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FLUORINATION OF SUBSTITUTED VERATROLES VIA REGIOSELECTIVE MERCURATION

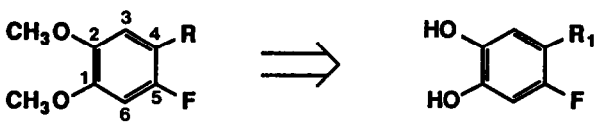
A. Luxen* and J.R. Barrio

UCLA School of Medicine, Los Angeles, California 90024

Abstract

A regioselective aromatic ring fluorination of substituted veratroles was achieved via a mercuration-fluorodemercuration reaction.

During the past decade, 6-fluorocatecholamines (2) have received considerable attention primarily due to their pharmacological and medicinal interest.[1] The simplest synthetic approach



1a-e **2**

R_1 = $CH_2CH(NH_2)COOH$; $CH_2CH_2NH_2$;

$CHOHCH_2NH_2$; $CHOHCH_2NHCH_3$

to these derivatives is the direct fluorination with dilute fluorine or acetylhypofluorite (AcOF), a procedure attempted for the preparation of 6-fluoro-3,4-dihydroxyphenylalanine.[2] However it is difficult to prepare 2 in a regioselective manner by this method and a mixture of isomers is always obtained. Site-specific fluorination has rested largely on the Balz-Schiemann reaction, that often serves as a general route for the preparation of 5-fluoro-4-substituted veratroles 1(a-e)[3], considered the most useful synthetic precursors of 2. We report here a simple, general method for the preparation of 1(a-d): a regioselective organomercuration of substituted veratroles 3(a-e) followed by an efficient aromatic fluorodemercuration reaction (Scheme I).

Mercuric trifluoroacetate in ethanol reacted with 3(a-e)[4] at room temperature to give the 5-mercurio derivatives 4(a-e) in good yields (Table 1). The products 4(c-e) precipitated during

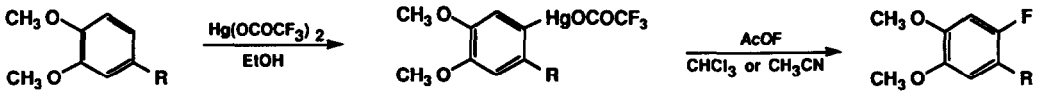
the reaction and were obtained in pure form after filtration, whereas 4a,b were recovered aftersolvent evaporation and recrystallization. Regioselectivity of organomercury substitution was assessed by iodination of the products 4(a-e), and subsequent comparison with authentic standards.[6] Mercuration was, as expected, dependent upon solvent conditions. For example, mercuration of veratraldehyde (3e) in acidic solvents (acetic acid or trifluoroacetic acid) lacked regioselectivity, yielding mixtures of 3,5 and 6 isomers.

TABLE 1

Compound	MP,°C	Yield %	^{1}H NMR[a]
4a	123-125	53	($CDCl_3$/TMS) 1.26 (t,3), 3.1-3.3 (m,2), 3.88 (s,6), 4.22 (dq,2), 4.82 (q,1), 6.75 (s,1), 6.79 (s,1), 7.2 (m,1).
4b	125-127	50	Same as 4a.
4c	127-128	94	($CDCl_3$/TMS) 1.27 (t,3), 3.55 (s,2), 3.88 (s,3), 3.90 (s,3), 4.17 (q,2), 6.85 (s,1), 6.87 (s,1).
4d	174-175	61	($CDCl_3$/TMS) 2.92 (t,2), 3.63 (t,2), 3.88 (s,3), 3.90 (s,3), 6.79 (s,1), 6.84 (s,1).
4e	177-178	64	($CDCl_3$/TMS) 4.0 (s,6), 7.09 (s,1), 7.35 (s,1), 9.96 (s,1).
1a	90-91	40	($CDCl_3$/HMDS) 1.31 (t,3), 3.15-3.35 (m,2), 3.81 (s,3), 3.85 (s,3), 4.24, 4.25 (dq,2), 4.75-4.85 (m,1), 6.53 (d, J = 7.02 Hz,1), 6.61 (d, J = 11.3 Hz,1), 6.8-7 (m,1H).
1b	92-93	35	Same as 1a.
1c	Oil	32	($CDCl_3$/TMS) 1.27 (t,3), 3.58 (s,2), 3.84 (s,6), 4.16 (q,2), 6.63 (d, J = 11.7 Hz, 1), 6.73 (d, J = 7.2 Hz,1).
1d	120-122 (lit. 130-131)[3c]	31	($CDCl_3$/TMS) 2.87 (t,2), 3.60 (t,2), 3.84 (s,3), 3.86 (s,3), 6.33 (bs,1), 6.62 (d, J = 5.2 Hz,1), 6.64 (d, J = 11.9 Hz,1).

[a] ^{1}H NMR spectra were recorded on a Bruker 360 MHz spectrometer.

The usefulness of the organomercury derivatives as synthetic intermediates was demonstrated by converting them into the corresponding monofluorinated veratroles. Thus, reaction of AcOF, generated in the gas phase[7], with 4(a-d) in chloroform, freon/chloroform (9:1) or acetonitrile at room temperature gave 1(a-d) in moderate yields. It should be noted, however, that in the presence of deactivating groups on the aromatic ring (e.g. 4e), fluorodemercuration could not be achieved, in agreement with similar earlier observations.[9b] In contrast to the successful application of AcOF, fluorination of 4(a-e) with dilute fluorine gas (1% in neon) in chloroform, acetonitrile or acetic acid at 0°C or -70°C was ineffective to produce the desired fluorinated products 1(a-e).



3a-e 4a-e 1a-e

a R = L -CH_2-CH(NHCOCF$_3$)-COOEt;

b R = D -CH_2-CH(NHCOCF$_3$)-COOEt;

c R = -CH_2-COOEt;

d R = -CH_2-CH_2-NHCOCF$_3$;

e R = -CHO

Scheme I

The following procedure is representative for the mercuration-fluorodemercuration reaction: The L-dopa derivative 3a (6.7 g, 19 mmole) dissolved in ethanol (80 mL) was stirred with one equivalent of $Hg(OCOCF_3)_2$ (8.2 g) at room temperature. Conversion to the organomercury derivative 4a was optimal at 72 hours. Yield: 6.7 g (53%); mp 123-125°C (petroleum ether-ether). Regiospecific fluorodemercuration was effected by bubbling AcOF prepared in the gas phase[7] (500 µmol) through a solution of 4a (500 mg, 756 µmol) in $CHCl_3$/freon (1:9) (40 mL) at room temperature. After washing with 1N $Na_2S_2O_3$ and water, the organic phase was dried over anhydrous $MgSO_4$ and the residue chromatographed on silica gel (CH_2Cl_2:MeOAc, 90:10) to afford 1a in 40% yield (mp: 90-91°C).

Selection of the organomercury precursors[8,9] as starting materials for regioselective fluorination was based on various experimental observations with arylmetallic compounds. For example, it has been shown in a comparative study[10] that fluoro-demetallation yields increase in the order Si < Ge < Sn. However, the applicability of aryltrialkylstannanes as substrates for regiospecific fluorination reactions is reduced to starting materials without sensitive functionalities because the reported synthesis of aryltrialkylstannanes are based on Grignard and organolithium reactions. Direct electrophilic mercuration avoids these conditions and therefore permits, for example, to obtain pure L- or D- 6-fluorodopa without racemization during

the preparative process.[11] In summary, this work reports efficient conditions for the regiospecific mercuration of substituted veratroles with sensitive functionalities, and application of the fluorodemercuration reaction to the synthesis of catechols of biological interest. Moreover, the reactions reported in this work are a valuable alternative to the Balz-Schiemann reaction.

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4. Compound 3(a and b) were prepared from L- or D-dopa, respectively, through the following sequence[5]: 1) $HCOOH/CH_3CO_2COCH_3$; 2) $(CH_3)_2SO_4/KOH$; 3) EtOH/HCl gas; 4) $CF_3CO_2COCF_3$/ 2 hr/RT. Compound 3d: R.W. Gray, A.S. Dreiding, Helv. Chim. Acta, 63, 315 (1980).
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11. Deprotection of 1a and 1b with 47% HBr (2 hr, reflux) provides L- and D- 6-fluorodopa, respectively. Their enantiomeric purity was determined by ligand exchange chromatography. (Serva Column 4.6 mm x 250 mm. ChiralPro = Si 100 Polyol; 50 mM KH_2PO_4, 1 mM $CuSO_4$, pH 4; flow rate, 1 ml/min.; k'D = 2.1, k'L = 7.3).

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