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Efficient continuous flow-synthesis of novel spiro-naphthalene-1,2'-[1,3,4]oxadiazol-4-ones

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Abstract

The highly efficient cycloaddition reaction of hydrazonyl chlorides with 2,3-dichloro-1,4-naphthoquinone yielded pharmaceutically important spiro-naphthalene-1,2'-[1,3,4]oxadiazol-4-ones with moderate to good yields under batch and flow synthesis methods. The obtained products were elucidated by IR, ^{1}H NMR, ^{13}C NMR, HRMS and single crystal X-ray diffraction technique (only for **6h**). The synthesized molecules have been subjected to theoretical analysis by quantum chemical calculations at B3LYP/6-31G(d,p) level, which provided supporting data for the experimental findings.

Keywords

naphthoquinones; flow chemistry; batch chemistry; cycloaddition reaction; spiran 1,3,4-oxadiazole, DFT, and X-ray diffraction.

Introduction

The synthesis of organic molecules has been achieved via traditional techniques **[1]** for centuries. However, new methods including microwave, mechanochemistry, ball milling, flow chemistry, and electrochemical synthesis, etc. have gained much interest in organic synthesis **[2-6]**. The advantages of flow chemistry **[7,8]** over conventional methods range from easy scaling up, advanced control of reaction conditions such as heat, flow rate, pressure, managing hazardous wastes and reagents, full recovery of unreacted reagents. Additionally, it also has fewer side impurities and is a greener approach

to synthesis as compared to traditional wet lab chemistry and industrial synthesis. In laminar flow conditions, mixing occurs by diffusion and since diffusion time is proportional to distance squared, therefore over short distances, diffusion is fast and reproducible.

The cycloaddition reaction of 1,3-dipoles with dipolarophiles such as unsaturated double or triple bonds to form five-membered heterocycles is a convergent and convenient route in batch chemistry. However, the application and comparison of this chemistry to flow systems is rare. **[9-14]** Pan et al research on CuACC demonstrated a significant transformation in a continuous-flow system vs the batch process in terms of of productivity, scale-up, reproducibility and safety synthesis (some of which are crucial in the preparation of pharmaceutical products). Hetero-spiro compounds are molecules with two or more rings sharing one atom and containing non-carbon atom(s). Over the years, due to their biological activities, they have gained recognition among chemists. Good examples of heterospiro compounds are MI-888 and NITD609, which are presently at preclinical evaluation for the treatment of human cancer (tumor) and malaria, respectively. **[15-18]**

1,3,4-oxadiazole containing molecules have also attracted significant attention in the field of drug discovery for decades due to their broad spectra of biological activities such as antifungal**[19]**, antibacterial**[20]**, analgesic**[21]**, anti-inflammatory**[22]**, antitumor**[23]**, anticonvulsant and muscle-relaxing activities**[24]**. The synthesis and biological evaluation of novel 1,3,4-oxadiazole derivatives has been accelerated in the last two decades. **[25]** In recent studies, 1,3,4-oxadiazoles can be obtained by direct annulation of hydrazides with methyl ketones**[26]**, the oxidative reaction of hydrazides with alkenes or alkynes in the presence of iodine followed by cyclization and deacylation**[27]**, cationic Fe(III)/TEMPO-catalyzed oxidative cyclization of aroyl hydrazones in the presence of oxygen**[28]**, using a catalytic quantity of $Cu(OTf)_2$ an imine C-H functionalization of N-arylidenearoylhydrazide**[29]**, condensation of semicarbazide/ thiosemicarbazide with aldehydes followed by I_2-mediated oxidative C-O/C-S bond formation. **[30]**.

Despite the biological and pharmaceutical interest of many chemists on the synthesis of 1,3,4-oxadiazoles, there are no studies to date on the preparation of cycloaddition reaction of hydrazonyl chlorides to naphthoquinones which produce spiro-1,3,4-oxadiazoles with better yields via flow chemistry with respect to batch chemistry. The reason might be the reagent streams are continuously pumped into the flow reactor where mixing and reacting occur in there, therefore, producing a cleaner target molecule. The efficiency and reproducibility of flow chemistry for the synthesis of spiro-1,3,4-oxadiazoles is reported in this study.

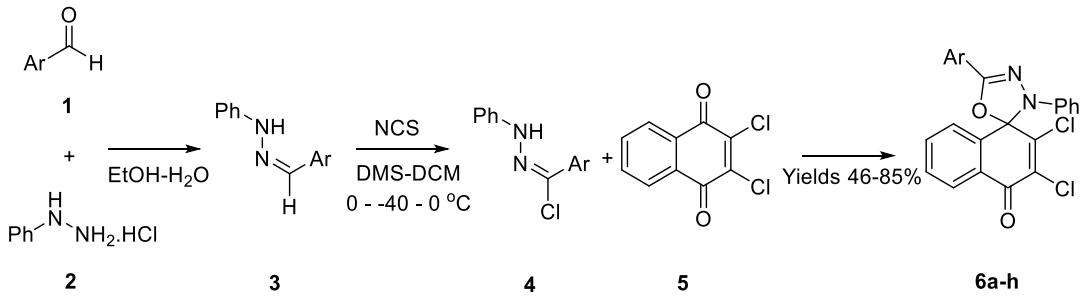
Results and Discussion

The hydrazonyl chlorides **(4a-h)** were prepared according to literature methods. **[31]** The synthesis of the desired products 5'-aryl-2,3-dichloro-3'-phenyl-2,3-dihydro-3'H,4H-spiro[naphthalene-1,2'-

[1,3,4]oxadiazol]-4-ones **(6a-h)** as accomplished *via* batch and flow chemistry. In the batch process, compounds **(6a-h)** were achieved by reacting an equimolar concentration of 2,3-dichloro-1,4-naphthoquinones **(5)** and hydrazonyl chlorides **(4a-h)** in the presence of 2 equivalent Et_3N in MeCN, precipitates were formed, solvents were decanted, then solids washed with water and MeCN respectively. Comparatively, compounds **(6a-h)** were obtained under flow chemistry conditions when the solution of reactants passes through cartridge packed with a base and the collected reaction mixtures in their respective solvents, which were subsequently evaporated and recrystallized from MeCN.

IR spectra of obtained compounds **6a-h** showed C=O stretching vibration from 1672-1682 cm^{-1}. Furthermore, C=N and ArC-H stretching vibrations could be seen from 1592-1601 cm^{-1} and 3026-3071 cm^{-1} respectively. ^1H NMR results for compounds **6a-h**, signals of all protons reported are at the aromatic regions except for **6h** with a methyl group at the para position with a singlet showed a signal at 2.48 ppm. N-phenyl protons signals in compounds **6a-h** were observed at 6.63-7.19 ppm. Additionally, ^{13}C NMR for carbonyl and quaternary carbon signals were observed at 174.9-175.4 ppm and 94.8-96.5 ppm respectively. The cyano- carbon signal on compound **6d** was observed at 118 ppm. All four fluorine to carbon coupling in the ^{13}C spectrum of **6g** were observed. All carbon and proton signals were matching with suggested molecules and are all reported in the supporting material section.

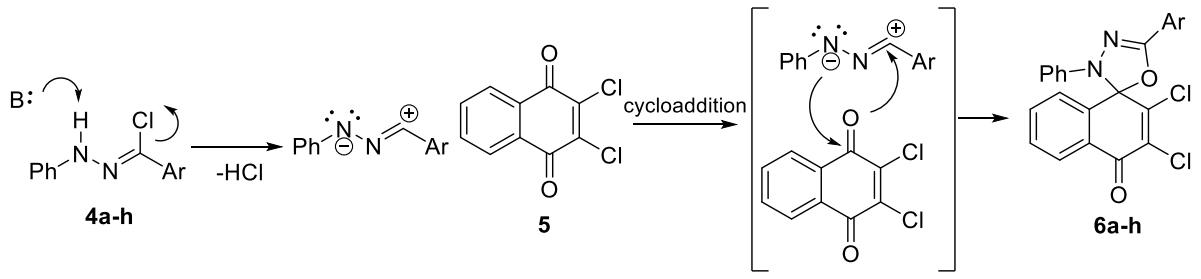
Table 1: General reaction scheme for **6a-h**



Entry	Ar	Compound	Flow rate (mL/min)**	Base*/**	Pressure (bar)**	Temperature (°C)*/**	Solvent */**	Yield (%)*/**
1	4-ClC_6H_4	6a	0.1	$Et_3N/NaHCO_3$	10	25/80	MeCN/EtOAc	58/85
2	4-BrC_6H_4	6b	0.1	Et_3N/Et_3N	10	25/80	MeCN/MeCN	46/82
3	4-$NO_2C_6H_4$	6c	0.5	Et_3N/Al_2O_3	10	25/80	MeCN/MeCN	68/74
4	4-CNC_6H_4	6d	0.3	Et_3N/ K_2CO_3	10	25/80	MeCN/EtOAc	53/79
5	2,4-diClC_6H_3	6e	0.3	Et_3N/K_2CO_3	10	25/80	MeCN/MeCN	67/80
6	2,6-diClC_6H_3	6f	0.2	Et_3N/Na_2CO_3	10	25/80	MeCN/MeCN	66/76
7	4-FC_6H_4	6g	0.3	Et_3N/K_2CO_3	10	25/80	MeCN/MeCN	60/78
8	4-MeC_6H_4	6h	0.5	Et_3N/Na_2CO_3	10	25/80	MeCN/MeCN	65/84

* Conventional Method, ** Flow Chemistry and Ar: Aromatic

Table 1 shows a summarized overall view on the formation and comparison of **6a-h** molecules preparation via batch vs flow chemistry. In batch chemistry, compounds **6a-h** were similarly synthesized with identical base and solvent, while certain optimization was required under flow chemistry such as the utilization of different flow rates, bases and solvents. Improved yields were observed in flow chemistry, all synthesized compounds were obtained in moderate to good yields.



Scheme 2: A proposed reaction mechanisms for compounds **6a-h**

One of the plausible pathways to the novel compounds **6a-h** has been proposed in Scheme 2. Firstly, a base deprotonates hydrazonyl chloride resulting into the nitrile imine, following cycloaddition to one of the carbonyl on a napthaquinone. Attempts to use two or three equivalence of hydrazonyl chlorides did not furnish two-sided cycloaddition product due to electron demand on the napthaquinone after cycloaddition may not be sufficient for another nitrilimine cyclization.

Additionally, as depicted in Fig. 1A, the solid state structure of compound **6h** were unambiguously elucidated by single-crystal X-ray analysis in order to gain more insights into the molecular structure. The 1,3,4-oxadiazole ring adopting an envelope conformation is nearly perpendicular to the adjacent 2,3-dichloro-4-oxo-naphthalene moiety with an dihedral angle (θ) of 86.67°. The major intermolecular interactions are identified as non-classical C─H···Cl (C24···Cl1 = 3.566 Å, C17···Cl2 = 3.696 Å) and C─H···O (C1···O2 = 3.570 Å) hydrogen bonding interactions (Fig. 1B and 1C). In addition, short Cl2···N2 (3.245(2) Å < r_{vdw}(Cl) + r_{vdw}(N) = 3.30 Å) contacts also link two molecules along the *a*-axis. Furthermore, moderate intermolecular π···π aromatic interactions (3.844 Å, Fig. 1D) between the aromatic ring along the b-axis contributed to the stabilization of 3D supramolecular network (Fig. 1E).

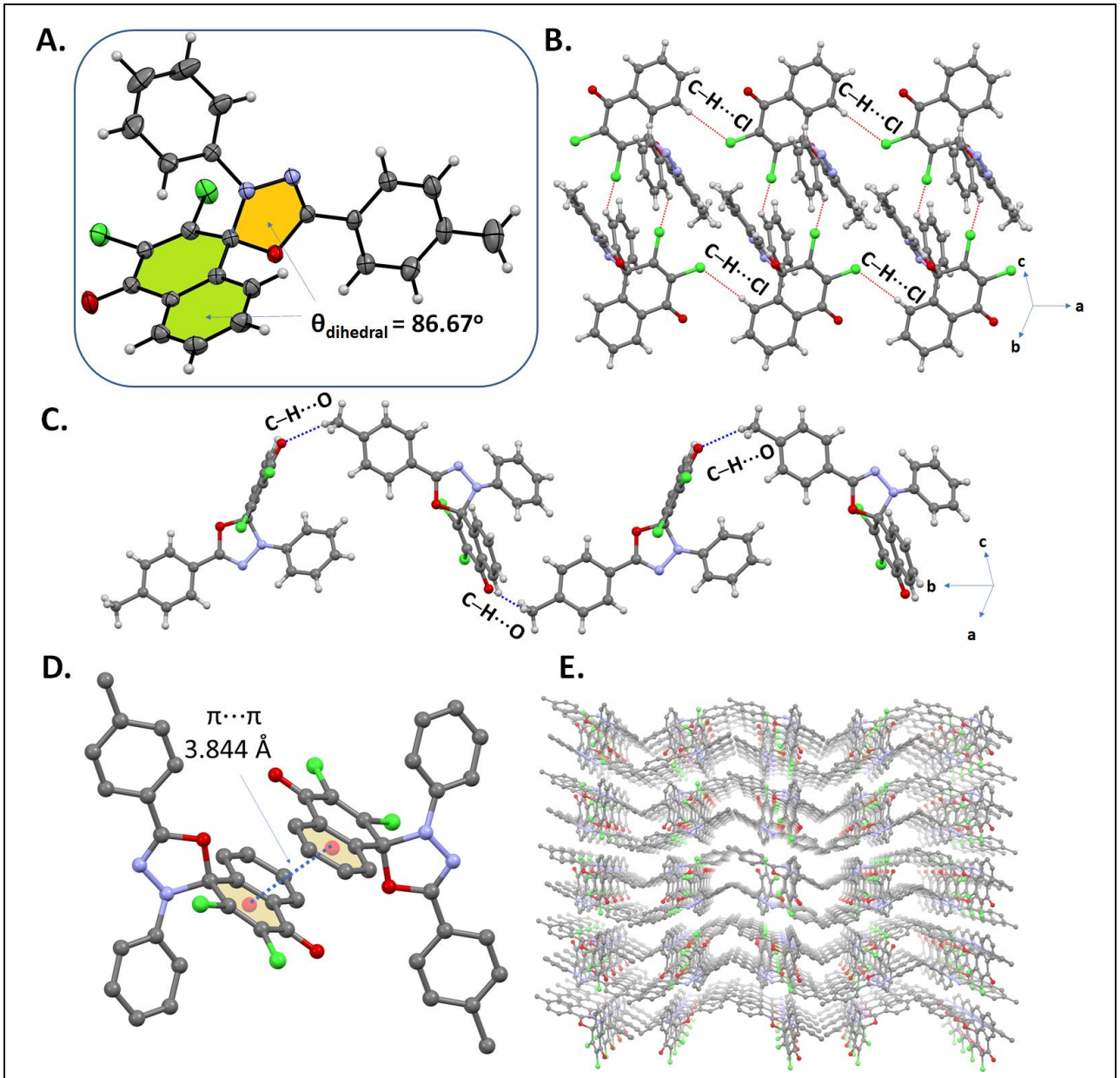


Figure 1. (A) Crystal structures of compound **6h** with displacement ellipsoids (30% probability level) showing the perspective view of inter-ring dihedral angle between 1,3,4-oxadiazole ring (gold coloured) and naphthalene moiety (lime green). (B) A view of classical intermolecular CH···Cl (red dotted lines along the *a*-axis). (C) A view of CH···O (blue dotted lines along the *b*-axis) intermolecular hydrogen bonding interactions (D) Perspective view of intermolecular π···π stacking interactions. (E) Illustration of three-dimensional crystal network of **6h** viewed down the *c*-axis.

Structural Optimization

All calculations were performed using ORCA**[32]** code. The initial coordinates in ground state were optimized using density functional theory (DFT) at B3LYP level with def2-TZVP basis sets. To get the minimum energy structure, a tight SCF method was used for all the calculations. The structure

of the molecule was visualized with VESTA**[33]**. **Figure 2** represent the optimized structure of **6h,** while figures **of 6a-g** optimized structures can be found in supporting information.

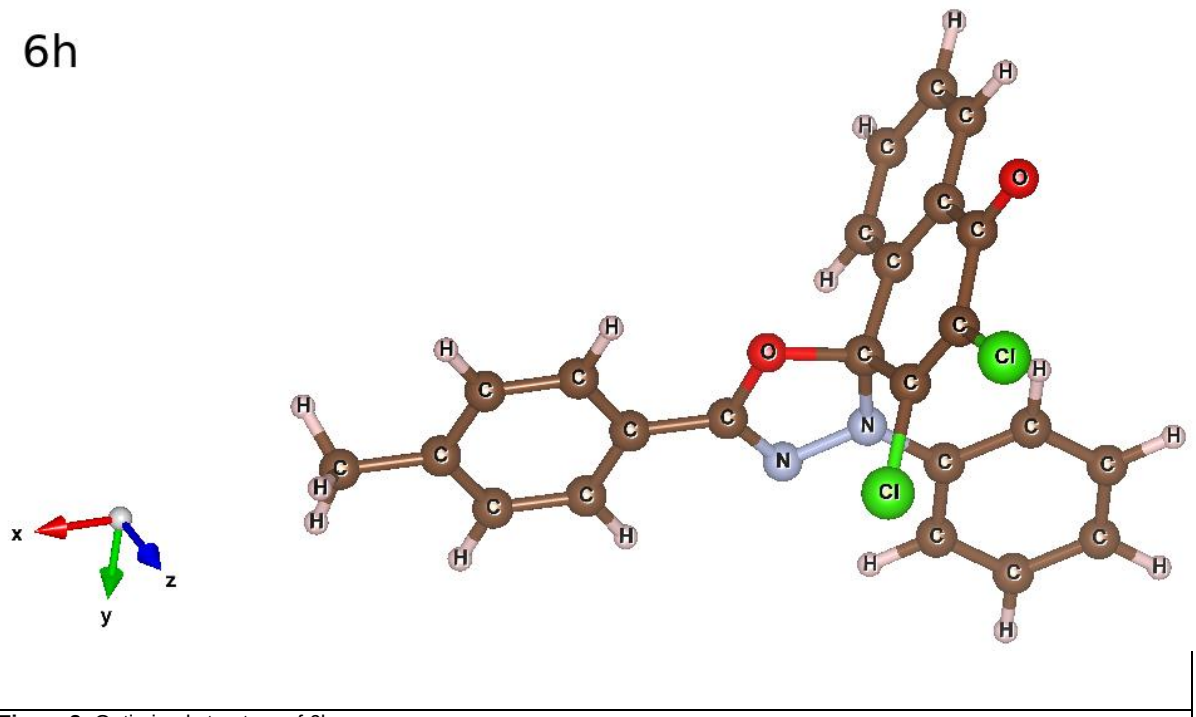


Figure 2: Optimized structure of 6h.

The structural parameters for **6h** calculated were compared with the parameters of structure obtained from single crystal X-ray analysis as summarized in Table 1. The calculated bond lengths and angles were well matched with experimental data. The difference between experimental and calculated data were found to be less than 2.17% and 2.15% within the acceptable limit for bond length and bond angle calculations, which confirm the structure is well optimized and energetically in most stable coordinates for the atoms are obtained.

Table 1: Some selected experimental and calculated bond lengths and bond angles for **6h**.

Bond	**Bond Length (Å)**	
	Experiment	**Calculation**
N-N	1.4068	1.3769
C'-O (bridge)	1.3866	1.3869
C"-O (bridge)	1.4354	1.4573
C-O (carbonyl)	1.2214	1.2252
Bonds	**Bond Angle (Degree)**	
O-C-O	107.0293	107.1516
N-N-C'	106.3280	106.7342
N-N-C"	108.7904	111.1869

Electronic structure

In the electronic structure calculations, Mulliken charge analysis, dipole moment and charge density were calculated and given in **Table 2**. Contribution of the atoms to total charge density were decided by using these results.

Table 2: Mulliken atomic charges for **6h**.

0 C : -0.175983	10 Cl: -0.021402	20 N : 0.093936	30 H : 0.129837	40 H : 0.111114
1 C : -0.007304	11 Cl: -0.030665	21 C : -0.166939	31 C : -0.075149	41 H : 0.153906
2 C : -0.037818	12 O : -0.262805	22 C : 0.174829	32 C : -0.197073	42 C : -0.387265
3 C : -0.139716	13 O : -0.296285	23 C : -0.164626	33 C : 0.143659	43 H : 0.119771
4 C : -0.089692	14 H : 0.139011	24 C : -0.173728	34 C : -0.122894	44 H : 0.129391
5 C : -0.110013	15 H : 0.139733	25 C : -0.016724	35 C : -0.100014	45 H : 0.130248
6 C : 0.425524	16 H : 0.119082	26 C : -0.193844	36 C : -0.236337	
7 C : -0.031366	17 H : 0.118889	27 H : 0.107744	37 H : 0.109924	
8 C : 0.067013	18 C : 0.287016	28 H : 0.108285	38 H : 0.122208	
9 C : 0.142342	19 N : -0.274079	29 H : 0.129494	39 H : 0.108766	

Calculated dipole moments for all the structures are given in Table 3, and as shown in the table, all the structures have net dipole moment so, vibrational properties can be calculated

Table 3: Dipole moment in x,y and z directions for **6a-h.**

Structure	x	y	z
6a	-0.36262	0.36273	-1.12640
6b	-0.42293	0.34542	-1.10538
6c	-2.28749	-0.04620	-0.48388
6d	-2.01521	0.01998	-0.58273
6e	-0.39644	0.73115	-1.23165
6f	0.68775	0.72414	-1.40276
6g	-0.19945	0.38836	-1.17590
6h	0.61818	0.55052	-1.43814

Vibrational calculations

The vibrational properties of the compound and obtained IR modes and frequencies were calculated herein. There was not any negative frequency for any compound so, this indicates that all structures are well optimized and at minimum energy state. Since our basis set (def2-TZVP) underestimates frequency values, it is needed to use correction factor. For def2-TZVP, correction factor**[34]** is used to be taken as 1.0377.

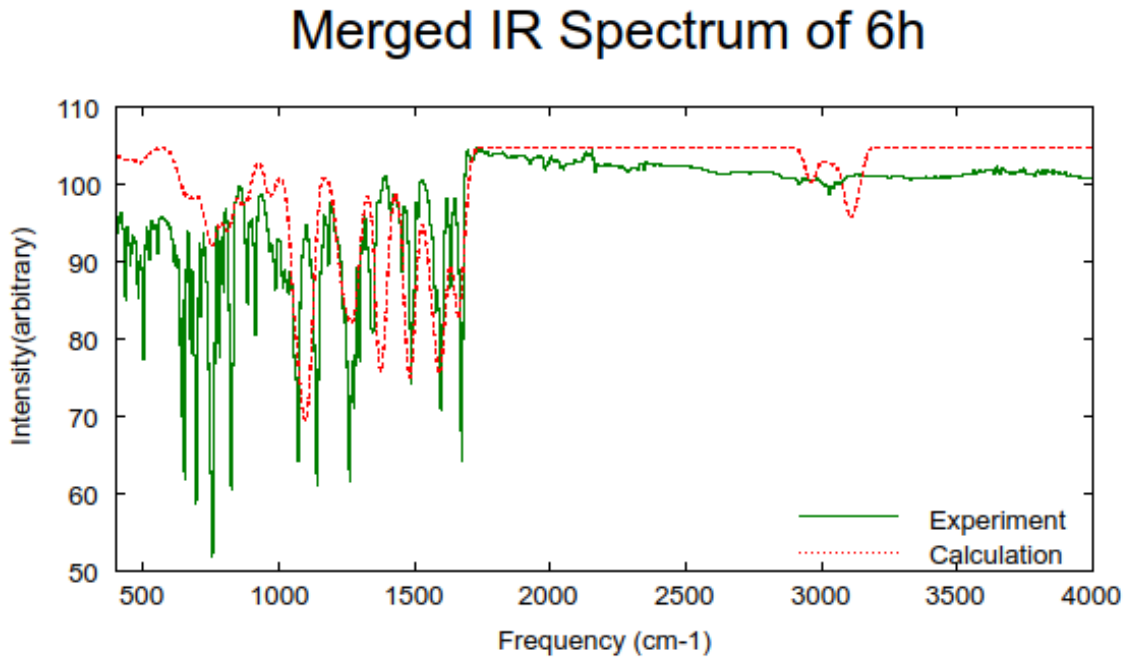


Figure 3: The calculated (red dashed) IR spectrum plot for 6h given along with the experimental (green) spectrum. These results shows good similarity with the experimental spectrum, which supports that, our calculations are in very good agreement with the experiment at characteristic vibrations. More of this merged IR results are given in supporting information.

Conclusions

In summary, we have compared the yield, bond angle and length of synthesized spiro-naphthalene-1,2'-[1,3,4]oxadiazol-4-ones both under batch and flow methods, with full provided characterization by IR, ^{1}H NMR, ^{13}C NMR, HRMS, single crystal X-Ray diffraction and DFT. The use of the flow method turned out to be beneficial both for simplicity and efficiency in terms of improved yields and product purity.

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