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AN ECO-FRIENDLY PREPARATION OF 2,6-DIARYLPIPERIDIN-4-ONES USING A GLUCOSE-CHOLINE CHLORIDE DEEP EUTECTIC SOLVENT

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ABSTRACT

Deep Eutectic Solvent (DES) made with Glucose & Choline Chloride is an environmentally safe and sustainable technique for 2,6-diaryl piperidine-4-ones preparation. Starting with benzaldehyde, 2 or 4-hydroxybenzaldehyde, the preparation was carried out in ammonia using different ketones such as 2-pentanone, 3-pentanone, 2-propanone, 2-butanone. Under an atom-efficient method, all of the derivatives (a–f) were synthesized in good to outstanding yields. FT-IR, ^{1}HNMR, ^{13}CNMR, and GC-MS spectral methods were used to characterize the synthesized compounds. Choline chloride-glucose DES as a solvent has benefits over volatile organic solvents commonly utilized in similar processes.

Keywords: Glucose-Choline Chloride DES, 2,6-diaryl piperidine-4-ones, GC-MS, FT-IR, ^{13}C NMR.

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INTRODUCTION

Deep Eutectic Solvents (DESs) were liquids with physicochemical qualities comparable to ionic liquids (ILs), without some of their drawbacks. Because of their low volatility, DESs are more environmentally benign than typical organic solvents, implying that they could be effective alternatives.[1-13] According to recent research, eutectic combinations of quaternary ammonium salts with hydrogen donors exhibit unusual solvent properties.[14-16] Due to their biological activity in nature, heterocyclic molecules having a piperidone backbone are fascinating targets for chemical synthesis.[17-19] The piperidone pharmacophore is found in numerous alkaloids, pharmaceuticals, agrochemicals, and synthetic intermediates.[20-24] We may note such significant properties as antibacterial,[25] antifungal,[26] antiviral,[27] anti-tumor,[28] analgesic,[29] anti-inflammatory, anesthetic,[30] and depressant activities.[31] In the present work, a DES formed from glucose and choline chloride was chosen for the preparation of title compounds, starting from the appropriate ketone, benzaldehyde derivatives, and ammonia.[32-34] All of the 2,6-diarylpiperidin-4-one compounds (a-f) were synthesized in very good to excellent yields (range 85-90%, median 87%) using an atom economy pathway having green features associated with DESs.

EXPERIMENTAL

Material and Methods

Analytical grade chemicals were used in the synthesis. In open capillaries, melting points were determined. The AT-FT-IR spectrometer was used to record IR spectra. At a Bruker model, ^{1}HNMR spectra at 400MHz and ^{13}CNMR spectra at 100MHz were collected with DMSO-d_6 as a solvent. The internal reference used in all NMR spectra was tetramethylsilane (TMS). The Clarus680 GCMS spectrometer from Perkin Elmer was used to collect GCMS data for the samples. The Perkin Elmer2400 series CHN Analyzer was used to do the elemental analysis.

DES Preparation

Glucose (melting point: 146ºC) and Choline chloride (melting point: 302ºC) were mixed at a 1:2 weight ratio to make a Glucose-Choline chloride eutectic combination. This combination was heated to 80ºC for 1

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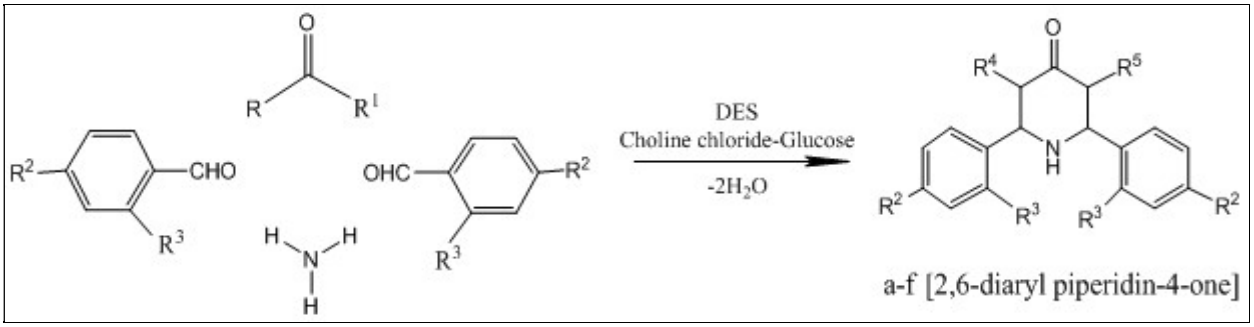
hour until it produced a homogeneous translucent colorless liquid. After 24 hours at room temperature, it remained a homogeneous liquid.



Scheme-1: Synthetic Pathway for the Preparation of Compounds

Compound a- R(CH_3), R^1(CH_3), R^2(H), R^3(H), R^4(H), R^5(H)
Compound b- R(CH_3), R^1(CH_3CH_2), R^2(H), R^3(H), R^4(H), R^5(CH_3)
Compound c- R(CH_3CH_2), R^1(CH_3CH_2), R^2(H), R^3(H), R^4(CH_3), R^5(CH_3)
Compound d- R(CH_3), R^1($CH_3CH_2CH_2$), R^2(H), R^3(H), R^4(H), R^5(CH_3CH_2)
Compound e- R(CH_3CH_2), R^1(CH_3CH_2), R^2(H), R^3(OH), R^4(CH_3), R^5(CH_3)
Compound f- R(CH_3), R^1($CH_3CH_2CH_2$), R^2(OH), R^3(H), R^4(H), R^5(CH_3CH_2)

Preparation of 2, 6–Diarylpiperidin-4-ones

According to the Scheme-1, In a round-bottom flask benzaldehyde/2-hydroxybenzaldehyde/4-hydroxy benzaldehyde (20 mL) and an appropriate ketone (10 mL), (2– Propanone, 2–Butanone, 2–Pentanone & 3–Pentanone) were taken with a saturated ammonia solution (10 mL)[32-34] and Glucose- Choline Chloride DES (20 mL). The contents of the flask were refluxed at 100°C-120°C, over a hot plate with stirring. Once the reaction mixture had turned red-orange, the heating was turned off, and the solution was cooled before adding conc. HCl (10 mL). Precipitation was then recovered and diffused in water. To make a transparent solution, saturated aqueous ammonia (10 mL) has been added and then transferred into cold water. A product was filtered and then rinsed lavishly with water. After drying, the final product was recrystallized from alcohol.

Spectral Data

2,6-Diphenylpiperidin-4-one(a)

Melting point: 96ºC; yield: 85%; FT-IR (cm^{-1}): 828 (υ_{Ar-H}), 1283 (υ_{C-C}), 1410-1590 ($\upsilon_{C=C}$), 1710 ($\upsilon_{C=O}$), 2803-2907 (υ_{C-H} stretching), 3044 (υ_{N-H}); ^{1}H NMR (400MHz, DMSO-d_6): δ 2.345-2.688 (d, 1H, H–3,5), 3.580 (s, 1H, N–H), 4.918-4.942 (d, 1H, H–2,6), 6.795-7.964 (m, 8H, Ar–H); ^{13}C NMR (100MHz, DMSO-d_6): δ 39.33-40.58 (C–3,5), 59.82 (C–2,6), 126.14-143.28 (C–Ar), 204.34 (C=O); GCMS (EI) m/z (%): 250.9709 (100) [M^+]; *Anal.* Calcd. for $C_{17}H_{17}NO$: C (81.24), H (6.82), N (5.57) and found: C (80.99), H (7.12), N (5.62).

3-Methyl-2,6–diphenylpiperidin-4-one(b)

Melting point: 112ºC; yield: 90%; FT-IR (cm^{-1}): 750 (υ_{Ar-H}), 1098-1241(υ_{C-H} in CH_3), 1405-1505 ($\upsilon_{C=C}$), 1717 ($\upsilon_{C=O}$), 2366-2697 ($\upsilon_{C-H,}$ cyclic), 2810-2907 (υ_{C-H} stretching), 3044 (υ_{N-H}); ^{1}HNMR (400MHz, DMSO-d_6): δ 1.127-1.245 (d, 3H, CH_3), 2.654-2.691(d, 1H, H–3), 3.371 (s, 1H, N–H), 3.502-3.534 (d, 1H, H–5), 4.960 (s, 1H, H–2,6), 7.413-7.966 (m, 8H, Ar–H); ^{13}CNMR (100MHz, DMSO-d_6): δ 15.86 (CH_3), 39.36-40.61(C–3), 44.98 (C–5), 59.78 (C–6), 65.10 (C–2), 128.92-136.20 (C–Ar), 202.79 (C=O); GCMS (EI) m/z (%): 263.9046 (70) [M^+]; *Anal.* Calcd. for $C_{18}H_{19}NO$: C (81.47), H (7.22), N (5.28) and found: C (81.54), H (7.42), N (5.20).

3,5-Dimethyl-2,6–diphenylpiperidin-4-one(c)

Melting point: 184ºC; yield: 82%; FT-IR (cm^{-1}): 750 (υ_{Ar-H}), 1222-1396 (υ_{C-H} in CH_3), 1446-1492 ($\upsilon_{C=C}$), 1697 ($\upsilon_{C=O}$), 2800-3020 (υ_{C-H} stretching), 3209 (υ_{N-H}); ^{1}HNMR (400MHz, DMSO-d_6): δ 0.988-1.443 (q, 3H, CH_3), 3.467 (s, 1H, N–H), 3.746-3.757 (d, 1H, H–3,5), 4.003-4.038 (dd, 1H, H–2,6), 6.811-7.754 (m, 8H, Ar-–H); ^{13}CNMR (100MHz, DMSO-d_6): δ 11.12 (CH_3), 39.33-40.58 (C–3,5), 79.12-79.79 (C–2,6), 115.65-

132.40 (C–Ar), 204.77(C=O); *Anal.* Calcd. for $C_{19}H_{21}NO$: C (81.68), H (7.58), N (5.01) and found: C (81.62), H (7.64), N (4.78).

3-Ethyl-2,6-diphenylpiperidin-4-one(d)
Melting point: 242ºC; yield: 85%; FT-IR (cm^{-1}): 756 (υ_{Ar-H}), 1096-1203 (υ_{C-H} in CH_3), 1296-1448($\upsilon_{C=C}$), 1701 ($\upsilon_{C=O}$), 2886-3024 (υ_{C-H} stretching), 3244 (υ_{N-H}); ^{1}HNMR (400MHz, DMSO-d_6): δ 0.688-0.704 (t, 3H, CH_3), 1.986 (q, 2H, CH_2), 2.434-2.466 (d, 2H, H–5), 2.677-2.775 (m, 1H, H–3), 3.376 (s, 1H, N–H), 3.583-3.611(d, 1H, H–2), 4.032-4.058 (d, 1H, H–6), 7.243-7.501(m, 8H, Ar–H); ^{13}CNMR (100MHz, DMSO-d_6): δ 10.80 (CH_3), 17.96 (CH_2), 39.37-40.62 (C–3), 51.05(C–5), 61.13 (C–6), 68.14 (C–2), 127.07-143.76(C–Ar), 209.40 (C=O); GCMS (EI) m/z (%): 278.8560 (100) [M^+]; *Anal.* Calcd. for $C_{19}H_{21}NO$: C (81.68), H (7.58), N (5.01) and found: C (81.40), H (7.54), N (5.02).

2,6-Bis(2-hydroxyphenyl) 3,5-dimethylpiperidin-4-one (e)
Melting point: 342ºC; yield: 90%; FT-IR (cm^{-1}): 750 (υ_{Ar-H}), 1028-1237 (υ_{C-H} in CH_3), 1403-1504 ($\upsilon_{C=C}$), 2702-2914 (υ_{C-H} stretching), 3047 (υ_{N-H}), 3388(υ_{O-H}), 1722($\upsilon_{C=O}$); ^{1}HNMR (400MHz, DMSO-d_6): δ 0.598-0.723 (dd, 3H, CH_3), 0.935-1.509 (m, 1H, H–3,5), 3.007- 3.354 (m, 2H, H–2.6), 3.833 (s, 1H, N–H), 6.695 (s, 1H, O–H), 6.737-8.861 (m, 8H, Ar–H); ^{13}CNMR (100MHz, DMSO-d_6): δ 11.22 (CH_3), 39.35-40.60 (C–3,5), 49.22-53.62 (C–2,6), 116.29-136.88 (C–Ar), 156.01(ortho C–OH), 210.86 (C=O); *Anal.* Calcd. for $C_{19}H_{21}NO_3$: C (73.29), H (6.80), N (4.50) and found: C (73.44), H (6.72), N (4.56).

3-Ethyl-2,6-bis(4-hydroxyphenyl) piperidin-4-one (f)
Melting point: 320ºC; yield: 90%; FT-IR (cm^{-1}): 754 (υ_{Ar-H}), 1031-1242 (υ_{C-H} in CH_3), 1404-1513 ($\upsilon_{C=C}$), 1716 ($\upsilon_{C=O}$), 2695-2915 (υ_{C-H} stretching), 3046 (υ_{N-H}), 3396 (υ_{O-H}); ^{1}HNMR (400MHz, DMSO-d_6): δ 0.593-0.697 (t, 3H, CH_3), 1.373-1.443 (q, 2H, CH_2), 2.413-2.450 (d, 2H, H–5), 2.606-2.778 (m, 1H, H–3), 3.446 (s, 1H, N–H), 3.682-3.708 (d, 1H, H–2), 4.003-4.038 (dd, 1H, H–6), 4.275 (s, 1H, O–H), 7.238-7.957 (m, 8H, Ar–H); ^{13}CNMR (100MHz, DMSO-d_6): δ 12.40 (CH_3), 18.13 (CH_2), 39.35-40.60 (C–3), 51.24 (C–5), 62.88 (C–6), 66.45 (C–2), 127.05-144.00 (C–Ar), 168.00 (para C–OH), 209.21(C=O); GCMS (EI) m/z (%): 311.0444 (100) [M^+]; *Anal.* Calcd. for $C_{19}H_{21}NO_3$: C (73.29), H (6.80), N (4.50) and found: C (73.54), H (7.06), N (4.36).

RESULTS AND DISCUSSION

The characterization data supported the proposed structures. All of the compounds that gave satisfactory elemental analysis, GCMS, FT-IR, ^{1}HNMR, and ^{13}CNMR data were consistent with the piperidine-4-one system. The eco-friendliness was suggested by the Sheldon E-factor calculation for the formation of 3-methyl-2,6-diphenylpiperidin-4-one (compound b) using the data from a representative synthetic run.

$$\text{E-factor} = \frac{\text{Kg(waste)}}{\text{Kg (product)}} = \frac{\text{Amount of waste in Kg}}{\text{Amount of the final product in Kg}} = \frac{1.582*10^{-3}\text{Kg}}{1.985*10^{-3}\text{Kg}} = 0.797$$

Total amount of reactants: 2.088g+0.805g+0.674g = 3.567g
Quantity of the final product: 1.985g
Quantity of waste: 3.567g-1.985g =1.582g

It is generally accepted [35] that a Sheldon E-factor in this range is desirable. The calculated environmental factor (E-factor) is less than one. It highlights the smaller amount of waste produced in the synthesis.
A simple and direct work-up approach is possible using this DES solvent system. In the end, the products were easily recovered by precipitation with acid and washing with water. After removal of the product, the DES was present in the filtrate, dissolved in water, and could be recycled by the evaporation of the water.

CONCLUSION

Finally, we have proven the importance of the DES formed from choline chloride and glucose in the preparation of 2,6-diarylpiperidin-4-ones fully described here. The DES obviates the need for volatile organic solvents and supplies very good yields of the desired products. We hope that our method will find further applications in the synthesis of heterocyclic compounds.

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