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APPLICATIONS OF 2,5-BIS(TRIMETHYLSTANNYL)THIOPHENE.
SYNTHESIS OF 3-METHOXY-17α-(5-IODOTHIEN-2-YL)-ESTRA-1,3,5(10)TRIEN-17β-OL

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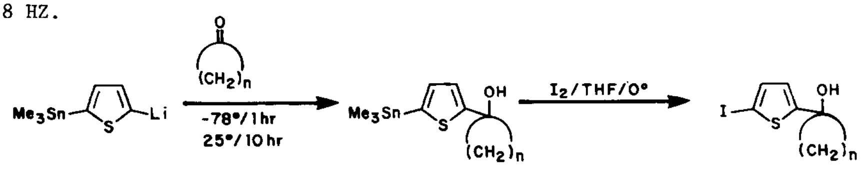
Abstract. Monotransmetallation of 2,5-bis(trimethylstannyl)thiophene followed by the addition of estrone 3-methyl ether and iodine yields 3-methoxy-17α-(5-iodothien-2-yl)estra-1,3,5(10)trien-17β-ol.

We have sought to employ bis(trialkylstannyl)ethylenes and -arenes as synthetic intermediates in which sequential replacement of the trialkylstannyl moieties results in the incorporation of the biologically active moiety and a radionuclide. Initially the synthesis of E-1,2-bis(tributylstannyl)ethylene[1] as well as its use in the preparation of radiolabeled iodovinyl estrogens[2,3] and the synthesis of 2,5-bis(trimethylstannyl)thiophene and its functionalization[4] were described. We wish to report here the preparation of 17α-substituted estrogen capable of being radiolabeled in high specific activity.

Before the synthesis of the target compound was undertaken, cyclopentanone and cyclohexanone were chosen as model compounds to explore the addition reaction of 2-lithio-5-trimethylstannylthiophene (1) to ketones. Thus, (1) was generated as previously described and allowed to react with the ketone in THF (Scheme 1). Compounds (2) (bp: 130-131°C; 0.5 torr) and (3) (mp: 54.5-56.5°C) could be readily isolated by reversed phase column chromatography in 63% and 66% yields respectively. The reaction of the 1-(5-trimethylstannylthien-2-yl)-cycloalkan-1-ols with 0.1 M iodine in THF resulted in an immediate discharge of the brown color. The reaction mixture was washed with an aqueous sodium thiosulfate solution and the products (4) and (5) were isolated in 90% and 93% yields after filtration through silica gel. The ^{1}H-NMR spectra displayed distinct doublets corresponding to the C-3 and C-4 protons with J = 3.8 HZ.



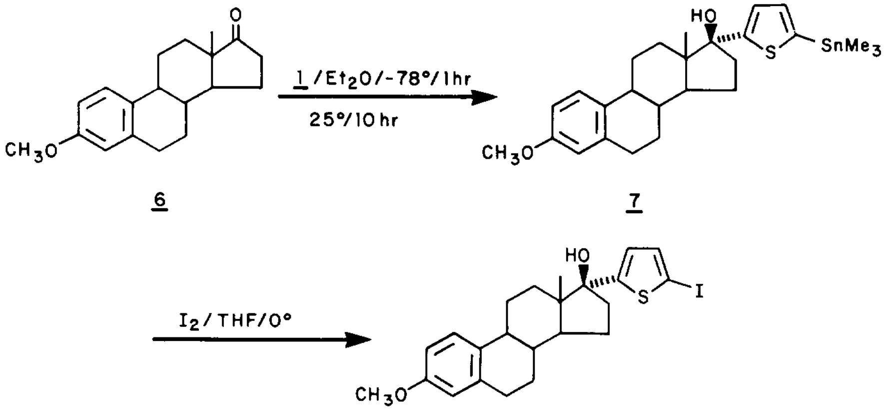
1

2 n = 4
3 n = 5

4 n = 4
5 n = 5

Scheme 1

In the same fashion, (1) reacted with 3-methoxyestra-1,3,5(10)trien-17-one (6) to give the 17α-derivative (7) (mp: 84-87°C) in 50% yield after reversed phase chromatography (Scheme 2). The ^{1}H-NMR spectrum of (7) showed characteristic peaks at 0.35 ppm (s, 9H) due to the trimethylstannyl group, at 1.05 ppm (s, 3H) for the angular methyl and at 3.70 ppm (s, 3H) for the methyl ether[5]. The infrared spectrum displayed a hydroxy stretching band at 3600 cm^{-1} and the compound exhibited optical activity $[\alpha]^{25}_{546} = +61^{\circ}$. Therefore, the stereochemical assignment at the C-17 position as shown would be sufficient based on the demonstrated tendency of organometallic reagents to undergo α-addition to the 17-ketone of estrone[6,7]. The subsequent addition of iodine in THF at $0^{\circ}C$ gave intermediate destannylation and the target compound (mp: 110-112°C) was isolated in 90% yield after filtration through silica gel[8]. As anticipated (8) showed optical activity with $[\alpha]^{25}_{546} = +88^{\circ}$.



Scheme 2

8

Therefore we have illustrated the utility of the bis(trimethylstannyl)arene for the synthesis of functionalized compounds. The ease with which the trialkylstannyl moiety can be replaced by a radiohalogen will allow for the facile preparation of the corresponding radiolabeled derivatives in high specific activity.

Acknowledgement

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5. 7: IR (CCl_4-cm^{-1}): 3600,3050,2920,1610,1550,1500; ^{1}H-NMR ($CDCl_3$-TMS; ppm): 0.35(s, 9H), 1.05(s, 3H), 1.20-3.02(br, 16H), 3.7 (s, 3H), 6.50-7.20(m, 5H); $[\alpha]^{25}_{546}$ ($CHCl_3$): $+61^{\circ}$; m/e:532 (m + 1); TLC (KC 18F): $R_f = 0.22(H_2O: CH_3OH = 1:4)$
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8. 8: IR ($CHCl_3$-cm^{-1}): 3600,3010,2920,1600,1500; ^{1}H-NMR ($CDCl_3$-TMS, ppm): 1.03(s, 3H), 1.22-3.03(br, 16H), 3.70(s, 3H), 6.60-7.08(m, 5H); $[\alpha]^{25}_{546}$ ($CHCl_3$): $+88^{\circ}$; m/e:495(m + 1); TLC (KC 18F): R_f = 0.28 (hexane: ether = 4:1)

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