

Synthesis of 2-Oxazolines from Diketene Using DAST via Beckmann Rearrangement

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Abstract: A novel synthesis of 2-oxazolines from diketene by using DAST via Beckmann rearrangement as been described. The route involves a one-pot amidation of diketene with different amines at 70°C in the presence of toluene to form corresponding amides followed by reacting the amides with K₂CO₃ and DMF at room temperature to form corresponding carboxamides and carboxylates. The carboxamides and carboxylates are then reacted with NH₂OH·HCL and NaOAc in presence of ethanol and water to form Ketoximes which are then reacted in one pot synthesis with DAST and dichloromethane at room temperature to form corresponding oxazolines via Beckmann rearrangement. Ketoximes are one of the most popular functional groups and are readily prepared by a number of methods. The initial step of our study was the strategic formation of the ketoxime from carboxamides species which would then be converted to corresponding oxazolines via Beckmann rearrangement. Each new compound has been elucidated through ¹H-NMR and ¹³C-NMR. The Characterization data of compound was also agrees with the molecular masses of HRMS (ESI-TOF). Indeed, all the corresponding products were obtained with a good yield. The studies utilizing this strategy for the production of oxazolines are ongoing in our laboratory. Further expansion of the substrate scope, elucidating the mechanism and exploring the applications of this transformation are now under investigation in our laboratory. We are hopeful; the synthesis of 2-oxazolines from diketene by using DAST via Beckmann rearrangement will be useful in many scientific researches.

Keywords: 2-Oxazoline, DAST, Beckmann Rearrangement

1. Introduction

The chemistry of oxazoline compounds is one of the most complex and fascinating branches of organic chemistry. The first oxazoline was formulated in 1884 by Andreasch [1]. His notion was that the compound ensuing from the dehydrohalogenation of allylurea bromide contained a new cyclic structure, but failed to deduce its accurate formula. Gabriel [2] established and characterized the oxazoline formula five years (1889) later thus commencing an extensive study of the chemistry of this heterocyclic system. Numerous expansive views of heterocyclic chemistry have since been published as disciplines of broad significance that

entrench on nearly all aspects of modern organic chemistry, medicinal chemistry, and biochemistry. As described in a review by Donaldson [3], the oxazoline ring unit exists in a significant number of biologically active natural products and pharmaceuticals [2-5]. Many reagents have been used in the synthesis of 2-oxazolines as is shown in the literature survey of this report. This report mainly focuses on the use of DAST in the synthesis of oxazolines. N,N-Dialkylaminosulfur trifluorides, first prepared in 1964 [6], have been established as mild, easily handled fluorinating agents [7]. DAST, which is the most widely used member of this family of reagents, is

a pale yellow liquid that reacts violently with water. DAST is known to be thermally unstable due to the fact that it undergoes either explosion or detonation when heated to $>90^{\circ}\text{C}$ [8]. The main use of DAST has been synthesis of organo fluorine compounds in the pharmaceutical and agrochemical industries [9], with efforts intended for the development of simple, safe and efficient methods for their synthesis [10]. The conversion of carbon–oxygen to carbon–fluorine bonds by nucleophilic fluorinating sources (deoxofluorination) such as DAST epitomizes one such technique which has been extensively used for the selective introduction of fluorine into organic molecules. [11]. DAST has also been used broadly for fluorodehydroxylation reactions, converting alcohols to the subsequent fluorides under mild conditions and in the presence of a variety of functional groups [12]. Treatment of aldehydes and ketones with DAST usually yields gem-difluoro-alkanes [7]. Another major utilization of DAST has been in activation of alcohols. An example of this has been treatment of β -hydroxy amides and β -hydroxy thioamides with DAST to obtain oxazolines and thiazolines, respectively [13]. DAST has also been found to effectively activate sugar-derived alcohols towards intramolecular substitution. Such reactions were found to occur stereo selectively to yield polyoxygenated tetrahydrofurans [14]. The occurrence of a fluorine atom in the locality of the anomeric position in saccharides reinforces the glycosidic bond, which further improves the therapeutic value of sugar- or nucleoside based pharmaceuticals. It should be noted that fluorination of optically active alcohols by using DAST usually proceeds with inversion of configuration [15] ($\text{S}_{\text{N}}2$ mechanism). In some hindered substrates, products with retained configuration could be attained [16]. Much as DAST has been used majorly for fluorination of compounds and activation of alcohols, it should also be noted that some papers have recently reported its use in the synthesis of oxazolines. Jean-Paul Lellouche et al on the other hand communicated an effective reaction of acyclic 1,2-amido alcohols (β -hydroxy amides under mild reaction conditions) with a minor excess of (diethyl amino)sulfur trifluoride (DAST) to produce corresponding 2-oxazolines [17] in excellent yields. Okuma [18] and group recently reported a simple, rapid and efficient green synthesis of aryl methoxylated benzamides and 2-oxazolines from renewable Eucalyptus biomass–tar derivatives. William's group reported mild and highly efficient for the cyclodehydrative conversion of β -hydroxy amides to oxazolines at relatively low temperature [19]. Loiseleuret al

reported a protocol involving a diethylaminosulfur trifluoride (DAST)-mediated cyclization of α , α -disubstituted- α -acylaminoketones [20]. Earlier studies by Jones and group had demonstrated that diethylaminosulfur trifluoride (DAST) is capable of transforming β -hydroxy amides to oxazolines under mild reaction conditions [21]. Recently Pouliot and group illustrated the preparation of 2-oxazolines and related N-containing heterocycles from the corresponding hydroxyamides utilizing Xtal Fluor-E ($[\text{Et}_2\text{NSF}_2] \text{BF}_4$) as a cyclodehydration agent providing a broad range of heterocycles under mild conditions in relatively excellent yields [22]. The Xtal Fluor- E was used as an important substitute to DAST and DeoxoFluor in deoxofluorination reaction was used due to its crystallinity and improved thermal stability [23].

Beckmann rearrangement is one of the more effective methods mainly used for conversion of Ketoximes to N-substituted amides (oxazoles) though the potential to afford a variety of products is dependent on prudent selection of the catalyst/reagent. Beckmann rearrangement discovered in 1886 and named after the German chemist Ernst Otto Beckmann, is an acid-catalyzed rearrangement of oximes to amides [24]. The Beckmann rearrangement is one of the oldest and well recognized transformations in organic chemistry and has been reviewed Numerous times. What turned out to be identified as the Beckmann fragmentation was in fact first observed by Wallach in 1889 [25], but was not advanced extensively until 1960. The Beckmann rearrangement has been used in many applications with the major one being the conversion of cyclohexanone oxime into ϵ -caprolactam, the monomer of nylon-6, which is of great industrial importance [26]. Much as a significant number of methods to synthesize substituted oxazoles have been published as is shown in the pathway and strategic synthesis of oxazoline sections of this report, fewer articles where oxazolines are synthesized using DAST have been published [27-29] and to the best of our knowledge there is no publication involving synthesis of stable 2-oxazolines via Beckmann rearrangement using DAST. This lack of published articles coupled with confrontational challenges like severe reaction conditions, long reaction time, low yield, and poor functional group tolerance; makes the ratio of efficient methods to the number of published methods rather low, leaving this area of endeavor still in a relatively primitive state of development. This conundrum led our group to synthesize cyclized oxazolines via Beckmann rearrangement using DAST as showed in figure 1.

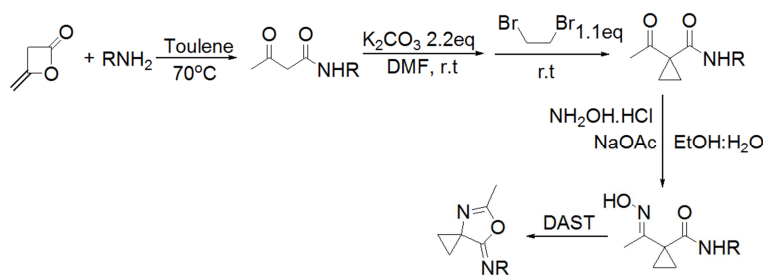


Figure 1. Synthesis of Oxazolines.

2. Experimental Procedures

2.1. Materials

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. TLC was performed on Quindao Haiyang plastic silica gel plates and products were purified by column chromatography over ZCX-II 300-400 mesh silica gel. Petroleum ether (PE) refers to the fraction boiling in the 30-60°C range. Melting points were obtained using a Yuhua X-4 apparatus. ¹H (500 MHz) and ¹³C (125 MHz) NMR spectra were recorded at 25°C using a Varian Unity 500 spectrometer, with TMS as internal standard. Mass spectra were recorded on an AutoflexIII Smart beam MS-spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker micro Tof using ESI method.

2.2. General Procedure for the Synthesis of Compounds

2.2.1. Synthesis of Amide

To an oven-dried 25 mL round-bottom flask with a stir bar was added naphthalen-1-amine (4.2 g, 10 mmol) and toluene (30 mL). The mixture was then stirred to mix the amine and the toluene; and then diketene 4-methyleneoxetan-2-one (0.77 mL/mmol, 30 mmol) was added one drop at a time, and the mixture stirred at a temperature of 70°C in an oil bath without exclusion of air. The reaction progress was monitored by TLC until the 4-methyleneoxetan-2-one was completely consumed.

Next, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and water solution (10 mL) and the mixture further stirred for an additional 15 minutes before the two resulting layers were separated. The organic layer was extracted with CH₂Cl₂ and collected in a clean beaker. The other layer containing water was discarded in the collecting vessel.

The organic layer was then evaporated in a steam bath. The contents in the beaker were let to evaporate until boiling stopped.

Finally, the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) = (15:1) to afford the product N-(naphthalen-1-yl)-3-oxobutanamide as a solid with orange colour.

2.2.2. Conversion of Amide to Carboxamides

To an oven-dried 25 mL round-bottom flask with a stir bar was added N-(naphthalen-1-yl)-3-oxobutanamide (2.27 g, 10 mmol) and DMF (10 mL). The mixture was then stirred to dissolve the amide and then Potassium carbonate (3.036 g, 2.2 eq) was, and the mixture stirred at room temperature of (25°C) without exclusion of air for 1 hour. Dibromomethane (0.957 mL/mol, 1.1 eq) was then added to the flask and stirring was continued. The reaction progress was monitored by TLC until the substrate was completely consumed.

Next, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and water solution (10 mL) and the mixture further stirred for an additional 15 minutes before the two resulting layers were separated. The organic layer was extracted with CH₂Cl₂ and collected in a clean beaker. The other layer containing water

was discarded in the collecting vessel.

The organic layer was then evaporated in a steam bath. The contents in the beaker were let to evaporate until boiling stopped.

Finally, the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) = (10:1) to afford the product 1-acetyl-N-(naphthalen-1-yl) cyclopropanecarboxamide.

2.2.3. Conversion of Carboxamides to Ketoximes

To an oven-dried 25 mL round-bottom flask with a stir bar was added cyclopropanecarboxamide (1.638 g, 6.5 mmol) and EtOH:H₂O (20:1 ratio). The mixture was then stirred to dissolve the cyclopropanecarboxamide and then NH₂OH·HCl (0.877 g, 2.2 eq) was added followed by NaOAc (1.168 g, 2.5 eq). The mixture stirred at room temperature (25°C) without exclusion of air. The reaction progress was monitored by TLC until the substrate was completely consumed. The TLC monitoring generally indicated that the ketoxime had a higher polarity than the cyclopropanecarboxamide. Next, ice crystals were added to a clean beaker (washed with water to avoid traces of acetone) followed by NaCl and then stirred with a clean glass rod. The mixture from the round bottomed flask was then added gradually with continuous stirring until it was finished from the round bottomed flask. The mixture in the beaker was then filtered with a funnel connected to a suction pump and the ketoxime was obtained as a white solid.

2.2.4. Procedure for the Preparation of the Oxazoline

To an oven-dried 25 mL round-bottom flask with a stir bar was added Ketoxime (0.5 mmol). Dichloromethane was then added and the mixture was then stirred to dissolve the ketoxime and then DAST (1.5 eq) was added one drop at a time, and the mixture stirred at room temperature (25°C) without exclusion of air. The reaction progress was monitored by TLC until the ketoxime was completely consumed. The TLC monitoring generally indicated that the oxazoline had a lower polarity than the ketoxime.

Next, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and water solution (10 mL) and the mixture further stirred for an additional 15 minutes before the two resulting layers were separated. The organic layer was extracted with CH₂Cl₂ and collected in a clean beaker. The other layer containing water was discarded in the collecting vessel.

The organic layer was then evaporated in a steam bath. The contents in the beaker were let to evaporate until boiling stopped.

Finally, the residue was purified by silica gel column chromatography (petroleum ether: ether) = (10: 1) to the oxazoline as a white solid.

2.3. Proposed Mechanism for the Synthesis of Oxazoline

The first step is the nucleophilic displacement of fluorine in DAST by the oxygen of the oximino substrate with elimination of hydrogen fluoride. Next, the elimination of Diethylaminosulfinio fluoride from the intermediate causes the bond cleavage and gives a nitrogen-intermediate.

The reaction then proceeds through a Beckmann Rearrangement which consists of formation of an iminocarbocation through partial ionization of the nitrogen-oxygen bond of an oxime with a concurrent intramolecular migration of the group anti to the leaving hydroxyl group. This then leads to the formation of the 2-oxazolinem.

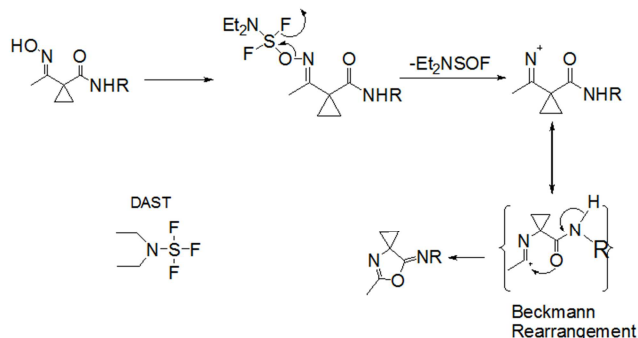


Figure 2. Formation of Oxazoline via Beckmann Rearrangement.

2.4. Analytical Data of the Ketoximes

1-(1-(hydroxyimino)ethyl)-N-phenylcyclopropanecarboxamide (4a)

Ketoxime 4a

Was made as a white solid from an amide as shown in the general procedure. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.14 (d, J = 40 Hz, 2H), 1.56 (d, J = 41.5 Hz, 2H), 1.95 (s, 3H), 7.09 (d, J = 14.5 Hz, 1H), 7.28 (d, J = 25.5 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 8.03 (s, 1H), 8.68 (s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 8.7, 17.4, 31.20, 121.3, 128.0, 128.9, 163.9, 180.2; HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1134 Found 219.1130.

N-benzyl-1-(1-(hydroxyimino) ethyl) cyclopropanecarboxamide (4b)

Ketoxime (4b)

Was made as a white solid from an amide as shown in the general procedure. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.04 (d, J = 10.0 Hz, 2H), 1.47 (d, J = 11.5 Hz, 2H), 1.91 (s, 3H), 2.31 (s, 2H), 4.44 (d, J = 5.5 Hz, 2H), 7.32 (d, J = 14.5 Hz, 3H), 8.15 (s, 1H), 8.59 (s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 7.7, 17.8, 30.1, 43.5, 126.7, 126.8, 128.3, 163.9, 180.6; HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$ 223.1290 Found 223.1288.

1-(1-(hydroxyimino) ethyl)-N-(p-tolyl) cyclopropanecarboxamide (4c)

Ketoxime 4c was made as a white solid from an amide as shown in the general procedure. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.16 (d, J = 11.5 Hz, 2H), 1.58 (d, J = 11.5 Hz, 2H), 1.91 (s, 3H), 2.18 (s, 3H), 7.25 (d, J = 9 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.80 (s, 1H), 9.11 (s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 6.9, 17.1, 21.0, 30.9, 121.2, 129.7, 136.3, 139.1, 163.9, 180.4; HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$ 223.1290 Found 223.1293.

1-(1-(hydroxyimino)ethyl)-N-(naphthalen-1-yl)cyclopropanecarboxamide (4d)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.16 (d, J = 11.0 Hz, 2H), 1.64 (d, J = 10 Hz, 2H), 1.93 (s, 3H), 7.44 (m, J = 25 Hz, 3H),

7.63 (d, J = 8.0 Hz, 1H), 7.81 (m, J = 7.0 Hz, 2H), 7.94 (d, J = 7.0 Hz, 1H), 8.29 (s, 1H), 9.69 (s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 12.6, 15.2 (2C), 29.7, 120.3, 120.8, 125.6, 126.2, 127.0, 128.6, 132.7, 134.0, 158.2, 169.7; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$ 269.1290 Found 269.1296.

N-(tert-butyl)-1-(1-(hydroxyimino)ethyl)cyclopropanecarboxamide (4e)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 0.96 (d, J = 11.0 Hz, 2H), 1.34 (d, J = 10 Hz, 2H), 1.35 (s, 3H), 1.96 (m, 9H), 5.97 (s, 1H), 8.66 (s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 8.4, 16.9, 30.1, 33.4, 57.3, 164.6, 180.0; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$ 200.1525 Found 200.1501.

2.5. Analytical Data of 2-Oxazolines

(Z)-N-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-ylidene) aniline (5a)

Purified by flash column chromatography (eluent: petroleum ether / EtOAc = 25:1); white solid (83.41 mg, 83%); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.48 (d, J = 12.5 Hz, 2H), 1.53 (d, J = 25.5 Hz, 2H), 1.85 (s, 3H), 7.23 (t, J = 28.0 Hz, 3H), 7.32 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 14.9, 18.7, 49.5, 127.7, 124.3, 128.6, 145.2, 161.7, 162.1. HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 201.1028 Found 201.0837.

(Z)-4-methyl-N-(5-methyl-6-oxa-4-azaspiro [2.4] hept-4-en-7-ylidene) aniline (5b)

Purified by flash column chromatography (eluent: petroleum ether / EtOAc = 25:1); white solid (77.40 mg, 72%); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.54 (d, J = 7.0 Hz, 2H), 1.61 (d, J = 3.5 Hz, 2H), 2.19 (s, 3H), 2.32 (s, 2H), 7.03 (m, 1H), 7.12 (m, 4H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 8.8, 17.0, 28.9, 49.4, 125.2, 126.4, 127.0, 139.1, 161.6, 163.8. HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 215.1184 Found 215.1181.

(Z)-4-methyl-N-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-ylidene)aniline (5c)

Purified by flash column chromatography (eluent: petroleum ether / EtOAc = 25:1); white solid (103.2 mg, 96%); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.35 (d, J = 6.0 Hz, 2H), 1.38 (d, J = 6.1 Hz, 2H), 2.12 (s, 3H), 2.34 (s, 3H), 7.13 (d, J = 25.0 Hz, 2H), 7.22 (d, J = 20.5 Hz, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 14.9, 18.6, 20.9, 49.5, 122.7, 129.3, 133.9, 142.6, 161.3, 162.2. HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 215.1184 Found 215.1174.

(Z)-N-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-ylidene) naphthalen-2-amine (d)

Purified by flash column chromatography (eluent: petroleum ether / EtOAc = 25:1); white solid (75.30 mg, 60%); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.72 (m, 4H), 2.14 (s, 3H), 7.18 (d, J = 7.5 Hz, 1H), 7.44 (m, 3H), 7.61 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 9.5 Hz, 1H), 8.03 (d, J = 9.5 Hz, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 14.9, 19.0 (2C), 49.7, 116.8, 123.4, 124.2, 125.4, 125.6, 125.9, 127.8, 128.0, 134.0, 141.8, 162.4, 162.5. HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 251.1184 Found 251.1108.

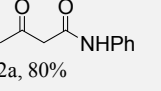

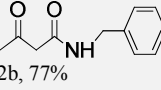
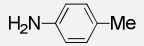
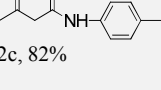
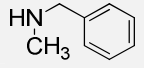
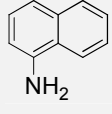
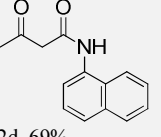
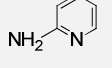
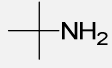
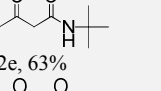
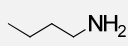
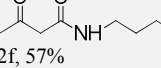
(Z)-2-methyl-N-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-ylidene)propan-2-amine

Purified by flash column chromatography (eluent: petroleum ether / EtOAc = 25:1); white solid (72.0 mg, 80%); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ = 1.56 (s, 9H), 1.62 (m, 2H), 1.71 (d, J = 8.0 Hz, 2H), 2.18 (s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ = 10.1, 18.2, 29.9, 30.1, 30.7, 53.2, 158.2, 164.4. HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_{17}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 181.2542 Found 181.1540.

3. Result and Discussion

From the results in Table 1 above, the 4-methyleneoxetan-2-one reacted with the various amines to give corresponding amides with good yields. All the results of this reaction are laid out in the Table 1. However there was no reaction between the 4-methyleneoxetan-2-one with *N*-methyl-1-phenylmethanamine and pyridin-2-amine as shown in (Table 1, entries 4-6) respectively.

Table 1. Conversion of Diketene to amide from corresponding amine.

Entry	Diketene	Amine	Amide
1	1a	NHPh	 2a, 80%
2	1a		 2b, 77%
3	1a		 2c, 82%
4	1a		No reaction
5	1a		 2d, 69%
6	1a		No reaction
7	1a		 2e, 63%
8	1a		 2f, 57%

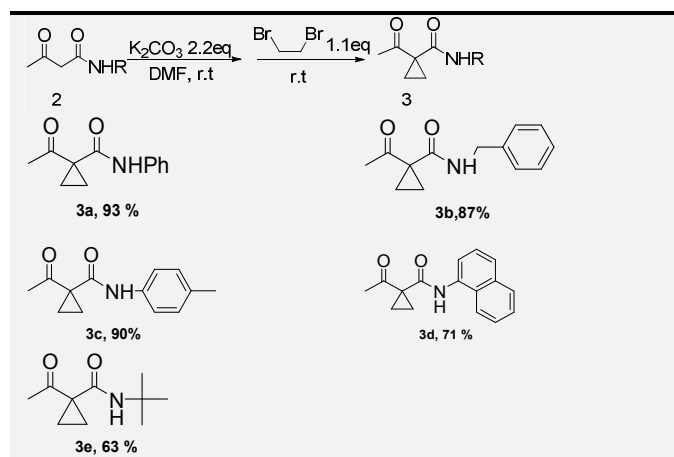
Reactions were performed with 4-methyleneoxetan-2-one (30 mmol), Amines (30 mmol), with toluene (30ml) solvent in an oil bath at a temperature of 70°C.

There was no reaction in (Table 1, entry 4) due to lack of α -hydrogenation or isotope exchange. Therefore there was no tautomerism due to the lack of the α -hydrogen. There was reaction in (Table 1, entry 8) to give butan-1-amine but isolation of a substantial butan-1-amine was not possible.

Results in Table 2 discloses that good to excellent yields of cyclopropane carboxamides can be obtained when an amide 2a is first reacted with K_2CO_3 with DMF and then treated

with dibromomethane after 1 hour at room temperature. The Table 2 compounds (3a-e) show the cycloaddition products; namely 3a 1-acetyl-N-phenylcyclopropanecarboxamide, 3b 1-acetyl-N-benzylcyclopropanecarboxamide, 3c 1-acetyl-N-(p-tolyl) cyclopropanecarboxamide, 3d 1-acetyl-N-(naphthalen-1-yl) cyclopropanecarboxamide, finally 3e 1-acetyl-N-(tert-butyl) cyclopropanecarboxamide respectively. It can be observed from the table above that the best yield of 3c 1-acetyl-N-(p-tolyl) cyclopropanecarboxamide was realized at a relatively slightly longer time (4 h). The cycloaddition of the cyclopropane significantly increases the functionality of the cyclopropanecarboxamide. This is as a result of the triangular structure of cyclopropane having bond angles between carbon-carbon bonds to be 60°C as opposed to the thermodynamically most stable angle of 109.5° (intended for bonds between atoms with sp^3 hybridized orbitals). This significant ring strain in addition to the torsional strain due to the eclipsed conformation of its hydrogen atoms causes bonds between the carbon atoms to be considerably weaker than in a typical alkane, resulting in much higher reactivity.

Table 2. Synthesis of Carboxamides.



Amides (10 mmol), reacted with 2.2 equiv K_2CO_3 and 10ml DMF. 1.1 equiv. Dibromomethane is added after 1 hour under room temperature.

Table 3. Synthesis of Ketoximes.

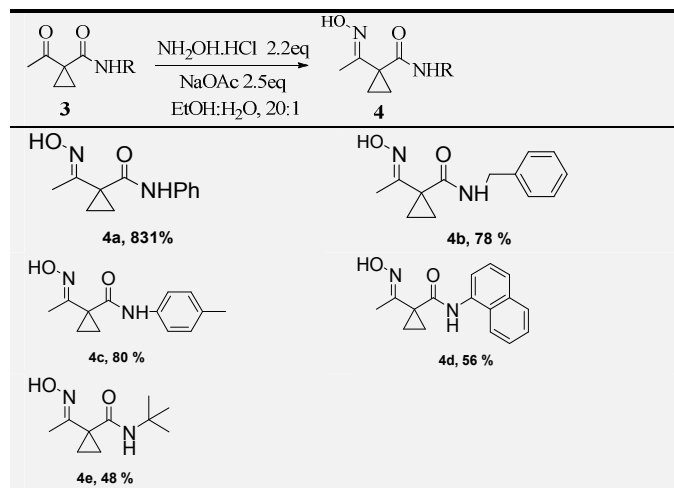
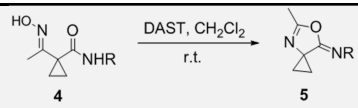
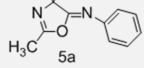
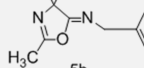
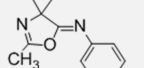
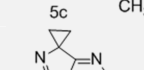



Table 4. Synthesis of 2-Oxazolines.^a

				
Entry	Substrate	Time (h)	Product	Yield (%)
1	4a	3.5		83
2	4b	5		72
3	4c	8		96
4	4d	11		60
5	4e	5		80

^aThe reaction was carried out using 0.5 mmol of ketoxime, DAST (1.5 equiv) in the indicated solvent CH₂Cl₂. ^b The yields were determined by NMR. ^c The reaction was conducted at room temperature and progress monitored by TLC.

Results in Table 4 disclose that good to excellent yields of oxazoline ((Z)-4-methyl-N-(5-methyl-6-oxa-4-azaspiro [2.4]

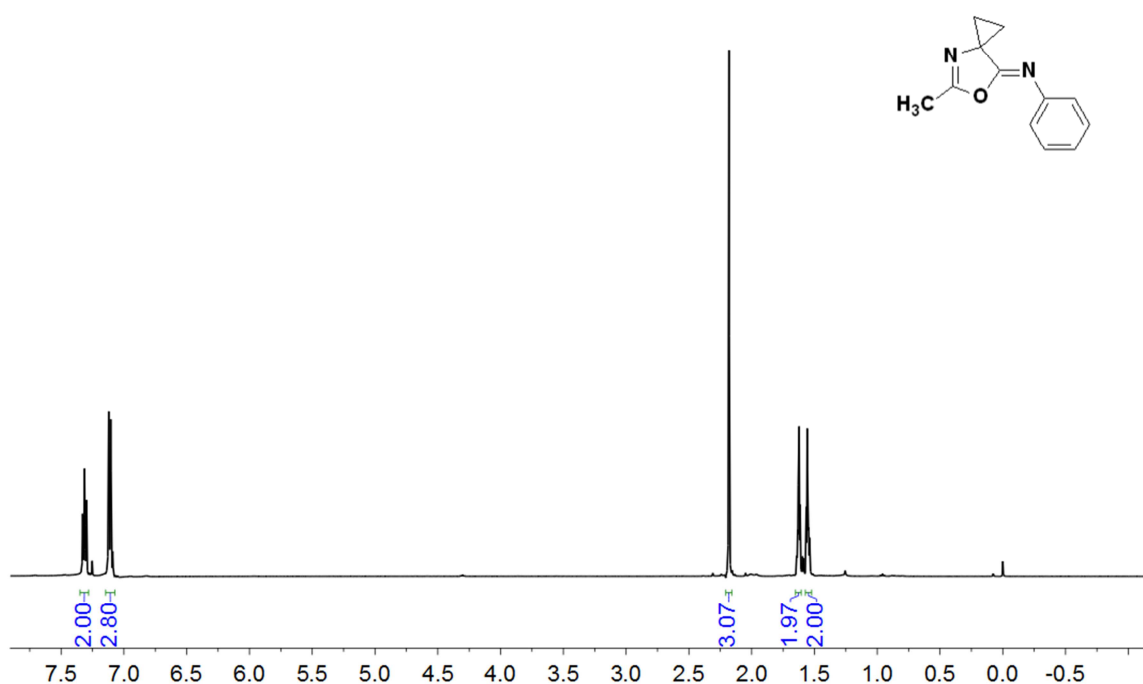
hept-4-en-7-ylidene) aniline) can be obtained via Beckmann rearrangement, when ketoxime 4c is treated with DAST and dichloromethane under room temperature as shown in entry 3 96% of compound 5c. It should be noted that the flow time for the formation of 5c was 8 hours. It can be observed from (Table 4 entry 1) that a good yield of 5a ((Z)-N-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7 ylidene)aniline) was achieved at a relatively short time (3.5 h) compared to the synthesis of compound 5d. The products 5b and 5e were obtained respectively with 72 % and 80 % of yield when the reaction time was set at 5 hours. the rest whose products were achieved at relatively.

4. Conclusion

Synthetic organic chemists today therefore seemed to be very enamored with novel efficient systems in managing their searches for modern synthetic processes. It therefore follows that the next few years on the incessant use of the route would enable researchers prevail over most limitations experienced in the use of other types of systems. In this article, we have discernibly shown a highly efficient system for the conversion of Ketoximes to various 2-oxazoline derivatives.

Supplementary Materials

¹H-HMR and ¹³C-NMR spectra copies

5a**Figure 3.** ¹H-HMR of product 5a.

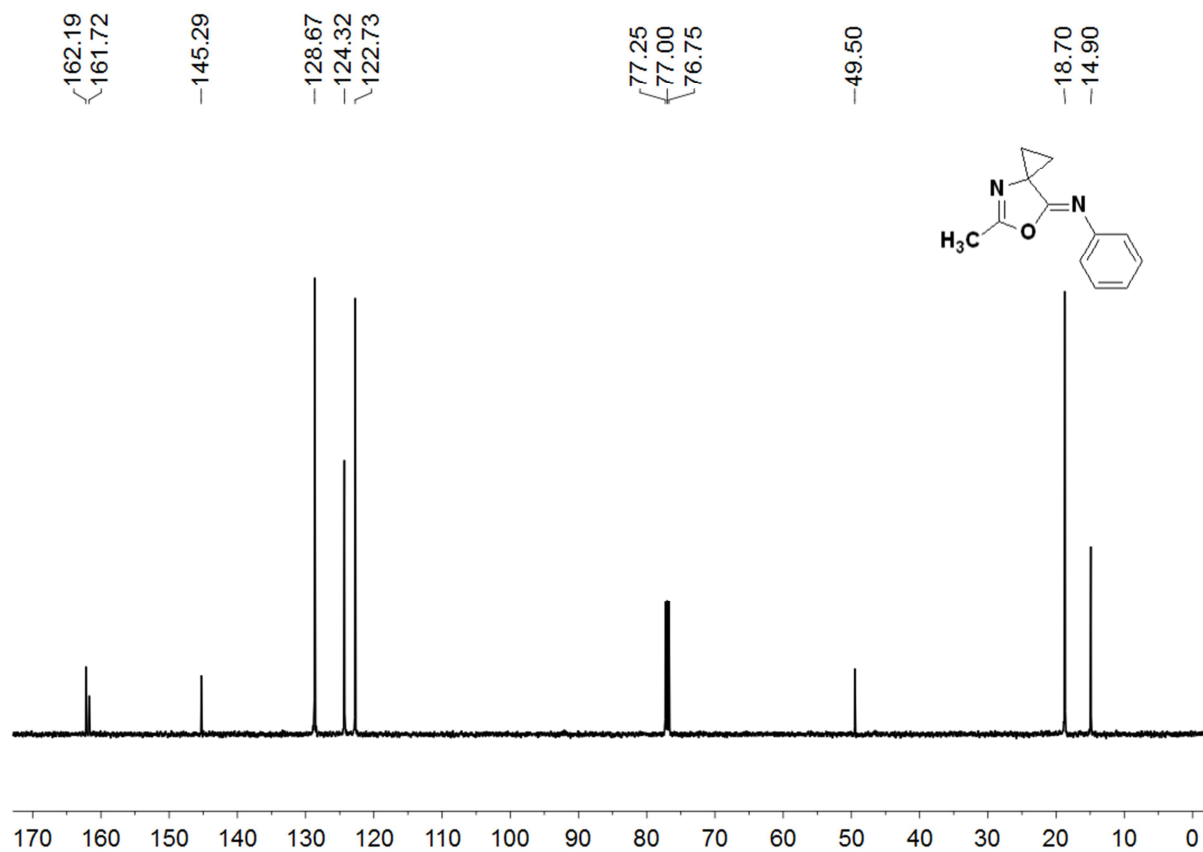


Figure 4. ¹³C-NMR spectra of product 5a.

5b

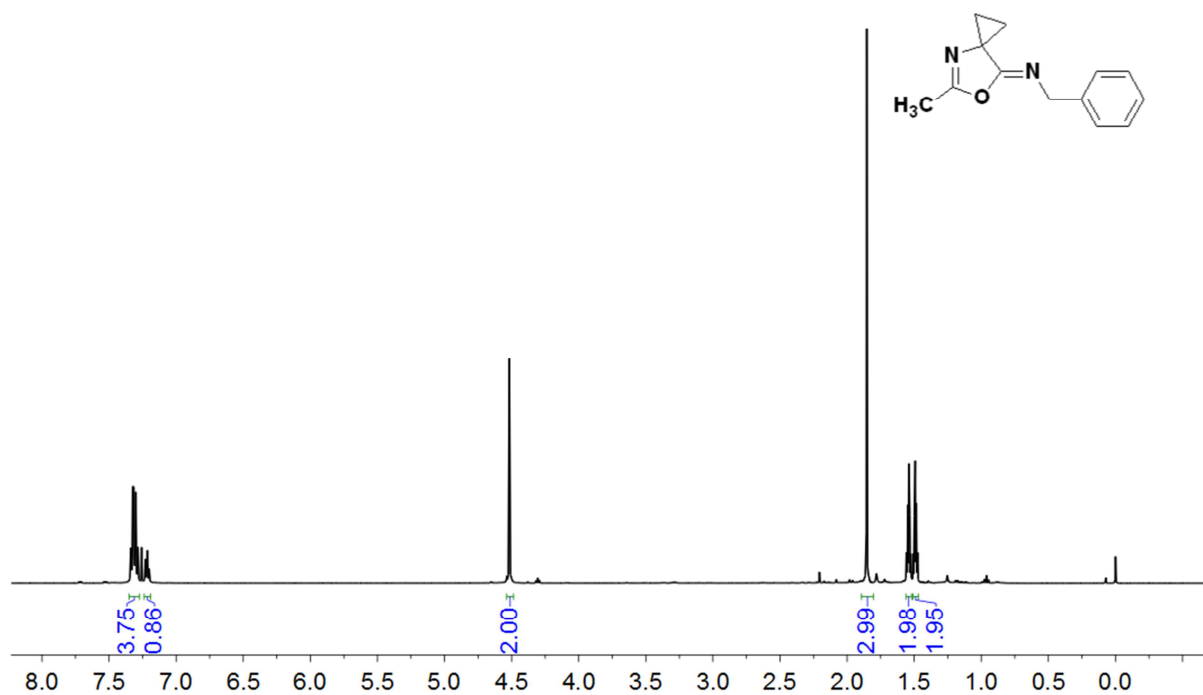


Figure 5. ¹H-NMR of product 5b.

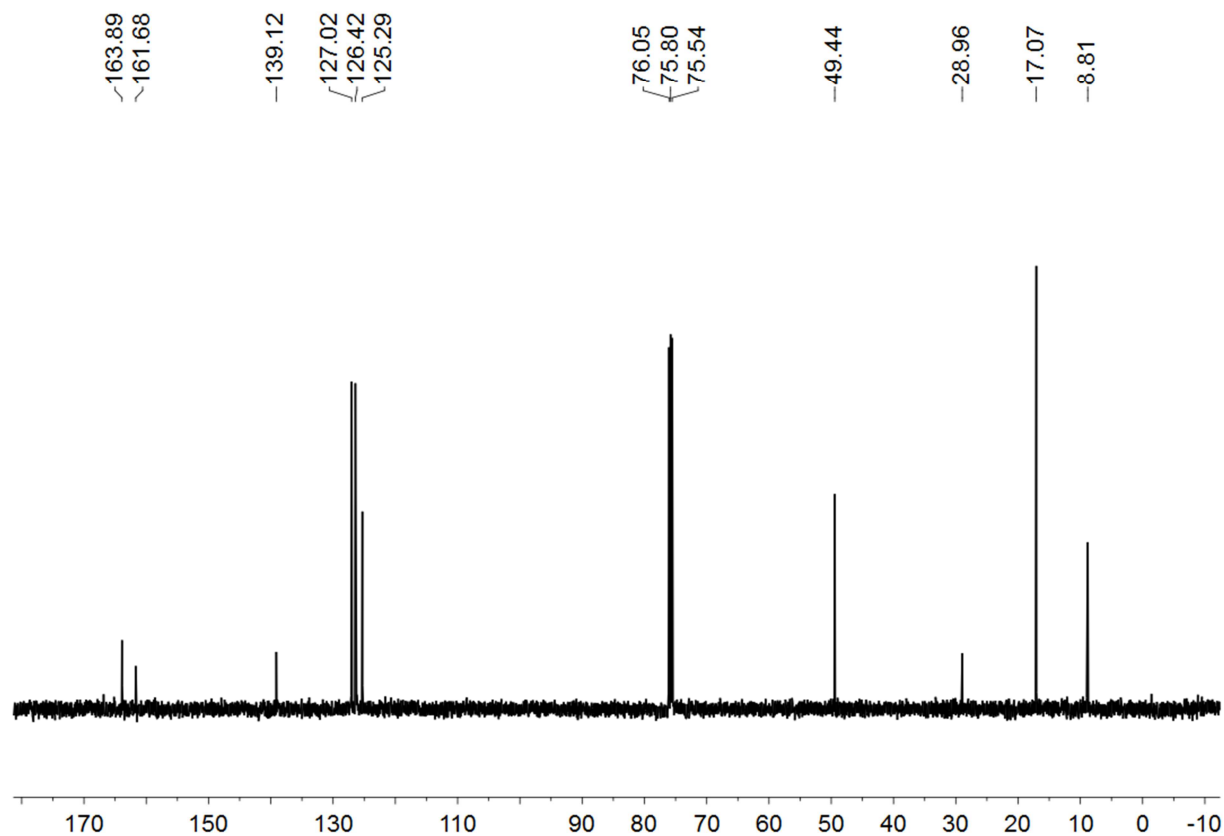


Figure 6. ¹³C-NMR spectra of product 5b.

5c

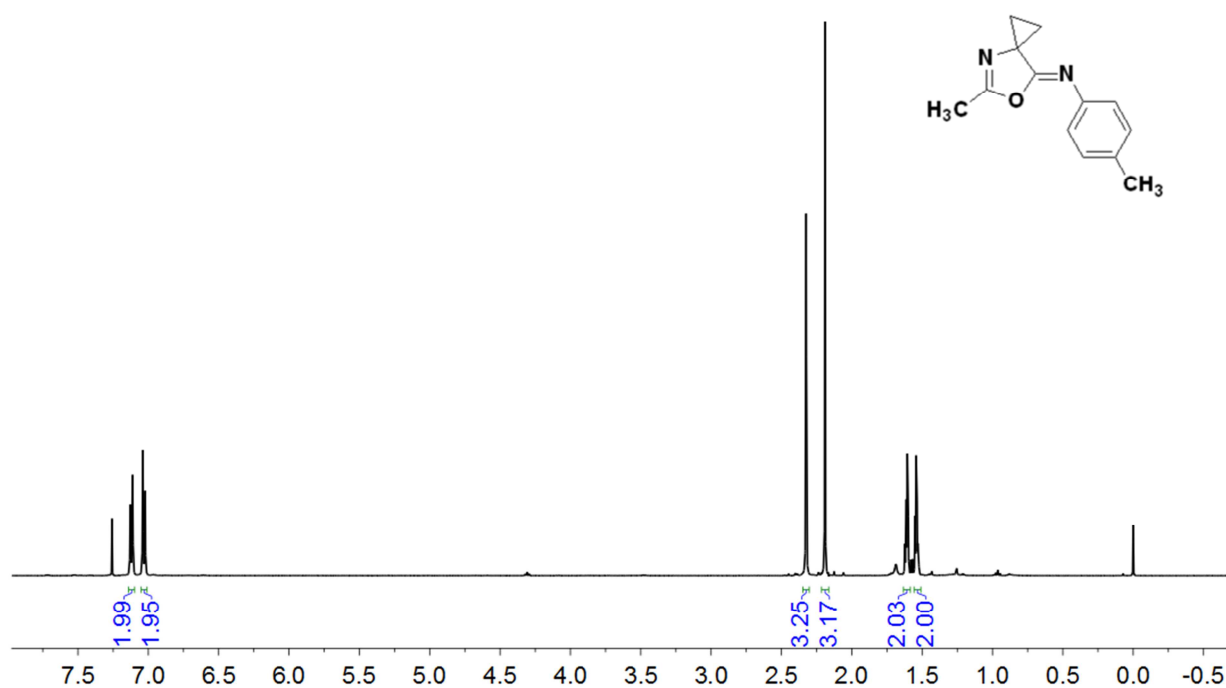


Figure 7. ¹H-NMR of product 5c.

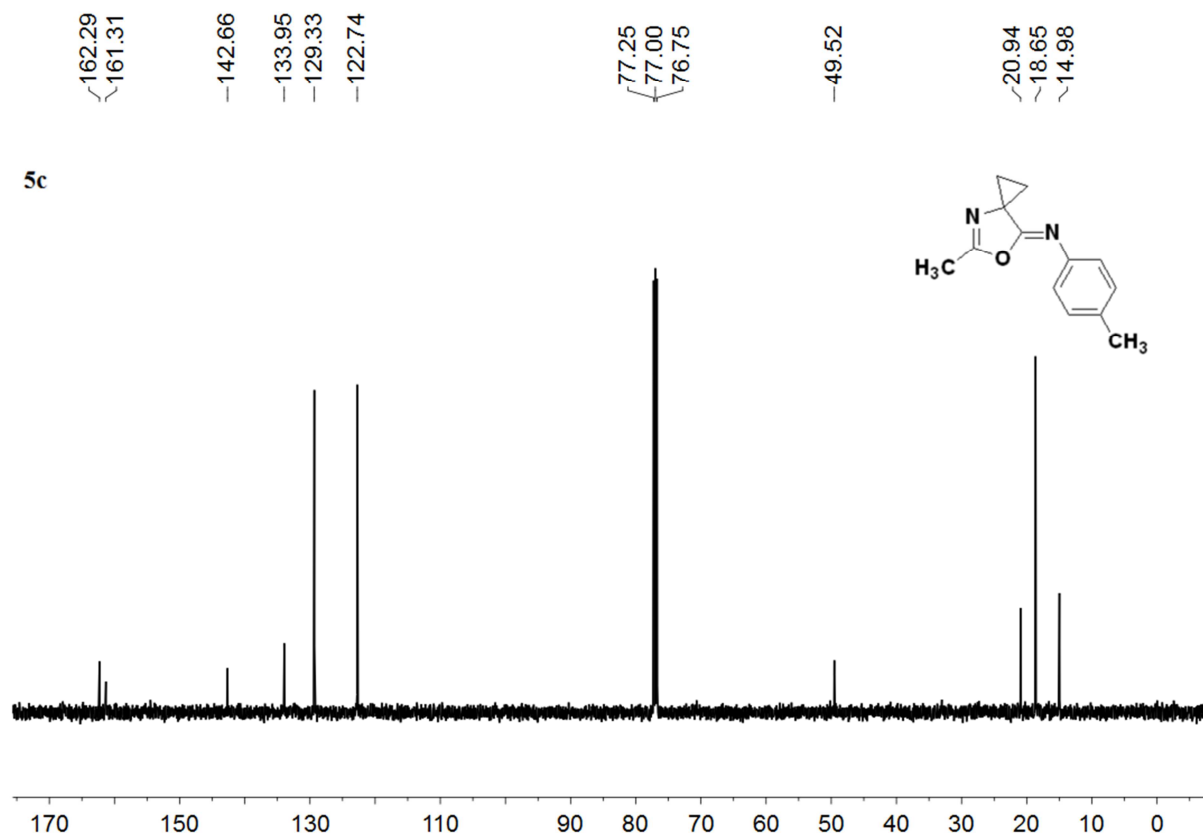


Figure 8. ¹³C-NMR spectra of product 5c.

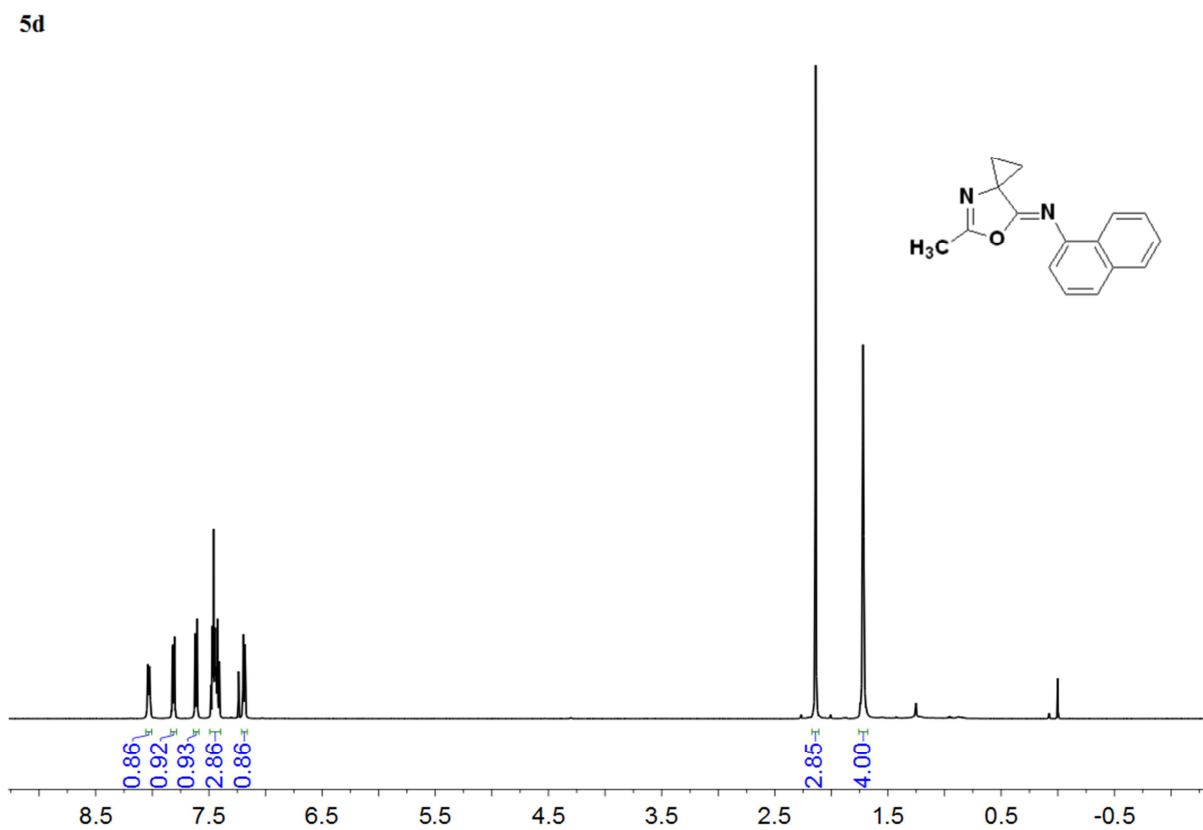
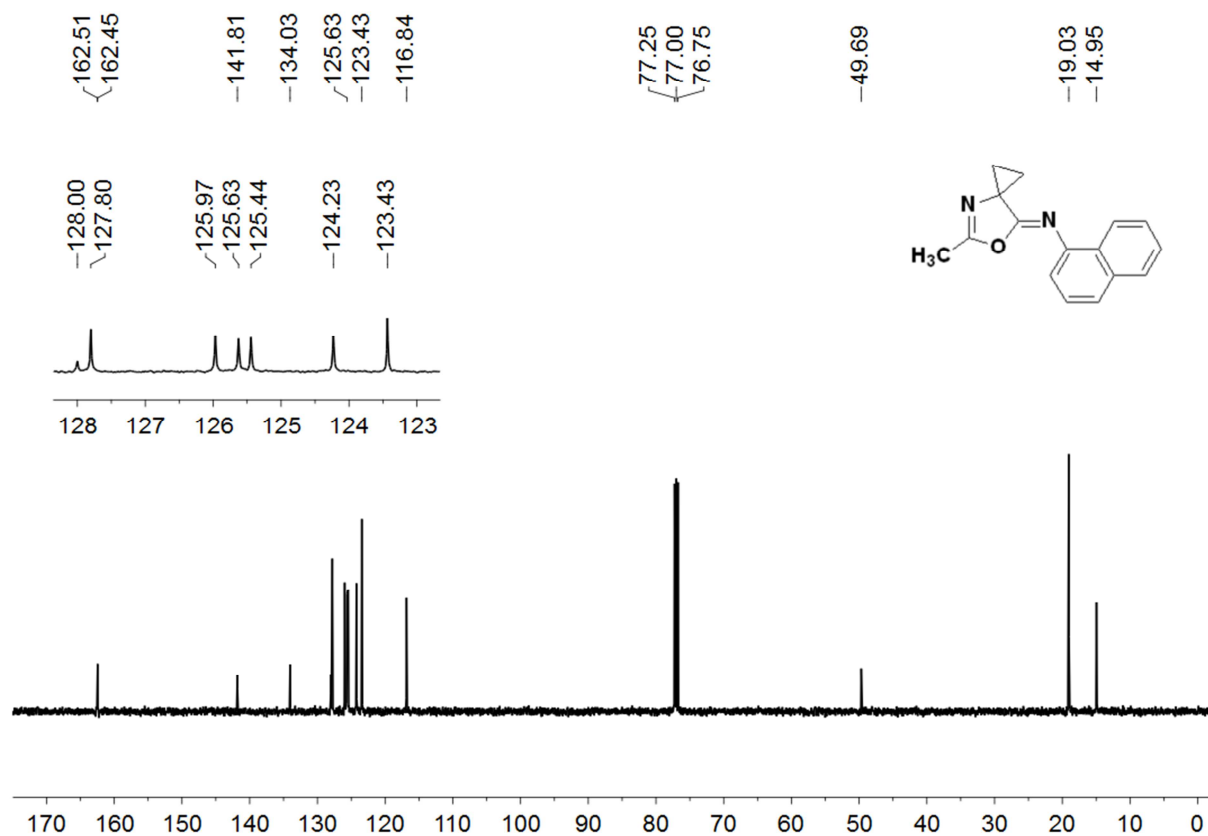
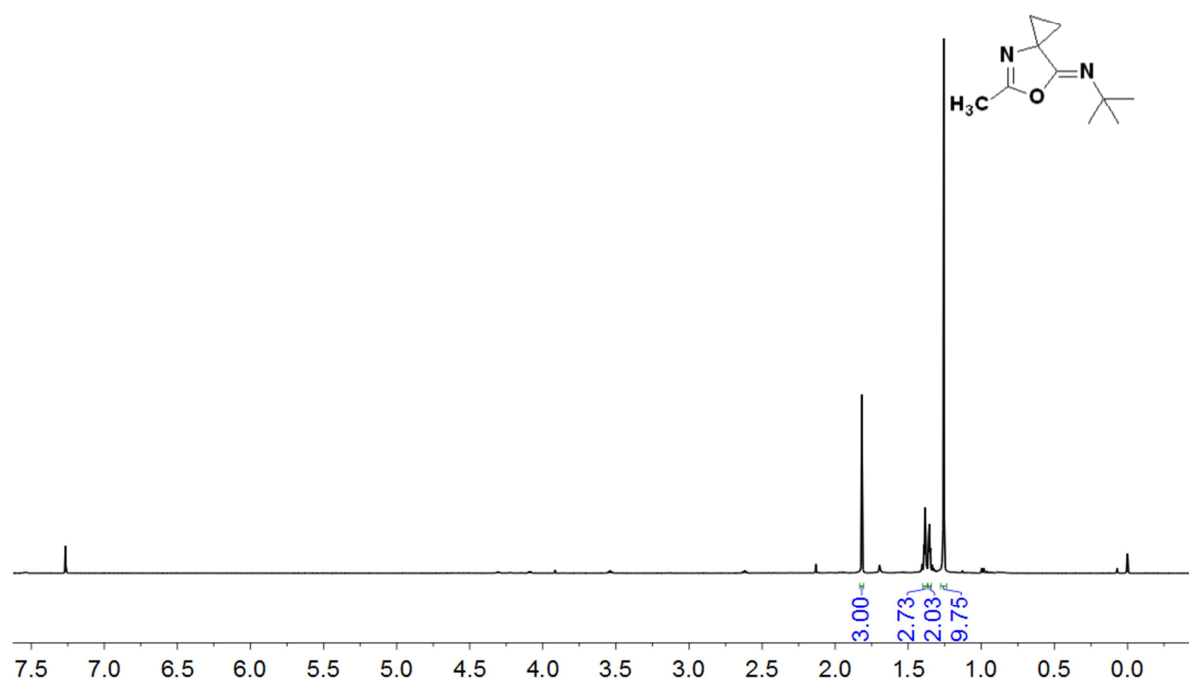


Figure 9. ¹H-NMR of product 5d.

Figure 10. ^{13}C -NMR spectra of product 5d.

5e

Figure 11. ^1H -NMR of product 5e.

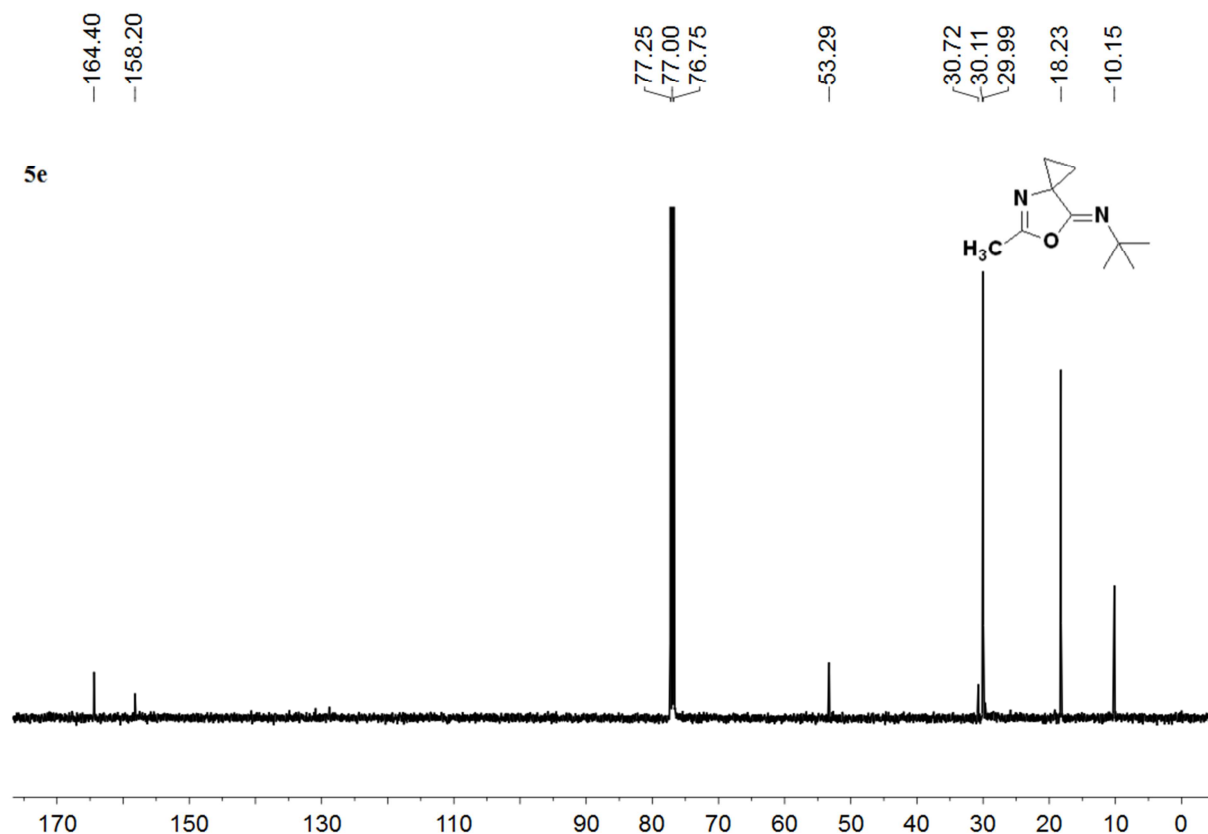


Figure 12. ^{13}C -NMR spectra of product **5e**.

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