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SYNTHESIS OF C-16 EXOCYCLIC DIPOLAROPHILES VIZ. (E)-16-ARYLIDENE ESTRONES

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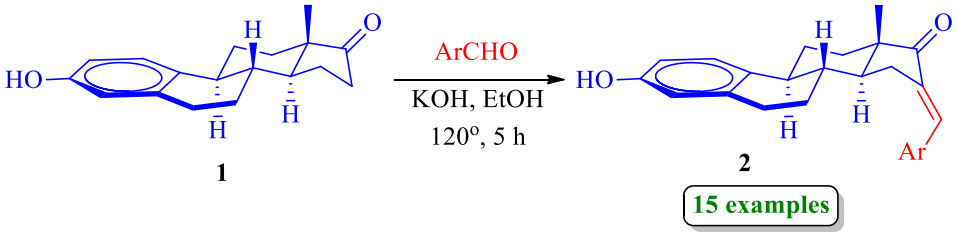
Abstract

In the present work, the C-16 exocyclic dipolarophiles *viz*. (*E*)-16-arylidene estrones **2** were synthesized from the reaction of estrone **1** with various aromatic aldehydes (**Scheme 1**). An equivalent mixture of estrone and the appropriate aldehyde were dissolved in ethanol followed by the addition of alcoholic potassium hydroxide. The mixture was boiled to reflux for 5 h and the completion of the reaction was realized when the (*E*)-16-arylidene estrones **2** precipitated out of the reaction mixture as yellow solid, which was filtered and washed with water. A total of fifteen (*E*)-16-arylidene estrones **2a–o** were synthesized in almost quantitative yields (>91 %, **Table 1**). However, the reaction failed to occur with aliphatic aldehydes.

Introduction



Steroids form a group of structurally related compounds, which are widely distributed in animals and plants. They possess a lipophilic cyclopentanoperhydro-phenanthrene skeleton (**Figure 1**), or a derivative thereof.[4] Steroidal hormones (chemical messengers) play a critical role in endocrine systems which control the regulation of metabolic processes. These hormones stimulate biological responses in an extensive range of tissues to influence endocrine processes such as sexual differentiation, reproductive physiology, and maintenance of salt balance and sugar metabolism.[5]

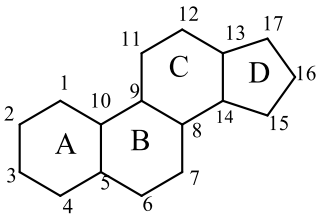


Figure 1. Steroid skeleton, numbering and ring notation

The most important classes of steroids are the sex hormones (estrogens and androgens), progestins, mineralcorticoids, glucocorticoids, vitamin D and its derivatives, bile acids, and sterols found in cell membranes (**Figure 2**). Synthetic derivatives of steroids have also attracted a good deal of attention for the purpose of developing drugs to treat hormone related disease.

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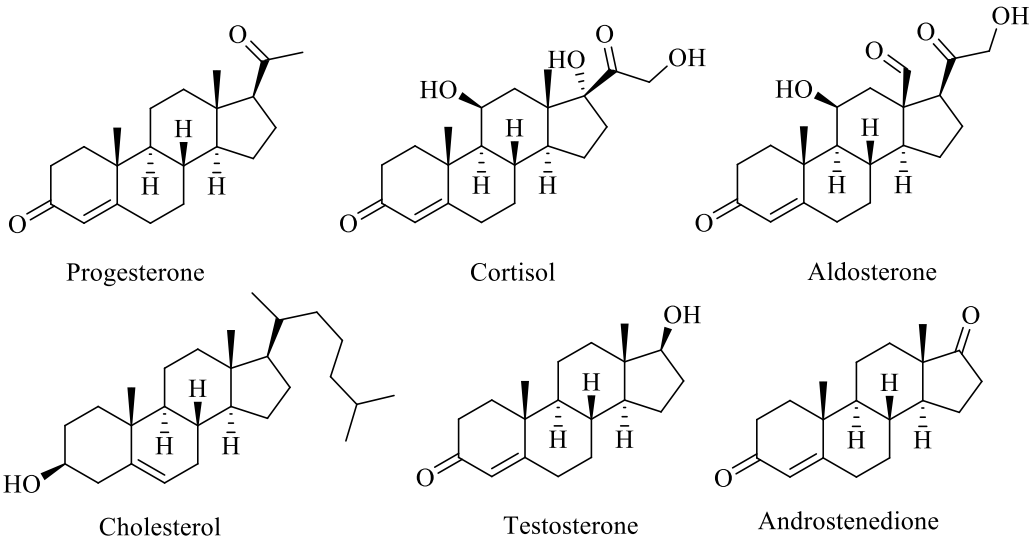

Figure 2. Some naturally occurring steroids

Significances of estrone

Estrone (oestrone) was the first estrogenic hormone to be isolated in crystalline form from the urine of pregnant women. Estrone is secreted by the ovary as well as adipose tissue. Estrone sulfate acts as a pool of estrone which can be converted as needed to the more active estradiol. In pre-menopausal adult women, more than 50% of estrone is secreted by the ovary. In pre-pubertal children, men and post-menopausal women, the major portion of estrone is derived from peripheral tissue conversion of androstenedione. During pregnancy, large amounts of estrone are synthesized in the placenta from dehydroepiandrosterone sulfate (DHEA-S) which originates from the maternal circulation and from the fetal adrenal gland.

Estrone is very a important steroid that have key role in many biological processes. Numerous derivatives have been made from these steroids and some are used as drug for medical applications. Improved methods for the synthesis of new modified estrone derivatives with biological applications receive considerable attention. Estrone is used as potent inhibitors of 17β-hyroxysteroid dehydrogenase type1 (17β-HSDs),[6] steroid sulfatase inhibitors(STS),[7] estrone sulfatase inhibitors[8] and also exhibits antiproliferative,[9] anticancer,[10] antimicrobial and antifungal activities.[11] Many of the drugs for menopausal estrogen therapy contain estrone core.[12] These drugs are used for the treatments of menopausal disorders, particularly estradiol, estradiol valerate, estriol, estropipate, mestranol (**Figure 3**).

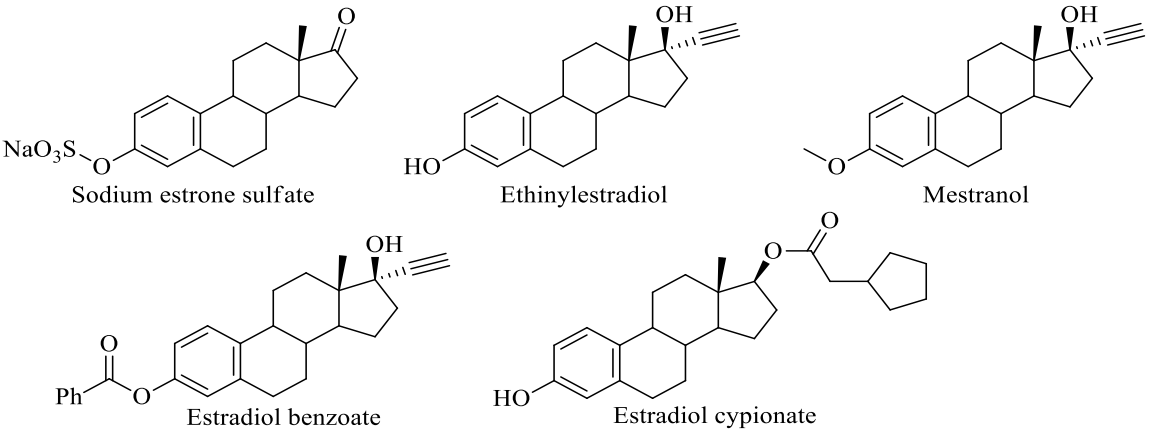

Figure 3. Drugs for menopausal estrogen therapy

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Scheme 1. Synthesis of (*E*)-16-arylmethylidene-estrones **2**

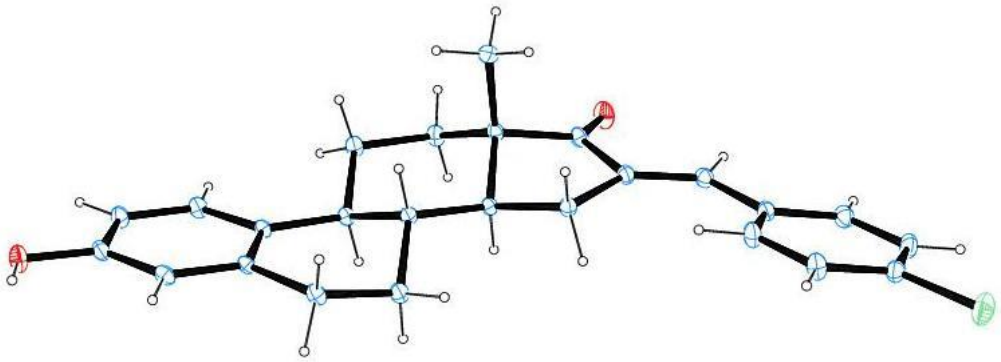

Figure 4. ORTEP diagram of 2b

Table 1. Yield of 2

Entry	Comp	Ar	Yield[a] (%)
1	**2a**	C_6H_5	93
2	**2b**	4-ClC_6H_4	95
3	**2c**	4-FC_6H_4	92
4	**2d**	4-BrC_6H_4	97
5	**2e**	4-$CH_3C_6H_4$	95

[a]Yields were quantitative except for the loss during workup

Structural elucidation of (*E*)-16-arylidene estrones

The structure of these dipolarophiles **2** was elucidated with the help of NMR spectroscopy. Moreover, the NMR spectra of (*E*)-16-arylidene estrones **2** and estrone **1** were similar except for the presence of new signals in the ^1H and ^{13}C NMR spectra of **2** due to the aromatic ring and benzylidene protons and carbons. Further, the DEPT-135 spectrum of **2** reveals the absence of one 'CH_2' carbon and appearance of new signals due to aromatic 'C' and 'CH' carbons. The structure of **2** assigned from NMR spectroscopy was further confirmed from single crystal X-ray studies. The ORTEP diagram of **2b** reveals (*E*)-configuration for the D-ring C-16 exocyclic alkene (**Figure 4**).[12]

Conclusions

In the present work, the C-16 exocyclic dipolarophiles *viz*. (*E*)-16-arylidene estrones **2** were synthesized from the reaction of estrone **1** with various aromatic aldehydes. the reaction was realized when the (*E*)-16-arylidene estrones **2** precipitated out of the reaction mixture as yellow solid, which was filtered and washed with water. A total of fifteen (*E*)-16-arylidene estrones **2a–o** were synthesized in almost quantitative yields

Experimental

General

The melting points were measured in open capillary tubes and are uncorrected. The ^1H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and

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$CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (□-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. The single crystal X-ray data of **2b** were collected on Enraf–Nonius (CAD4) diffractometer with Mo K□ (□□0.71073 Å) radiation. Scan range was $2.02^o \leq \theta \leq 24.97^o$. SHELXTL software was used for structure solution and refinement. Silica gel-G plates (Merck) were used for tlc analysis with a mixture of petroleum ether (60–80ºC) and ethyl acetate as eluent. All the chemicals were purchased from Aldrich and used without any further purification.

General procedure for the synthesis of 16-(*E*)-arylidene-estrones 2.

A mixture of estrone **1** (1 mmol) and aromatic aldehyde (1 mmol) were dissolved in ethanol (5 mL) to which an alcoholic solution of potassium hydroxide (20%) was added. The mixture was refluxed on an oil bath with continuous stirring for 5 hours and the progress of the reaction was monitored by TLC intermittently. After completion of the reaction, the mixture was allowed to cool. The precipitated solid was filtered, washed with water (100 mL) and dried under vacuum to afford the product **2** as yellow solid. The yields of the 16-(*E*)-arylidene-estrones **2** were almost quantitative except for the loss during work-up.

Isolated as pure white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.32 (s, 3H), 0.50–0.60 (m, 1H), 0.95–0.97 (m, 1H), 1.04–1.18 (m, 2H), 1.23–1.33 (m, 1H), 1.60–1.61 (m, 2H), 1.62–1.68 (m, 2H), 1.80–1.84 (m, 1H), 2.01–2.05 (m, 1H), 2.50–2.51 (m, 1H), 2.54–2.69 (m, 2H), 2.82–2.95 (m, 2H), 3.63 (d, *J* = 6.6 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H, 7.04–7.34 (m, 7H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H).

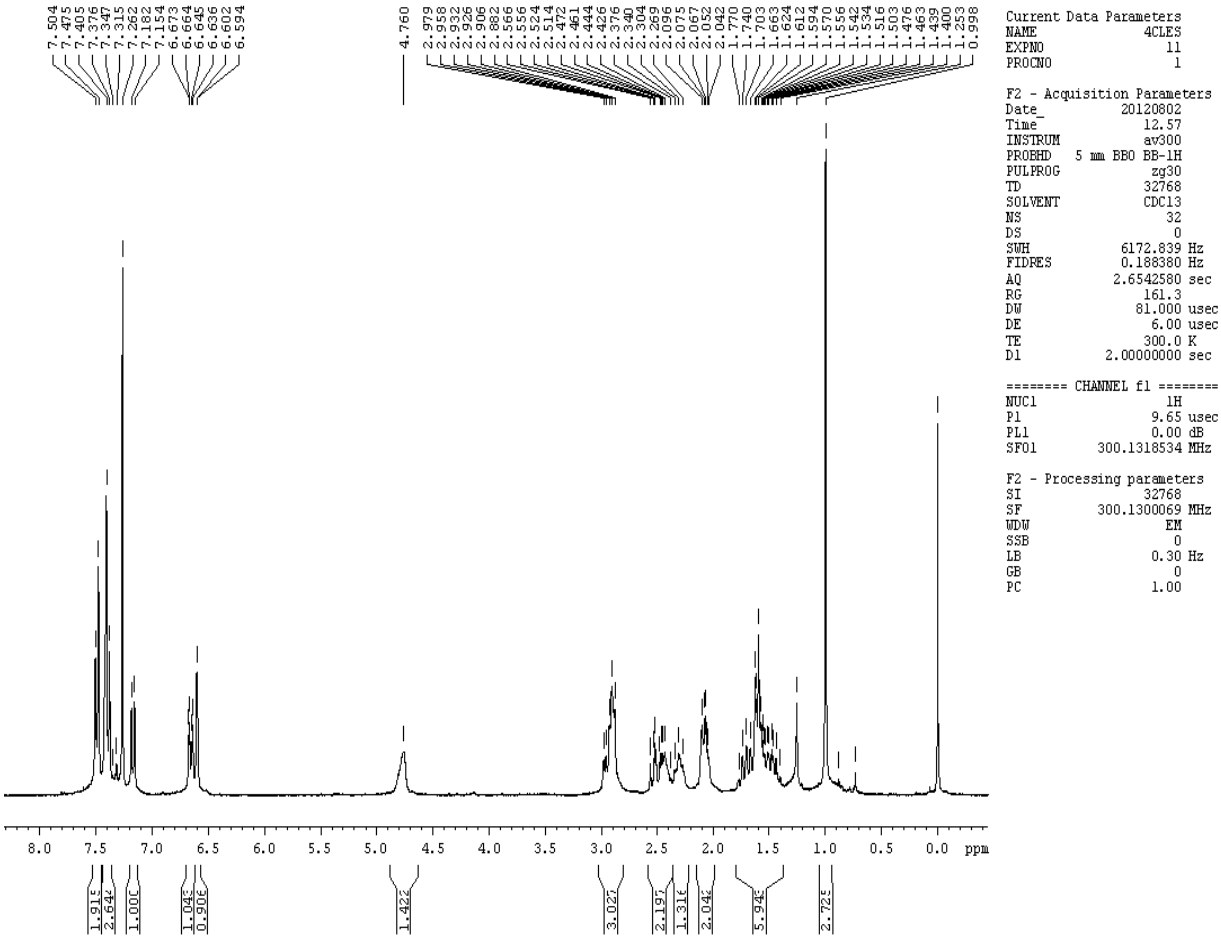

Figure 5. ^{1}H NMR spectra of **2b**

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