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Mechanism study of cycloaddition reaction toward the synthesis of 1,3-oxazepane-4,7-diones

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ABSTRACT

The one-step reaction of succinic anhydride with 3-((alkylimino)methyl)phenol in dry benzene gave 2-(3-hydroxyphenyl)-3-alkyl-1,3-oxazepane-4,7-diones in good yields. The mechanism of reaction show that the imine gave the dipolar intermediate which undergoes the cyclization of 7-membered heterocyclic ring.

KEYWORDS

Cycloaddition reaction;
Mechanism;
1,3-oxazepane-4,7-diones.

INTRODUCTION

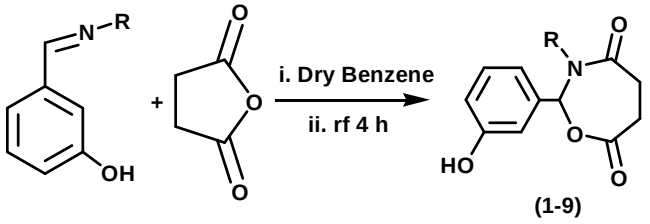
It has well been documented that the 1,4-, 4,1-, and 1,5-benzoxazepines are important heterocyclic compounds which have a wide range of biological activities[1-7]. There are no general procedures existing for the synthesis of these compounds. The six-membered ring heterocyclic ring system i.e. the 1,3-oxazine-4,6-diones has already been reported and thoroughly reviewed in the literature[8-11]. Maleic, arylmaleic and substituted maleic anhydrides react with trimethylsilyl azide to give 1,3-oxazine-2,6-diones[12-14]. It was found that *N*-acylimine or immonium ions that are capable of tautomerization undergo intramolecular Diels-Alder reaction to give dihydro-1,3-oxazine[15]. The discovery of the activity of 1,4-benzodiazepine on the central nervous system (CNS)[16] encouraged chemists to look for more effective ways to build up the seven-membered heterocyclic ring system. It is known that Schiff bases react with acid chlorides to give the corresponding addition products[17]. Recently, we prepared a series of 1,3-oxazepinediones[18]. In this paper, we reported a mechanism of reaction of the new compounds 3-alkyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-diones. The hydroxyphenyl and the terminal alkyl chain are attached to the oxazepane ring. The *N* atom of the heterocyclic ring was linked to the alkyl chain next to two of the 1,3-oxazepane fragments. The reaction between cyclic anhydride with imine have been studied in this paper.

RESULTS AND DISCUSSION

All title compounds are solid with sharp melting points. The synthetic routes towards formation of compounds 1-9 are shown in Scheme 1, while the mechanism is shown in Scheme 2. The analytical and selected FT-IR, ^{1}H and ^{13}C-NMR data for compounds are summarized in experimental section.

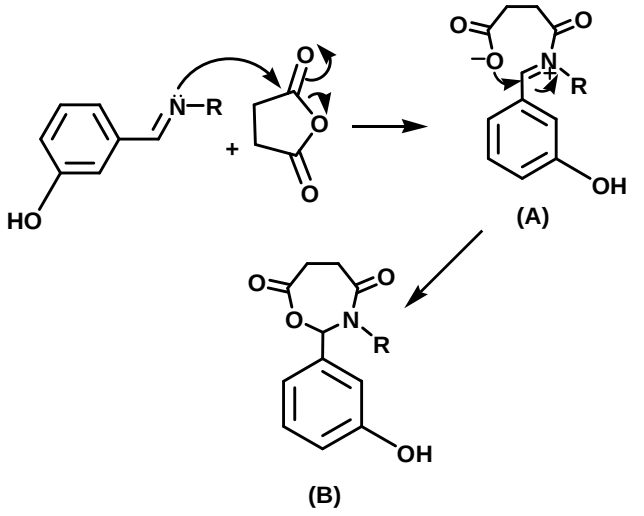
The reaction of the succinic anhydride with 3-((alkylimino)methyl)phenol gives the dipolar intermediate (A) which underwent the cyclization leading to the formation of 7-membered heterocyclic ring B (Scheme

2). The cyclization is a ring formation process that results from the addition of bond with either σ or π, forming new σ bonds. This class of reaction encompasses a large number of individual types[1]. Generally, Huisgen[19], is a useful classification of diverse cycloaddition in terms of the number of the new σ bond. This cycloaddition reaction can be classified as 2 + 5-7, which is the first cycloaddition of this type. Although, one would predict that the butadienyl cation might add to an olefin through a 4n+2 transition state to yield the cycloheptenyl cation[20]. The molecular structures of the title compounds are investigated in the solid state by using the infrared spectral analysis prior to adopting the advanced NMR techniques finding the compounds present in solution.



Compounds	R
1	C_2H_5
2	C_4H_9
3	C_6H_{13}
4	C_8H_{17}
5	$C_{10}H_{21}$
6	$C_{12}H_{25}$
7	$C_{14}H_{29}$
8	$C_{16}H_{33}$
9	$C_{18}H_{37}$

Scheme 1 : Synthesis, reagent and condition for the general procedure towards formation if compounds 1-9



Scheme 2 : Mechanism route towards formation of compounds 1-9

EXPERIMENTAL

Material

The 3-((alkylimino)methyl)phenol derivatives used, were already prepared in our laboratory. Succinic anhydride was purchased from Aldrich and was used without further purification. Thin layer chromatography (TLC) was performed on silica-gel plates. The ^1H, ^{13}C NMR and DEPT135 spectra along with two-dimensional COSY, ^1H- ^{13}C HMQC and HMBC spectra have been described elsewhere[21].

Physical measurements

Melting points were recorded by GALLENKAMP digital melting point apparatus. The elemental microanalyses (CHN) were performed using a Perkin Elmer 2400 LS Series CHNS/O analyzer. The FT-IR spectra of the title compounds 1-9 were recorded by using a Perkin Elmer 2000-FT-IR spectrophotometer in the frequency range 4000-400 cm^{-1}. The FT-IR measurement was carried out with the samples made up in KBr discs. The NMR spectra were recorded in deuterated methyl sulphoxide (DMSO-d_6) at 298 K on a Bruker 400 MHz Ultrashied™ FT-NMR spectrometer equipped with a 5 mm BBI inverse gradient probe. Chemical shifts were referenced to internal tetramethylsilane (TMS). The concentration of solute molecules was 50 mg in 1.0 ml of (DMSO-d_6). Standard Bruker pulse programs[22] were used throughout the entire experiment.

General procedure to synthesis of 1,3- oxazepane-4,7- diones derivatives

All the above mentioned compounds were synthesized by the same method. The synthetic method will be described by based on the compound 6:

A solution of succinic anhydride (0.01 mol) in dry benzene (10 ml) was added dropwise to a hot solution of 3-((dodecylimino)methyl)phenol (0.01 mol) in benzene (20 ml) in a round bottom flask equipped with a double surface condenser fitted with calcium chloride guard tube. The reaction mixture, monitored by TLC,

was refluxed for 4 h. Then, the solvent was removed in vacuo and the solid product obtained was filtered and washed with cold water. The resulting solid was re-crystallized twice from 1,4-dioxane. Yield 61 % m.p. 112-113 °C. Anal: Found for $C_{23}H_{35}NO_4$ (%): C 70.80, H 9.65, N 3.60. Calc (%) C 70.92, H 9.65, N 3.60. IR: υ_{max}(KBr) (cm^{-1}): 3316, 3018, 2945, 2920, 2850, 2838, 1717, 1544, 1520, 1401, 1311, 3213, 2593, 1078, 875, 824, 790. ^{1}H NMR δ (ppm) (DMSO): 9.92 (s, OH), 7.89 (s, H7), 7.25 (t, *J* =8.9 Hz, H5), 7.15 (s, H2), 7.05 (d, *J* =7.5 Hz, H4), 6.82 (d, *J* =8.2 Hz, H6), 3.01 (t, H12), 2.48 (t, *J* =7.8 Hz, H10), 2.30 (t, *J* =7.2 Hz, H9), 1.76 (q, H13), 1.29 (Hx), 1.25 (m, H14-H15-21), 0.85 (Hy); ^{13}C NMR δ (ppm) (DMSO): 174.73 (C11), 171.58 (C8), 158.83 (Ar-C-O), 138.49-114.48 (Ar-C), 68.34 (C7), 39.36 (C12), 34.60-27.80 (C14-C21), 29.67 (C13), 29.52 (C10), 27.68 (C9), 22.53 (Cx), 15.00 (Cy).

3-ethyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (1)

Yield 35 %. m.p. 86-88 °C. Anal: Found for $C_{13}H_{15}NO_4$ (%): C 62.72 H 6.19, N 5.51. Calc (%) C 62.64, H 6.07, N 5.62. IR: υ_{max}(KBr) (cm^{-1}): 3405, 3042, 2961, 2942, 2870, 2756, 1682, 1594, 1533, 1454, 1310, 3213, 2710, 1090, 880, 780, 725. ^{1}H NMR δ (ppm) (DMSO): 9.50 (s, OH), 7.65 (s, H7), 7.41 (t, *J* =8.8 Hz, H5), 7.15 (s, H2), 7.10 (d, *J* =7.4 Hz, H4), 6.67 (d, *J* =8.4 Hz, H6), 3.12 (q, H12), 2.40 (t, *J* =7.6 Hz, H10), 2.21 (t, *J* =7.1 Hz, H9), 1.74 (t, H13); ^{13}C NMR δ (ppm) (DMSO): 175.64 (C11), 172.35 (C8), 158.43 (Ar-C-O), 137.22-114.10 (Ar-C), 70.58 (C7), 40.15 (C12), 30.41(C13), 29.50 (C10), 28.58 (C9).

3-butyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (2)

Yield 47% m.p. 92-94 °C. Anal: Found for $C_{15}H_{19}NO_4$ (%): C 64.81, H 6.82, N 5.14. Calc (%) C 64.97, H 6.91, N 5.05. IR: υ_{max}(KBr) (cm^{-1}) 3459, 3018, 2966, 2941, 2869, 2751, 1690, 1544, 1527, 1432, 1318, 3215, 2560, 1084, 847, 740, 703. ^{1}H NMR δ (ppm) (DMSO): 9.50 (s, OH), 7.60 (s, H7), 7.41 (t, *J* =8.7 Hz, H5), 7.15 (s, H2), 7.10 (d, *J* =7.6 Hz, H4), 6.67 (d, *J* =8.7 Hz, H6), 3.22 (t, H12), 2.42 (t, *J* =7.4 Hz, H10), 2.35 (t, *J* =7.0 Hz, H9), 1.73 (q, H13), 1.28 (Hx), 0.94 (Hy); ^{13}C NMR δ (ppm) (DMSO): 176.32 (C11), 172.05 (C8), 158.72 (Ar-C-O), 138.10-114.95 (Ar-C), 70.50 (C7), 40.15 (C12), 29.50 (C10), 28.80 (C9), 22.50 (Cx), 20.51 (C13), 13.80 (Cy).

3-hexyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (3)

Yield 58% m.p. 98-100 °C. Anal: Found for $C_{17}H_{23}NO_4$ (%): C 66.71, H 7.41, N 4.41. Calc (%) C 66.86, H 7.59, N 4.59. IR: υ_{max}(KBr) (cm^{-1}): 3301, 3090, 2955, 2926, 2864, 2858, 1693, 1570, 1554, 1435, 1337, 3208, 2646, 1050, 865, 785, 765. ^{1}H NMR δ (ppm) (DMSO): 9.23 (s, OH), 7.62 (s, H7), 7.38 (t *J* =8.8 Hz, H5), 7.14 (d, *J* =7.3 Hz, H4), 7.12 (s, H2), 6.68 (d, *J* =8.8 Hz, H6), 3.10 (t, H12), 2.41 (t, *J* =7.7 Hz, H10), 2.27 (t, *J* =7.1 Hz, H9), 1.71 (q, H13), 1.32 (Hx), 1.30 (m, H14-H15), 0.86 (Hy); ^{13}C NMR δ (ppm) (DMSO): 176.70 (C11), 172.12 (C8), 161.06 (Ar-C-O), 138.10-115.80 (Ar-C), 70.03 (C7), 40.03 (C12), 34.40-27.12 (C14-C15), 30.30 (C13), 29.70 (C10), 27.20 (C9), 22.80 (Cx), 14.04 (Cy).

3-octyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (4)

Yield 61% m.p. 103-104 °C. Anal: Found for $C_{19}H_{27}NO_4$ (%): C 68.66, H 8.10, N 4.16. Calc (%) C 68.44, H 8.16, N 4.20. IR: υ_{max}(KBr) (cm^{-1}): 3381, 3069, 2953, 2927, 2861, 2848, 1707, 1587, 1526, 1403, 1317, 3235, 2725, 1050, 862, 789, 758. ^{1}H NMR δ (ppm) (DMSO): 9.19 (s, OH), 7.64 (s, H7), 7.38 (t, *J* =8.9 Hz, H5), 7.14 (s, H2), 7.11 (d, *J* =7.2 Hz, H4), 6.74 (d, *J* =8.7 Hz, H6), 3.13 (t, H12), 2.43 (t, *J* =7.5 Hz, H10), 2.25 (t, *J* =7.1 Hz, H9), 1.70 (q, H13), 1.31 (Hx), 1.25 (m, H14-H17) 0.87 (Hy); ^{13}C NMR δ (ppm) (DMSO): 174.71 (C11), 171.54 (C8), 158.85 (Ar-C-O), 138.50-115.50 (Ar-C), 67.56 (C7), 40.06 (C12), 30.85 (C13), 34.93-27.77 (C14-C17), 29.98 (C10), 28.08 (C9), 23.12 (Cx), 15.01 (Cy).

3-decyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (5)

Yield 64% m.p. 104-105 °C. Anal: Found for $C_{21}H_{31}NO_4$ (%): C 69.80, H 8.71, N 3.81. Calc (%) C 69.78, H 8.64, N 3.87. IR: υ_{max}(KBr) (cm^{-1}): 3430, 3015, 2940, 2925, 2860, 2830, 1710, 1560, 1528, 1405, 1310, 3220, 2769, 1090, 810, 760, 710. ^{1}H NMR δ (ppm) (DMSO): 9.81 (s, OH), 7.93 (s, H7),

7.39 (t, *J* =8.6 Hz, H5), 7.14 (s, H2), 7.09 (d, *J* =7.4 Hz, H4), 6.70 (d, *J* =8.9 Hz, H6), 3.21 (t, H12), 2.45 (t, *J* =7.7 Hz, H10), 2.26 (t, *J* =7.1 Hz, H9), 1.76 (q, H13), 1.27 (Hx), 1.24 (m, H14-H19), 0.88 (Hy); ^{13}C NMR δ (ppm) (DMSO): 175.54 (C11), 172.05 (C8), 158.65 (Ar-C-O), 138.65-115.01 (Ar-C), 67.92 (C7), 39.80 (C12), 30.03 (C13), 29.81 (C10), 34.70-27.65 (C14-C19), 27.70 (C9), 22.94 (Cx), 15.03 (Cy).

3-tetradecyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (7)

Yield 69 % m.p. 102-104 °C. Anal: Found for $C_{25}H_{39}NO_4$ (%): C 71.86, H 9.58, N 3.28. Calc (%) C 71.91, H 9.41, N 3.35. IR: υ_{max}(KBr) (cm^{-1}): 3314, 3018, 2953, 2918, 2850, 2839, 1695, 1582, 1545, 1471, 1312, 3204, 2589, 1079, 824, 794, 784. ^{1}H NMR δ (ppm) (DMSO): 9.91 (s, OH), 7.93 (s, H7), 7.24 (t, *J* =8.7 Hz, H5), 7.10 (s, H2), 7.06 (d, *J* =7.5 Hz, H4), 6.81 (d, *J* =8.7 Hz, H6), 3.03 (t, H12), 2.40 (t, *J* =7.8 Hz, H10), 2.28 (t, *J* =7.2 Hz, H9), 1.73 (q, H13), 1.29 (Hx), 1.24 (m, H14-H15-23), 0.85 (Hy); ^{13}C NMR δ (ppm) (DMSO): 174.64 (C11), 171.92 (C8), 158.88 (Ar-C-O), 138.74-115.08 (Ar-C), 68.62 (C7), 39.83 (C12), 32.50-26.40 (C14-C23), 29.60 (C13), 29.53 (C10), 27.27 (C9), 22.91 (Cx), 14.82 (Cy).

3-hexadecyl-2-(3-hydroxyphenyl)-1,3-oxazepane-4,7-dione (8)

Yield 74 % m.p. 124-126 °C. Anal: Found for $C_{27}H_{43}NO_4$ (%): C 72.82, H 9.61, N 3.09. Calc (%) C 72.77, H 9.73, N 3.14. IR: υ_{max}(KBr) (cm^{-1}): 3443, 3018, 2954, 2920, 2850, 2834, 1694, 1558, 1517, 1450, 1344, 3209, 2523, 1078, 824, 794, 766. ^{1}H NMR δ (ppm) (DMSO): 9.92 (s, OH), 7.92 (s, H7), 7.36 (t, *J* =8.6 Hz, H5), 7.24 (s, H2), 7.11 (d, *J* =7.4 Hz, H4), 6.92 (d, *J* =8.9 Hz, H6), 3.01 (t, H12), 2.42 (t, *J* =7.5 Hz, H10), 2.29 (t, *J* =7.2 Hz, H9), 1.71 (q, H13), 1.30 (Hx), 1.23 (m, H14-H15-25), 0.85 (Hy); ^{13}C NMR δ (ppm) (DMSO): 174.71 (C11), 171.56 (C8), 158.82 (Ar-C-O), 137.16-115.49 (Ar-C), 69.86 (C7), 39.90 (C12), 33.57-27.44 (C14-C25), 29.96 (C13), 29.56 (C10), 27.25 (C9), 22.95 (Cx), 14.76 (Cy).

3-octadecyl-2-(3-hydroxyphenyl)- 1,3-oxazepane-4,7-dione (9)

Yield 70 % m.p. 119-121 °C. Anal: Found for $C_{29}H_{47}NO_4$ (%): C 73.39, H 10.05, N 2.81. Calc (%) C 73.53, H 10.00, N 2.96. IR: υ_{max}(KBr) (cm^{-1}): 3449, 3017, 2954, 2919, 2850, 2839, 1693, 1558, 1516, 1404, 1312, 3265, 2614, 1077, 875, 824, 790. ^{1}H NMR δ (ppm) (DMSO): 9.94 (s, OH), 7.91 (s, H7), 7.38 (t, *J* =8.9 Hz, H5), 7.21 (s, H2), 7.08 (d, *J* =7.5 Hz, H4), 6.94 (d, *J* =8.8 Hz, H6), 3.05 (t, H12), 2.41 (t, *J* =7.7 Hz, H10), 2.28 (t, *J* =7.3 Hz, H9), 1.75 (q, H13), 1.28 (Hx), 1.23 (m, H14-H15-27), 0.86 (Hy); ^{13}C NMR δ (ppm) (DMSO): 174.64 (C11), 171.57 (C8), 158.83 (Ar-C-O), 138.13-115.54 (Ar-C), 69.21 (C7), 39.85 (C12), 33.87-27.80 (C14-C27), 29.95 (C13), 29.51 (C10), 27.23 (C9), 22.90 (Cx), 14.89 (Cy).

CONCLUSION

In this paper we present some new heterocyclic compounds with 1,3-oxazepane cores, the mechanism of this reaction have been discussed. The reaction of the succinic anhydride with 3-((alkylimino)methyl)phenol gave the dipolar intermediate which has undergone the cyclization leading to the formation of 7-membered heterocyclic ring.

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