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Ultrasound-promoted preparation of disteryl ethers catalyzed by montmorillonite K 10

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Abstract

In the presence of montmorillonite K 10, 5(6)-unsaturated sterols (**1**) were heated under ultrasound at 45°C in dichloromethane for 2–5.5 h to provide 3β,3′β-5(6)/5′(6′)-unsaturated disteryl ethers (**2**) in 35–79% yield. Meanwhile, 3α,3′α-diandrost-5-en-17-one-3-yl ether (**3a**) and 3α,3′α-dipregn-5-en-20-one-3-yl ether (**3b**) were also obtained as by-products from 3β-hydroxyl-androst-5-en-17-one (**1a**) and 3β-hydroxyl-pregnan-5-en-20-one (**1b**) respectively.

Keywords: Ultrasound; Disteryl ethers; Preparation

1. Introduction

Under some conditions, disteryl ethers are formed by dehydration of sterols, e.g. cholesterol, stigmasterol and sitosterol [1–6]. They are also formed from the industrial refining of fats and oils where they are presumably formed by the action of acidic bleaching earth on sterols that are minor constituents of fats and oils [7–9]. Therefore, the detection of disteryl ethers in fats and oils may be useful as evidence of industrial bleaching [10,11].

There are several publications describing the formation of disteryl ethers during various chemical reactions of sterols [1–6]. We have recently shown that several side-chain-varied disteryl ethers have been obtained from the corresponding sterols in 69–73% yield catalyzed by montmorillonite K 10 at refluxing temperature in dichloromethane for 6–13 h [12]. The stereochemistry of the disteryl ethers at C-3 was 3β,3′β-configuration from the reported reactions [1–6,12].

Recently, many organic reactions have been accelerated under ultrasound irradiation [13–19]. This prompted us to study the possibility of the preparation of disteryl ethers catalyzed by montmorillonite under ultrasound. We report here the dimerisation of sterols under ultrasonic irradiation catalyzed by montmorillonite K 10.

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2. Method

2.1. Apparatus and analysis

Melting points were uncorrected. IR spectra were recorded on a Perkin Elmer 983G spectrometer. ^{1}H NMR spectra were measured on INOVA-500 spectrometer and spectrometers (TMS, $CDCl_3$). Mass spectra were determined on a VG-7070E spectrometer (EI, 70 eV). Montmorillonite K 10 was purchased from Aldrich and dried at 100°C for 1 h prior to use. Sonication was performed in a Shanghai Branson–CQX ultrasonic cleaner with a frequency of 25 Hz and a nominal power of 250 W. The reaction flask was located at the maximum energy area in the cleaner and the temperature of the water bath was controlled by addition or removal of water.

2.2. General procedure

A mixture of sterol (**1**, 1.00 mmol), montmorillonite K 10 (300 mg) in dichloromethane (20 ml) was irradiated in the water bath of an ultrasonic cleaner at 42–46°C for the length of time as indicated in Table 1 until the substrate disappeared (TLC). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give a light yellow solid. The crude product was subjected to chromatography on silica (200–300 mesh), eluted with petroleum ether

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Table 1
Preparation of disteryl ethers from sterols catalyzed by montmorillonite K 10 under ultrasound (U.S.)

Entry	R^1	R^2	Reaction time (h)		Product		Isolated yield (%)		mp (°C)
			K 10*	K 10/U.S.	K 10	K 10/U.S.	K 10	K 10/U.S.	(Lit.)
1a	R^1R^2=O		11	5	**2a**	**2a**	73	40	270–272 (272–274) [12]
						3a		17	140–143
1b		H	12	4	**2b**	**2b**	71	35	224–227 (225–227) [12]
						3b		23	103–105
1c		H	13	5.5	**2c**	**2c**	72	72	192–194 (192–194) [6,12]
1d		H	6	2	**2d**	**2d**	73	79	198–200 (197–200) [6,12]
1e		H	8	4	**2e**	**2e**	69	69	202–204 (206–209) [12]

*Catalyzed by montmorillonite in absence of ultrasound.

(b.p. 60–90°C) or a mixture of petroleum ether and diethyl ether to give **3** and **2** successively. The melting points and ^{1}H NMR data of **2a**, **2b**, **2c**, **2d** and **2e** agreed well with those reported [6,12].

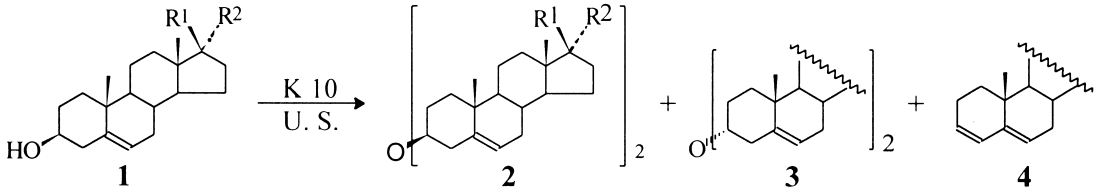
2a: R_f=0.33, petroleum ether–diethyl ether (2/1, v/v) as eluent. **3a**: R_f=0.62, mp 140–143°C (colorless needles from dichloromethane); ν_{max} 2940, 1738, 1458, 1372, 1100 cm^{-1}; δ_H (500 MHz) 0.888(6H, s, 18, 18′–H), 1.030(6H, s, 19, 19′–H), 3.164(2H, m, $W_{1/2}$=16 Hz, 3β, 3β′–H), 5.380(2H, m, 6,6′–H) ppm; m/z (%): 316(25), 271(10), 270(42), 261(70), 255(35), 231(74), 213(26), 199(8), 160(4), 145(16), 121(28), 105(30), 85(100).

2b: R_f=0.47, petroleum ether–diethyl ether (2/1, v/v) as eluent. **3b**: R_f=0.56, mp 103–105°C (colorless needles from dichloromethane); ν_{max} 2940, 1700, 1430, 1352, 1095 cm^{-1}; δ_H (200 MHz) 0.63(6H, s, 18,18′–H), 1.00(6H, s, 19,19′–H), 2.13(6H, s, 21,21′–H), 3.16(2H, m, $W_{1/2}$=16 Hz, 3β,3′β–H), 5.38(2H, m, 6,6′–H) ppm; m/z (%): 428(2), 396(5), 358(8), 344(22), 314(12), 298(60), 283(32), 259(31), 213(32), 145(36), 121(28), 105(35), 85(100), 85(66), 43(100).

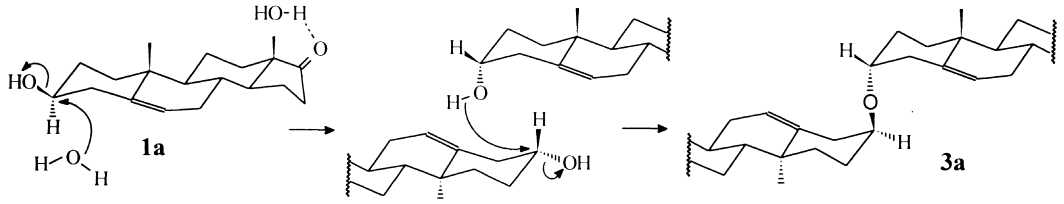
3. Results and discussion

As shown in Table 1 and Scheme 1, several side-chain-varied sterols (**1a**–**1e**) were catalyzed by montmorillonite K 10 at 42–46°C in dichloromethane for 2–5.5 h to give the corresponding disteryl ethers (**2a**–**2e**) in 35–79% yield under irradiation of ultrasound. The use of ultrasound affords a shorter reaction time (2–5.5 h) than the reported procedure (6–13 h) [12] and gives a comparable yield (35–79%). In the absence of ultrasound, the configuration of C-3 in the products was 3β,3′β-disteryl ethers (**2**). Irradiation with ultrasound facilitates the formation of some 5(6),5′(6′)-unsaturated 3α,3′α-disteryl ethers. For example, 3β-hydroxy-5-androsten-17-one (**1a**) provided, except for 3β,3′β-diandrost-5-en-17-one-3-yl ether (**2a**) in 40% yield, 3α,3′α-diandrost-5-en-17-one-3-yl ether (**3a**) in 17% yield. Under the same conditions, pregnenolone (**1b**) provided 3α,3′α-dipregn-5-en-20-one-3-yl ether (**3b**) in 23% yield, together with 3β,3′β-dipregn-5-en-20-one-3-yl ether (**2b**) in 35% yield. In the other three cases, sitosterol (**1c**), cholesterol (**1d**) and stigmasterol (**1e**) provided only 3β,3′β-disteryl ethers (**2c**–**2e**) in 69–79% yield.

Compounds **3a** and **3b** have larger R_f values on TLC than their 3β,3′β-isomers, **2a** and **2b**, respectively. This implies they might have an 3α,3′α-ether function. Even so, the stereochemistry of **3a** and **3b** was mainly assigned by their high resolution ^{1}H NMR (500 MHz) spectra. The C-3 protons in **3a** and **3b** were both at δ 3.16 (m, $W_{1/2}$=16 Hz) ppm, whereas those of **2a** and **2b** were both at δ 3.29 (m, $W_{1/2}$>20 Hz) ppm. These illustrated that C-3 protons in **3a** and **3b** occupied equatorial positions and thus the stereochemistry of **3a** and **3b** was 3α,3′α-disteryl ether (Scheme 2). There were two methyls resonance signals in **3a** and three methyls resonance



Scheme 1. Preparation of disteryl ethers.



Scheme 2. Plausible mechanism for the formation of **3a**.

signals in **3b** indicated that both **3a** and **3b** had symmetric structure and therefore the possibility of a structure of 3α,3′β-configuration could be excluded.

The electron impact mass spectra of **3a** and **3b** show no molecular ions, while their 3β,3′β-isomers **2a** and **2b** show molecular ions, although in very low intensities [12]. However, some fragments were detected, such as m/z 316 (30%), 301 (2%), 270 (45%) and 231 (75%) in **3a** and m/z 428 (3%), 396 (6%), 358 (8%) and 344 (20%) in **3b**. These results implied that **3a** and **3b** were less stable than their 3β,3′β-isomers **2a** and **2b**.

It was very interesting that no 3α,3′α-disteryl ethers (**3c**–**3e**) were isolated from the three long alkyl side chained sterols **1c**–**1e**. This suggests that the long side chain of a sterol prohibited the formation of unstable 3α,3′α-disteryl ethers. The reason for these results is unclear. A plausible mechanism is proposed in Scheme 2. This mechanism might involve a two-step SN_2 with water participation. Ketone groups in **1a** and **1b** might favour the association with water due to hydrogen bonding. Steroidal-3,5-dienes (**4**) are by-products, yield 5–10%, from the above reactions.

4. Conclusion

In conclusion, ultrasound can accelerate the formation of 3β,3′β-disteryl ethers catalyzed by montmorillonite K 10. 3α,3′α-Diandrost-5-en-17-one-3-yl ether (**3a**) and 3α,3′α-dipregn-5-en-20-one-3-yl ether (**3b**) are obtained as by-products from dehydroisoandrostone (**1a**) and pregnenolone (**1b**) respectively.

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