Clean and Efficient Synthesis of Isoxazole Derivatives in Aqueous Media

Guolan Dou 1,*, Pan Xu 2, Qiang Li 3, Yukun Xi 2, Zhibin Huang 2 and Daqing Shi 2,*

1 School of Safety Engineering, China University of Mining & Technology, Xuzhou 221116, China
2 Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China
3 Hainan Chuntch Pharmaceutical Company Limited, Hainan Province Seaport Bonded Area 6th Workshop, Haikou 570216, China

* Authors to whom correspondence should be addressed; E-Mails: gldoucmt@163.com (G.D.); dqshi@suda.edu.cn (D.S.); Tel.: +86-512-6588-0049 (D.S.); Fax: +86-512-6588-0089 (D.S.).

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Abstract: A series of 5-arylisoxazole derivatives were synthesized via the reaction of 3-(dimethyl-amino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in aqueous media without using any catalyst. This method has the advantages of easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure.

Keywords: 5-arylisoxazole; without catalyst; aqueous media; synthesis

1. Introduction

The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods [1]. One of the most promising approaches is the use of water as the reaction medium [2]. Compared to organic solvents the aqueous medium is less expensive, less dangerous, and more environmentally friendly. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [3–5]. Many important types of heterocycles, such as furans, pyridines, quinolines, indoles, triazines, acidines, pyrazines, and pyrimidines have been synthesized in aqueous media [6–15]. The synthesis of new and other important type of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.
Nitrogen-containing heterocyclic building blocks are of great importance to both medical and organic chemists, and their synthesis continues to represent a challenge from both academic and industrial perspectives [16]. Isoxazole derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their significant and wide spectrum of biological activities, including potent and selective antagonism of the NMDA receptor [17] and anti-HIV activity [18]. Many syntheses of isoxazoles have been developed [19,20]. However, these syntheses are usually carried out in organic solvents. As part of our current studies on the development of new routes to heterocyclic systems in aqueous media [21–28], we now report an efficient and clean synthetic route to isoxazole derivatives via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in aqueous media.

2. Results and Discussion

When an equivalent mixture of an 3-(dimethylamino)-1-arylprop-2-en-1-one derivative 1 and hydroxylamine hydrochloride (2) was stirred at 50 °C in aqueous media, 5-arylisoxazole derivatives 3 were obtained in good yields (Scheme 1). The results are summarized in Table 1.

**Scheme 1.** The synthesis of 5-arylisoxazole derivatives in aqueous media.

![Scheme 1](image)

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

| Entry | Product | Ar       | R | Isolated Yield (%) |
|-------|---------|----------|---|---------------------|
| 1     | 3a      | 4-ClC₆H₄ | H | 88                  |
| 2     | 3b      | 4-CH₃OC₆H₄| H | 93                  |
| 3     | 3c      | 4-BrC₆H₄ | H | 89                  |
| 4     | 3d      | Naphthen-2-yl | H | 84                  |
| 5     | 3e      | C₆H₆     | CH₃| 88                  |
| 6     | 3f      | 4-CH₃OC₆H₄| CH₃| 92                  |
| 7     | 3g      | 4-CH₃C₆H₄ | CH₃| 89                  |
| 8     | 3h      | 4-BrC₆H₄ | CH₃| 90                  |
| 9     | 3i      | 4-ClC₆H₄ | CH₃| 86                  |
| 10    | 3j      | 4-CH₃OCOC₆H₄| CH₃| 84                  |
| 11    | 3k      | 4-BocNHC₆H₄| CH₃| 86                  |
| 12    | 3l      | Thiophen-2-yl | CH₃| 93                  |

As shown in Table 1, this protocol could be applied to the 3-(dimethylamino)-1-arylprop-2-en-1-ones with both electron-withdrawing groups (such as halide groups) and electron-donating groups (such as methyl or methoxyl groups). Polysubstituted 3-(dimethylamino)-1-arylprop-2-en-1-ones could also be used in this synthesis. We concluded that the electronic nature of the substituent on the aromatic ring of 3-(dimethylamino)-1-arylprop-2-en-1-ones had no significant effect on this reaction. This synthesis was confirmed to follow the group-assisted-purification chemistry process [29–31], which can avoid
traditional chromatography and recrystallization purification, that is, all the pure products can be obtained only by suction filtration without further purification. All the products 3 were identified from their IR, ¹H-NMR, and HRMS spectra.

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of 5-arylisoxazoles 3 could be explained by the reaction sequence presented in Scheme 2. First, the Michael addition of 3-(dimethylamino)-1-arylprop-2-en-1-ones 1 and hydroxylamine 2 gives the intermediate A, which then eliminates one molecule of dimethylamine to give the intermediate B, which upon intramolecular cyclization and dehydration gives rise to the final product 3.

**Scheme 2.** The proposed mechanism for the synthesis of 5-arylisoxazoles.

3. Experimental

All reagents were purchased from commercial suppliers and used without further purification. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm⁻¹. ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian Inova-300 MHz or Varian Inova-400 MHz in CDCl₃ solution. J Values are in Hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. High-resolution mass spectra (HRMS) were obtained using Bruker microTOF-Q instrument.

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

A solution of substituted acetophenone (2 nmol) in N,N-dimethylformamide dimethyl acetal or N,N-dimethylacetamide dimethyl acetal (10 mL) was refluxed for 20 h during which time some methanol was formed and removed through a reflux condenser. After cooling, the precipitate was collected by suction to give compounds 1.

1-(4-Chlorophenyl)-3-(dimethylamino)prop-2-en-1-one (1a). Mp: 84–86 °C; IR (KBr) ν: 2916, 2804, 1648, 1580, 1545, 1433, 1411, 1353, 1279, 1237, 1118, 1088, 1053, 1010, 980, 899, 837, 790, 678 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 2.89 (s, 3H, NCH₃), 3.12 (s, 3H, NCH₃), 5.63 (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, 128.2, 128.8, 128.8, 136.8, 138.7, 154.4, 187.0; HRMS calcd. for C₁₁H₁₃ClNO [M+H]+: 210.0686; found: 210.0685.

3-(Dimethylamino)1-(4-methoxyphenyl)prop-2-en-1-one (1b). Mp: 92–94 °C; IR (KBr) ν: 2905, 2838, 1643, 1603, 1583, 1432, 1358, 1305, 1242, 1175, 1117, 1057, 1026, 901, 774 cm⁻¹; ¹H-NMR (400 MHz,
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CDCl₃ δ (ppm) 2.89 (s, 3H, NCH₃), 3.05 (s, 3H, NCH₃), 3.80 (s, 3H, CH₃O), 5.66 (d, J = 12.4 Hz, 1H, CH), 6.86–6.88 (m, 2H, ArH), 7.74 (d, J = 12.4 Hz, 1H, CH), 7.86–7.88 (m, 2H, ArH); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 37.1, 44.8, 55.2, 91.5, 113.1, 129.3, 132.9, 153.7, 161.8, 187.2; HRMS calcd. for C₁₂H₁₆NO₂ [M+H]⁺: 206.1181; found: 206.1205.

1-(4-Bromophenyl)-3-(dimethylamino)prop-2-en-1-one (1c). Mp: 81–83 °C; IR (KBr) ν: 2910, 2808, 1649, 1575, 1540, 1435, 1357, 1304, 1271, 1120, 1056, 1003, 895, 847, 808, 775, 760, 673 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 2.88 (s, 3H, NCH₃), 3.11 (s, 3H, NCH₃), 5.62 (d, J = 12.4 Hz, 1H, CH), 7.50 (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, 91.6, 125.4, 129.1, 131.3, 139.3, 154.6, 187.2; HRMS calcd. for C₁₁H₁₃BrNO [M+H]⁺: 254.0181; found: 254.0182.

3-(Dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one (1d). Mp: 94–95 °C; IR (KBr) ν: 2927, 2898, 2809, 1636, 1554, 1427, 1291, 1253, 1189, 1111, 1045, 909, 863, 826, 781, 759 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 2.91 (s, 3H, NCH₃), 3.09 (s, 3H, NCH₃), 5.85 (d, J = 12.4 Hz, 1H, CH), 7.46–7.53 (m, 2H, ArH), 7.82–7.87 (m, 3H, ArH), 7.92 (t, J = 6.8 Hz, 1H, CH), 8.00–8.03 (m, 1H, ArH), 8.40 (s, 1H, ArH); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 37.3, 45.0, 92.4, 124.7, 126.2, 127.2, 127.7, 127.8, 129.2, 134.7, 137.9, 154.3, 188.4; HRMS calcd. for C₁₅H₁₅NO [M+H]⁺: 226.1232; found: 226.1234.

3-(Dimethylamino)-1-(4-methoxyphenyl)but-2-en-1-one (1f). Mp: 134–136 °C; IR (KBr) ν: 2961, 2835, 1671, 1574, 1460, 1307, 1167, 1081, 1025, 917, 865, 782, 746, 694 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 2.55 (m, 2H, CH₂), 2.62 (s, 3H, CH₃), 3.02 (s, 6H, N(CH₃)₂), 3.81 (s, 3H, CH₃O), 5.64 (s, 1H, CH), 6.86 (d, J = 8.4 Hz, 2H, ArH), 7.18 (d, J = 7.6 Hz, 2H, ArH); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 16.3, 21.4, 40.0, 92.6, 121.9, 127.3, 128.7, 140.3, 140.5, 163.6, 187.1; HRMS calcd. for C₁₃H₁₈NO₂ [M+H]⁺: 220.1338; found: 220.1341.

1-(4-Bromophenyl)-3-(dimethylamino)but-2-en-1-one (1h). Mp: 88–92 °C; IR (KBr) ν: 2931, 2808, 1660, 1577, 1561, 1450, 1357, 1300, 1277, 1122, 1066, 1000, 899, 847, 775, 760, 673 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ (ppm) 2.63 (s, 3H, CH₃), 3.06 (s, 6H, N(CH₃)₂), 5.58 (s, 1H, CH), 7.49 (d, J = 8.4 Hz, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 16.5, 40.1, 92.0, 124.6,
128.4, 128.9, 131.1, 131.8, 141.8, 186.7; HRMS calcd. for C\textsubscript{12}H\textsubscript{14}BrNO [M+H]\textsuperscript{+}: 267.0259; found: 267.0256.

\textit{1-(4-Chlorophenyl)-3-(dimethylamino)but-2-en-1-one} (1i). Mp: 82–84 °C; IR (KBr) \(\nu\): 3039, 2961, 2804, 1676, 1537, 1411, 1379, 1351, 1278, 1224, 1166, 1089, 1024, 1010, 921, 862, 772, 739, 712, 678 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 2.62 (s, 3H, CH\(_3\)), 3.04 (s, 6H, N(CH\(_3\))\(_2\)), 5.57 (s, 1H, CH), 7.31 (d, \(J = 8.4\) Hz, 2H, ArH), 7.76 (d, \(J = 8.4\) Hz, 2H, ArH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 16.4, 40.1, 92.0, 128.0, 128.6, 136.0, 141.3, 164.3, 186.5; HRMS calcd. for C\textsubscript{12}H\textsubscript{14}ClNO [M+H]\textsuperscript{+}: 224.0842; found: 224.0861.

\textit{Methyl 4-(3-dimethylamino)but-2-enoyl)benzoate} (1j). Mp: 103–106 °C; IR (KBr) \(\nu\): 2951, 1720, 1620, 1600, 1569, 1434, 1282, 1217, 1110, 1037, 868, 825, 759, 725 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 2.64 (s, 3H, CH\(_3\)), 3.06 (s, 6H, N(CH\(_3\))\(_2\)), 3.89 (s, 3H, CH\(_3\)), 5.61 (s, 1H, CH), 7.85 (d, \(J = 8.0\) Hz, 2H, ArH), 8.01 (d, \(J = 8\) Hz, 2H, ArH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 16.5, 40.1, 52.1, 92.5, 127.1, 129.3, 131.2, 147.0, 164.6, 166.7, 186.9; HRMS calcd. for C\textsubscript{14}H\textsubscript{17}NO\textsubscript{3} [M+H]\textsuperscript{+}: 248.1287; found: 248.1292.

\textit{tert-Butyl (4-(3-dimethylamino)but-2-enoyl)phenyl)carbamate} (1k). Mp: 218–220 °C; IR (KBr) \(\nu\): 3242, 3087, 2963, 1721, 1615, 1482, 1361, 1310, 1269, 1245, 1152, 1085, 1050, 1022, 866, 788, 690 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 1.50 (s, 9H, C(CH\(_3\))\(_3\)), 2.62 (s, 3H, CH\(_3\)), 3.04 (s, 6H, N(CH\(_3\))\(_2\)), 5.65 (s, 1H, CH), 6.83 (s, 1H, NH), 7.37 (d, \(J = 8.4\) Hz, 2H, ArH), 7.81 (d, \(J = 8.8\) Hz, 2H, ArH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 16.4, 28.3, 40.0, 80.6, 92.3, 117.3, 128.4, 137.4, 140.4, 152.5, 163.5, 187.2; HRMS calcd. for C\textsubscript{17}H\textsubscript{25}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 305.1865; found: 305.1866.

\textit{3-(Dimethylamino)-1-(thiophen-2-yl)but-2-en-1-one} (1l). Mp: 90–91 °C; IR (KBr) \(\nu\): 3078, 2919, 1862, 1620, 1569, 1434, 1282, 1217, 1110, 1037, 921, 868, 825, 759, 725 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 2.59 (s, 3H, CH\(_3\)), 3.01 (s, 6H, N(CH\(_3\))\(_2\)), 5.65 (s, 1H, CH), 6.83 (s, 1H, CH), 7.37 (d, \(J = 8.4\) Hz, 2H, ArH), 8.30 (d, \(J = 2.0\) Hz, 1H, C\(_3\)-H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 16.4, 28.3, 40.0, 80.6, 92.3, 117.3, 128.4, 137.4, 140.4, 152.5, 163.5, 187.2; HRMS calcd. for C\textsubscript{17}H\textsubscript{25}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 305.1865; found: 305.1866.

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.

\textit{5-(4-Chlorophenyl)isoxazole} (3a). Mp: 85–87 °C (lit. [19] 84–85 °C); IR (KBr) \(\nu\): 1601, 1447, 1264, 1128, 1109, 1088, 802 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 6.52 (d, \(J = 2.0\) Hz, 1H, C\(_4\)-H), 7.45 (d, \(J = 8.4\) Hz, 2H, ArH), 7.73 (d, \(J = 8.4\) Hz, 2H, ArH), 8.30 (d, \(J = 2.0\) Hz, 1H, C\(_3\)-H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 98.9, 125.6, 127.0, 129.2, 136.1, 150.8, 168.1; HRMS calcd. for C\textsubscript{9}H\textsubscript{7}ClNO [M+H]\textsuperscript{+}: 180.0216; found: 180.0215.

\textit{5-(4-Methoxyphenyl)isoxazole} (3b). Mp: 60–62 °C (lit. [19] 64–65 °C); IR (KBr) \(\nu\): 3002, 1605, 1510, 1446, 1251, 1175, 1020, 906, 877, 675 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 3.86 (s, 3H, CH\(_3\)O),
6.39 (d, J = 1.6 Hz, 1H, C4-H), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.73 (d, J = 8.8 Hz, 2H, ArH), 8.25 (d, J = 1.6 Hz, 1H, C3-H); 13C-NMR (75 MHz, CDCl3) δ (ppm) 55.3, 97.2, 114.3, 120.0, 127.3, 150.7, 161.0, 169.2; HRMS calcd. for C10H10NO2 [M+H]+: 176.0712; found: 176.0718.

5-(4-Bromophenyl)isoxazole (3c). Mp: 112–114 °C (lit. [19] 114–116 °C); IR (KBr) ν: 1629, 1427, 1077, 1021, 846, 775 cm−1; 1H-NMR (400 MHz, CDCl3) δ (ppm) 6.53 (d, J = 1.6 Hz, 1H, C4-H), 7.60 (d, J = 8.4 Hz, 2H, ArH), 7.66 (d, J = 8.8 Hz, 2H, ArH), 8.30 (d, J = 1.6 Hz, 1H, C3-H); 13C-NMR (75 MHz, CDCl3) δ (ppm) 99.0, 124.5, 126.0, 127.2, 132.2, 150.9, 168.2; HRMS calcd. for C9H7BrNO [M+H]+: 223.9711; found: 223.9716.

5-(Naphthalen-1-yl)isoxazole (3d). Mp: 90–92 °C; IR (KBr) ν: 3049, 1562, 1449, 1360, 1265, 1190, 910, 808, 738 cm−1; 1H-NMR (300 MHz, CDCl3) δ (ppm) 6.63 (d, J = 1.6 Hz, 1H, C4-H), 7.53–7.56 (m, 2H, ArH), 7.84–7.93 (m, 4H, ArH), 8.30–8.34 (m, 2H, C3-H and ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 98.9, 122.8, 124.3, 125.5, 126.8, 127.2, 127.7, 128.5, 128.8, 132.9, 133.8, 150.8, 169.3; HRMS calcd. for C13H10NO [M+H]+: 196.0762; found: 196.0768.

3-Methyl-5-phenylisoxazole (3e). Mp: 67–69 °C (lit. [32] 67 °C); IR (KBr) ν: 3056, 2983, 1600, 1424, 1258, 1039, 897, 766, 683 cm−1; 1H-NMR (400 MHz, CDCl3) δ (ppm) 2.36 (s, 3H, CH3), 6.37 (s, 1H, C4-H), 7.42–7.48 (m, 3H, ArH), 7.75–7.77 (m, 2H, ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 11.4, 100.1, 125.6, 127.4, 128.8, 129.9, 160.2, 169.5; HRMS calcd. for C10H10NO [M+H]+: 160.0762; found: 160.0770.

5-(4-Methoxyphenyl)-3-methylisoxazole (3f). Mp: 99–101 °C; IR (KBr) ν: 2936, 1612, 1510, 1430, 1253, 1174, 1022, 787, 680 cm−1; 1H-NMR (400 MHz, CDCl3) δ (ppm) 2.33 (s, 3H, CH3), 3.85 (s, 3H, CH3O), 6.24 (s, 1H, C4-H), 6.96 (d, J = 8.8 Hz, 2H, ArH), 7.69 (d, J = 8.8 Hz, 2H, ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 11.4, 55.2, 98.7, 114.2, 120.3, 127.2, 127.6, 128.8, 129.5, 160.2, 169.5; HRMS calcd. for C11H12NO2 [M+H]+: 190.0868; found: 190.0862.

3-Methyl-5-(4-methylphenyl)isoxazole (3g). Mp: 88–90 °C (lit. [33] 92 °C); IR (KBr) ν: 3063, 2961, 1603, 1415, 1259, 1114, 1044, 956, 895, 792, 680 cm−1; 1H-NMR (400 MHz, CDCl3) δ (ppm) 2.13 (s, 3H, CH3), 2.18 (s, 3H, CH3), 6.09 (s, 1H, C4-H), 7.04 (d, J = 8.4 Hz, 2H, ArH), 7.43 (d, J = 8.0 Hz, 2H, ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 11.4, 21.3, 99.5, 124.8, 125.6, 129.5, 140.1, 160.2, 169.7; HRMS calcd. for C11H12NO [M+H]+: 174.0919; found: 174.0914.

5-(4-Bromophenyl)-3-methylisoxazole (3h). Mp: 126–128 °C; IR (KBr) ν: 2978, 1598, 1467, 1404, 1256, 1061, 14, 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.67 (d, J = 8.0 Hz, 2H, ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 11.4, 100.4, 125.9, 126.9, 129.1, 135.9, 160.4, 168.4; HRMS calcd. for C10H9NO2 [M+H]+: 194.0373; found: 194.0378.

5-(4-Chlorophenyl)-3-methylisoxazole (3i). Mp: 88–89 °C (lit. [34] 90–91 °C); IR (KBr) ν: 1600, 1451, 1400, 1249, 1092, 1053, 833cm−1; 1H-NMR (400 MHz, CDCl3) δ (ppm) 2.34 (s, 3H, CH3), 6.34 (s, 1H, C4-H), 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.67 (d, J = 8.0 Hz, 2H, ArH); 13C-NMR (75 MHz, CDCl3) δ (ppm) 11.4, 100.4, 125.9, 126.9, 129.1, 135.9, 160.4, 168.4; HRMS calcd. for C10H9ClNO [M+H]+: 194.0373; found: 194.0378.
Methyl 4-(3-methylisoxazol-5-yl)benzoate (3j). Mp: 88–90 °C; IR (KBr) \(\nu\): 2945, 1720, 1601, 1419, 1274, 1182, 1105, 774 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 2.36 (s, 3H, CH\(_3\)), 3.93 (s, 3H, CH\(_3\)O), 6.46 (s, 1H, C\(^4\)-H), 7.81 (d, \(J = 8.4\) Hz, 2H, ArH), 8.10 (d, \(J = 8.4\) Hz, 2H, ArH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 11.4, 52.2, 101.6, 125.5, 130.1, 131.1, 131.2, 160.4, 166.2, 168.3; HRMS calcd. for C\(_{12}\)H\(_{12}\)NO\(_3\) [M+Na]\(^+\): 240.0637; found: 240.0650.

tert-Butyl 4-(3-methylisoxazol-5-yl)phenylcarbamate (3k). Mp: 120–121 °C; IR (KBr) \(\nu\): 3363, 3005, 2978, 1701, 1520, 1413, 1237, 1160, 835, 772 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 1.48 (s, 9H, (CH\(_3\))\(_3\)C), 2.25 (s, 3H, CH\(_3\)), 6.71 (s, 1H, C\(^4\)-H), 7.59 (d, \(J = 8.8\) Hz, 2H, ArH), 7.71 (d, \(J = 8.4\) Hz, 2H, ArH), 9.65 (s, 1H, NH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 11.5, 80.9, 99.2, 118.3, 122.1, 126.6, 140.0, 152.4, 160.3, 169.3; HRMS calcd. for C\(_{15}\)H\(_{19}\)N\(_2\)O\(_3\) [M+H]\(^+\): 275.1396; found: 275.1392.

3-Methyl-5-(thiophen-2-yl)isoxazole (3l). Oil; IR (KBr) \(\nu\): 2933, 1605, 1422, 1033, 899, 792, 706 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 2.33 (s, 3H, CH\(_3\)), 6.24 (s, 1H, C\(^4\)-H), 7.11 (t, \(J = 4.4\) Hz, 1H, ArH), 7.43 (d, \(J = 4.8\) Hz, 1H, ArH), 7.48 (d, \(J = 3.6\) Hz, 1H, ArH); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) 11.4, 100.0, 126.7, 127.7, 128.0, 129.4, 160.3, 160.4; HRMS calcd. for C\(_8\)H\(_8\)NOS [M+H]\(^+\): 166.0327; found: 166.0322.

4. Conclusions

In conclusion, we have developed an efficient synthesis of isoxazole derivatives via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in aqueous media without using any catalyst. This method has the advantages of an easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure.

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Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds 3 are available from the authors.

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