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Synthesis and Characterization of Piperidin-4-one Derivatives Using Green Solvent

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A deep eutectic solvent of glucose-urea was found to be an inexpensive and effective reaction medium in the synthesis of piperidin-4-one derivatives. In this work, 3-methyl-2,6-diphenyl piperidin-4-one (**4a**), 3,5-dimethyl-2,6-diphenylpiperidin-4-one (**4b**), 2,6-diphenylpiperidin-4-one (**4c**), piperidin-4-one (**4d**), 3,5-dimethylpiperidin-4-one (**4e**), 3-methyl-2,6-di(2-hydroxyphenyl)piperidin-4-one (**4f**), 3,5-dimethyl 2,6-di(2-hydroxyphenyl)piperidin-4one (**4g**) were synthesized using a deep eutectic solvent (DES) of glucose and urea with the percentage composition of 60:40. The yields of these products were 82, 78, 75, 68, 72, 70 and 70 %, respectively. The products obtained were characterized by FT-IR and ^{1}H NMR spectroscopic techniques. A synthesis of piperidin-4-one derivatives by using this green solvent was considered to be new environmentally safe synthetic method.

Keywords: Deep eutectic solvent, Piperidin-4-one derivatives, Glucose-urea.

INTRODUCTION

In recent years, deep eutectic solvents (DES) are emerging type of environment friendly green solvents. Deep eutectic solvents have been made to eliminate the consumption of volatile organic solvents as reaction media which contribute to major source of environmental pollution. Even though the problems associated with conventional volatile organic solvents are well studied, the usage of green and biorenewable solvents still remains an endless challenge [1]. In this sense, advantages of using DES as reaction medium is highlighted from the fact that they are biodegradable, non-toxic recyclable and could be easily prepared using inexpensive raw materials [2-6]. Deep eutectic solvents (DES) have been studied in a variety of applications including metal dispositions, metalloid dissolution, purification of biodiesel, biotransformation, different synthetic processes and metal catalyses organic reactions [7-15]. In recent years, low melting mixtures and inorganic salts have been introduced as new alternative sustainable solvents for organic transformation [16-22]. Our focus is on glucose-urea based DES, where urea acts as a hydrogen bond acceptor (HBA) and is combined with hydrogen bond donor (HBD) like glucose [23-25] in order to form a low melting point eutectic mixture of glucose-urea. In this work, glucose-urea DES used as a reaction medium for the synthesis of some piperidin-4-one derivatives. Among the wide variety of heterocyclic compounds that have been explored for developing pharmaceutically important molecules piperidin-4-ones exhibit various biological activities like analgesic, antihypertensive, central nervous system depressant, antiviral, bactericidal and fungicidal activities [26-30]. Numerous pharmacological activities of substituted piperidin-4-ones trigger to synthesis these products by using DES. In traditional method, high toxic organic solvents are used for the synthesis of piperidin-4-one derivatives [31,32] herein, a new solvent (glucose + urea DES) is identified to synthesize these compounds without producing harmful byproducts and environmental friendly benign method.

EXPERIMENTAL

The melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on AT-FT-IR spectrometer. ^{1}H NMR spectra were recorded at BRUKER (500 MHz, 400 MHz) spectrometer using $CDCl_3$ & DMSO as solvent and TMS as standard.

Preparation of glucose-urea DES: The mixture of glucose and urea (60:40) was heated up to 73 ºC until a homogenous

transparent colourless liquid was formed. Thus glucose-urea DES was prepared.

General procedure for synthesis of piperidin-4-one derivatives: A deep eutectic solvent of glucose-urea was found to be an inexpensive and effective reaction medium in the synthesis of piperidin-4-one derivatives. In this work piperidin-4-one derivatives (**4a-g**) were synthesized using a deep eutectic solvent (DES) of glucose and urea with the percentage composition of 60:40. In this synthesis various ketones (**1**) (acetone, ethyl methyl ketone and diethyl ketone) (6 mL:0.1 mol), aldehydes (**2**) (0.1 mol) (benzaldehyde, formaldehyde, salicylaldehyde) (12 mL, 0.2 mol) and ammonia solution (**3**) (20 mL) taken in round bottom flask containing glucose and urea DES. The mixture is refluxed at 60-70 °C in a water bath with occasional shaking until the colour changes into red orange. The product formed was monitored by TLC. The solution is cooled and then conc. HCl (10 mL) is added. A precipitate obtained was dispersed in water and excess ammonia was added until a clear solution formed. Then the clear solution was poured into ice cold water and then precipitate was filtered. The product formed was washed several times with water and dried. Then the product **4** was recrystallized with alcohol (**Scheme-I**). Synthesized compounds (**4a-g**) were characterized by FT-IR and ^{1}H NMR spectroscopic techniques.

3-Methyl-2,6-diphenylpiperidin-4-one (4a): Yield: 82 %; m.p.: 112 ºC; m.f.: $C_{18}H_{19}NO$; FT-IR (cm^{-1}): 3316 ν(N-H), 3033-2801 ν(C-H), 1708 ν(C=O), 1452-1218 ν(C=C), 756 ν(Ar-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.243-7.465 (m, 10H, Ar-H), 4.069-4.098 (dd, 2H, H-2,6 position), 3.607-3.628 (q, 1-H, H-3 position), 2.630-2753 (d, 2H, H-5 position), 2.113 (s, 1H, N-H), 0.840 (s, 3H, CH_3).

3,5-Dimethyl 2,6-diphenylpiperidin-4-one (4b): Yield: 78 %; m.p.: 140 ºC; m.f.: $C_{19}H_{21}NO$; FT-IR (ν_{max}, cm^{-1}): 3209 ν(N-H), 3061-2981 ν(C-H in phenyl ring), 2638 ν(C-H in aliphatic), 1692 ν(C=O), 1495-1451 ν(C=C), 760 ν(Ar-H). ^{1}H NMR (400 MHz, DMSO): δ 6.556-7.961 (m, 10H, Ar-H), 4.121-4.234 (d, 2H, H-2,6 position), 3.375 (s, 1H, NH), 2.018-2.178 (dq, 2H, H-3,5 position), 0.656-0.711 (dd, 6H, CH_3).

2,6-Diphenylpiperidin-4-one (4c): Yield: 75 %; m.p.: 96 ºC; m.f.: $C_{17}H_{17}NO$; FT-IR (ν_{max}, cm^{-1}): 3053 ν(N-H), 3023-2854 ν(C-H), 1701 ν(C=O), 1495-1447 ν(C=C), 755 ν(Ar- H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.686- 8.194 (m, 10H, Ar-H), 4.362-5.249 (m, 2H, H-2,6 position), 3.830-3.852 (d, 2H, H-3,5 position), 2.871 (s, N-H).

Piperidin-4-one (4d): Yield: 68 %; m.p.: 79 ºC; m.f.: C_5H_9NO; FT-IR (ν_{max}, cm^{-1}): 3351 ν(N-H), 3027 ν(C-H), 1649 ν(C=O), 1247-1130 ν(C-C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.603 (dd, 4H, H-2,6 position), 1.257 (dd, 4H, H-3,5 position), 2.185 (s, 1H, NH).

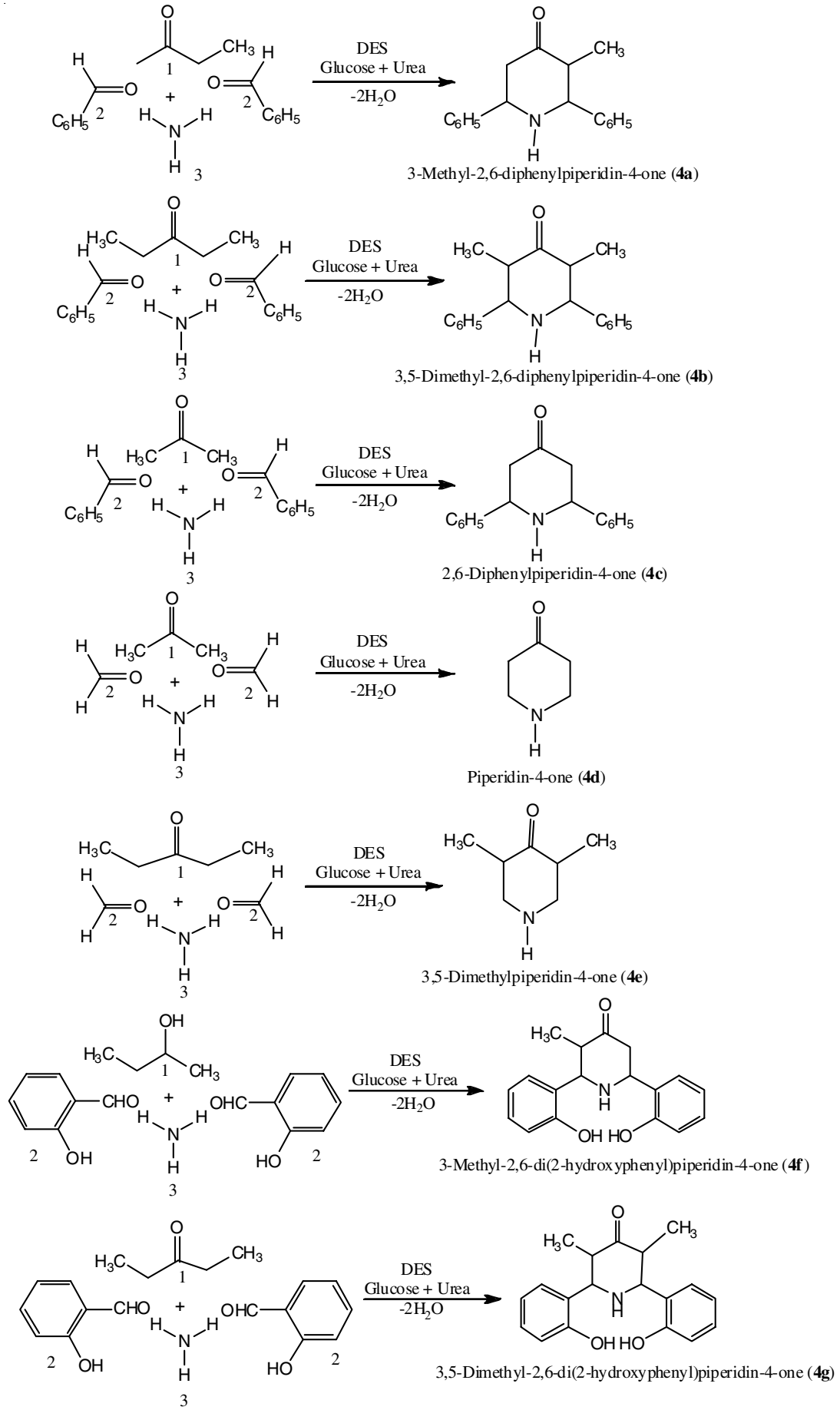
3,5-Dimethyl piperidin-4-one (4e): Yield: 72 %; m.p.: 86 ºC; m.f.: $C_7H_{13}NO$; FT-IR (ν_{max}, cm^{-1}): 3332 ν(N-H), 3136 ν(C-H), 1658 ν(C=O), 1519-1394 ν(C-C). ^{1}H NMR (400 MHz, DMSO): δ 4.440-4.727 (dd, 2H, H-2,6 equatorial proton), 3.222-3.468 (dd, 2H, H-2,6 axial position), 2.245-2.2841 (dq, 2H, H-3,5 position), 3.726 (s, 1H, NH), 1.091-1.971 (d, 6H, CH_3).

3-Methyl-2,6-di(2-hydroxyphenyl)piperidin-4-one (4f): Yield: 70 %; m.p.: 220 ºC; m.f.: $C_{18}H_{19}NO_3$; FT-IR (ν_{max}, cm^{-1}): 3396 ν(O-H), 3208 ν(N-H), 2920 ν(C-H), 1705-1659 ν(C=O), 1456-1403 ν(C=C), 756 ν(Ar-H). ^{1}H NMR (400 MHz, DMSO): δ 6.853-7.440 (m, 8H, Ar-H), 6.853-6.894 (m, 4H, *ortho* proton to OH), 6.951-6.989 (m, 4H, *para* proton to OH), 7.193-7.440 (m, 4H, *meta* proton to OH), 5.460 (s, 1H, phenolic proton), 3.377 (s, 1H, NH), 2.207-2.310 (dd, 2H, H-2,6 position), 1.797-1.972 (q, 1H, H-3 position), 1.50-1.579 (d, 2H, H-5 position), 0.6648-0.6808 (d, 3H, CH_3).

3,5-Dimethyl-2,6-di(2-hydroxyphenyl)piperidin-4-one (4g): Yield: 70 %; m.p.: 242 °C; m.f.: $C_{19}H_{21}NO_3$; FT-IR (ν_{max}, cm^{-1}): 3208 ν(O-H), 3076 ν(N-H), 2974-2936 ν(C-H), 1695-1622 ν(C=O), 1486-1455 ν(C=C), 758 ν(Ar-H). ^{1}H NMR (400 MHz, DMSO): δ 6.803-7.313 (m, 8H, Ar-H), 6.803-6.883 (m, 4H, *ortho* proton to OH), 6.974-6.995 (m, 4H, *para* proton to OH), 7.048-7.313 (m, 4H, *meta* proton to OH), 4.980 (s, 1H, phenolic proton), 3.939-3.957 (dd, 2H, H-2,6 position), 3.364 (s, 1H, NH), 1.880-1.894 (dq, 1H, H-3,5 position), 0.666-1.064 (d, 6H, CH_3).

RESULTS AND DISCUSSION

In this work, piperidin-4-one derivatives (**4a-g**) were synthesized by glucose-urea DES as a green solvent. The synthesized 3-methyl-2,6-diphenylpiperidin-4one (**4a**) showed strong absorption at 3316 cm^{-1} for N-H, 1708 cm^{-1} for carbonyl group and 756 cm^{-1} for aromatic group in FT-IR spectrum. ^{1}H NMR in $CDCl_3$ spectrum in showed the multiplet at δ 7.243-7.465 for aromatic proton, singlet in δ 2.113 for N-proton and singlet in δ 0.840 for methyl proton. These spectral data very much agree with the structure of compound **4a**. The FT-IR spectrum of 3,5-dimethyl-2,6-diphenylpiperidin-4-one (**4b**) showed strong absorption at 3209 cm^{-1} for N-H, 1692cm^{-1} for carbonyl group and 760 cm^{-1} for aromatic group. ^{1}H NMR in DMSO spectrum showed the multiplet at δ 6.556-7.961 for aromatic proton, singlet in δ 3.375 for N-proton and doublet in δ 0.656-0.711 for methyl proton in 3,5-position. These spectral data supported the structure of compound **4b**. 2,6-Diphenylpiperidin-4-one (**4c**) showed strong absorption at 3053 cm^{-1} for N-H, 1701 cm^{-1} for carbonyl group and 755 cm^{-1} for aromatic group in FT-IR spectrum. ^{1}H NMR in $CDCl_3$ spectrum showed the multiplet at δ 6.686- 8.194 for aromatic proton, singlet in δ 2.871 for N-proton revealed the structure of compound **4c**. The FT-IR spectrum of piperidin-4-one (**4d**) showed absorption at 3351 cm^{-1} for N-H, 1649 cm^{-1} for carbonyl group. ^{1}H NMR in $CDCl_3$ spectrum showed the absence of multiplet for aromatic substituent 2,6-position, singlet in δ 2.185 for N-proton confirmed the structure of compound **4d**. The structure of 3,5-dimethylpiperidin-4-one (**4e**) confirmed by the FT-IR absorption at 3332 cm^{-1} for N-H, 1658 cm^{-1} for carbonyl group and ^{1}H NMR spectrum in DMSO showed the absence multiplet for aromatic substituent, singlet in δ 3.726 for N-proton and double quintet at δ 2.245-2.2841 for methyl proton 3,5-position. In 3-methyl 2,6-di(2-hydroxyphenyl)piperidin-4-one (**4f**) FT-IR spectrum absorptions were observed at 3396 cm^{-1} for O-H, 3208 cm^{-1} for N-H, 1659-1705 cm^{-1} for carbonyl group & 756 cm^{-1} for aromatic group and ^{1}H NMR spectrum in DMSO showed multiplet at δ 6.853-7.440 for aromatic proton, δ 5.460 for phenolic proton δ 3.377 for N-proton and double quintet at ä 2.245-2.2841 for methyl proton in 3-position. The structure



Scheme-I: Synthetic route of piperidin-4-one derivatives (**4a-g**) using glucose-urea as green solvent

of 3,5-dimethyl 2,6-di(2-hydroxyphenyl)piperidin-4-one (**4g**) confirmed by the FT-IR absorption at 3208 cm^{-1} for O-H, 3076 cm^{-1} for N-H, 1622-1695 cm^{-1} for carbonyl group & 758 cm^{-1} for aromatic group and ^1H NMR spectrum in DMSO showed multiplet at δ 6.803-7.313 for aromatic proton, δ 4.980 for phenolic proton, δ 3.364 for N-proton and double quintet at δ 1.880-1.894 for methyl proton in 3,5-position. The above results confirmed the structure of synthesized piperidin-4-one derivatives (**4a-g**).

Conclusion

In this study, newer green solvent of glucose-urea DES was used for the synthesis of piperidin-4-one derivatives. The products were synthesized in good yields and excellent purities. When compared to the conventional synthetic method, deep eutectic solvent synthesis is environmental friendly and volatile chemical usage is minimized with good yields. Pharmaceutically important piperidin-4-one derivatives were synthesized by using glucose-urea DES method is benign for green synthetic method against the volatile organic solvents.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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