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(Diacetoxyiodo)Benzene Mediated Copper (II) Triflate Catalyzed Synthesis of Oxazole

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Research Scholars

Rashtrasant Tukadoji Maharaj Nagpur University (RTMNU), Nagpur Abstract:

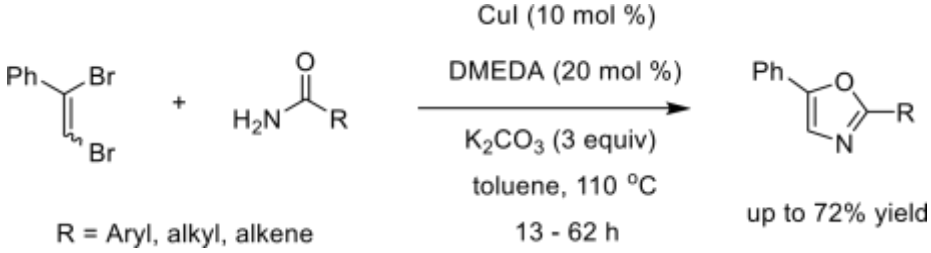
Oxazole ring system is present in many naturally found biologically active organic compound. Due to its immense importance, it is necessary to develop new methods for the synthesis of this compound. Therefore, in this article we are reporting new method for the synthesis of oxazole. In this method enamide is treated with (diacetoxyiodo)benzene in presence of copper(II) triflate catalyst to afford oxazole in excellent yield. Easily prepared starting material, commercially available reagent, short reaction time and mild reaction condition are the advantages of this method.

Keywords:

Oxazole, (diacetoxyiodo)benzene, copper(II) triflate, enamide, heterocyclic compound **Introduction:**

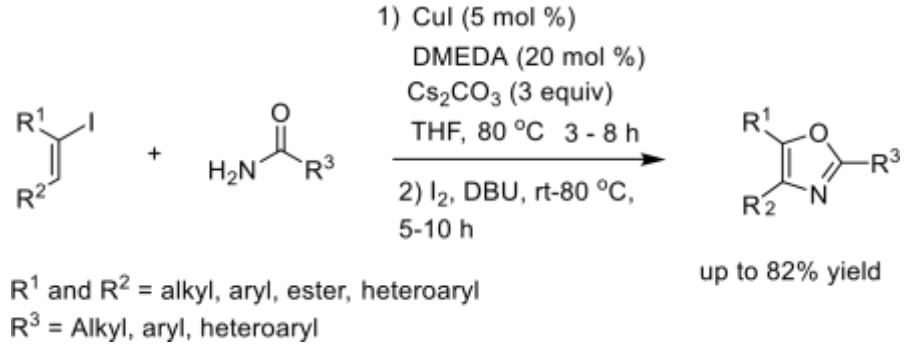
Oxazole is the core structural unit in many naturally found biologically active organic compound.[1] They show various pharmacological activity like antifungal, antiviral, antileukemia, antibacterial, and enzyme inhibitory activities.[2] Some trisubstituted and 2,5-disubstituted oxazoles have been proved to show antidiabetic activity.[3] Due to its immense importance, it is necessary to discover some alternative way for the synthesis of oxazole.

In literature there are number of methods for the synthesis of oxazole. In 2007 Glorius et al reacted different primary amides with 1,2-dibromophenylethylene in presence copper(I) iodide to afford oxazole in good yield.[4]



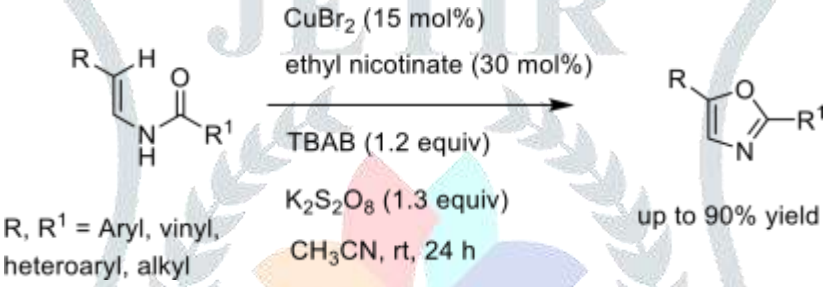
Scheme. 1: Synthesis of oxazole from primary amides and 1,2-dibromophenylethylene

Later in the same year Buchwald et al developed method for the synthesis of highly substituted oxazoles by a Cu-catalyzed amidation of vinyl halides followed by intramolecular cyclization promoted by iodine.[5]



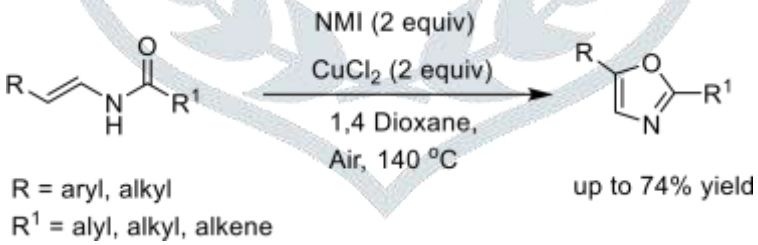
Scheme. 2: Cu-catalyzed amidation of vinyl halides followed by intramolecular cyclization

In 2012 same group reported Room Temperature Copper(II)-Catalyzed Oxidative Cyclization through Vinylic C−H Functionalization of Enamides for the synthesis of 2,5-Disubstituted Oxazoles at room temperature.[6]



Scheme. 3: Copper(II)-Catalyzed Oxidative Cyclization through Vinylic C−H Functionalization of Enamides

In the same year stahl group reported copper(II)-mediated oxidative cyclization of enamides in presence of N-methyl imidazole in 1,4 dioxane for the synthesis of 2,5-disubstituted oxazoles.[7]

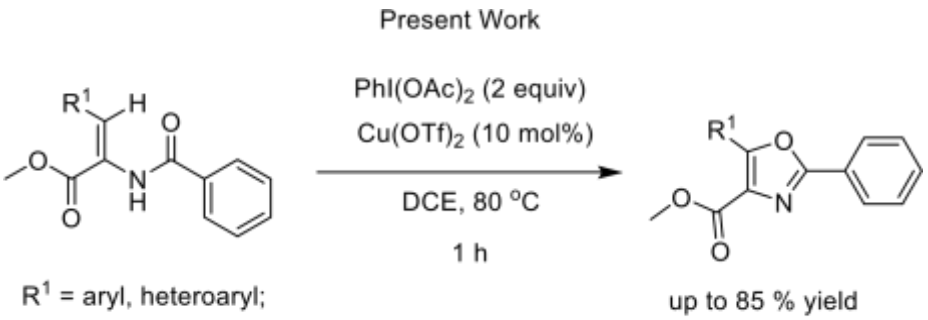


Scheme. 4: copper(II)-mediated oxidative cyclization of enamides

In the same year zhao et al reported oxidative cyclization of enamide by using (diacetoxyiodo)benzene and boron trifluoride etherate under reflux condition in DCE.[8]

Scheme. 5: oxidative cyclization of enamide by using (diacetoxyiodo)benzene and boron trifluoride etherate

In this article we reported Oxidative cyclization of enamide by using (diacetoxyiodo)benzene and catalytic amount of copper(II) triflate.

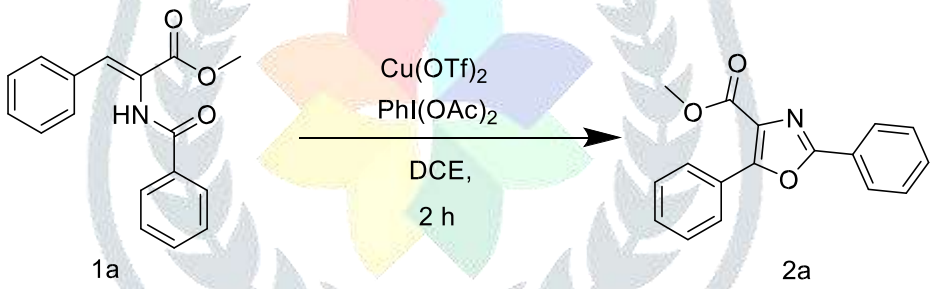


Scheme. 6: Present work

Result and discussion:

At first, we are trying the synthesis of indole from imidazole by using stochiometric amount of copper(II) triflet as a catalyst along with 2 equivalents of (Diacetoxyiodo)Benzene in dichloroethane as a solvent. But it was found that instead of indole we were getting oxazole in this reaction. Then we tried to optimize the reaction condition under different condition (table 1). At first, we were used stoichiometric amount of copper(II) triflet. In later experiment we reduced the stoichiometry of copper (II) triflet to catalytic amount and we found that reaction is equally efficient with catalytic amount of copper (II) triflet.

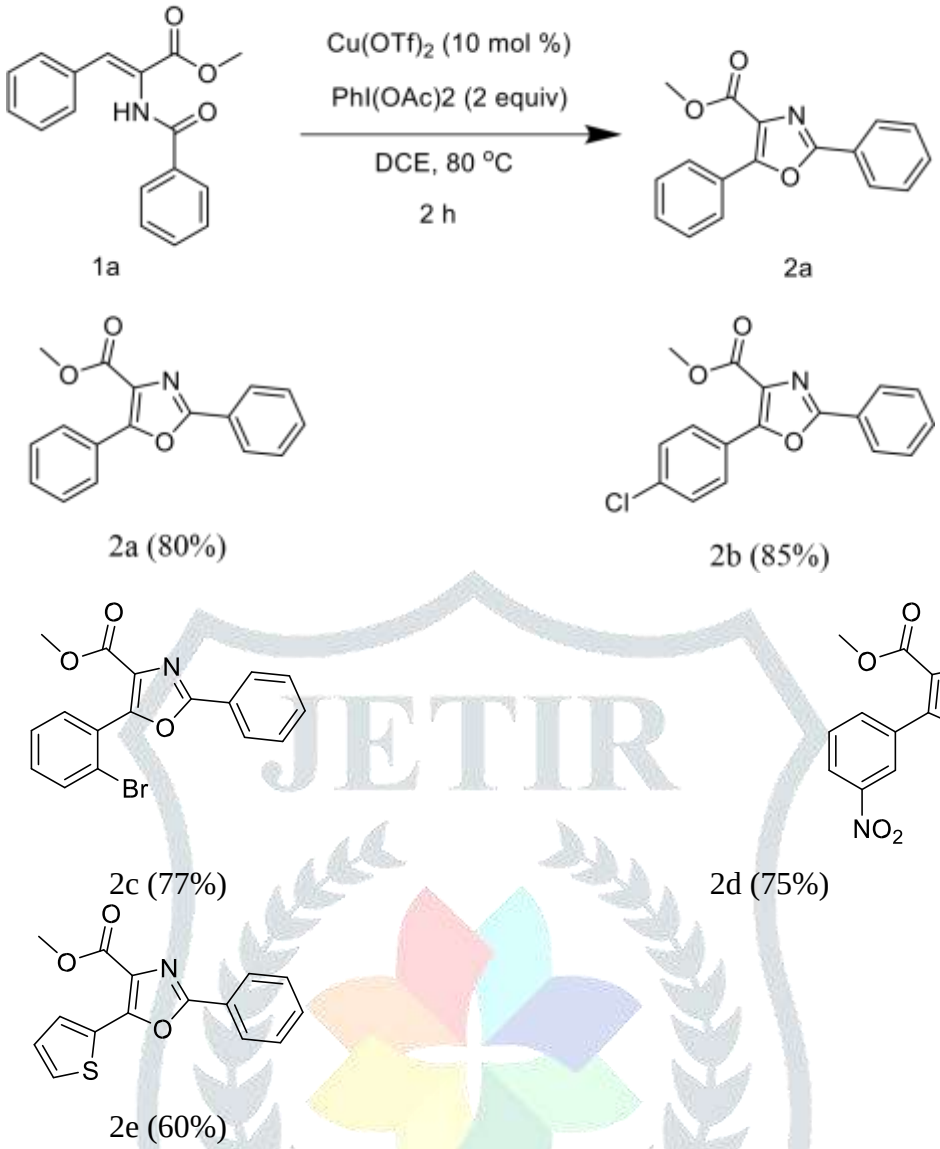
Table. 1: Optimization of reaction condition



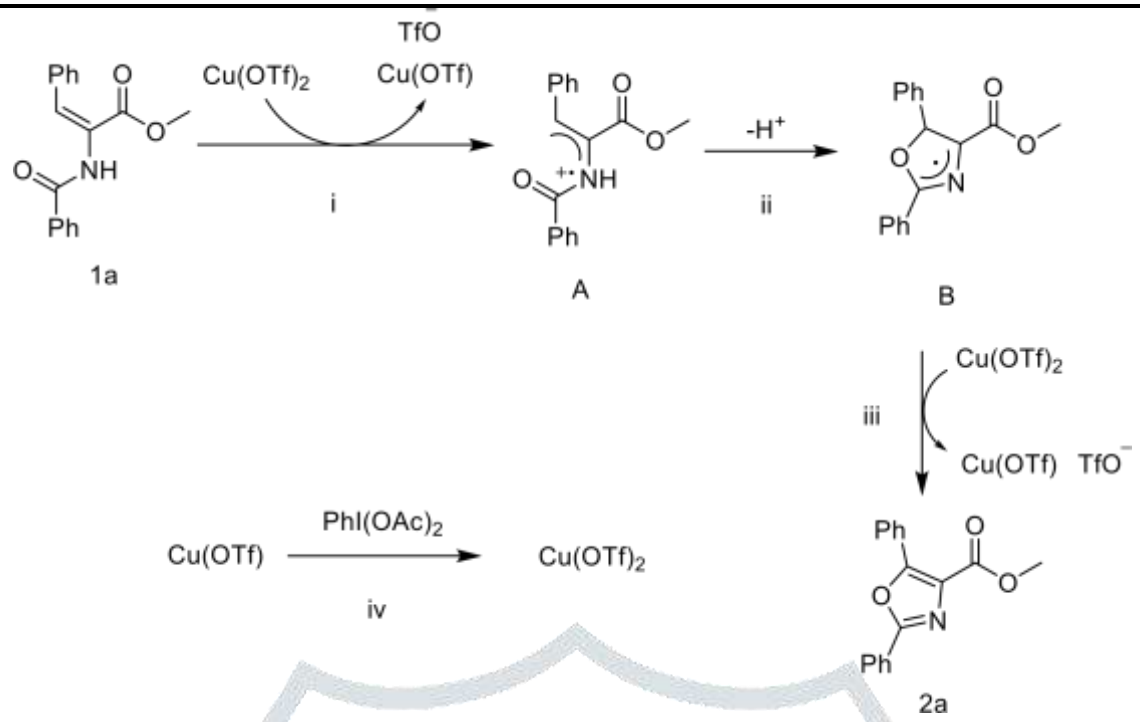
Entry	Reagent	Catalyst	Temperature	Yield %
1	$PhI(OAc)_2$ (1 equiv)	$Cu(OTf)_2$ (1 equiv)	80 °C	80
2	$PhI(OAc)_2$ (2 equiv)	$Cu(OTf)_2$ (0.3 equiv)	80 °C	85%
3	**$PhI(OAc)_2$ (2 equiv)**	**$Cu(OTf)_2$ (0.1 equiv)**	**80 °C**	**85%**
4	$PhI(OAc)_2$ (2 equiv)	$Cu(OTf)_2$ (0.1 equiv)	rt	trace

Then we checked substrate scope for this rection. Electron rich as well as electron deficient enamides are smoothly converted in to the corresponding oxazole in good yield. Heterocyclic enamides are also transformed in to corresponding oxazole.

Table. 2: Substrate scope of reaction



Plausible reaction mechanism for this reaction is similar to the mechanism proposed by Buchwald group in 2012 for the similar transformation.[6] This mechanism can be explained as at first copper(II) triflate removes one electron from enamide to afford radical cation A. This radical cation A undergo deprotonation to give free radical intermediate B. Then second molecule of copper(II) triflate will take one electron from intermediate B followed by deprotonation of this intermediate will give title product (2a). Then the reduced copper(I) triflet was oxidized to copper(II) triflet by the (Diacetoxyiodo)Benzene regenerating the catalyst to carry out second catalytic cycle.



Scheme. 7: Plausible mechanism of oxazole formation from enamides **Material and method:**

All reactions were done in oven-dried glassware. All commercially available reagents were used as it is without further purification. All the reactions were monitored by thin-layer chromatography (TLC) were visualized by a UV lamp; product was purified by using silica gel column chromatography. ^{1} H/^{13}C NMR spectra were recorded on Bruker Advance Neo 500 MHz spectrometers at 500/125 MHz, respectively, in CDCl3 and Dimethyl Sulphoxide-d6 unless otherwise stated, using TMS as internal standard. Unit of chemical shifts are ppm (parts per million). Mass spectra were obtained from shimadzu LCMS-8040 by electrospray ionization time-of-flight (ESI-TOF) mass spectrometry. Melting points were determined using Thiele's tube. Column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) and petroleum ether (PE) as mobile phase.

General procedure for Synthesis of 2,4,5-Trisubstituted Oxazoles(2a-2e): In 100 ml round bottom flask enamide (compound 1a) (300 mg, 1.07 mmol, 1 equiv) was dissolved in 1,2-dichloro ethane (5 mL) and copper(II) triflate (38 mg, 0.10 mmol, 0.1equiv) was added. To this mixture (Diacetoxyiodo)Benzene (687 mg, 2.13 mmol, 2 equiv) was added. The reaction mixture was heated at 80 ^{o}C for 2 h. Reaction completion was monitored by using TLC plate. After the reaction completion rection mixture was cooled to room temperature and then quenched water. The resulting mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced

pressure. The resulting crude product is purified by silica gel column chromatography using mobile phase petroleum ether & ethyl acetate (13:1) affording pure title compound (238 mg, 80%)

Methyl 2,5-diphenyloxazole-4-carboxylate (2a): White solid; mp 77-79 ºC yield: 238 mg, 80 % (ethyl acetate/petroleum ether = 1/13); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm) = 8.17 - 8.13 (m, 4H), 7.51 - 7.47 (m, 6H), 3.98 (s, 3H); ^{13}C NMR (126 MHz, CDCl3, 300 K) δ (ppm) = 162.7, 159.8, 155.3, 131.2, 130.4, 128.9, 128.9, 128.5, 127.9, 127.0, 126.9, 126.3, 52.4; IR: 2922, 2850, 1710, 1559, 1485, 1442, 1212, 1094, 765, 678 cm^{-1}.[8]

Methyl 5-(4-chlorophenyl)-2-phenyloxazole-4-carboxylate (2b): White solid; mp 130-132 ºC; yield: 238 mg, 85 % (ethyl acetate/petroleum ether = 1/12); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm) = 8.16 - 8.13 (m, 4H), 7.52 - 7.47 (m, 5H), 3.99 (s, 3H); ^{13}C NMR (126 MHz, CDCl3, 300 K) δ (ppm) = 162.8, 160.1, 154.3, 136.6, 131.5, 129.9, 129.0, 129.0, 128.4, 127.0, 126.3, 125.6, 52.7, 29.8; IR: 2948, 1712, 1588, 1560, 1483, 1215, 1086, 1006, 833, 781, 706, 688 cm^{-1} HRMS (ESI): m/z calcd for- $[C_{17}H_{12}ClO_3N+Na]^+$: - 336.0398, found: - 336.0386.

Methyl 5-(2-bromophenyl)-2-phenyloxazole-4-carboxylate (2c): White solid; mp 134-136 ºC yield: 238 mg, 77 % (ethyl acetate/petroleum ether = 1/13); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm) = 8.17-8.14 (m, 2H), 7.73 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.59 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.51 - 7.46 (m, 3H), 7.44 (dd, *J* = 2.9, 8.3 Hz, 1H), 7.38 (dt, *J* = 1.8, 8.1 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 300 K) δ (ppm) = 161.9, 161.1, 154.0, 133.2, 132.5, 131.8, 131.3, 130.4, 129.0, 128.9, 127.1, 127.0, 126.4, 123.8, 52.3; IR: 2920, 1717, 1625, 1428, 1207, 1000, 755, 675 cm^{-1}.

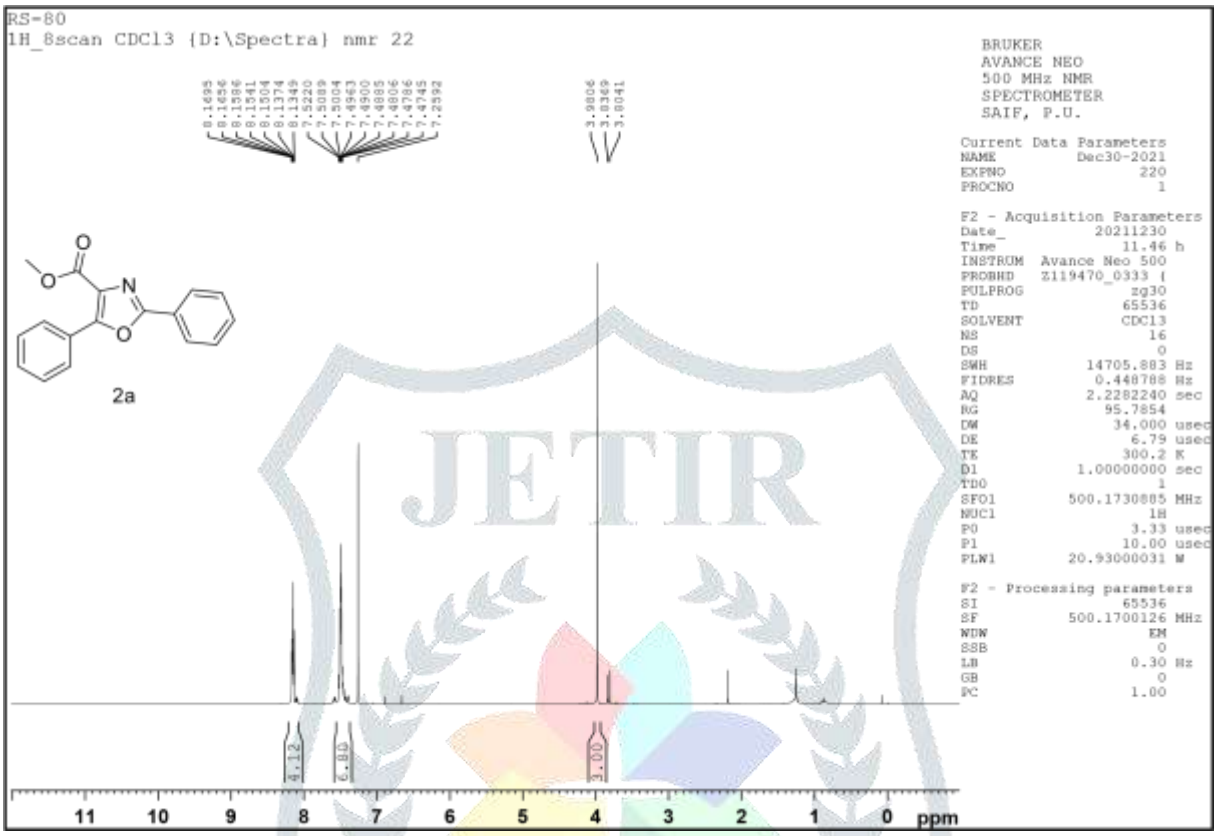
Methyl 5-(3-nitrophenyl)-2-phenyloxazole-4-carboxylate (2d): White solid; mp 172-174 ºC yield: 229 mg, 75 % (ethyl acetate/petroleum ether = 1/11); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm) = 9.07 (t, *J* = 1.9 Hz, 1H), 8.57 (td, *J* = 1.2, 8.1 Hz, 1H), 8.32 (ddd, *J* = 1.0, 2.2, 8.2 Hz, 1H), 8.20 - 8.15 (m, *J* = 6.7 Hz, 2H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.56 - 7.50 (m, 3H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ (ppm) = 162.4, 160.7, 152.4, 148.4, 134.0, 131.7, 129.7, 129.7, 129.0, 128.5, 127.1, 125.8, 124.7, 123.3, 52.8; IR: 3103, 1714, 1525, 1346, 1236, 1103, 1023, 803, 700 cm^{-1} HRMS (ESI): m/z calcd for- $[C_{17}H_{12}N_2O_5+H]^+$: - 325.0819, found: - 325.0812.

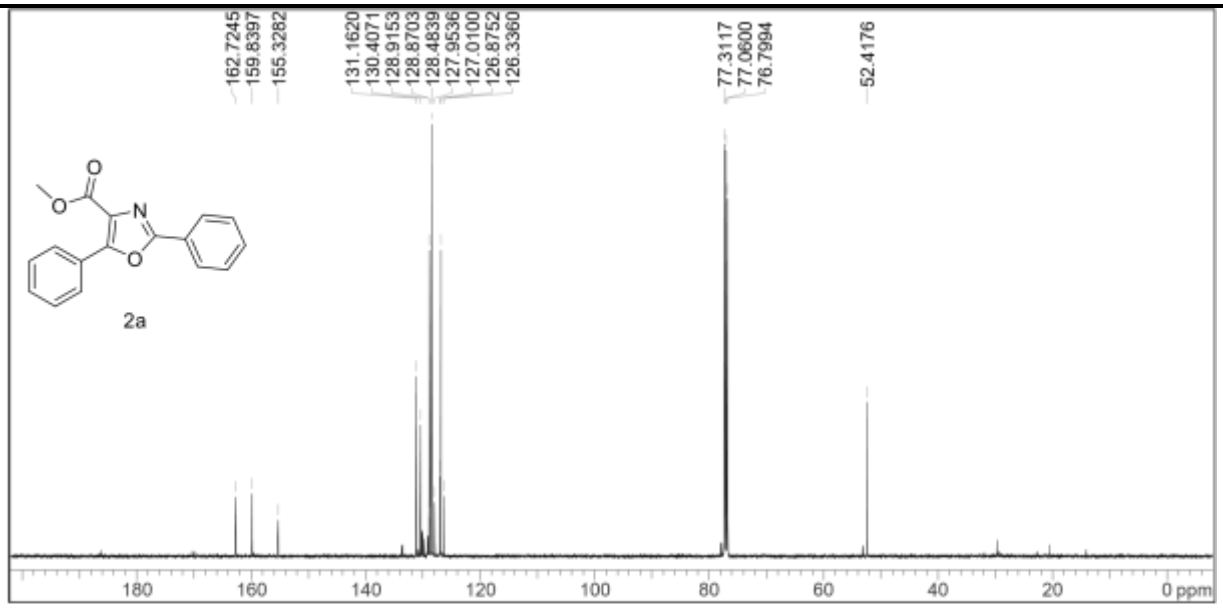
Methyl 2-phenyl-5-(thiophen-2-yl) oxazole-4-carboxylate (2e): White Solid; mp 125-127 ºC; yield: 261 mg, 60 % (ethyl acetate/petroleum ether = 1/19); ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm) = 8.16 - 8.13 (m, 3H), 7.56 (dd, *J* = 1.2, 5.0 Hz, 1H), 7.51 - 7.47 (m, 3H), 7.19 (dd, *J* = 3.8, 4.9 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ (ppm) = 162.6, 159.0, 151.2, 131.2, 130.3, 129.7, 128.9, 128.5, 127.8, 126.9, 126.1, 52.4; IR: 2944, 1702, 1613, 1577, 1487, 1440, 1239, 1203, 1092, 1052, 779, 735, 703 cm^{-1}; LCMS (ESI): m/z calcd for- $[C_{15}H_{11}NO_3S+H]^+$: 286, found: 286.

[1] H and ^{13}C NMR spectra of synthesized compounds

Conclusion:

We successfully developed simple one-pot protocol for the synthesis of oxazole. Easily prepared precursor, commercially available reagent and catalyst, short reaction time, mild reaction condition and excellent yield are the advantages of our protocol.

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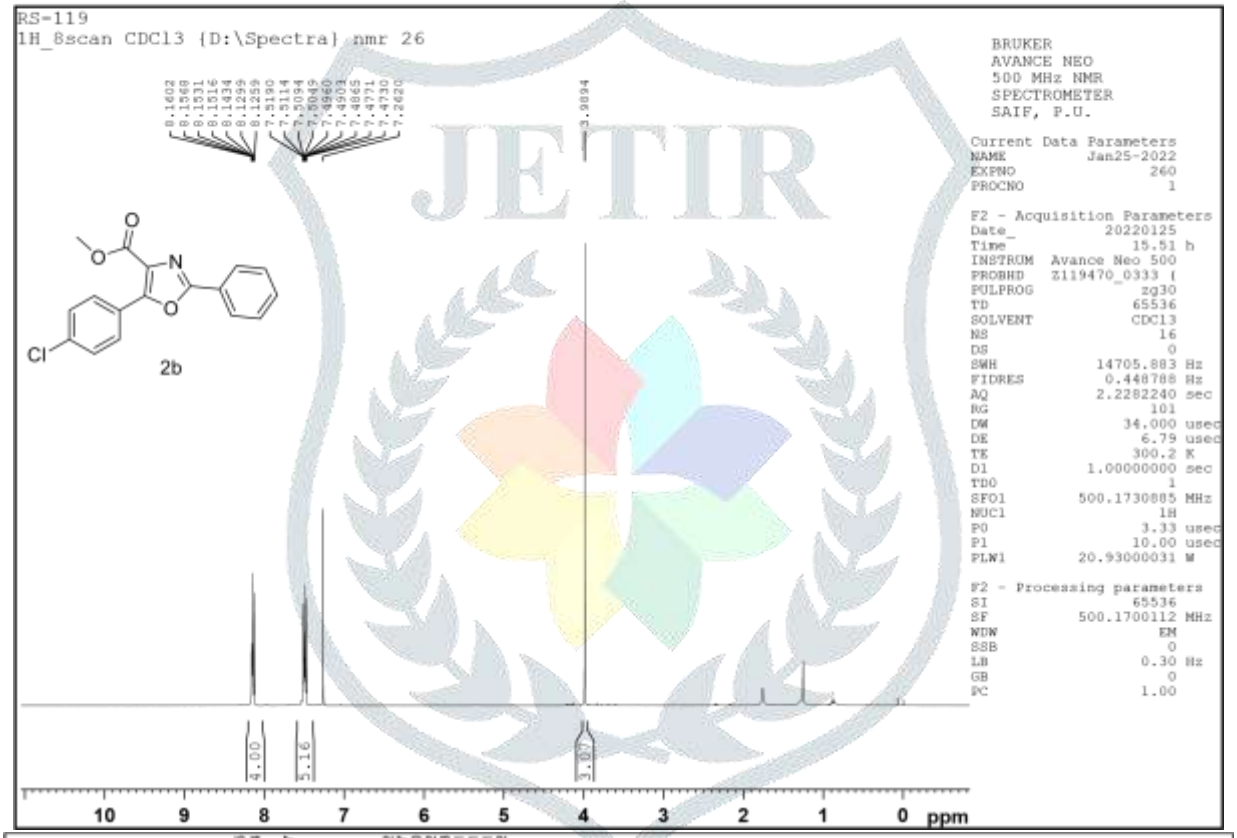
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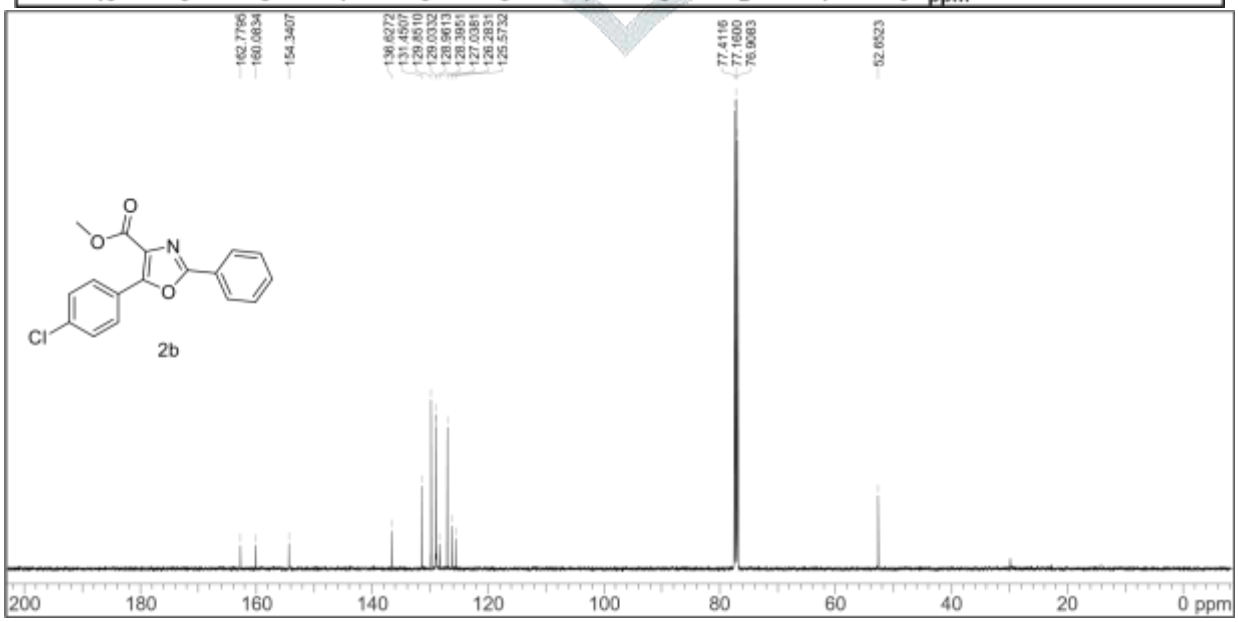
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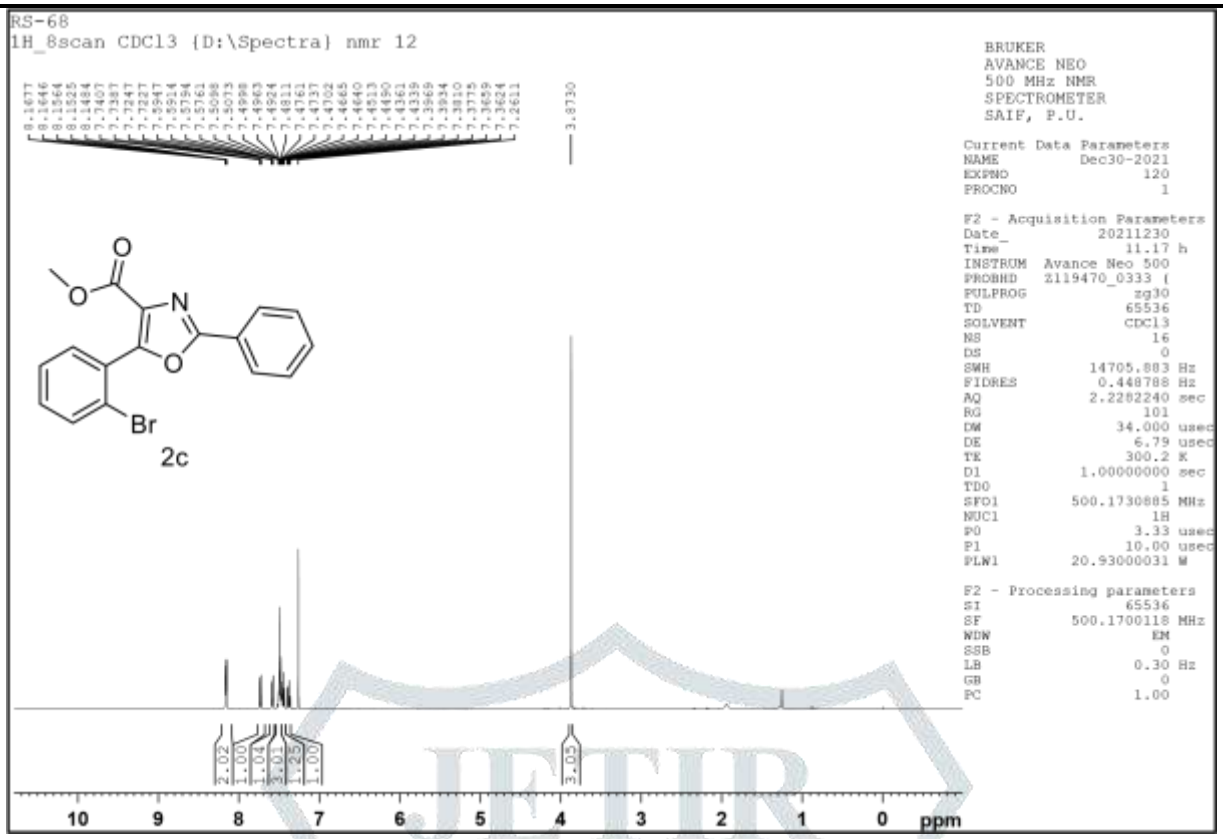
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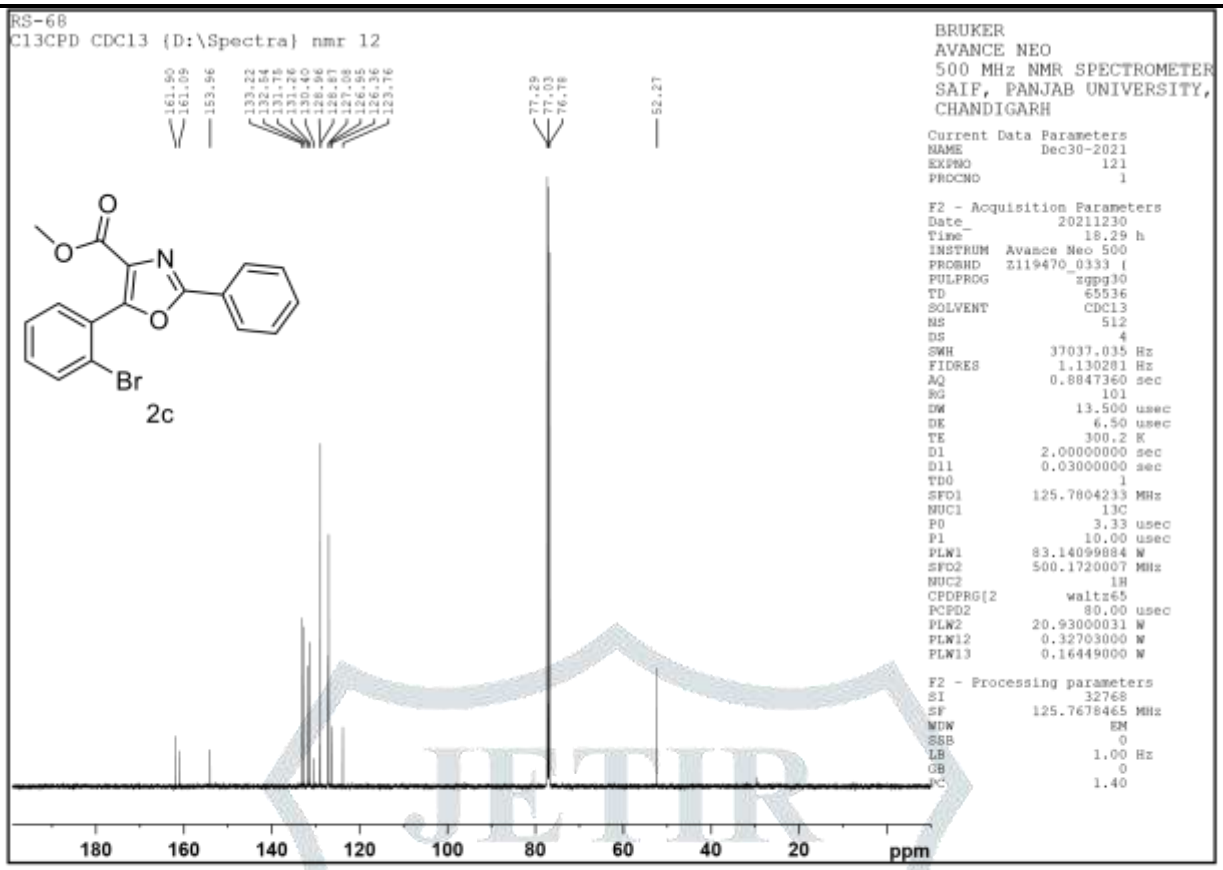
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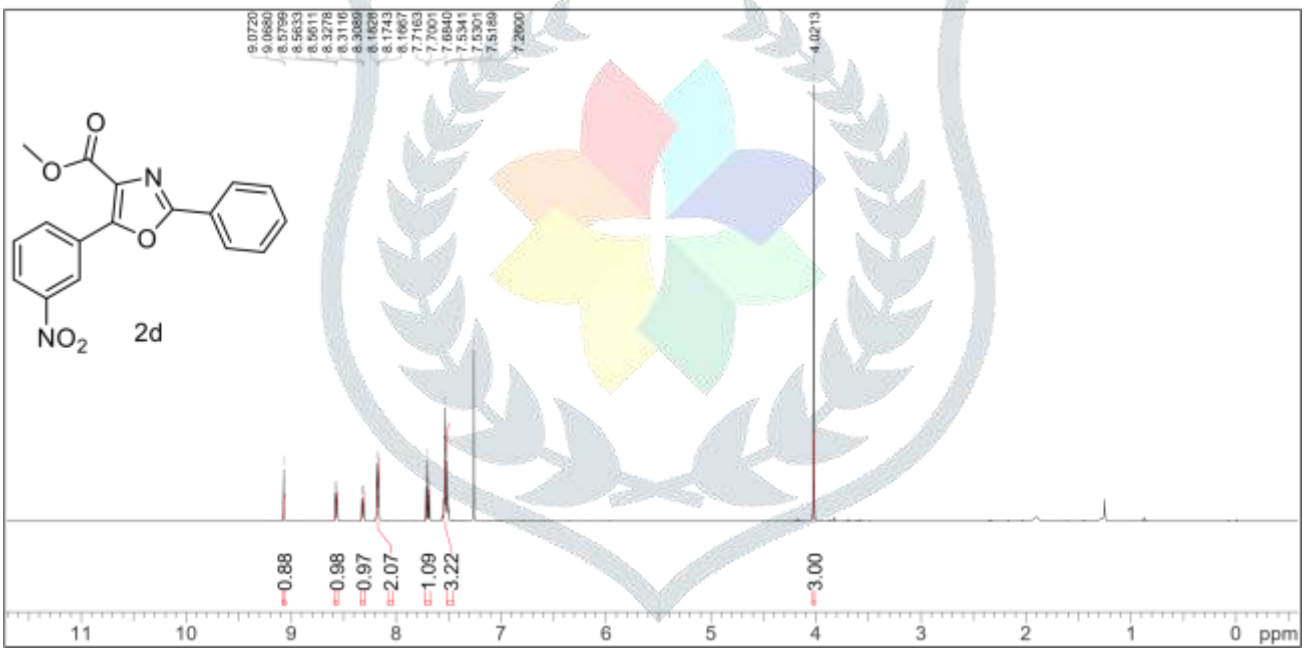
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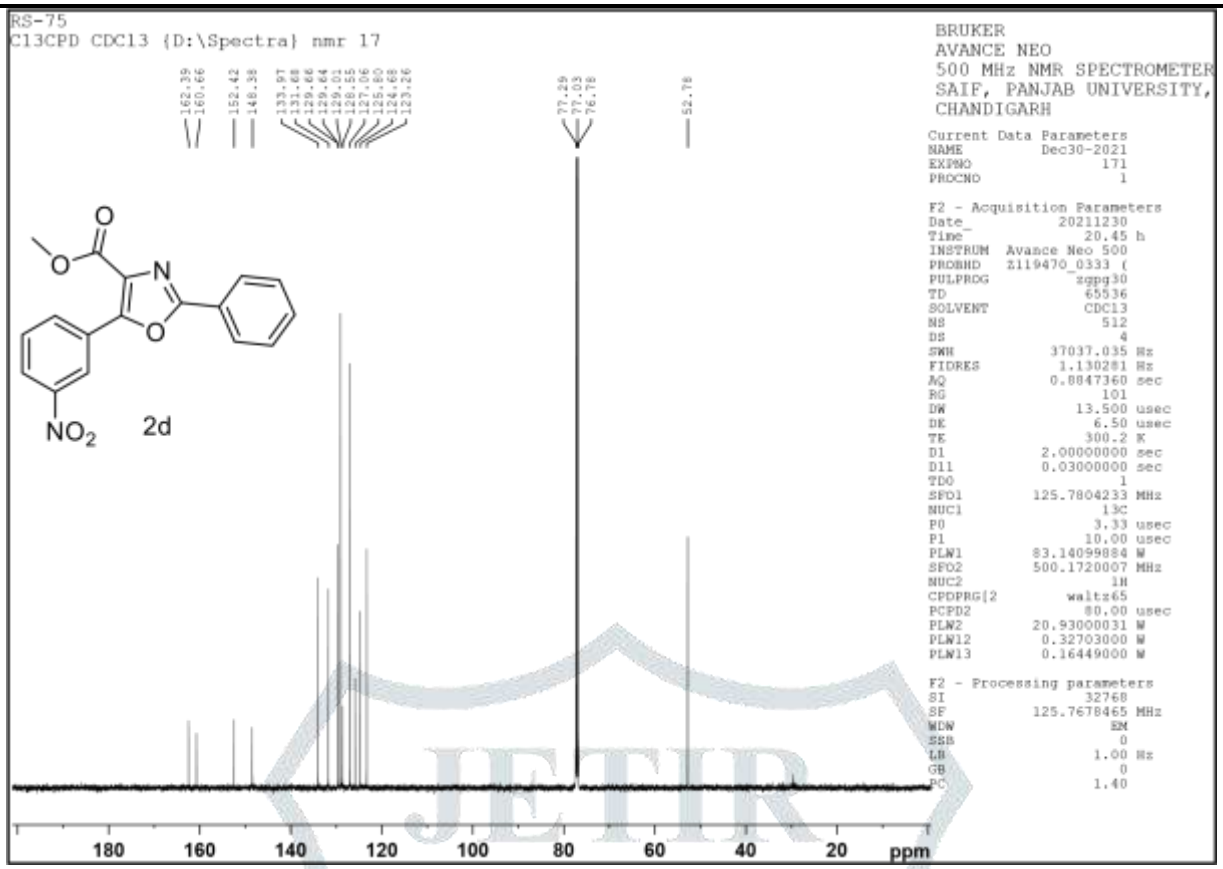
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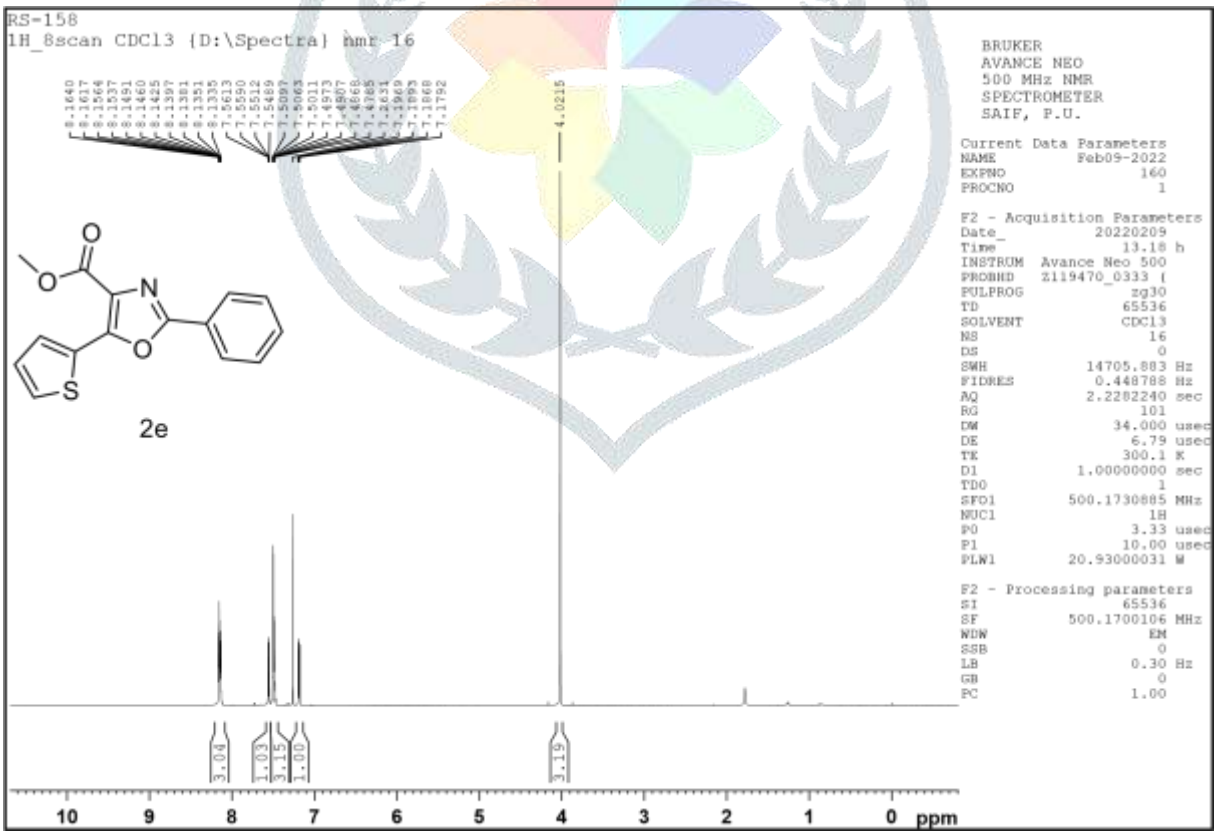
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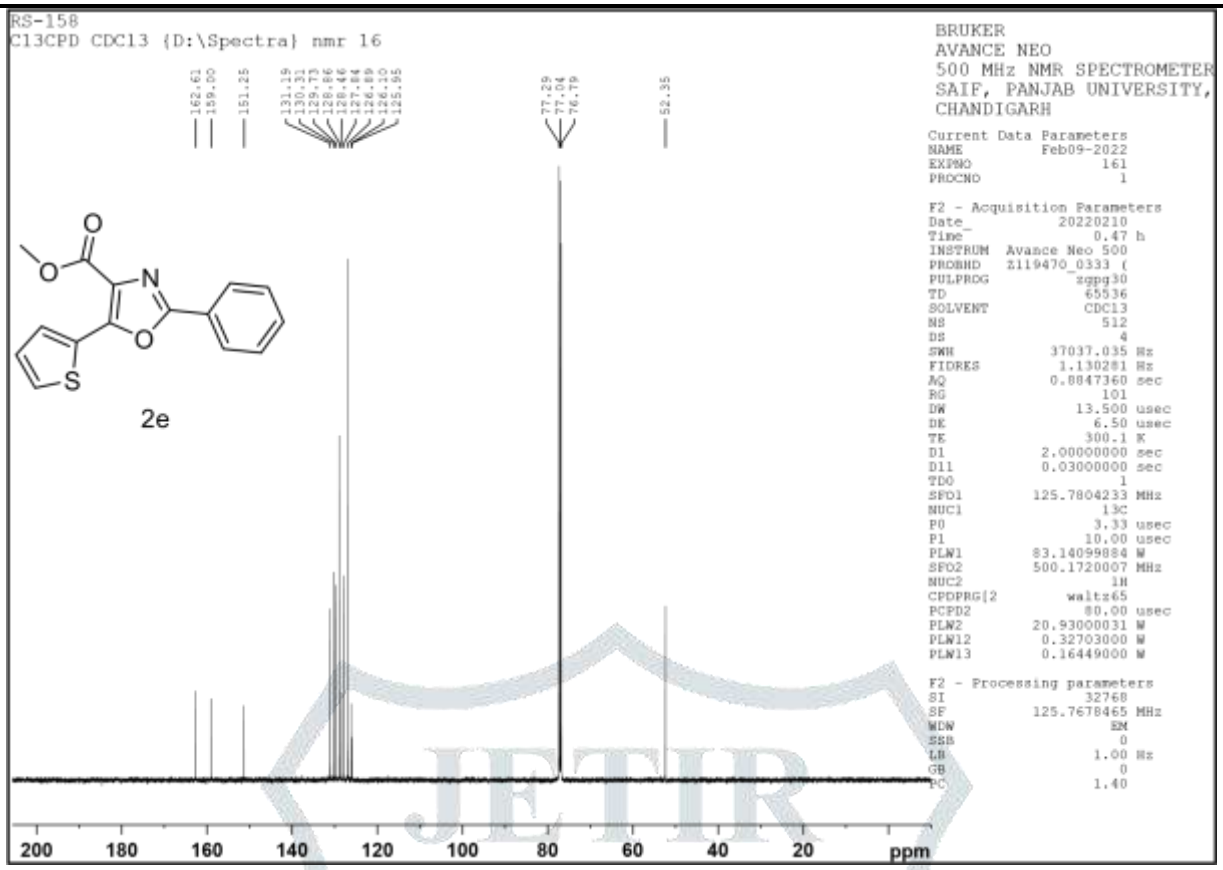

Acknowledgement:

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