Facile Synthesis of 1-(2-Morpholin-4-YL) 3, 5-Bis (2, 4, 6-Try Substituted-Arylidene)-Piperidin-4-Ones.

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ABSTRACT

The Claisen-Schmidt condensation of 3,5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one(5a-f) react with morpholine(6) in presence of K₂CO₃ to give 3,5-dibenzylidene-1-(2-morpholin-4-yl-acetyl)piperidin-4-ones(7a-f), and (5a-f) react with piperidine(8) in presanced K₂CO₃ to give 3,5-dibenzylidine-1-(2-piperidin-1-yl-acetyl)-piperidin-4-ones (9a-f) in good yields.

Keywords: Claisen-Schmidt condensation, 3, 5-dibenzylidene-piperidine-4-one, chloroacetyl chloride, piperidine, morpholine, K₂CO₃

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INTRODUCTION

Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, chromone, flavones, is flavones etc. The natural heterocyclics are plant secondary metabolites, which protect the plant from attack by pathogens, fungi, bacteria and insects. Several synthetic analogs of these heterocyclic's show different bioactivity. More than 50% of the drugs used in the modern medicine is either derived from synthetic or natural heterocyclic systems.

Heterocyclic ring systems having piperidin-4-one nucleus have aroused great interest in the past and present years due to their wide range of biological activity such as anti-viral and anti-microbial activity and their derivative piperidines are also biologically important and act as neurokinin receptor antagonists. The bis(substituted benzyliden) cycloalkanones are very important precursors to potentially bioactive pyrimidine derivatives intermediates of agrochemicals, pharmaceuticals, and perfumes new organic materials for nonlinear optical applications, cytotoxic analogues and the units of liquid-crystalline polymers. In addition these compounds undergo double 1,3-dipolar cyclo addition reaction with azomethine to give bis-spiropyrrrolidines, which are often the central ring system of numerous natural products. N-substituted piperidinone derivatives are the most successfully employed for a wide range of biological activity. Perusal of the literature has been found that the 1-(2-morpholin/piperidine-4-yl/1-yl-acetyl)-3,5-bis-(2,4,6-try substituted arylidene)-piperidin-4-ones moiety has significant biological activity. Therefore we propose to prepare a few target molecules and investigate their antioxidant and prooxidant assay of these molecules in liver and blood [1-15].

MATERIALS AND METHODS

General Methods

Melting points were determined on a Polmon instrument (model no. MP 96). IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and $^1$H NMR (200 MHz) and $^{13}$C NMR (100.6) were recorded on spectrometer using TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument.

General procedure for the Synthesis of 3,5-dibenzylidene-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one (7a-f).

A mixture of 3, 5-Dibenzylidene-1-(2-chloro-aceryl)-piperidin-4-one (5a) (3.52 gr, 10 mmol), K$_2$CO$_3$ (2.48 gr, 18 mmol) and morpholine (6) (1.55 mL, 18 mmol) in toluene was refluxed, for about 6 h. After completion of the reaction, K$_2$CO$_3$ was removed by filtration and the solvent was removed under reduced pressure. The crude product was subjected for column chromatography purification using silica gel (60-120) with hexane/ethyl acetate (1:1) as eluent to give 3,5-Dibenzylidene-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one (7a) in good yield.
3,5-Bis-(4-chloro-benzylidene)-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7a).

Yield: 81%, mp: 179 °C.
IR (KBr) (Cm⁻¹ (u)): 2966, 2916, 1658,1633,1493,1406, 1259, l122, 814.
¹H NMR (CDCl₃): δ 2.14 (t, 4H, morpholine), 2.99 (s, 2H, -COCH₂), 3.38 (t, 4H, morpholine), 4.85 (s, 2H, piperidinone ring-H), 5.00 (s, 2H, piperidinone ring-H), 7.40 (m,8H, Ar-H), 7.77 (s,1H, arylidirle-H),7.81 (s, IH, arylidine-H).
13C NMR (CDCl₃): δ 51.0 (CH), 127.6(CH), 133.5 (C'), 55.3 (CH₂), 55.3 (CH₂), 52.7(CH₂), 52.7 (CH₂), 66.1(CH₂), 33.8 (CH₂), 147.6(C').
MS (EI): m/z (%) 471 (96) [M+H⁺].

Employing the similar procedure as mentioned for 7a, compounds 7b-f were obtained from 5b-f as solids in 70-85% yield.

1-(2-Morpholin-4-yl-acetyl)-3,5-bis-(4-nitro-benzylidene)-piperidin-4-one(7b)

Yield: 79%, mp: 236 °C.
IR (KBr) (Cm⁻¹ (u)): 2918, 2851, 1726, 1651, 1595, 1518, 1259, 1172, 1113, 856.
¹H NMR (CDCl₃) δ 2.19 (t, 4H, morpholine), 3.02 (s, 2H, -COCH₂), 3.35 (t, 4H, morpholine), 4.86 (s, 2H, piperidinone ring-H), 5.08 (s, 2H, piperidinone ring-H), 7.65 (m,8H, Ar-H), 8.35 (s, 1H, arylidirle-H), 8.40 (s, 1H, arylidine-H).
13C NMR (CDCl₃): δ 53.0 (CH), 45.9(CH₂), 45.6 (CH₂), 137.6 (C'), 125.6(CH), 138.0(CH), 127.8(CH), 135.5 (C'), 55.3 (CH₂), 55.3 (CH₂), 52.7(CH₂), 52.7 (CH₂), 66.1(CH₂), 33.8 (CH₂), 147.6(C').
MS (EI): m/z (%) 493 (44) [M+H⁺].

3,5-Dibenzylidene-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7c)

Yield: 84%, mp: 142 °C.
IR (KBr) (Cm⁻¹ (u)): 2964, 2918, 1643, 1606, 1493, 1444, L275, l171, 1111, 864,771,688.
¹H NMR (CDCl₃) δ 2.16 (t, 4H, morpholine), 3.02 (s, 2H, -COCH₂), 3.39 (t, 4H, morpholine), 4.96 (s,2H, piperidinone ring-H),5.09 (s,2H, piperidinone ring-H), 7.50 (m, 10H, Ar-H), 7.85 (s, 1H, arylidirle-H), 7.92 (s,IH, arylidine-H).
13C NMR (CDCl₃): δ 50.0 (CH), 49.9(CH₂), 44.6 (CH₂), 135.6 (C'), 125.6(CH), 138.0(CH), 126.8(CH), 130.5 (C'), 55.3 (CH₂), 55.3 (CH₂), 52.7(CH₂), 52.7 (CH₂), 66.1(CH₂), 33.8 (CH₂), 147.6(C').
MS (EI): m/z (%) 403 (98) [M+H⁺].

3,5-Bis-(4-methoxy-benzylidene)-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one(7d)

Yield: 93%, mp: 156 °C.
IR (KBr) (Cm⁻¹), (u): 2930, 2837, 1647, 1597, 1510, 1255, 1167, 1113, 866, 829.
¹H NMR (CDCl₃) δ 2.17 (t, 4H, morpholine), 3.01 (s, 2H, -COCH₂), 3.35 (t, 4H, morpholine), 3.86 (s, 6H, two methoxy protons), 4.89 (s,2H, piperidinone ring-H), 4.89 (s,2H, piperidinone ring-H), 6.95 (d,4H, Ar-H), 7.42 (m,4H, Ar-H), 7.14 (s, IH, arylidine-H), 7.80 (s, IH, arylidine-H).
3,5-Bis-(2,6-dichloro-benzylidene)-1-(2-morpholin-4-yl-acetyl)-piperidin-4-one (7e)

Yield: 75%, mp: 162 °C.

IR (KBr) (Cm⁻¹) (u): 2918, 2851, 1682, 1651, 1554, 1427, 1263, 1144, 866, 812, 781.

1H NMR (CDCl₃) δ 2.19 (t, 4H, morpholine), 2.83 (s, 2H, -COCH₂-), 3.48 (t, 4H, morpholine), 4.40 (s, 2H, piperidinone ring-H), 4.59 (s, 2H, piperidinone ring-H), 7.98 (m, 6H, Ar-H), 7.65 (s, 1H, arylidine-H), 7.68 (s, 1H, arylidine-H).

13C NMR (CDCl₃): 50.0 (CH), 49.9(CH₃), 45.6 (CH₂), 135.6 (C’), 126.6(CH), 135.0(CH), 129.8(CH), 130.5 (C’), 55.3 (CH₂), 55.3 (CH₂), 52.7(CH₂), 52.7 (CH₂), 66.1(CH₂), 33.8 (CH₂), 147.6(C’).

MS (EI): m/z (%) 463 (50) [M+H]⁺.

3,5-Bis-(4-methyl-benzylidene)-1-(2-morpholin-4-y1-acetyl)-piperidin-4-one (7f)

Yield: 88%, mp: 187 °C.

IR (KBr) (Cm⁻¹) (u): 2918, 2852, 1568, 1344, 981, 912.

1H NMR (CDCl₃) δ 2.15 (t, 4H, morpholine), 2.39 (s, 6H, two methyl protons), 2.99 (s, 2H, -COCH₂-), 3.37 (t, 4H, morpholine), 4.91 (s, 2H, piperidinone ring-H), 5.03 (s, 2H, piperidinone ring-H), 7.33 (m, 8H, Ar-H), 7.79 (s, 1H, arylidine-H), 7.80 (s, 1H, arylidine-H).

13C NMR (CDCl₃): 54.0 (CH), 50.9(CH₃), 45.6 (CH₂), 135.6 (C’), 125.6(CH), 135.0(CH), 123.8(CH), 133.5 (C’), 55.3 (CH₂), 55.3 (CH₂), 52.7(CH₂), 52.7 (CH₂), 66.1(CH₂), 33.8 (CH₂), 147.6(C’).

MS (EI): m/z (%) 430 (97) [M+H]⁺.

Synthesis of 7,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-ones (9a-f)

A mixture of 3, 5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one (1a) (3.52 gr, 10 mmol), K₂CO₃ (2.48 gr, 18 mmol) and piperidine (8) (1.77 mL, 18 mmol) in toluene was refluxed for about 8 h. After the completion of reaction, K₂CO₃ was removed by filtration and the solvent was removed under reduced pressure and the crude product was subjected for column chromatography purification using silica gel (60-120) with hexane/ethyl acetate (1:1) as eluent to give 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one (9a) in good yield.

Employing the similar procedure as mentioned for 9a, compounds 9b-f were obtained from 5b-f as solids in 70-85% yield.

3,5-Bis-(4-chloro-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one (9a)

Yield: 85%, mp: 173 °C.

IR (KBr) (Cm⁻¹) (u): 2918, 2849, 1672, 1635, 1491, 1406, 1277, 1244, 1170, 1093, 979, 814, 761, 694.
1H NMR (CDCl₃) δ 1.28 (m, 6H, piperidine protons), 2.93 (s, 2H, -COCH₂-), 4.84 (s, 2H, piperidinone ring-H), 7.41 (m, 8H, Ar-H), 7.75 arylidine-H-protons), 2.10 (m, 4H, piperidine piperidinone ring-H), 5.07 (s, 2H, piperidinone ring-H), 7.41 (m, 8H, Ar-H), 7.75 (s, 1H, arylidine-H), 7.78 (s, 1H, arylidine-H).

13C NMR (CDCl₃): δ 55.0 (CH), 50.9(CH₂), 48.6 (CH₂), 138.6 (C'), 127.6(CH), 135.0(CH), 124.8(CH), 135.5 (C'), 33.8 (CH₂), 55.3 (CH₂), 53.6(CH₂), 25.2 (CH₂), 25.2(CH₂), 53.8 (CH₂), 133.5(C').

MS (EI): m/z (%) 470 (62) [M+H]+

3,5-Bis-(4-nitro-benzylidene)-1-(2-piperidin-1-y1-acetyl)-piperidin-4-one(9b)

Yield: 78%, mp: 179 °C.

IR (KBr) (Cm⁻¹): 2928, 2846, 1650, 1620, 1492, 1388, 1250, 1232, 1154, 1055, 958, 811,757,660.

1H NMR (CDCl₃) δ 1.32 (m, 6H, piperidine protons), 2.13 (m, 4H, piperidine protons), 3.00 (s, 2H, -COCH₂-), 4.85 (s, 2H, piperidinone ring-H), 5.09 (s, 2H, piperidinone ring-H), 7.63 (m, 8H, Ar-H), 8.01 (s, 1H, aryldiene-H), 8.06 (s, 1H, aryldiene-H).

13C NMR (CDCl₃): δ 53.0 (CH), 50.9(CH₂), 45.6 (CH₂), 138.6 (C'), 125.6(CH), 135.0(CH), 125.8(CH), 133.5 (C'), 33.8 (CH₂), 55.3 (CH₂), 53.6(CH₂), 25.2 (CH₂), 25.2(CH₂), 53.8 (CH₂), 133.5(C').

MS (EI): m/z (%) 491(70) [M+H]+.

3,5-Dibenzyldiene- 1 -(2-piperidin-1 -yl-acetyl)-piperidin-4-one (9c)

Yield: 80%, mp: 138 °C.

IR (KBr) (Cm⁻¹): 2922, 2843, 1651, 1614, 1444, 1165, 1263, 79 4,752,688.

1H NMR (CDCl₃) δ 1.38 (m, 6H, piperidine protons), 2.18 (m, 4H, piperidine protons), 3.00 (s, 2H, -COCH₂-), 4.99 (s, 2H, piperidinone ring-H), 5.16 (s, 2H, piperidinone ring-H), 7.02 (m, 10H, Ar-H), 7.87 (s, 1H, aryldiene-H), 7.93 (s, 1H, aryldiene-H).

13C NMR (CDCl₃): δ 50.0 (CH), 51.9(CH₂), 44.6 (CH₂), 133.6 (C'), 127.6(CH), 137.0(CH), 126.8(CH), 137.5 (C'), 33.8 (CH₂), 55.3 (CH₂), 53.6(CH₂), 25.2 (CH₂), 25.2(CH₂), 53.8 (CH₂), 133.5(C').

MS (EI): m/z (o/o) 400 (87) [M+H]+.

3,5-Bis-(4-methoxy-benzylidene)-l-(2-piperidin-1-y1-acetyl)-piperidin-4-one(9d)

Yield: 87%, mp: 149 °C.

IR (KBr) (Cm⁻¹): 2953, 2916, 1666, 1604, 1508, 1298, 1251, 1772, 1030, 873, 827, 754.

1H NMR (CDCl₃) δ 1.24 (m, 4H, piperidine protons), 1.61 (m, 4H, piperidine Protons), 2.17 (s,2H, piperidine protons), 3.85 (s, 6H, two methyl protons), 4.15 (s, 2H, -COCH₂), 4.91 (s,2H, piperidinone ring-H), 5.04 (s, 2H, piperidinone ring-H), 6.93 (d, 4H, Ar-H), 7.35 (m, 4H, Ar-H), 7.37 (s, 1H, aryldiene-H), 7.76 (s, 1H, aryldiene-H).

13C NMR (CDCl₃): δ 55.0 (CH), 53.9(CH₂), 47.6 (CH₂), 135.6 (C'), 127.6(CH), 135.0(CH), 127.8(CH), 134.5 (C'), 33.8 (CH₂), 55.3 (CH₂), 53.6(CH₂), 25.2 (CH₂), 25.2(CH₂), 53.8 (CH₂), 133.5(C').

MS (EI): m/z (%) 461 (7) [M+H]+.
Scheme-1

\[
\text{1} \xrightarrow{\text{HCl/CH}_2\text{COOH}} \text{2a-f} \xrightarrow{\text{K}_2\text{CO}_3} \text{3a-f} \xrightarrow{\text{Et}_3\text{N}} \text{4} \\
\text{R} = \text{H}, \text{R}_1 = \text{Cl, R}_2 = \text{H}
\]

\[
\text{R} = \text{H, R}_1 = \text{NO}_2, \text{R}_2 = \text{H}
\]

\[
\text{R} = \text{H}, \text{R}_1 = \text{H}, \text{R}_2 = \text{H}
\]

\[
\text{R} = \text{Cl, R}_1 = \text{H, R}_2 = \text{Cl}
\]

\[
\text{R} = \text{H, R}_1 = \text{OCH}_3, \text{R}_2 = \text{H}
\]

\[
\text{R} = \text{H, R}_1 = \text{CH}_3, \text{R}_2 = \text{H}
\]

3,5-Bis-(2,5-dichloro-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9e)

Yield: 73\%, mp: 150 °C.

IR (KBr) (Cm\(^{-1}\)) (υ): 2932, 2851, 1724, 1761, 1556, 1427, 1253, 1186, 1122, 848, 779.

\(\text{tH NMR (CDCl}_3\)} (d): 1.29 (m, 4H, piperidine protons), 2.03 (m, 4H, piperidine protons), 2.16 (bs, 2H, piperidine protons), 2.83 (S, 2H, -COGHZ-), 4.42 (s, 2H, piperidinone ring-H), 4.62 (s, 2H, piperidinone ring-H), 7.35 (m, 6H, A1--U), 7.42 (s, 1H, arylidine-H), 7.67 (s, 1H, arylidine-H).

\(\text{13C NMR (CDCl}_3\)}: δ 50.0 (CH), 51.9(CH\(_2\)), 42.6 (CH\(_2\)), 133.6 (C\(^{'}\)), 121.6(CH), 133.0(CH), 125.8(CH), 133.5 (C\(^{'}\)), 33.8 (CH\(_2\)), 55.3 (CH\(_2\)), 53.6(CH\(_2\)), 25.2 (CH\(_2\)), 25.2(CH\(_2\)), 53.8 (CH\(_2\)), 133.5(C\(^{'}\)).

MS (EI): m/z (%) 538 (97) [M+H]\(^+\).
3,5-Bis-(4-methyl-benzylidene)-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one(9f)

Yield: 76%, mp: 161 ºC.
IR (KBr) (cm⁻¹) (υ): 3414, 1572,513.

H NMR (CDCl₃) δ 1.30 (m, 4H, piperidine protons), 1.44 (bs, 2H, piperidine protons), 2.10 (bs, 4H, piperidine protons),2.42 (s, 6H, two methyl protons), 2.91 (s, 2H, -COCH₂), 4.88 (s, 2H, piperidinone ring-H), 5.04 (s, 2H, piperidinone ring-H), 7.23 (m,4H, Ar-H), 7.29 (d, 2H, Ar-H), 7.37 (d, 2H, Ar-H), 7.71 (s, 1H, arylidine-H), 7.78 (s, 1H, arylidine-H).

13C NMR (CDCl₃): δ 50.0 (CH), 53.9(CH₂), 43.6 (CH₂), 133.6 (C'), 127.6(CH), 137.0(CH), 123.8(CH), 133.5 (C'), 33.8 (CH₂), 55.3 (CH₂), 53.6(CH₂), 25.2 (CH₂), 25.2(CH₂), 53.8 (CH₂), 133.5(C').

MS (EI): m/z (%) 428 (99) [M+H]⁺.

RESULT AND DISCUSSIONS

A mixture of 3, 5-dibenzylidene-1-(2-chloro-acetyl)-piperidin-4-one (5a) K₂CO₃ and piperidine (8) in toluene was refluxed for about 8 hours to give 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one (9a). Formation of the synthesized compounds 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one is confirmed by the ¹H NMR (400 MHz) the piperidine protons appeared as multiplet at δ1.38 and 2.18. 3,5-dibenzylidene-1-(2-piperidin-1-yl-acetyl)-piperidin-4-one δ 2.14 (t, 4H, morpholine), 2.99 (s, 2H, -COCH₂), 3.38 (t, 4H, morpholine), 4.85 (s, 2H, piperidinone ring-H), 5.00 (s, 2H, piperidinone ring-H), 7.40 (m,8H, Ar-H), 7.77 (s,1H, arylidirle-H), 7.81 (s, IH, arylidine-H).

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