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Article type : Special Issue Research Article

Photochemical behavior of some estrone aryl and methyl sulfonates in solution: Preparative and mechanistic studies†

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†This article is part of a Special Issue commemorating the XIV ELAFOT Conference held from November 11th to 14th, 2019 in Viña del Mar, Chile.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/PHP.13272

ABSTRACT

Direct irradiation of estrone aryl and methyl sulfonates in different organic solvents under nitrogen atmosphere was investigated under steady-state conditions. The estrone derivatives reacted efficiently through the photo-Fries rearrangement reaction involving [1;3]-sulfonyl migration providing the *ortho*-sulfonyl estrone derivatives and estrone as the photoproducts. In addition, estrone and 2-arylsulfonyl estrone derivatives were epimerized involving a Norrish Type I reaction. Chemical quenching and photosensitization experiments on the photoreaction have been also carried out to establish the photo reactive excited state. Likewise, the solvent effect and the nature of the sulfonyl group on the photoreactions have been also studied.

INTRODUCTION

Estrone and estradiol are steroidal sex hormones possessing significant physiological activity and have attracted the attention of organic chemists promoting the development of new and challenging total synthesis (1, 2). These estrogens are involved in many biological processes and certainly, drugs bearing steroidal motifs are used for the treatment of different medical conditions (3). Thus, novel potent inhibitors of 17β-hydroxy steroids dehydrogenase type 1 (17β-HSD) bear the estrone motif where the position at carbon 6, 16, or 17 have been modified (4). This enzyme can be found in all classical steroidogenic tissues, all peripheral tissues, including the skin and breast, and moreover, it is highly expressed in malignant breast cells (5). 3-Hydroxyestra-1,3,5(10)-trienyl toluene-*p*-sulfonate was found to be one of the best inhibitors of estrone sulfatase activity exhibiting an inhibitory activity close to that of estrone-3-methylthiophosphonate (E1-3-MTP), one of the classical potent inhibitor known (6). Likewise, alkylsulfonate derivatives of estrone; i.e., the methanesulfonate, the ethanesulfonate and the butanesulfonate, all showed some inhibition of estrone sulfatase but not at levels of the estrone toluene-*p*-sulfonate (7). Therefore, sulfonylation of the estrone moiety could provide a new family of derivatives with the potential ability to inhibit the estrone sulfatase activity in regulating estrogen production. The synthetic 17α-ethinylestradiol, a phenolic steroid, is responsible for the development of secondary sexual characteristics in female vertebrates (8).

The photochemical behavior of steroids in solution was completely studied in terms of photorearrangement, photoaddition, photoreduction and photooxidation reactions throughout the years (9), and photochemical approaches toward the synthesis of natural products have been applied with success (10). The photochemistry of steroids have been studied in terms of preparative, mechanistic and taking into account the stereospecificity of the photoreaction and some interesting examples are depicted in Scheme 1 (11-19). Indeed, photoinduced lactonization reaction of some cholestan-6-one derivatives provided efficiently 6-oxa-B-homocholestan-7-ones with retention of the configuration at C-5 (12). Likewise, direct irradiation of 3α-(dimethylphenylsilyloxy)-5α-androstane-6,17-dione and its 3β isomer gave two distinct photoproducts arising from the photoreduction and the Norrish type I

reactions of the steroids. An antenna-photosensitization process from the arylsilyloxy group to the carbonyl groups through triplet and singlet energy transfers accounts for this particular behavior (16).

Direct irradiation of estrone and estrone 3-methyl ether showed the epimerization of methyl group at C-13 located at ring D of the steroids involving a Norrish Type I reaction (see Scheme 1). Also, seco-steroids as byproducts were formed when anhydrous THF was used as solvent (20). Irradiation of estrone with UV-B (280 – 320 nm) led to the almost complete conversion into lumiestrone in acetonitrile as well as in water under aerobic conditions (21). These results confirmed that 13α-epimerization reaction occurred through the Norrish type I mechanism which is typically observed with cyclic ketone moiety (22). The photocatalytic azolylation reaction of estrone methyl ether, a precursor leading to an FDA approved oral contraceptive (mestranol), have been reported by Weaver and co-workers and they were able to isolate the desired estrone derivative in 37% yield as a single regioisomer in which the benzothiazolylation occurred at C_4 position of the estrone 3-methyl ether (23). Recently, the photodegradation of estrone and 17α-ethinylestradiol with HCO_3^-, NO_3^- and 254 nm photolysis has been reported (24) because these steroids are considered as toxic contaminants of emerging concerns (CECs) for water reused applications. Estrogens were also photooxidized efficiently with humic acids in the presence of Mn(III) (25) and the application of alkene cyclopropanation with chloromethyl silicate through a visible-light-mediated redox neutral catalysis of vinylphosphonate derived from estrone took place efficiently and the photoproduct was isolated in 92% yield (26).

<Insert Scheme 1>

However, the direct irradiation (254 nm) of estrone arylsulfonate and estrone methylsulfonate was not previously reported yet in the literature, we were encouraged to undertake a more extensive work and to study accurately the reaction mechanism for which we chose as the substrates the estrone derivatives that are shown on Chart I.

<Insert Chart I>

These estrone derivatives **1** – **4** bearing a sulfonic ester group on the phenyl ring of the steroids, became interesting substrates to study the possible photo-Fries rearrangement under direct irradiation (λ_{exc} = 254 nm). Anderson and Reese (27) have discovered the photo-Fries rearrangement reaction in 1960 and later it was demonstrated that the photoreaction involves the homolytic fragmentation of the carbon–heteroatom bond, *i.e.*, C-O, C-S and C-N, characteristic bonds present in esters, thioesters and amides, respectively (28). Usually, the photoreaction provided the *ortho*- and *para*-regioisomers along with the corresponding phenols, thiophenols or amines, depending on the nature of the carbon-heteroatom bond cleaved (29). Also, it was established that the photoreaction involved an in-cage radical mechanism and it is known that the singlet state is the photo reactive excited state (29). The preparation of griseofulvin (30), daunomycinone (31) and flavonoids (32) have successfully employed the photo-Fries rearrangement reaction, however, most of the studies have been devoted to elucidating the mechanism of the reaction rather than its application as a synthetic methodology. In addition, we have also contributed to show how important is the application of the photo-Fries rearrangement reaction in the preparation of 2,2-dimethyl-4-chromanone derivatives (33, 34) and carbazole derivatives (35, 36). Recently, we were able to show the selectivity and the effect of surfactant micelles on the photo-Fries reaction of an assortment of substituted acetamides (37) as well as substituted aryl benzoates (38) and also, the photochemical behavior of 3-aryloxy estrone derivatives in solution (39).

Therefore, we present herein our work on the direct irradiation of estrone derivatives **1** – **4** (see Chart I) in term of product distribution, triplet photosensitization and chemical quenching of the photochemical reaction.

MATERIALS AND METHODS

Materials and equipment. Estrone, tetramethyl-diazodiazetine dioxide, benzene sulfonyl chloride, pyridine, *p*-methylphenyl sulfonyl chloride and acetone were obtained from commercial sources. Spectroscopic grade solvents were used as received but pyridine was first distilled and immediately stored over KOH pellets. A Fisher Jones apparatus was used to determine the Melting Points and were

not corrected. NMR spectra were recorded on a 500 MHz spectrometer using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in parts per million (ppm), relative to the internal standard signal of tetramethylsilane. 2D NMR spectra (HSQC and HMQC sequences) were also recorded in $CDCl_3$ on the same spectrometer. All the mono and bi-dimensional measurements were carried out using standard pulse sequences and the coupling constant (*J*) values were given in Hz. A Shimadzu UV-1203 spectrophotometer was used to record the UV-visible spectra using two-faced stoppered quartz cuvettes (1 mm x 1 mm) at 298 K. HR-MS (ESI) analyses were performed on a Bruker micrOTOF-Q-11 instrument. Quadrupole – time of flight analyzer that provides exact masses with an error less than 3 ppm in EM and less than 5 ppm in EM/MS.

General Procedure for the Synthesis of estrone aryl and methane sulfonates 1, 3 and 4. Estrone (1.85 mmol) was dissolved in pyridine (10 mL) and the solution was placed in an ice-bath. Then, the corresponding sulfonyl chloride (2.22 mmol) was added dropwise to the solution during 10 minutes under gentle stirring. The solution was stirred at 25 ºC until positive control by TLC. Then, the reaction mixture was extracted with dichloromethane (10 mL) and washed with a solution of diluted HCl (10 mL). The organic phase was washed with water, dried over sodium sulfate, filtrated off and finally, was evaporated under vacuum. The solid was washed with 10 mL of methanol at 0/5 °C and it was dried in the air. The corresponding sulfonates were obtained in good yields. Compounds **1, 3** and **4** were fully characterized by physical and spectroscopic data (^1H and ^{13}C NMR) (see Supporting Information).

General Procedure for the Synthesis of estrone 4-fluorophenyl sulfonate 2. 4-Fluorobenzene-1-sulfonyl chloride was prepared following the methodology previously reported in the literature with some slight modifications (40). Preparation of estrone 4-fluorophenyl sulfonate **2** with the 4-fluorobenzene-1-sulfonyl chloride in pyridine was performed by the sulfonylation method previously described giving **2** as a white solid after purification by flash chromatography on silica gel using mixtures of hexane and ethyl acetate as the eluent (0.46 g, 88%). Compounds 4-fluorobenzene-1-sulfonyl chloride and **2** were fully characterized by physical and spectroscopic data (^1H and ^{13}C NMR) (see Supporting Information).

General Procedure for the Synthesis of compounds 7, 8 and 9. The preparation of compound **7** was performed according to the methodology reported in the literature (39). Next, the preparation of *nor*estrone phenyl sulfonate **8** and *nor*estrone methane sulfonate **9** with benzenesulfonyl chloride and methanesulfonyl chloride, respectively, was performed according to the method previously described giving compounds **8** and **9** in good yields and these compounds were fully characterized by physical and spectroscopic data (^{1}H and ^{13}C NMR) (see Supporting Information).

General procedure for the irradiation of estrone aryl and methane sulfonates. The general procedure for the irradiation of compounds **1 – 4, 8** and **9** were performed according to the methodology reported in the literature (39). The photoproducts were isolated and characterized by mean of physical and spectroscopic methods (see Supporting Information).

General Procedures for Potentiometric Titrations. A stock solutions of sulfonates (**1**, **3** and **4**, 0.106 mmol) in acetonitrile or methanol were irradiated for 15, 30, 60, 120 and 150 min, under nitrogen atmosphere. Known volumes of these irradiated solutions were diluted to 100 mL with deionized water. The extent of photoacid generation was determined by titration using a validated solution of NaOH 0.0212 N. Potentiometric titrations were performed using a standard proton glass electrode and a pH meter Cole-Parmer Chemcadet 5986-50.

Preparation of the relative yield profiles. The relative yield profiles were constructed as follow. Aliquots of the reaction mixture were picked up at different irradiation times and each aliquot was evaporated leading to a solid residue that was dissolved in deuterated chloroform. Then, the ^{1}H-NMR spectra of the solutions were recorded. Finally, the aromatic protons of the aryl ring of the steroid derivatives were chosen as the diagnostic signals and, after integration of these signals, the yields were calculated.

RESULTS

Irradiation of estrone aryl sulfonate in solution.

Direct irradiation with λ_{exc} = 254 nm of estrone benzene sulfonate (**1**), estrone p-fluorobenzene sulfonate (**2**) and estrone p-methylbenzene sufonate (**3**) in cyclohexane and methanol under nitrogen atmosphere gave the following photoproduct distribution which are the expected ones from the photo-Fries rearrangement, viz. the *ortho* regioisomers (**1a** and **1b** from compound **1**, **2a** and **2b** from compound **2** and **3a** and **3b** from compound **3**), and estrone (**5**). Additionally, lumiestrone (**6**) was detected in the reaction mixtures and compounds **1c**, **2c** and **3c** were also detected in the reaction mixture after irradiation of estrone benzene sulfonate (**1**), estrone p-fluorobenzene sulfonate (**2**) and estrone p-methylbenzene sulfonate (**3**), respectively. The photo-Fries rearrangement reactions of the estrone sulfonate derivatives are depicted in Scheme 2.

<Scheme 2>

On the other hand, when the irradiations of the estrone aryl sulfonates (**1** – **3**) were carried out in acetonitrile the product distribution was completely different. Indeed, estrone (**5**) and lumiestrone (**6**) were the only products detected in the reaction mixtures being estrone the main product in all the cases. Also, irradiation with UV-light (254 nm) of compound **1** in tetrahydrofuran provided lumiestrone **6** in quantitative yield. These polar aprotic solvents (acetonitrile and tetrahydrofuran) change completely the course of the photoreaction favoring the photoinduced solvolysis of the sulfonic esters **1**, **2** and **3** providing exclusively estrones **5** and **6** and cancelling the [1;3]-migration of the arylsulfonyl group to give the *ortho*-regioisomers. We have selected three different reaction solvents showing distinct polarity and proticity properties in order to study their effect on the photochemical behavior of the estrone sulfonate derivatives, a procedure that is often applied when photochemical reactions are studied for the first time.

Table 1 shows the chemical yields of the photoproducts formed. It is apparent from the data that the *ortho*-regioisomers are the main photoproducts obtained when the reaction solvent was cyclohexane. In fact, the (**a**+ **b** + **c**) / (**5** + **6**) ratios change from 3.1 to 4.2, always favoring the formation of the *ortho*-regioisomers over the estrones, but the ratios change only from 1.1 to 1.7 when the solvent is methanol. On the other hand, the data displayed in the table also shows that the [1;3]-migration of the arylsulfonyl group is preferred to position 4 of the aryl moiety over the migration of the same group to position 2 and certainly does not depend significantly on the reaction solvent as can

be seen from the (**b**/**a**) ratio that have a 2.3 mean value in both reaction solvents. The low selectivity of the migration observed for the aryl sulfonyl group to carbon 2 can be attributed to the steric electronic effect due to the ring B of the steroid.

<Insert Table 1>

The quantum yields (ϕ_R) assigned to the consumption of estrone arylsulfonates (**1**, **2** and **3**) were also measured (see Table 1). The ϕ_R values of estrone **1** move from 0.010 to 0.020 in all the solvents used while for esters **2** and **3** the ϕ_R values are 3 to 5 times lower than 0.02 when the irradiations were carried out in acetonitrile and cyclohexane, respectively. However, these ϕ_R values mean that the photochemical reaction took place smoothly and could compete with radiative and non-radiative pathways.

The photochemical reaction of the estrone aryl sulfonates **1** – **3** were followed by UV-visible and NMR spectroscopies. Figure 1(a) and (b) shows the variation of the UV-visible absorption spectra with the irradiation time of the photochemical reaction of estrone *p*-fluorobenzene sulfonate (**2**) in methanol and estrone *p*-methylbenzene (**3**) in cyclohexane. A new absorption band situated at 300 nm is formed and rises with irradiation time in the above-mentioned solvents. The new bands were assigned to the electronic transition of the sulfonyl group of the *ortho*-regioisomers (42) and it was found that the position of the new band was not affected upon solvent polarity change. Similar spectroscopic behavior was observed for estrone benzene sulfonate (**1**) in both cyclohexane and methanol.

Figure 1(c) outlines the course of the photochemical reaction of ester **2** in methanol measured by NMR spectroscopy where it can be deduced that the migration of the *p*-fluorobenzene sulfonyl group is the main reaction pathway providing *ortho*-regioisomers **2a**, **2b** and **2c**. Diagnostic signals (aromatic protons) of the estrone derivatives (**2**, **2a**, **2b**, **2c**, **5** and **6**) were accurately selected and, after integration of these signals, the yields were calculated. Similar results were obtained when the course of the photoreaction was carried out in cyclohexane. Notably, the sum of the yields of estrone (**5**) and lumiestrone (**6**), respectively, was lower than 22% in cyclohexane while in methanol was lower than 43%. Figure 1(d) shows the relative formation of compounds **2a, 2b** and **2c** finding that similar relative rates were obtained in methanol as well as in cyclohexane. The finding leads to the

conclusion that radiative and non-radiative decay competitively with the photochemical reaction pathway.

<Insert Figure 1>

On the other hand, it is apparent from the relative yield profile shown in Figure 1(c) that the photoinduced Norrish Type I reaction competes with the photo-Fries rearrangement reaction during the irradiation of estrone **2**. Effectively, both photoproducts **2a** and **5**, respectively, reached a maximum yield value at *ca.* 60 minutes and then, each compound was consumed at distinct rate. This behavior was attributed to the epimerization of the methyl group at C-13 of the nucleus D of the estrone moiety in compounds **2a** and **5**, respectively. Indeed, irradiation of compound **2a** at 254 nm provides efficiently compound **2c** in 11% through a Norrish Type I mechanism involving the epimerization of methyl group (see Scheme 3). No epimerization of region isomer **2b** occurred during irradiation of ester **2**. Likewise, estrone (**5**) was converted smoothly to lumiestrone (**6**) during the irradiation of estrone *p*-fluorobenzene sulfonate (**2**) because of the easily epimerization of the methyl group attached on the ring D of the steroid (see Scheme 3) (20, 21). The epimerization reaction observed on compounds **2a** and **5**, respectively, involves a homolytic fragmentation of the Cα attached to the carbonyl group at ring D providing a biradical intermediate as is depicted in Scheme 3. Then, an intramolecular cyclization pathway provided the epimerized photoproducts, viz. **2c** and **6**, respectively. A similar behavior was observed for estrone aryl sulfonates **1** and **3**, where compounds **1a**, **3a** and estrone **5** epimerized efficiently during the photochemical reaction providing compounds **1c**, **3c** and lumiestrone **6**, respectively.

<Insert Scheme 3>

Figure 2 shows the course of the epimerization of estrone **5** into lumiestrone **6** which are formed during the irradiation of estrone *p*-fluorophenyl sulfonate **2** in methanol followed by ^{1}H-NMR spectroscopy. It is apparent from the stacked spectra that the signal with chemical shift at 0.90 ppm assigned to the methyl group at C-13 of estrone **5** diminishes as the reaction time increases while a new signal with chemical shift of 1.05 ppm that was assigned to the methyl group of lumiestrone **6**,

increases. Therefore, these results demonstrate once again that the epimerization of compound **5** involves the homolytic fragmentation of the α carbon through the Norrish Type I reaction mechanism.

<Insert Figure 2>

The noticeable photo stability observed for compounds **1b**, **2b** and **3b** during irradiation of estrone sulfonates **1**, **2** and **3** can be ascribed to the strong intramolecular hydrogen bonding between the thionyl group and the hydroxy group of the β-hydroxysulfone moiety which is present in the aromatic ring A of the steroid (see Scheme 4). Excitation with light of 254 nm of compounds **1b**, **2b** and **3b** bearing a β-hydroxy sulfone group in their structures, the π,π* excited states are populated efficiently where the thionyl group becomes more basic and the phenolic group usually becomes more acidic favoring the excited state intramolecular proton transfer (ESIPT) process that then follows the deactivation pathways (radiative and non-radiative pathways). Therefore, the epimerization of the methyl group at C-13 of compounds **1b**, **2b** and **3b**, respectively, was not observed and no competition with deactivation pathways occurred. A similar behavior has been early observed for 3-acyl estrone derivatives (39). On the other hand, epimerization of compounds **1a**, **2a** and **3a** to photoproducts **1c**, **2c** and **3c**, respectively, is due to the non-planarity of the arylsulfonyl group with the benzene moiety disfavoring the intramolecular hydrogen bonding between the thionyl group and the hydroxyl group. Therefore, in these cases the ESIPT process is not a competitive pathway and the epimerization reaction of the carbonyl group proceeds smoothly because an intramolecular triplet photosensitization process occurs from the aryl moiety to the carbonyl group at C-17 of compounds **1c**, **2c** and **3c** accordingly with was previously reported in the literature for 3α-dimethylphenylsilyloxy androstanone derivatives (16, 43) and 3-acylestrone derivatives (39).

<Insert Scheme 4>

Chemical quenching and photoinduced sensitization of the photo-Fries rearrangement of estrone aryl sulfonates.

The multiplicity of the photo reactive excited state that led to the photo-Fries rearrangement reaction of estrone phenyl sulfonate (**1**) was determined performing triplet sensitization of the photoreaction with acetone and triplet energy quenching with tetramethyl-1,2-diazetine dioxide (TMDO). Triplet photosensitization of photo-Fries rearrangement of estrone **1** was carried out in acetone because acetone was the triplet energy donor while estrone **1** was the triplet energy acceptor. Indeed, the E_T of acetone (44) is 74 kcal.mol^{-1} while the E_T of estrone phenyl sulfonates was assumed to be 69.4 kcal.mol^{-1} (45) considering the phenyl sulfonate group does not modify substantially the value of the estrone moiety. Therefore, the triplet energy transfer pathway was a thermodynamically feasible process by *ca.* 5 kcal.mol^{-1}. Then, irradiation of estrone phenyl sulfonate **1** was carried out with λ_{exc} = 310 nm in acetone and the results are collected in Table 2. The data in the Table 2 indicates that irradiation of estrone **1** in acetone provided a distinct photoproduct distribution when compared with the results obtained in cyclohexane. Indeed, the photosensitized reaction provided estrone **5** and lumiestrone **6** as the sole photoproducts while the *ortho*-regioisomers **1a** and **1b** were not formed. Noteworthy, the yield of estrone **5** increased four times while the yield of lumiestrone **6** was doubled under acetone photosensitization.

<Insert Table 2>

We have also studied the quenching of the photo-Fries rearrangement by tetramethyl-1,2-diazetine dioxide (TMDO) which is a triplet energy quencher (E_T = 54.0 kcal.mol^{-1})(36) and we were able to show that the energy gap between its triplet state and that of estrone **1** was of *ca.* 15 kcal.mol^{-1} and we concluded that the triplet energy transfer pathway is hence possible. Then, irradiation of estrone phenyl sulfonate **1** in cyclohexane but in the presence of increasing amounts of TMDO showed that the photo-Fries rearrangement reaction proceeded efficiently while the yields of estrone **5** and lumiestrone **6** diminished significantly (see Table 2). Therefore, after accurate rationalization of the results, we can conclude that: (i) the excited triplet state of estrone phenyl sulfonate **1** is not the photo reactive state in the photo-Fries rearrangement reaction and, (ii) the conversion of estrone **5** into lumiestrone **6** certainly involves the triplet excited state because the photoepimerization reaction was efficiently quenched by TMDO. The photoepimerization reaction of estrone **5** is in agreement with

similar results reported in the literature such as the involvement of a triplet state in the photoepimerization reaction of cyclic ketones (16, 43, 46). Likewise, we have previously demonstrated that direct irradiation of estrone methyl ether furnished lumiestrone methyl ether involving the photoepimerization of methyl group at C-13 through a Norrish type I mechanism (39). Furthermore, we have also assessed that the photoepimerization reaction of estrone methyl ether was efficiently quenched by TMDO and was sensitized by acetone confirming that the triplet excited state is the photo reactive excited state of the photoreaction. Finally, we can conclude from these experiments that the photo-Fries rearrangement reaction of estrone aryl sulfonates takes place from the singlet excited state (S_1) while the photo epimerization of estrone proceeds from the triplet excited state (T_1).

Irradiation of estrone methyl sulfonate (4) in homogeneous media.

Surprisingly, irradiation with λ_{exc} = 254 nm of estrone methane sulfonate **4** in different solvents under nitogen atmosphere did not provide the expected photo-Fries photoproducts, instead, a noticeable distinct product distribution was obtained, viz. compounds **4a**, **4b** and lumiestrone **6** as it is depicted in Scheme 5(a). Table 3 also showed the chemical yields of the photoproducts.

<Insert Scheme 5>

Table 3 showed that direct irradiation of estrone methane sulfonate **4** in cyclohexane and acetonitrile gave compound **4a** in good yield being the main photoproduct. In the case the reaction was carried out in acetonitrile, lumiestrone **6** was also detected but in only 7% yield. The conversion of **4** into **4a** was attributed to the photo epimerization of the methyl group (the C-13 located at the ring D of compound **4**) through a Norrish Type I photoreaction that proceeded efficiently in both reaction solvents. Furthermore, formation of lumiestrone **6** turned out to be the hydrolysis of compound **4a** as well as the starting material (**4**).

<Insert Table 3>

The course of the photoreaction of estrone **4** in acetonitrile was measured by NMR spectroscopy as it is outlined in Figure 3 where the epimerization of the methyl group at C-13 is the main reaction pathway providing photoproduct **4a**. The relative yield profile was constructed choosing the methyl protons of the steroid derivatives (**4**, **4a** and **6**) and the yields of the steroids were calculated after integration of the signals.

<Insert Figure 3>

When the photoreaction was carried out in methanol compound **4b** was formed in 70% yield along with **4a** and **6** in lower yields (up to 15%). Interestingly, the origin of compound **4b** and **4a** involves the same biradical intermediate **A** which is obtained through a Norrish type I mechanism. Meanwhile, intermediate **A** evolves to **4a** through an epimerization pathway, it is apparent that the same intermediate is able to involve competitively an intermolecular hydrogen abstraction from the reaction solvent releasing intermediate **B**. Oxidation of intermediate **B** by residual molecular oxygen and further reaction with methanol, affords compound **4b** (see Scheme 5(b)). This photochemical behavior was also observed during irradiation of estrone methyl ether (39).

Irradiation of 17-norestrone phenyl sulfonate (8) and 17-norestrone methyl sulfonate (9) in homogeneous media

We decided to synthetize 17-*nor*estrone phenyl sulfonate **8** and 17-*nor*estrone methyl sulfonate **9** as probe compounds with the aim to demonstrate that the carbonyl group (C-17 at the ring D of the steroid) is responsible of the competitive Norrish type I reaction during the irradiation of estrones **1**, **2** and **3**. The preparation of both compounds **8** and **9** involves the application of the Wolf-Kischner reaction on estrone **5** providing 17-*nor*estrone **7** in good yield (91%) (39). Then, treatment of 17-*nor*estrone **7** with benzenesulfonyl chloride in pyridine at room temperature gave compound **8** in 88% yield while treatment of compound **7** with methanesulfonyl chloride compound **9** was obtained in 95% yield (see Scheme 6).

<Insert Scheme 6>

Irradiation of 17-*nor*estrone benzene sulfonate (**8**) in methanol and cyclohexane (λ_{exc} = 254 nm) under nitrogen atmosphere provided the *ortho*-regioisomers **8a** and **8b** and the corresponding 17-*nor*estrone (**7**) (see Scheme 6) as the sole photoproducts when the ester **8** was consumed in up to 90% yield because compound **8** does not bear a carbonyl group at C-17 and, therefore, no photo epimerization of the photoproducts occurred. The selectivity of the benzene sulfonyl group migration did not depend on the reaction solvent used because the **8a**/**8b** ratio was found to be ca. 1.2 in both solvents. On the other hand, irradiation of estrone methane sulfonate **9** in methanol provided the expected *ortho*-regioisomers (**9a** and **9b**) in good yield and no epimerization reaction was observed. The quantum yields of consumption (ϕ_R) of **8** and **9** were also measured and were found to be similar (see Scheme 6). Taking into account that the obtained ϕ_R values are ten-times lower than those obtained for compounds **1** and **4**, respectively, we can suggest that the photo-Fries rearrangement of compounds **8** and **9** proceeded smoothly and radiative and non-radiative decay processes are the solely pathways that compete with the photochemical reaction.

Estrone sulfonates as photoacid generators in acetonitrile.

In order to explain the distinct photochemical behavior observed for estrone aryl and methane sulfonates in acetonitrile (see Tables 1 and 3), we decided to measure potentiometrically the amount of sulfonic acid evolved at different irradiation time when solutions of estrones **1**, **3** and **4** were irradiated with light of 254 nm in acetonitrile. Figure 4(a) shows the potentiometric titration curves of compound **1** at different irradiation time using a validated solution of NaOH 0.0212 mol.dm^{-3}. Certainly, this plot turns out that an acidic photoproduct is formed as the irradiation time increases from 15 to 180 min. Indeed, we can suggest that upon irradiation of estrone benzene sulfonate (**1**) in acetonitrile, benzene sulfonic acid was released as well as estrone (**5**) that, in turn, estrone (**5**) was converted into lumiestrone (**6**) upon irradiation (see Scheme 7). Similar results were obtained for the other two estrone derivatives.

<Insert Scheme 7>

On the other hand, Figure 4(b) depicts a nice representation of sulfonic acids formed to estrones molar ratio as a function of irradiation time of estrone derivatives **1**, **3** and **4** in acetonitrile and in methanol. It is apparent from the plot that during irradiation of the estrone derivatives the acidity of the solution increases with irradiation time. Therefore, the sulfonic acids released to the medium promoted the hydrolysis of the starting materials and consequently, estrone **5** is the main photoproduct formed along with lumiestrone **6** (see Scheme 7). It is apparent from the plots depicted in Figure 4(b) that estrone aryl sulfonates **1** and **3** reacted efficiently and rapidly in acetonitrile than estrone **4** did. However, when the solvent is methanol, estrone benzenesulfonate **1** did not released efficiently significant amounts of the corresponding phenyl sulfonic acid. Similar photochemical acid generators behavior of aryl sulfonate derivatives have been reported in the literature.(47),(48)

<Insert Figure 4>

DISCUSSION

As hinted above, it was found that the direct irradiation (254 nm) of estrone aryl sulfonates **1**, **2** and **3** reacted efficiently in cyclohexane and methanol under nitrogen atmosphere (see Scheme 2 and Figure 1) giving the [1;3]-sulfonyl migrated photoproducts together with estrone (**5**) (see Table 1). Additionally, photo epimerization of **1a, 2a** and **3a** to give compounds **1c, 2c** and **3c**, respectively, occurred efficiently as well as estrone (**5**) was converted into lumiestrone (**6**) during irradiation. This behaviour shows that during the irradiation of sulfonates **1**, **2** and **3** two reaction pathways certainly operate: i) the photo-Fries rearrangement reaction and, ii) the Norrish type I reaction. Based on our results, Scheme 8 depicts the proposed reaction mechanism for the direct irradiation of estrone aryl sulfonates.

<Insert Scheme 8>

Population of the singlet excited state of estrone aryl sulfonates (**1**, **2** and **3**) was achieved upon direct irradiation with light of 254 nm. The singlet excited state is the photo reactive state because the

triplet energy quenching of estrone **1** with TMDO and photosensitization experiments with acetone (see Table 2) have demonstrated that the triplet excited state is not involved in the photo-Fries rearrangement of the estrone derivatives. Then, S-O bond cleavage of the sulfonic ester group (***path (a)***) takes place efficiently from the excited state and the fragmentation pathway competes with fluorescence and prompt-heat processes from the same excited state (k_d). Two radical species are thus formed in the solvent cage after S-O bond was broken, viz. the arylsulfonyl and the phenoxy radicals. These radical species evolve to photoproducts across two competitive pathways: (i) in-cage [1;3] arylsulfonyl radicals migration to positions 2 and 4 affording the expected *ortho*-regioisomers (***path (b)*** in Scheme 8) and, (ii) diffusion of the radical species from the solvent cage giving estrone **5** as well as the aryl sulfonic ester (***path (c)*** in Scheme 8). Indeed, the phenoxy radical captures a hydrogen atom from the solvent furnishing estrone (**5**) while aryl sulfonic acids arise from the reaction of the aryl sulfonyl radical with residual water contained in the organic solvents. Noteworthy, the photochemical behavior of the *ortho*-regioisomers are quite different. In fact, regioisomers **1b**, **2b** and **3b** were photo stable compounds upon irradiation with λ = 254 nm while regioisomers **1a**, **2a** and **3a** were not. This strong photo stability is attributed to the ESIPT process (excited state intramolecular proton transfer) between the thionyl group and the hydroxy group of the β-hydroxysulfone moiety which is present in the aromatic ring A of the steroid (see Scheme 4) causing the deactivation of these *ortho*-regioisomers through radiative and non-radiative pathways. On the other hand, photo-epimerization reaction of compounds **1a**, **2a** and **3a** took place smoothly providing compounds **1c - 3c** due to out-of-plane deviation of the arylsulfonyl group from the co-planarity of the aromatic ring and consequently, disfavoring the intramolecular proton transfer process. Therefore, a singlet-singlet energy transfer occurred efficiently between the aryl moiety and the carbonyl group (C-17) during direct irradiation (254 nm) of compounds **1a** – **3a** promoting the population of the triplet excited state of the carbonyl group (C-17) (see later in the text) (41). Once the triplet state was populated, two competitive deactivation processes arose: (i) deactivation of the triplet state (k''_d in Scheme 8) that restores compounds **1a- 3c** in their ground states and, (ii) the Norrish Type I photoreaction. Thus, the Norrish Type I reaction promotes the fragmentation of the C_α-C=O bond at the ring D of compounds **1a** – **3a** (***path (d)***) providing the corresponding biradical intermediates that then, epimerize the methyl

group at C-13 to give the observed compounds **1c – 3c** (***path (e)***). Similar conclusions can be drawn for the conversion of estrone **5** into lumiestrone **6** (***paths (f)*** and ***(g)*** in Scheme 8) via a Norrish Type I photoreaction (see also Figure 2) (16, 20). Indeed, quenching with TMDO and photosensitization with acetone of the Norrish Type I photoreaction of **5** (Table 2) confirm the involvement of a triplet excited state which is located on the carbonyl group (C-17) of the D ring of the steroid. Therefore, we concluded that the triplet state of the carbonyl group (C-17) is involved in the photoinduced epimerization reaction of compounds **1a**, **2a**, **3a** and **5**. The way the carbonyl group populates the triplet excited state was achieved as follows: selective excitation of the phenolic moiety (the *antenna* chromophore) to its singlet excited state populates efficiently the carbonyl group (C-17; the *acceptor* chromophore) singlet excited state through a singlet-singlet energy transfer because this pathway is a feasible thermodynamic process (see Scheme 9) (39). Then, the triplet excited state (n,π^*) of the carbonyl group is formed through the intersystem crossing process that can compete with the fluorescence emission process. Finally, we can conclude that the photo-epimerization reaction of the methyl group took place smoothly from the triplet excited state ($T_1(n,\pi^*)$) of the carbonyl group through a Norrish Type I reaction mechanism. A similar photochemical behavior has been recently reported for 3-acyl estrone derivatives (39).

<Insert Scheme 9>

Surprisingly, it was observed that direct irradiation of estrone methane sulfonate **4** in cyclohexane, acetonitrile and methanol under N_2 atmosphere did not provide the expected photo-Fries photoproducts while a noticeable distinct product distribution was obtained depending on the reaction solvent (see Table 3 and Scheme 5). This photochemical behavior was attributed to the intramolecular singlet-singlet energy transfer from the *antenna* chromophore (the phenolic moiety) to the carbonyl group (C-17; the acceptor chromophore) that evolved to the selective population of the triplet excited state (n,π^*) of the last group. Then, C(O)-C_α homolytic fragmentation from the triplet excited state occurred and epimerization of the methyl group proceeded smoothly via the Norrish Type I reaction mechanism. Therefore, the photo-Fries rearrangement of compound **4** did not compete with the intramolecular singlet-singlet energy transfer.

Concurrently, it was found that irradiation of estrone aryl sulfonates in acetonitrile released aryl sulfonic acid behaving as efficient photoacid generators (PAGs). Indeed, after excitation of the estrone derivatives, consecutive ***path (a)*** and ***path (c)*** in Scheme 8 proceeded efficiently giving estrone (**5**) and aryl sulfonic acids as the sole photoproducts and no competition of the [1;3]-migration aryl sulfonyl group (***path (b)***) was observed (see Table 1 and Scheme 7). The apparent photo-solvolysis observed in acetonitrile can be ascribed to the significant increase of the acidity in the reaction medium with irradiation time (see Figure 4). Then, a thermal hydrolysis of the estrone aryl sulfonates (***path (h)***) took place very efficiently promoting cleanly the formation of estrone (**5**) that in turn, after absorption of a photon, was converted into lumiestrone (**6**) according to ***path (f)*** in Scheme 8. The photochemical/thermal behavior described above in acetonitrile was also observed for the irradiation of compound **1** in tetrahydrofuran (see Table 1).

Finally, direct irradiation (254 nm) of 17-*nor*estrone benzene sulfonate (**8**) and methane sulfonate (**9**) in methanol and cyclohexane gave the expected *ortho*-regioisomers in good yield and 17-*nor*estrone (**7**) (see Scheme 6). No epimerization of the photoproducts was observed because the carbonyl group at C-17 was absence and consequently, the Norrish Type I reaction does not compete with the photo-Fries rearrangement reaction. Certainly, these results confirmed that if there is no a carbonyl group at the ring D, no intramolecular singlet-singlet energy transfer occurs and thence, no epimerization of the methyl group takes place. We suggest that this methodology would be useful in the synthesis of other kinds of aryl and alkyl sulfone steroid derivatives belonging to the family of estrone through the photo-Fries rearrangement without interference of the Norrish Type I reaction.

CONCLUSIONS

The photochemical behavior of estrone aryl and alkyl sulfonate derivatives examined in this work proceeds efficiently giving the *ortho*-regioisomers and estrone via the photo-Fries rearrangement reaction and the formation of the *ortho*-regioisomers depends on the solvent reaction. We were able to demonstrate that the photoreaction occurs from the singlet excited state through photosensitization and chemical quenching experiments. The S-O bond cleavage gives in-cage sulfonyl and phenoxyl

radicals and competes with the excited state deactivation pathways. These radicals can couple in-cage through a [1;3]-sulfonyl migration to give the desired *ortho*-regioisomers (see Scheme 8) or can diffuse to the bulk and give estrone. Compounds **1b**, **2b** and **3b** were found to be photo stable photoproducts due to the efficient ESIPT processes under UV irradiation (see Scheme 4). On the other hand, irradiation of estrone (**5**) and compounds **1a**, **2a** and **3a** with UV light (254 nm) are found to photoepimerize via a Norrish Type I reaction mechanism (see Schemes 3 and 8) involving the triplet excited state of the carbonyl group (C-17) (see Scheme 9). Surprisingly, irradiation of estrone methane sulfonate **4** did not provide the expected photo-Fries photoproducts while a noticeable distinct product distribution (**4a**, **4b** and **6**) was obtained depending on the reaction solvent (see Table 3 and Scheme 5). This behavior was attributed to the intramolecular singlet-singlet energy transfer process followed by the C(O)-C_α homolytic bond fragmentation that finally, the methyl group epimerizes via a Norrish Type I reaction. Concurrently, irradiation of estrone aryl and methyl sulfonates in acetonitrile released aryl and methane sulfonic acids behaving as efficient photoacid generators (PAGs) (Table 1 and Figure 4). Indeed, the increase of the acidity in the reaction medium with irradiation time (see Figure 4) promotes a thermal hydrolysis of the estrone aryl and methyl sulfonates giving cleanly estrone (**5**) that in turn, was converted into lumiestrone (**6**) (Scheme 8). Finally, the photochemistry of 17-*nor*estrone benzene sulfonate (**8**) and methane sulfonate (**9**) in methanol and cyclohexane gives smoothly the expected *ortho*-regioisomers in good yields along with 17-*nor*estrone (**7**) (see Scheme 6) and no epimerization of the photoproducts was observed because there is no carbonyl group at the ring D of the steroid. Therefore, the Norrish Type I reaction does not compete with the photo-Fries rearrangement reaction. Therefore, we can suggest that this synthetic methodology would be useful in the preparation of other kinds of aryl and alkyl sulfone steroid derivatives belonging to the family of estrone through the photo-Fries rearrangement without interference of the Norrish Type I reaction. Further studies on the preparation of fused 4-chromanone estrone derivatives applying the photo-Fries rearrangement reaction of 3-(3-methylbutenyloxy) estrone derivatives are currently in progress in our laboratory and will be reported in due course.

ACKNOWLEDGEMENTS*:* Partial support for this work from the University of Buenos Aires, Subsidio 20120160100124BA-Programa: 2017 – 2020. SMB and JAR are research members of CONICET. MIQ thanks CONICET for doctoral scholarship (Doctorate Program).

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

UV-visible spectral change vs time of compound **1** and relative absorbance at 330 nm (A/A_∞) of formation of *ortho*-rearranged photoproducts (**1a, 1b** and **1c**) in cyclohexane, physical and spectroscopical data of substrates and photoroducts and copies of 1D and 2D NMR spectra of substrates and photoproducts.

REFERENCES

1. Blickenstaff, R. T., A. C. Ghosh and G. C. Wolf (1974) Total Synthesis of Steroids. (Edited by A. T. Blomquist and H. Wasserman). Academic Press, New York.

2. Daniewski, A. R., T. Kowalcyzk-Przewloka (1985) Total synthesis of aromatic steroids. J. Org. Chem. 50, 2976 - 2980.

3. Liu, L.; B. Kim and S. D. Taylor (2007) Synthesis of 4-formyl estrone using a potential protecting group and its conversion to other C-4-substituted estrogens. J. Org. Chem. 72, 8824 – 8830.

4. Allan, G. M., H. R. Lawrence, J. Cornet, Ch. Bubert, D. S. Fischer, N. Vicker, A. Smith, H. J. Tutill, A. Purohit, J. M. Day, M.F. Mahon, M. J. Reed and B. V. L. Potter (2006) Modification of estrone at the 6, 16, and 17 positions: Novel potent inhibitors of 17β-hydroxysteroid dehydrogenase Type 1. J. Med. Chem. 49, 1325 – 1345.

5. Tremblay, M. R., R. P. Boivin, V. Luu-the and D. Poirier (2005) Inhibitors of type 1 17β-hydroxysteroide dehydrogenase with reduced estrogenic activity: modifications of the positions 3 and 6 of estradiol. J. Enzyme Inhibition and Medicinal Chem. 20, 153-163.

6. Howarth, N. M., A. Purohit, M. J. Reed and B. V. L. Potter (1997) Estrone sulfonates as inhibitors of estrone sulfatase. Steroids, 62, 346- 350.

7. Henriques, R. G., T. S. Widlanski, T. Xu and J. D. Lambeth (1992) Inhibition of steroids biosynthesis by steroids sulfonates. J. Am. Chem. Soc. 114, 7311-7313.

8. Chan, K. Y., B. Courtois, K. Loose and P. M. Hare (2013) Solvent-dependent fluorescence lifetime of estrone, 17β-estradiol and 17α-ethinylestradiol. Photochemistry and Photobiology 89, 294–299.

9. Waters, J. A., Y. Kondo and B. Witkop (1972) Photochemistry of steroids, J. Pharm. Sciences. 61, 321–334.

10. Karkas, M. D., J. A. Porco and C. R. J. Stephenson (2016) Photochemical approaches to complex chemotypes: applications in natural product synthesis. Chem. Rev. 116, 9683 – 9747.

11. Vulliet, E., M. Falletta, P. Marote, T. Lomberget, J. O. Païssé and M. F. Grenier-Loustalot (2010) Light induced degradation of testosterone in waters. Sci. Total Environ. 408, 3554 – 3559.

12. Tiver, S. and P. Yates (1988) Photochemistry of cyclic α-hydroxy ketones. I. The nature and genesis of the photoproducts from steroidal 5-hydroxy 6-keto steroids and related compounds. Can. J. Chem. 66, 214 – 226.

13. Young, R. B., D. E. Lotch, D. B. Mawhinney, T. H. Nguyen, J. C. C. Davis and T. Borch (2013) Direct photodegradation of androstenedione and testosterone in natural sunlight: inhibition by dissolved organic matter and reduction of endocrine disrupting potential. Environ. Sci. Techno. 47, 8416–8424.

14. Bellus, D., D. R. Kearns and K. Schaffner (1969) Photochemische reaktionen. 52. Mitteilung [1]. ZurPhotochemie von α,β-ungesättingtencyclishenketonen: spezifische reaktionen der n,π* und π,π*-triplettzutstände von O-acetyl-tetosteron und 10-methyl-$\Delta^{1,9}$-octalon-(2). Helv. Chim. Acta 52, 971 – 1009.

15. Vulliet, E., B. Giroud, B. and P. Marote (2013) Determination of testosterone and its photodegradation products in surface waters using solid-phase extraction followed by LC-MS/MS analysis. Environ. Sci. Pollut. Res. 20, 1021 – 1030.

16. Wu, Zh.-Zh., and H. Morrison (1992) Organic photochemistry. 95. Antenna-initiated photochemistry of distal groups in polyfunctional steroids. Intramolecular singlet and triplet energy

transfer in 3α-(dimethylphenylsiloxy)-5α-androstan-17-one and 3α-(dimethylphenylsiloxy)-5α-androstane-11,17-dione. J. Am. Chem. Soc. 114, 4119-4128.

17. Blandon, P., W. McMeekin and I. A. Williams (1963) Steroids Derived from Hecogenin. Part III. The Photochemistry of Hecogenin Acetate. J. Chem. Soc. 5727 – 5737.

18. Jeger, O. and K. Schaffner (1970) On photochemical transformations of steroids. Pure Appl. Chem. 20, 247 – 262.

19. Lai, W.-Ch., B. Danko, J. Csabi, Z. Kele, F. R. Chang, M. L. Pascu, T. Gati, A. Simon, A.; L. Amaral, G. Toth and A. Hunyadi (2014) Rapid, laser-induced conversion of 20-hydroxyecdysone. Follow-up study on the products obtained. Steroids 89, 56 – 62.

20. Watcher, M. P., R. E. Adams, M. A. Cotter, and J. A. Settepani (1979) Lumi-mestranol and epi-lumi-mestrano. Steroids 33, 287 – 294.

21. Trudeau, V. L., B. Heyne, J. M. Blais, F. Temussi, S. K. Atkinson, F. Pakdel, J. T. Popesku, V. L. Marlatt, J. C. Scaiano and L. Previtera, D. R. S. Lean (2012) Lumiestrone is photochemically derived from estrone and may be released to the environment without detection. Frontiers in Endocrinology **2012,** doi: 10.3389/fendo.2011.00083.

22. Whidbey, Ch. M., K. E. Daumit, T. H. Nguyen, D. D. Ashworth, J. C. C. Davis and D. E. Latch (2012) Photochemical induced changes of in vitro estrogenic activity of steroid hormones. Water Res. 46, 5287-5296.

23. Arora, A. and J. D. Weaver (2016) Photocatalytic generation of 2-azolyl radicals: intermediates for the azolylaation of arenes and heteroaarenes cia C-H functionalization. Org. Lett. 18, 3996−3999.

24. Huang, Y., M. Kong, D. Westerman, E. G. Xu, S. Coffin, K. H. Cochran, Y. Liu, S. D. Richardson, D. Schlenk and D. D. Dionysiou (2018) Effects of HCO_3^- on degradation of toxic contaminants of eemerging concern by UV/NO·. Environ. Sci. Technol. 52, 12697−12707.

25. Wang, X., J. Yao, S. Wang, X. Pan, R. Xiao, Q. Huang, Z. Wang and R. Qu (2018) Phototransformation of estrogens mediated by Mn(III), not byreactive oxygen species, in the presence of humic acids. Chemosphere, 201, 224 – 233.

26. Guo, T., L. Zhang, X. Liu, Y. Fang, X. Jin, Y. Yang, Y. Li, B. Chen and M. Ouyang (2018) Visible-light promoted redox-neutral cyclopropnation reactions of a-substituted vinylphosphonates

and other Michael acceptors with chloromethyl silicate as methylene transfer reagent. Adv. Synth. Catal. 360, 4459 – 4463.

27. Anderson, J. C. and C. B. Reese (1960) Photo-induced Fries rearrangement. Proc. Chem. Soc. London. 217.

28. Bellus, D. (1971) Photo-Fries rearrangement and related photochemical [1,j]-shifts (j = 3, 5, 7) of carbonyl and sulfonyl groups. *Adv. Photochem.* 8, 109-159.

29. Miranda, M. A. and F. Galindo (2004) Photo-Fries rearrangement. In CRC Handbook of Organic Photochemistry and Photobiology (Edited by W. Horspool and M. Lenci), p. 42-1-42-11. CRC Press, Boca Raton, FL.

30. Taub, D., C. Kuo, H. L. Slates and N. L. Wendler (1963) A total synthesis of griseofulvin and its optical antipode. Tetrahedron 19, 1-17.

31. Kende, A. S., J. Belletrie, T. J. Bently, E. Hume and J. Airey (1975) Regiospecific total synthesis of (±)-9-deoxydaunomycinone. J. Am. Chem. Soc. 97, 4425 – 4427

32. Ramakrisham, V. T. and J. Kagan (1970) Photochemical synthesis of 2'-hydroxychalcones from phenyl cinnamates. J. Org. Chem. 35, 2901 – 2904.

33. Iguchi, D., R. Erra Ballsels and S. M. Bonesi (2014) Expeditious photochemical reaction toward the preparation of substituted chroman-4-one. Tetrahedron Lett. 55, 4653 – 4656.

34. Iguchi, D., R. Erra Ballsels and S. M. Bonesi (2016) Formation of 2,2-dimethylchroman-4-ones during the photoinduced rearrangement of some aryl 3-methyl-2-butenoate esters. A mechanistic insight. Tetrahedron 72, 1903 – 1910.

35. Bonesi, S. M. and R. Erra Balsells (1991) Product study of the photolysis of N-acetyl carbazole in ethanol and dichloromethane solution. Part I. J. Photochem. Photobiol. A. Chem. 56, 55 – 72.

36. Bonesi, S. M. and R. Erra Balsells (1997) Photochemistry of N-acetyl and N-benzoyl carbazoles: photo-Fries rearrangement and photoinduced single electron transfer. J. Photochem. Photobiol. A: Chem. 110, 271 – 284.

37. Iguchi, D., R. Erra Ballsels and S. M. Bonesi (2016) Photo-Fries rearrangement of aryl acetamides: regioselectivity induced by the aqueous micellar green environment. Photochem. Photobiol .Sci. 15, 105 – 116.

38. Siano, G., S. Crespi, M. Mella and S. M. Bonesi (2019) Selectivity in the Photo-Fries Rearrangement of Some Aryl Benzoates in Green and Sustainable Media. Preparative and Mechanistic Studies. J. Org. Chem. 84, 4338- 4352.

39. Quindt, M. I., G. F. Gola, J. A. Ramirez and S. M. Bonesi (2019) Photo-Fries Rearrangement of Some 3-Acylestrones in Homogeneous Media: Preparative and Mechanistic Studies. J. Org. Chem. 84, 7051- 7065.

40. Morizur, V., S. Olivero, J. R. Desmurs, P. Knauth and E. Duñach (2014) Novel lithium and sodium salts of sulfonamides and bis(sulfonyl)imides: synthesis and electrical conductivity. *New J. Chem.* 38, 6193-6197.

41. Goldstein, S. And J. Rabani (2008) The ferrioxalate and iodide-iodate actinometers in the UV region. J. Photochem. Photobiol., A: Chem. 193, 50-55.

42. Fehnel, E. and M. Karmak (1950) The ultraviolet absorption spectra of organic sulfur compounds. IV. Substituted phenyl sulfones. J. Am. Chem. Soc. 72, 1292-1297.

43. Wu, Z.-Z., J. Nash and H. Morrison (1992) Antenna-initiated photochemistry in polyfunctional steroids. Photoepimerization of 3α-(dimethylphenylsilyloxy)-5α-androstane-6,17-dione and its 3β-isomer by through-bond exchange energy transfer. *J. Am. Chem. Soc.* 114, 4119 – 4128.

44. Murov, L. S., I. Carmichael and G. L. Hug (1993) Handbook of Photochemistry. Marcel Dekker, New York.

45. Weinreb, A. and A. Werner (1974) On the luminescence of estrogens. Photochem. Photobiol. 20, 313 – 321.

46. Wagner, P. J. (1976) Chemistry of excited triplet organic carbonyl compounds. Top. Curr. Chem. 66, 1 – 52.

47. Andraos, J; G. G. Barclay, D. R. Medeiros, M. V. Baldovi, J. C. Scaiano and R. Sinta (1998) Model studies on the photochemistry of phenolic sulfonate photoacid generators. Chem. Mater. 10**,** 1694-1699.

48. Torti, E., S. Protti, S. Bollanti, F. Flora, A. Torre, G. Brusatin, A. Gerardino, L. Businaro, M. Fagnoni, G. Della Giustina and L. Mezi (2018) Aryl Sulfonates as Initiators for Extreme Ultraviolet Lithography: Applications in Epoxy-Based Hybrid Materials. ChemPhotoChem, 2, 425-432.

FIGURE CAPTIONS

Figure 1. Figure 1. (a) UV-visible spectral change vs time of **2** in methanol. Blue line: initial time; red line: 14 min. (b) UV-visible spectral change vs time of **3** in cyclohexane. Blue line: initial time; red line: 32 min. (c) Relative yield profile vs time of **2** in methanol: **2, 2a, 2b, 2c, 5, 6**. (d) Relative absorbance at 290 nm (A/A_∞) of formation of *ortho*-rearranged photoproducts (**2a**, **2b** and **2c**) in: cyclohexane (blue squares) and methanol (black circle).

Figure 2. Figure 2. Evolution of the consumption of estrone 5 into lumiestrone 6 during the irradiation of estrone 2 in methanol followed by NMR spectroscopy.

Figure 3. Relative yield profile vs time of **4** in acetonitrile: **4**, **4a** and **6**.

Figure 4. (a) Potentiometric titration curves of estrone benzene sulfonate (**1**) at different irradiation time. (b) Sulfonic acid formed to estrone molar ratio as a function of irradiation time in different solvents.

SCHEME CAPTIONS

Scheme 1. Photochemistry of some steroidal derivatives.

Chart I. Structures of the arylsulfonyl and alkylsulfonyl estrone derivatives.

Scheme 2. The photo-Fries rearrangement of estrone aryl sulfonate (1 – 3).

Scheme 3. The Norrish Type I photoreaction of compound (2a) and estrone (5) in organic solvents.

Scheme 4. Intramolecular proton transfer and radiationless processes of compounds **1b** - **3b**.

Scheme 5. (a) Product distribution obtained after irradiation of estrone methyl sulfonate (4) and (b) Plausible reaction mechanism for the formation of photoproduct **4b**.

Scheme 6. Preparation and irradiation of 17-norestrone **8** and **9**.

Scheme 7. Sulfonic acid release upon irradiation of estrone derivatives **1**, **3** and **4**.

Scheme 8. Proposed reaction mechanism of estrone aryl sulfonates **1**, **2** and **3**.

Scheme 9. Plausible mechanism for intramolecular energy transfer for aryl antenna to the C17-keto group of estrone derivatives (**5**; **1a**; **2b**; **3a**).

Table 1. Irradiation of estrone arylsulfonates **1** – **3** in different solvents under N_2 atmosphere. Yield of photoproducts[a] and reaction quantum yield (ϕ_R).[b]

Estrone arylsulfonates	Solvent	Yields (%)					ϕ_R
		1a	**1b**	**1c**	**5**	**6**	
1	MeOH	17	32	-	13	30	0.010
	Cyclohexane	14	48	4	11	7	0.020
	MeCN	-	-	-	60	15	0.010
	THF	-	-	-	-	100	NM[c]
		2[a]	**2b**	**2c**	**5**	**6**	ϕ_R
2	MeOH	16	40	1	24	10	0.011
	Cyclohexane	15	39	5	10	4	0.006
	MeCN	-	-	-	22	15	0.003
		3[a]	**3b**	**3c**	**5**	**6**	
3	MeOH	15	35	-	18	22	0.002
	Cyclohexane	11	47	11	14	8	0.004
	MeCN	-	-	-	40	8	0.003

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of 3-acyl estrone: 5.0×10^{-3} M. [b]Actinometer: KI (0.6 M), KIO_3 (0.1 M) and $Na_2B_2O_7.10H_2O$ (0.01 M) in water; $\phi(I_3^-) = 0.74$; $\lambda_{exc} = 254$ nm.(41) Error: ± 0.001. [c]Not Measured.

Table 2. Irradiation of estrone phenyl sulfonate in cyclohexane, acetone and the presence of TMDO under N_2 atmosphere.[a]

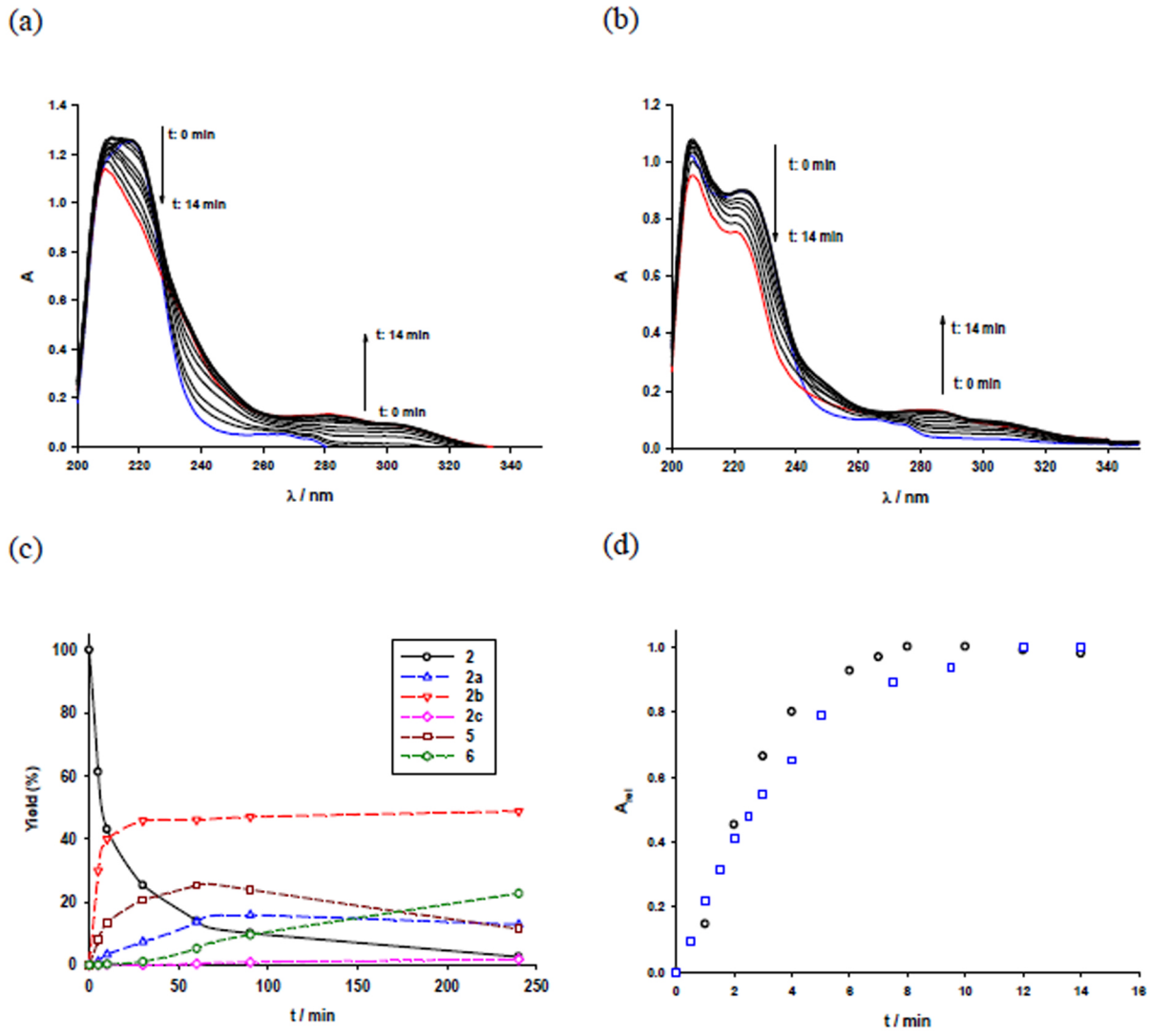
		Additive	Yield (%)				
Estrone	Solvent	**TMDO**[b] ($mol.dm^{-3}$)	**1a**	**1b**	**1c**	**5**	**6**
	Cyclohexane	---	14	48	4	11	7
	Acetone[c]	---	-	-	-	41	15
1	Cyclohexane	$5.0x10^{-4}$	23	43	7	5	2
		$1.0x10^{-3}$	26	51	5	1	-
		$1.5x10^{-3}$	28	56	-	-	-

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of estrone phenyl sulfonate: $1.0x10^{-3}$ M. Irradiation with λ_{exc} = 254 nm. [b]Tetramethyl-1,2-diazetina dioxide (TMDO). [c]Irradiation with λ_{exc} = 310 nm.

Table 3. Irradiation of estrone methane sulfonate **4** in different solvents under N_2 atmosphere. Yield of photoproducts[a] and reaction quantum yield (ϕ_R).[b]

Solvent	Yields (%)			ϕ_R
	4a	**4b**	**6**	
MeOH	15	70	12	0.003
Cyclohexane	56	---	---	0.010
MeCN	80	---	7	0.002

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of estrone methane sulfonate: 5.0×10^{-3} M. [b]Actinometer: KI (0.6 M), KIO_3 (0.1 M) and $Na_2B_2O_7.10H_2O$ (0.01 M) in water; $\phi(I_3^-) = 0.74$; $\lambda_{exc} = 254$ nm.(41); Error: ± 0.001.



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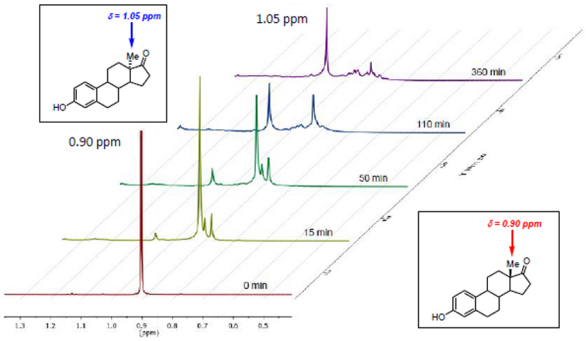

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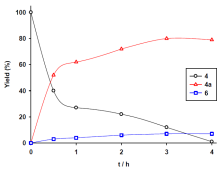

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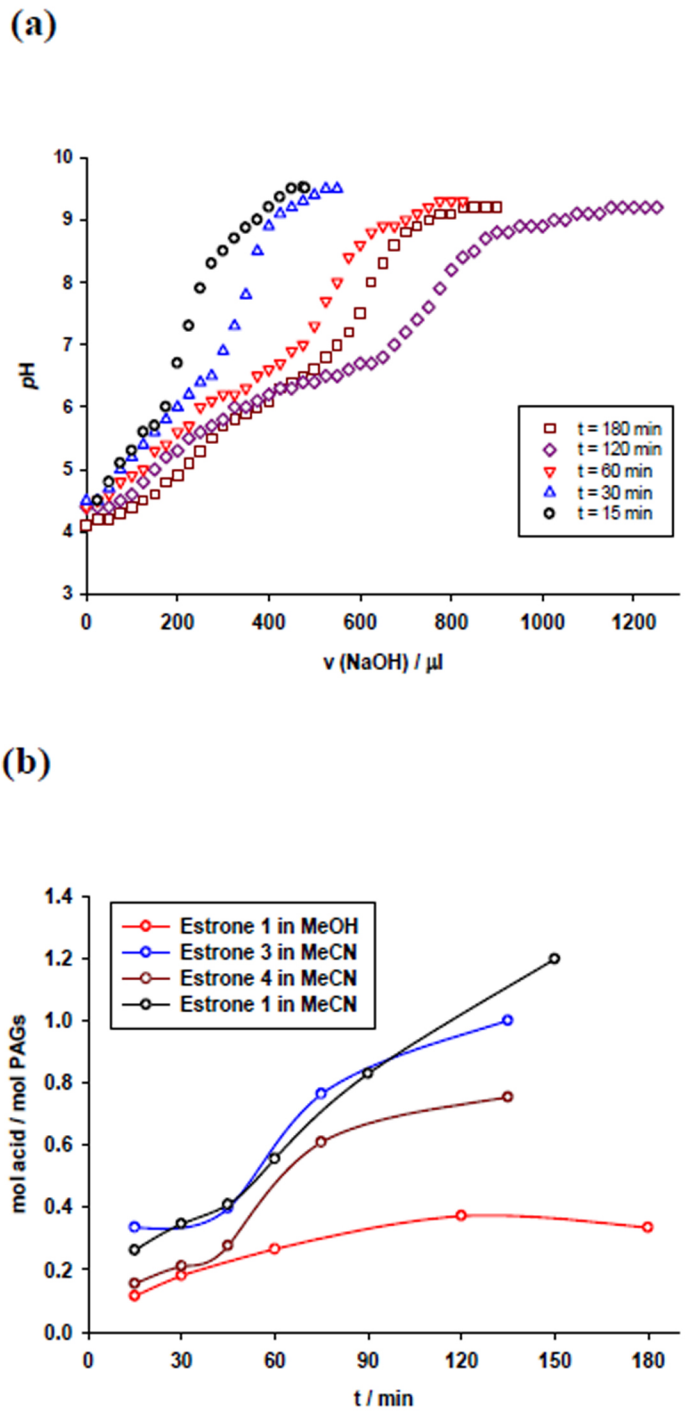

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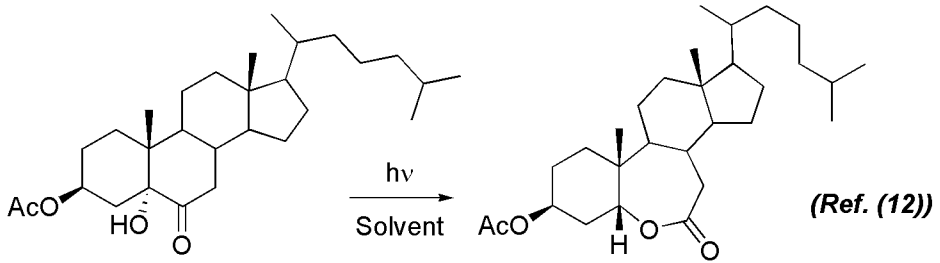
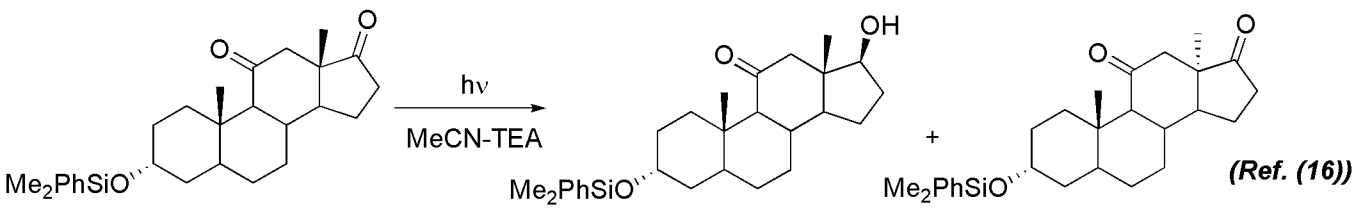


3β-acetoxy-5-hydroxy-5α-cholestane-6-one

6-oxa-B-homocholestan-7-ones

(Ref. (12))

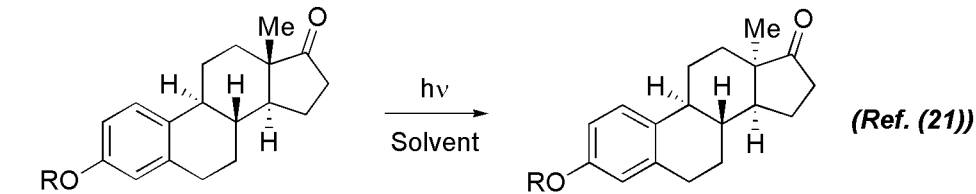


3α-dimethylphenylsilyloxy-5α-androstane-11,17-dione

3α-dimethylphenylsilyloxy-17β-hydroxy-5α-androstan-11-one

3α-dimethylphenylsilyloxy-5α,13α-androstane-11,17-dione

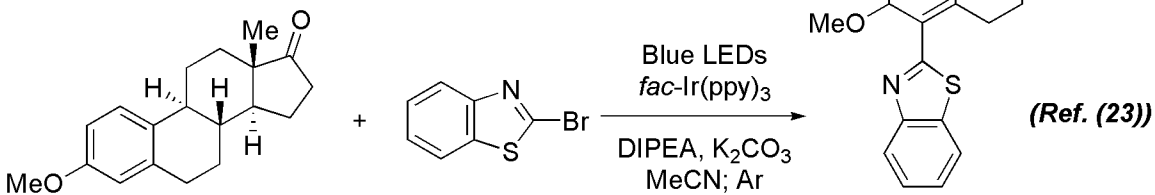
(Ref. (16))



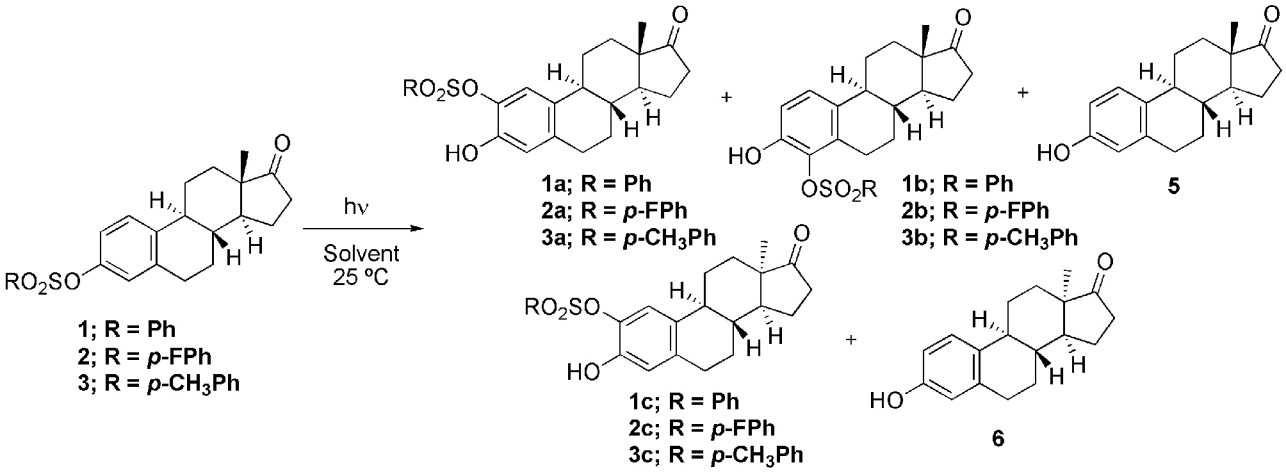
R = H; ***estrone***
R = Me; ***estrone methyl ether***

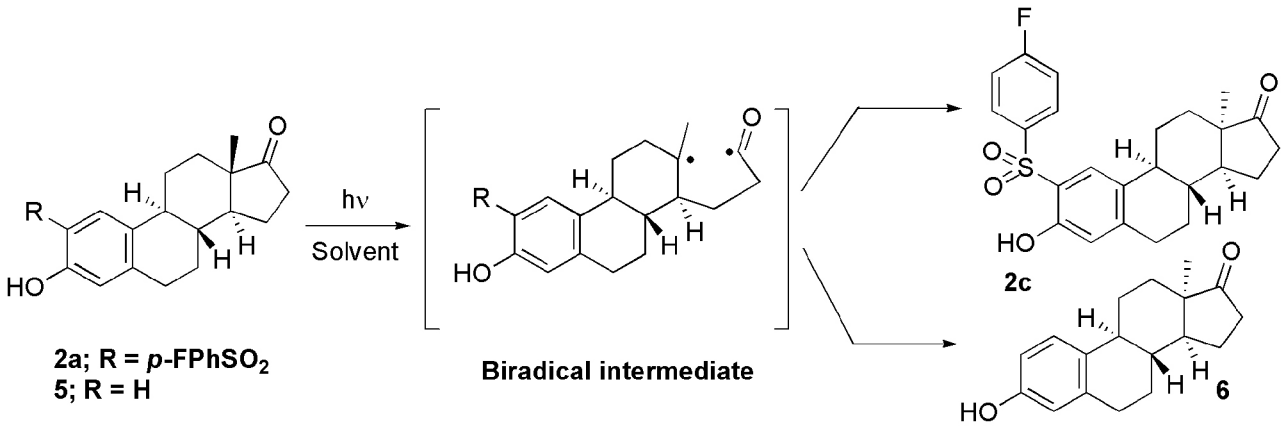
R = H; ***lumiestrone***
R = Me; ***lumiestrone methyl ether***

(Ref. (21))



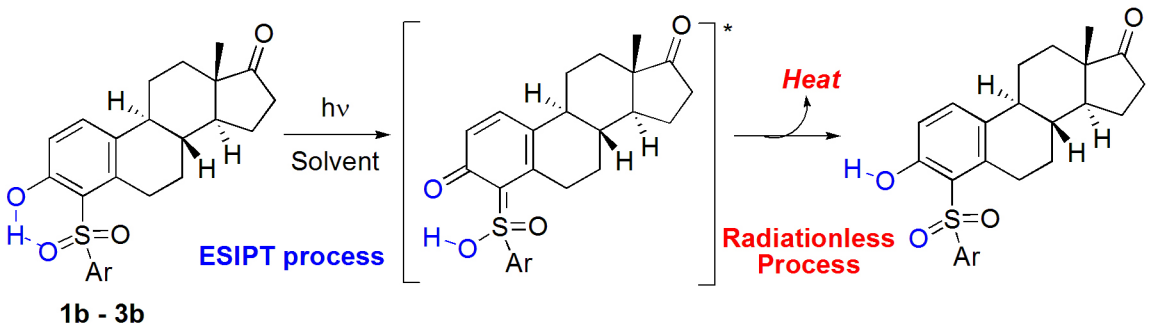
(Ref. (23))

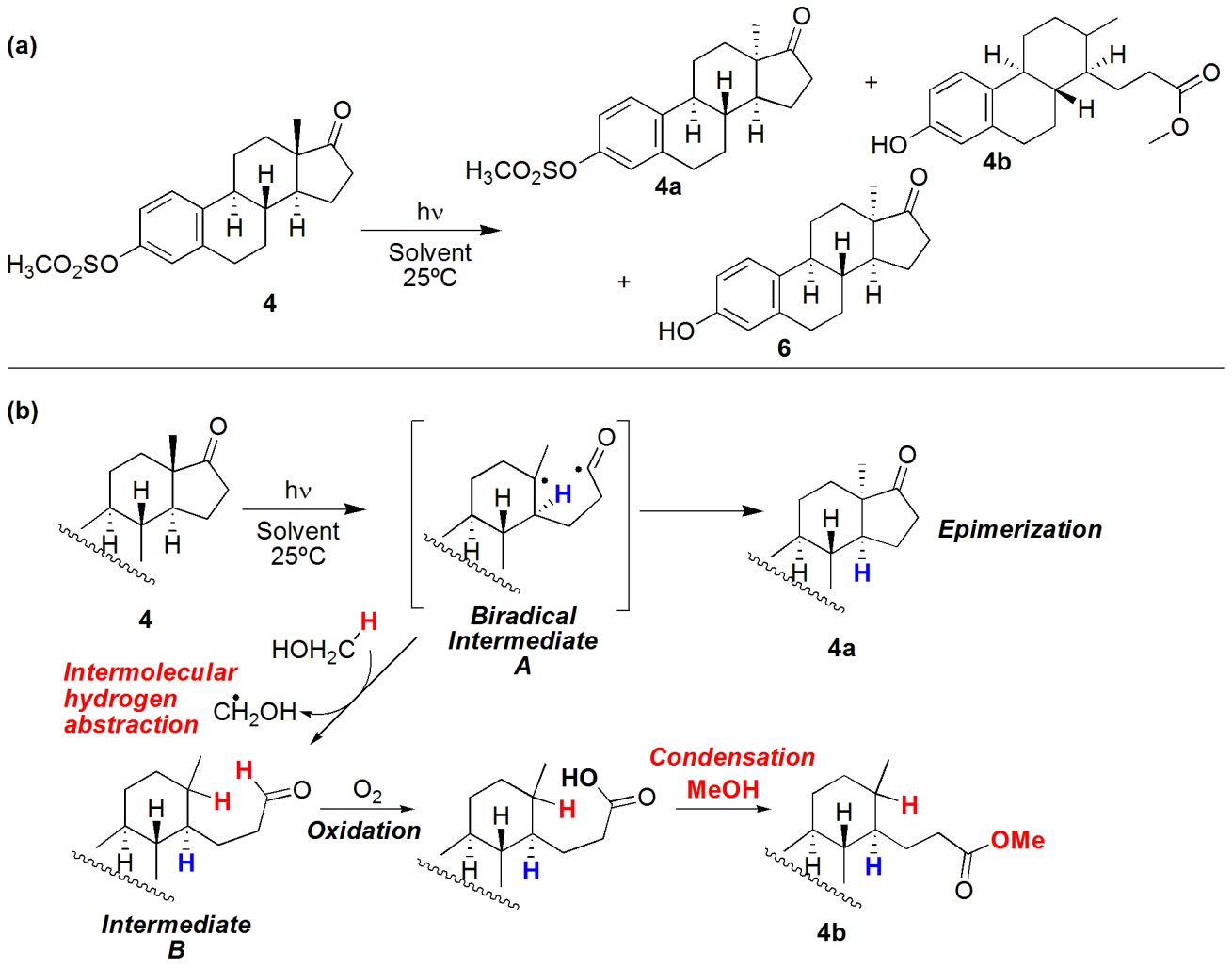

RO2SO
O
H
H
H
hν
Solvent
25 °C
1; R = Ph
2; R = p-FPh
3; R = p-CH3Ph
HO
1a; R = Ph
2a; R = p-FPh
3a; R = p-CH3Ph
OSO2R
1b; R = Ph
2b; R = p-FPh
3b; R = p-CH3Ph
5
1c; R = Ph
2c; R = p-FPh
3c; R = p-CH3Ph
6

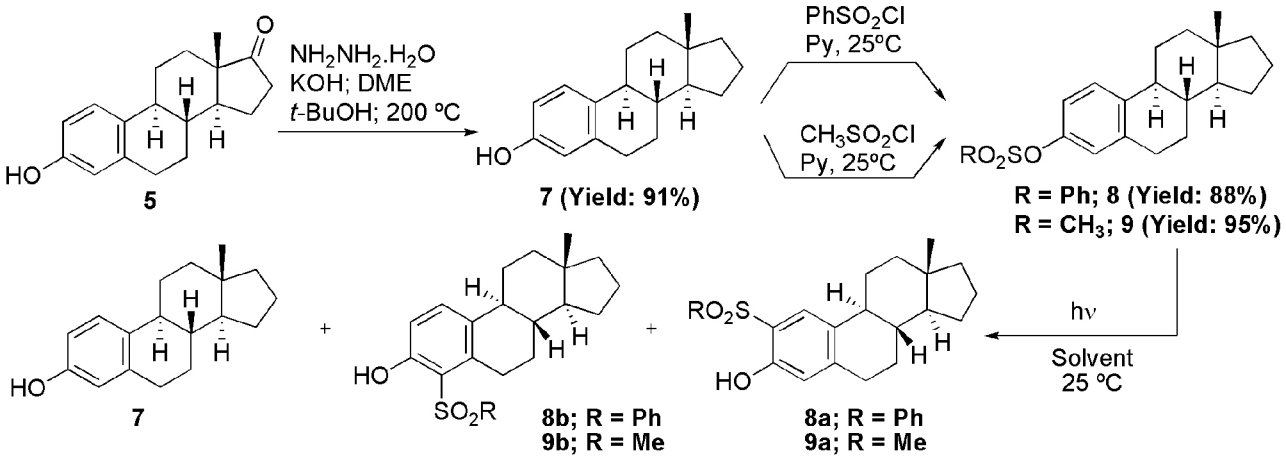


2a; R = *p*-FPhSO$_2$
5; R = H

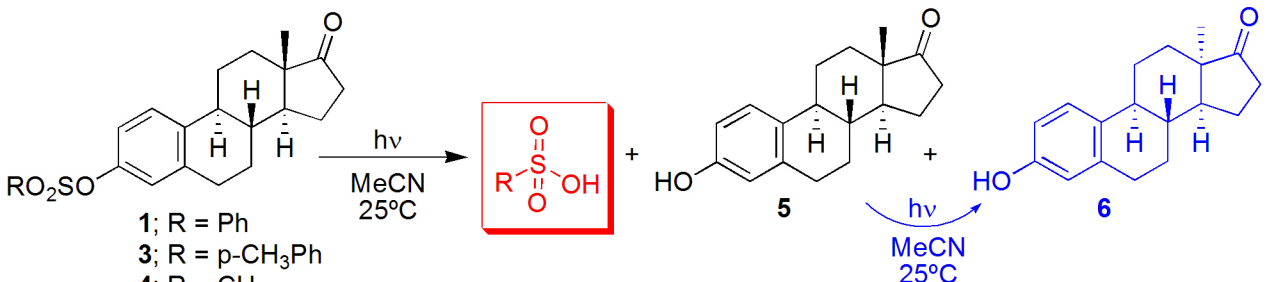
Biradical intermediate


hν
Solvent
ESIPT process
Heat
Radiationless
Process
Ar
Ar
Ar
1b - 3b

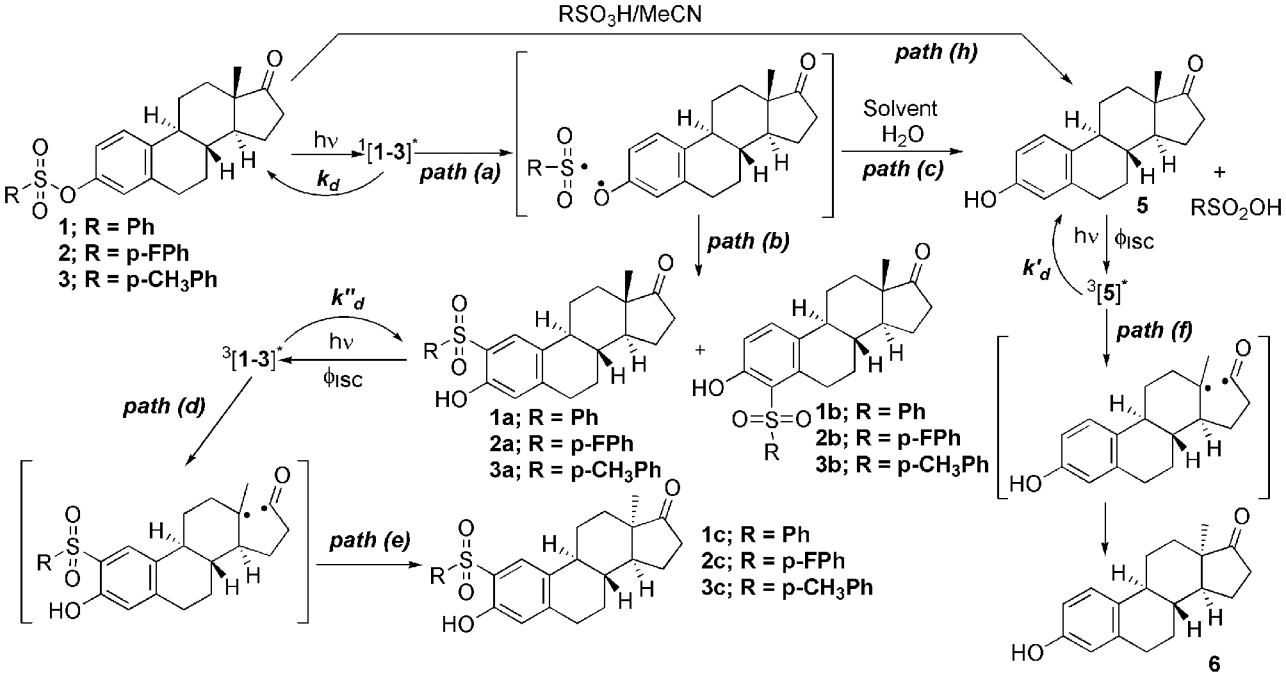

(a)
H3CO2SO
4
hν
Solvent
25ºC
4a
4b
6
HO
(b)
4
Biradical
Intermediate
A
Epimerization
4a
Intermolecular
hydrogen
abstraction
HOH2C
CH2OH
Intermediate
B
O2
Oxidation
Condensation
MeOH
OMe
4b

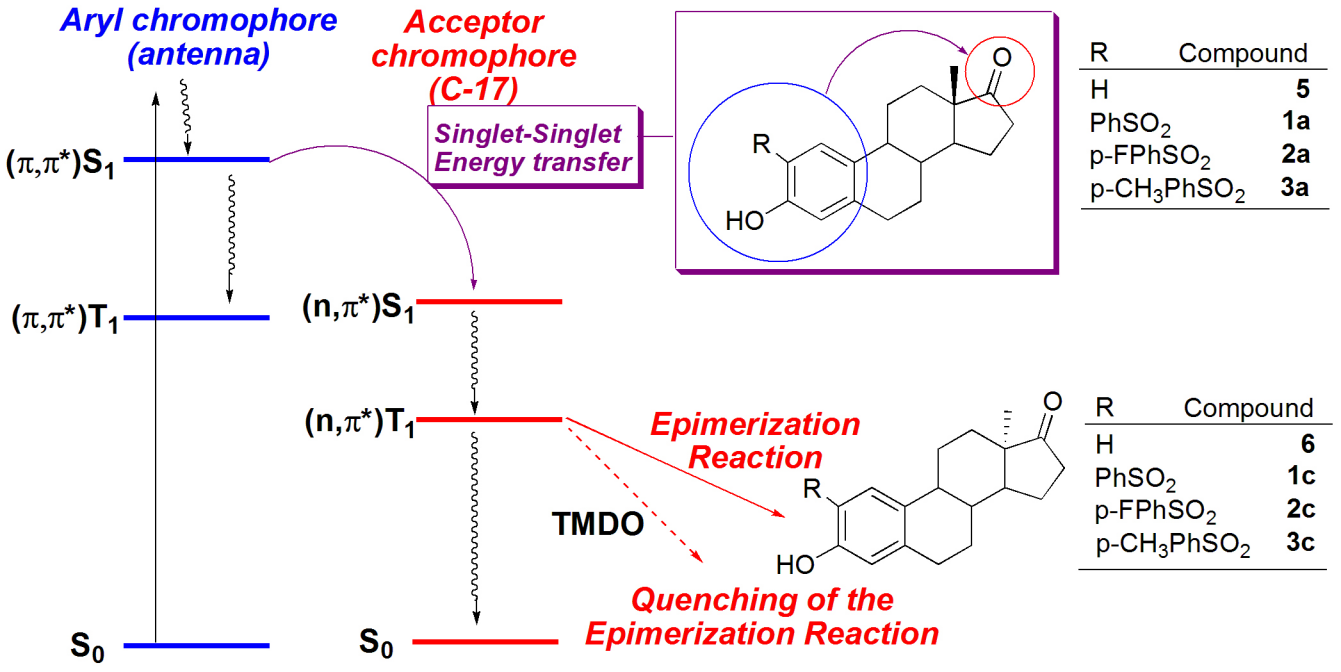


Estrone	Solvent	Yield (%) 8a	8b	7	ϕ_R
8	MeOH	30	24	16	0.002
	Cyclohexane	31	25	31	0.002
9	MeOH	35	33	0	0.001



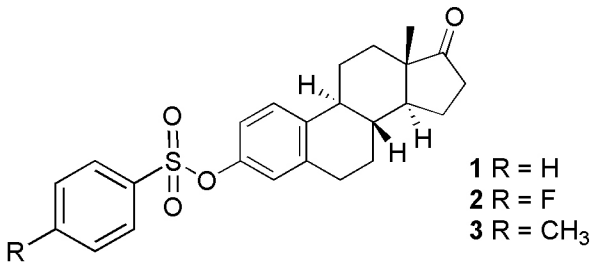
1; R = Ph
3; R = p-CH_3Ph
4; R = CH_3


RSO3H/MeCN
path (h)
hν
1[1-3]*
kd
path (a)
Solvent
H2O
path (c)
5
+
RSO2OH
1; R = Ph
2; R = p-FPh
3; R = p-CH3Ph
path (b)
k''d
hν
ϕisc
3[1-3]*
path (d)
1a; R = Ph
2a; R = p-FPh
3a; R = p-CH3Ph
1b; R = Ph
2b; R = p-FPh
3b; R = p-CH3Ph
k'd
hν
ϕisc
3[5]*
path (f)
path (e)
1c; R = Ph
2c; R = p-FPh
3c; R = p-CH3Ph
6

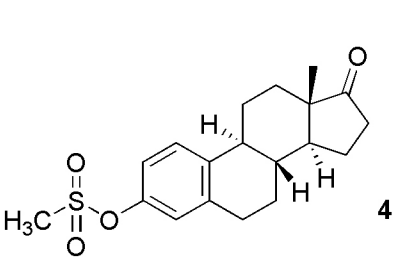


R	Compound
H	**5**
$PhSO_2$	**1a**
p-$FPhSO_2$	**2a**
p-CH_3PhSO_2	**3a**

R	Compound
H	**6**
$PhSO_2$	**1c**
p-$FPhSO_2$	**2c**
p-CH_3PhSO_2	**3c**



1 R = H
2 R = F
3 R = CH_3



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