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A SITE-SPECIFIC METHOD FOR DEUTERATION: REDUCTION OF ARYL HALIDES WITH SODIUM BORODEUTERIDE AND PALLADIUM CHLORIDE

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Sodium borohydride-transition metal systems produce reductions not achieved by sodium borohydride alone,[1,2] such as dehalogenation of aryl halides. The demand for deuterium labeled compounds in organic chemical[3] and biomedical[4] research stimulated us to develop a convenient method for introducing a deuterium atom into an aromatic system. With the appropriate choice of aryl halide, a wide variety of specifically deuterated aromatic compounds can be prepared (Table 1).

The following procedure for the preparation of 4-deuterobenzoic acid is representative. A dry 25 ml roundbottom flask was flushed with nitrogen and immersed in a water bath at 20°. 4-Chlorobenzoic acid-d_1 (0.157 g, 1.0 mmole), prepared by successive dioxane-D_2O exchanges, was dissolved in 7.0 ml of methanol-d_1 and then solid palladium chloride (0.355 g, 2.0 mmoles) was added. Solid sodium borodeuteride (98% D) (0.418 g, 10.0 mmoles) was then added in small portions to the stirred solution and stirring was continued for 1 hr. The reaction mixture was poured into 80 ml of water containing 5 ml of 5N hydrochloric acid. Extraction of the aqueous phase with 3 X 30 ml of ethyl ether, drying the combined ether extracts with anhydrous $MgSO_4$, filtration, and removal of the ether under reduced pressure, yielded the crude product. Recrystallization from water gave 0.102 g, 83% of colorless plates, mp 122°; nmr ($CDCl_3$) δ 7.73 (q, 4, J=4Hz, aromatic) and δ 12.06 (s, 1, COOH).

The data in Table 1 shows the greater ease of deuteration of ortho and para substituted aryl halides relative to the corresponding meta derivative, and the greater reactivity of bromo as opposed to chloro derivatives.

TABLE 1

SITE-SPECIFIC DEUTERIUM LABELING

COMPOUND DEUTERATED	TEMPERATURE	% Yield[a]	% DEUTERIUM[b]
2-Bromobenzoic acid	20°	70	>95
2-Chlorobenzoic acid	20°	62	>95
3-Chlorobenzoic acid	20°	48	>95
4-Chlorobenzoic acid	20°	83	>95
3,4-Dichlorobenzoic acid	20°	55	>95
3-Bromoanisole	20°	46	>95
4-Chloronitrobenzene[c]	-10°	70	>95
3-Bromobenzo[b]thiophene[d]	-10°	70	>95
5-Bromoindole[d]	-10°	85	>95
4-Chlorophenoxyacetic acid	20°	73	>95
1-(4-Chlorophenyl)-2-methyl-aminopropane	20°	85	>95

[a] All compounds were pure by GLC and gave mass spectra consistent with their structures. [b] Determined by 100 MHz nmr which gave splitting patterns consistent with deuterium incorporation at the site of the halogen in the starting material. [c] The deuterated product was 4-deuteroaniline. [d] Small amounts (3-5%) of dihydro products were obtained at 20°.

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