

Environmentally Sustainable and Highly Effective Synthesis of Isoxazole Derivatives in Aqueous Solutions

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Abstract : A series of 5-arylisoxazole derivatives were prepared through the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in water, without the need for any catalysts. This approach offers several benefits, including simplified work-up procedures, mild reaction conditions, high yield, and an environmentally friendly process.

(Keywords : 5-arylisoxazole; hydroxylamine hydrochloride, without catalyst; aqueous solution)

Introduction

The necessity to minimize toxic waste and byproducts generated from chemical processes highlights the importance of utilizing less harmful and environmentally friendly materials in the development of new synthetic methodologies¹. One of the most promising strategies is employing water as the reaction medium². Aqueous environments are generally more economical, safer, and environmentally sustainable compared to organic solvents. In recent years, there has been a growing acknowledgment of water as a suitable medium for various organic reactions³. Numerous significant heterocycles, including furans, pyridines, quinolines, indoles, triazines, acridines, pyrazines, and pyrimidines, have been successfully synthesized in aqueous media^{4,5}. The ongoing synthesis of novel and essential heterocyclic compounds in water continues to garner considerable interest among synthetic chemists.

Nitrogen-containing heterocyclic compounds are highly significant for both

medicinal and organic chemists, and their synthesis remains a challenge from both academic and industrial viewpoints⁶. Isoxazole derivatives constitute a vital class of heterocyclic pharmaceuticals and bioactive natural products, exhibiting a wide range of biological activities, including potent and selective antagonism of the NMDA receptor⁷ and anti-HIV properties⁸. Numerous methods for synthesizing isoxazoles have been developed^{9,10}; however, these procedures are typically conducted using organic solvents. In line with our ongoing research aimed at creating new pathways for heterocyclic compounds in aqueous media¹¹, we present an efficient and environmentally friendly synthetic method for isoxazole derivatives, achieved through the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in water.

Experimental

All reagents were obtained from commercial sources and utilized without any further purification. Melting points were recorded uncorrected. Infrared (IR) spectra were measured using a Varian F-1000 spectrometer in KBr, with absorptions reported in cm⁻¹. Proton (¹H-NMR) and carbon (¹³C-NMR) nuclear magnetic resonance spectra were recorded on a Varian Inova-300 MHz or Varian Inova-400 MHz spectrometer in CDCl₃ solution, with J values expressed in Hertz. Chemical shifts were indicated in parts per million relative to the internal standard tetramethylsilane (TMS). High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF-Q instrument.

3.1. 3.1.General Procedure for the Synthesis of 3- (Dimethylamino)-1-arylprop-2-en-1-ones 1a-l

Solution of the substituted acetophenone (2 nmol) in N,N-dimethyl-formamide dimethyl acetal or N,N-dimethylacetamide dimethyl acetal (10 mL) was refluxed for 20 hours, during which methyl alcohol was generated and removed using a reflux condenser. After cooling, the resulting ppt. was collected by suction filtration to yield the desired compounds.

1-(4-Chlorophenyl)-3-(dimethylamino) prop-2-en-1-one (1a)

Melting Point: 84–86 °C

IR (KBr) ν (cm⁻¹): 2916, 2804, 1648, 1580, 1545, 1433, 1412, 1353, 1279, 1237, 1118, 1088, 1053, 1010, 981, 899, 837, 790, 742, 678
¹H-NMR (400 MHz, CDCl₃) δ (ppm): 2.89 (s, 3H, NCH₃), 3.11 (s, 3H, NCH₃), 5.64 (d, J = 12.4 Hz, 1H, CH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.78 (d, J = 12.8 Hz, 1H, CH), 7.81 (d, J = 8.4 Hz, 2H, ArH)

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 37.2, 45.0, 91.6, 128.3, 128.8, 136.8, 138.7, 154.4, 187.1

HRMS calculated for C₁₁H₁₃ClNO [M+H]⁺: 210.0686; found: 210.0685.

3-(Dimethylamino)-1-(4-methoxyphenyl) prop-2-en-1-one(1b)

Melting Point: 92-94 °C

IR (KBr) ν (cm⁻¹): 2904, 2838, 1643, 1603, 1583, 1432, 1358, 1305, 1242, 1175, 1117, 1057, 1025, 901, 775

¹H-NMR(400MHz,CDCl₃) δ (ppm): 2.89(s,3H,NCH₃),3.06(s,3H,NCH₃),3.80(s,3H,CH₃O), 5.66(δ ,J=12.4Hz,1H,CH),6.86- 6.87 (m,2H,ArH),7.74(d,J=12.4Hz,1H, CH),7.86-7.88(m,2H,ArH)

¹³C-NMR(75MHz,CDCl₃) δ (ppm): 37.0, 44.8,55.2,91.5,113.2,129.3,132.9,153.7, 161.8,187.1

HRMS calculated for C₁₂H₁₆NO₂ [M+H]⁺: 206.1181; found : 206.1205.

1-(4-Bromophenyl)-3-(dimethylamino)prop-2-en-1-one (1c)

Melting Point: 81–83 °C

IR (KBr) ν (cm⁻¹): 2910, 2808, 1649, 1575, 1541, 1435, 1357, 1304, 1271, 1237, 1120, 1056, 1003, 895, 847, 808, 774, 760, 673

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 2.88 (s, 3H, NCH₃), 3.12 (s, 3H, NCH₃), 5.62 (d, J=12.4 Hz, 1H, CH), 7.60 (d, J=8.4 Hz, 2H, ArH), 7.73 (s, 1H, CH), 7.75–7.79 (m, 2H, ArH)

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 37.3, 45.1, 91.5, 125.4, 129.1, 131.3, 139.4, 154.6, 187.2

HRMS calculated for C₁₁H₁₃BrNO [M+H]⁺: 254.0181; found: 254.0182.

3-(Dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one (1d)

Melting Point: 94–95 °C

IR(KBr) ν (cm⁻¹): 2928, 2898, 2809, 1636, 1554, 1427, 1291, 1253, 1189, 1111, 1045, 909, 863, 826, 781, 759

¹H-NMR(400MHz,CDCl₃) δ (ppm): 2.90(s,3H,NCH₃),3.09(s,3H,NCH₃),5.85 (δ ,J=12.4Hz,1H,CH),7.46-7.53 (m,2H, ArH),7.82-7.88(m,3H,ArH),7.92 (t, J=6.8Hz, 1H,CH),8.00-8.04 (m,1H,ArH),8.40 (s,1H, ArH)

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 37.3, 45.1, 92.4, 124.6, 126.2, 127.2, 127.7, 127.8, 129.2, 132.8, 134.7, 137.9, 154.3, 188.4

HRMS calculated for C₁₅HNO[M+H]⁺: 226.1232; found : 226.1234.

3-(Dimethylamino)-1-phenylbut-2-en-1-one (1e)

State: Oil

IR (KBr) ν (cm⁻¹): 2911, 1650, 1555, 1500, 1450, 1357, 1311, 1267, 1027, 1067, 1000, 900, 857, 775, 761, 673

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 2.64 (s,3H, CH), 3.02 (s, 6H, N(CH₃)), 5.69 (s, 1H, CH), 333 37.0, 44.8, 55.2, 91.5, 113.2, 129.3, 132.9, 153.7, 7.13 (s, 1H, ArH), 7.41 (t, J = 6.4 Hz, 2H, ArH),

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 19.5, 42.7, 52.3, 117.3, 128.2, 130.0, 130.6, 133.9, 151.6, 166.1, 172.4

HRMS calculated for $C_{12}H_{15}NO$ $[M+H]^+$ 190.1232; found: 190.1245.

3-(Dimethylamino)-1-(4-methoxyphenyl)but-2-en-1-one (1f)
HRMS calculated for $C_{12}H_{14}BrNO$ $[M+H]^+$: 2-en-1-one (1f)

Melting Point: 134–136 °C

IR (KBr) ν (cm^{-1}): 2961, 2835, 1671, 1574, 1461, 1307, 1167, 1081, 1025, 917, 865, 782, 746, 694

^1H -NMR (400 MHz, $CDCl_3$) δ (ppm):

2.62 (s, 3H, CH_3), 3.01 (s, 6H, $N(CH_3)_2$), 3.81 (s, 3H, CH_3O), 5.64 (s, 1H, CH), 6.86 (d, $J = 8.4$ Hz, 2H, ArH), 7.84 (d, $J = 8.4$ Hz, 2H, ArH)

^{13}C -NMR (75 MHz, $CDCl_3$) δ (ppm): 16.2, 39.9, 55.2, 92.1, 113.0, 129.0, 135.5, 161.3, 163.3, 187.0

HRMS calculated for $C_{12}H_{14}NO$ $[M+H]^+$: 220.1338; found: 220.1341.

3-(Dimethylamino)-1-(4-methylphenyl)but-2-en-1-one (1g)

Melting Point: 94–96 °C

IR (KBr) ν (cm^{-1}): 2913, 2808, 1660, 1577, 1561, 1451, 1357, 1300, 1277, 1122, 1066, 1000, 899, 847, 775, 760, 673

^1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 2.37 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 5.67 (s, 1H, CH), 7.18 (d, $J = 7.6$ Hz, 2H, ArH), 7.76 (d, $J = 8.0$ Hz, 2H, ArH)

^{13}C -NMR (75 MHz, $CDCl_3$) δ (ppm): 16.4, 21.4, 40.0, 92.6, 127.3, 128.7, 140.4, 140.5, 163.6, 188.0

HRMS calculated for $C_{13}H_{15}NO$ $[M+H]^+$: 204.1388; found : 204.1386.

1-(4-Bromophenyl)-3-(dimethylamino)but-2-en-1-one (1h)

Melting Point: 88–92 °C

IR (KBr) ν (cm^{-1}): 2932, 1721, 1616, 1500, 1420, 1385, 1354, 1220, 1161, 1069, 1030, 1007, 849, 769, 680, 627

^1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 2.63 (s, 3H, CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 5.58 (s, 1H, CH), 7.49 (d, $J = 8.4$ Hz, 2H, ArH), 7.71 (d, $J = 8.4$ Hz, 2H, ArH)

^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) :16.5, 40.1, 92.0, 124.6, 128.4, 128.9, 131.2, 131.8, 141.8, 186.6

HRMS calculated for $C_{12}H_{14}BrNO$ $[M+H]^+$: 267.0259; found:267.0256.

3.2.General Procedure for the Synthesis of Isoxazole Derivatives 3a–l

3-(Dimethylamino)-1-arylprop-2-en-1-one 1 (1 nmol), hydroxylamine hydrochloride 2 (1 nmol) and water (5 mL) were added to a 25-mL round-bottom flask. The mixture was then stirred at 50°C for 2 h. After completion of the reaction, the mixture was then cooled to room temperature. The precipitate was collected by suction filtration to give products 3 without further purification.

Isoxazole Compounds Data

1. 5-(4-Chlorophenyl)isoxazole (3a)

- o Melting Point (Mp): 85–87 °C (lit. 84–85°C)
- o IR (KBr) ν (cm^{-1}): 1601, 1447, 1264, 1128, 1109, 1088, 802
- o ^1H -NMR ($CDCl_3$, 400 MHz): δ 6.52 (1H, C4-H), 7.45 (2H, ArH), 7.73 (2H, ArH), 8.31 (1H, C3-H)
- o ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 98.9, 125.6, 127.1, 129.2, 136.1, 150.8, 168.0
- o HRMS: calcd. 180.0216; found 180.0215

2. 5-(4-Methoxyphenyl)isoxazole (3b)

- o **Mp:** 60–62 °C (lit. 64–65 °C)
- HRMS calculated for $C_{13}H_{13}NO$ $[M+H]^+$:**
- o IR ν (cm^{-1}): 3001, 1605, 1510, 1446, 1251, 1175, 1020, 906, 787, 675 204.1388; found: 204.1386.

- o ^1H -NMR: d 3.86 (3H, CH O), 6.39 (1H, C4-H), 6.97(2H, ArH), 7.73 (2H, ArH), 8.25 (1H, C3-H) o ^{13}C -NMR: δ 55.3, 97.2, 114.3, 120.0, 127.2, 150.7, 161.1, 169.2

- o **HRMS: calcd. 176.0712; found 176.0718**

3. 5-(4-Bromophenyl)isoxazole (3c)

- o **Mp:** 112–114 °C (lit. 114–116 °C)
- o IR ν (cm^{-1}): 1629, 1427, 1077, 1021, 846, 774
- o ^1H -NMR: d 6.53 (1H, C4-H), 7.60 (2H, ArH), 7.66 (2H, ArH), 8.31 (1H, C3-H)

$^{13}\text{C-NMR}$: δ 99.1, 124.5, 126.0, 127.2, 132.2, 150.9, 168.1

HRMS : calcd. 223.9711; found 223.9716

4. 5-(Naphthalen-1-yl)isoxazole(3d)

o Mp: 90–92°C

o IR (cm^{-1}): 3049, 1562, 1449, 1360, 1265, 1190, 910, 808, 738

o $^1\text{H-NMR}$: δ 6.63 (1H, C4-H), 7.53–7.56 (2H, ArH), 7.84–7.93 (4H, ArH), 8.31–8.34 (2H, C3-H and ArH)

o $^{13}\text{C-NMR}$: δ 98.9, 122.8, 124.3, 125.5, 126.8, 127.2, 127.7, 128.5, 128.8, 132.9, 133.8, 150.8, 169.2

o HRMS: calcd. 196.0762; found 196.0768

5. 3-Methyl-5-phenylisoxazole (3e)

Mp: 67–69°C (lit. 67°C)

IR (cm^{-1}): 3056, 2983, 1600, 1424, 1258, 1039, 897, 766, 683

o $^1\text{H-NMR}$: δ 2.36 (3H, CH₃), 6.37 (1H, C4-H), 7.42–7.47 (3H, ArH), 7.75–7.77 (2H, ArH)

o $^{13}\text{C-NMR}$: δ 11.4, 100.1, 125.6, 127.4, 128.8, 129.9, 160.2, 169.5

o HRMS: calcd. 160.0762; found 160.0770

6. 5-(4-Methoxyphenyl)-3-methylisoxazole (3f)

o Mp: 99–101°C

o IR (cm^{-1}): 2936, 1612, 1510, 1430, 1253, 1174, 1022, 787, 6803

o $^1\text{H-NMR}$: δ 2.34 (3H, CH₃), 3.85 (3H, CH₃O), 6.24 (1H, C4-H), 6.96 (2H, ArH), 7.68 (2H, ArH)

o $^{13}\text{C-NMR}$: δ 11.5, 55.2, 98.7, 114.2, 120.3, 127.2, 160.2, 160.8, 169.4

o HRMS: calcd. 190.0868; found 190.0862

7. 3-Methyl-5-(4-methylphenyl)isoxazole (3g)

o Mp: 88–90°C (lit. 92°C)

o IR (cm^{-1}): 3064, 2961, 1603, 1415, 1259, 1114, 1044, 956, 895, 792, 680

o $^1\text{H-NMR}$: δ 2.14 (3H, CH₃), 2.18 (3H, CH₃), 6.09 (1H, C4-H), 7.03 (2H, ArH), 7.43 (2H, ArH)

o $^{13}\text{C-NMR}$: δ 11.3, 21.3, 99.5, 124.8, 125.6, 129.5, 140.1, 160.1, 169.6

o HRMS: calcd. 174.0919; found 174.0914

8. 5-(4-Bromophenyl)-3-methylisoxazole (3h)

o Mp: 126–128°C

o IR (cm^{-1}): 2978, 1598, 1467, 1404, 1257, 1061

o $^1\text{H-NMR}$: δ 2.26 (3H, CH₃), 6.14 (1H, C4-H), 7.40 (2H, ArH), 7.68 (2H, ArH)

o $^{13}\text{C-NMR}$: δ 11.3, 100.4, 125.9, 126.9, 129.0, 135.9, 160.4, 168.3

o HRMS: calcd. 194.0372; found 194.0379

Results and Discussion

When an equimolar mixture of a 3-(dimethylamino)-1-arylprop-2-en-1-one derivative and hydroxylamine hydrochloride was stirred at 50 °C in an aqueous medium, the 5-aryl isoxazole derivatives were successfully synthesized in high yields (Scheme 1). The outcomes of this reaction are represented in Table 1.

Scheme 1. The synthesis of 5-aryl isoxazole derivatives in aqueous solution.

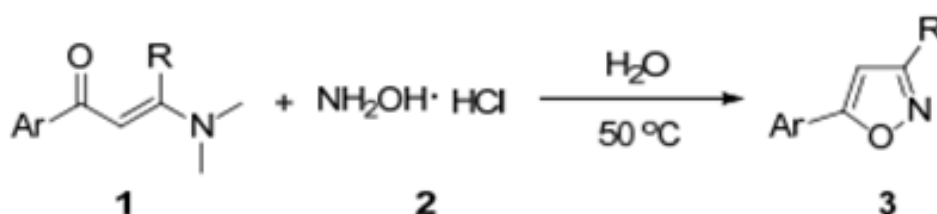


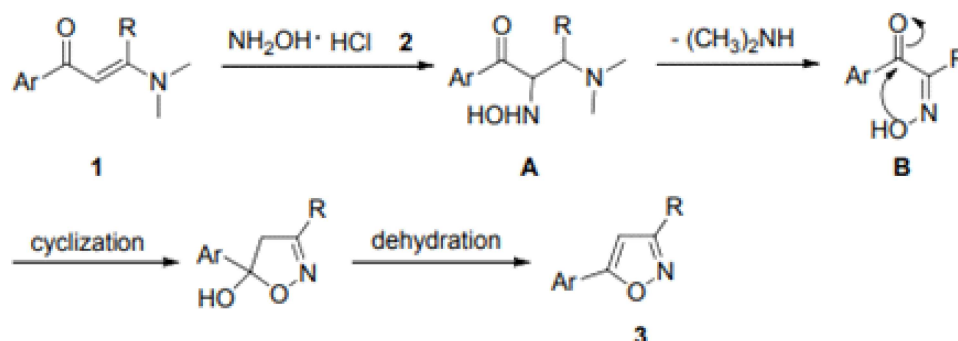
Table 1. The synthetic results of 5-arylisoxazole derivatives in aqueous solution

Entry	Product	Ar	R	Isolated Yield (%)
1	3a	4-ClC ₆ H ₄	H	88
2	3b	4-CH ₃ OC ₆ H ₄	H	93
3	3c	4-BrC ₆ H ₄	H	89
4	3d	Naphthen-2-yl	H	84
5	3e	C ₆ H ₅	CH ₃	88
6	3f	4-CH ₃ OC ₆ H ₄	CH ₃	92
7	3g	4-CH ₃ C ₆ H ₄	CH ₃	89
8	3h	4-BrC ₆ H ₄	CH ₃	90

As illustrated in Table 1, this method is applicable to 3-(dimethylamino)-1-arylprop-2-en-1-ones containing both electron-withdrawing groups (such as halides) and electron-donating groups (such as methyl or methoxy). Additionally, polysubstituted 3-(dimethylamino)-1-arylprop-2-en-1-ones were also suitable for this synthesis. Our findings indicated that the electronic characteristics of the substituents on the aromatic ring of the 3-(dimethylamino)-1-arylprop-2-en-1-ones did not significantly influence the reaction. This synthesis adhered to the principles of group-assisted purification chemistry[12,13], which enables the avoidance of traditional chromatography and recrystallization methods, allowing for the isolation of pure products solely through suction filtration without further

purification. All products (**3**) were characterized using their IR, ¹H-NMR, and HRMS spectra.

While the detailed mechanism of this reaction has yet to be fully elucidated, the formation of 5-arylisoxazoles can be understood through the reaction sequence outlined in Scheme 2. Initially, a Michael addition occurs between 3-(dimethylamino)-1-arylprop-2-en-1-ones and hydroxylamine, resulting in the formation of intermediate A. This intermediate then undergoes the elimination of one molecule of dimethylamine to produce intermediate B. Following this, intramolecular cyclization and dehydration take place, ultimately yielding the final product, 5-arylisoxazole (**3**). Scheme 2 illustrates the proposed mechanism for the synthesis of these compounds 5-arylisoxazole.



Conclusions

In summary, we successfully established a streamlined method for synthesizing isoxazole derivatives through the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in aqueous

solution, eliminating the need for any catalyst. This approach offers several benefits, including simpler work-up procedures, mild reaction conditions, high yields, and environmentally friendly practices.

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