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Preliminary communication

IODODESTANNYLATION. POSITION-SPECIFIC SYNTHESIS OF IODOTAMOXIFEN

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Summary

A procedure has been developed for the synthesis of iodotamoxifen 3 from tamoxifen (1), an anti-estrogenic agent currently employed in the treatment of breast cancer. Ortho-directed metalation of tamoxifen with sec-butyllithium at -78°C followed by addition of tri-n-butyltin chloride gave the stannyl derivative 2 in 98% isolated yield. Iododestannylation of 2 at 0°C with iodine afforded the desired iodotamoxifen 3 in quantitative yield. The dimethylaminoethoxy group appears to be more strongly activating for ortho metalation than methoxy.

Tamoxifen (1), an anti-estrogenic compound currently employed in the treatment of estrogen-dependent breast carcinoma, is thought to act by competing with endogenous estradiol for binding to cytoplasmic estrogen receptor proteins [2]. This cytoplasmic drug-receptor complex is then translocated to the nucleus [3]. The use of radiolabeled tamoxifen should therefore effect a higher concentration of the isotope in the nuclei of tumor cells than in normal tissues, a necessary condition for the therapeutic use of an internally emitting radionuclide in the treatment of cancer. A radioactive label ideally

suited for this purpose is ^{125}I, an Auger electron emitter which produces an extremely localized deposition of energy. The radiotoxicity of ^{125}I incorporated into DNA as 5-[^{125}I]-iododeoxyuridine has been demonstrated by cell death and DNA strand breaks in bacteria and in mammalian cells [4]. As part of a program to synthesize and evaluate position-specific radiolabeled agents for diagnostic and therapeutic use, we required the iodinated and ^{125}I-radioiodinated derivatives 3 of tamoxifen.

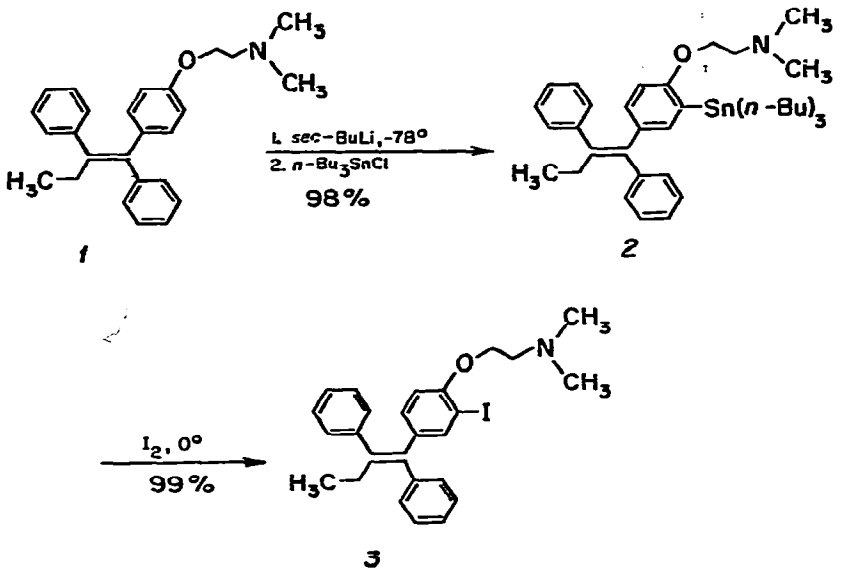
Iodination techniques based on electrophilic substitution often suffer from lack of regiospecificity and may afford complex mixtures of products. This renders the synthesis and isolation of a single derivative, substituted at a specific position, potentially difficult. Indeed, all attempts at direct iodination of tamoxifen using iodine, iodine monochloride or sodium iodide and chloramine-T gave complex and unresolvable mixtures. Iodination procedures utilizing mercury (II) acetate or thallium (III) trifluoroacetate were likewise unsuccessful.

The tributylstannyl derivative 2, however, is an attractive precursor to 3. The striking reactivity of aryltrialkylstannanes has been utilized synthetically to introduce a variety of electrophiles onto otherwise unreactive aromatic systems [5]. A particularly noteworthy feature of these destannylation reactions is the obtention of only a single isomer. Regiochemical control in the synthesis of 3 would therefore be assured by the preparation of 2.

The heteroatom-facilitated ortho metalation of benzene derivatives is a well established reaction and has become a powerful tool for synthesizing 1,2-disubstituted aromatic compounds [6]. A wide variety of functional groups, including ethers, amines, imines, amides, sulfonamides and oxazolines, are capable of directing ortho metalation. The dimethylaminoethoxy group seems particularly suited to activate tamoxifen toward ortho metalation by a combination of inductive and coordination effects associated with an ether oxygen, and possible 1:1 complexation of the alkyllithium by the bidentate aminoether. The rate of a number of ortho metalation reactions has been greatly increased by the addition of tetramethylethylenediamine (TMEDA), a chelating agent which forms 1:1 complexes with n-butyllithium and sec-butyllithium [7].

Reaction of tamoxifen (1) with sec-butyllithium in a mixture of tetrahydrofuran and cyclohexane at -78° C for seven hours followed by addition of tri-n-butyltin chloride gave the desired stannyl derivative 2 [8] in 98% yield after purification by column chromatography (Scheme 1). Metalation of 1 could also be accomplished with n-butyllithium in a mixture of tetrahydrofuran and hexane at 0° C for seven hours. Thus, the dimethylaminoethoxy group appears to be more strongly activating for ortho metalation than methoxy [9] but less activating than a tertiary benzamide [10]. The rate of the metalation using n-butyllithium or sec-butyllithium appeared to be insensitive to

SCHEME 1



added TMEDA, an observation which supports the postulated complexation of alkyllithium with the internal bidentate ligand, dimethylaminoethoxy.

Treatment of 2 at 0°C with iodine in chloroform afforded the desired iodotamoxifen 3 essentially instantaneously in quantitative yield. No double bond isomerization was observed on exposure of tamoxifen to the iodination conditions employed for conversion of 2 to 3. The ortho relationship of the substituents in 2 and 3 was established by ^{1}H and ^{13}C NMR. Significantly, 3 is formed devoid of any uniodinated tamoxifen, an essential condition for accurate measurement of receptor binding affinity.

Because of the number of biologically active molecules containing an appropriately functionalized aromatic residue capable of ortho-directed metalation, this two step procedure for the position-specific introduction of an electrophile, such as iodine, is highly recommended. Our own further efforts in this area, including the details of the synthesis, biodistribution, cellular uptake and cytotoxicity of ^{125}I-iodotamoxifen 3, will be described in due course. The application of this method to other dialkylaminoethoxy substituted compounds is currently being investigated.

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