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

K. Hemalatha¹ and D. Ilangeswaran²,*,

¹Department of Chemistry, Justice Basheer Ahmed Sayeed College for Women (Autonomous), Teynampet-600018 (Chennai), India
²Department of Chemistry, Rajah Serfoji Government College (Autonomous), Thanjavur-613005, (Affiliated to Bharathidasan University, India)

*Corresponding Author: dhailangeswaran@gmail.com

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, ¹HNMR, ¹³CNMR, 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-diarylpiperidine-4-ones, GC-MS, FT-IR, ¹³C NMR.

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, ¹HNMR spectra at 400MHz and ¹³CNMR spectra at 100MHz were collected with DMSO-d₆ 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: 146°C) and Choline chloride (melting point: 302°C) were mixed at a 1:2 weight ratio to make a Glucose-Choline chloride eutectic combination. This combination was heated to 80°C for 1 hour. The mixture was then cooled to room temperature and used as a solvent for the synthesis.
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 | R(CH₂)₃ | R¹(CH₂)₂ | R²(H) | R³(H) | R⁴(H) | R⁵(H) |
|----------|---------|----------|-------|-------|-------|-------|
| a        | R(CH₃)  | R¹(CH₃)  | R²(H) | R³(H) | R⁴(H) | R⁵(CH₃) |
| b        | R(CH₃)  | R¹(CH₃CH₂) | R²(H) | R³(H) | R⁴(H) | R⁵(CH₃) |
| c        | R(CH₂CH₃) | R¹(CH₂CH₃) | R²(H) | R³(H) | R⁴(H) | R⁵(CH₃) |
| d        | R(CH₃)  | R¹(CH₃CH₂) | R²(H) | R³(H) | R⁴(H) | R⁵(CH₃) |
| e        | R(CH₂CH₃) | R¹(CH₂CH₃) | R²(H) | R³(H) | R⁴(H) | R⁵(CH₃) |
| f        | R(CH₃)  | R¹(CH₃CH₂) | R²(OH) | R³(H) | R⁴(H) | R⁵(CH₃) |

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: 96°C; yield: 85%; FT-IR (cm⁻¹): 828 (ν Ar-H), 1283 (ν C=O), 1410-1590 (νC–C), 1710 (νC=O), 2803-2907 (νC-H stretching), 3044 (ν N-H); H NMR (400MHz, DMSO-d₆): 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); ¹³C NMR (100MHz, DMSO-d₆): δ 39.33-40.58 (C–3,5), 79.12-79.79 (C–2,6), 126.14-143.28 (C–Ar), 204.34 (C=O); GCMS (EI) m/z (%): 250.9709 (100) [M⁺]; Anal. Calcd. for C₁₇H₁₇NO: 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: 112°C; yield: 90%; FT-IR (cm⁻¹): 750 (ν Ar-H), 1098-1241 (νC=O in CH₃), 1405-1505 (νC–C), 1717 (νC=O), 2366-2697 (νC-H cyclic), 2810-2907 (νC-H stretching), 3044 (ν N-H); ¹H NMR (400MHz, DMSO-d₆): δ 1.127-1.245 (d, 3H, CH₃), 2.654-2.691(d, 1H, H–3), 3.376 (s, 1H, N–H), 3.502-3.534 (dd, 1H, H–2,6), 4.960 (s, 1H, H–2,6), 7.413-7.966 (m, 8H, Ar–H); ¹³C NMR (100MHz, DMSO-d₆): δ 15.86 (CH₃), 39.26-40.161(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 C₁₉H₁₈NO: C (81.47), H (6.82), N (5.57) and found: C (81.54), H (7.72), N (5.57).

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

Melting point: 184°C; yield: 82%; FT-IR (cm⁻¹): 750 (ν Ar-H), 1222-1396 (νC=O in CH₃), 1446-1492 (νC–C), 1697 (νC=O), 2800-3020 (νC-H stretching), 3209 (νN=O); ¹H NMR (400MHz, DMSO-d₆): δ 0.988-1.443 (q, 3H, CH₃), 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); ¹³C NMR (100MHz, DMSO-d₆): δ 11.12 (CH₃), 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_{10}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: 242°C; yield: 85%; FT-IR (cm⁻¹): 756 (v_{Ar-H}), 1096-1203 (v_{C-H} in CH₃), 1296-1448 (v_{C-C}), 1701 (v_{C=O}), 2886-3024 (v_{C-H stretching}), 3244 (v_{N-H}); ¹H NMR (400MHz, DMSO-d₆): δ 0.688-0.704 (t, 3H, CH₃), 1.986 (q, 2H, CH₂), 2.434-2.466 (d, 2H, H−5), 2.677-2.775 (m, 1H, H−3), 3.376 (s, 1H, N−H), 3.853-3.611(d, 1H, H−2), 4.032-4.058 (d, 1H, H−6), 4.275 (s, 1H, O−H), 7.238-7.957 (m, 8H, Ar−H); ¹³CNMR (100MHz, DMSO-d₆): δ 10.80 (CH₃), 17.96 (CH₃), 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_{10}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: 342°C; yield: 90%; FT-IR (cm⁻¹): 750 (v_{Ar-H}), 1028-1237 (v_{C-H} in CH₃), 1403-1504 (v_{C-C}), 2702-2914 (v_{C=C stretching}), 3047 (v_{N-H}), 3388 (v_{O-H}), 1722 (v_{C=O}); ¹H NMR (400MHz, DMSO-d₆): δ 0.598-0.723 (dd, 3H, CH₃), 0.935-1.509 (m, 8H, Ar−H), 2.606-2.778 (m, 2H, H−2), 2.738-3.957 (m, 8H, Ar−H); ¹³CNMR (100MHz, DMSO-d₆): δ 11.22 (CH₃), 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_{23}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: 320°C; yield: 90%; FT-IR (cm⁻¹): 754 (v_{Ar-H}), 1031-1242 (v_{C-H} in CH₃), 1404-1513 (v_{C-C}), 1716 (v_{C=O}), 2695-2915 (v_{C=C stretching}), 3046 (v_{N-H}), 3396 (v_{O-H}); ¹H NMR (400MHz, DMSO-d₆): δ 0.593-0.697 (t, 3H, CH₃), 1.373-1.443 (q, 2H, CH₂), 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); ¹³CNMR (100MHz, DMSO-d₆): δ 12.40 (CH₃), 18.13 (CH₂), 39.35-40.60 (C−3, 5), 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_{23}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, ¹H NMR, and ¹³CNMR 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.

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

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 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.
ACKNOWLEDGEMENT

The author is grateful to the Vellore Institute of Technology for recording spectra.

REFERENCES

1. J. Earle and R. Seddon, Pure and Applied Chemistry, 72, 1391(2000), http://dx.doi.org/10.1351/pac200072071391
2. A. Abbott, G. Capper, L. Davies, H. Munro, K. Rasheed and V. Tambyrajah, Chemical Communication, 2001(2010-2011), http://dx.doi.org/10.1039/b106357j
3. A. Abbot, G. Capper, L. Davies, and K. Rasheed, American Chemical Society, 126, 9142(2004), https://doi.org/10.1021/ja048266j
4. Manurung, Renita, Liang and Alexander, Rasayan Journal of Chemistry, 11(4), 1519(2018), http://dx.doi.org/10.31788/RJC.2018.1143079
5. Q. Zhang, K. D. O. Vigier, S Royer and F. Jerome, Chemical Society Reviews, 41, 7108(2012), https://doi.org/10.1039/c2cs35178a
6. M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, Science, 297, 807(2002), https://dx.doi.org/10.1126/science.297.5582.807
7. R. D. Rogers, K. R. Seddon, Science, 302, 792(2003), https://doi.org/10.1126/science.1090313
8. Jairton Dupont, Roberto F. de Souza and Paulo A. Z. Suarez, ACS Chemical Reviews, 102, 3367(2002), https://doi.org/10.1021/cr010338r
9. P. Wasserscheid, W. Keim and Angew, Angewandte Chemie - International Edition, 39, 3772(2000), https://doi.org/10.1002/1521-3772(20001103)39:21%3C3772::aid-anie3772%3E3.0.co;2-5
10. K. Ghandi, Green and Sustainable Chemistry, 4, 44(2014), http://dx.doi.org/10.1021/jct.8b01622
11. M. Francisco, A. van den Bruinhorst and M.C. Kroon, Angewandte Chemie International Edition, 52, 3074 (2013), https://doi.org/10.1002/anie.201207548
12. Yingga Cui, Changleping Li, Jingmei Yin, Shenmin Li, Yingping Jia and Ming Bao, Journal of Molecular Liquids, 236, 338(2017), https://doi.org/10.1016/j.molliq.2017.04.052
13. Q. Abbas and L. Binder, Journal of chemical society Transactions, 33, 49(2010), http://dx.doi.org/10.1149/1.3484761
14. A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, Journal of the American Chemical Society, 126, 9142(2004), https://doi.org/10.1021/ja048266j
15. Moghimi, Marzieh and Roosta, Aliakbar, The Journal of Chemical Thermodynamics, 129(2018), http://dx.doi.org/10.1016/j.jct.2018.09.029
16. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, Chemical Communication, 70 (2003), http://dx.doi.org/10.1021/ja048266j
17. B. Selvakumar and R. Venkataraman, Rasayan Journal of Chemistry, 3, 260(2010)
18. K. Kamesu, G. Mohan and K. Rajasekhar, Rasayan Journal of Chemistry, 13(1), 494(2020), http://dx.doi.org/10.31788/RJC.2020.1315392
19. S. Balasubramanian, G. Aridoss, P. Parthiban, C. Ramalingan and S. Kabilan, Biological and Pharmaceutical Bulletin, 29, 125(2006), http://dx.doi.org/10.1248/bpb.29.12520
20. J J. Chakkaravarthy, G. Muthukumaran and K. Pandiarajan, Journal of Molecular Structure, 889, 297(2008), http://dx.doi.org/10.1016/j.molstruc.2007.12.021
21. A. Paiva, R. Craveiro, I. Aroso, M. Martins, R.L. Reis and A.R.C. Duarte, ACS Sustainable Chemical Engineering, 2, 1063(2014), http://dx.doi.org/10.1021.sc500096j
22. N. Rameshkumar, A. Veena, R. Ilavarasan, M. Adiraj, P. Shanmugapandiyan and S. K. Sridhar, Biological and Pharmaceutical Bulletin, 26, 188(2003), http://dx.doi.org/10.1248/bpb.26.188
23. K. Selvaraju and A. Manimekalai, Rasayan Journal of Chemistry, 10, 25(2011)
24. R. Revathi, R.V. Perumal, K.S.R. Pai, G. Arunkumar, D. Sriram and S. Kini, Drug Design, Development and Therapy, 2015, 3779(2015), http://dx.doi.org/10.2147/DDDT.S83047
25. P. Parthiban, S. Balasubramanian, G. Aridoss, and S. Kabilan, Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy, 70, 24(2008), http://dx.doi.org/10.1016/j.saa.2007.07.059
26. C. Ramalingam, Y. T. Park and S. Kabilan, European Journal of Medicinal Chemistry, 41, 683(2006), http://dx.doi.org/10.1016/j.ejmech.2006.02.005
27. Gopalakrishnan, Mounega, J. Thanusu and V. Kanagarajan, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **24**, 669(2008), [http://dx.doi.org/10.1080/14756360802323902](http://dx.doi.org/10.1080/14756360802323902)

28. P. Parthiban, G. Aridoss, P. Rathika, V. Ramkumar and S. Kabilan, *Bioorganic & Medicinal Chemistry Letters*, **19**, 2981(2009), [http://dx.doi.org/10.1016/j.bmcl.2009.10.042](http://dx.doi.org/10.1016/j.bmcl.2009.10.042)

29. S. Savithiri, M. Arockia doss, G. Rajarajan and V. Thanikachalam, *Journal of Molecular Structure*, **1075**, 430(2014), [http://dx.doi.org/10.1016/j.molstruc.2014.06.096](http://dx.doi.org/10.1016/j.molstruc.2014.06.096)

30. C.R. Noller and V. Baliah, *Journal of American Chemical Society*, **70**, 3853(1948), [http://dx.doi.org/10.1021/ja01191a092](http://dx.doi.org/10.1021/ja01191a092)

31. G. Aridoss, S. Amirthaganesan, M. S. Kim, J. T. Kim and Y. T. Jeong, *European Journal of Medicinal Chemistry*, **44**, 4199(2009), [http://dx.doi.org/10.1107/S1600536809033674](http://dx.doi.org/10.1107/S1600536809033674)

32. K. Hemalatha and D. Ilangeswaran, *Asian Journal of Chemistry*, **32**, 981(2020), [http://dx.doi.org/10.14233/ajchem.2020.22589](http://dx.doi.org/10.14233/ajchem.2020.22589)

33. K. Hemalatha and D. Ilangeswaran, *Materials Today: Proceedings*, **33**, 2671(2020), [http://dx.doi.org/10.1016/j.matpr.2020.01.345](http://dx.doi.org/10.1016/j.matpr.2020.01.345)

34. K. Hemalatha and D. Ilangeswaran, *Materials Today: Proceedings*, **33**, 4255(2020), [http://dx.doi.org/10.1016/j.matpr.2020.07.353](http://dx.doi.org/10.1016/j.matpr.2020.07.353)

35. Maja Molnar, Ivana Periš and Mario Komar, *European Journal of Organic Chemistry*, **15**, 2688(2019), [http://dx.doi.org/10.1002/ejoc.201900249](http://dx.doi.org/10.1002/ejoc.201900249)

[RJC-6321/2021]