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Synthesis and Identification of 1,3-Oxazepine derivatives by reaction of Schiff Bases with Anhydride derivative of Cycloheptatriene

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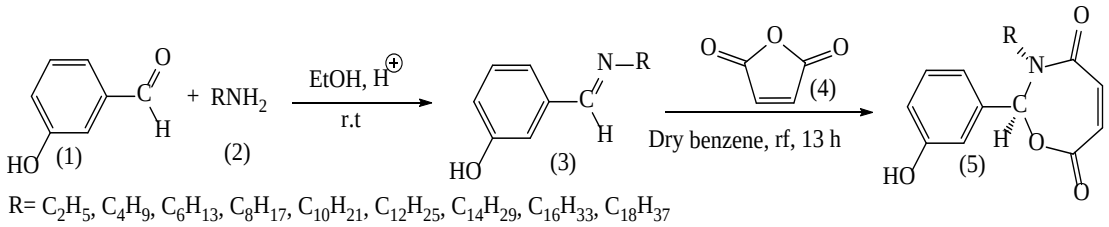
Abstract:

In this work, 1,3-oxazepine derivatives (14-19) were synthesized from reaction of Schiff bases with anhydride derivative of cycloheptatriene in two steps, in the one step Schiff bases Compound (6-11) were prepared by reaction of aniline with some aromatic aldehydes using H_2SO_4 as a catalyst and ethanol as a solvent at room temperature, also prepared anhydride derivative of cycloheptatriene from reaction of maleic anhydride (4) with cycloheptatriene (12) without using any solvent to give excellent yields of Compound (13), in the two step Compound (13) was reacted with Schiff bases Compound (6-11) in refluxing benzene dry to give 1,3-oxazepine derivatives (14-19), Compounds (14-19) have been identified by spectroscopic methods, IR, UV, ^{1}H-NMR, ^{13}C-NMR (DEPT 90 + DEPT 135) and elemental analysis (C.H.N).

Key words: oxazepine, Schiff base, cycloheptatriene, aromatic aldehyde, maleic anhydride.

1. INTRODUCTION

Recently, the chemistry of unsaturated seven-membered heterocyclic compounds especially 1,3-oxazepine has attracted attention due to their reactivity and showed various biological activities such as antibacterial [1], inhibitors for some enzymes action [2], the oxazepane rings is still preferred owing to its importance as pharmaceutical drugs and active substances in biological system [3-4], the design and synthesis of heterocyclic compounds having a ring size with 7 atoms received great attention in synthetic organic chemistry and this can be ascribed to their application in biologically active natural products [5], drugs [6], synthetic materials [7] and catalysts [8], Some of oxazepane derivatives are used in another applied fields [9-10], 1,3-oxazepine containing oxygen atom in position 1, nitrogen atom in position 3, in edition of five carbonsm, [11] 1,3-Oxazepine derivatives were prepared by reaction of 3-hydroxybenzaldehyde (1) with primary amines (2) to give Schiff Bases (3), then in new step reaction between Schiff bases (3) and malic anhydride (4) to give 1,3-Oxazepine derivatives (5). [12]



R= C_2H_5, C_4H_9, C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$, $C_{18}H_{37}$

2. EXPERIMENTAL

2.1. Apparatus measurements

Infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S instrument, and were calibrated using a polystyrene film. Solid compounds were recorded in potassium bromide disks (KBr). Ultraviolet (UV) spectra were recorded on Shimadzu UV-1800 spectrophotometer, ^{1}H-NMR spectra were recorded on 500 MHz AV III-HD-800 Bio Spin spectrometer while ^{13}C-NMR were recorded on 500 MHz Bruker spectrometer instrument using dimethyl sulfoxide (DMSO-d6) as a solvent solution, using tetramethylsilane (TMS) as an internal standard. Chemical shifts were quoted in parts per million (ppm) downfield from TMS. Elemental analysis was performed on the CHN elemental (Eur Vector EA 3000A) Germany.

2.2. Organic Preparations

2.2.1. General procedure for the synthesis of Schiff bases (6-11).

These compounds were prepared as previously reported. [13] To a solution of aromatic aldehydes (5 mmol) in ethanol (5ml) one drop of H_2SO_4 was added with stirring, after 0.5 h aniline (5 mmol) was added dropwise for 2 hours in room temperature and monitored by TLC until reactions were completed. In each time, Solid products separated out were filtered of and recrystallized to give compounds (6-11) respectively. see Scheme (1).

2.2.2. preparation of anhydride derivative of cycloheptatriene (13).

This compound was prepared as previously reported. [14] maleic anhydride (4) (10.65g, 0.1 mol) was mixed with cycloheptatriene (12) (10g, 0.1 mol) and refluxed for 4 h without using any solvent, and monitored by TLC until reactions was completed, Reaction mixture was cooled to room temperature, hexane was added to mixture and washed, The product was recrystallized from ethylacetate: hexane (3:1), which gave white crystals of (13), m.p., 104 C^o [Lit.104.2 C^o][13] and (Yield: 18.59g , 90%).

2.2.3. General procedure for the synthesis of 1,3-oxazepine derivatives (14-19).

To a solution of anhydride derivative of cycloheptatriene (13) (10 mmol) in dry benzene (5ml) solution of Schiff bases (6-11) (10 mmol) in dry benzene also (5ml) was added, the mixture was refluxed and monitored by TLC until reactions were completed, Solid products separated out were filtered of and recrystallized to give compounds (14-19) respectively see Scheme (2) and table (1).

6(R,6aR,7aS,8S)-3,4-diphenyl-3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa [4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (14).

(C. H. N.) (Found: C% = 75.85, H% = 6.12, N%= 3.91, $C_{24}H_{21}NO_3$; Requires C% = 77.61, H% = 5.70, N%= 3.77). λ_{max} (EtOH) : 194 , 205 , 234 , 284 nm. υ (KBr): 3030 (CH-aromatic.) ; 2970 , 2890 (CH-aliph.) ; 1740 (C=O-ester) ; 1660 (C=O-amide) ; 1600 (C=C) ; 1340 (C-N) ; 1290 cm^{-1} (C-O). ^{1}H-NMR (DMSO-d_6) : δ 1.01 (1H, p, H_7) ; 1.19 (1H, p, H_8) ; 1.39 (1H, t, H_9 endo) ; 1.45 (1H, t, H_9 exo) ; 2.90 (1H, d, H_3) ; 2.96 (1H, q, H_2) ; 3.08 (1H, q, H_6) ; 3.35 (1H, d, H_5) ; 5.75 (1H, t, H_1) ; 5.78 (1H, t, H_4) ; 7.25 (5H, s, H_{19-23}) ; 7.35 (5H, s, H_{24-28}) ; 7.60 ppm (1H, s, H_{12}). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 35.9 (C_6) ; 40.8 (C_3) ; 42.0 (C_5) ; 89.2 (C_{12}) ; 124.3 ($C_{19,23}$) ; 127.2 (C_{21}) ; 129.1 ($C_{20,22}$) ; 127.1 ($C_{24,28}$) ; 128.7 ($C_{25,27}$) ; 128.9 (C_{26}) ; 127.6 ($C_{1,4}$) ; 137.6 (C_{18}) ; 137.9 (C_{17}) ; 169.9 (C_{10}) ; 173.7 ppm (C_{14}).

(R,6aR,7aS,8S)-3-(4-hydroxyphenyl)-4-phenyl-6 3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa[4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (15).

(C. H. N.) (Found: C% = 75.12, H% = 5.33, N%= 3.24, $C_{24}H_{21}NO_4$; Requires C% = 74.40, H% = 5.46, N%= 3.62). λ_{max} (EtOH) : 198 , 202 , 225 , 286 nm. υ (KBr): 3400 (O-H) ; 3020 (CH-aromatic.) ; 2980 , 2900 (CH-aliph.) ; 1730 (C=O-ester) ; 1655 (C=O-amide) ; 1600 (C=C) ; 1350 (C-N) ; 1280 cm^{-1} (C-O). ^{1}H-NMR (DMSO-d_6) : δ 1.07 (1H, p, H_7) ; 1.18 (1H, p, H_8) ; 1.40 (1H, t, H_9 endo) ; 1.44 (1H, t, H_9 exo) ; 2.85 (1H, d, H_3) ; 2.95 (1H, q, H_2) ; 3.11 (1H, q, H_6) ; 3.40 (1H, d, H_5) ; 5.73 (1H, t, H_1) ; 5.75 (1H, t, H_4) ; 6.73-7.32 (4H, dxd, $H_{24,25,27,28}$) ; 7.39 (5H, s, H_{19-23}) ; 7.61 (1H, s, H_{12}) ; 8.99 ppm (1H, s, H_{29}). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 35.9 (C_6) ; 40.8 (C_3) ; 42.1 (C_5) ; 89.3 (C_{12}) ; 115.7 ($C_{25,27}$) ; 124.4 ($C_{19,23}$) ; 127.2 (C_{21}) ; 127.5 (C_1) ; 128.0 ($C_{24,28}$) ; 128.4 (C_4) ; 129.0 ($C_{20,22}$) ; 129.1 (C_{18}) ; 138.3 (C_{17}) ; 158.2 (C_{26}) ; 169.9 (C_{10}) ; 173.5 ppm (C_{14}).

(R,6aR,7aS,8S)-3-(4-chlorophenyl)-4-phenyl-6P 3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa[4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (16).

(C. H. N.) (Found: C% = 70.22, H% = 4.76, N%= 3.55, $C_{24}H_{20}ClNO_3$; Requires C% = 71.02, H% = 4.97, N%= 3.45). λ_{max} (EtOH) : 191 , 203 , 234 , 283 nm. υ (KBr): 3010 (CH-aromatic.) ; 2990 , 2880 (CH-aliph.) ; 1735 (C=O-ester) ; 1650 (C=O-amide) ; 1610 (C=C) ; 1330 (C-N) ; 1285 (C-O) ; 1070 cm^{-1} (C-Cl). ^{1}H-NMR (DMSO-d_6) : δ 1.03 (1H, p, H_7) ; 1.14 (1H, p, H_8) ; 1.40 (1H, t, H_9 endo) ; 1.44 (1H, t, H_9 exo) ; 2.88 (1H, d, H_3) ; 3.05 (1H, q, H_2) ; 3.17 (1H, q, H_6) ; 3.43 (1H, d, H_5) ; 5.74 (1H, t, H_1) ; 5.78 (1H, t, H_4) ; 7.25 (5H, s, H_{19-23}) ; 7.34-7.51 (4H, dxd, $H_{24,25,27,28}$) ; 7.65 ppm (1H, s, H_{12}). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 35.9 (C_6) ; 40.8 (C_3) ; 42.3 (C_5) ; 88.9 (C_{12}) ; 124.4 ($C_{19,23}$) ; 126.8 (C_{21}) ; 127.5 (C_1) ; 127.9 ($C_{24,28}$) ; 128.3 (C_4) ; 129.0 ($C_{20,22}$) ; 129.1 ($C_{25,27}$) ; 133.0 (C_{26}) ; 136.4 (C_{18}) ; 138.3 (C_{17}) ; 169.9 (C_{10}) ; 173.6 ppm (C_{14}).

(R,6aR,7aS,8S)-3-(4-bromophenyl)-4-phenyl-6 3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa[4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (17)

(C. H. N.) (Found: C% = 63.72, H% = 4.56, N%= 3.31, $C_{24}H_{20}BrNO_3$; Requires C% = 64.01, H% = 4.48, N%= 3.11). λ_{max} (EtOH) : 194 , 206 , 234 , 284 nm. υ (KBr): 3035 (CH-aromatic.) ; 2970 , 2890 (CH-aliph.) ; 1730 (C=O-ester) ; 1665 (C=O-amide) ; 1630 (C=C) ; 1350 (C-N) ; 1270 (C-O) ; 1040 cm^{-1} (C-Br). ^{1}H-NMR (DMSO-d_6) : δ 1.03 (1H, p, H_7) ; 1.14 (1H, p, H_8) ; 1.40 (1H, t, H_9 endo) ; 1.44 (1H, t, H_9 exo) ; 2.88 (1H, d, H_3) ; 3.05 (1H, q, H_2) ; 3.15 (1H, q, H_6) ; 3.43 (1H, d, H_5) ; 5.74 (1H, t, H_1) ; 5.78 (1H, t, H_4) ; 7.25 (5H, s, H_{19-23}) ; 7.45-7.53 (4H, dxd, $H_{24,25,27,28}$) ; 7.65 ppm (1H, s, H_{12}). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 36.0 (C_6) ; 40.8 (C_3) ; 42.5 (C_5) ; 89.3 (C_{12}) ; 121.9 (C_{26}) ; 124.4 ($C_{19,23}$) ; 127.1 (C_{21}) ; 127.9 ($C_{24,28}$) ; 128.0 (C_1) ; 128.4 (C_4) ; 129.1 ($C_{20,22}$) ; 131.8 ($C_{25,27}$) ; 137.0 (C_{18}) ; 138.3 (C_{17}) ; 169.9 (C_{10}) ; 173.6 ppm (C_{14}).

(R,6aR,7aS,8S)-3-(3-hydroxyphenyl)-4-phenyl-6 3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa[4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (18).

(C. H. N.) (Found: C% = 74.11, H% = 4.82, N%= 4.13, $C_{24}H_{21}NO_4$; Requires C% = 74.40, H% = 5.46, N%= 3.62). λ_{max} (EtOH) : 192 , 204 , 234 , 285 nm. υ (KBr): 3450 (O-H) ; 3030 (CH-aromatic.) ; 2950 , 2880 (CH-aliph.) ; 1740 (C=O-ester) ; 1650 (C=O-amide) ; 1630 (C=C) ; 1320 (C-N) ; 1300 cm^{-1} (C-O). ^{1}H-NMR (DMSO-d_6) : δ 1.07 (1H, p, H_7) ; 1.18 (1H, p, H_8) ; 1.40 (1H, t, H_9 endo) ; 1.44 (1H, t, H_9 exo) ; 2.86 (1H, d, H_3) ; 2.96 (1H, q, H_2) ; 3.10 (1H, q, H_6) ; 3.38 (1H, d, H_5) ; 5.75 (1H, t, H_1) ; 5.73 (1H, t, H_4) ; 6.66 (1H, d, H_{26}) ; 6.97 (1H, s, H_{28}) ; 7.13 (1H, t, H_{25}) ; 7.22 (1H, d, H_{24}) ; 7.35 (5H, s, H_{19-23}) ; 7.56 (1H, s, H_{12}) ; 9.30 ppm (1H, s, H_{29}). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 35.9 (C_6) ; 40.8 (C_3) ; 42.1 (C_5) ; 89.3 (C_{12}) ; 114.0 (C_{28}) ; 115.8 (C_{26}) ; 119.3

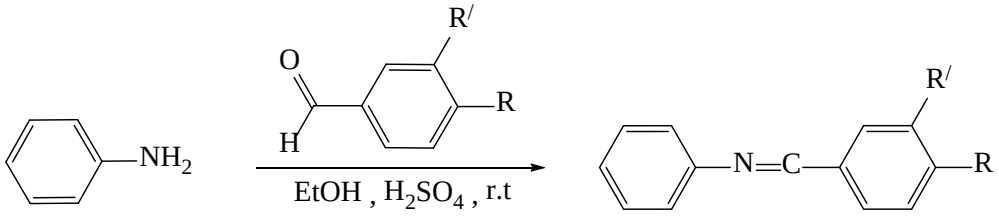
(C_{24}) ; 124.4 ($C_{19,23}$) ; 127.2 (C_{21}) ; 127.5 (C_1) ; 128.4 (C_4) ; 129.0 ($C_{20,22}$) ; 129.9 (C_{25}) ; 138.0 (C_{18}) ; 138.3 (C_{17}) ; 157.2 (C_{27}) ; 169.9 (C_{10}) ; 173.5 ppm (C_{14}).

6(R,6aR,7aS,8S)-3-(4-hydroxy-3-methoxyphenyl)-4-phenyl-3,4,6,6a,7,7a,8,8a-octahydro-1H-6,8-ethenocyclopropa[4,5]benzo[1,2-e][1,3]oxazepine-1,5(5aH)-dione (19).

(C. H. N.) (Found: C% = 72.23, H% = 5.34, N%= 3.22, $C_{25}H_{23}NO_5$; Requires C% = 71.93, H% = 5.55, N%= 3.36). λ_{max} (EtOH) : 196 , 205 , 234 , 285 nm. υ (KBr): 3500 (O-H) ; 3050 (CH-aromatic.) ; 2980 , 2870 (CH-aliph.) ; 1730 (C=O-ester) ; 1660 (C=O-amide) ; 1630 (C=C) ; 1310 (C-N) ; 1280 , 1200 cm^{-1} (C-O). ^{1}H-NMR (DMSO-d_6) : δ 1.00 (1H, p, H_7) ; 1.14 (1H, p, H_8) ; 1.41 (1H, t, H_9 endo) ; 1.47 (1H, t, H_9 exo) ; 2.80 (1H, d, H_3) ; 2.95 (1H, q, H_2) ; 3.13 (1H, q, H_6) ; 3.49 (1H, d, H_5) ; 3.81 (3H, s, H_{31}) ; 5.73 (1H, t, H_1) ; 5.76 (1H, t, H_4) ; 6.77 (1H, d, H_{25}) ; 6.99 (1H, d, H_{24}) ; 7.02 (1H, s, H_{28}) ; 7.27 (5H, s, H $_{19-23}$) ; 7.62 (1H, s, H $_{12}$) ; 8.34 ppm (1H, s, H $_{29}$). ^{13}C-NMR (DMSO-d_6) : δ 14.6 (C_9) ; 16.1 (C_7) ; 16.2 (C_8) ; 34.5 (C_2) ; 35.9 (C_6) ; 40.8 (C_3) ; 42.3 (C_5) ; 56.1 (C_{31}) ; 89.5 (C_{12}) ; 111.0 (C_{28}) ; 115.1 (C_{25}) ; 121.0 (C_{24}) ; 124.3 ($C_{19,23}$) ; 127.1 (C_{21}) ; 128.0 (C_1) ; 128.3 (C_4) ; 129.1 ($C_{20,22}$) ; 129.2 (C_{18}) ; 138.3 (C_{17}) ; 146.8 (C_{26}) ; 147.4 (C_{27}) ; 169.9 (C_{10}) ; 173.5 ppm (C_{14}).

3. RESULTS AND DISCUSSION

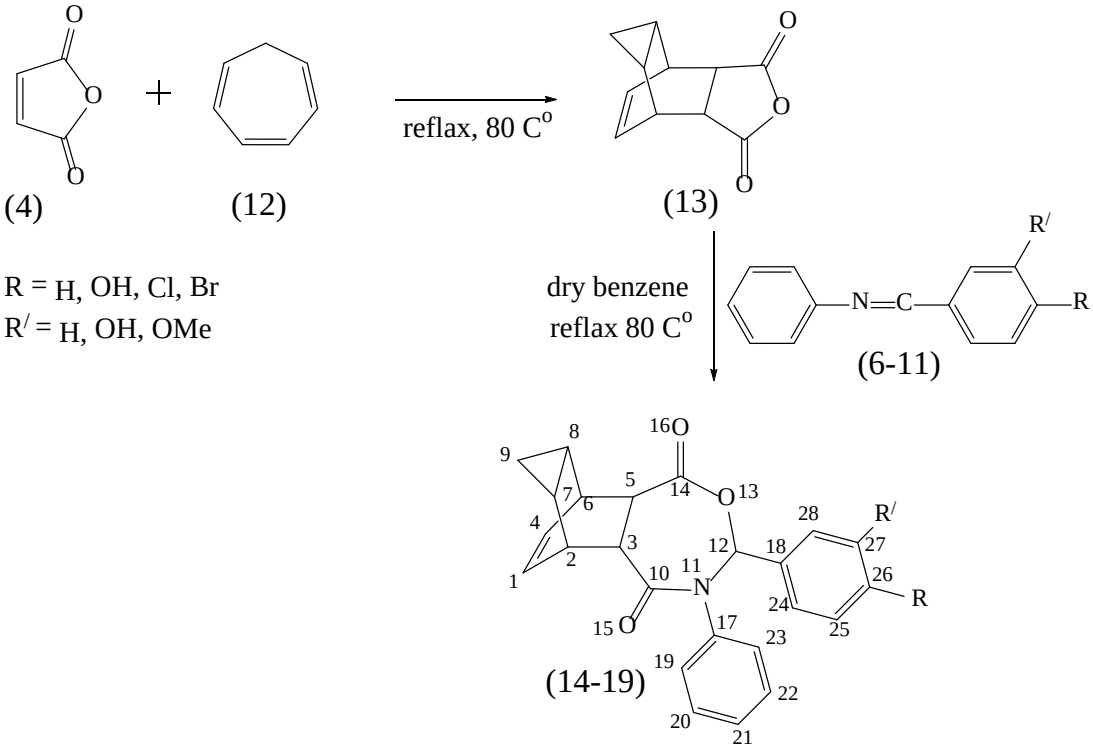
In our study, reactions of aromatic aldehydes with aniline in the presence of H_2SO_4 as a catalyst and ethanol as a solvent in room temperature gave Schiff bases (6-11) respectively, this compound was prepared as previously reported. [13] see scheme (1).



R = H, OH, Cl, Br
R/ = H, OH, OMe

(6-11)

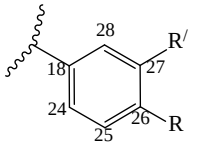
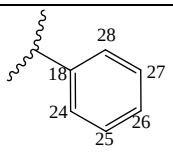
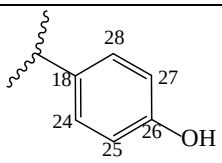
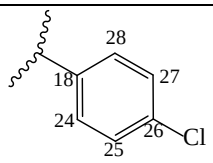
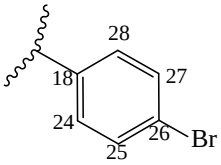
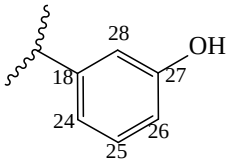
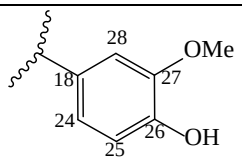
Scheme (1).



R = H, OH, Cl, Br
R/ = H, OH, OMe

Scheme (2).

Table (1). Crystalliztion solvent, reaction time, some physical properties and yields of compounds (14-19).

Compd. No.		Crystallization Solvent	Reaction time [hr]	Color	M.P. [C°]	Yield [%]
14		Ethyl acetate	2	Yellow	263-5	70
15		Ethyl acetate	4	Pink	245-7	62
16		Ethyl acetate	5	White	276 .d	42
17		Ethyl acetate	6	White	286 .d	48
18		Ethyl acetate	3	Pink	236-8	65
19		Ethyl acetate	2	Yellow	254-6	80

Besides the importance of maleic anhydride and its derivatives as biologically active agents, they are also useful synthons and building block for many heterocyclic products, so in new step maleic anhydride (4) was reacted with cycloheptatriene (12) without using any solvent to give anhydride derivative of cycloheptatriene (13), this compound also was prepared as previously reported. [13] Condensation of anhydride derivatives and Schiff bases has been extensively used for the preparation of 7-membered ring heterocyclic compounds especially in the preparation 1,3-oxazepine derivatives.

Heterocycliczation of the synthesized compounds (14-19) was achieved by refluxing anhydride derivative of cycloheptatriene (13) with Schiff bases (6-11) in dry benzene. see scheme (2). Formation of the products (14-19) was confirmed by IR, UV, ^{1}H-NMR, ^{13}C-NMR (DEPT 90 + DEPT 135) and elemental analysis (C.H.N).

From this study, It was observed that yields were moderate to good. see table (1).

4. CONCLUSIONS

In conclusion, we have developed an exceedingly simple, mild and clean synthetic protocol for the synthesis of 1,3-oxazepine derivatives.

In this method, the reaction of schiff bases with anhydride derivative of cycloheptatriene and anti-oxidant Ability for this derivative has been described.

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