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Microwave Assisted Organic Synthesis (MWAOS) of a series of Dihydroquinazolinones and Dihydrocinnolinols.

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ABSTRACT

The present study concentrates on the synthesis of a series of dihydroquinazolinones and dihydrocinnolinols by applying the green concept Microwave Assisted Organic Synthesis (MWAOS) with high atom economy and the effect of substituents on deciding the product. A series of phenyl substituted 2-(phenylmethylidene) amino phenols are coupled with isatoic anhydride using a Microwave oven. A systematic computational study was conducted in designing and modelling the products and the reaction conditions. The practical application of artificial intelligence in designing the reactions was successfully tested and implemented.

Keyword: Solvent free synthesis; Microwave Assisted Organic Synthesis (MWAOS); isatoic anhydride; 2-(phenylmethylidene) amino phenols.

INTRODUCTION

The synthesis has charming beauty in the field of organic chemistry and especially attracted the interests of scientists. The field of organic synthesis is undergoing swift development through different novel methods for synthesising organic compounds of interest by the introduction of computers and computer assisted designing. The effective use of artificial intelligence in designing the molecules and the routes to achieve the target molecules in the shortest and economic pathways are the theme of modern research [1, 2]. The Microwave assisted organic synthesis has revolutionized the field of organic synthesis and particularly revolutionized the field of drug synthesis that can be achieved in a fraction of time when compared to the conventional method [3].

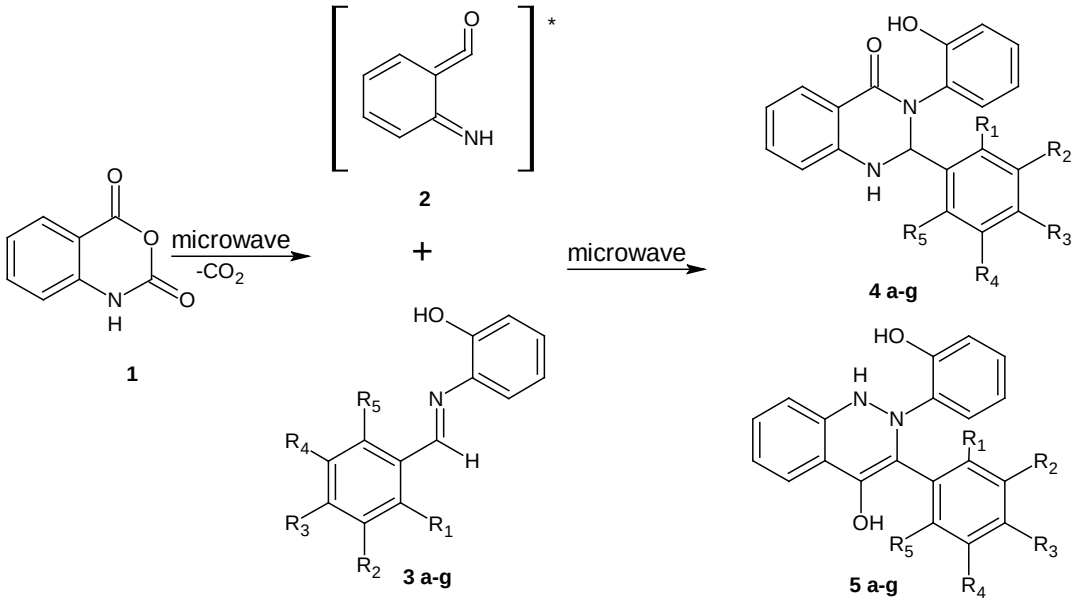
The first reported Diels Alder reaction in 1931 was a perfect green one as the inventors used the most popular green solvent water[4,5].The usual traditional conditions for Diels Alder type reactions need refluxing for nearly 90 min but the aid of microwaves it has been achieved in a fraction of minutes. Many microwave assisted Diels Alder type reactions were also found reported with solvents like DMF, diglyme and even in water and is even the theme of modern research [6,7]. But recent microwave assisted synthesis in many cases adopts the concept of solvent free synthesis. If a solvent is needed much care is to be given while selecting the apt solvent for Microwave Assisted Organic Synthesis (MWAOS). Most organic reactions requiring heat and have been heated using traditional heat transfer equipment such as oil baths, sand baths or heating mantles. These techniques are rather slow and create a temperature gradient within the sample. Moreover, the hot surface of the reaction vessel may result in localized overheating leading to product, substrate and reagent decomposition when heated for prolonged periods. In contrast, when using microwave dielectric heating (the theory behind Microwave heating) the energy is introduced into the chemical reactor remotely and there is no direct contact between the energy source and the reaction mixture [8]. Microwave radiation passes through the walls of the vessel heating the contents directly by taking advantage of the ability of some liquids and solids to transform electromagnetic radiation into heat. The present study concentrates on the synthesis of quinazolinones by applying the green concept Microwave Assisted Organic Synthesis (MWAOS).

Many of the quinazolinones have medicinal applications and are well known as choleretic and antidiabetic agents that traditionally prepared using anthranilic acid and thionyl chloride in dry benzene [9, 10, 11]. The most possible defect of MWAOS is the explosion due to overheating but which can be effectively controlled by handling the oven professionally.

Experimental section

The essential designing and modelling of the proposed molecules were achieved using available leading software ArgusLab. The HOMO-LUMO interactions were studied

believing that the HOMO and LUMO electrons are involved in the Diels Alder reactions. The conditions for systematic laboratory synthesis were carefully studied using available computational methods and finally developed a novel concept. The chemicals (Isatoic anhydride and solvents) used for the synthesis were purchased from Merck and used as such. Azomethines were prepared according to the reported procedures and recrystallized from methanol [12]. IR spectra were recorded on a Schimadzu instrument and the absorbencies were reported in cm -1. The NMR spectra were recorded in Bruker 400MHz FT-NMR spectrometer using CDCl3 as solvent. CHN analysis was carried out in a Perkin Elmer CHNS-analyzer. The reaction was monitored using Thin Layer Chromatography and visualized using UV-chamber. Microwave reactions were performed on a domestic oven of Samsung make where 10Sec intervals of heating time controller which can be even stopped in a fraction of 1Sec in between if needed. The equipment has a power source of 220V, 50Hz and microwave energy output 850W. A series of dihydroquinazolones were prepared as per the Scheme 1. An equimolar mixture of isatoic anhydride and corresponding azamethine were powdered together in a mortar and transferred in to 50mL beaker of Schott Duran make. The mixture was then microwave irradiated without solvent for 120-540Sec at a temperature of 65-70^{0}C (may not be accurate as measured outside the oven) and the molten mass was worked up as reported [13].



Scheme 1

Compound	R	Yield (%)
3a, 4a, 5a	R1=R2=R3=R4=R5=H	95
3b, 4b, 5b	R1=OH; R2=R3=R4=R5=H	90
3c, 4c, 5c	R1=H; R2=OH; R3=R4=R5=H	85
3d, 4d, 5d	R1=R2=H; R3=OH; R4=R5=H	92
3e, 4e, 5e	R1=NO_2; R2=R3=R4=R5=H	95
3f, 4f, 5f	R1=H; R2=NO_2; R3=R4=R5=H	85
3g, 4g, 5g	R1=H; R2=OH; R3=O-CH_3; R4=R5=H	78

Characterization

The characterizations were done using instruments like IR-spectrometer, CHN-analyzer and ^{1}HNMR. The structures were conformed based on obtained spectral data. The colour varies from light orange to dark red as the colour of azomethines. The products 4a, 4c and 4d & 5b, 5e, 5f and 5g were found formed.

4a) Spectral data for 3-(2-hydroxyphenyl) -2-phenyl-2, 3-dihydroquinazolin-4(1H)-one:

IR (KBr, cm^{-1}) 3450 (OH str) 3350 (NH str), 1648 (C=O str), 1512, 1485, 1391, 1310, 1256, 1162, 1034, 872, 751, 703,629, 548.

Elemental Analysis Calculated for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86%. Found: C, 78.04; H, 5.00; N, 9.01%.

4c) Spectral data* for *3-(2-hydroxyphenyl)-2-(3 -hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one:
IR (KBr, cm^{-1}) 3340 (broad NH str, OH), 1645 (C=O str), 1520, 1246, 1165, 1035, 856, 754, 713, 568.

Elemental Analysis Calculated for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%. Found: C, 74.00; H, 4.58; N, 8.62%.

4d) Spectral data for 3-(2-hydroxyphenyl)-2-(4-hydroxyphenyl)- 2,3-dihydroquinazolin-4(1H)-one:
IR (KBr, cm^{-1}) 3380(broad OH str), 3328 (broad NH str, OH), 1638 (C=O str), 1512, 1246, 1156, 1045, 855, 756, 710, 555.

Elemental Analysis Calculated for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%. Found: C, 74.00; H, 4.58; N, 8.52%.

5b) Spectral data for 2,3-bis(2-hydroxyphenyl)-1,2-dihydrocinnolin-4-ol:
IR (KBr, cm^{-1}) 3332 (broad NH str, OH), 1743(weak), 1590(Sharp with shoulder C=Cstr, enolic), 1501, 1455, 1286, 1232, 1162, 899, 755, 676, 634, 570, 459.

Elemental Analysis Calculated for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43%. Found: C, 74.20; H, 4.62; N, 8.60%.

5e) Spectral data for 2-(2-hydroxyphenyl)-3-(2-nitrophenyl)-1,2-dihydrocinnolin-4-ol:
IR (KBr, cm^{-1}) 3560(OH str) 3290 (NH str), 1645 (Sharp with shoulder C=C str), 1534-1454 (NO_2), 1392, 1312, 1256, 1168, 1028, 872, 751, 718, 548.

Elemental Analysis Calculated for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63%. Found: C, 67.26; H, 4.28; N, 12.17%.

5f) Spectral data for 2-(2-hydroxyphenyl)-3-(3-nitrophenyl)-1,2-dihydrocinnolin-4-ol:
IR (KBr, cm^{-1}) 3629 (OH str), 3298 (NH str), 1648 (Sharp with shoulder C=C str), 1526-1448 (NO_2), 1382, 1338, 1246, 1164, 1038, 872, 754, 700, 560.

Elemental Analysis Calculated for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63%. Found: C, 67.26; H, 4.28; N, 12.17%.

5g) Spectral data for 3-(3-hydroxy-4-methoxyphenyl)-2-(2-hydroxyphenyl)-1,2-dihydrocinnolin-4-ol:
IR (KBr, cm^{-1}) 3565 (OH), 3295 (NH str), 1645 (Sharp with shoulder C=C str), 1512, 1392, 1302, 1265, 1038, 874, 754, 708, 556.

Elemental Analysis Calculated for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%. Found: C, 69.26; H, 4.98; N, 8.17%.

^{1}HNR (δ, ppm) Data: The ^{1}HNR were recorded in $CDCl_3$ as solvent and D_2O as clearing and clarifying solvent. The compounds 4a, 4c and 4d showed O**H** singlets in between 5.30 to 5.00 and N**H** broad singlets in between 4.20 to 4.00 and no peaks were observed beyond 12.00. The peaks were found D_2O exchangeable. The compounds 5b, 5e, 5f and 5g also showed O**H** singlets in between 5.30- 5.00 and N**H** broad singlets between 4.20- 4.00. The characteristic O**H** and N**H** singlet peaks were found D_2O exchangeable along with peaks observed between 13.20 and 13.00 in compounds 5b, 5e, 5f and 5g. The characteristic deshielded aromatic protons were also observed between 6.70 and 8.40 (δ, ppm).

RESULTS AND DISCUSSION

The computational studies of many reported cyclo addition reactions based on their HOMO-LUMO interactions lead to a new concept (Distribution of Active Electrons) that helped in designing and modelling the reaction conditions. The predicted nature of the products and reaction conditions were found supportive and helpful in laboratory synthesis. This research supports the formation of substituted quinasolinon products by the in situ Diels Alder addition of isatoic anhydride with azomethines applying the concept of MWAOS. The method adopted gave a better yield (75-90%) in a lesser time interval (less than 180Sec) than the traditional method. The possible mechanism may be the following one represented in **scheme 1** in which the isatoic anhydride **1** forms an unisolable hetero diene **2** when exposed to microwave and azomethine **3a-g** as dienophile.

The present study reveals that substituents on the either part of the azomethines have considerable effect on the product formation as also evident from computational studies. The NMR-data of the characteristic proton C**H** was expected as a doublet but found to be a singlet and N**H** is found as a broad singlet. The proton from C**H** was not found to be shifted to the C=O to make its enol form C-O**H**. This was supported by the D_2O exchange data in 4**a**, 4**c** **&** 4**d** where only the N**H** and other phenolic O**H** were found vanished. Enolic O**H** peaks were clearly observed in between 13.20 to 13.00 in compounds 5**b**, 5**e**, 5**f** **&**5**g** that were found D_2O exchangeable along with the N**H** and other phenolic O**H**. The characteristic enolic C=C stretching observed in compounds 5**b**, 5**e**, 5**f** **&**5**g** in the recorded IR-spectra was in support to the formation of enols. These results were found in acceptance with the outcomes of computational studies. The time taken for the reaction to occur in microwave conditions varies as the difference in visual

colour change of the reaction medium. This clearly supports the effect of substituents at the aldehydic part of the azomethines. The theoretical bases of the designing and the predictions of the plausible products were in accordance to the developed concept called Distribution of Active Electrons.

CONCLUSION

The microwave assisted organic synthesis of a series of compounds (ketones and enoles) was achieved in short time duration with good yield and better atom economy. The process was successfully achieved with the substituted N-(phenylmethylidene) aminophenols at the phenyl group. The computational and theoretical studies lead to an entirely new concept termed Distribution of Active Electrons. The present studies of designing the reactions were based on those theoretical bases and they even helped to predict the feasibility of the reaction. The present study clearly reveals the importance of substituents on the either part of the azomethines on the product formation.

REFERENCES

1. M. Kaushal, R.S.Dehal, A.Kaur, Overview of Artificial Intelligence, World of Computer Science and Information Technology Journal (WCSIT), 1(4) (2011) 157-161.
2. M.A.Hussain, C.R.C. Hassan, K.S.Loh, K.W. Mah, Application of Artificial Intelligence Techniques in Process Fault Diagnosis, Journal of Engineering Science and Technology, 2(3) (2007) 260-270.
3. F. Mavandadi, Ake Pilotti, The impact of microwave-assisted organic synthesis in drug discovery, Drug Discovery Today, 11(3-4) (2006) 165-174.
4. O. Diels, K. Alder, Synthesen in der hydroaromatichen Reihe. XII. Mitteilung, Liebigs, Annalen der Chemie, 490(1) (1931) 243-257.
5. R. Woodward, H.Baer, The reaction of furan with maleic anhydride, Journal of the American Chemical Society, 70(3) (1948) 1161-1166.
6. M. Wiessler, W.Waldeck, C.Kliem, R. Pipkorn, K. Braun, The Diels-Alder-Reaction with inverse- Electron-Demand, a very efficient versatile Click-Reaction Concept for proper ligation of variable molecular Partners, International Journal of Medical Sciences, 7(1) (2010) 19-28.
7. G.V.R. Sharma, A.R. Robert, Synthetic Strategies to Quinazolinones, IJPBC, 1(3) (2012) 2277-4688.
8. D. Stuerga, Microwave- Material Interactions and Dielectric Properties, Key Ingredients for Mastery of Chemical Microwave Processses-Microwaves in Organic Synthesis, 2nd Edn, A.Loupy, Wiley VCH, Weinheim, 2006.
9. T.L. Levien, D.E. Baker, New Drugs in Development for the Treatment of Diabetes, Diabetes Spectrum, 22(2) (2009) 92-106.
10. Y.A. Ammar, Synthesis of Some Biologically Active 4(3H0-Quinazolinones Derived from 2, 3-Pyridine dicarboxylic anhydride, Chemical Sciences Journal, (2011) 1-10.
11. R. Arora, N.S. Gill, A. Kapoor, Synthesis of Quinazolinone Based Schiff Bases as Potential Anti-inflammatory and Analgesic Agents, Journal of Pharmacy and Allied Health Sciences, (2012) 1-9.
12. B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell, Vogel's text book of practical organic chemistry, ELBS, London, 1980.
13. Abhilash Mullasseril, Substituent Effects on Solvent Free Synthesis (MWAOS) of Dihydroquinazolinones by the Addition of Isatoic Anhydride to a series of Phenyl Substituted N-(Phenylmethylidene) Anilines, Journal of Chemistry, (2013) 1-4.