Synthesis of 17α-(Iodovinyl)estradiol and Analogous Derivatives by Iododestannylation of Insoluble Polymer-Supported Organotin Precursors

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Keywords: Polymer-supported organotin hydride / Steroids / Iodinated estrogens

Iodoestrogen derivatives were prepared by iododestannylation of insoluble polymer-supported organotin precursors.

Introduction

Radiopharmaceuticals are drugs containing unstable nuclei which emit nuclear particles or photons. These medical imaging agents are of interest for diagnosis and radiotherapy of various diseases.

Compounds bearing γ-emitting radioisotopes such as ^{123}I are commonly used in SPECT (Single Photon Emission Computerized Tomography) detection. Radioiodinated derivatives are frequently prepared from organotin precursors.[1][2] The iododestannylation reaction is fast, as well as regio- and stereoselective. Furthermore, high yields can be obtained under mild conditions.

However, the complete elimination of these precursors or their by-products can be difficult. In order to avoid traces of polluting organotin residues in the reaction products, the organotin precursor can be anchored onto an insoluble solid support;[3][4] the radiopharmaceutical will be released into solution. Few papers report the utilization of these reagents.[5−8]

Studies of some breast and ovarian cancers have shown the presence of selective estrogen receptors in the tumorous cells. Therefore, radioiodinated estrogens like 17α-(iodovinyl)estradiol and analogous derivatives have been used as imaging agents due to their high specificity and their stability in vivo.[9] These compounds are prepared by iododestannylation of organotin compounds. For the reasons previously reported, we have prepared iodinated estrogens from insoluble polymer-supported organotin precursors.

Results and Discussion

In this study, we have used an insoluble polymer-supported organotin hydride, P−$[CH_2]_4SnBu_2H$ (**1**; P: polystyrene),[10] in order to perform the hydrostannation of 17α-ethynylestradiol (**2**),[11][12] and its derivatives mestranol (**3**)[13] and moxestrol (**4**)[14] (Scheme 1).

These hydrostannation reactions were performed with the polymer **1** (tin hydride content: 0.83 mmol/gram of polymer) in the presence of AIBN in refluxing THF for 8 h. The conversion rates (80%, 82% and 75% for **2**, **3** and **4**, respectively) have been evaluated from the amounts of recovered starting estrogen derivatives.

Iododestannylation reactions were performed in dichloromethane solution, for 15 h at room temperature, with excess iodine (4 equiv.) because of partial adsorption on the polymer. Under these conditions, using 17α-(tributylstannylvinyl)estradiol [prepared from 17α-ethynylestradiol (**2**) and tributyltin hydride], we have checked that iododestannylation retains the configuration of the C=C bond. Iodosteroids, easily recovered from the reaction mixture by simple filtration, were analyzed by HPLC.

The iododestannylation of the estradiol adduct **5** led to a mixture of diastereoisomers **8a** (*E*) and **8b** (*Z*), (**8a**/**8b** ≈ 98:2); we have also observed the presence of a small amount of 17α-vinylestradiol (**11**; Scheme 2) generated by protodestannylation of **5** (Table 1).

On the other hand, the iododestannylation of adducts **6** and **7**, prepared from mestranol (**3**) and moxestrol (**4**), respectively, led to the formation of *E* (**9a**, **10a**), *Z* (**9b**, **10b**) and *gem* (**9c**, **10c**) (Scheme 2) isomers (Table 1). In all cases, the *E* isomers were the major compounds.

The configurations of iodovinyl compounds have been determined using ^1H and ^{13}C NMR, based on the characteristic coupling constants ($^3J_{HH}$) between vinylic hydrogen atoms: approximately 14 Hz for *E* isomers and 8.6 Hz for *Z* isomers (Table 2).

Conclusion

This report shows that polymer-supported organotin intermediates can be used as precursors for (iodovinyl)estradiol and related compounds. The iodide derivatives were obtained directly in good yields, free of organotin groups, as proved by HPLC and ^1H NMR, without later purification. This method can be applied to the preparation of radioiodinated compounds as described in a previous paper.[15] Indeed, the utilization of polymer-supported reagents strongly improves the purification of compounds

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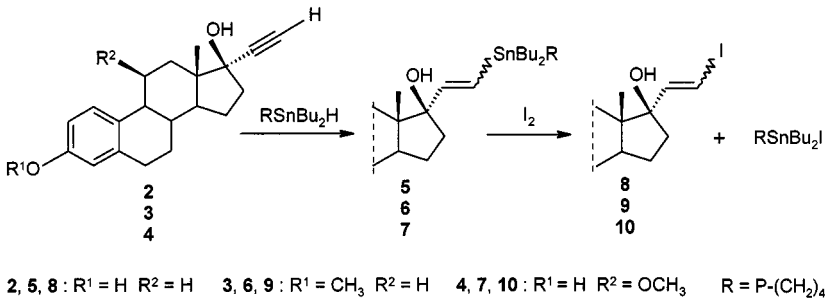
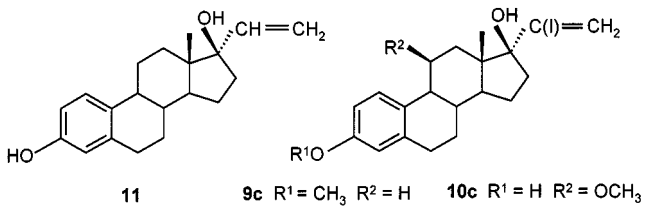


Scheme 1. Hydrostannation of estrogen derivatives **2**, **3** and **4** and iododestannylation of polymer-supported adducts **5**, **6** and **7**



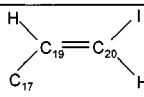
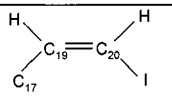
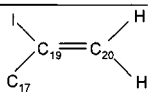
Scheme 2. By-products formed during the iododestannylation of **5**, **6**, and **7**

Table 1. Iododestannylation of polymer-supported organotin precursors **5**, **6** and **7**

Polymer-supported organotin precursors	Yield (%)	Isomers (%) *E*	*Z*	others
5	61	**8a** (95%)	**8b** (2%)	**11**[a] (3%)
6	40	**9a** (83%)	**9b** (14%)	**9c**[b] (3%)
7	48	**10a** (83%)	**10b** (10%)	**10c**[b] (7%)

[a]17α-Vinylestradiol. − [b]*gem* isomers.

Table 2. NMR data (^{1}H and ^{13}C) of iodoestrogen derivatives **8**, **9** and **10**

				
8	δ_H	6.75 and 6.23	6.73 and 6.43	
	J_{HH} (Hz)	14.3	8.6	
	δ_C (C_{19} C_{20})	152.4 74.8	145.0 77.4	
9	δ_H	6.84 and 6.34	6.89 and 6.42	6.46 and 6.18
	J_{HH} (Hz)	14.5	8.6	2.3
	δ_C (C_{19} C_{20})	150.4 74.6	143.3 87.4	73.3 126.9
10	δ_H	6.87 and 6.36	6.85 and 6.43	6.48 and 6.19
	J_{HH} (Hz)	14.5	8.6	2.3
	δ_C (C_{19} C_{20})	151.1 75.5	144.3 88.0	75.4 128.8

and leads to a very low level of tin pollution as shown by atomic absorption and ICP−MS.[16]

Experimental Section

General: NMR spectra were recorded with a Bruker AC 250 spectrometer operating at 250 and 62.9 MHz for ^{1}H and ^{13}C resonance frequencies, respectively. Products were dissolved in [D_6]DMSO. Tetramethylsilane was used as internal standard. − HPLC analyses were performed on column A (Nucleosil phenyl, 7 μm, 250 × 4.6 mm), column B (Nucleosil C 18, 5 μm, 250 × 4.6 mm) or column C (Nucleosil C 18, 10μm, 250 × 4.6 mm).

Polymer-Supported Tin Hydride: Compound **1** was prepared from Amberlite XE 305, a monofunctional macroporous polystyrene cross-linked with divinylbenzene (Rohm and Haas).[10] The SnH content (0.83 mmol per gram of polymer) was evaluated from the amount of decane formed during the reduction of 1-bromodecane by **1**.

Addition of 1 to Estrogen Derivatives: In a Schlenck tube, under nitrogen, a mixture of polymer **1** (2.10 g, 1.74 mmol SnH), 17α-ethynylestradiol (**2**; 0.43 g, 1.45 mmol), AIBN (0.014g, 0.08 mmol) and dry THF (30 mL) was stirred and heated at reflux for 8 h. After 4 h, a second portion of AIBN (0.08 mmol) was added. The polymer was filtered and washed several times with THF. After evaporation of the solvent, the amount (0.086 g, 0.29 mmol) of 17α-ethynylestradiol recovered allows for the evaluation of the conversion yield (80%). The polymer was dried in vacuo at 60°C. Polymer **5** (2.4 g) containing 1.16 mmol of the estradiol moiety was obtained. Similar procedures were used for mestranol (**3**) and moxestrol (**4**).

Preparation of 17α-(Iodovinyl)estradiol (8): In a Schlenck tube, under nitrogen, in the dark, polymer **5** (2.0 g, 0.97 mmol estradiol), iodine (0.98 g, 3.88 mmol) and dichloromethane (25 mL) were stirred at room temperature for 15 h. After filtration, the polymer was washed several times with dichloromethane. The organic layers were washed with a solution (0.1 M) of sodium thiosulfate and water and then dried with sodium sulfate. After evaporation of the solvent, the crude 17α-(iodovinyl)estradiol (**8**; yield: 61%) was analyzed. HPLC: column A; eluent: MeOH (85%), H_2O (15%), 1 mL/min; retention times: 4.0 min [17α-vinylestradiol (**11**)], 4.4 min (*E* isomer **8a**), 5.2 min (*Z* isomer **8b**). − ^{1}H NMR of vinylic protons: δ = 6.23 and 6.75, $^3J_{HH}$ = 14.3 Hz for **8a**; δ = 6.43 and 6.73, $^3J_{HH}$ = 8.6 Hz for **8b**. − ^{13}C NMR: δ = 152.0 (C-19) and 74.8 (C-20) for **8a**; δ = 145.0 (C-19) and 77.4 (C-20) for **8b**; the other NMR data are in agreement with those of the estrogen skeleton. NMR data of **11** have been compared with those of 17α-vinylestradiol prepared by protodestannylation of 17α-(tributylstannylvinyl)estradiol.

Preparation of 17α-(Iodovinyl)mestranol (9): In a similar procedure, the crude product **9** was prepared from polymer **6** (yield: 40%). HPLC: column B; eluent: MeOH, 1.2 mL/min; retention times: 3.3 min (*gem* isomer **9c**), 4.0 min (*E* isomer **9a**), 4.3 min (*Z* isomer **9b**). − ^{1}H NMR of vinylic protons: δ = 6.34 and 6.84, $^3J_{HH}$ = 14.5 Hz for **9a**; δ = 6.42 and 6.89, $^3J_{HH}$ = 8.6 Hz for **9b**; δ = 6.18 and 6.46, $^2J_{HH}$ = 2.3 Hz for **9c**. − ^{13}C NMR : δ = 150.4 (C-19) and 74.6 (C-20) for **9a**; δ = 143.3 (C-19) and 87.4 (C-20) for **9b**; δ = 73.3 (C-19) and 126.9 (C-20) for **9c**.

Preparation of 17α-(Iodovinyl)moxestrol (10): In a similar procedure, the crude product **10** was prepared from polymer **7** (yield: 48%). HPLC: column C; eluent: MeOH (90%), H_2O (10%), 1 mL/min; retention times: 4.2 min (*E* isomer **10a**), 5.1 min (*gem* isomer

10c), 5.5 min (*Z* isomer **10b**). – ^{1}H NMR of vinylic protons: δ = 6.36 and 6.87, $^3J_{HH}$ = 14.5 Hz for **10a**; δ = 6.43 and 6.85, $^3J_{HH}$ = 8.6 Hz for **10b**; δ = 6.19 and 6.48, $^2J_{HH}$ = 2.3 Hz for **10c**. – ^{13}C NMR : δ = 151.1 (C-19) and 75.5 (C-20) for **10a**; δ = 144.3 (C-19) and 88.0 (C-20) for **10b**; δ = 75.4 (C-19) and 128.8 (C-20) for **10c**.

Acknowledgments

The authors are grateful to the Conseil Régional d′Aquitaine for financial support and to Rohm and Haas for the gift of Amberlite XE 305.

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Received August 28, 1998
[O98395]