Synthesis And Characterization Of New 1,2,4-Triazine Based On 2,5-Dihydrazino-1,3,4-Thiadiazole

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Abstract

The chemistry of 1,2,4-triazine derivatives received a great deals of attention in recent year due to the use of such ring system as the core structure in many heterocyclic compound covering wide range of applications in many different field especially in industrial and biological fields. An efficient aza Diels-Alder reaction have been used in this presentation to prepare the hetero adducts represented by N2,N5-di(3,5,6-tri aryl-5,6-dihydro-1,2,4-triazine-4(3H)-yl)-1,3,4-thiadiazole-2,5-diamino( 9-20) from hetero dienes and hetero dienophile. However the preparation starting form 1,3,4-thiadiazole-2,5-dithaiole (1) which converted directly to the dihydrazino derivatives(2) which then afford under condensation reaction hetero dienophile represented by 2,5-bis Schiff bases of 1,3,4-thiadiazole(3-6) by its reaction with substituted benzaldehyde . The last compound were reacted through one-pot free solvent aza Diels-Alder reaction with appropriate hetero diene hydrazine with substituted benzaldehyde in ratio 1:2 (7&8 ) to afford 1,2,5-triazine derivatives (9-20) using grinding and MWI techniques as a types of green chemistry approaches.

Keywords: aza Diels-Alder, 1,2,4-triazine, 1,3,4-thiadiazole, hetero diene, hetero dienophile , Schiff bases , MWI.

1-Introduction

The triazine derivatives one of the most important heterocyclic which appear in three different isomers 1,2,3-triazin, 1,2,4-triazine, and 1,3,5-triazine .The most interesting one is 1,2,4-triazine due to its wide applications in many different fields(Agostinis 2019, Ntombela and Mahlambi 2019). They show in industries field (Samy and Taha 2018, Yang, Clark et al. 2019, Cui, Li et al. 2021) special activity in textile industry as in polyurethane polymerization(Hou, Chen et al. 2021), in azodyes(Miladinova and Lukanova 2017, El-Sedik, Abd Elmegied et al. 2019), paints(Gladis, Eggert et al. 2010), plastic and rubber(Khan, Yadav et al. 2015). Also, they possess wide application in agricultural field(Jason Krutz, Shaner et al. 2010) as fungicides (Parikh and Vyas 2012) and insecticide. Besides this 1,2,4-triazine derivatives shown wide spectrum of biological activity including anticancer (Bernat, Mieszkowska et al. 2021, Gornowicz, Szymanowska et al. 2021), anti –HIV (Patel, Kumari et al. 2012, Arshad, Bhat et al. 2014) and antifungal (Li, Jiao et al. 2018, Karnwal 2021) ,anti-inflammatory(Makki,
Bakhotmah et al. 2018, Rafiq, Nazir et al. 2019), analgesic (Naganagowda, Thamyongkit et al. 2011, Majid, Lawal et al. 2020) and antihypertensive(Husain, Rashid et al. 2013). 1,2,4-triazines prepared in many different synthetic pathways: one of the most important one that used 1,2-dicarbonyl compounds as active reagent especially when it reacted with mono acyl hydrazide followed by ring closure with alcoholic ammonia to afford substituted 1,2,4-triazine(Kushwaha and Sharma 2020). Other synthesized method involving the reaction of amidrazone with1,4-benzoquinonone moiety in presence of N2 atmospheric(Abu Emaileq 2014). Now days, a recent and important trend in the synthesis of new hetero adducts represented by compounds 1,2,4-triazines through Diels-Alder reaction and also especially when it proceed through green chemistry technique such as microwave irradiation (MWI), which is used for variety of applications including organic synthesis where in chemical reaction accounted because of selective absorption of microwave energy by polar molecules, nonpolar molecules being inert of the microwave dielectric loss. In this presentation anew series of 1,2,5-triazine derivatives as hetero adducts were prepared according to the green chemistry environmentally solvent-free approaches, firstly by grinding method then via microwave irradiation technique using (720 watt) in suitable time, starting from 2,5-dihydrazino-1,3,4-thiadiazole and substituted benzoaldehyde to afforded hetero dienophile represented by di Schiff bases (3-6) which then reacted with hetero dienes represented by diarylidine hydrazines (7,8) through Diels-Alder reaction to give the hetero adducts represented by substituted 1,2,4-triazine (9-20).

2-Experimental :-

Starting material and solvents were procured from Fluka,BDH and Aldrich companies and used without further purification. Melting points (M.P.) were measured on Electrothermal SMP30- Stuart melting point apparatus and were uncorrected. 1H-NMR spectra were recorded using Bruker Bio Spin GmbH Spectrophotometer (400 MHz by using TMS as internal standard and using DMSO-d6 as a solvent) in University of Gazi Othman Basha, Turkey, [s] singlet, (d) doublet, (m) multiplet]. Infrared (FT-IR) spectra were recorded using FT-IR Spectrophotometer, Shimadzu 8400s (Japan). Ultraviolet (U.V) spectra were performed on (Jasco V-630 UV–Vis) Spectrophotometer using methanol as a solvent. The Thin-layer chromatography (TLC) was carried out on an eastman chromatogram sheet (20x20) cm, 13181 silica gel with the fluorescent indicator (No. 6060) using solvent system benzene: methanol in the ratio (80:20).

Synthesis of 2,5-dimercabto-1,3,4-thiadiazole(1)(Salimon, Salih et al. 2010):

A solution of carbon disulphide (0.020 mole/15ml) with pyridine (5ml) was added drop wise with stirring to the ethanolic solution of hydrazine hydrate (80%) (0.020 mole/5ml) in (5ml) ethanol. The reaction mixture was then heated under reflux for (1 hour), cooled down and left overnight at lab. temp. then poured into crashed-ice water, acidify by hydrochloric acid to remove the excess of pyridine. The resulting product filtered off and followed by washing with water several times then recrystallized from ethanol to afford the compound (1), pale yellow powder with M.P.(163-165°C), yield (60%) and T.L.C. (Rf=0.785).

Synthesis of 2,5-dihydrazino-1,3,4-thiadiazole(2)(Salimon, Salih et al. 2010):

An ethanolic solution of (0.018 mole of hydrazine hydrate (80%)) with catalytic amount of tri ethylamine (3 drops) was added drop wise with stirring to the ethanolic solution of (0.01 mole/1.5gm) of compound (1), the reaction mixture was heated under reflux for (6 hrs), cooling and poured into crashed-ice water followed by acidify with hydrochloric acid. The resulting precipitate was filtered off and washed thoroughly with water followed by recrystallization from ethanol to afford compound (2), yellowish powder with M.P.(195-197°C), yield (58%) and T.L.C. (Rf=0.534). FT-IR(v cm⁻¹): NH₂(3210), NH(3124), C≡N(1480), C-N(1092) and C-S(855).

Synthesis of 2,5-diarylidine hydrazino-1,3,4-thiadiazole (3-6): (Sharma and Chow 2008)

A mixture of substituted benzaldehyde (0.001 mole) and compound (2) (0.005 mole.0.730g) in the presence of glacial acetic acid (3 drops) and ethanol (15 ml) was refluxed for (2 hrs), cooling and poured into crashed-ice water followed by filtration and washed thoroughly with cold water, and finally recrystallized from ethanol.
2,5-diphenyldiene hydrazino-1,3,4-thiadiazole (3): Brown, M.P. (79-81°C), yield (62%) and T.L.C.(Rf 0.651). FT-IR(ν cm⁻¹): NH 3052, C=N (acycl.) 1653, C=C 1624, C=N(cyclic)1574, C-O-C asym. 1447 & sym.1072, C-N 1211, N-N 1020 and C-S 856.

2,5-di(4-chloro phenyl) hydrazino-1,3,4-thiadiazole (4): Yellow, M.P.(213-215°C), yield (67%) and T.L.C.(Rf 0.493). FT-IR(ν cm⁻¹): NH 3050, C=N (acycl.) 1625, C=C 1618, C=N(cyclic) 1587, C-N 1294, N-N 1089, C-S 826 and C-S 816.

2,5-di(4-methoxy phenyl) hydrazino-1,3,4-thiadiazole(5): Yellow, M.P.(167-169 °C), Yield (84%) and T.L.C.(Rf 0.625). FT-IR(ν cm⁻¹): NH 3142, CH₃ asym. 2927 & sym. 2839, C=N (acycl.) 1618, C=C 1602, C=N(cyclic)1508, C-O-C asym. 1301 & sym.1109, C-N 1250, N-N 1026, C-S 833.

2,5-di(4-N,N-dimethyl amino phenyl) hydrazino-1,3,4-thiadiazole (6): Orange, M.P.(244-247 °C), Yield (74%) and T.L.C.(Rf 0.588). FT-IR(ν cm⁻¹): NH 3316, CH₃ asym. 2912 & sym. 2622, C=N (acycl.) 1653, C=C 1601, C=N(cyclic)1578, C-N 11171, N-N 1062, C-S 821.

Synthesis of diarylidine hydrazines (7&8): (Sharma and Chow 2008)

These compounds were prepared using a previously reported method, in the literature mentioned above and at room temperature.

Synthesis of (9-20): (Lenardao, Lara et al. 2007) Equimolare of compounds (3-6) and dibenzylidene hydrazine(7&8) were grinding for (30min) followed by irradiation in a microwave oven for suitable time at (720 watt). Cooling then cold water was added to the reaction mixture, and the solid product was then filtered off and recrystallized from ethanol. The completion of the reaction (as monitored by TLC).

N²,N²-di(5-phenyl-3,6-di(2,4-dimethoxyphenyl)-5,6-dihydro-1,2,4-triazine-4-yl) -1,3,4-thiadiazole (9): Irradiation time (15 minute), pale yellow M.P.(185-187°C), yield (90%) and T.L.C.(Rf=0.739). UV λmax (nm): 313& 390. FT-IR (ν cm⁻¹): NH 3078, CH₃ asym.2932& sym.2839, C=N 1624, N=N 1018, C-O-C asym. 1273 sym.1140 and C-S 754. ¹H-NMR (δ ppm): NH(s,2.51m2H), OCH₃(s,3.83OCH₃), phenyl(m,7.07-7.53m 5H), di OCH₃:phenyl( m,7.88-7.91,3H), triazine ( m,8.65-8.73,3H)

N²,N²-di(5-(p-chloro phenyl)-3,6-di(2,4-dimethoxy phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(10): Irradiation time (15 minute), off-white, M.P.(178-179 °C), yield (67%) and T.L.C.(Rf=0.729). UV λmax (nm): 302 & 388. FT-IR(ν cm⁻¹): NH 3416, CH₃ asym.2945& sym.2837 C=N 1610, N-N 1028, C-O-C asym.1269 & asym. 1028, C-S 824 and C-Cl 860

N²,N²-di(5-(p-methoxy phenyl)-3,6-di(2,4-dimethoxy phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole (11): Irradiation time (15 minute), brown, M.P.(179-181°C), yield (77%) and T.L.C.(Rf=0.833). UV λmax (nm): 287 & 397. FT-IR(ν cm⁻¹): NH 3406, CH₃ asym.2974 & sym.2839, C=N 1605, N-N 1161, C-O-C asym.1251 & sym. 1030 and C-S 826.

N²,N²-di(5-(p,N,N-dimethyl amino phenyl)-3,6-di(2,4-dimethoxy phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole (12): Irradiation time (2 minute), orange, M.P. (172-174°C), yield(86%) and T.L.C.(Rf=0.741). UV λmax (nm): 298 &410. FT-IR(ν cm⁻¹): NH 3466, CH₃ asym.2928. sym. 2839, C=N 1603, N-N 1018, C-O-C asym.1269 & sym. 1161 and C-S 812. ¹H-NMR (δ ppm): N(CH₃)₂ (s,3.00,4CH₃) , OCH₃ ( s,3.83,8OCH₃) , AB system p-N,N-di methyl(d,d,6.75-7.09,4H) , di OCH₃ phenyl (m,7.33-7.69)3H), triazine (m,8.50-8.64) 3H), NH(s,2.52,2H).

N²,N²-di(5-(p,N,N-dimethyl amino phenyl)-3,6-di(2,4-dimethoxy phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole (13): Irradiation time (5 minute), orange,M.P. (180-182°C), yield (88%) and T.L.C.(Rf=0.690). UV λmax (nm): 291 &381. FT-IR(ν cm⁻¹): NH 3416, CH₃ asym.2918 & sym. 2866, C=N 1605, N-N 1177, C-O-C asym.1368 & sym. 1067 and C-S 814.
N\textsuperscript{2},N\textsuperscript{3}-di(5-(p-chloro phenyl)-3,6-di(p-N,N-dimethyl amino phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(14): Irradiation time (15 minute), green, M.P.(212-214°C), yield(73%) and T.L.C.(R\textsubscript{f}=0.755). UV \( \lambda_{\text{max}} \) (nm): 395 & 412. FT-IR(\nu cm\textsuperscript{-1}): NH 3428, CH\textsubscript{s} asym.2913& sym. 2855, C=N 1601, N=N 1177, C-O-C asym.1366 & sym. 1087, C-S 814 and C-C 1143).

N\textsuperscript{2},N\textsuperscript{3}-di(5-(p-methoxy phenyl)-3,6-di(p-N,N-dimethyl amino phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole (15): Irradiation time (15 minute), green, M.P.(222-225°C), yield (68%) and T.L.C.(R\textsubscript{f}=0.811). UV \( \lambda_{\text{max}} \) (nm): 397 & 421. FT-IR(\nu cm\textsuperscript{-1}): NH 3428, CH\textsubscript{s} asym.2913& sym. 2857, C=N 1601, N=N 1177, C-O-C asym. 1364 & sym. 1026 and C-S 814. 1\textsuperscript{H}-NMR (\delta ppm): N(CH\textsubscript{3})\textsubscript{2} (s,3.00,8CH\textsubscript{3}) ,OCH\textsubscript{3}(s,3.93,2OCH\textsubscript{3}) , AB system p-N,N-di methyl (d-d,6.76-7.07,4H) , AB system p-OCH\textsubscript{3}(d-d,7.64-7.84,4H) , triazine (m,8.50-8.62,2H) , NH(s,2.60,2H).

N\textsuperscript{2},N\textsuperscript{3}-di(5- ( p-N,N-dimethyl amino phenyl)-3,6-di(p-N,N-dimethyl amino phenyl) -5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole (16): Irradiation time (2 minute), deep yellow, M.P.(265\textdegree C), yield(95%) and T.L.C.(R\textsubscript{f}= 0.800). UV \( \lambda_{\text{max}} \) (nm): 318 & 378. FT-IR(\nu cm\textsuperscript{-1}): NH 3472, CH\textsubscript{s} asym. 2913& sym. 2857, C=N 1601, N=N 1177 and C-S 814.

N\textsuperscript{2},N\textsuperscript{3}-di(5-( phenyl-3,6-di(o-chloro phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(17): Irradiation time (15minute), yellow, M.P.(73-75\textdegree C), yield (89%) and T.L.C.(R\textsubscript{f}=0.590). UV \( \lambda_{\text{max}} \) (nm): 318 & 378. FT-IR(\nu cm\textsuperscript{-1}): NH 3472, C=N 1616, N=N 1049, C-S 858 and C-C 750.

N\textsuperscript{2},N\textsuperscript{3}-di(5-(p-chloro phenyl)-3,6-di(o-chloro phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(18): Irradiation time (15minute), yellow M.P.(140-141\textdegree C), yield(84%) and T.L.C.(R\textsubscript{f}=0.811). UV \( \lambda_{\text{max}} \) (nm): 289 & 381. FT-IR(\nu cm\textsuperscript{-1}): NH 3482, C=N 1618, N=N 1088, C-S 821 and C-Cl 750. 1\textsuperscript{H}-NMR (\delta ppm): NH(s,3.24,2H), AB system p-Cl(d-d, 7.88-8.17,4H) , o-Cl phenyl( m,7.46-7.61,4H) , triazine ( m,8.68-8.96,3H).

N\textsuperscript{2},N\textsuperscript{3}-di(5-(p-methoxy phenyl)-3,6-di(o-chloro phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(19): Irradiation time (15minute), brown, M.P.(111-112\textdegree C), yield (44%) and T.L.C.(R\textsubscript{f}=0.692). UV \( \lambda_{\text{max}} \) (nm): 311 & 389. FT-IR(\nu cm\textsuperscript{-1}): NH 3482, CH\textsubscript{s} asym.2938& sym.2837, C=N 1605, N=N 1167, C-O-C asym.1254 & sym. 1026, C-S 831 and C-Cl 752.

N\textsuperscript{2},N\textsuperscript{3}-di(5-( p-N,N-dimethyl amino phenyl)-3,6-di(o-chloro phenyl)-5,6-dihydro-1,2,4-triazine-4-yl)-1,3,4-thiadiazole(20): Irradiation time (15minute), brown, M.P.(149-151\textdegree C), yield(65%)and T.L.C.(R\textsubscript{f}=0.821). UV \( \lambda_{\text{max}} \) (nm): 325 & 385. FT-IR(\nu cm\textsuperscript{-1}): NH 3462, CH\textsubscript{s} asym.2920& sym. 2855, C=N 1603, N=N 1175, C-O-C asym.1366 & sym.1049, C-S 816 and C-Cl 752.

3-Results and discussion

It was found that the hetero dienophile must be prepared firstly although the reaction between 2,5-dihydrazino -1,3,4-thiadiazole and substituted benzaldehyde in acidic media in ratio (1:2) under reflux condition for (2 hrs) , whereas the hetero diene prepared at room temperature with stirring between hydrazine hydrate and substituted benzaldehyde in ratio (1:2) these two starting materials hetero diene and dienophile were undergoes Diels-Alder reaction via grinding and MWI technique as summarized in the following Scheme:
Scheme (1): Synthetic pathway for substituted 1,2,4-triazine derivatives
Firstly, Schiff bases prepared through condensation reaction in acidic media. The structure of Schiff bases (3-6) were established on the bases of their spectroscopic data, they show in FT-IR spectroscopy stretching vibration bands at (1653-1618 cm\(^{-1}\)) due to the C≡N functional group and stretching vibration band at (3316-3050 cm\(^{-1}\)) due to the only NH functional group. Actually these Schiff bases were underwent Diels-Alder reaction with hetero dienes (7,8) under grinding for (30min) and then free-Solvent MWI with power (720 watt) at specific time to offered the hetero adducts (9-20) through one step intercyclization reaction, as shown in Scheme (1). The structure of these adducts were illustrated on the bases of their spectroscopic data, so, they gave in UV spectra two type of electronic transitions at (287-397) and at (378-421) due to the π→π* and n→π* respectively. Whereas in FT-IR spectra an absorption bands of (1177-1018 cm\(^{-1}\)) were appeared and also this due to the cyclic (N=N) functional group additionally to the other absorption bands which listed in the experimental part. The disappearance of the (C≡N) for Schiff bases and the appearance of the (N=N) absorption bands gave clear evidence of the desired products. On the other hand, in \(^1\)H-NMR spectra the compounds (9,12,15 & 18) shown characteristic signals as mentioned in experimental part, all these compounds shown NH-thiadiazole and 1,2,4-triazine protons additionally to the other absorption peaks which came in agreement with suggested structures.
4-Conclusion

In this presentation we prepared Schiff bases which utilized as a hetero dienophile and diarylidine hydrazine which utilized as a hetero diene which then used to prepare the aza Diels-Alder products (cyclo hetero adducts) and also it was successfully accomplished under green chemistry solvent free approaches firstly by grinding and then by MWI technique. This method reducing the reaction time and gave a high purity product.

References