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Rapid communication

Rapid synthesis of long chain fatty acid esters of steroids in ionic liquids with microwave irradiation: Expedient one-pot procedure for estradiol monoesters

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ABSTRACT

We report the rapid synthesis (1 min) in high yield of fatty acid ester (FAE) derivatives of several steroids under microwave irradiation in an ionic liquid (IL). An expedient regioselective hydrolysis at C-3 of estradiol diesters is also reported.

1. Introduction

Fatty acid esters (FAE) of steroid hormones occur naturally in the human body. They are potent hormones, they act as a hormone reservoir and can release active hormone to the target tissues by the action of esterase [1,2]. They participate in important biological processes. The sex hormone FAE has a role in the intracrinology of breast cancer cells [3]. Fatty acid esterification is one of the few metabolic transformations that augment hormone activity. Estradiol fatty acid esters are most potent mammalian estrogens [4]. The role of FAE of steroid hormones in atherosclerosis is presently under active study. Studies have shown that E2 FAE in blood can protect lipoproteins against oxidation [5] and take part in reverse cholesterol transport mechanism as well [6]. These findings indicate that these compounds may reduce the risk of cardiovascular diseases.

Estradiol 17-esters have previously been synthesized from estradiol with the corresponding acyl chloride under anhydrous conditions. While the major product was estradiol-3,17-diester, also estradiol-3-ester, estradiol-17-ester and unreacted estradiol were detected [7]. This mixture was isolated and then hydrolyzed with $NaHCO_3$ to remove the ester function at C-3. This process suffers from sluggishness and often results in low yield [7–10]. We describe here a rapid, high yielding procedure for estradiol esters applicable to other steroid esters as well.

Application of microwaves in organic synthesis has become popular over the past few years. In many instances microwave heating results in rapid reactions, high yields and lower amounts of side products. Microwave heating depends on the microwave power absorbing ability of the molecules present in the reaction mixture. Under microwave irradiation the reaction mixture undergoes dielectric heating, a process occurring by two mechanism: dipolar polarization and ionic conduction. Thus polar and ionic compounds can absorb microwave energy very efficiently and are heated up fast [11,12].

Due to their ionic structure ionic liquids (IL) are very efficient in absorbing microwave energy. In addition, they can dissolve a wide range of organic, inorganic and organometallic compounds and are thermally stable [13–15]. Therefore ionic liquids should be ideal solvents for microwave assisted organic synthesis.

In spite of all these advantages IL have not been used extensively for microwave induced synthesis, and never in steroid chemistry. As is evident from the number of publications in the last few years, although much research has been done in IL and MW synthesis separately, organic syntheses combining the two techniques have not been widely explored. For example, studies on the esterification reaction using IL/MW are so far limited only to the Fischer esterification with simple model compounds where Brønsted acidic IL was tested as catalyst [16,17] or as solvent in domestic microwave oven [18]. There are no studies on the hydrolysis of esters under IL/MW conditions.

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Table 1
One-pot synthesis of estradiol 17β-monoesters: esterification followed by KOH hydrolysis in IL *in situ*.

Substrate	Product (%yield[a])
Estradiol **1**	*In situ* reaction in IL and MW irradiation 1 + 1 min Estradiol 17β-monooleate **2** (88%) Estradiol 17β-monolinoleate **3** (87%) Estradiol 17β-monostearate **4** (86%) Estradiol 17β-palmitate **5** (91%)

[a] Isolated yield.

Here we report the rapid one-pot synthesis of estradiol-17β-stearate, estradiol-17β-palmitate, estradiol-17β-oleate and estradiol-17β-linoleate in a microwave reactor using neutral IL. All of these monoesters occur in human body. Using IL/MW methodology long chain fatty acid esters of testosterone, dehydroepiandrosterone and 5α-androstane-3β,17β-diol were also synthesized in high yield. Use of IL as heating aid enhances the reaction rate and provides a fast and high yielding procedure.

2. Experimental

2.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 MHz spectrometer. Mass spectra were obtained with a JEOL JMS SX102 mass spectrometer. Reactions under microwave irradiation were carried out in CEM Discover instrument. Estradiol, 5α-androstane-3β,17β-diol, and 4-androsten-17β-ol-3-one (testosterone) were purchased from Steraloids. Dehydroepiandrosterone was purchased from Fluka. Fatty acid chlorides were purchased from Sigma. 1-Butyl-3-methylimidazolium chloride [Bmim]Cl was prepared in our laboratory [19]. Magnetic resonance data are included for some known compounds where such data have not been previously reported. All final products were homogenous by TLC (Merck siliga gel 60 F_{254} plates and visualized with UV light and with a mixture of vanillin and sulfuric acid in ethanol).

2.2. General procedure for the synthesis of 17β-monoesters of estradiol

20 mg (0.07 mmol) of estradiol, 1 mg (0.008 mmol) of 4-(dimethylamino)pyridine (DMAP) and about 70 mg of [Bmim]Cl were taken in a microwave vial and 0.1 ml of pyridine was added to it. Then 2.4 molar equivalent of the fatty acid chloride was added to the vial. The mixture was microwave irradiated at 40 °C with 20 W power for 1 min. After that 71 mg (1.4 mmol) of KOH and 1 ml of toluene was added to the vial. The mixture was again microwave irradiated at 80 °C for 1 min and then poured into ice-cold water, neutralized with 1N HCl and extracted three times with 7 ml of EtOAc. Combined organic phase was washed successively with $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The crude product was purified on a silica gel column with n-hexane/EtOAc eluent. For yields see Table 1.

2.2.1. Estradiol 17β-monooleate **2**

Colorless solid, R_f in 3:1 n-hexane/EtOAc is 0.51. ^{1}H NMR ($CDCl_3$) δ: 7.13 (d, 1H, H-1, J = 8.4 Hz), 6.63 (dd, 1H, H-2, J = 8.4 Hz, 2.7 Hz), 6.56 (d, 1H, H-4, J = 2.7 Hz), 5.34 (m, 2H, H-9′ and H-10′), 4.7 (t, 1H, H-17, J = 8.4 Hz), 0.88 (t, 3H, H-18′, J = 6.75 Hz), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.72 (C-1), 112.92 (C-2), 153.68 (C-3), 115.47 (C-4), 132.71 (C-5), 27.81 (C-7), 38.79 (C-8), 43.99 (C-9), 138.37 (C-10), 26.43 (C-11), 37.14 (C-12), 43.18 (C-13), 49.99 (C-14), 23.49 (C-15), 27.39 (C-16), 82.72 (C-17), 12.31 (C-18), 174.33 (C-1′), 34.84 (C-2′), 25.33 (C-3′), 29.33–29.97 (C-6, C-4′–C-7′ and C-12′–C-15′), 130.22, 129.97 (C-9′, C-10′), 22.89 (C-17′), 14.32 (C-18′). MS m/z (relative intensity) 536 M^+ (9), 255 (32), 159 (14), 133 (7).

2.2.2. Estradiol 17β-monolinoleate **3**

Colorless solid, R_f in 3:1 n-hexane/EtOAc is 0.5. ^{1}H NMR ($CDCl_3$) δ: 7.14 (d, 1H, H-1, J = 8.2 Hz), 6.63 (dd, 1H, H-2, J = 8.2 Hz, 2.5 Hz), 6.56 (d, 1H, H-4, J = 2.5 Hz), 5.35 (m, 4H, H-9′, H-10′, H-12′, H-13′), 4.7 (t, 1H, H-17, J = 8.4 Hz), 0.89 (t, 3H, H-18′, J = 6.75 Hz), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.75 (C-1), 112.92 (C-2), 153.61 (C-3), 115.47 (C-4), 138.41 (C-5), 27.83 (C-7), 38.8 (C-8), 44.01 (C-9), 132.79 (C-10), 26.45 (C-11), 37.16 (C-12), 43.20 (C-13), 50.02 (C-14), 23.50 (C-15), 27.42 (C-16), 82.72 (C-17), 12.33 (C-18), 174.3 (C-1′), 34.85 (C-2′), 25.34 (C-3′), 29.35–29.82 (C-6, C-4′–C-7′ and C-12′–C-15′), 130.45, 130.28 (C-9′, C-13′), 128.28, 128.15 (C-10′, C-12′), 22.79 (C-17′), 14.29 (C-18′). MS m/z (relative intensity) 534 M^+ (25), 255 (63), 159 (32), 133 (14).

2.2.3. Estradiol 17β-monostearate **4**

R_f in 11:1 n-hexane/EtOAc is 0.55. ^{1}H NMR ($CDCl_3$) δ: 7.13 (d, 1H, H-1, J = 8.4 Hz), 6.62 (dd, 1H, H-2, J = 8.4 Hz, 2.7 Hz), 6.56 (d, 1H, H-4, J = 2.4 Hz), 4.7 (t, 1H, H-17, J = 8.7 Hz), 2.31 (t, 2H, H-2′, J = 7.05 Hz), 0.88 (t, 3H, H-18′, J = 6.8 Hz), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.7 (C-1), 112.91 (C-2), 153.66 (C-3), 115.46 (C-4), 132.7 (C-5), 27.80 (C-7), 38.79 (C-8), 43.99 (C-9), 138.35 (C-10), 26.43 (C-11), 37.13 (C-12), 43.18 (C-13), 49.99 (C-14), 23.48 (C-15), 27.39 (C-16), 82.73 (C-17), 12.31 (C-18), 174.39 (C-1′), 34.85 (C-2′), 25.34 (C-3′), 29.35–29.9 (C-4′–C-15′), 32.12 (C-16′), 22.89 (C-17′), 14.31 (C-18′). MS m/z (relative intensity) 538 M^+ (80), 510 (14), 255 (12), 159 (12).

2.2.4. Estradiol 17β-monopalmitate **5**

R_f in 3:1 n-hexane/EtOAc is 0.24. ^{1}H NMR ($CDCl_3$) δ: 7.13 (d, 1H, H-1, J = 8.1 Hz), 6.61 (dd, 1H, H-2, J = 8.1 Hz, 2.5 Hz), 6.56 (d, 1H, H-4, J = 2.4 Hz), 4.69 (t, 1H, H-17, J = 8.4 Hz), 2.30 (t, 2H, H-2′, J = 7.5 Hz), 0.88 (t, 3H, H-18′, J = 6.3 Hz), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.65 (C-1), 112.98 (C-2), 153.86 (C-3), 115.51 (C-4), 132.5 (C-5), 27.80 (C-7), 38.79 (C-8), 43.99 (C-9), 138.26 (C-10), 26.43 (C-11), 37.13 (C-12), 43.18 (C-13), 49.98 (C-14), 23.49 (C-15), 27.41 (C-16), 82.17 (C-17), 12.31 (C-18), 174.54 (C-1′), 34.85 (C-2′), 25.34 (C-3′), 29.35–29.89 (C-4′–C-13′), 32.13 (C-14′), 22.89 (C-15′), 14.31 (C-16′). MS m/z (relative intensity) 510 M^+ (12), 282 (50), 259 (25).

2.3. General procedure for esterification

0.07 mmol of steroid, 1 mg (0.008 mmol) of 4-(dimethylamino)pyridine (DMAP), and about 70 mg of [Bmim]Cl were taken in a microwave vial and 0.1 ml of pyridine was added. Then 0.105 mmol (1.2 molar equivalent per OH or 2.4-fold excess for diesters) of the fatty acid chloride was added to the vial. The mixture was microwave irradiated at 40 °C with 20 W power for 1 min. After the reaction, the mixture was poured into ice-cold water and neutralized with 1N HCl. The aqueous phase was extracted with EtOAc (3 × 7 ml). Combined organic phase was washed successively with $NaHCO_3$ solution and brine and dried over Na_2SO_4. The crude product was purified on silica gel column with n-hexane/EtOAc eluent. For yields see Table 2.

2.3.1. Estradiol dioleate **6**

Colorless liquid, R_f in 5:1 n-hexane/EtOAc is 0.65. ^{1}H NMR ($CDCl_3$) δ: 7.27 (d, 1H, H-1, J = 8.2 Hz), 6.83 (dd, 1H, H-2, J = 8.2 Hz, 2.5 Hz), 6.77 (d, 1H, H-4, J = 2.5 Hz), 5.35 (m, 4H, H-9′ and H-10′), 4.7 (dd, 1H, H-17, J = 8.85 Hz, 7.65 Hz), 2.02 (m, 8H, H-8′, H-11′), 0.88 (t, 6H, H-18′, J = 6.9 Hz), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.55 (C-1), 118.79 (C-2), 148.72 (C-3), 121.7 (C-4), 138.31 (C-5), 29.97 (C-6), 27.81 (C-7), 38.44 (C-8), 44.2 (C-9), 137.93 (C-10), 26.26 (C-11), 37.12 (C-12), 43.13 (C-13), 50.07 (C-14), 23.49 (C-15), 27.25 (C-16),

Table 2
Synthesis of fatty acid esters of steroids synthesized in IL/MW.

Entry	Substrate	Product	Yield (%)[a]
1	Estradiol **1**	Estradiol dioleate **6**	89%
		Estradiol dilinoleate **7**	92%
		Estradioldistearate **8**	90%
		Estradiol dipalmitate **9**	91%
2	Dehydroepiandrosterone **10**	5-Androsten-3β-ol-17-one oleate **11**	85%
		5-Androsten-3β-ol-17-one linoleate **12**	92%
3	5α-androstane-3β,17β-diol **13**	5α-Androstane-3β,17β-diol dioleate **14**	85%
		5α-Androstane-3β,17β-diol dilinoleate **15**	74%
4	Testosterone **16**	4-Androsten-17β-ol–3-one oleate **17**	83%
		4-Androsten-17β-ol–3-one linoleate **18**	79%

[a] Isolated yields.

82.57 (C-17), 12.29 (C-18), 174.10, 172.78 (C-1′), 34.81, 34.63 (C-2′), 25.33, 25.20 (C-3′), 29.33–29.9 (C-4′–C-7′ and C-12-C-15′), 130.23, 129.95 (C-9′, C-10′), 22.88 (C-17′), 14.31 (C-18′). MS m/z (relative intensity) 800 M^+(3), 536 (44), 272 (22), 255 (50), 159 (16), 133 (8).

2.3.2. Estradiol dilinoleate **7**

Colorless liquid, R_f in 5:1 n-hexane/EtOAc is 0.62. ^{1}H NMR ($CDCl_3$) δ: 7.27 (d, peak overlapped with $CHCl_3$ peak, 1H, H-1), 6.83 (dd, 1H, H-2, J = 8.4 Hz, 2.4 Hz), 6.77 (d, 1H, H-4, J = 2.4 Hz), 5.35 (m, 8H, H-9′, H-10′, H-12′, and H-13′), 4.7 (t, 1H, H-17, J = 8.4 Hz), 2.77 (t, 4H, H-11′, J = 5.55 Hz), 2.04 (m, 8H, H-8′, H-14′), 0.89 (t, 6H, H-18′), 0.82 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 126.56 (C-1), 118.79 (C-2), 148.73 (C-3), 121.7 (C-4), 138.31 (C-5), 27.82 (C-7), 38.45 (C-8), 44.2 (C-9), 137.94 (C-10), 26.26 (C-11), 37.12 (C-12), 43.14 (C-13), 50.06 (C-14), 23.49 (C-15), 27.25 (C-16), 82.59 (C-17), 12.3 (C-18), 174.10, 172.77 (C-1′), 34.81, 34.63 (C-2′), 25.32, 25.20 (C-3′), 29.34–29.8 (C-6, C-4′–C-7′ and C-12′–C-15′), 130.43, 130.25 (C-9′, C-13′), 128.23, 128.12 (C-10′, C-12′), 22.78 (C-17′), 14.28 (C-18′). MS m/z (relative intensity) 796 M^+(8), 534 (40), 272 (48), 255 (100), 159 (37), 133 (17).

2.3.3. 5-Androsten-3β-ol-17-one oleate **11**

Colorless liquid, R_f in 5:1 n-hexane/EtOAc is 0.58. ^{1}H NMR ($CDCl_3$) δ: 5.41 (d, 1H, H-6, J = 4.5 Hz), 5.34 (m, 2H, H-9′and H-10′), 4.6 (m, 1H, H-3), 2.27 (t, 2H, H-2′, J = 7.5 Hz), 2.00 (m, 4H, H-8′and H-11′), 1.05 (s, 3H, H-19), 0.88 (overlapped peaks, 6H, H-18 and H-18′). ^{13}C NMR ($CDCl_3$) δ: 37.15 (C-1), 27.94 (C-2), 73.62 (C-3), 38.32 (C-4), 140.22 (C-5), 122.01 (C-6), 31.68 (C-7), 31.62 (C-8), 50.4 (C-9), 36.94 (C-10), 20.52 (C-11), 30.98 (C-12), 47.71 (C-13), 51.92 (C-14), 22.07 (C-15), 36.01 (C-16), 221.18 (C-17), 13.73 (C-18), 19.54 (C-19), 173.47 (C-1′), 34.98 (C-2′), 25.23 (C-3′), 29.28–29.96 (C-4′–C-7′ and C-12′–C15′), 27.36 (C-8′), 27.94 (C-11′), 130.2, 129.96 (C-9′ and C-10′), 32.09 (C-16′), 22.87 (C-17′) 14.3 (C-18′). MS m/z (relative intensity) 552 M^+(very small), 270 (31), 255 (14), 145 (8), 121 (23), 107 (11).

2.3.4. 5-Androsten-3β-ol-17-one linoleate **12**

Colorless liquid, R_f in 3:1 n-hexane/EtOAc is 0.73. ^{1}H NMR ($CDCl_3$) δ: 5.39–5.25 (d, 1H and m, 4H overlapped, H-6 and H-9′, H-10′, H-12′, H-13'), 4.6 (m, 1H, H-3), 2.74 (t, 2H, H-11′, J = 5.7 Hz), 2.03 (m, 4H, H-8′ and H-14′), 2.27 (t, 2H, H-2′, J = 7.5 Hz), 1.02 (s, 3H, H-19), 0.86 (overlapped peaks, 6H, H-18 and H-18′). ^{13}C NMR ($CDCl_3$) δ: 37.16 (C-1), 27.96 (C-2), 73.64 (C-3), 38.34 (C-4), 140.2 (C-5), 122.02 (C-6), 31.64 (C-7), 31.7 (C-8), 50.38 (C-9), 36.96 (C-10), 20.54 (C-11), 30.99 (C-12), 47.72 (C-13), 51.93 (C-14), 22.09 (C-15), 36.05 (C-16), 221.19 (C-17), 13.75 (C-18), 19.55 (C-19), 173.46 (C-1′), 34.89 (C-2′), 25.24 (C-3′), 29.3–29.8 (C-4′–C-7′), 27.4 (C-8′), 130.42, 130.26, 128.25, 128.12 (C-9′, C-10′, C-12′ and C-13′), 22.78 (C-17′), 14.27 (C-18′). MS m/z (relative intensity) 550 M^+ (9), 270 (93), 255 (47), 145 (30), 121 (63).

2.3.5. 5α-Androstane-3β,17β-diol dioleate **14**

Colorless liquid, R_f in 5:1 n-hexane/EtOAc is 0.64. ^{1}H NMR ($CDCl_3$) δ: 5.34 (m, 4H, H-9′ and H-10′), 4.69 (m, 1H, H-3), 4.59 (t, 1H, H-17, J = 8.4 Hz), 2.25 (q, 4H, H-2′, J = 16.2 Hz, 7.8 Hz), 2.01 (m, 8H, H-8′, H-11′), 0.83 (s, 3H, H-19), 0.77 (s, 3H, H-18), 0.88 (t, 6H, H-18′, J = 6.45 Hz). ^{13}C NMR (acetone-d_6) δ: 37.62 (C-1), 25.92 (C-2), 73.75 (C-3), 2.73 (C-4), 43.56 (C-5), 28.38 (C-6), 32.38 (C-7), 37.93 (C-8), 55.19 (C-9), 36.41 (C-10), 21.55 (C-11), 36.22 (C-12), 45.56 (C-13), 51.62 (C-14), 24.22 (C-15), 30.57 (C-16), 83.02 (C-17), 12.64 (C-18), 173.62, 173.20 (C-1′), 35.05 (C-2′), 25.83 (C-3′), 28.38–30.57 (C-4′, C-5′, C-6′, C-7′, C-12′, C-13′, C-14′, C-15′), 130.69, 130.61 (C-9′ and C-10′), 27.88 (C-8′ and C-11′), 30.68 (C-16′), 23.42 (C-17′), 14.46 (C-18′ and C-19). MS m/z (relative intensity) 820 M^+(very small), 539 (16), 265 (21), 257 (46), 163 (14), 95 (18).

2.3.6. 5α-Androstane-3β,17β-diol dilinoleate **15**

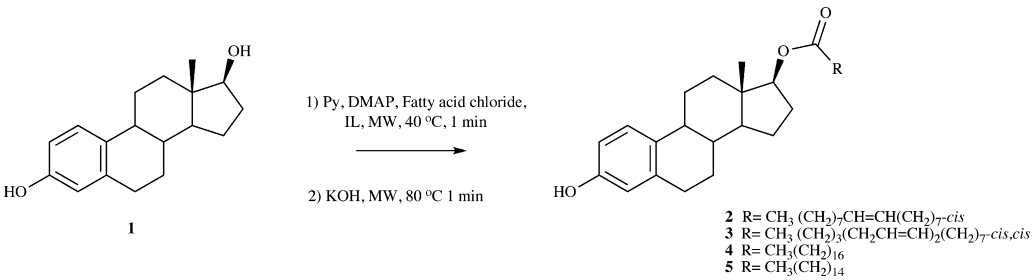
Colorless liquid, R_f in 4.5:1 n-hexane/EtOAc is 0.62. ^{1}H NMR ($CDCl_3$) δ: 5.35 (m, 8H, H-9′, H-10′, H-12′, H-13′), 4.54 (m, 1H, H-3), 4.52 (q, 1H, H-17, J = 9 Hz, 7.8 Hz), 2.77 (t, 4H, H-11′, J = 5.85 Hz), 2.26 (m, 4H, H-2′), 2.04 (m, 8H, H-8′, H-11′), 0.77 (s, 3H, H-18), 0.83 (s, 3H, H-19), 0.89 (t, 6H, H-18′, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 37.14 (C-1), 27.41 (C-2), 73.54 (C-3), 34.81 (C-4), 42.9 (C-5), 34.26 (C-7), 35.77 (C-8), 54.39 (C-9), 35.49 (C-10), 20.88 (C-11), 37.14 (C-12), 44.86 (C-13), 50.91 (C-14), 23.76 (C-15), 31.73 (C-16), 82.77 (C-17), 12.43 (C-18), 174.11, 173.62 (C-1′), 34.96 (C-2′), 25.31 (C-3′), 27.79–29.55 (C-6, C-4′, C-5′, C-6′, C-7′, C-15′), 130.43, 130.27 (C-9′ and C-10′), 128.25, 128.13, (C-12′ and C-13′), 27.7 (C-8′ and C-14′), 25.84 (C-11′), 29.80 (C-16′), 22.78 (C-17′), 14.27 (C-18′ and C-19). MS m/z (relative intensity) 816 M^+(1), 537 (1.5), 257 (11.5).

2.3.7. 4-Androsten-17β-ol-3-one oleate **17**

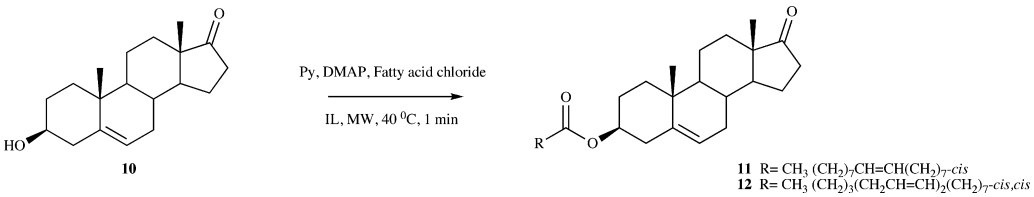
Colorless liquid, R_f in 5:1 n-hexane/EtOAc is 0.23. ^{1}H NMR ($CDCl_3$) δ: 5.73 (s, 1H, H-4), 5.34 (m, 2H, H-9′ and H-10′), 4.61 (q, 1H, H-17, J = 9.15 Hz, 7.65 Hz), 2.29 (t, 2H, H-2′, J = 7.55 Hz), 2.00 (m, 4H, H-8′ and H-11′), 1.19 (s, 3H, H-19), 0.88 (t, 3H, H-18′, J = 6.75 Hz), 0.84 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$) δ: 35.63 (C-1), 34.76 (C-2), 199.58 (C-3), 124.16 (C-4), 171.08 (C-5), 32.94 (C-6), 32.10 (C-7), 35.63 (C-8), 53.93 (C-9), 38.81 (C-10), 20.75 (C-11), 36.86 (C-12), 42.72 (C-13), 50.47 (C-14), 23.69 (C-15), 27.71 (C-16), 82.36 (C-17), 12.26 (C-18), 17.6 (C-19), 174.03 (C-1′), 34.12 (C-2′), 25.3 (C-3′), 29.30–29.96 (C-4′, C-5′, C-6′, C-7′, C-12′, C-13′, C-14′, and C-15′), 130.20, 129.94 (C-9′ and C-10′), 27.37, 27.42 (C-8′ and C-11′), 31.70 (C-16′), 22.87 (C-17′), 14.31 (C-18′). MS m/z (relative intensity) 552 M^+ (14), 271 (38), 147 (6).

2.3.8. 4-Androsten-17β-ol-3-one linoleate **18**

Colorless liquid, R_f in 3:1 n-hexane/EtOAc is 0.30. ^{1}H NMR ($CDCl_3$) δ: 5.73 (s, 1H, H-4), 0.84 (s, 3H, H-18), 1.19 (s, 3H, H-19), 5.35 (m, 4H, H-9′, H-10′, H-12′ and H-13′), 4.6 (q, 1H, H-17, J = 9.3 Hz, 7.5 Hz), 2.77 (t, 2H, H-11′, J = 5.55 Hz), 2.29 (t, 2H, H-2′,



Scheme 1. Estradiol, DMAP and ionic liquid were dissolved in dry pyridine and fatty acid chloride was added. The mixture was irradiated in microwave for 1 min at 40 °C. Then toluene and KOH was added and reaction mixture was again irradiated at 80 °C for 1 min to saponify the ester at C-3.



Scheme 2. DHEA (**10**) DMAP and ionic liquid was taken in a microwave vial and dissolved in dry pyridine. Fatty acid chloride was added and the mixture was irradiated in microwave for 1 min at 40 °C to furnish fatty acid esters of DHEA.

J = 7.5 Hz), 2.03 (m, 4H, H-8′ and H-14′), 0.89 (t, 3H, H-18′, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 35.61 (C-1), 34.74 (C-2), 199.65 (C-3), 124.15 (C-4), 171.15 (C-5), 32.93 (C-6), 31.7 (C-7), 35.9 (C-8), 53.91 (C-9), 38.8 (C-10), 20.73 (C-11), 36.84 (C-12), 42.7 (C-13), 50.45 (C-14), 23.68 (C-15), 27.71 (C-16), 82.36 (C-17), 12.25 (C-18), 17.59 (C-19), 174.03 (C-1′), 34.1 (C-2′), 25.28 (C-3′), 130.42, 130.22 (C-9′ and C-13′), 128.25, 128.1 (C-10′ and C-12′) 25.82 (C-11′), 14.25 (C-18′). MS m/z (relative intensity) 550 M^+ (20), 271 (37), 253 (8.5), 147 (8).

3. Results and discussion

In the human body estradiol is found esterified exclusively at the C-17OH of the steroid nucleus. Previously [20] we have synthesized the 17β-monoesters in two steps, by way of the diester followed by selective saponification, each reaction requiring at least 1 h for completion and isolation of the product in each step. We have now developed a one-pot method for the synthesis of estradiol 17β-monoesters: the diester prepared in IL is mixed *in situ* with KOH and toluene and the mixture again microwave irradiated (Scheme 1). The entire sequence requires only 2 min. In the absence of toluene the reaction is slower. When the synthesis of estradiol 17β-monoester was performed without ionic liquid keeping other conditions the same, only the corresponding diesters (**6**–**9**) were isolated and no estradiol-17β monoesters were formed (Table 1). Thus in the selective hydrolysis of a diester, toluene and IL are needed to dissolve the diester. Here the IL may act as a phase transfer agent as well as heat transfer medium. The high yield, short reaction time and elimination of the diester isolation step make this reaction much more efficient than a conventional synthesis or a microwave synthesis without IL. In the absence of IL, the formation of estradiol dilinoleate, using DMAP, pyridine and MW irradiation takes 60 min [20]. Similarly, the selective hydrolysis at C-17 of estradiol FA esters, using KOH, *t*-BuOH and MW irradiation requires a 60 min. reaction time.

The oleate and linoleate esters of DHEA (**10**), 5α-androstane-3β,17β-diol (**13**) and testosterone (**16**) are available in a short reaction time (1 min.) in very good yields by irradiating a mixture of the steroid, fatty acid chloride, pyridine, DMAP, and IL in a closed vial (Scheme 2, Table 2.). At the end of the reaction IL forms a separate phase, allowing the separation and reuse of IL. Both [bmim]Cl and [bmim]Br worked well. Many of the steroid fatty acid esters are known as hormonal constituents but have not been previously reported as synthetic products in the literature, or in the few instances where synthetic work has been carried out, no information on yields is given [21,22]. Quite often reaction times are from a few hours up to 20 h [21–23].

Therefore it can be concluded that IL/MW give excellent rate enhancement of both the esterification reaction as well as the regioselective saponification reaction.

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