. Chem. 1955, 594, 137.
2) Ladd, D.L., Weinstock, J. J. Org. Chem. 1981, 46, 203.
3) Kirk, K.L., Catacuzene, D., Collins, B., Chen, G.T., Nimit, Y., Creveling, C.R. J. Med. Chem. 1982, 25, 680.
4) Hawthorne, M.F., J. Org. Chem. 1957, 22, 1001.
5) Biphenyls 3 and 6 gave satisfactory elemental analysis and spectral data. Selected physical and spectral data are as follows:
2-Fluoro-6-methoxy-2'-hydroxy-3'-methoxy biphenyl 3 m.p. = 74-76°C; ^{1}H NMR $(CDCl_3)$: δ 7.45-6.70 (m, 6H) 5.72 (s, 1H), 3.92 (s, 3H), 3.79 (s, 3H); MS m/e 248 (M^+, base); IR (KBr): 3500 $cm.^{-1}$; Analysis $C_{14}H_{13}O_3F$ (C,H,F).
2-Fluoro-6-methoxy-2',3'-dimethoxy biphenyl 6 m.p. = 89-90°C; ^{1}H NMR $(CDCl_3)$: δ 7.45-6.65 (m, 6H), 3.90 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H); MS m/e 262 (M^+, base); Analysis $C_{15}H_{15}O_3F$ (C,H,F).

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