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ARTICLE

Evaluation of sodium acetate trihydrate-urea DES as a benign reaction media for the Biginelli reaction. Unexpected synthesis of methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones), hexahydroxanthene-1,8-diones and hexahydroacridine-1,8-diones

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Camilo A. Navarro,[a] Cesar A. Sierra[a] and Cristian Ochoa-Puentes[a]*

In this work, the low melting mixture sodium acetate trihydrate-urea was synthesized and the eutectic composition was determined and characterized using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The physical properties of the deep eutectic solvent (DES) such as viscosity, electrical conductivity, density, pH and refractive index were mesured and analyzed as function of temperature. To explore the use of this DES as a reaction media, the Biginelli one-pot reaction for the obtention of polyhydroquinoxaline derivatives was studyied and unexpectedly methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones) and hexahydroxanthene-1,8-diones were obtained when the reaction was performed at 60 °C and hexahydroacridine-1,8-diones when the reaction was conducted at 100 °C. Our results showed that the nature of the obtained products can be tuned by increasing the temperature of the reaction.

Introduction

Organic solvents are widely used in chemical laboratories and the chemical industry as liquid media in which different processes like synthesis, extraction, separation, purification and drying of chemical products take place. They also serve as medium to perform some analytical, spectroscopic and spectrometric methods and for the determination of physicochemical properties. Due to their extensive use, hazardous and toxic properties, many organic solvents are considered as dangerous waste by-products. As alternative for common organic solvents, a new class of "green reaction media" which include ionic liquids, water, perfluorinated biphasic solvents, supercritical liquids, carbonic esters and deep eutectic solvents (DESs) have emerged.[1]

A DES would be defined as a mixture of two or more components (hydrogen bond donors and hydrogen-bond acceptors) which may be solid or liquid with a particular composition (eutectic composition) that present a high melting point depression.[2] DESs can be formed by mixing the starting components under moderate temperatures and many of them can be obtained from cheap, readily available, and toxicologically well characterized starting materials.[3] Recent advances in the use of DES include processes of extraction,[4, 5] dissolution and separation,[6] catalysis,[7] preparation of materials,[8] electrochemistry and organic synthesis.[3, 9] In this last field, the low melting mixtures have been introduced as reaction media for a variety of organic C–C-coupling reactions. Diels-Alder, Perkin, aldol, Biginelli and Pictet–Spengler reaction, Knoevenagel condensation, addition of organolithium and Grignard reagents to ketones, metal-catalysed reactions like Suzuki, Heck, and Sonogashira reactions, and the Huisgen 1,3-dipolar cycloaddition are some examples of successfully conducted reactions.[9, 10]

The Biginelli reaction is one of the most important multicomponent reactions based on acid-catalyzed three-component condensation of a β-dicarbonyl compound, an aldehyde and urea or thiourea.[11] This remarkable reaction offers straightforward access to biologically active dihydropyrimidones[12] and therefore in the last decades many improved procedures with new catalysts, building blocks and solvents have been reported.[13]

Recently König et al. introduced the use of tartaric acid-N,N-dimethyl urea DES for the synthesis of several nitrogenated hereocycles,[14] including dihydropyrimidones.[15] Interestingly, these reports show that this DES acts as solvent, catalyst and reactant allowing the efficient construction of highly functionalized nitrogenated heterocycles in good to excellent yields.

Based on the aforementioned results and the recent reports about the base-catalyzed Biginelli reaction,[16, 17] we hypothesized that the sodium acetate trihydrate-urea DES may promote the reaction between dimedone, aldehydes and urea to obtain polyhydroquinoxaline derivatives of biological significance via Biginelli reaction,[18] and herein we report the unexpected results obtained during this multicomponent reaction.

[a] Grupo de Investigación en Macromoléculas, Departamento de Química, Universidad Nacional de Colombia–Sede Bogotá, Carrera 45 # 26-85, A.A. 5997, Bogotá, Colombia, E-mail: cochoapu@unal.edu.co; Tel.: +57-1-3165000
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Results and discussion

Thermal analysis (DSC/TGA)

The sodium acetate trihydrate-urea DES was first reported as a eutectic mixture composed by $CH_3COONa{\cdot}3H_2O$ and $CO(NH_2)_2$ in the mass ratio 0.4:0.6, with a melting point of 30 °C.[19] Based on this, we decided to prepare this low melting system to be used as DES in organic synthesis, but during several experiments a non-homogenous mixture with dispersed solids was obtained. Then, we focused on study the mixture by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) in order to determine the eutectic point and the thermal stability of the mixture. Figure 1 shows the phase diagram constructed with 11 samples of $CH_3COONa{\cdot}3H_2O/CO(NH_2)_2$ of different molar composition (1:0; 0.8:0.2; 0.6:0.4; 0.5:0.5; 0.4:0.6; 0.3:0.7; 0.2:0.8; 0.15:0.85; 0.1:0.9; 0.05:0.95 and 0:1).

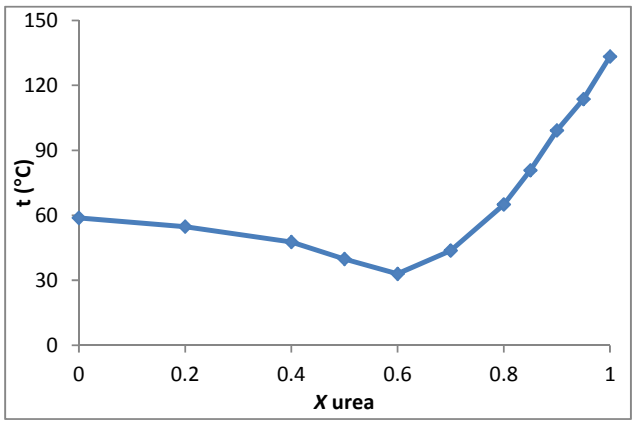

Figure 1. Phase diagram for sodium acetate trihydrate-urea mixtures.

The eutectic point found for the mixture was 33 °C with a molar composition of 0.4:0.6 $CH_3COONa{\cdot}3H_2O/CO(NH_2)_2$, which is different from the reported by Li and co-workers.[19] This depression of the melting point might arise from the interaction between urea molecules and acetate ions as shown by the crystallographic data for the adduct $[(CH_3)_3N^+CH_2CH_2OH\text{-}]_2C_2O_4^{2-}{\cdot}2(NH_2)_2CS$, where a hydrogen bonding between the oxalate anion and the thiourea has been described.[20] The thermogravimetric analysis (Figure 2) shows that the DES loses 61.7 wt% in four consecutive steps. The first three steps correspond to mass loss of 8.03 % (71 °C), 7.91 % (108 °C) and 6.69 % (131 °C), which is consistent with the release of the three crystallization water molecules present in the acetate. Decomposition of urea starts at 133 °C and ends at 214 °C, where only sodium acetate anhydride remains. DSC and TGA analysis allows concluding that the DES can be used as reaction media at temperatures between 33 and 130 °C, where no decomposition of its components is present.

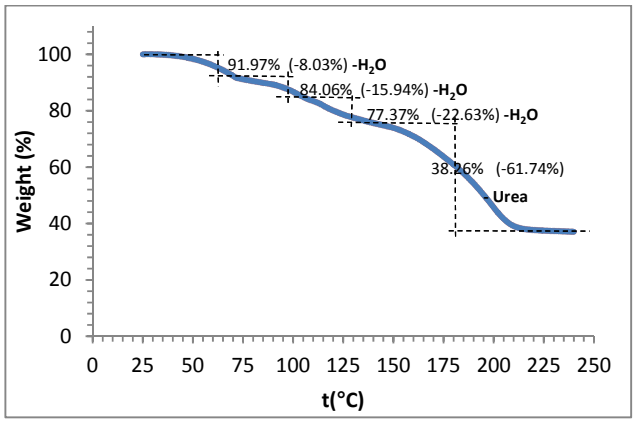

Figure 2. TGA profile in N_2 atmosphere for the sodium acetate trihydrate-urea DES.

Once the thermal stability of the DES was established, and to better understand the role of this solvent in the model reaction and other future applications, some physicochemical properties such as density, refractive index, pH, viscosity and electrical conductivity as function of temperature were studied.

Density

It is well known that the composition and the temperature of a liquid notoriously affect density.

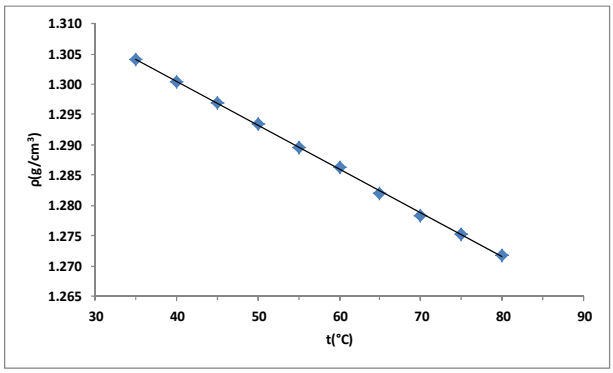

Figure 3. Density (ρ) of sodium acetate trihydrate-urea DES as a function of temperature.

Density measurements for the $CH_3COONa{\cdot}3H_2O/CO(NH_2)_2$ DES (Figure 3) were performed at temperatures ranging from 35 to 80 °C, and it was observed that this property decreases linearly with temperature. The increase in molecules-ions mobility in the DES by changes in temperature has been attributed to molecular rearrangements caused by the vibrations when the components absorbed the energy given to the system.[21] This increases the solution molar volume which reduces density. In addition, the loose of some water content during heating decreases the mass and also

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contribute to have lower density values. The variation of density with temperature was modeled according to equation 1.

$$\rho(g/cm^3) = a(t/^oC) + b \quad (1)$$

where ρ is the density, t is the temperature, a and b are constants (Table 1).

Refractive index

Refractive index (n_D) of the DES was measured as a function of temperature and is shown in Figure 4.

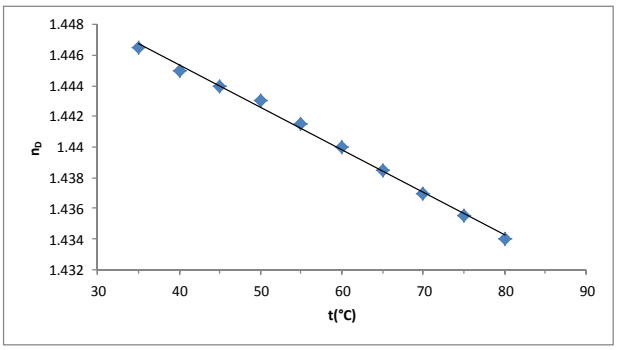

Figure 4. Refractive index (n_D) of sodium acetate trihydrate-urea DES as a function of temperature.

The refractive index (n_D) of the DES lies within the range of 1.446-1.430 for the temperature range of 35-80 °C and decreases with increasing temperature. This behavior was the expected due to its proportionality with the square root of electrical permittivity and magnetic permeability which change nonlinearly.[22] The relationship between refractive index and temperature was fitted linearly according with the general equation

$$n_D = a(t/^oC) + b \quad (2)$$

where n_D is the refractive index, t is the temperature, a and b are unitless parameters shown in Table 1.

pH

pH is a physical property that may influence the selection of a solvent for potential biochemical and industrial applications. The relationship of the measured pH values for the DES at different temperatures (35-80 °C) is presented in Figure 5.

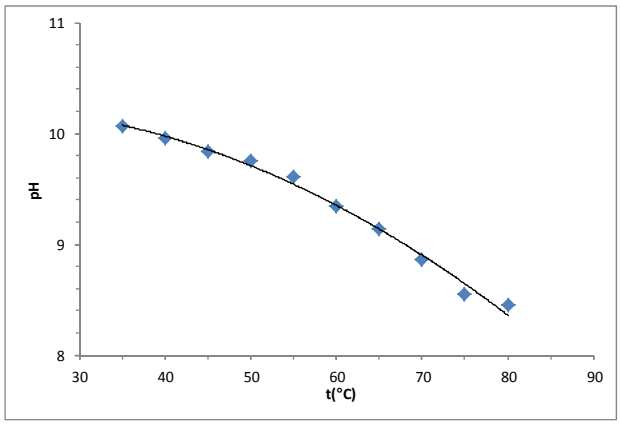

Figure 5. pH for sodium acetate trihydrate-urea DES as a function of temperature.

As shown in Figure 5, the increase of temperatures decreases the pH in the DES showing values for the pH in the range of 10.07 to 8.45. The variation of pH with temperature was fitted by the general second-order polynomial equation

$$pH = a(t/^oC)^2 + b(t/^oC) + c \quad (3)$$

where t is the temperature, a, b and c are unitless parameters shown in Table 1.

Table 1. Values of parameters a, b, c and correlation coefficient for equations 1-3.

Physical properties	a	b	c	R^2
ρ	$-7x10^{-4}$	1.3293		0.9993
n_D	$-3x10^{-4}$	1.4565		0.9963
pH	$-5x10^{-3}$	0.0147	10.126	0.9919

Viscosity

The viscosity (η) is defined as the internal friction measurement of a moving fluid which describes the resistance of a substance to flow. The viscosity strongly influences the ability of a liquid to transport compounds within it, and therefore is directly related with the conversion of reagents into products in a chemical reaction. The viscosity of the DES was studied in the same range of temperatures as the other physicochemical properties (Figure 6).

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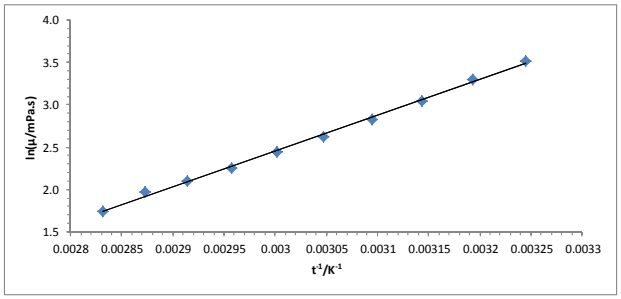

Figure 6. Viscosity change for sodium acetate trihydrate-urea DES as a function of temperature.

The viscosity of the DES is higher in comparison to other common organic solvents, but has lower values compared to other DES based on choline chloride and tetrabutylammonium bromide.[5, 22, 23] DES viscosity reduces with an increase in temperature, and although its graph is non-linear (see supporting information), this result is consistent with the reports for other DES. Heating will increase the kinetic energy and as a result the attractive forces between molecules and ions in the DES may weaken. In addition, the water content and the size of the molecules might benefit the fluidity due to smaller size species moves with diminished resistance. The viscosity of the DES was modeled according with the expression

$$\text{Ln } \eta = ln\ \eta_0 + (E_\eta/RT) \quad (4)$$

where η_0 is a constant, E_η is the activation energy of a viscous flow, R is the gas constant, and T is the temperature in Kelvin. Values of η_0 and E_η/R are shown in Table 2.

Electrical conductivity

Electrical conductivity (k) is defined as the ability to conduct an electric current. Conductivity of the DES was studied at different temperatures (35-80 ^{o}C) and it is illustrated in Figure 7.

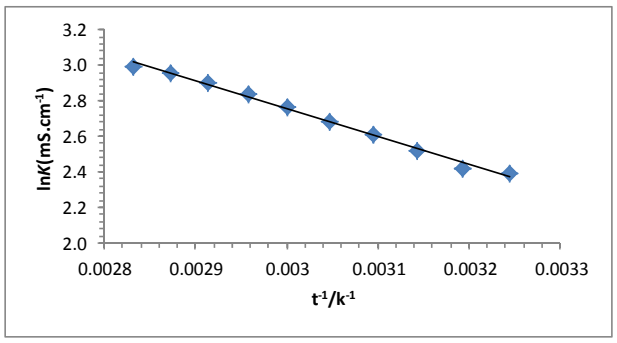

Figure 7. Conductivity as a function of temperature for sodium acetate trihydrate-urea DES.

As shown in Figure 7, the ionic conductivity of the DES increases with temperature. This behavior may be explained by two factors: first, the increased kinetic energy rise the frequency of collisions between molecules which weakens the intermolecular forces,[24] and second, the high movement of the small charge carriers due to the decreases in viscosity increase the ionic conductivity as described by the Walden Rule.[25] The temperature dependence of the experimental conductivity was correlated using

$$\text{Ln } k = ln\ k_0 - (E_k/RT) \quad (5)$$

Where k_0 is a constant and E_k is the activation energy of conductivity. Values of k_0 and E_k/R are shown in Table 2.

Table 2. Values found for η_0, E_η/R, k_0, E_k/R and correlation coefficients for equations 4 and 5.

Physical properties	η_0	E_η/R	k_0	E_k/R	R^2
η	3.58x10^{-5}	4229.8			0.9969
k			1741.1	1569	0.9938

Once the physicochemical properties of the sodium acetate trihydrate-urea DES were studied as function of temperature, the DES was evaluated in the Biginelli reaction for the synthesis of polyhydroquinoxaline derivatives. TGA analysis and the variation of density and viscosity as function of temperature showed that the sodium acetate trihydrate-urea DES may be used at high temperatures (under 130 ^{o}C) were the mobility of substrates is favored and no decomposition of the components is present. Therefore, dimedone (**1**) (1 mmol), 4-chlorobenzaldehyde (**2**) (1 mmol) and urea (**3**) (1 mmol) were added to 2 g of the DES and the reaction mixture was heated at 90 ^{o}C during 6 h. After reaction completion (monitoring by thin layer chromatography) water was added and the solid product was filtered and recrystallized from ethanol. The structure of the obtained compound which was elucidated by FT-IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis (see supporting information) indicates that the polyhydroquinoxaline expected (**4**) was not synthesized, and instead, under the reaction conditions the hexahydroxacridine-1,8-dione (**5a**) was obtained (Scheme 1).

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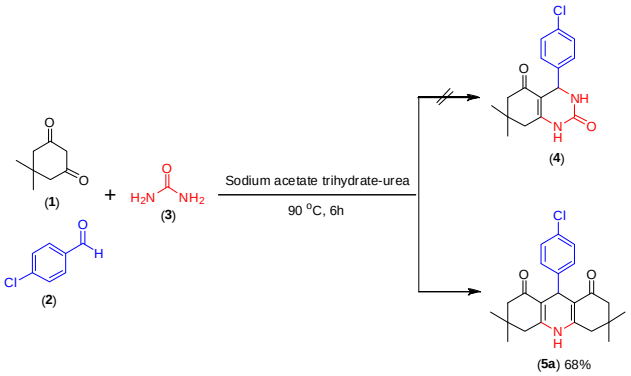
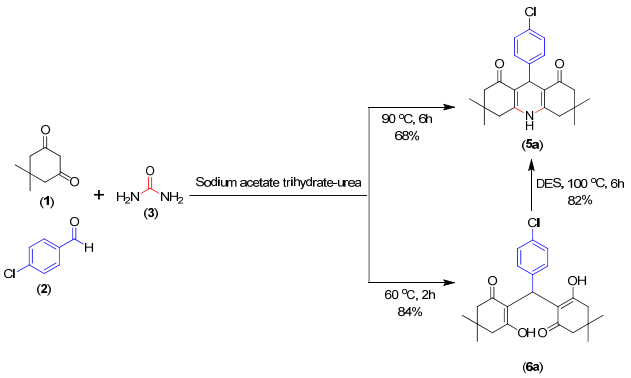


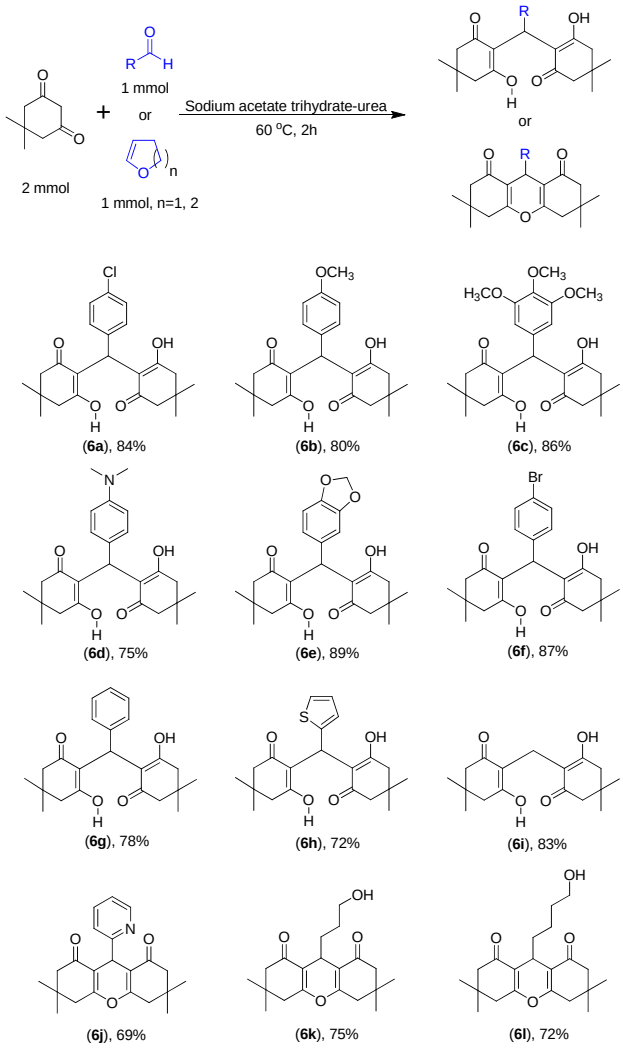
Scheme 1. Unexpected one-pot multicomponent synthesis of the hexahydroxacridine-1,8-dione (**5a**).

The unexpected synthesis of the hexahydroxacridine-1,8-dione (**5a**) led us to hypothesize that the high temperature and the time of the reaction promoted the decomposition of urea, yielding the ammonia needed for the formation of (**5a**). Therefore the same reaction was performed at 60 °C and after 2h a white solid labeled as (**6a**) was obtained (Scheme 2). FT-IR, ^{1}H-NMR, ^{13}C-NMR spectra and elemental analysis showed that the structure of (**6a**) corresponds to a bis-hydroxy compound[26] (see supporting information) which may be formed by the Michael addition of one equivalent of dimedone to the Knoevenagel aduct of 4-chlorobenzaldehyde and a second equivalent of dimedone.[27] This result shows that the urea does not react under these conditions and although heating was extended for 12h the formation of (**5a**) did not take place.



Scheme 2. Synthesis of the bis-hydroxy derivative (**6a**) and the hexahydroxacridine-1,8-dione (**5a**) in sodium acetate trihydrate-urea DES under different conditions.

The same type of bis-hydroxy derivatives were obtained in moderate to good yields when the reactivity of different aldehydes was studied under the same reaction conditions using 2 mmol of dimedone (Scheme 3). Similar results were found by Azizi and co-workers using a choline chloride-urea DES.[28] Interestingly, the hexahydroxanthene-1,8-diones (**6j**-**6l**) were obtained when 2-pyridinecarboxaldehyde, 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran were used. These compounds may be obtained by an intramolecular cyclization-dehydration of the corresponding bis-hydroxy intermediate,[29] which could not be isolated from the reaction mixture.



Scheme 3. Synthesis of bis-hydroxy derivatives (**6a**-**6i**) and hexahydroxanthene-1,8-diones (**6j**-**6l**).

In order to confirm that compound (**6a**) is an intermediate for the obtention of (**5a**), this bis-hydroxy derivative was added to the DES and the mixture was heated to 100 °C during 6h obtaining the hexahydroxacridine-1,8-dione (**5a**) in good yield (Scheme 2).

The obtention of the bishydroxy derivative (**6a**) and its conversion to the hexahydroxacridine-1,8-dione (**5a**) under the reaction conditions here explored, indicates that the reaction may proceed following one of the three possible mechanisms proposed for the Biginelli reaction[17, 30] (Scheme 4).

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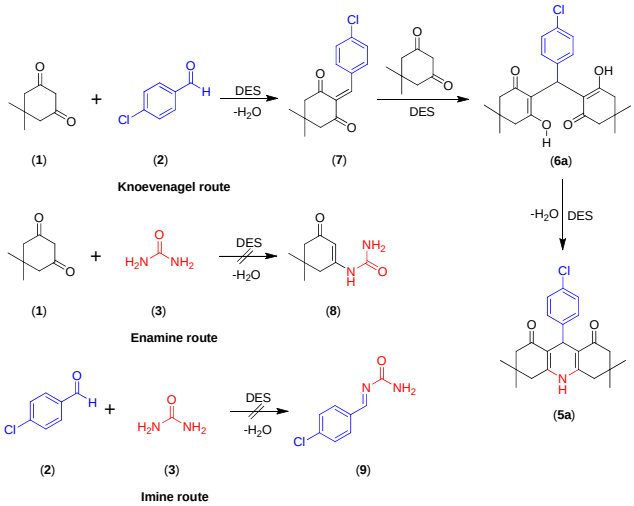


Scheme 4. Possible synthetic routes to obtain (**5a**) by the Biginelli reaction.

As shown in Scheme 4, only the Knoevenagel route will promote the formation of the bis-hydroxy derivative (**6a**). The obtention of (**6a**) may be attributed to the high reactivity of the 2-arylidenedimedone intermediate (**7**) which preferably reacts with dimedone affording (**6a**)[31] and its further reaction with ammonia may yield (**5a**) (Scheme 4). This is consistent with one of the proposed mechanisms for the Hantzsch dihydropyridine synthesis.[32]

Intrigued by the results, the reaction was studied by ^{1}H-NMR in DMSO-6d (Figure 8).

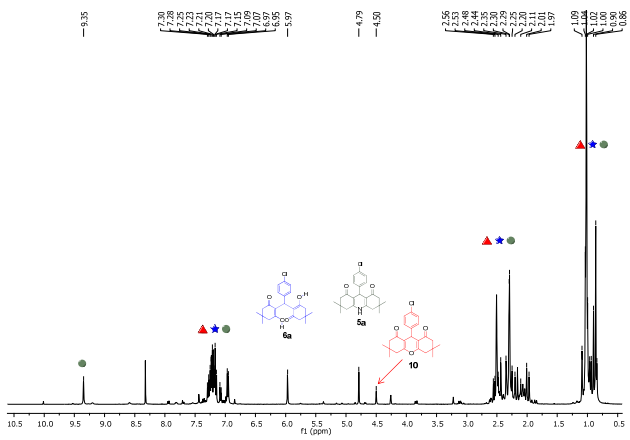
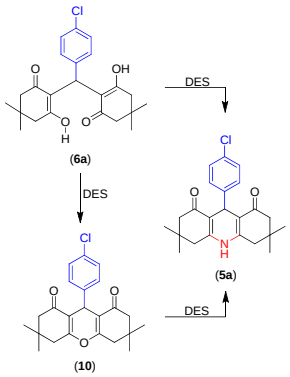


Figure 8. Crude ^{1}H NMR spectra for the reaction forming **5a**.

After 4h the spectrum showed characteristic signals for the methinic protons belonging to both the bis-hydroxy intermediate (**6a**) at 5.97 ppm (singlet), and the hexahydroacridine-1,8-dione (**5a**) at 4.79 ppm (singlet). Interestingly, a signal (singlet) at 4.50 ppm was detectable and assigned to the methinic proton of the hexahydroxanthene-1,8-dione (**10**)[33] which suggests that this compound is formed from the bis-hydroxy derivative (**6a**) during the reaction and the hexahydroxacridine-1,8-dione (**5a**) would be obtained from both (**6a**) and (**10**) (Scheme 5). Other possible intermediates like (**8**) and (**9**) were not detected from the crude reaction mixture by ^{1}H-NMR and after completion of reaction the intermediates (**6a**) and (**10**) were not detected (TLC) when compared with authentic samples.



Scheme 5. Bis-hydroxy derivative (**6a**) and hexahydroxanthene-1,8-dione (**10**) as intermediates for the synthesis of the hexahydroacridine-1,8-dione (**5a**).

All these results show that although the TGA indicates that the DES is stable below 130 ^{o}C, the eutectic mixture decomposes at lower temperature yielding ammonia under the reaction conditions here employed, and affording the hexahydroxacridine-1,8-dione (**5a**). This finding is in agreement with the recent report of Simeonov and Afonso[34] which shows the obtention of dihydropyridines via Hantzsch reaction in sorbitol-urea DES. In this study the decomposition of urea (source of ammonia for the reaction) occur below 100 ^{o}C and is enhanced in diols based DES by the formation of carbonates.

Hexahydroxacridine-1,8-diones are extensively studied nitrogenated heterocycles with biological activity as SITR1 inhibitors,[35] DNA intercalator,[36] calcium,[37] and potassium[38] channel modulators, antimicrobial[39] and antifungal agents,[40] and carbonic anhydrase inhibitors.[41] In addition, the interesting photophysical and photochemical properties of several acridinediones have promoted their use as laser dyes,[42] initiators in photopolymerization,[43] chemosensors,[44] fluorescent probes for monitoring of polymerization processes,[45] in the preparation of blue light-emitting devises,[46] and dye-sensitized solar cells.[47]

In spite of the different synthetic methodologies reported for the synthesis of hexahydroxacridine-1,8-diones,[48] their known biological activity and photophysical properties have inspired the design of new synthetic strategies to obtain this versatile heterocyclic compound. Motivated for the few reports concerning the synthesis of dihydropyridine derivatives and related compounds under Biginelli conditions,[49] the unexpected formation of (**5a**) led us to synthesize a series of hexahydroxacridine-1,8-diones starting from dimedone and different aromatic aldehydes (Scheme 6).

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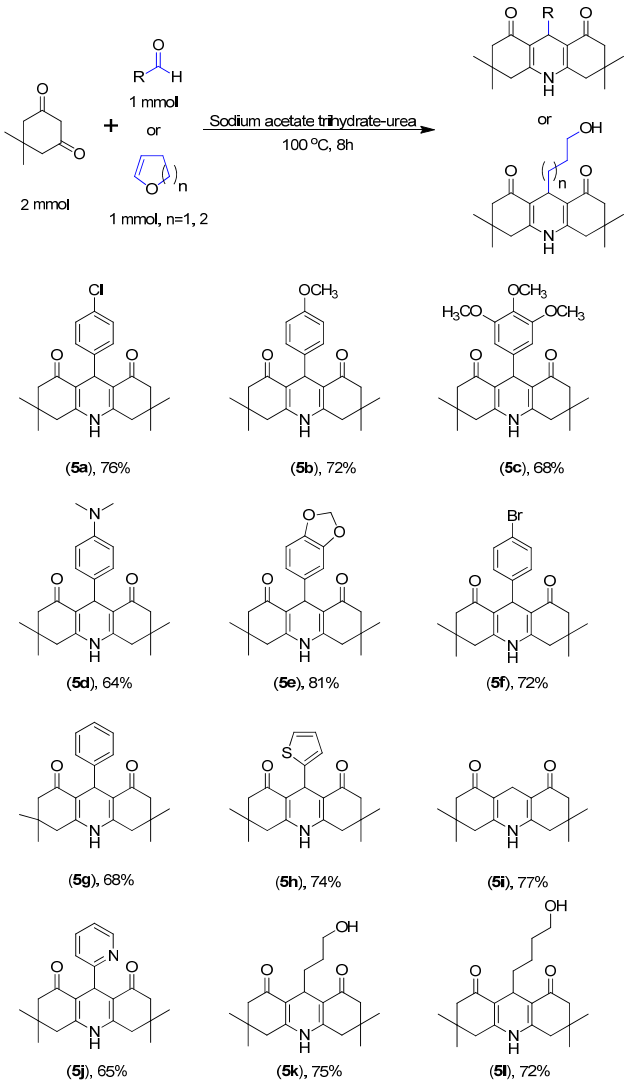

Scheme 6. Synthesis of hexahydroxacridine-1,8-diones (**5a**-**5l**).

All hexahydroxacridine-1,8-diones (**5a**-**5l**) were obtained in moderate to good yields after purification by recrystallization from ethanol. The masked aldehydes dihydrofuran and dihydropyran also reacted under the reaction conditions employed here to give the corresponding hexahydroxacridine-1,8-diones (**5k**) and (**5l**) which to the best of our knowledge have not been reported before. As mention previously, when these masked aldehydes and 2-pyridinecarboxaldehyde were used in the reaction at 60°C the bis-hydroxy derivatives were not obtained and instead of this, the xanthenes (**6j**-**6l**) were formed. Therefore the synthesis of compounds (**5j**-**5l**) also supports the fact that these hexahydroxacridine-1,8-diones are formed from the reaction of (**6j**-**6l**) with ammonia, which was further confirmed when these xanthenes were heated in the DES for 6h. Similar results have been reported recently.[50]

Experimental

General information

All the chemicals and solvents were purchased from commercial suppliers and used without further purification. Melting points, reported without correction, were measured using a Stuart SMP10 apparatus. The FT-IR spectra were obtained with a Shimadzu IR prestige 21 spectrophotometer (Columbia, MD, USA). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE III system operating at 400 MHz, using residual and deuterated solvent peaks of $CDCl_3$ (δH 7.26; δC 77.0) and DMSO (δH 2.50; δC 39.5) as reference standards. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J, are reported in Hertz (Hz). Elemental analyses were performed on a Thermo Scientific Flash 2000 CHNS/O analyser and their results were found to be in agreement with the calculated values. For the DSC analysis, 11 samples of $CH_3COONa\cdot 3H_2O/CO(NH_2)_2$ of different molar composition (1/0; 0.8/0.2; 0.6/0.4; 0.5/0.5; 0.4/0.6; 0.3/0.7; 0.2/0.8; 0.15/0.85; 0.1/0.9; 0.05/0.95 and 0/1) were formed by heating and stirring between 35 and 120°C until a liquid was formed. A portion of each warm mixture liquid was loaded into a hermetically sealed aluminum pan. The sample was then cooled to -60°C and then heated to 145°C at 1°C/min under a nitrogen atmosphere on a differential scanning calorimeter DSC 1 STAR^{e} System (Mettler Toledo). TGA analysis for the DES was run in nitrogen (40 mL/min) atmosphere using a TGA 1 STAR^{e} System (Mettler Toledo). Programmed heating rate was 2°C/min starting from 25°C until 240°C. The density of the DES was measured using a liquid densitometer (Anton Paar DMA4500M). An Abbe type refractometer (model 2WAJ equipped with a sodium D1 line) was used to measure the DES refractive. The pH of the synthesized DES was measured at different temperatures using Jenway 370 pH/mV hand-held meter. The viscosity was determined using a Oswalt (Cannon-Fenske Routine Type) viscometer. The conductivity and its temperature dependence were determined using a Jenway 470 portable conductivity/TDS meter calibrated by measuring the conductivities of aqueous solutions of KCl at different concentrations. The variation of the temperature for the determination of the physical properties was done by using a Lauda Alpha water circulator.

General procedure for the synthesis of bis-hydroxy derivatives (6a-6i) and hexahydroxanthene-1,8-diones (6j-6l).

1.5g of sodium acetate trihydrate-urea DES (0.4 : 0.6) was heated to 35 °C to obtain a clear melt. To this melt a mixture of dimedone (2.00 mmol) and aromatic aldehydes (1.00 mmol) was added and the reaction was stirred at 60 °C for 2h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by adding water while still hot, cooled to room temperature and the crude solid was filtered, washed with water (3 x 5 mL) and recrystallized from ethanol to afford the pure product.

2,2'-((4-Chlorophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6a). White solid, mp: 145 - 147 °C, IR ν_{max}/cm^{-1}: 2957 (CH), 1581 (C=O), 1491 (C=C), 1374 (HCH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.87 (s, 1H, OH), 7.23 (d, *J* = 8.5 Hz, 2H, H-Ar), 7.01 (d, *J* = 8.0 Hz, 2H, H-Ar), 5.47 (s, 1H,CH), 2.49 - 2.28 (m,

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8H, $4CH_2$), 1.22 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 189.5, 136.9, 131.7, 128.5, 128.4, 115.5, 47.2, 46.6, 32.58, 31.6, 29.7, 27.6. Anal. calcd for $C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75; found: C, 68.84; H, 6.76.

2,2'-((4-Methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6b). White solid, mp: 143 - 145 °C, IR ν_{max}/cm^{-1}: 2960 (CH), 1599 (C=O), 1509 (C=C), 1377 (HCH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.91 (s, 1H, OH), 6.99 (d, *J* = 8.1 Hz, 2H, H-Ar), 6.81 (d, *J* = 8.8 Hz, 2H, H-Ar), 5.48 (s, 1H, CH), 3.77 (s, 3H, OCH_3), 2.39 (m, 8H, $4CH_2$), 1.22 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 190.5, 189.5, 157.8, 130.0, 127.9, 115.9, 113.8, 55.3, 47.2, 46.6, 32.2, 31.54, 29.8, 27.5. Anal. calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59; found: C, 72.03; H, 7.41.

2,2'-((3,4,5-Trimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6c). White solid, mp: 190 - 191 °C, IR ν_{max}/cm^{-1}: 2954 (CH), 1582 (C=O), 1508 (C=C), 1374 (HCH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 12.02 (s, 1H, OH), 6.34 (s, 2H, H-Ar), 5.49 (s, 1H, CH), 3.81 (s, 3H, OCH_3), 3.75 (s, 6H, $2OCH_3$), 2.46 – 2.32 (m, 8H, $4CH_2$), 1.24 (s, 6H, $2CH_3$), 1.12 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 190.5, 189.4, 153.0, 133.9, 115.7, 104.3, 61.0, 56.0, 47.2, 46.5, 32.9, 31.3, 30.2, 27.0. Anal. calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47; found: C, 67.94; H, 7.41.

2,2'-((4-(Dimethylamino)phenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6d). Yellow solid, mp: 198 - 200 °C, IR ν_{max}/cm^{-1}: 2961 (CH), 1599 (C=O), 1522 (C=C), 1370 (HCH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.92 (s, 1H, OH), 6.97 (d, *J* = 8.2 Hz, 2H, H-Ar), 6.74 (s, 2H, H-Ar), 5.47 (s, 1H, CH), 2.92 (s, 6H, $N(CH_3)_2$), 2.47 – 2.26 (m, 8H, $4CH_2$), 1.22 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 189.4, 127.7, 116.0, 113.2, 46.9, 41.3, 32.0, 31.5, 29.8, 27.4. Anal. calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40; found: C, 72.85; H, 8.03; N, 3.34.

2,2'-(Benzo[*d*][1,3]dioxol-5-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6e). White solid, mp: 177 - 180 °C, IR ν_{max}/cm^{-1}: 2960 (CH), 1584 (C=O), 1520 (C=C), 1373 (HCH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H, OH), 6.70 (d, *J* = 8.1 Hz, 1H, H-Ar), 6.57 (s, 1H, H-Ar), 6.54 (dd, *J* = 8.2, 1.2 Hz, 1H, H-Ar), 5.91 (s, 2H, OCH_2O), 5.45 (s, 1H, CH), 2.48 - 2.27 (m, 8H, $4CH_2$), 1.21 (s, 6H, $2CH_3$), 1.09 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 189.5 , 147.8, 145.7, 132.0, 119.8, 115.8, 108.0, 107.7, 101.0, 47.2, 46.5, 32.6, 31.5, 29.7, 27.6. Anal. calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84; found: C, 69.44; H, 6.64.

2,2'-((4-Bromophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6f). White solid, mp: 174 - 176 °C, IR ν_{max}/cm^{-1}: 2957 (CH), 1583 (C=O), 1486 (C=C), 1371 (HCH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H, OH), 7.38 (d, *J* = 8.5 Hz, 2H, H-Ar), 6.96 (d, *J* = 7.8 Hz, 2H, H-Ar), 5.45 (s, 1H, CH), 2.49 - 2.28 (m, 8H, $4CH_2$), 1.21 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 189.5, 137.4, 131.4, 128.7, 119.7, 115.4, 47.1, 46.5, 32.6, 31.5, 29.7, 27.5. Anal. calcd for $C_{23}H_{27}BrO_4$: C, 61.75; H, 6.08; found: C, 61.33; H, 6.08.

2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6g). White solid, mp: 192 - 194 °C, IR ν_{max}/cm^{-1}: 2961 (CH), 1591 (C=O), 1491 (C=C), 1372 (HCH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H, OH), 7.32 - 7.26 (m, 2H, H-Ar), 7.18 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.11 (d, *J* = 8.3 Hz, 2H, H-Ar), 5.56 (s, 1H, CH), 2.51 - 2.29 (m, 8H, $4CH_2$), 1.25 (s, 6H, $2CH_3$), 1.11 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 189.5, 138.2, 128.3, 126.9, 125.9, 115.7, 47.2, 46.6, 32.8, 31.5, 29.7, 27.5. Anal. calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66; found: C, 74.63; H, 7.55.

2,2'-(Thiophen-2-ylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6h). White solid, mp: 155 - 157 °C, IR ν_{max}/cm^{-1}: 2967 (CH), 1581 (C=O), 1447 (C=C), 1376 (HCH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H, OH), 7.10 (s, 1H, H-Ar), 6.92 - 6.80 (m, 1H, H-Ar), 6.67 - 6.57 (m, 1H, H-Ar), 5.63 (s, 1H, CH), 2.44 – 2.28 (m, 8H, $4CH_2$), 1.22 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 189.6, 143.8, 126.5, 124.7, 123.6, 116.1, 47.1, 46.3, 31.3, 30.5, 30.1, 26.9. Anal. calcd for $C_{21}H_{26}O_4S$: C, 67.35; H, 7.00; S, 8.56; found: C, 67.21; H, 7.08; S, 8.54.

2,2'-Methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (6i). White solid, mp: 192 - 194 °C, IR ν_{max}/cm^{-1}: 2968 (CH), 1608 (C=O), 1579 (C=C), 1379 (HCH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (s, 1H, OH), 3.15 (s, 2H, CH_2), 2.29 (s, 4H, $2CH_2$), 2.28 (s, 4H, $2CH_2$), 1.05 (s, 12H, $4CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 113.6, 46.1, 31.9, 29.6, 27.2, 16.0. Anal. calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; found: C, 69.61; H, 8.21.

3,3,6,6-Tetramethyl-9-(pyridin-2-yl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (6j). Yellow solid, mp: 175 - 178 °C, IR ν_{max}/cm^{-1}: 2932(CH), 1657(C=O), 1625(C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 4.1, 1H, H-Ar), 7.62 – 7.57 (m, 2H, H-Ar), 7.01 (m, 1H, H-Ar), 4.86 (s, 1H, CH), 2.54 (d, *J* = 17.9 Hz, 2H, CH_2), 2.45 (d, *J* = 17.5 Hz, 2H, CH_2), 2.23 (d, *J* = 16.2 Hz, 2H, CH_2), 2.16 (d, *J* = 16.2 Hz, 2H, CH_2), 1.09 (s, 6H, $2CH_3$), 1.00 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 197.1, 163.6, 161.7, 148.9, 135.9, 125.3, 121.6, 114.3, 50.8, 41.0, 34.5, 32.4, 29.4, 27.3. Anal. calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99; found: C, 74.71; H, 6.90; N, 3.61.

9-(3-Hydroxypropyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (6k). White solid, mp: 129 - 130 °C; IR ν_{max}/cm^{-1}: 3428 (OH), 1651 (C=O), 1616 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 3.80 (t, *J* = 4.5, 1H, CH), 3.60 (t, *J* = 6.6, 2H, CH_2), 2.38 (s, 4H, $2CH_2$), 2.30 (d, *J* = 16.2, 2H, CH_2), 2.25 (d, *J* = 16.2, 2H, CH_2), 1.90 (s, 1H, OH), 1.58 – 1.53 (m, 2H, CH_2), 1.41 – 1.34 (m, 2H, CH_2), 1.10 (s, 12H, $4CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 197.4, 164.1, 115.0, 62.8, 51.0, 41.0, 32.1, 30.6, 29.5, 28.9, 27.5, 24.7. Anal. calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; found: C, 72.61; H, 8.50.

9-(4-Hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (6l). White solid, mp: 125 - 127 °C; IR ν_{max}/cm^{-1}: 3390 (OH), 1664 (C=O),. 1643 (C=O), 1616 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 3.78 (t, *J* = 4.5, 1H, CH), 3.55 (t, *J* = 6.5, 2H, CH_2), 2.37 (s, 4H, $2CH_2$), 2.30 (d, *J* = 16.2, 2H, CH_2), 2.24 (d, *J* = 16.2, 2H, CH_2), 1.60 (bs, 1H, OH), 1.55 (m, 2H, CH_2), 1.57 - 1.46 (m, 2H, CH_2), 1.18 - 1.12 (m, 2H, CH_2), 1.10 (s, 12H, $4CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 197.2, 164.0, 114.9, 62.7, 50.9, 40.9, 33.6, 32.6, 32.0, 29.4, 27.3, 25.2, 21.5. Anal. calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; found: C, 72.53; H, 8.68.

General procedure for the synthesis of hexahydroxacridine-1,8-diones (5a-5l).

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1.5g of sodium acetate trihydrate-urea DES (0.4 : 0.6) was heated to 35 ^{o}C to obtain a clear melt. To this melt a mixture of dimedone (2.00 mmol) and aromatic aldehydes (1.00 mmol) was added and the reaction was stirred at 100 ^{o}C for 8h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by adding water while still hot, cooled to room temperature and the crude solid was filtered, washed with water (3 x 5 mL) and recrystallized from ethanol to afford the pure product.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5a). Yellow solid, mp: 298 - 300 °C, IR ν_{max}/cm^{-1}: 3278 (NH), 1649 (C=O), 1608 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.35 (s, 1H, NH), 7.28 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.15 (d, *J* = 7.9 Hz, 2H, H-Ar), 5.05 (s, 1H, CH), 2.33 (d, *J* = 16.3 Hz, 2H, CH_2), 2.27 – 2.21 (m, 4H, $2CH_2$), 2.15 (d, *J* = 16.3 Hz, 2H, CH_2), 1.07 (s, 6H, $2CH_3$), 0.95 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 195.8, 148.8, 145.2, 131.7, 129.6, 128.2, 113.3, 50.8, 41.1, 33.5, 32.8, 29.7, 27.2 Anal. calcd for $C_{23}H_{26}ClNO_2$: C, 71.96; H, 6.83; N, 3.65; found: C, 71.99; H, 6.81; N, 3.63.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5b). Yellow solid, mp: 270 - 273 °C, IR ν_{max}/cm^{-1}: 3275 (NH), 1673 (C=O), 1604 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.93 (s, 1H, NH), 7.26 (s, 2H, H-Ar), 6.74 (s, 2H, H-Ar), 5.06 (s, 1H, CH), 3.69 (s, 3H, OCH_3), 2.26 - 2.14 (m, 8H, $4CH_2$), 1.08 (s, 6H, $2CH_3$), 0.97 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 196.2, 157.8, 149.1, 139.3, 129.1, 113.5, 113.4, 55.1, 51.0, 40.8, 32.9, 32.7, 29.7, 27.2. Anal. calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; found: C, 75.97; H, 7.63; N, 3.87.

3,3,6,6-Tetramethyl-9-(3,4,5-trimethoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5c). Yellow solid, mp: 258 - 261 °C, IR ν_{max}/cm^{-1}: 3225 (NH), 1591 (C=O), 1604 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 9.29 (s, 1H, NH), 6.42 (s, 2H, H-Ar), 4.79 (s, 1H, CH), 3.65 (s, 6H, $2OCH_3$), 3.57 (s, 3H, OCH_3), 2.45 (d, *J* = 17.0 Hz, 2H, CH_2), 2.33 (d, *J* = 17.1 Hz, 2H, CH_2), 2.19 (d, *J* = 16.1 Hz, 2H, CH_2), 2.03 (d, *J* = 16.1 Hz, 2H, CH_2), 1.02 (s, 6H, $2CH_3$), 0.91 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, DMSO-d_6): δ(ppm) 194.5, 152.2, 149.4, 142.8, 135.5, 111.2, 104.9, 59.9, 55.6, 50.3, 32.6, 32.1, 29.1, 26.4. Anal. calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19, found: C, 70.81; H, 7.64; N, 3.06.

9-(4-(Dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5d). Yellow solid, mp: 264 - 266 °C, IR ν_{max}/cm^{-1}: 3277 (NH), 1647 (C=O), 1603 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.67 (s, 1H, NH), 7.18 (d, *J* = 8.4 Hz, 2H, H-Ar), 6.57 (d, *J* = 8.1 Hz, 2H, H-Ar), 4.99 (s, 1H, CH), 2.81 (s, 6H, $N(CH_3)_2$), 2.28 - 2.09 (m, 8H, $4CH_2$), 1.05 (s, 6H, $2CH_3$), 0.95 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 196.2, 149.0, 148.7, 128.8, 113.8, 113.7, 112.5, 51.1, 40.8, 40.8, 32.7, 32.6, 29.7, 27.4. Anal. calcd for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14, found: C, 76.07; H, 8.24; N, 7.12.

9-(Benzo[*d*][1,3]dioxol-5-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5e). Yellow solid, mp >300 °C, IR ν_{max}/cm^{-1}: 3271 (NH), 1643 (C=O), 1605 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.84 (s, 1H, H-Ar), 6.78 (d, *J* = 7.9 Hz, 1H, H-Ar), 6.73 (s, 1H, NH), 6.63 (d, *J* = 7.9 Hz, 1H, H-Ar), 5.83 (s, 2H, OCH_2O), 4.99 (s, 1H, CH), 2.39 - 2.15 (m, 8H, $4CH_2$), 1.08 (s, 6H, $2CH_3$), 0.99 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 195.8, 148.1, 147.4, 145.7, 141.0, 121.3, 113.9, 109.1, 107.9, 100.8, 50.9, 41.5, 33.5, 32.8, 29.6, 27.4. Anal. calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56, found: C, 73.24; H, 6.92; N, 3.58.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5f). Yellow solid, mp 299 - 300 °C, IR ν_{max}/cm^{-1}: 3277 (NH), 1645 (C=O), 1608 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.31 (d, *J* = 8.4 Hz, 2H, H-Ar), 7.21 (d, *J* = 8.5 Hz, 2H, H-Ar), 7.00 (s, 1H, NH), 5.03 (s, 1H, CH), 2.34 (d, *J* = 16.7 Hz, 2H, CH_2), 2.27 – 2.20 (m, 4H, $2CH_2$), 2.15 (d, *J* = 16.3 Hz, 2H, CH_2), 1.08 (s, 6H, $2CH_3$), 0.96 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 195.7, 148.6, 145.7, 131.2, 130.0, 120.0, 113.3, 50.8, 41.2, 33.6, 32.8, 29.6, 27.3. Anal. calcd for $C_{23}H_{26}BrNO_2$: C, 64.49; H, 6.12; N, 3.27, found: C, 64.12; H, 6.11; N, 3.24.

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5g). Yellow solid, mp: 191 - 193 °C, IR ν_{max}/cm^{-1}: 3281 (NH), 1638 (C=O), 1605 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.59 (s, 1H, NH), 7.33 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.18 (t, *J* = 7.3 Hz, 2H, H-Ar), 7.06 (t, *J* = 7.1 Hz, 1H, H-Ar), 5.09 (s, 1H, CH), 2.32 (d, *J* = 16.9 Hz, 2H, CH_2), 2.24 (d, *J* = 16.8 Hz, 4H, $2CH_2$), 2.15 (d, *J* = 16.3 Hz, 2H, CH_2), 1.07 (s, 6H, $2CH_3$), 0.95 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 196.0, 149.2, 146.7, 128.2, 128.1, 126.1, 113.5, 51.0, 40.9, 33.8, 32.7, 29.7, 27.2. Anal. calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01, found: C, 78.85; H, 7.73; N, 3.84.

3,3,6,6-Tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5h). White solid, mp: >300 °C, IR ν_{max}/cm^{-1}: 3277 (NH), 1638 (C=O), 1605 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 9.43 (s, 1H, NH), 7.13 (d, *J* = 4.9 Hz, 1H, H-Ar), 6.79 (t, *J* = 4.10 Hz 1H, H-Ar), 6.65 (d, *J* = 2.6 Hz, 1H, H-Ar), 5.14 (s, 1H, CH), 2.44 (d, *J* = 17.2 Hz, 2H, CH_2), 2.32 (d, *J* = 17.2 Hz, 2H, CH_2), 2.21 (d, *J* = 16.1 Hz, 2H, CH_2), 2.07 (d, *J* = 16.1 Hz, 2H, CH_2), 1.02 (s, 6H, $2CH_3$), 0.94 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, DMSO-d_6): δ(ppm) 194.3, 151.0, 149.6, 126.2, 123.0, 122.8, 110.9, 50.2, 39.5, 32.1, 29.2, 27.3, 26.5. Anal. calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02, found: C, 70.72; H, 7.10; N, 4.22; S, 9.11.

3,3,6,6-Tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5i). Light green solid, mp: 150 - 152 °C, IR ν_{max}/cm^{-1}: cm^{-1}: 3220 (NH), 1691 (C=O), 1587 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 8.86 (s, 1H, NH), 2.82 (s, 2H, CH_2), 2.24 (s, 4H, $2CH_2$), 2.13 (s, 4H, $2CH_2$), 0.99 (s, 12H, $4CH_3$).). ^{13}C-NMR (100 MHz, DMSO-d_6): δ(ppm) 194.9, 150.2, 107.2, 50.0, 39.6, 32.0, 27.9, 18.4. Anal. calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12, found: C, 74.60; H, 8.34; N, 5.39.

3,3,6,6-Tetramethyl-9-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5j). Red solid, mp >300 °C, IR ν_{max}/cm^{-1}: 3281 (NH), 1624 (C=O), 1605 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 8.39 (d, *J* = 4.1 Hz, 1H, H-Ar), 7.59 (d, *J* = 7.6 Hz, 1H, H-Ar), 7.53 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.01 - 6.95 (m, 1H, H-Ar), 6.91 (s, 1H, NH), 5.21 (s, 1H, CH), 2.38 - 2.11 (m, 8H, $2CH_2$), 1.07 (s, 6H, $2CH_3$), 0.98 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 195.8, 163.8, 149.0, 148.7, 135.9, 124.5, 121.3, 112.5, 50.9, 41.3, 36.7, 32.9, 29.6, 27.2. Anal. calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99, found: C, 75.17; H, 7.44; N, 8.09.

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9-(3-Hydroxypropyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5k). Yellow solid, mp: 282 - 285 °C, IR ν_{max}/cm^{-1}: 3261 (NH), 1616 (C=O), 1599 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 9.03 (s, 1H, NH), 4.25 (m, 1H, CH), 3.80 (s, 1H, OH), 3.22 (m, 2H, OCH_2), 2.36 (d, *J* = 17.1 Hz, 2H, CH_2), 2.23 (d, *J* = 17.2 Hz, 2H, CH_2), 2.17 (d, *J* = 16.0 Hz, 2H, CH_2), 2.07 (d, *J* = 16.0 Hz, 2H, CH_2), 1.21 (s, 4H, $2CH_2$), 1.01 (s, 12H, $4CH_3$). ^{13}C-NMR (100 MHz, DMSO-d_6): δ(ppm) 194.7, 150.4, 111.5, 61.3, 50.4, 31.9, 31.3 29.3, 28.7, 26.5, 26.0. Anal. calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4,23, found: C, 72.60; H, 8.84; N, 4.14.

9-(4-Hydroxybutyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5l). Yellow solid, mp: 246 - 248 °C, IR ν_{max}/cm^{-1}: 3283 (NH), 1618 (C=O), 1608 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 9.01 (s, 1H, NH), 4.22 (t, *J* = 4.5 Hz, 1H, CH), 3.79 (s, 1H, OH), 3.29 - 3.22 (m, 2H, OCH_2), 2.35 (d, *J* = 17.0 Hz, 2H), 2.23 (d, *J* = 17.2 Hz, 2H), 2.17 (d, *J* = 16.0 Hz, 2H), 2,07 (d, *J* = 16.0 Hz, 2H), 1.29 – 1.20 (m, 4H, $2CH_2$), 1.08 – 1.01 (m, 14H, $4CH_3$, CH_2). ^{13}C-NMR (100 MHz, DMSO-d_6): δ(ppm) 194.7, 150.3, 111.6, 60.8, 50.4, 34.9, 33.0, 32.0, 29.3, 26.4, 26.2, 21.2. Anal. calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05, found: C, 73.31; H, 9.10; N, 3.97.

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The main text of the article should appear here with headings as appropriate.

Conclusions

In conclusion, we have synthesized, determined the eutectic composition and study different physical properties of the low melting mixture sodium acetate trihydrate-urea as function of temperature. This deep eutectic solvent was used as reaction media for the Biginelli reaction of dimedone, aromatic aldehydes and urea obtaining unexpectedly bis-hydroxy derivatives and hexahydroxanthene-1,8-diones when the reaction was performed at 60 °C and hexahydroacridine-1,8-diones when the reaction was conducted at 100 °C. These results show that the nature of the obtained products can be tuned by increasing the temperature of the reaction. All compounds were obtained in moderate to good yields. The study of the crude reaction mixture by ^{1}H-NMR allows concluding that under the conditions here employed the bis-hydroxy derivatives and hexahydroxanthene-1,8-diones are formed during the reaction and the hexahydroacridine-1,8-diones might be obtained from the reaction of these intermediates with ammonia which is generated from the in situ decomposition of urea. To the best of our knowledge, there are few reports about the obtention of hexahydroacridine-1,8-diones under Biginelli contitions and the method here developed provided an opportunity to use a benign, inexpensive and convenient solvent for its synthesis.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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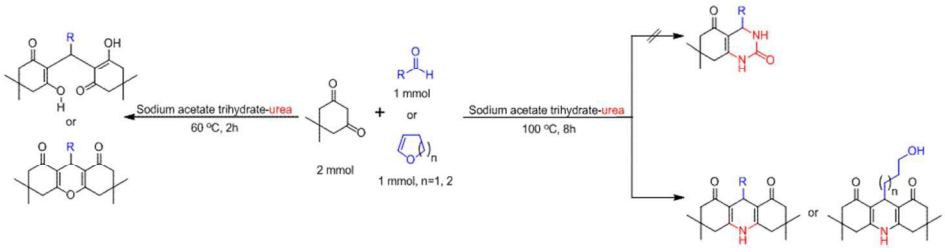

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