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Design and Synthesis of Some Isoxazolidine moieties

Nedhal Abdullah Heatham Ali[1], Mohammed Al-Ghorbani[2,3*], Adel Gubran Al-Saeedi[4]
[1]Department of Chemistry, Education College, Aden University, Yemen
[2]Department of Chemistry, College of Science and Arts, Ulla, Taibah University, Medina, Saudi Arabia
[3]Department of Chemistry, College of Education, Thamar University, Thamar, Yemen
[4]Department of Chemistry, Education College – Yafea - Aden University, Yemen
***Corresponding Author: E-Mail: malghorbani@yahoo.com**

ABSTRACT

A series of isoxazolidine moieties were synthesized by 1,3-dipolar cycloaddition reaction in two refluxing methods. $NiCl_2$ was used as a catalyst in the cycloaddition reaction. The result showed that the catalytic method was more operative than the refluxing method which showed a high yield in less time. Most of the synthesized compounds were characterized by IR, NMR, mass spectroscopic techniques.

KEY WORDS: Nitrone, Cyclo addition reaction, Isoxazolidine.

1. INTRODUCTION

Nitrones are an intermediate for the synthesis of many natural products and serve to develop a wide range of 1,3-dipolar cycloaddition synthesis and were the significant entrance to various biological applications (Efremova, 2021; Cai, 2021; Loh, 2010; Teterina, 2019; Marx, 1997; Meng, 2007). The condensation reaction of two and more molecules in one framework structure has been used as an effective approach for designing new bioactive molecules. The 1,3-dipolar cycloaddition reaction of nitrones with olefins is an atom-economic approach for the yielded isoxazolidines which were crucial precursors in several natural molecules such as alkaloids, amino acids, and β-lactams **(**Martin and Jones, 2003). The isoxazolidine moiety represents one of the favored structures in medicinal chemistry, and there is a vast number of reported studies on isoxazolidine and isoxazolidine-containing compounds. Nitrone-olefin cycloaddition reactions have been used in the synthesis of numerous isoxaolidine substances which involve of various potential antimicrobial agents (Kumar, 2003: Mullen, 1988). Encouraged by current literature studies, some new isoxaolidine analogs were synthesized by 1,3-dipolar cycloaddition reaction of several nitrones and dipolarphiles, leading to remarkable heterocyclic frames that are most valuable for the design of varied drug-like molecules for biological examination.

2. MATERIALS AND METHODS

The FT-IR was recorded on a Bruker spectrophotometer (KBr/cm^{-1}). NMR spectra were performed on Bruker AVANCE HD Spectrometer (^1H, 500 MHz and ^{13}C, 125 MHz) at SAIF, IIT Madras, Chennai, India. LC-MS (m/z,%) was recorded on an Agilent Model 8890 GC System spectrometer at SAIF, IIT Madras, Chennai, India. Elemental analyses (E.A) were determined utilizing LECO Truspec Micro Analyzer.

General procedure preparation of nitrones 3a-c: A mixture of nitrobenzene (12.5g, 0.1mol) in 50 ml of ethanol, and NH_4Cl (6.25 g, 0.1mol) in 50 ml of water was added to the mixture. The reaction mixture was stirred in an ice bath while adding zinc dust (15.5g, 0.2mol) in 3 g portions every 3 to 5 min. after stirring for 25 min at 10 to 15^0C, the formed white suspension was treated with substituted amides (formamide, benzamide, and *N*-phenylacetamide) (0.1mol) in 50 ml of acetic acid. A clear yellow solution was immediately obtained, after 15 min, the nitrone began to precipitate, the reaction mixture was stirred for 30 min at room temperature, the reaction mixture was monitored by TLC, then poured into 200 ml of toluene, the toluene was washed with two 150 ml portions of water,150 ml of saturated aqueous sodium bicarbonate and again with 150 ml of water most of the toluene was then evaporated at reduced pressure and the remaining warm solution poured into 200ml of cyclohexane while stirring and cooling, the crude nitrone was collected by filtration and recrystallized from benzene.

N-phenyl-α-phenyl–α-amino nitrone (3b): ^1H NMR (500MHz, DMSO-d_6): δ 7.36-7.97 (m, 10H, Ar-H), 7.21 (s, 2H, NH_2); LC-MS: m/z calculated for $C_{13}H_{12}N_2O$: 213.02 (M+1). Anal. Calcd C, 73.56; H, 5.70; N, 13.20; Found: C, 73.32; H, 5.56; N, 13.11 %.

Synthesis of Isoxazolidines (5a-k): To a mixture of nitrone (0.0025mol) in 20 ml of toluene, amides (0.0025mol) was added and the mixture was heated under reflux until TLC analysis showed complete consumption, typically 21–48 h. Then the cooled solution was evaporated and 20 mL of water was added to the residue and extracted with DCM (3x15). The DCM layer was dried over magnesium sulfate and evaporated to give a crude mixture. Then it was purified by column chromatography using EtOAc/hexanes (1:3) as eluent to afford the final products (5a-k).

3-Amino-2,3-diphenylisoxazolidine-5-carboxamide (5c): ^1H NMR (500MHz, DMSO-d6): δ 2.54-2.56 (d, 2H, CH_2), 4.18-4.29 (d, 1H, CH), 5.57-5.60 (d, 2H, NH_2), 6.04-6.08 (d, 1H, Ar-H), 6.11-6.21 (d, 1H, Ar-H), 6.29-6.32 (d, 1H, Ar-H), 7.07 (d, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 7.42-7.45 (d, 2H, NH_2), 7.49-7.52 (d, 1H, Ar-H), 7.86-7.87 (d, 2H, Ar-H), 7.97 (d, 1H, Ar-H). Anal. Calcd.: C, 67.83; H, 6.05; N, 14.83; Found: C, 67.71; H, 5.05; N, 14.83%.

3-Amino-2,3-diphenyl-isoxazoldine-5-carboxylic acid (5e): ^{1}H NMR (500MHz, DMSO-d6): δ 5.59-5.90 (d, 2H, NH_2), 6.9-6.08 (d, 1H, Ar-H), 6.11-6.21 (d, 1H, Ar-H), 6.29-6.32 (d, 1H, Ar-H), 7.07 (d, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 7.42-7.45 (d, 2H, NH_2), 7.49-7.52 (d, 1H, Ar-H), 7.86-7.87 (d, 2H, Ar-H), 7.97 (d, 1H, Ar-H). Anal. Calcd.: C, 67.83; H, 6.05; N, 14.83; Found: C, 67.71; H, 5.05; N, 14.83%.

3-Methyl-2-phenyl-3-(phenylamino)isoxazolidine-5-carboxamide (5f): IR ν_{max} (KBr): 3294, 3135, 3060, 1664, 1556, 1435, 1368, 1263, 1040, 906, 756, 694, 509; 1 H NMR (500MHz, DMSO-d6): δ 2.03 (s, 3H, CH3), 3.36 (s, 2H, CH_2), 6.99-7.03 (t, 2H, Ar-H), 7.25-7.29 (t, 4H, Ar-H), 7.55-7.56 (t, 4H, Ar-H); ^{13}C NMR (500MHz, DMSO-d_6): δ 24.43, 119.48, 123.34, 129.09, 139.77, 168.74. Anal. Calcd.: C, 68.67; H, 6.44; N, 14.13; Found: C, 68.45; H, 6.32; N, 14.02 %.

3-Methyl-*N*,2-diphenyloctahydrobenzo[d]isoxazol-3-amine (5g): ^{1}H NMR (500MHz, DMSO-d_6): δ 3.44 (s, 2H, CH_2), 3.73 (s, 3H, CH_3), 4.75 (s, 2H, CH), 6.89-6.91(d, 2H, Ar-H), 6.92-6.95 (d, 1H, Ar-H), 6.99-7.00 (d, 2H, Ar-H), 7.21-7.24 (d, 2H, NH_2), 7.37-7.38 (d, 3H, Ar-H), 7.49 (d, 1H, Ar-H). Anal. Calcd.: C, 77.89; H, 7.84; N, 9.08; Found: C, 77.71; H, 7.68; N, 9.01 %.

3-Methyl-2-phenyl-3-(phenylamino)-4-(phenylcarbamoyl)isoxazolidine-5-carboxylic acid (5K): ^{1}H NMR (500MHz, DMSO-d_6): δ 2.02 (s, 3H, CH_3), 3.38 (s, 2H, CH), 6.29-6.31 (d, 1H, Ar-H), 6.45-6.47 (d, 1H, Ar-H), 6.99-7.03 (t, 1H, Ar-H), 7.07-7.10 (d, 1H, Ar-H), 7.25-7.34 (m, 6H, Ar-H), 7.54-7.56 (m, 4H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 9.91 (s, 2H, NH), 10.41 (s, 1H, OH). Anal. Calcd.: C, 69.05; H, 5.55; N, 10.07; Found: C, 68.87; H, 5.35; N, 10.02 %.

5-(Bromomethyl)-3-methyl-N,2-diphenylisoxazolidin-3-amine (5i): ^{1}H NMR (500MHz, DMSO-d_6): δ 2.03 (s, 3H, CH_3), 3.39 (s, 2H, $2CH_2$), 6.99-7.33 (d, 1H, Ar-H), 7.25-7.29 (d, 2H, Ar-H), 7.55-7.57 (m, 2H, Ar-H), 9.91 (s, 1H, NH); LC-MS: m/z 348.08 (M+1). ; LC-MS: m/z calculated for C_{17} $H_{19}BrN_2O$**:** 348.08 (M+ 1). Anal. Calcd.: C, 58.80; H, 5.52; Found: C, 58.65; H, 5.34 %.

Scheme.1. Synthesis of nitrones (3a-c)

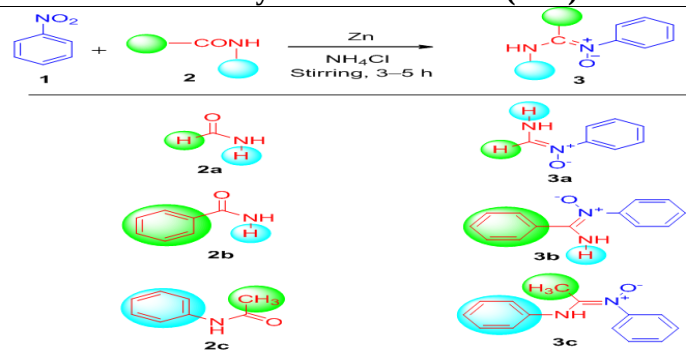

Table.1. Physical properties of nitrones (3a-c)

Comp No.	Molecular formal	State	M.P/ ºC	Time/h (Stirring)	Yield %
3a	$C_7H_8N_2O$	Reddish dark	liquid	3h	67
3b	$C_{13}H_{12}N_2O$	White crystals	122-125	3h	35
3c	$C_{14}H_{14}N_2O$	Brown solid	105-108	3h	58

Scheme 2. Synthesis of isoxazolidine derivatives (5a-b); Reagents and conditions: (i) Toluene, reflux at 110ºC, 21-48h (ii) $NiCl_2$, toluene, reflux at 110ºC, 3-5h.

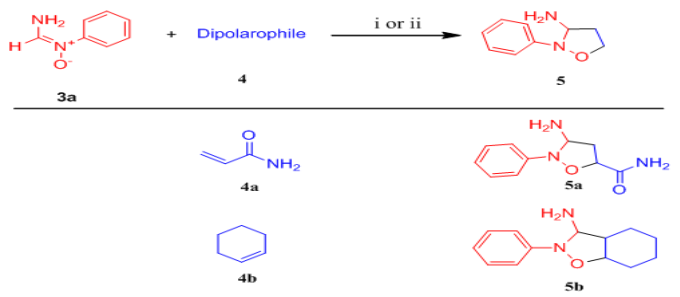

Table 2. Physical properties of isoxazolidine derivatives (5a -b)

Comp. No.	M. F.	State	M.P/ºC	Time/ h (Uncatalyzed: Catalyzed)	Yield %
5a	C_{10} $H_{14}N_3O_2$	Colorless crystal	>200	48: 3	66: 80
5b	$C_{13}H_{19}N_2O$	Dark red thick liquid	liquid	44: 3	63:75

Scheme 3. Synthesis of isoxazolidine derivatives 5c-e: Reagents and conditions: (i) Toluene, reflux at 110ºC, 21-48h (iii) $NiCl_2$, toluene, reflux at 110ºC, 3-5h.

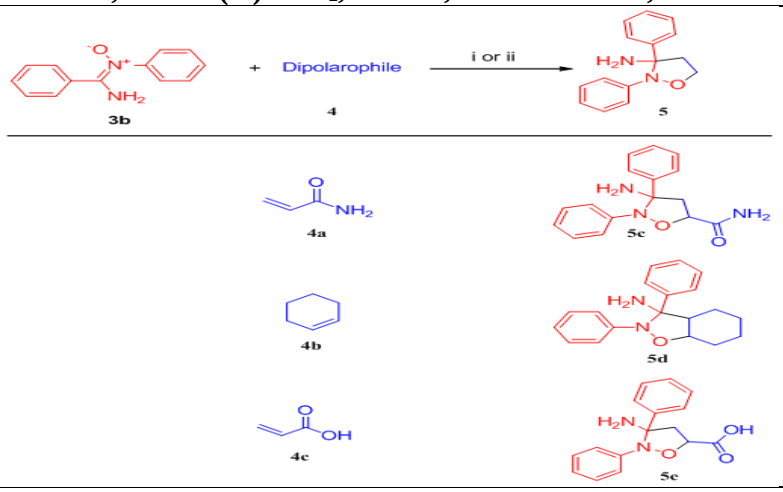

Table 3. Physical properties of isoxazolidine derivatives (5c-e)

Comp. No.	M.F.	State	M.P/ ºC	Time/ h (Uncatalyzed: Catalyzed)	Yield %
5c	$C_{16}H_{17}N_3O_2$	White solid	116-118	31: 3	44: 66
5d	$C_{19}H_{22}N_2O$	White solid	125-127	21 : 3	43: 70
5e	$C_{16}H_{16}N_2O_3$	Yellow solid	125-126	34 :3	84: 87

Scheme 4. Synthesis of isoxazolidines 5f-k: Reagents and conditions: (i) Toluene, reflux at 110ºC, 21-48h (ii) (iii) $NiCl_2$, toluene, reflux at 110ºC, 3-5h.

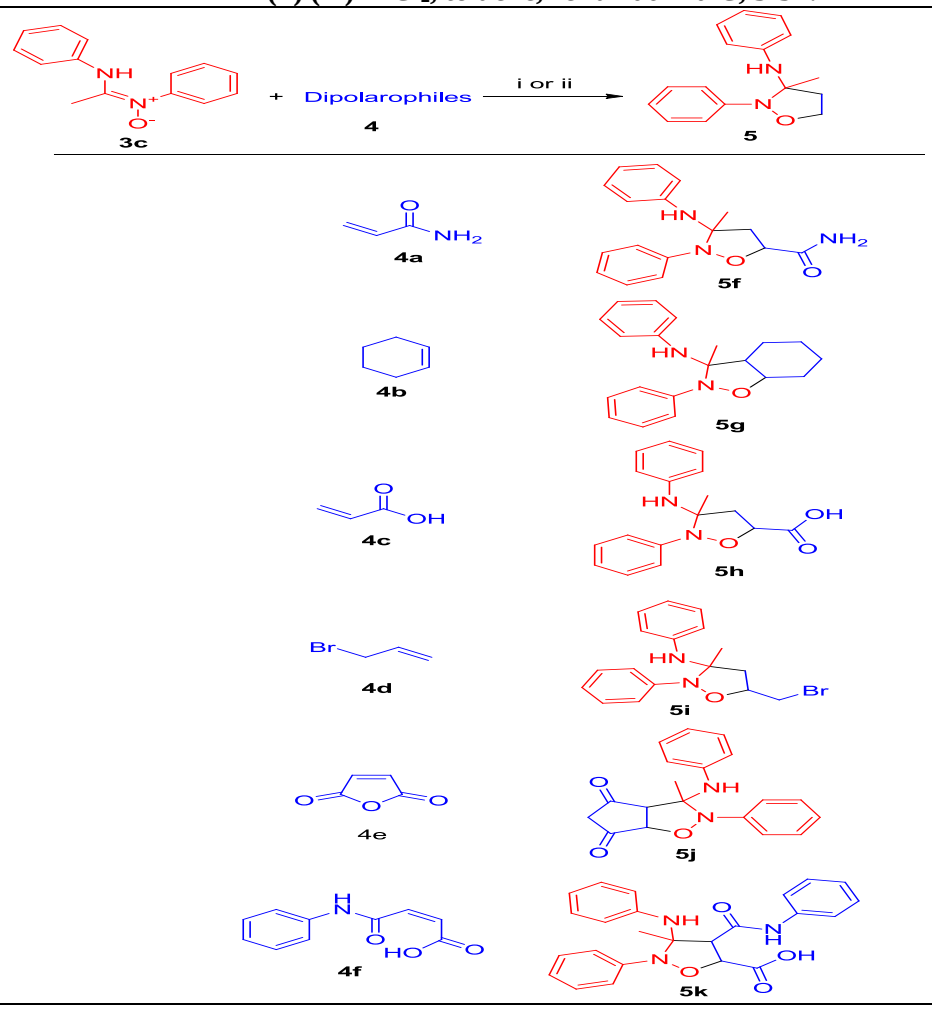

Table 4. Physical properties of isoxazolidine derivatives (5f-k)

Comp. No.	M. F.	State	M.P/ ºC	Time/h (Uncatalyzed: Catalyzed)	Yield %
5f	$C_{16}H_{17}N_3O_2$	White solid	112-114	22: .3	41: 60
5g	$C_{19}H_{19}N_2O_3$	Yellow solid	126-128	24: 3	71: 80
5h	$C_{24}H_{23}N_3O_4$	White solid	121-123	42: 3	44: 65
5i	$C_{17}H_{19}BrN_2O$	Brown solid	108-110	26: 3	65: 79
5j	$C_{16}H_{16}N_2O_3$	White crystal	109-111	27: 3	77: 80
5k	$C_{19}H_{22}N_2O$	Brown solid	111-113	25: 3	62: 88

3. RESULTS AND DISCUSSION

The synthesis of the isoxazolidine derivatives was performed in two-step reactions outlined in schemes 1, 2. The green synthesis of nitrones (3a-c) was established by stirring nitrobenzene in the presence of Zn, NH_4Cl (Scheme 1). The formed precipitate was treated with substituted amides (formamide, benzamide, and *N*-phenyl acetamide) without further purification according to the reported method (Pfeiffer 2009). The cyclo addition reactions were accomplished by two methods using nitrone analogs (3a-c) and dipolarphiles (4a-f) such as Acrylamide, cyclohexene, maleic anhydride, acrylic acid, allyl bromide, and *N*-phenyl maleamic acid in 1:1 mixture which was refluxing in toluene at 110ºC for 21-48h. In addition, the $NiCl_2$ was used as a catalyst for the cycloaddition reaction in toluene for 3-5h (Scheme 2, 3, 4). From the results, we found that the catalytic method was more operative than the refluxing method which showed a high yield in less time. On the other hand, the yield is not increased when we increased the temperature and time of refluxing method.

We observed that the presence of phenyl group on nitrones 3b-c showed less yield, in addition, isoxazolidine 5e bearing carboxyl as the withdrawing group on C5 of isoxazolidine ring gives a relatively higher yield. Furthermore, the cycloaddition reaction of 3d with cycloalkenes such as furan-2,5-dione and cyclohexene showed a moderate yield. The structures of the most synthesized compounds were confirmed by IR, mass, NMR spectra analysis.

4. CONCLUSION

The isoxazolidine derivatives 5a-k were synthesized by the 1,3-dipolar cyclo addition reaction of Nitrones 3a-c and dipolarphiles 4a-f in or without the catalyst. The catalytic method was more operative than the refluxing method which showed a high yield in less time.

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