

Efficient Synthesis of 2-Methoxy- and 4-Methoxy-estrogens

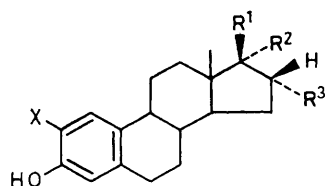
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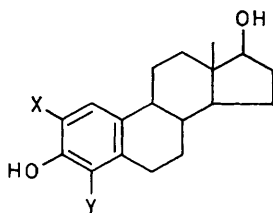
2-Methoxy- and 4-methoxy-estrogens are easily prepared from the corresponding 2-iodo or 4-bromo derivatives in high yields by a halogen-methoxy group exchange reaction using sodium methoxide-copper(II) chloride.

The physiological significance of catechol estrogens, a group of major estrogen metabolites formed by aromatic hydroxyla-

tion of primary estrogens at either the C-2 or C-4 position, is now well documented.¹ Catechol estrogens are further metab-



- (1) R¹ = OH, R² = R³ = H, X = H
 (2) R¹ = OH, R² = R³ = H, X = Br
 (3) R¹ = OH, R² = R³ = H, X = I
 (4) R¹ = OH, R² = R³ = H, X = OMe
 (5) R¹, R² = O, R³ = H, X = I
 (6) R¹, R² = O, R³ = H, X = OMe
 (7) R¹ = R³ = OH, R² = H, X = I
 (8) R¹ = R³ = OH, R² = H, X = OMe



- (9) X = Y = Br
 (10) X = H, Y = Br
 (11) X = H, Y = OMe

olized to their monomethyl ethers, in which 2-methylation^{1a,b} or 4-methylation² generally predominates. The biological activity of the 2-methyl ethers is becoming increasingly evident.³

A practical synthesis of 2-methoxy-estrogens was first reported by Fishman.⁴ Since then many synthetic procedures have been reported for the 2-methoxy⁵ and 4-methoxy^{5a,b} derivatives, the most interesting of which^{5d} involves a direct conversion of 2-bromoestradiol (2) into the corresponding methoxy derivative (4); this procedure, however, requires a long reaction time (22 h), and the yield is not satisfactory (50%). We now describe a new, efficient, and simple method for introducing a methoxy group at C-2 and C-4 of estrogens via the corresponding 2-iodo-⁷ or 4-bromo-estrogens, which can be obtained regioselectively in high yields.

When 2,4-dibromoestradiol (9) was catalytically hydrogenated over 5% palladium-on-charcoal (EtOH, 1 atm, room temp.) until absorption of hydrogen (ca. 1 equiv.) stopped, selective debromination occurred at the C-2 position to give 4-bromoestradiol (10)⁸ (80%).

Treatment^{5d} of 2-iodoestradiol (3) with NaOMe (10 mol. equiv.) in MeOH-dimethylformamide (DMF) in the presence of CuI (0.33 mol. equiv.) unexpectedly gave the reductively dehalogenated product, estradiol (50%), along with the desired 2-methoxy compound (4) (3%). When the iodide (3) was submitted to the same reaction using CuCl₂⁹ instead of CuI, however, the methoxyestrogen (4) [m.p. 188–189 °C (lit.⁴ 188–190 °C); ¹H n.m.r. δ (CDCl₃-CD₃OD) 0.80 (3H, s, 3 × 18-H), 3.87 (3H, s, 2-OCH₃), 6.64 (1H, s, 4-H), and 6.80 (1H, s, 1-H)] was quantitatively obtained after only brief treatment (5 min). Other 2-iodo compounds (5) and (7) were also converted into the corresponding methoxyestrogen (6) (30%) [m.p. 185–187 °C (lit.⁴ 188–191 °C), ¹H n.m.r. δ (CDCl₃) 0.90 (3H, s, 3 × 18-H), 3.83 (3H, s, 2-OCH₃), 6.62 (1H, s, 4-H), and 6.75 (1H, s, 1-H)] and (8) (45%) [m.p. 212–214 °C (lit.^{5b} 211–214 °C), ¹H n.m.r. δ (CDCl₃-CD₃OD) 0.74 (3H, s, 3 × 18-H), 3.79 (3H, s, 2-OCH₃), 6.54 (1H, s, 4-H), and 6.70 (1H, s, 1-H)] using the same reaction (Table 1). Furthermore, the yield of the

Table 1. Conversion of halogeno into methoxy compounds.^a

Substrate	Conditions		Product (isolated yield, %)
	Solvent	t/min	
(3)	DMF	5	(4) (95) ^b
(3)	Pyridine	20	(4) (1.3) ^c
(5)	DMF	15	(6) (30) ^c
(5)	Pyridine	30	(6) (65) ^b
(7)	DMF	10	(8) (44) ^b
(7)	Pyridine	15	(8) (20) ^c
(10)	DMF	75	(11) (75) ^b

^a Substrate (1 mmol) was dissolved in 4 ml of solvent. To this solution were added 2.0 ml of a 5.1 M solution of NaOMe in MeOH and CuCl₂ (0.33 mmol) and the reaction mixture was refluxed under an N₂ atmosphere. ^b The crude product obtained after the usual work-up was crystallized to give a pure product. ^c The product was purified by column chromatography.

methoxyestrogen (6) (only) was much improved (65%) when pyridine was used as a solvent (Table 1).

When 4-bromoestradiol (10) was treated similarly with NaOMe in DMF, the corresponding 4-methoxyestradiol (11) [m.p. 166–168 °C (lit.⁸ 167–169 °C), ¹H n.m.r. δ (CDCl₃-CD₃OD) 0.75 (3H, s, 3 × 18-H), 3.78 (3H, s, 4-OCH₃), 6.73 (1H, d, *J* 9 Hz, 2-H), and 6.98 (1H, d, *J* 9 Hz, 1-H)] was obtained in 75% yield.

In addition to its simplicity and the high yields obtained, the obvious advantages of this sequence are that substrates, 2-iodo- or 4-bromo-estrogens, can be obtained regioselectively in high yields and that catechol estrogens can be synthesized from primary estrogens in a relatively short step through the demethylation^{5b} of the 2- or 4-methoxy derivatives.†

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† In a recent report (X. U.-Z. Zheng, W. L. Wang, Z.-Z. Zhong, Z.-B. Xu, and H.-M. Zhao, *Steroids*, 1982, 40, 121) 2,4-dibromoestradiol (9) was converted into the 2,4-dimethoxy analogue using NaOMe-CuI-benzo-15-crown-5-DMF in 40% yield. It is interesting to speculate on the results when using a crown ether in the reactions described in the present communication.