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Synthesis of 4-Stannylated Tamoxifen Analogues; Useful Precursors to Radiolabelled Idoxifene and Aziridinyl 4-Iodotamoxifen

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SUMMARY

The 4-stannylated tamoxifen analogues (*E*)-1-[4-[2-(*N*-pyrrolidino)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene and (*E*)-1-[4-[2-(aziridin-1-yl)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene have been synthesised as precursors to radiolabelled idoxifene, an important new drug for the treatment of breast cancer, and to aziridinyl 4-iodotamoxifen, a potentially useful biological research tool for studying the action of tamoxifen, respectively.

Keywords: (*E*)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene, Idoxifene, Tamoxifen, Aziridinyl 4-iodotamoxifen, Stannylation, Radioiodination.

INTRODUCTION

(*E*)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (Idoxifene, **1**) is an analogue of tamoxifen which incorporates an iodine atom in the 4-position, together with a pyrrolidinoethoxy side-chain[1]. The 4-iodine substituent prevents metabolic 4-hydroxylation, yet enhances binding affinity for the target estrogen receptor (ER)[2]. Idoxifene has a number of additional advantages over tamoxifen for the chemotherapy of breast cancer including higher antagonism of calmodulin-dependent processes[3], lower partial agonist activity, and increased cytotoxicity to breast cancer cells[4]. Idoxifene is presently in clinical trials for the treatment of breast cancer and it is important to develop a precursor to radioiodinated idoxifene to investigate its biodistribution. Radiolabelled idoxifene also has important potential applications in tumour imaging of estrogen receptor positive tissues such as the breast and uterus, and in targetted selective radiotherapy, since the

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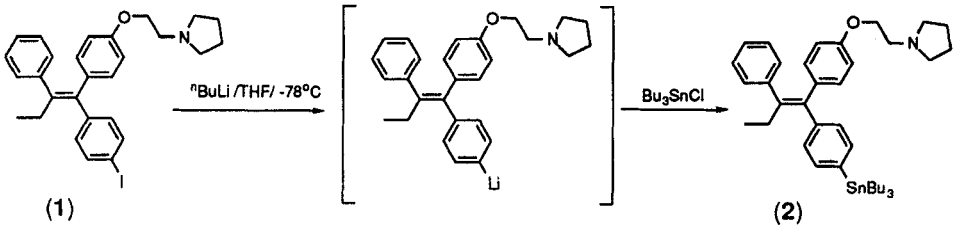
estrogen receptor, to which idoxifene has high affinity, is a nuclear hormone receptor which binds directly to DNA and would thereby allow the radio-emitter to be brought into close proximity to the nuclear DNA[5].

Scheme I



(1) (2)

RESULTS AND DISCUSSION

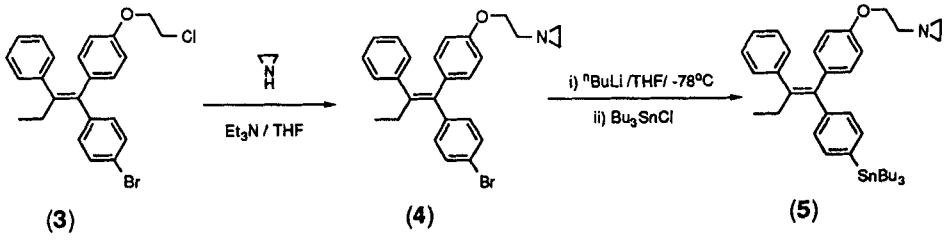
In order to specifically incorporate radioactive iodine into the 4-position we sought to prepare the 4-stannylated compound (*E*)-1-[4-[2-(*N*-pyrrolidino)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene (**2**), since it has previously been shown that arylstannanes undergo facile iodine exchange, that is iododestannylation, when treated with an electrophilic iodine source, such as iodine, iodine monochloride, or sodium iodide in the presence of a mild oxidising agent[6]. Indeed, this approach has been employed in the preparation of a stannylated tamoxifen analogue for radioiodination of the ortho position of the alkoxy-bearing phenyl ring[7]. However, this ortho-iodinated tamoxifen analogue has decreased affinity for the ER, and increased non-specific binding[8]. Idoxifene is an ideal candidate for incorporation of the radiolabel in the iodine atom, since the labelled compound is structurally identical to the unlabelled parent drug, and thus its biodistribution can be faithfully monitored. This is especially important in this type of receptor binding drug where subtle structural changes can have large effects on receptor binding[2] and hence biodistribution. Furthermore, the iodine atom of idoxifene should not be susceptible to metabolic displacement, since all the identified metabolites of the related compound 4-iodotamoxifen have the iodine atom present[9].

The required 4-stannylated compound **2** was prepared using pure *E*(*trans*) idoxifene itself as starting material. Treatment of idoxifene at low temperature with *n*-butyllithium generated the intermediate 4-lithio compound which was quenched with tributyltin chloride (Scheme I). Some tamoxifen derivatives are susceptible to olefinic stereomutation in the presence of radicals and since organostannanes can form radicals it was necessary to consider the possibility of stereoisomerisation in

the formation of **2**. It is crucial that the precursor for radioiodination is prepared in an isomerically pure form to avoid having to separate geometric isomers of the labelled compound. Importantly, this reaction afforded **2** as the desired *E*(*trans*) isomer without any unwanted interconvertion to the *Z*(*cis*) isomer, and the product is stereochemically stable. Additionally, this approach allowed introduction of the tin substituent specifically into the 4-position, without any unwanted ortho-stannylation[6] of the alkoxy-bearing phenyl ring. This was possible since butyllithium mediated lithiodehalogenation of a soft halogen, such as iodine or bromine, occurs much faster than lithiodeprotonation.

The aziridinyl 4-iodotamoxifen precursor (*E*)-1-[4-[2-(aziridin-1-yl)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene (**5**) was also required as a potentially useful biological research tool to further investigate the precise mechanisms of action of tamoxifen *in vitro*, since the radioiodinated product would be anticipated to bind covalently and hence irreversibly to receptor proteins, by alkylation through ring-opening of the aziridine group.

Scheme II



(3) (4) (5)

Synthesis of **5** was achieved via *E*(*trans*) aziridinyl 4-bromotamoxifen **4** (Scheme II). The starting material for this route (*E*)-1-(4-bromophenyl)-1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butene (**3**) has been previously prepared in stereochemically pure form by our stereoselective bromide trapping reaction[10]. However, in order to prepare larger quantities of this material it was found to be more convenient to use a modification of our method employed to prepare (*E*)-4-bromotamoxifen[2] by reaction of 4-bromophenyllithium with 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone[11] and separation of the resultant stereoisomers by crystallisation. Reaction of **3** with aziridine proceeded very slowly at room temperature and required the use of a higher reaction temperature (80°C) and a sealed vessel to achieve appreciable conversion to **4**. Triethylamine was also required in this reaction to protect the aziridinyl group from ring-opening. In the final step, despite the presence of the reactive aziridinyl group in **4**, lithiation occurred without attack of butyllithium on the aziridine ring, and the desired *E*(*trans*) 4-stannylated product **5** was obtained in good yield (67%).

EXPERIMENTAL

Tetrahydrofuran (THF) was the commercially available anhydrous grade from Aldrich Chemical Co. Ltd., and aziridine was obtained from Serva Feinbiochemica. (*E*)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene[2] (Idoxifene, **1**) and 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone[11] (**3**) were prepared as previously described. NMR spectra were recorded on a Bruker AC 250 instrument with TMS as internal standard, and mass spectra (MS, electron impact, 70 eV) on a VG7070H spectrometer with a VG2235 data station. Melting points were determined on a hot stage and are uncorrected. Petrol refers to light petroleum (b.p. 60-80° C). Ether refers to diethyl ether. Chromatography refers to column chromatography on silica gel (Merck 15111) with the eluent indicated applied at a positive pressure of 0.5 atm. TLC's were performed using fluorescent silica plates (Merck 5735) with the developing solvent indicated, and viewed using a mini-UV light (Camlab). Elemental analyses were carried out by CHN Analysis Ltd., South Wigston, Leicester, England.

(*E*)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene (2). To a solution of (*E*)-1-[4-[2-(*N*-pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene[2] **1** (2.00 g, 3.82 mmol) in dry THF (15 ml), under an argon atmosphere, and cooled to -78°C using an acetone/cardice bath, was added *n*-butyllithium (2.5 M; 1.7 ml, 4.20 mmol). After 5 min at -78°C a solution of tributyltin chloride (1.49 g, 4.58 mmol) in dry THF (4 ml) was added and the reaction mixture allowed to reach ambient temperature. The product (R_F 0.3) and starting material (R_F 0.2) could be distinguished by TLC (petrol-ether-triethylamine 4:4:1). The reaction mixture was then partitioned between ether (50 ml) and aqueous Na_2CO_3 (0.5 M; 50 ml). The organic phase was separated, dried (Na_2CO_3), and concentrated. Chromatography, on elution with petrol-ether-triethylamine (50:5:1) afforded the title compound **2** as a colourless oil (1.58 g, 60%). ^{1}H-NMR ($CDCl_3$) δ 0.87-1.09 (18H, m, $BuCH_2CH_3$ and $EtCH_3$), 1.27-1.62 (12H, m, $BuCH_2CH_2$), 1.89 (4H, m, $N(CH_2CH_2)_2$), 2.48 (2H, q, *J* 7.4 Hz, $EtCH_2$), 2.82 (4H, m, $N(CH_2CH_2)_2$), 2.99 (2H, t, *J* 5.6 Hz, OCH_2CH_2), 4.09 (2H, t, *J* 5.6 Hz, OCH_2CH_2), 6.55 (2H, d, *J* 8.8 Hz, ArH *ortho* to OR), 6.78 (2H, d, *J* 8.8 Hz, ArH *meta* to OR), 7.09-7.21 (7H, m, ArH), 7.42 (2H, d, *J* 7.8 Hz, ArH *ortho* to Sn). MS *m/z* 687 (M^+; ^{120}Sn). Found: C, 70.09; H, 8.60; N, 1.98. $C_{40}H_{57}NOSn$ [686.56] requires C, 69.97; H, 8.37; N, 2.04%.

(*E*)-1-(4-Bromophenyl)-1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butene (3). To a solution of 1,4-dibromobenzene (29.49 g, 125 mmol) in dry THF (150 ml), under a nitrogen atmosphere, and cooled to -78°C, was added *n*-butyllithium (2.5 M; 48 ml, 120 mmol). After 15 min a solution of 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone[11] (34.5 g, 114 mmol) in dry THF (100 ml) was added, and after 5 min the reaction mixture allowed to reach ambient temperature. The mixture was diluted with ethanol (250 ml), conc. HCl added (2 ml), and heated under reflux for 15 min then allowed to cool. The product (R_F 0.5) and the intermediate tertiary alcohol (R_F 0.2) could be distinguished by TLC (petrol-dichloromethane 1:1). The reaction mixture was then partitioned between ether (500 ml) and water (500 ml). The organic phase was separated, dried ($MgSO_4$), and concentrated to give the crude product as a mixture of *E* and *Z* isomers. Recrystallisation from petrol gave the product with an isomeric ratio (*E*/*Z*) of 15:1 (25.2 g, 50%). A second recrystallisation from petrol afforded the pure *E*(*trans*) isomer (19.6 g, 39%), spectroscopically identical to authentic material[10].

(*E*)-1-(4-Bromophenyl)-1-[4-[2-(aziridin-1-yl)ethoxy]phenyl]-2-phenyl-1-butene (4). To a solution of (*E*)-1-(4-bromophenyl)-1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butene **3** (896 mg, 2.03 mmol) in THF (50 ml) was added triethylamine (1.0 ml) followed by aziridine (1.5 ml) and the mixture heated in a steel bomb (Parr Scientific) at 80°C for 12h and allowed to cool. The reaction mixture was then partitioned between ether (50 ml) and water (25 ml). The organic phase was separated, dried (Na_2CO_3), and concentrated. Chromatography, on elution with petrol-ether (20:1) gave firstly unreacted starting material (750 mg, 84% recovery). Further elution with petrol-ether-triethylamine (25:25:1) afforded the title compound **4** (128 mg, 14% yield; 86% based on consumed starting material) which gave white crystals from hexane at -20°C, mp 90-92°C. ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, t, *J* 7.4 Hz, $EtC\underline{H}_3$), 1.22 and 1.78 (4H, 2 x m, $N(C\underline{H}_2)_2$), 2.45 (2H, q, *J* 7.4 Hz, $EtC\underline{H}_2$), 2.55 (2H, t, *J* 5.6 Hz, $OCH_2C\underline{H}_2$), 4.01 (2H, t, *J* 5.6 Hz, $OC\underline{H}_2CH_2$), 6.58 (2H, d, *J* 8.9 Hz, Ar<u>H</u> *ortho* to OR), 6.74 (2H, d, *J* 8.9 Hz, Ar<u>H</u> *meta* to OR), 7.09-7.20 (7H, m, Ar<u>H</u>), 7.47 (2H, d, *J* 8.4 Hz, Ar<u>H</u> *ortho* to Br). Found: C, 70.05; H, 5.94; N, 3.11. $C_{26}H_{26}BrNO$ [448.39] requires C, 69.64; H, 5.84; N, 3.12%.

(*E*)-1-[4-[2-(Aziridin-1-yl)ethoxy]phenyl]-1-[4-(tributylstannyl)phenyl]-2-phenyl-1-butene (5). To a solution of (*E*)-1-(4-bromophenyl)-1-[4-[2-(aziridin-1-yl)ethoxy]phenyl]-2-phenyl-1-butene **4** (64 mg, 0.14 mmol) in dry THF (2 ml), under an argon atmosphere, and cooled to -78°C, was added *n*-butyllithium (1.6 M; 0.1 ml, 0.16 mmol) via a μ-syringe through a septum inlet. After 5 min at -78°C a solution of tributyltin chloride (56 mg, 0.17 mmol) in dry THF (1 ml) was added and

after 20 min the reaction mixture was allowed to reach ambient temperature. The product (R_F 0.5) and starting material (R_F 0.3) could be distinguished by TLC (petrol-ether-triethylamine 4:4:2). The reaction mixture was then partitioned between ether (15 ml) and saturated aqueous $NaHCO_3$ (15 ml). The organic phase was separated, dried (Na_2CO_3), and concentrated. Chromatography, on elution with petrol-ether-triethylamine (20:2:1) afforded the title compound **6** as a colourless oil (62 mg, 67%). ^{1}H-NMR ($CDCl_3$) δ 0.86-1.09 (18H, m, $BuCH_2CH_3$ and $EtCH_3$), 1.27-1.62 (12H, m, $BuCH_2CH_2$), 1.20 and 1.77 (4H, 2 x m, $N(CH_2)_2$), 2.50 (2H, q, *J* 7.4 Hz, $EtCH_2$), 2.54 (2H, t, *J* 5.6 Hz, OCH_2CH_2), 4.00 (2H, t, *J* 5.6 Hz, OCH_2CH_2), 6.57 (2H, d, *J* 8.8 Hz, ArH *ortho* to OR), 6.78 (2H, d, *J* 8.8 Hz, ArH *meta* to OR), 7.09-7.19 (7H, m, ArH), 7.41 (2H, d, *J* 7.8 Hz, ArH *ortho* to Sn). Found: C, 69.82; H, 8.54; N, 2.46. $C_{38}H_{53}NOSn$ [658.50] requires C, 69.31; H, 8.11; N, 2.13%.

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