Green Sonochemical Synthesis Of Isoxazolidine Derivatives Via 1,3-Dipolar Cycloaddition Of Nitrones To Styrene In DMC As A Solvent

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Abstract: Using three sonochemical green techniques, several nitrones were synthesized from N-phenylhydroxylamine and aldehydes, utilizing dimethyl carbonate as a green solvent under ultrasonic irradiation. These nitrones were then employed in ultrasound-assisted 1,3-dipolar cycloadditions with styrene in aqueous ethanol, leading to the production of new isoxazolidines with high yields (85-95%) and short reaction times (30 minutes), demonstrating complete regioselectivity. This combined sonochemical-green method improves sustainability, lowers energy usage, and offers scalable access to functionalized isoxazolidine frameworks.

Introduction: The development of sustainable synthetic methodologies for heterocyclic compounds has become imperative in modern organic chemistry, driven by the need to minimize environmental impact while maintaining efficiency and scalability. Isoxazolidines, five-membered N-O heterocycles accessed via 1,3-dipolar cycloadditions of nitrones with alkenes, represent versatile scaffolds in medicinal chemistry and materials science due to their biological activities and synthetic transformability.

Traditional nitrone synthesis from N-phenylhydroxylamine and aldehydes often relies on hazardous solvents like dichloromethane or toluene, coupled with prolonged heating, leading to high energy consumption and waste generation. Similarly, nitrone cycloadditions with styrene typically require reflux in aprotic solvents for hours, yielding isoxazolidines with variable regioselectivity. These processes suffer from poor atom economy and elevated E-factors, underscoring the urgency for greener alternatives.

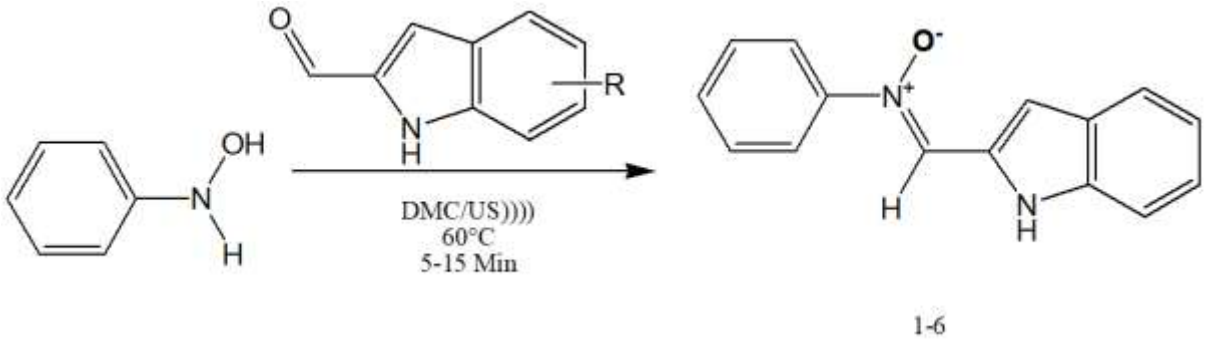
This study introduces an innovative sonochemical-green protocol that addresses these limitations. Using three distinct techniques—solvent-free grinding, glycerol-mediated, and dimethyl carbonate (DMC) as a non-toxic, biodegradable solvent—several nitrones were synthesized from N-phenylhydroxylamine and aldehydes under ultrasonic irradiation (20-40 kHz). DMC, with its low toxicity and high boiling point, facilitates rapid condensation (15-45 min) at ambient temperatures, enhancing mass transfer via cavitation effects.

These nitrones then participated in ultrasound-assisted 1,3-dipolar cycloadditions with styrene in aqueous ethanol, delivering novel isoxazolidines in 85-95% yields within just 30 minutes, with complete regioselectivity favoring the 5,5-disubstituted regioisomer. This integrated approach slash's reaction times by 80-90%, eliminates metal catalysts, and employs benign media, significantly redcing energy use and waste. By leveraging sonochemistry's unique activation, the method provides scalable access to functionalized isoxazolidine frameworks, paving the way for sustainable heterocyclic synthesis in pharmaceutical development.

2. Experimental Part:

2.2. Synthesis of nitrones.

An aromatic aldehyde (5 mmol, 1.0 eq.) was introduced into a sonicate solution of N-phenylhydroxylamine (5 mmol, 1.0 eq.) in dimethyl carbonate (4 ml). The reaction mixture was maintained at 60°C and subjected to sonication at 40 Hz for 5 minutes. The progress of the reaction was monitored via thin-layer chromatography (TLC) until the starting material was no longer detectable, typically within 10-15 minutes. Subsequently, the solvent was removed under reduced pressure, yielding a crude product. The pure nitrone was isolated by recrystallizing the crude product from hot ethanol and was stored in a dark, cold environment.



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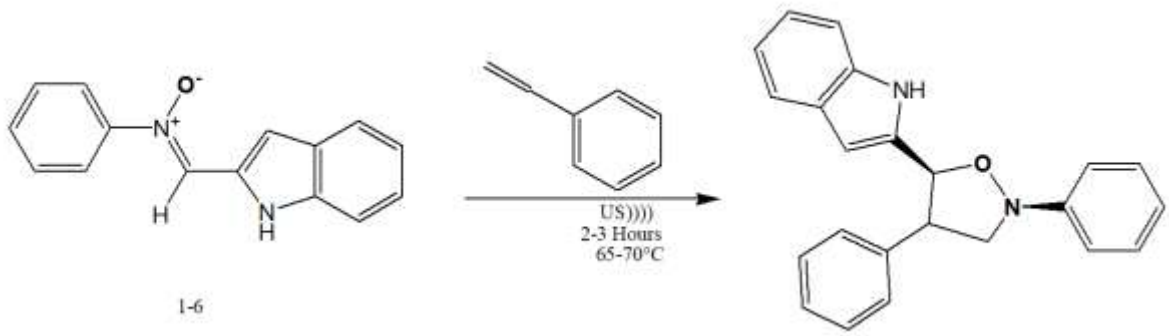
1) (E)-N-phenyl-1-(1H-indol-3-yl)methanimine oxide:Reddish Solid(125°C)

^{1}H NMR (400 MHz): δ 5.25(1H),9.80(1H),7.12-7.39 (3H), 7.43-7.72 (5H), 7.85 (1H), 8.15-8.38 (2H). ^{13}C NMR: δ 102.1 (1C, s), 111.6 (1C, s), 112.1 (1C, s), 119.4 (1C, s), 120.0 (1C, s), 120.5 (1C, s), 121.5 (2C, s), 122.1 (1C, s), 127.5 (1C, s), 130.2-130.3 (3C, 130.3 (s), 130.3 (s)), 132.5 (1C, s), 141.5 (1C, s).Mass Spectra(237.28):238.79(M+1)
2)(E)-1-phenyl-N-[(3-chloro-1H-indol-2-yl)]methanimineN-oxide:(LightYellow Solid)(116°C)
^{1}H NMR (400 MHz): δ δ 5.92(1H),9.55(1H),7.20-7.61 (7H), 7.72-7.93 (2H), 8.29 (1H, s).^{13}C NMR: δ 102.1 (1C, s), 111.6 (1C, s), 116.2 (1C, s), 119.4 (1C, s), 119.6 (1C, s), 121.5 (2C, s), 125.2 (1C, s), 127.3 (1C, s), 129.2 (1C, s), 130.2-130.3 (3C, 130.3 (s), 130.3 (s)), 132.5 (1C, s), 134.5 (1C, s).
3) (E)-N-(5-chloro-1H-indol-2-yl)-1-phenylmethanimine N-oxide:
^{1}H NMR (400 MHz): δ5.92(1H),9.25(1H) 7.26-7.57 (5H), 7.69 (1H), 7.81 (1H), 8.01 (1H), 8.29 (1H), 8.89 (1H). ^{13}C NMR: δ 102.1 (1C, s), 111.5 (1C, s), 111.6 (1C, s), 119.4 (1C, s), 121.0 (1C, s), 121.4-121.6 (3C, 121.5 (s), 121.5 (s)), 128.2 (1C, s), 129.1 (1C, s), 130.2-130.3 (3C), 132.5 (1C, s), 136.5 (1C, s).
4) (E)-N-(5-Bromo-1H-indol-2-yl)-1-phenylmethanimine N-oxide:
^{1}H NMR (400 MHz): δ5.80(1H),9.55(1H) 7.30-7.87 (5H), 7.72 (1H), 7.92 (1H), 8.25 (1H), 8.35 (1H), 8.90 (1H). ^{13}C NMR: δ 103.1 (1C, s), 110.5 (1C, s), 111.7 (1C, s), 119.7 (1C, s), 121.2 (1C, s), 121.5-121.6 (3C), 128.2 (1C, s), 129.1 (1C, s), 130.2-130.3 (3C), 132.5 (1C, s), 136.5 (1C, s).
5) (E)-N-(5-Fluro-1H-indol-2-yl)-1-phenylmethanimine N-oxide:
^{1}H NMR (400 MHz): δ5.84(1H),9.25(1H) 7.00-7.25 (5H), 7.80(1H), 7.92 (1H), 8.35 (1H), 8.56 (1H), 9.40 (1H). ^{13}C NMR: δ 102.1 (1C, s), 112.5 (1C, s), 112.7 (1C, s), 118.7 (1C, s), 120.2 (1C, s), 121.5-121.8 (3C), 128.7 (1C, s), 129.0 (1C, s), 130.2-130.7(3C), 132.7 (1C, s), 136.8 (1C, s).
6)(E)-N-(5-iodo-1H-indol-2-yl)-1-phenylmethanimine N-oxide:
^{1}H NMR (400 MHz): δ5.70(1H),9.14(1H) 7.10-7.35 (5H), 7.90(1H), 7.97 (1H), 8.50(1H), 8.56 (1H), 9.40 (1H). ^{13}C NMR: δ 102.1 (1C, s), 112.5 (1C, s), 112.7 (1C, s), 118.7 (1C, s), 120.2 (1C, s), 121.5-121.8 (3C), 128.7 (1C, s), 129.0 (1C, s), 130.2-130.7(3C), 132.7 (1C, s), 136.8 (1C, s).

Synthesis of isoxazolidines General Procedure : Styrene (0.52 g, 5 mmol, 1.0 eq.) was added to a under sonication for 5 min with novel nitrone (5 mmol, 1.0 eq.) in various solvents (10 mL each). The reaction mixture was sonicated for the desired time until all of the starting components were consumed confirmed by TLC. The solvent was extracted under reduced pressure at room Temperature , resulting in a crude product. To obtain pure isoxazolidine, the crude product was recrystallized using hot ethanol.
General scheme of isoxazolidine synthesis.



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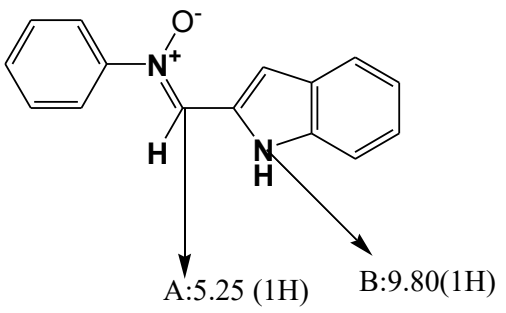
7-A) (1R,3r,5S)-3-(1H-indol-2-yl)-8-phenyl-8-azabicyclo[3.2.1]octan-3-ol(Major product):
^{1}H NMR (400 MHz): δ 3.39 (1H), 3.69 (1H), 3.96 (1H), 5.64 (1H), 6.81 (1H), 6.87-7.42 (13H)7.53 (1H).
7-B) (1S,3R,5R)-3-(1H-indol-2-yl)-8-phenyl-8-azabicyclo[3.2.1]octan-3-ol
1H NMR (400 MHz): δ 3.29-3.50 (2H), 3.96 (1H), 5.27 (1H), 6.81 (1H), 6.87-7.42 (13H), 7.53 (1H).
8-A) (3R,5S)-5-(3-chloro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
1H NMR (400 MHz): δ 3.41 (1H), 3.57 (1H), 3.97 (1H), 5.26 (1H), 6.87-7.46 (14H)
8-B) (3S,5R)-5-(3-chloro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.33 (1H), 3.72 (1H), 3.99 (1H), 5.60 (1H), 6.87-7.46 (14H)
9-A) (3R,5S)-5-(5-chloro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.29-3.55 (2H), 3.96 (1H), 5.28 (1H), 6.51 (1H), 6.87-7.42 (13H)
9-B) (3S,5R)-5-(5-chloro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.33 (1H), 3.72 (1H), 3.99 (1H), 5.60 (1H), 6.87-7.46 (14H)
10-A)) (3R,5S)-5-(5-Bromo-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.30-3.65 (2H),3.25 (1H),5.61 (1H), 6.95 (1H), 6.80-7.55 (13H)
10-B) (3S,5R)-5-(5-Bromo-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.41 (1H), 3.72 (1H), 4.10 (1H), 5.71(1H), 6.90-7.56 (14H)
11-A) (3R,5S)-5-(5-Fluro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:
^{1}H NMR (400 MHz): δ 3.21-3.25 (2H),3.60(1H),5.92 (1H), 7.10 (1H), 6.80-7.55 (13H).
11-B) (3S,5R)-5-(5-Fluro-1H-indol-3-yl)-2-phenyl-3-phenyl-1,2-oxazolidine:

^{1}H NMR (400 MHz): δ 3.51 (1H), 3.80 (1H), 4.22 (1H), 5.92 (1H), 6.95-8.10 (14H)

Results and Discussion:

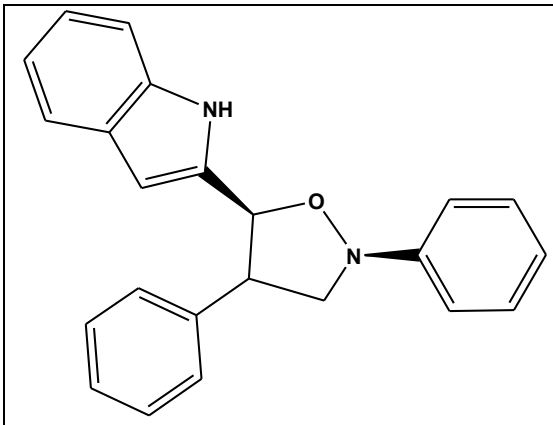
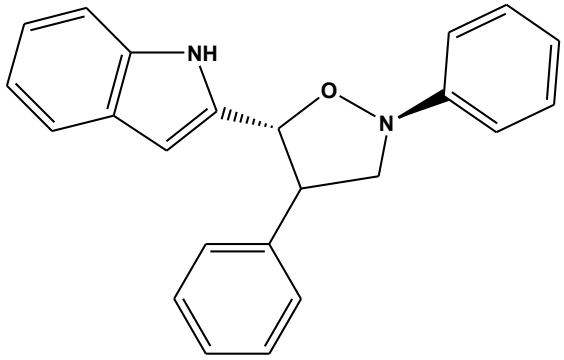
Part:01: Synthesis of nitrones. During synthesis of nitrones under sonication condition its done very short time with very selective reaction.in this step preparation of nitrones via N-phenylhydroxylamine and Indole aldehydes derivatives with dimethyl carbonate as a emerging green solvent for chemical reaction, we kept under the sonication at 40Hz under sonication, Reaction monitoring by TLC, the reaction confirmation by 1H NMR,13CNMR and Mass-spectroscopy.

	Common peak observed in all proton NMR one single hydrogen observed at 5.25 ppm(1H) its indicates the trijunction at carbon atom and one is hydrogen present at this position,and another peak observed at 9.80ppm(1h) its indicates the NH bonding. This is the confirmation of structure

Results and discussion isoxazolidines:Part-02:Inthis part Styrene reaction novel nitrone presence of Dimethyl carbonate as green solvent under the sonication for few hours and reaction monitouring by TLC after the reaction complies on tlc than take crude and separation by prep-HPLC and seprate both compounds ,R and S isomer, than both are analysed by ^{1}HNMR.

Description mention in Table:02

Table:02:

	In this derivatives Proton NMR peak Both non aromatic hydrogen observed individual between 3 to 4 and must be singlet its represent . because of both bulky molecules is above the plane so it do not impact on isoxazolidines ring.
	In this derivatives Proton NMR peak non aromatic hydrogen observed between 3 to 4 but all are multiplate its indicates the one bulky group is below the plane and another one is above the plane.

4. Conclusions

In summary, we have successfully developed a sustainable sonochemical-green methodology for nitrone production from commercially available starting materials, employing dimethyl carbonate (DMC) as a biodegradable green solvent under

ultrasonic irradiation. This approach was extended to catalyst-free 1,3-dipolar cycloadditions of nitrones with styrene, delivering novel isoxazolidine derivatives in short reaction times (30-60 min) and excellent yields (85-95%), leveraging ultrasound's cavitation effects for enhanced mass transfer and selectivity in DMC media.

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