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Directed *ortho*-Lithiation Reactions: Position-Specific Introduction of Tributylstannyl Derivative onto β-[*N,N*-Dimethylamino]ethoxybenzenes

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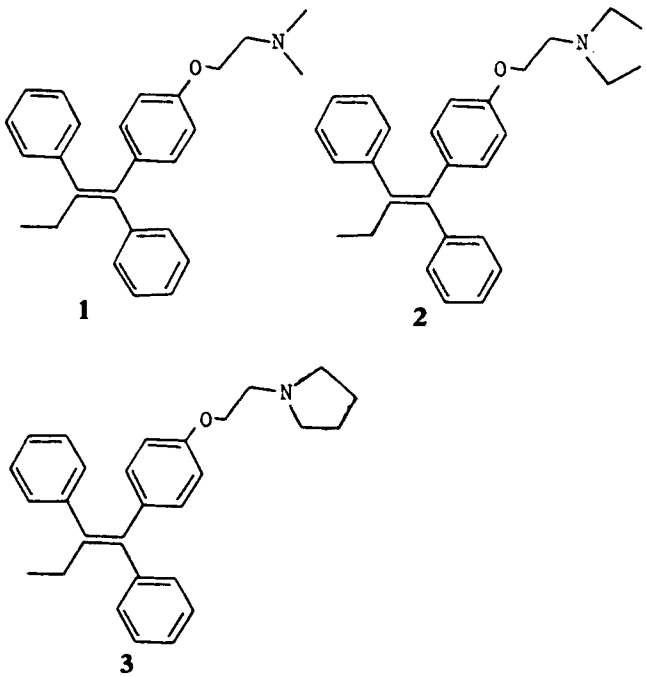
ABSTRACT

This article presents the position-specific introduction of substituents onto substituted phenolic rings via electrophilic destannylation of trialkylstannyl derivatives of β-[N,N-dialkylamino]ethoxybenzenes.

INTRODUCTION

The multifaceted nature of heteroatom-facilitated lithiation of aromatic compounds [1] is suggestive of broad synthetic applicability; recently numerous studies have been reported in the literature [2–6] utilizing the *ortho*-lithiation methodology for these reactions. Moreover, the high degree of regioselectivity and the relative facility of this type of reaction, combined with the high reactivity of the new organolithium species toward a variety of electrophilic substrates, contribute to the attractiveness of heteroatom-facilitated lithiation as a synthetic tool.

In earlier works [7, 8] we reported on a procedure for the introduction of tritium and iodine into the molecule of tamoxifen **1**, an antiestrogen agent currently employed in the treatment of breast cancer. The method introduces a trialkyltin moiety into a functionalized organic molecule and selectively replaces it via electrophilic destannylation. A series of model studies with β-[*N,N*-dialkylamino]-ethoxybenzenes was performed initially both to determine the best reaction conditions and to assess accurately the activating effect of the β-[*N,N*-dialkylamino]ethoxy ligand for orthometallation.



1 **2** **3**

The β-[*N,N*-dialkylamino]ethoxy ligand was chosen for activation of orthometallation because of its structural resemblance to a partial structure

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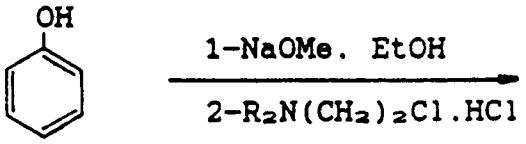
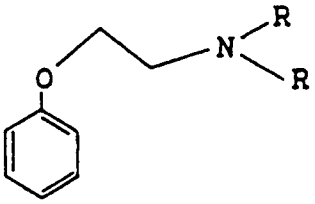
of the antiestrogenic compounds tamoxifen **1** [9], clomiphene **2** [10], and nafoxidine **3** [11], respectively, upon which interest has been focused because of their potential for controlling the growth of estrogen-dependent neoplasms, particularly breast cancer [12].

RESULTS AND DISCUSSION

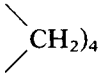
The β-[*N*,*N*-dialkylamino]ethoxy compounds **4**, **5**, and **6** are available in one step upon treatment of phenol and the commercially available β-[*N*,*N*-dialkylamino]ethyl chloride hydrochloride with ethanolic sodium methoxide.





4 R = CH_3–

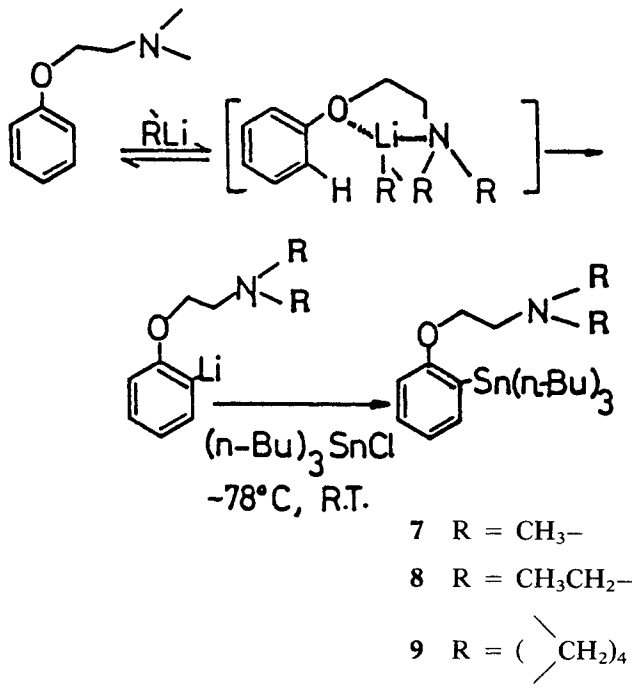
5 R = CH_3CH_2–

6 R = 

Stannylation of these phenoxyethyldialkylamines was performed via initial *ortho*-lithiation. Tetrahydrofuran has been the solvent of choice for *sec*-butyllithium, which was the organometallic reagent mainly used in our lithiation reaction. This is because the organometallic compound is considered to be present as a dimer in this solvent. Also, it is well known that tetramethylethylenediamine (TMEDA) tends to deaggregate these oligomers by complexation with the lithium. Thus, we thought that the dialkylaminoethoxy group might serve the same purpose in our studies (Figure 1).

The transmetallations of the lithio-derivatives of **4**, **5**, and **6** were performed in situ using tri(*n*-butyl)tin chloride and were instantaneous. Each reaction was quenched with 7 M aqueous potassium fluoride to precipitate tri-*n*-butyltin fluoride. The resulting compounds (**7**, **8**, and **9** from **4**, **5**, and **6**, respectively) were characterized in the usual way.

Aryl-, vinyl-, and allyltrialkylstannanes are smoothly transformed into a desirable functionalized derivative on treatment with the appropriate electrophile [13, 14]. The efficiency of such an approach was proven by the synthesis of deuterated and tritium-labelled tamoxifen [8]. 2-[Phenylseleno]phenoxy-β-[*N*,*N*-diethyl]ethylamine] **10** has now been prepared by the addition of **8** to a solution of phenylselenyl bromide in tetrahydrofuran (prepared in situ from diphenyl diselenide and bromide) to give, after chromatographic separation, the *ortho*-phenylseleno derivative **10**. This paves the way for the development of specifically substituted radioligands as therapeutic and/or diagnostic agents, since ^{75}Se is of interest in this regard.

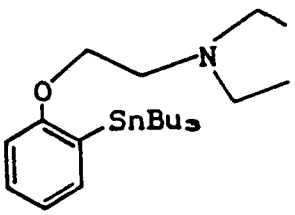


7 R = CH_3–

8 R = CH_3CH_2–

9 R =

FIGURE 1 *Ortho*-Stannylation of the Dialkylaminoethoxybenzens



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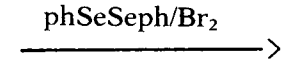

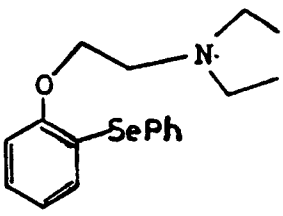

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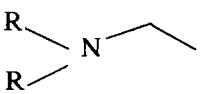
TABLE 1 Preparation and Stannylation of the β-[*N,N*-dialkylaminol]-ethoxy Derivatives of Phenols



	Yield %	Compound No.	Yield %	Compound No.
R = CH_3	85	4	75	7
R = CH_3CH_2	93	5	72	8
R + R = $(CH_2)_4$	78	6	63	9

The general reactivity of the organotin compound toward electrophilic destannylation is mainly confined to reactions of the tin–carbon bond in comparison with the corresponding bond between carbon and other group XIV elements (specially Se). Metal carbon bond strengths have been reviewed by Skinner [15] who noted that mean bond dissociation energies follow the order D (C–Se) > (C–H) > (C–Sn), and this is the main reason for the ease with which different electrophiles can be introduced via electrophilic destannylation. The cleavage of the aryl group in trialkyltin compounds by PhSeBr (**8** → **10**) thus proceeds via a simple electrophilic aromatic substitution mechanism similar to the cleavage by iodine in carbon tetrachloride [16].

EXPERIMENTAL

General Materials

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately prior to use. The phenol and the dialkylaminoethoxy derivatives were also distilled prior to use. *sec*-Butyllithium was purchased from Aldrich Chemical Company as 1.4 M or 1.2 M solutions in cyclohexane. All moisture-sensitive reactions were performed under a stream of N_2. Microdistillations were performed with a Kugelrohr distillation apparatus. Melting and boiling points are uncorrected. Infrared (IR) spectra were determined with a Perkin Elmer 567 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined using either a 60-MHz or a 100-MHz instrument, and chemical shifts are expressed in ppm downfield from tetramethylsilane. Significant ^{1}H-NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet), number of protons, coupling constant(s) in Hz. Flash chromatography was performed according to the procedure of Still [17] (silica gel 60, 240–400 mesh). Analytical thin layer chromatography (TLC) was performed using Merck 60 F-254 or Analtech GHLF precoated silica gel plates (0.25-mm layer thickness). Microanalyses were performed by Galbraith Laboratories, Knoxville, TN, and Spang Microanalytical Laboratory, Eagle Harbor, MI.

N-*2-Phenoxyethyl*-N,N-*dialkylamines* (**4, 5, 6**). To a solution of phenol (20 mmol) in 30 mL of ethanol was added sodium methoxide (40 mmol), and the reaction mixture was stirred for 30 min under N_2. β-[*N,N*-dimethylamino]ethyl chloride hydrochloride (20 mmol) was added in one portion followed by 30 mL of toluene. The reaction mixture was refluxed for 4 h under nitrogen and then cooled to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate. The organic phase was washed with 1 N sodium hydroxide solution and 2 N hydrochloric acid. The combined hydrochloric acid washes were made basic with solid sodium hydroxide. The aqueous phase was reextracted with ethyl acetate, and the combined organic extracts were washed with water and brine, and then dried with sodium sulfate. The solvent was removed under reduced pressure affording a yellow oil. Distillation of the product (Kugelrohr) gave **4**, **5**, and **6** as colorless oils in 85, 93, and 78% yield, respectively.

N-*2-Phenoxyethyl*-N,N-*dimethylamine* (**4**). 85%: ^{1}H-NMR ($CDCl_3$, 60 MHz, δ 2.25 (6H, s), 2.68 (2H, t, J = 6 Hz), 4.15 (2H, t, J = 6 Hz), 6.8–7.4 (5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 45.84, 58.24, 65.77, 114.21, 120.57, 159.10. Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.67; H, 9.17. Found: C, 72.44; H, 9.15.

N-*2-Phenoxyethyl*-N,N-*diethylamine* (**5**). 93%: ^{1}H-NMR ($CDCl_3$, 60 MHz, δ 1.2 (6H, t, J = 7 Hz); 2.70 (4H, q, J = 7 Hz), 2.95 (2H, t, J = 6 Hz), 4.18 (2H, t, J = 6 Hz); 6.85 (5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 22.01, 47.92, 51.88, 66.50, 114.22, 120.60, 129.31, 159.11. Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.55; H, 9.92. Found: C, 74.34; H, 9.97.

N-*2-Phenoxyethyl Pyrrolidine* (**6**). 78%: ^{1}H-NMR ($CDCl_3$, 60 MHz, δ 1.70 (4H, m), 2.59 (4H, m), 2.82 (2H, t, J = 6 Hz), 4.05 (2H, t, J = 6 Hz); 6.75–7.45 (5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 23.44, 54.67, 55.06, 66.88, 114.23, 120.57, 159.11. Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.33; H, 8.98. Found: C, 75.09; H, 9.06.

N-*2-(2-tri*-n-*butylstannylphenoxy)*-N,N-*dialkylamine* (**7, 8, 9**). To a solution of 4 mmol of the *N*-2-phenoxyethyl-*N,N*-dialkylamine in 10 mL of tetrahydrofuran at −78°C under N_2 was added a solution containing 6 mmol of *sec*-butyllithium dropwise via a syringe. After 7 h of stirring at −78°C, 6 mmol of tri-*n*-butylstannyl chloride was added. The reaction mixture was warmed to room temperature and 2 mL 7 M aqueous potassium fluoride was added. The reaction mixture was extracted with ethyl acetate, washed with water, and dried (sodium sulfate). Chromatography of the product on silica gel using a mixture of chloroform–methanol (9:1) as eluent followed by distillation (Kugelrohr) afforded the tributylstannyl derivatives **7**, **8**, and **9** respectively, as yellow oils.

N-*2(2-tri-butylstannylphenoxy)ethyl*-N,N-*dimethylamine* (**7**). 75%: ^{1}H-NMR ($CDCL_3$, 60 MHz, δ 0.8–1.7 (27H, m, *n*-Bu), 2.28 (6H, s), 2.7 (2H, t, J = 6 Hz), 4.5 (2H, t, J = 6 Hz); 6.7–7.5 (4H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 9.80, 13.70, 27.40, 29.15 (*n*-Bu), 46.03, 58.37, 65.90, 109.54, 120.12, 129.10, 137.22, 164.10. Anal. Calcd. for $C_{22}H_{41}ONSn$: C, 58.17; H, 9.10; N, 0.03. Found: C, 58.38; H, 9.24; N, 0.03.

N-*2(2-tri-n*-butylstannylphenoxy)ethyl-N,N-*diethylamine* (**8**). 72%: ^{1}H-NMR ($CDCl_3$, 60 MHz, δ 0.7–1.8 (27H, m, *n*-Bu and 6H, m), 2.64 (4H, q, J = 7 Hz), 2.82 (2H, t, J = 6 Hz); 4.2 (2H, t, J = 6 Hz), 6.7–7.5 (4H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 9.79, 13.79, 27.44, 29.25 (*n*-Bu), 22.20, 48.10, 52.10, 66.60, 109.61, 120.92, 129.63, 137.05, 162.0. Anal. Calcd. for $C_{24}H_{41}ONSn$: C, 59.77; H, 9.40; N, 0.03. Found: C, 59.99; H, 9.39; N, 0.03.

N-*2(2-tri*-n-*butylstannylphenoxy)ethyl Pyrroldine* (**9**). 63%: ^{1}H-NMR ($CDCl_3$, 60 MHz, δ 0.7–1.7 (27H, m, *n*-Bu), 1.8 (4H, m), 2.64 (4H, m), 2.95 (2H, t, J = 6 Hz), 4.15 (2H, t, J = 6 Hz); 6.75–7.5 (4H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 9.82, 13.76, 27.46, 29.22 (for *n*-Bu), 23.50, 54.67, 55.06, 66.55, 109.60, 120.91, 129.66, 137.07, 162.91. Anal. Calcd. for $C_{24}H_{43}ONSn$: C, 60.12; H, 9.02; N, 0.03. Found: C, 60.31; H, 9.33; N, 0.03.

2-[Phenylseleno]phenoxy)-[N,N-*diethyl]-ethylamine* (**10**). To a solution of 0.33 mmol of diphenyl diselenide in THF (3 mL) at 0°C, 0.314 mmol of bromine was added followed by 0.331 mmol of the *o*-stannylated derivative **8**. The reaction mixture was stirred at 0°C for 5 h and then warmed to room temperature, and 2 mL of 7 M aqueous potassium fluoride were added. The reaction mixture was extracted with ethyl acetate and washed with 10% hydrochloride acid. The combined hydrochloric acid washes were made basic and extracted with ethyl acetate. The organic layer was washed with water, dried (sodium sulfate), and concentrated to give an oil. Chromatography using a mixture of hexane and acetone (92:8) followed by distillation (Kugelrohr) gave 187.5 mg (78% yield) of **10** as yellow oil. ^{1}H-NMR ($CDCl_3$, 60 MHz), δ 1.22 (6H, t, J = 7 Hz), 2.78 (4H, q, J = 7 Hz), 3.0 (2H, t, J = 6 Hz), 4.2 (2H, t, J = 6 Hz), 6.8–7.88 (9H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ 23.57, 54.87, 68.00, 111.49, 121.62, 127.59, 127.98, 129.34, 130.70, 135.32: mass spectrum $M^+ \cdot$ 348. Anal. Calcd. for $C_{18}H_{23}ONSe$: C, 62.06; H, 6.66; N, 4.02. Found: C, 61.98; H, 6.60; N, 3.99.

ACKNOWLEDGMENTS

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