EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800356

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800356

Supported by ACES Asian Chemical Editorial Society

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10.1002/ejoc.201800356

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The use of switchable polarity solvents for the synthesis of 16-arylidene steroids *via* Claisen-Schmidt condensation

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Abstract: Switchable polarity recyclable solvent mixtures were applied as reaction medium and catalyst to replace the conventional base catalysts in the Claisen-Schmidt condensation of 17-oxo steroids with aromatic aldehydes. Reversibility between ionic and non-ionic forms of the new 2-*n*-butyl-1,1,3,3-tetramethylguanidine (nBu-TMG)/ethylene glycol/CO_2 and 2-tert-butyl-1,1,3,3-tetramethylguanidine (tBu-TMG)/ethylene glycol/CO_2 systems were proved by conductivity measurements. The structure of the ionic form was determined by ^{1}H NMR, IR measurements and quantum chemical calculations. The steroidal products with androstane and estrane skeleton were characterised with different spectroscopic methods (NMR, IR, MS).

Introduction

Switchable polarity solvents are capable to change their polarity reversibly between a non-ionic and an ionic form in the presence of an external trigger. As an example, a properly selected molecular solvent can be converted to an ionic liquid upon exposure to carbon-dioxide atmosphere. The reversed process, transformation of the ionic liquid to the starting molecular solvent occurs *via* removal of CO_2, e.g. under an inert gas (argon or nitrogen) atmosphere, or by heating.[1]

In the literature there are a wide range of examples for appropriate two component liquid mixtures for the construction of switchable systems: amidine/alcohol,[1] guanidine/alcohol,[2] amidine/primary amine[3] and guanidine/acidic alcohol[4] mixtures were described. There are also some representatives of one-component reversible zwitterionic liquids such as alkanol-guanidines,[5,6] alkanol-amidines,[5,6] secondary amines[7] and diamines.[5] In addition, siloxylated amines have also been shown to react with carbon-dioxide reversibly.[8] The use of such solvents can be advantageous in multistep processes requiring reaction media of varying polarity and there are several examples for applications in extraction, CO_2 capture or organic synthesis.[9] The properties of solvents containing 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) and 2-*n*-butyl-1,1,3,3-tetramethylguanidine (nBu-TMG) with different *n*-alkyl alcohols were studied thoroughly.[7] The exposure of an equimolar mixture of the two components to carbon-dioxide leads to an ionic alkylcarbonate derivative which causes a dramatic increase in the polarity of the material. This high polarity liquid is immiscible with apolar organic solvents which enables the removal of organic compounds of lower polarity *via* extraction. Base catalysed reactions may be carried out in the non-ionic form with the amine component serving as the catalyst. After completion of the reaction, the solvent can be "switched" to the high-polarity ionic liquid in carbon-dioxide atmosphere and the products can be extracted with apolar organic solvents. The catalyst can be made recyclable by triggering the mixture back to the molecular form. In spite of the great potential of the methodology, there are only a few reports describing its application in organic transformations, such as in cyanosilylation,[10] Michael addition[10] and transesterification.[11,12] Claisen-Schmidt condensation of butanone and benzaldehyde[10,13,14] was also performed in nBu-TMG and product separation and catalyst recycling could be realised with the help of the nBu-TMG/methanol/CO_2/octane system. Optimised yield (34%) was obtained at partial conversion of substrates due to a competing condensation process between the enone products and benzaldehyde.

Benzylidene derivatives obtained by the Claisen-Schmidt condensation of steroidal ketones may serve as starting materials for the synthesis of compounds of pharmacological importance[15-18] or may show favourable biological activity themselves.[19-24] The 16-arylidene group was found to be a good pharmacophore for cytotoxic activity. Derivatives of androst-5-en-3β-ol-17-one showed significant activity against MCF-7 (breast), NCI-H460 (lung) and SF-268 (central nervous system) cell lines[19,20] as well as against KB (human nasopharyngeal epidermoid carcinoma), T47D (human breast cancer) and SK-N-MC (human neuroblastoma) cells.[21] The cytotoxic potential of these compounds was greatly influenced by the position and nature of the substituent on the benzylidene pendant. Similar androstenedione derivatives were found to inhibit aromatase, an enzyme that plays a key role in estrogen-dependent breast cancer.[22] Some 16-arylidene estrone derivatives, especially those with 4-(*N*,*N*-dimethylamino)-phenyl- and thiophenyl groups, showed good selectivity for the type 1 isosyme of 17β-hydroxysteroid dehydrogenase (17β-HSD1), a promising target for the control of estrogen-dependent diseases.[23] Recently, 16-arylidene derivatives of

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androst-5-en-3β-ol-17-one and their 4-aza-analogues were reported to prevent the progression of lipopolysaccharide-induced neuroinflammation and subsequent neurodegeneration, so they represent a new class of neuroprotective agents for the treatment of Alzheimer's and Parkinson's diseases.[24] All arylidene derivatives were obtained from the corresponding steroidal 17-ketones and aromatic aldehydes in base-catalysed reactions in the presence of LDA,[15] KF/Al_2O_3,[16] or alkali-hydroxides.[17-24]

As part of our ongoing interest in using sustainable methods in the synthesis of steroid derivatives[25-27] our goal was the synthesis of 16-substituted androstane and estrane derivatives including promising 17β-HSD1 inhibitors mentioned above *via* a green approach, replacing traditionally used inorganic bases to a switchable polarity solvent mixture as catalyst and reaction medium.

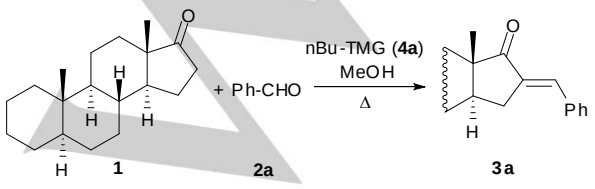
Results and Discussion

Claisen-Schmidt condensation of 17-oxo steroids in the presence of a nBu-TMG/MeOH switchable polarity solvent

Based on the earlier results reported by Hart et al.,[10] firstly the Claisen-Schmidt condensation of 5α-androstan-17-one (**1**) and benzaldehyde (**2a**) was carried out in the presence of nBu-TMG (**4a**) as catalyst and solvent (Scheme 1). However, no reaction took place at 50 °C and even an increase in the temperature to 80°C led to the product only in traces (Table 1, Entries 1-2). Interestingly, 40% conversion of the starting steroid was observed by GC (Entry 4) after 12 hours at 50 °C using a nBu-TMG (**4a**)/MeOH mixture in a molar ratio of 1/1. The increase of the ratio of MeOH (nBu-TMG (**4a**)/MeOH = 1/2) led to 66% and 88% conversion after 12 and 20 hours, respectively (Entries 5-6), which clearly shows the advantageous effect of the alcohol that enhances the polarity of the system and solubility of substrates.

The reusability of the switchable solvent system was also studied. The product was isolated by extraction with toluene after placing the reaction mixture under CO_2 atmosphere.

Then the ionic liquid was converted to the molecular liquid form at 70°C in vacuo. The substrate (**1**), benzaldehyde (**2a**) and MeOH were added to the neutral liquid and the reaction was repeated under the same conditions in 4 subsequent cycles. However, the results were poorly reproducible with conversions varying between 74-99% (Entries 7-9). It can be assumed that at 50 °C a partial and uncontrollable evaporation of MeOH took place. As the reaction had been found to be very susceptible to the MeOH/nBu-TMG (**4a**) ratio, this could lead to different conversion in each cycle. To reduce the evaporative loss of the solvent, ethylene glycol was chosen as the alcohol component. Under these conditions, a good yield could be obtained even using a shorter reaction time (Entry 10).



Scheme 1. Claisen-Schmidt condensation of 5α-adrostan-17-one (**1**) and benzaldehyde (**2a**)

Table 1. Claisen-Schmidt condensation of **1** and **2a** using different nBu-TMG (**4a**)/MeOH ratios.[a]

Entry	nBu-TMG (**4a**) /MeOH	Reaction time (h)	Conversion (%)[b]
1	1/0	5	no reaction
2[c]	1/0	5	10
3	1/1	5	10
4	1/1	12	40
5	1/2	12	66
6	1/2	20	88
7[d]	1/2	20	74
8[e]	1/2	20	99
9[f]	1/2	20	93
10[g]	1/2	4	87
11[h]	$5.6*10^{-4}$	4	traces
12[i]	$5.8*10^{-4}$	4	31

[a] Reaction conditions (unless otherwise stated): 0.2 mmol **1**, 0.4 mmol **2a**, 0.67 mmol nBu-TMG (**4a**), 50°C. [b] Determined by GC. [c] Reaction temperature: 80°C. [d] First reuse of the nBu-TMG (**4a**)/MeOH mixture. [e] Second reuse of the nBu-TMG (**4a**)/MeOH mixture. [f] Third reuse of the nBu-TMG(**4a**)/MeOH mixture. [g] 0.67 mmol nBu-TMG (**4a**), 1.34 mmol ethylene glycol (**5**). [h] 0.01 mmol nBu-TMG (**4a**), 1 ml ethylene glycol (**5**). [i] 0.01 mmol nBu-TMG (**4a**), 1 ml EtOH,

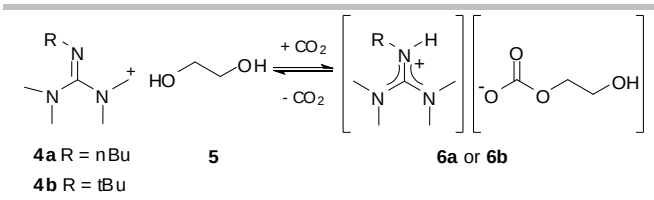
It should be mentioned that the product could be detected only in traces when a catalytic amount of nBu-TMG was used in ethylene glycol (**5**) as solvent (Entry 11) probably due to the very low solubility of the steroid substrate. When the solvent was changed to ethanol, **3a** was formed with moderate yield (Entry 12).

As a consequence, the nBu-TMG (**4a**)/ethylene glycol (**5**) system was chosen for further investigations. To the best of our knowledge, the properties of this switchable polarity system has not been investigated before, so structure and reversibility of the ionic form was studied first.

Investigation of the CO_2 capture of the nBu-TMG (**4a**)/ethylene glycol (5) mixture

The ionic liquid form of the two-component switchable polarity system was prepared by stirring a 1/2 mixture of nBu-TMG (**4a**)/ethylene glycol (**5**) for one hour under CO_2 atmosphere. The formed alkylcarbonate was characterised by ^{1}H-NMR, IR and MS measurements. According to these investigations, ethylene glycol forms an 1-1 adduct with nBu-TMG (**4a**) under these conditions, leading to alkylcarbonate **6a** (Scheme 2).

In the ^{1}H-NMR spectrum (Figure S1) the signals of the nonequivalent methylene protons of alkylcarbonate (**6a**) appeared as two multiplets between 3.91-3.96 ppm and 3.60-3.64 ppm. The presence of these non-equivalent groups proves that the anion is not symmetric, only one of the hydroxyl groups of ethylene glycol was converted to a carbonate.



4a R = nBu
4b R = tBu

5

6a or **6b**

Scheme 2. The formation of alkylcarbonates **6a** or **6b** under carbon-dioxide atmosphere

Similarly to a previous report on the nBu-TMG/methanol system,[28] convergence of the two singlets of $N(CH_3)_2$ groups was observed in the range of 2.81-2.97 ppm because of the formation of the ionic liquid. This phenomenon was explained with the resonance stabilisation of the double bond in guanidine, leading to rotation of the molecule across the bond.[28]

Absorption bands of the IR spectrum of nBu-TMG (**4a**), the nBu-TMG (**4a**)/ethylene glycol (**5**) molecular liquid and the ionic liquid form were compared (Figure 1). The assignment of the bands of the IR spectra was supported by quantum chemical calculations. The vibrational frequencies were calculated with the CAM-B3LYP density functional method using the 6-31G** basis set (Table S1).

In the spectrum of nBu-TMG (**4a**), the C=N stretching appeared at 1616 cm^{-1}, while after adding ethylene-glycol the wavenumber of this absorption was lowered to 1591 cm^{-1}. This suggests the formation of a hydrogen bond between ethylene-glycol and the imine nitrogen of nBu-TMG (**4a**) in the molecular solvent. (Table S1, Entries 1-2). Under CO_2 atmosphere, a splitting of the C=N band was observed, with two new absorptions at 1584 cm^{-1} and 1643 cm^{-1}. The band at 1584 cm^{-1} supports the formation of the ionic liquid which results in a delocalization in the guanidine skeleton. The other new band at 1643 cm^{-1} demonstrates the presence of the carbonate anion. The lower wavenumber compared to other carbonates can be explained by hydrogen bond formation. Although there are some differences between the observed and calculated wavenumbers, the similar tendency of signal shifts supports the proposed reaction route.

According to the results of the DFT calculations, the C=O stretching vibrational mode of the 2-hydroxyethyl carbonate anion can be found at 1834 cm^{-1}, whereas the wavenumber was lowered to 1693 cm^{-1} in the hydrogen bonded structure **6a** (Table S1, Entries 4-5). The band at 1281 cm^{-1} is assigned to

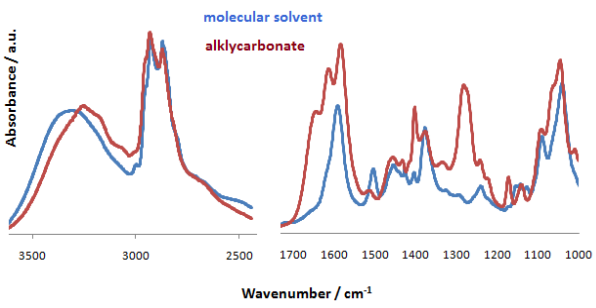


Figure 1. FT-IR spectra of molecular solvent mixture (nBu-TMG (**4a**) and ethylene glycol, (**5**) (blue line)) and alkylcarbonate **6a** (red line)

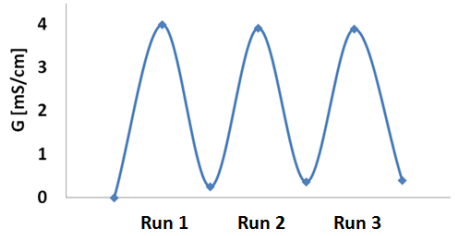


Figure 2. Monitoring the reversibility of the nBu-TMG (**4a**)/ethylene-glycol (**5**) system by conductivity measurements

the deformation vibration of the O-C-O skeleton. In the molecular solvent the signal due to methylene deformation of the *n*-butyl chain can be observed at 1403 cm^{-1}. After the formation of the ionic liquid its intensity increased. This phenomenon could be explained by the protonation of the nitrogen atom connected to the butyl group. The shift of the OH stretch from 3305 cm^{-1} to 3289 cm^{-1} serves as another proof for the presence of a not symmetric anion. The optimised structure of the ionic liquid is shown in Figure S3 using the CAM-B3LYP density functional with 6-31G** basis set.

The formation of alkylcarbonate **6a** was also supported by an ESI-MS measurement. The spectrum was obtained in negative ionization mode (Sampling cone voltage: 3 V). The peak observed at m/z = 105 corresponded to the alkylcarbonate anion of **6a**. On the contrary, no signals, corresponding to the $[M+H]^-$ (m/z=149) or $[M]^{2-}$ (m/z=74) ions of a bis(carbonate) structure, could be detected.

The formation of the ionic liquid was proved by conductivity measurements too, taking samples with equal volume from the switchable polarity solvent mixture. The samples were mixed with acetonitrile and their conductivity was measured (Figure 2). The conductivity of the starting components was 0 mS cm^{-1}. After stirring the nBu-TMG (**4a**)/ethylene glycol (**5**) mixture under CO_2 atmosphere for 1 hour to form the ionic liquid, conductivity increased to 4 mS cm^{-1}. In order to convert the system back to the starting molecular solvent, the mixture was stirred for 1.5 hour at 100 °C under vacuum (45 mmHg). The conductivity decreased totally to the starting value. Moreover, the maximum conductivity value did not change appreciably after the repeated absorption of CO_2.

Claisen-Schmidt condensation of 17-oxo steroids in the presence of guanidine/ethylene glycol switchable polarity solvents

The Claisen-Schmidt condensation of 5α-androstan-17-one (**1**) and benzaldehyde (**2a**) was carried out in the presence of a nBu-TMG (**4a**)/ethylene glycol (**5**) (molar ratio =1/2) mixture. Almost total conversion of **1** was observed by GC after 4 hours at 50 °C (Figure 3). Then the argon atmosphere was changed to CO_2 and after the formation of the ionic liquid the product was extracted with toluene. No nBu-TMG (**4a**) could be detected by GC in the toluene phase. No contamination of the product mixture with either the ionic liquid or the components of the low polarity form could be observed by NMR. A chromatographic purification led to the desired product in 87% yield.

The recyclability of the switchable solvent was also investigated: it was reused twice efficiently without a significant decrease in

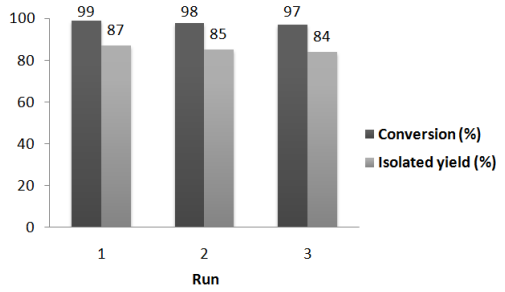
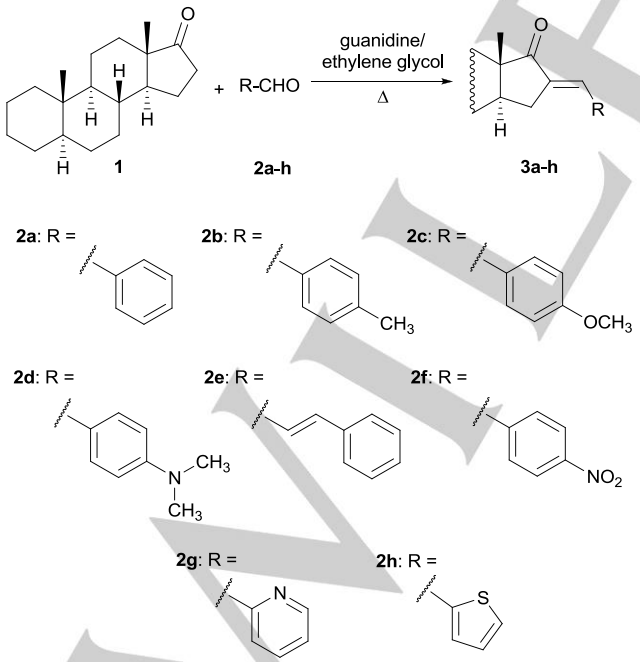


Figure 3. Reuse of nBu-TMG (**4a**)/ethylene glycol (**5**) mixture in the condensation of 5α-androstan-17-one (**1**) and benzaldehyde (**2a**).

the isolated yields (Figure 3). No measurable loss of the nBu-TMG (**4a**)/ethylene glycol (**5**) system could be detected after CO_2 had been expelled (weight loss <1%). The effect of different nBu-TMG (**4a**)/ethylene glycol (**5**) ratios on the outcome of the reaction was also studied (Table 2, Entries 1-3). A lower amount of ethylene glycol (nBu-TMG (**4a**)/ethylene glycol (**5**) = 1/0.5) caused a dramatic decrease in the conversion of the steroidal substrate (**1**) (Entry 2). A similar phenomenon was observed when the amount of ethylene glycol was the same as before, while the amount of nBu-TMG (**4a**) was higher (Entry 3).

Under the optimal conditions the condensation reaction of steroid **1** was carried out with different aromatic/unsaturated aldehydes (Scheme 3).

Aldehydes containing an electron donating substituent (**2b**-**d**) were less reactive compared to benzaldehyde (**2a**). In the presence of 4-methyl- (**2b**), 4-methoxy- (**2c**) and 4-(dimethylamino)benzaldehyde (**2d**) the desired products were isolated in moderate or low yields (Entries 4-7 and 9-10). On the



Scheme 3. Claisen-Schmidt condensation of steroid **1** with aromatic aldehydes

contrary, the condensation with aldehyde **2e** led to the steroid derivative **3e** in excellent yield (Entry 13). The reaction with compound **2f** containing the electron-withdrawing nitro group in para-position led to enone **3f** in 47% yield (Entry 14). Because of the disappearance of aldehyde **2f** from the reaction mixture, a side reaction of **2f** was supposed. Therefore **2f** was added in 3 equivalent portions to the reaction mixture at the beginning of the reaction and after the first and second hour and it was heated for an additional 6 hours at 50 °C. Consequently, the desired product (**3f**) was obtained in 77% yield (Entry 15).

Aldehydes of *N*- and *S*-heterocycles were also used as reagents. Condensation of 2-pyridinecarboxaldehyde (**2g**) and 2-thiophenecarboxaldehyde (**2h**) led to the products after 4 hours in 75 % (**3g**) and 43 % (**3h**) yield, respectively (Entries 16-17).

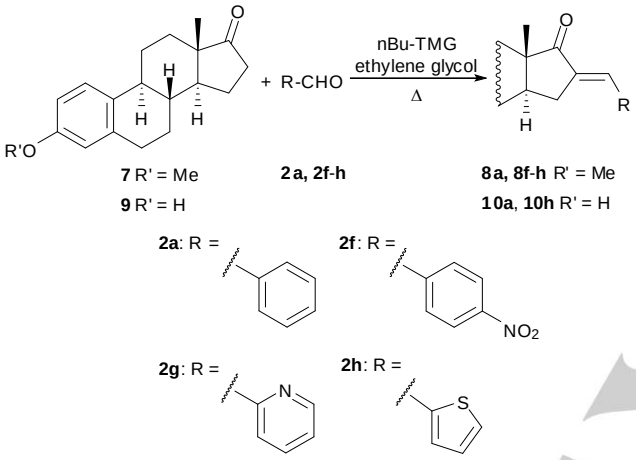
Table 2. Claisen-Schmidt condensation of steroid **1** with aromatic aldehydes (**2a**-**2h**) in the presence of guanidine/ethylene glycol mixture.[a]

Entry	Reagent	Reaction time (h)	Product	Yield (%)[b]
1	**2a**	4	**3a**	87
2[c]	**2a**	4	**3a**	n.d. (12)[d]
3[e]	**2a**	4	**3a**	n.d. (10)[d]
4	**2b**	4	**3b**	50
5	**2b**	8	**3b**	51
6	**2c**	4	**3c**	51
7	**2c**	8	**3c**	51
8[f]	**2c**	4	**3c**	85
9	**2d**	4	**3d**	11
10	**2d**	8	**3d**	10
11[f]	**2d**	4	**3d**	51
12[f]	**2d**	8	**3d**	65
13	**2e**	4	**3e**	98
14	**2f**	8	**3f**	47
15[g]	**2f**	8	**3f**	77
16	**2g**	4	**3g**	75
17	**2h**	4	**3h**	42
18	**2h**	8	**3h**	70

[a] Reaction conditions (unless otherwise stated): 0.2 mmol substrate **1**, 0.4 mmol aldehyde (**2a**-**2h**), 0.67 mmol nBu-TMG (**4a**), 1.34 mmol ethylene glycol, 50°C. [b] Yield = (mmol isolated product (**3a**-**3h**))/(mmol substrate **1**) x 100. [c] 0.67 mmol nBu-TMG (**4a**), 0.335 mmol ethylene glycol (ratio of nBu-TMG (**4a**)/ethylene glycol (**5**) = 1/0.5) [d] Isolated yield was not determined, conversion of **1** (GC) is indicated in brackets. [e] 2.68 mmol nBu-TMG (**4a**), 1.34 mmol ethylene gylcol (ratio of nBu-TMG (**4a**)/ethylene glycol (**5**) = 2/1). [f] tBu-TMG (**4b**) was used as base. [g] 0.4 mmol of **2f** was added to the reaction mixture in 3 portions, at the beginning of the reaction and after 1 and 2 hours.

In the latter case an increase in the reaction time to 8 hours led to the formation of **3h** in 70% yield (Entry 18).

In order to achieve higher yields in the condensation with aldehydes containing electron donating groups, the possibility of the use of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (tBu-TMG (**4b**)) as catalyst was investigated because of its higher basicity compared to nBu-TMG (**4a**). It was tested in the condensation of substrate **1** and aldehydes **2c**-**d**. The yields increased in both cases, proving that tBu-TMG (**4b**) is more effective under the same reaction conditions. Product **3c** was obtained after 4 hours in 85% (Entry 8), while **3d** was isolated in 65% yield applying longer reaction time (Entries 11-12). The ionic liquid was transformed to the molecular solvent at 70 °C, under vacuum (45 mmHg), after 6h.



Scheme 4. Claisen-Schmidt condensation of estrone-3-methylether (**7**) and estrone (**9**) with aromatic aldehydes

Beside androstane based steroids, the synthesis of additional derivatives with estrane skeleton was also planned, in order to obtain compounds with described biological activity.[23] Accordingly, 3-methoxy-estra-1,3,5(10)-triene-17-one (**7**, Scheme 4) was applied as the starting material in the condensation reaction with benzaldehyde (**2a**). Using the same reaction conditions as before (50 °C, 4 hours), product **8a** was isolated in excellent, 97% yield. Furthermore the switchable solvent was reused efficiently twice, leading to the 16-benzylidene derivative **8a** in 95% and 94% yield in the second and third runs, respectively (Figure 4).

Further three estrane derivatives were synthesized applying the same reaction conditions starting from steroid **7** and aldehydes **2f**-**h** (Scheme 4, Table 3).

In the presence of **2g** the desired product (**8g**) was obtained in 80% yield (Table 3, Entry 4). In case of aldehydes **2f** and **2h** the application of longer reaction time was needed, to obtain the products (**8f**, **8g**) in excellent yield (Entries 3 and 6).

Finally, the condensation of 3-hydroxy-estra-1,3,5(10)-triene-17-one (**9**) was carried out with benzaldehyde (**2a**) and 2-thiophenecarboxaldehyde (**2h**) leading to **10a** and **10h** derivatives in 93% and 84% yield (Entries 7 and 8). As according to earlier reports the latter product bears 17β-HSD1 and 17β-HSD2 inhibitory effect,[23] the method has been proved to be applicable in the synthesis of compounds with proved

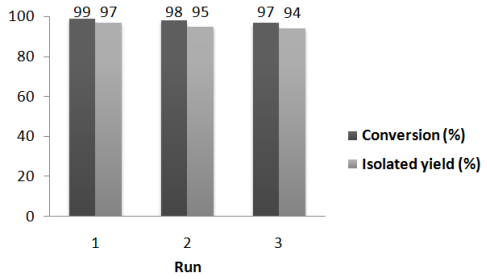


Figure 4. Reuse of nBu-TMG (**4a**)/ethylene-glycol (**5**) mixture in the condensation of estrone-3-methylether (**7**) and benzaldehyde (**2a**)

biological activity. (As a comparison, reaction of steroid **9** and benzaldehyde (**2a**) resulted in the formation of the 16-arylidene product **10a** under the usual basic conditions (5eq. NaOH in EtOH) at room temperature in 70% yield in 4h.)

Table 3. Synthesis of estrane based derivatives *via* Claisen-Schmidt condensation[a].

Entry	Substrate	Reagent	Product	Yield (%)[b]
1	**7**	**2a**	**8a**	97
2	**7**	**2f**	**8f**	54
3[c]	**7**	**2f**	**8f**	89
4	**7**	**2g**	**8g**	80
5	**7**	**2h**	**8h**	52
6[c]	**7**	**2h**	**8h**	90
7	**9**	**2a**	**10a**	93
8	**9**	**2h**	**10h**	84

[a] Reaction conditions: 0.2 mmol substrate (**7**, **9**), 0.4 mmol aldehyde, 0.67 mmol nBu-TMG (**4a**), 1.34 mmol ethylene glycol, 4 h, 50°C. [b] Yield = (mmol isolated product)/(mmol substrate) x 100. [c] Reaction time: 8h.

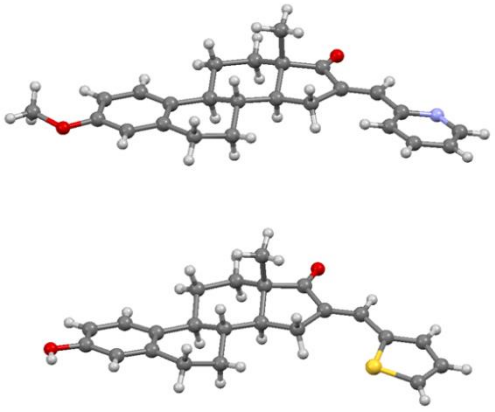


Figure 5. Solid state crystallographic structures of **8g** and **10h**.

All the steroidal products were characterised by ^{1}H, ^{13}C NMR, IR and HRMS measurements. In the case of **8g** and **10h** crystals suitable for X-ray measurement were grown and analysed. This confirmed the structures of the newly synthesised molecules. *E* configuration of the exocyclic double bond at C-16 could be established (Figure 5).

Conclusions

The nBu-TMG (**4a**)/ethylene-glycol (**5**) switchable solvent system was found to be an efficient catalyst for the Claisen-Schmidt condensation of 17-oxo-steroids. The products could easily be separated due to the reversible polarity change of the reaction media, and the nBu-TMG (**4a**)/ethylene glycol (**5**) mixture was reused. This method could be a green and effective tool for the synthesis of biologically relevant steroid derivatives.

Experimental Section

General information

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 500 spectrometer at 500.15 MHz and 125.78 MHz, or on a Bruker Avance 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). HRMS spectra were obtained using a Q-TOF Premier mass spectrometer (Waters Corporation, Milford, MA, USA), which was operated in positive electrospray ionization mode for the measurement of the products and in negative mode for the ionic liquid. IR spectra of steroid derivatives were made using a Thermo Nicolet Avatar 330 FT-IR instrument. Samples were prepared as KBr pellets. Infrared spectra of the nBu-TMG (**4a**)/ethylene glycol (**5**) system were recorded on a Bruker Vertex 70 type spectrometer with a Bruker Platinum ATR adapter at a resolution of 2 cm^{-1} with a room temperature DTGS detector (256 scans were co-added).
The synthesis of nBu-TMG (**4a**) was carried out according to Hart's and Huttenhower's PhD thesis.[28] The spectroscopic data of nBu-TMG (**4a**) corresponded well with the published findings. tBu-TMG (**4b**) was purchased from Sigma Aldrich. Steroid derivatives **8f**,[29] **10a** and **10h** are known compounds.[23]

Synthetic procedures

*General procedure for the Claisen-Schmidt condensation of androstane (**1**) and estrane (**7**, **9**) based steroids with different aldehydes (**2g**-**2h**) in the presence of nBu-TMG (**4a**)*

5α-Androstan-17-one (**1**), 3-methoxy-estra-1,3,5(10)-triene-17-one (**7**) or estra-1,3,5(10)-triene-17-one (**9**) (0.2 mmol) was placed under argon atmosphere in a Schlenk tube equipped with a magnetic stirrer, a septum inlet and a balloon on the top. nBu-TMG (**4a**) (0.67 mmol, 127 µl), ethylene glycol (**5**) (1.34 mmol, 75 µl) and 0.4 mmol aldehyde were added through the septum inlet. The reaction mixture was heated at 50 °C for 4 or 8 hours. The argon atmosphere was changed to carbon dioxide and the mixture was stirred for 1 hour while the ionic liquid was formed. The product was extracted with toluene (4 x 3 ml) from the ionic liquid. In order to convert the ionic liquid back to the starting molecular solvent, the mixture was stirred for 1.5 hour at 100 °C under vacuum (45 mmHg). The obtained molecular solvent was reused as solvent and catalyst in the next run. The extracted crude product was purified by column chromatograpy: silica, eluent *n*-hexane/EtOAc (6:1, v/v) (**3b**-**d**, **3f**-**h**), toluene/EtOAc (25:1, v/v) (**3a**, **3e**), toluene/EtOAc (15:1, v/v) (**8a**, **8f**, **8g**), toluene/EtOAc (25:1, v/v) (**8h**), toluene/EtOAc (5:1, v/v) (**10a**, **10h**). The condensation in the presence of tBu-TMG (**4b**) was carried out under the same reaction conditions. The ionic liquid was transformed to molecular solvent at 70 °C, under vacuum (45 mmHg) after 6h.

2-*n*-butyl-1,1,3,3-tetramethylguanidinium-2'-hydroxy-ethylcarbonate (**6a**):
^{1}H-NMR ($CDCl_3$, 400.13 MHz): δ = 3.97-4.02 (m, 2H, $^{-}O_3C$-$(CH_2)_2$-OH), 3.65-3.69 (m, 2H, $^{-}O_3C$-$(CH_2)_2$-OH), 3.58 (t, 2H, N-CH_2), 2.78-2.96 (brs, 12H, C-$(N(CH_3)_2)_2$), 1.49-1.60 (m, 2H, NCH_2CH_2), 1.21-1.32 (m, 2H, $N(CH_2)_2CH_2$), 0.84 (t, 3H, $N(CH_2)_3CH_3$).

2-*t*-butyl-1,1,3,3-tetramethylguanidinium-2'-hydroxy-ethylcarbonate (**6b**):
^{1}H-NMR ($CDCl_3$, 400.13 MHz): δ = 3.76-3.80 (m, 2H, $^{-}O_3C$-$(CH_2)_2$-OH), 3.45-3.49 (m, 2H, $^{-}O_3C$-$(CH_2)_2$-OH), 2.66-2.93 (brs, 12H, C-$(N(CH_3)_2)_2$), 0.84 (s, 9H, N-$(C(CH_3)_3)$).

16-Benzylidene-5α-androstan-17-one (**3a**):
Yield: 87%. White solid, mp. 144-145 °C, R_f: 0.69 (silica, toluene/EtOAc 25:1). IR (KBr, (cm^{-1})): 2922, 2854, 1718, 1636, 1448, 1377. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.53-7.59 (m, 2H, 2',6'-H), 7.34-7.48 (m, 4H, 3', 4', 5'-H, Ar-CH=), 2.85-2.94 (m, 1H, 15-H_a), 2.38-2.48 (m, 1H, 15-H_b), 0.76-2.00 (m, 20H, ring protons), 0.98 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.0, 136.4, 135.8, 132.8, 130.3 (2C), 129.1, 128.6 (2C), 55.0, 49.7, 47.7, 47.1, 38.6, 36.5, 34.8, 31.8, 31.3, 29.3, 29.0, 28.8, 26.8, 22.1, 20.2, 14.5, 12.3. HRMS: calculated for $C_{26}H_{35}O$ $[M+H]^+$ 363.2688, found 363.2683.

16-(4-Methyl-benzylidene)-5α-androstan-17-one (**3b**):
Yield: 51%. Light yellow solid, mp. 209-210 °C, R_f: 0.75 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2953, 2919, 2849, 1715, 1632, 1261, 1093, 1016, 800, 522. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.46 (d, *J* = 8.0 Hz, 2H, 3',5'-H), 7.41-7.44 (brs, 1H, Ar-CH=), 7.24 (d, *J* = 8.0 Hz, 2H, 2', 6'-H), 2.83-2.93 (m, 1H, 15-H_a), 2.40 (s, 3H, Ar-CH_3), 2.36-2.46 (m, 1H, 15-H_b), 0.76-2.00 (m, 20H, ring protons), 0.97 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.2, 139.4, 135.4, 133.0, 132.8, 130.4 (2C), 129.4 (2C), 55.0, 49.7, 47.6, 47.0, 38.6, 36.5, 34.8, 31.8, 31.3, 29.4, 29.0, 28.8, 26.8, 22.1, 21.4, 20.2, 14.6, 12.3. HRMS: calculated for $C_{27}H_{37}O$ $[M+H]^+$ 377.2844, found 377.2849.

16-(4-Methoxy-benzylidene)-5α-androstan-17-one (**3c**):
Yield: 55%. Light yellow solid, mp. 174-175 °C, R_f: 0.51 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2914, 2846, 1712, 1625, 1602, 1511, 1252, 1175, 1092, 1040, 1015, 831, 526. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.53 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 7.39-7.42 (brs, 1H, Ar-CH=), 6.96 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 3.87 (s, 3H, OCH_3), 2.83-2.91 (ddd, *J* = 1.2 Hz, 6.6 Hz, 15.5 Hz, 1H, 15-H_a), 2.34-2.44 (ddd, *J* = 2.9 Hz, 12.4 Hz, 15.5 Hz, 1H, 15-H_b), 0.77-2.00 (m, 20H, ring protons), 0.96 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.2, 160.4, 134.0, 132.6, 132.0 (2C), 128.5, 114.2 (2C), 55.4, 55.0, 49.8, 47.6, 47.1, 38.6, 36.5, 34.8, 31.8, 31.3, 29.3, 29.0, 28.8, 26.8, 22.1, 20.2, 14.6, 12.3. HRMS: calculated for $C_{27}H_{37}O_2$ $[M+H]^+$ 393.2794, found 393.2801.

16-(4-Dimethylamino-benzylidene)-5α-androstan-17-one (**3d**):
Yield: 11%. Yellow solid, mp. 208-209 °C, R_f: 0.41 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2917, 2849, 1700, 1603, 1100, 814. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.49 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 7.37-7.42 (brs, 1H, Ar-CH=), 6.73 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 3.04 (s, 6H, $N(CH_3)_2$), 2.83-2.91 (m, 1H, 15-H_a), 2.32-2.42 (m, 1H, 15-H_b), 0.75-1.98 (m, 20H, ring protons), 0.95 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.3, 150.9, 133.5, 132.1 (2C), 131.4, 123.7, 111.9 (2C), 55.1, 50.0, 47.5, 47.1, 40.1 (2C), 38.6, 36.6, 34.8, 31.9, 31.3, 29.4, 29.1, 28.9, 26.8, 22.2, 20.2, 14.7, 12.3. HRMS: calculated for $C_{28}H_{40}NO$ $[M+H]^+$ 406.3110, found 406.3113.

16-(3-Phenyl-2-propenylidene)-5α-androstan-17-one (**3e**):
Yield: 98%. Light yellow solid, mp. 142-145 °C, R_f: 0.55 (silica, toluene/EtOAc 25:1). IR (KBr, (cm^{-1})): 2920, 2847, 1712, 1611, 1590, 1448, 1279, 1098, 971, 760, 747. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.51 (d, *J* = 7.2 Hz, 2H, 2',6'-H), 7.38 (t, *J* = 7.2 Hz, 2H, 3',5'-H), 7.32 (t, *J* = 7.2 Hz, 1H, 4'-H), 7.13-7.19 (m, 1H, C(O)C=CH-), 6.88-6.98 (m, 2H, Ar-CH=, Ar-CH=CH-), 2.76-2.85 (ddd, *J* = 1.2 Hz, 6.4 Hz, 15.8 Hz, 1H, 15-H_a), 2.14-2.24 (ddd, *J*= 2.8 Hz, 12.7 Hz, 15.8 Hz, 1H, 15-H_b), 0.76-1.97 (m, 20H, ring protons), 0.93 (s, 3H, 19-H_3), 0.86 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.7, 140.6, 137.4, 136.6, 132.2, 128.8 (3C), 127.1 (2C), 124.8, 55.0, 49.2, 48.4, 47.1, 38.6, 36.5, 34.7, 31.7, 31.2, 29.0, 28.8, 27.1, 26.8, 22.1, 20.2, 14.5, 12.3. HRMS: calculated for $C_{28}H_{37}O$ $[M+H]^+$ 389.2844, found 389.2846.

16-(4-Nitro-benzylidene)-5α-androstan-17-one (**3f**):
Yield: 77%. Dark yellow solid, mp. 195-196 °C, R_f: 0.53 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2917, 2859, 1717, 1636, 1595, 1516, 1341, 852, 796. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 8.28 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 7.68 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 7.43-7.47 (brs, 1H, Ar-CH=), 2.84-2.92 (ddd, *J* = 1.5 Hz, 6.4 Hz, 16.1 Hz, 1H, 15-H_a), 2.41-2.51 (ddd, *J* = 3.2 Hz, 12.7 Hz, 16.1 Hz, 1H, 15-H_b), 0.76-2.03 (m, 20H, ring protons), 0.99 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.1, 147.5, 142.1, 140.4, 130.6 (2C), 129.9, 123.9 (2C), 54.9, 49.4, 47.8, 47.0, 38.6, 36.5, 34.8, 31.7, 31.2, 29.4, 29.0, 28.7, 26.7, 22.1, 20.1, 14.5, 12.3. HRMS: calculated for $C_{26}H_{34}NO_3$ $[M+H]^+$ 408.2539, found 408.2533.

16-(Pyridin-2-ylmethylene)-5α-androstan-17-one (**3g**):
Yield: 75%. Pale brown solid, mp. 145-147 °C, R_f: 0.29 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2922, 2849, 1717, 1638, 1585, 1565, 1467, 1451, 1081, 785. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 8.72 (d, *J* = 4.1 Hz, 1H, 6'-H), 7.69-7.75 (td, *J* = 1.6 Hz, 7.7 Hz, 1H, 4'-H), 7.46 (d, *J* = 7.7 Hz, 1H, 3'-H), 7.38-7.42 (m, 1H, Ar-CH=), 7.19-7.24 (dd, *J* = 4.1 Hz, 7.7 Hz, 1H, 5'-H), 3.26-3.34 (ddd, *J* = 1.4 Hz, 6.3 Hz, 16.8 Hz, 1H, 15-H_a), 2.43-2.53 (ddd, *J* = 3.1 Hz, 12.9 Hz, 16.8 Hz, 1H, 15-H_b), 0.76-2.01 (m, 20H, ring protons), 0.97 (s, 3H, 19-H_3), 0.86 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.5, 155.2, 149.9, 140.7, 136.2, 130.6, 126.4, 122.7, 55.0, 49.3, 47.8, 47.1, 38.6, 36.6, 34.9, 31.7, 31.3, 29.7, 29.0, 28.8, 26.8, 22.2, 20.2, 14.5, 12.3. HRMS: calculated for $C_{25}H_{34}NO$ $[M+H]^+$ 364.2640, found 364.2643.

16-(Thien-2-ylmethylene)-5α-androstan-17-one (**3h**):
Yield: 70%. Light yellow solid, mp. 157-160 °C, R_f: 0.63 (silica, *n*-hexane/EtOAc 6:1). IR (KBr, (cm^{-1})): 2965, 2939, 2916, 2887, 2849, 1713, 1619, 1451, 1280, 1259, 1246, 1097, 1016, 905, 832, 697. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.61-7.65 (brs, 1H, Ar-CH=), 7.52 (d, *J* = 4.9 Hz, 1H, 5'-H), 7.34 (d, *J* = 3.5 Hz, 1H, 3'-H), 7.14 (dd, *J*= 3.5 Hz, 4.9 Hz, 1H, 4'-H), 2.85-2.93 (ddd, *J* = 1.3 Hz, 6.6 Hz, 15.9 Hz, 1H, 15-H_a), 2.23-2.32 (ddd, *J* = 2.7 Hz, 12.4 Hz, 15.9 Hz, 1H, 15-H_b), 0.78-1.97 (m, 20H, ring protons), 0.95 (s, 3H, 19-H_3), 0.87 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.8, 140.1, 134.1, 132.1, 129.5, 127.8, 125.5, 55.0, 49.4, 48.1, 47.1, 38.6, 36.6, 34.7, 31.7, 31.3, 29.1, 29.0, 28.8, 26.8, 22.1, 20.2, 14.7, 12.3. HRMS: calculated for $C_{24}H_{33}OS$ $[M+H]^+$ 369.2252, found 369.2253.

3-Methoxy-16-benzylidene-estra-1,3,5(10)-triene-17-one (**8a**):
Yield: 93%. Light yellow solid, mp. 158-159 °C, R_f: 0.53 (silica, toluene/EtOAc 15:1). IR (KBr, (cm^{-1})): 2975, 2921, 2856, 2842, 1711, 1626, 1608, 1502, 1448, 1316, 1247, 1235, 1187, 1166, 1089, 1034, 943, 865, 822, 773, 687, 521. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.60 (d, *J* = 7.4 Hz, 2H, 2',6'-H), 7.49-7.54 (brs, 1H, Ar-CH=), 7.46 (t, *J* = 7.4 Hz, 2H, 3',5'-H), 7.40 (t, *J* = 7.4 Hz, 1H, 4'-H), 7.26 (d, *J* = 8.6 Hz, 1H, 1-H), 6.75-6.79 (dd, *J* = 2.3 Hz, 8.6 Hz, 1H, 2-H), 6.68-6.71 (m, 1H, 4-H), 3.82 (s, 3H, OCH_3), 1.44-3.08 (m, 13H, ring protons), 1.04 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.6, 157.7, 137.7, 136.1, 135.7, 133.2, 132.1, 130.3 (2C), 129.2, 128.7 (2C), 126.3, 114.0, 111.6, 55.2, 48.6, 47.9, 44.1, 38.0, 31.7, 29.7, 29.2, 26.9, 26.0, 14.6. HRMS: calculated for $C_{26}H_{29}O_2$ $[M+H]^+$ 373.2168, found 373.2166.

3-Methoxy-16-(4-nitro-benzylidene)-estra-1,3,5(10)-triene-17-one (**8f**)[29]:
Yield: 54%. Light yellow solid, mp. 218-219 °C, R_f: 0.47 (silica, toluene/EtOAc 15:1). IR (KBr, (cm^{-1})): 2932, 2853, 1717, 1633, 1596, 1513, 1500, 1461, 1340, 1276, 1257, 1107, 1086, 1053, 1018, 991, 851, 781, 687. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 8.30 (d, *J* = 8.6 Hz, 2H, 3',5'-H), 7.72 (d, *J* = 8.6 Hz, 2',6'-H), 7.50-7.53 (brs, 1H, Ar-CH=), 7.25 (d, *J* = 8.6 Hz, 1H, 1-H), 6.75-6.78 (dd, *J* = 2.4 Hz, 8.6 Hz, 1H, 2-H) 6.69 (d, *J* = 2.4 Hz, 1H, 4-H), 3.81 (s, 3H, OCH_3), 1.46-3.06 (m, 13H, ring protons), 1.05 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 208.7, 157.7, 147.6, 142.0, 140.0, 137.6, 131.8, 130.7 (2C), 130.3, 126.3, 123.9 (2C), 114.0, 111.7, 55.2, 48.4, 48.0, 44.0, 38.0, 31.7, 29.6, 29.2, 26.9, 25.9, 14.5. HRMS: calculated for $C_{26}H_{28}NO_4$ $[M+H]^+$ 418.2018, found 418.2015.

3-Methoxy-16-(pyridin-2-ylmethylene)-estra-1,3,5(10)-triene-17-one (**8g**):
Yield: 43%. Yellow solid, mp. 181-182 °C, R_f: 0.49 (silica, toluene/EtOAc 5:1). IR (KBr, (cm^{-1})): 2995, 2935, 2914, 2844, 1720, 1633, 1610, 1495, 1462, 1432, 1279, 1259, 1152, 1051, 868, 784, 619. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 8.74 (d, *J*=4.4 Hz, 1H, 6'-H), 7.71-7.76 (m, 1H, 4'-H), 7.49 (d, *J* = 7.7 Hz, 1H, 3'-H), 7.43-7.46 (brs, 1H, Ar-CH=), 7.22-7.27 (m, 2H, 5'-H, 1-H), 6.74-6.78 (dd, *J* = 2.4 Hz, 8.6 Hz, 1H, 2-H), 6.69 (d, *J* = 2.4 Hz, 1H, 4-H), 3.81 (s, 3H, OCH_3), 3.42-3.51 (m, 1H, 15-H_a), 1.43-3.04 (m, 12H, ring protons), 1.02 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 210.1, 157.6, 155.1, 149.9, 140.4, 137.8, 136.3, 132.2, 130.9, 126.7, 126.3, 122.8, 113.9, 111.6, 55.2, 48.3, 48.0, 44.1, 38.1, 31.7, 29.7, 29.6, 26.9, 26.0, 14.6. HRMS: calculated for $C_{25}H_{28}NO_2$ $[M+H]^+$ 374.2120, found 374.2115.

3-Methoxy-16-(thien-2-ylmethylene)-estra-1,3,5(10)-triene-17-one (**8h**):
Yield: 52%. Light yellow solid, mp. 178-179 °C, R_f: 0.41 (silica, toluene/EtOAc 25:1). IR (KBr, (cm^{-1})): 3110, 2972, 2920, 2858, 2844, 2821, 1708, 1615, 1503, 1464, 1449, 1417, 1376, 1316, 1235, 1187, 1166, 1102, 1086, 1034, 905, 863, 852, 822, 787, 717, 582, 517. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.65-7.72 (brs, 1H, Ar-CH=), 7.55 (d, *J* = 4.3 Hz, 1H, 5'-H), 7.35-7.41 (brs, 1H, 3'-H), 7.25 (d, *J* = 8.4 Hz, 1H, 1-H), 7.14-7.19 (m, 1H, 4'-H), 6.73-6.80 (m, 1H, 2-H), 6.67-6.73 (brs, 1H, 4-H), 3.82 (s, 3H, Ar-OCH_3), 1.44-3.10 (m, 13H, ring protons), 1.00 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.3, 157.7, 140.0, 137.7, 133.7, 132.4, 132.1, 129.6, 127.9, 126.3, 125.9, 114.0, 111.6, 55.2, 48.4, 48.2, 44.1, 38.0, 31.7, 29.7, 28.9, 26.9, 26.0, 14.7. HRMS: calculated for $C_{24}H_{27}O_2S$ $[M+H]^+$ 379.1732, found 379.1734.

16-Benzylidene-estra-1,3,5(10)-triene-17-one (**10a**)[23]:
Yield: 96%. White solid, mp. 248-250 °C, R_f: 0.49 (silica, toluene/EtOAc 5:1). IR (KBr, (cm^{-1})): 3361, 2933, 2918, 2874, 2853, 1703, 1611, 1505, 1491, 1456, 1216, 728, 694, 514. ^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.59 (d, *J* =7.4 Hz, 2H, 2',6'-H), 7.49-7.53 (m, 1H, Ar-CH=), 7.43-7.49 (m, 2H, 3',5'-H), 7.37-7.43 (m, 1H, 4'-H), 7.20 (d, *J* = 8.4 Hz, 1H, 1-H), 6.66-6.72 (m, 1H, 2-H), 6.61-6.66 (brs, 1H, 4-H), 4.86-5.09 (brs, 1H, OH), 1.23-3.08 (m, 13H, ring protons), 1.04 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.8, 153.6, 137.9, 136.0, 135.6, 133.4, 132.1, 130.3 (2C), 129.3, 128.7 (2C), 126.5, 115.3, 112.9, 48.7, 47.9, 44.1, 38.0, 31.7, 29.5, 29.1, 26.8, 26.0, 14.6. HRMS: calculated for $C_{25}H_{26}O_2Na$ $[M+Na]^+$ 381.1831, found 381.1832.

16-(Thien-2-ylmethylene)-estra-1,3,5(10)-triene-17-one (**10h**)[23]:
Yield: 84%. Pale yellow solid, mp. 260-261 °C, R_f: 0.46 (silica, toluene/EtOAc 5:1).
^{1}H-NMR ($CDCl_3$, 500.15 MHz): δ = 7.66-7.72 (brs, 1H, Ar-CH=), 7.55 (d, *J* = 4.7 Hz, 1H, 5'-H), 7.38 (d, *J* = 2.8 Hz, 1H, 3'-H), 7.14-7.23 (m, 2H, 1-H, 4'-H), 6.66-6.72 (m, 1H, 2-H), 6.61-6.66 (brs, 1H, 4-H), 4.83-4.93 (brs, 1H, OH), 1.24-3.08 (m, 13H, ring protons), 1.00 (s, 3H, 18-H_3). ^{13}C-NMR ($CDCl_3$, 125.78 MHz): δ = 209.4, 153.6, 140.0, 138.0, 133.7, 132.4, 132.1, 129.7, 127.9, 126.5, 126.0, 115.3, 112.9, 48.4, 48.2, 44.1, 38.0, 31.7, 29.5, 28.9, 26.8, 26.0, 14.7. HRMS: calculated for $C_{23}H_{25}O_2S$ $[M+H]^+$ 365.1575, found 365.1573.

Crystallography

Data were collected on a Gemini diffractometer (Oxford Diffraction Ltd) equipped with a Ruby CCD detector using Enhance Mo X-ray or Cu X-ray sources. Structure has been refined on F2 using the SHELXL-201430 suite of programs and data analysis was performed with PLATON.31A multi-scan procedure was applied to correct for absorption effects. Hydrogen atom positions were calculated and refined isotropically using a riding model. CCDC-1815277-1815278 entries contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Suitable crystals of **8g** and **10h** were grown from toluene/EtOAc (15:1, v/v) and toluene/EtOAc (5:1, v/v) mixture.

Computational Methods

Theoretical calculations were performed with the Gaussian 09 software package.[32] Molecular geometries were optimized using the long-range corrected hybrid density functional CAM-B3LYP33 and the standard 6-31G** basis set. The optimizations were performed without any symmetry constraint. The vibrational analysis yielded no imaginary frequencies verifying that each of the optimised structures is a true minimum on the potential energy surface. The vibrational frequencies were corrected with the scaling factor 0.97. For the visualisation of infrared spectra, the Molden program was used.[34]

Acknowledgements

The support of the National Research, Development and Innovation Office (OTKA 116727 and 120014) is acknowledged. This work is supported by the ÚNKP-17-2 New National Excellence Program of the Ministry of Human Capacities. X-ray diffraction data were recorded within the Plateforme de caractérisation PC2 at UNamur.

Keywords: alkylcarbonate • guanidine •green synthesis • ionic liquid • recyclability

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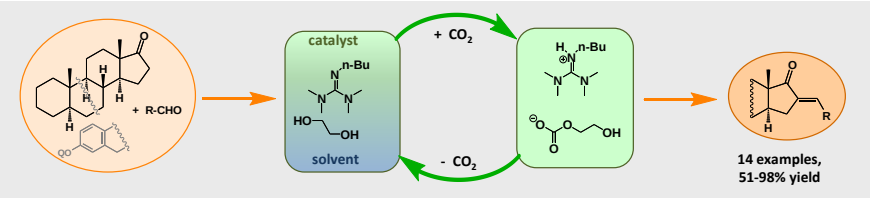

A recyclable guanidine/ethylene glycol catalyst/solvent system was used in the high-yielding synthesis of steroids with known and potential biological activity. The guanidine served as the catalyst in the condensation of 17-oxo steroids and aromatic aldehydes. The products were separated after switching the mixture into its ionic alkylcarbonate form with CO_2.

Green synthetic methods*

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The use of switchable polarity solvents for the synthesis of 16-arylidene steroids *via* Claisen-Schmidt condensation