Molecules **2013**, *18*, 13645-13653; doi:10.3390/molecules181113645

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

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: gldoucumt@163.com (G.D.); dqshi@suda.edu.cn (D.S.); Tel.: +86-512-6588-0049 (D.S.); Fax: +86-512-6588-0089 (D.S.).

Received: 5 August 2013; in revised form: 22 October 2013 / Accepted: 31 October 2013 / Published: 5 November 2013

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, acridines, 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.

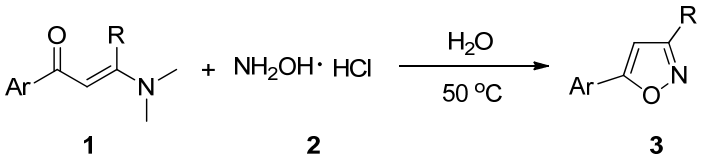


Table 1. The synthetic results of 5-arylisoxazole derivatives in aqueous media.

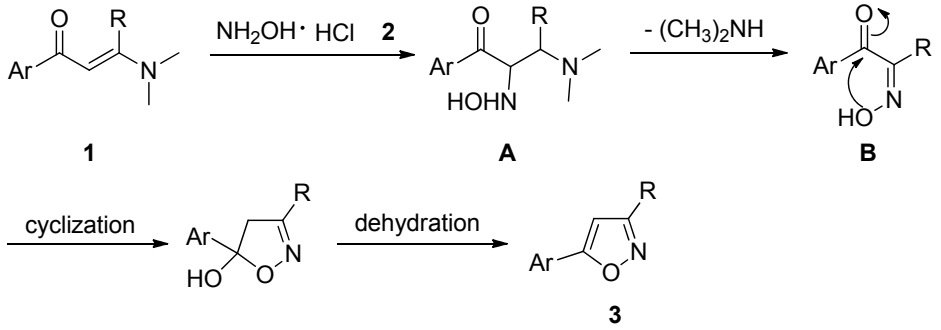
Entry	Product	Ar	R	Isolated Yield (%)
1	**3a**	4-ClC_6H_4	H	88
2	**3b**	4-$CH_3OC_6H_4$	H	93
3	**3c**	4-BrC_6H_4	H	89
4	**3d**	Naphthen-2-yl	H	84
5	**3e**	C_6H_5	CH_3	88
6	**3f**	4-$CH_3OC_6H_4$	CH_3	92
7	**3g**	4-$CH_3C_6H_4$	CH_3	89
8	**3h**	4-BrC_6H_4	CH_3	90
9	**3i**	4-ClC_6H_4	CH_3	86
10	**3j**	4-$CH_3OCOC_6H_4$	CH_3	84
11	**3k**	4-$BocNHC_6H_4$	CH_3	86
12	**3l**	Thiophen-2-yl	CH_3	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, ^{1}H-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}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Inova-300 MHz or Varian Inova-400 MHz in $CDCl_3$ 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) *v*: 2916, 2804, 1648, 1580, 1545, 1433, 1411, 1353, 1279, 1237, 1118, 1088, 1053, 1010, 980, 899, 837, 790, 742, 678 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.89 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 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); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 37.2, 45.0, 91.6, 128.2, 128.8, 136.8, 138.7, 154.4, 187.0; HRMS calcd. for $C_{11}H_{13}ClNO$ $[M+H]^+$: 210.0686; found: 210.0685.

3-(Dimethylamino)-1-(4-methoxyphenyl)prop-2-en-1-one (**1b**). Mp: 92–94 °C; IR (KBr) *v*: 2905, 2838, 1643, 1603, 1583, 1432, 1358, 1305, 1242, 1175, 1117, 1057, 1026, 901, 774 cm^{-1}; ^{1}H-NMR (400 MHz,

$CDCl_3$) δ (ppm) 2.89 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 3.80 (s, 3H, CH_3O), 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); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181; found: 206.1205.

1-(4-Bromophenyl)-3-(dimethylamino)prop-2-en-1-one (**1c**). Mp: 81–83 °C; IR (KBr) *v*: 2910, 2808, 1649, 1575, 1540, 1435, 1357, 1304, 1271, 1237, 1120, 1056, 1003, 895, 847, 808, 775, 760, 673 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.88 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 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); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 37.3, 45.1, 91.6, 125.4, 129.1, 131.3, 139.3, 154.6, 187.2; HRMS calcd. for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0181; found: 254.0182.

3-(Dimethylamino)-1-(naphthalen-2-yl)prop-2-en-1-one (**1d**). Mp: 94–95 °C; IR (KBr) *v*: 2927, 2898, 2809, 1636, 1554, 1427, 1291, 1253, 1189, 1111, 1045, 909, 863, 826, 781, 759 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.91 (s, 3H, NCH_3), 3.09 (s, 3H, NCH_3), 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); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 37.3, 45.0, 92.4, 124.7, 126.2, 127.2, 127.7, 127.8, 129.2, 132.8, 134.7, 137.9, 154.3, 188.4; HRMS calcd. for $C_{15}H_{15}NO$ $[M+H]^+$: 226.1232; found: 226.1234.

3-(Dimethylamino)-1-phenylbut-2-en-1-one (**1e**). Oil; IR (KBr) *v*: 2911, 1650, 1555, 1500, 1450, 1357, 1310, 1267, 1027, 1067, 1000, 900, 857, 775, 761, 673 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.64 (s, 3H, CH_3), 3.03 (s, 6H, $N(CH_3)_2$), 5.69 (s, 1H, CH), 7.13 (s, 1H, ArH), 7.41 (t, J = 6.4 Hz, 2H, ArH), 7.82 (d, J = 7.6 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 19.5, 42.7, 52.4, 117.3, 128.2, 130.0, 130.5, 133.9, 151.6, 166.1, 172.3; HRMS calcd. for $C_{12}H_{15}NO$ $[M+H]^+$: 190.1232; found: 190.1245.

3-(Dimethylamino)-1-(4-methoxyphenyl)but-2-en-1-one (**1f**). Mp: 134–136 °C; IR (KBr) *v*: 2961, 2835, 1671, 1574, 1460, 1307, 1167, 1081, 1025, 917, 865, 782, 746, 694 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.62 (s, 3H, CH_3), 3.02 (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) 16.3, 39.9, 55.2, 92.1, 113.0, 129.0, 135.5, 161.3, 163.3, 187.1; HRMS calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338; found: 220.1341.

3-(Dimethylamino)-1-(-4-methylphenyl)but-2-en-1-one (**1g**). Mp: 94–96 °C; IR (KBr) *v*: 2913, 2808, 1660, 1577, 1561, 1450, 1357, 1300, 1277, 1122, 1066, 1000, 899, 847, 775, 760, 673 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.37 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.06 (s, 6H, $N(CH_3)_2$), 5.67 (s, 1H, CH), 7.18 (d, J = 7.6 Hz, 2H, ArH), 7.77 (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, 140.3, 140.5, 163.6, 188.1; HRMS calcd. for $C_{13}H_{17}NO$ $[M+H]^+$: 204.1388; found: 204.1386.

1-(4-Bromophenyl)-3-(dimethylamino)but-2-en-1-one (**1h**). Mp: 88–92 °C; IR (KBr) *v*: 2931, 1721, 1616, 1500, 1420, 1385, 1354, 1220, 1161, 1069, 1030, 1007, 849, 769, 680, 627 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.63 (s, 3H, CH_3), 3.06 (s, 6H, $N(CH_3)_2$), 5.58 (s, 1H, CH), 7.49 (d, J = 8.4 Hz, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{14}BrNO$ $[M+H]^+$: 267.0259; found: 267.0256.

1-(4-Chlorophenyl)-3-(dimethylamino)but-2-en-1-one (**1i**). Mp: 82–84 °C; IR (KBr) *v*: 3039, 2961, 2804, 1676, 1620, 1537, 1411, 1379, 1351, 1278, 1224, 1166, 1089, 1024, 1010, 921, 862, 772, 739, 712, 678 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm) 16.4, 40.1, 92.0, 128.0, 128.6, 136.0, 141.3, 164.3, 186.5; HRMS calcd. for $C_{12}H_{14}ClNO$ $[M+H]^+$: 224.0842; found: 224.0861.

Methyl 4-(3-dimethylamino)but-2-enoyl)benzoate (**1j**). Mp: 103–106 °C; IR (KBr) *v*: 2951, 1720, 1620,1600, 1569, 1434, 1282, 1217, 1110, 1037, 1011, 921, 868, 825, 759, 725 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (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 $C_{14}H_{17}NO_3$ $[M+H]^+$: 248.1287; found: 248.1292.

tert-Butyl (4-(3-dimethylamino)but-2-enoyl)phenyl)carbamate (**1k**). Mp: 218–220 °C; IR (KBr) *v*: 3242, 3087, 2963, 1721, 1615, 1482, 1361, 1310, 1269, 1245, 1152, 1085, 1050, 1022, 922, 866, 788, 690 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (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 $C_{17}H_{25}N_2O_3$ $[M+H]^+$: 305.1865; found: 305.1866.

3-(Dimethylamino)-1-(thiophen-2-yl)but-2-en-1-one (**1l**). Mp: 90–91 °C; IR (KBr) *v*: 3078, 2919, 2815, 1694, 1622, 1543, 1422, 1380, 1345, 1228, 1170, 1085, 1064, 1028, 906, 860, 837, 771, 723 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.59 (s, 3H, CH_3), 3.01 (s, 6H, $N(CH_3)_2$), 5.60 (s, 1H, CH), 6.99 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.51 (s, 1H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 16.5, 40.0, 91.6, 127.2, 127.4, 129.4, 150.0, 163.8, 180.1; HRMS calcd. for $C_{10}H_{14}NOS$ $[M+H]^+$: 196.0796; found: 196.0807.

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.

5-(4-Chlorophenyl)isoxazole (**3a**). Mp: 85–87 °C (lit. [19] 84–85 °C); IR (KBr) *v*: 1601, 1447, 1264, 1128, 1109, 1088, 802 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm) 98.9, 125.6, 127.0, 129.2, 136.1, 150.8, 168.1; HRMS calcd. for C_9H_7ClNO $[M+H]^+$: 180.0216; found: 180.0215.

5-(4-Methoxyphenyl)isoxazole (**3b**). Mp: 60–62 °C (lit. [19] 64–65 °C); IR (KBr) *v*: 3002, 1605, 1510, 1446, 1251, 1175, 1020, 906, 787, 675 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.86 (s, 3H, CH_3O),

6.39 (d, *J* = 1.6 Hz, 1H, C^4-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, C^3-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 55.3, 97.2, 114.3, 120.0, 127.3, 150.7, 161.0, 169.2; HRMS calcd. for $C_{10}H_{10}NO_2$ $[M+H]^+$: 176.0712; found: 176.0718.

5-(4-Bromophenyl)isoxazole (**3c**). Mp: 112–114 °C (lit. [19] 114–116 °C); IR (KBr) *v*: 1629, 1427, 1077, 1021, 846, 775 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.53 (d, *J* = 1.6 Hz, 1H, C^4-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, C^3-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 99.0, 124.5, 126.0, 127.2, 132.2, 150.9, 168.2; HRMS calcd. for C_9H_7BrNO $[M+H]^+$: 223.9711; found: 223.9716.

5-(Naphthalen-1-yl)isoxazole (**3d**). Mp: 90–92 °C; IR (KBr) *v*: 3049, 1562, 1449, 1360, 1265, 1190, 910, 808, 738 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 6.63 (d, *J* = 1.6 Hz, 1H, C^4-H), 7.53–7.56 (m, 2H, ArH), 7.84–7.93 (m, 4H, ArH), 8.30–8.34 (m, 2H, C^3-H and ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{10}NO$ $[M+H]^+$: 196.0762; found: 196.0768.

3-Methyl-5-phenylisoxazole (**3e**). Mp: 67–69 °C (lit. [32] 67 °C); IR (KBr) *v*: 3056, 2983, 1600, 1424, 1258, 1039, 897, 766, 683 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.36 (s, 3H, CH_3), 6.37 (s, 1H, C^4-H), 7.42–7.48 (m, 3H, ArH), 7.75–7.77 (m, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 11.4, 100.1, 125.6, 127.4, 128.8, 129.9, 160.2, 169.5; HRMS calcd. for $C_{10}H_{10}NO$ $[M+H]^+$: 160.0762; found: 160.0770.

5-(4-Methoxyphenyl)-3-methylisoxazole (**3f**). Mp: 99–101 °C; IR (KBr) *v*: 2936, 1612, 1510, 1430, 1253, 1174, 1022, 787, 680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 3H, CH_3), 3.85 (s, 3H, CH_3O), 6.24 (s, 1H, C^4-H), 6.96 (d, *J* = 8.8 Hz, 2H, ArH), 7.69 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 11.4, 55.2, 98.7, 114.2, 120.3, 127.2, 160.2, 160.8, 169.5; HRMS calcd. for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0868; found: 190.0862.

3-Methyl-5-(4-methylphenyl)isoxazole (**3g**). Mp: 88–90 °C (lit. [33] 92 °C); IR (KBr) *v*: 3063, 2961, 1603, 1415, 1259, 1114, 1044, 956, 895, 792, 680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.13 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 6.09 (s, 1H, C^4-H), 7.04 (d, *J* = 8.4 Hz, 2H, ArH), 7.43 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 11.4, 21.3, 99.5, 124.8, 125.6, 129.5, 140.1, 160.2, 169.7; HRMS calcd. for $C_{11}H_{12}NO$ $[M+H]^+$: 174.0919; found: 174.0914.

5-(4-Bromophenyl)-3-methylisoxazole (**3h**). Mp: 126–128 °C; IR (KBr) *v*: 2978, 1598, 1467, 1404, 1256, 1061, C^4-H), 7.41 (d, *J* = 8.0 Hz, 2H, ArH), 7.67 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 11.4, 100.4, 125.9, 126.9, 129.1, 135.9, 160.4, 168.4; HRMS calcd. for $C_{10}H_9ClNO$ $[M+H]^+$: 194.0373; found: 194.0378.

5-(4-Chlorophenyl)-3-methylisoxazole (**3i**). Mp: 88–89 °C (lit. [34] 90–91 °C); IR (KBr) *v*: 1600, 1451, 1400, 1249, 1092, 1053, 833cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.34 (s, 3H, CH_3), 6.34 (s, 1H, C^4-H), 7.41 (d, *J* = 8.0 Hz, 2H, ArH), 7.67 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 11.4, 100.4, 125.9, 126.9, 129.1, 135.9, 160.4, 168.4; HRMS calcd. for $C_{10}H_9ClNO$ $[M+H]^+$: 194.0373; found: 194.0378.

Methyl 4-(3-methylisoxazol-5-yl)benzoate (**3j**). Mp: 88–90 °C; IR (KBr) *v*: 2945, 1720, 1601, 1419, 1274, 1182, 1105, 950, 774 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.36 (s, 3H, CH_3), 3.93 (s, 3H, CH_3O), 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, $CDCl_3$) δ (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) *v*: 3363, 3005, 2978, 1701, 1520, 1413, 1237, 1160, 835, 772 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, $(CH_3)_3C$), 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, $CDCl_3$) δ (ppm) 11.5, 28.2, 80.9, 99.2, 118.3, 122.1, 126.6, 140.0, 152.4, 160.3, 169.3; HRMS calcd. for $C_{15}H_{19}N_2O_3$ $[M+H]^+$: 275.1396; found: 275.1392.

3-Methyl-5-(thiophen-2-yl)isoxazole (**3l**). Oil; IR (KBr) *v*: 2933, 1605, 1422, 1033, 899, 792, 706 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm) 11.4, 100.0, 126.7, 127.7, 128.0, 129.4, 160.3, 160.4; HRMS calcd. for C_8H_8NOS $[M+H]^+$: 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.

Acknowledgments

We are grateful to The Joint Funds of the National Natural Science Foundation of China and Shenhua Group Corporation Limited (No. 51134020), the National Natural Science Foundation of China Youth Science Foundation (Grant No. 51204171 and 51004105), and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Amato, I. The slow birth of green chemistry. *Science* **1993**, *259*, 1538–1541.
2. Fringuell, F.; Piematti, O.; Pizzo, F.; Vaccaro, L. Recent advances in Lewis acid catalyzed Diels-Alder reactions in aqueous media. *Eur. J. Org. Chem*. **2001**, *2001*, 439–455.
3. Breslow, R. Hydrophobic effects on simple organic reactions in water. *Acc. Chem. Res*. **1991**, *24*, 159–164.
4. Li, C.J. Organic reactions in aqueous media—with a focus on carbon-carbon bond. *Chem. Rev*. **1993**, *93*, 2023–2035.

5. Li, C.J. Organic reactions in aqueous media with a focus on carbon-carbon bond formations: A decade update. *Chem. Rev*. **2005**, *105*, 3095–3166.
6. Dandia, A.; Arya, K.; Sati, M.; Sarangi, P. Green chemical synthesis of fluorinated 1,3,5-triaryl-s-triazines in aqueous medium under microwaves as potential antifungal. *J. Fluorine Chem.* **2004**, *125*, 1273–1277.
7. Wang, X.S.; Zhang, M.M.; Zeng, Z.S.; Shi, D.Q.; Tu, S.J.; Wei, X.Y.; Zong, Z.M. A simple and clean procedure for the synthesis of polyhydroacridine and quinoline derivatives: Reaction of Schiff base with 1,3-dicarbonyl compounds in aqueous medium. *Tetrahedron Lett*. **2005**, *46*, 7169–7173.
8. Cho, C.S.; Kim, J.S.; Oh, B.H.; Kim, T.J.; Shim, S.C.; Yoon, N.S. Ruthenium-catalyzed synthesis of quinolines from anilines and allylammonium chlorides in an aqueous medium via amine exchange reaction. *Tetrahedron* **2000**, *56*, 7747–7750.
9. Khadikar, B.M.; Gaikar, V.G.; Chitnavis, A.A. Aqueous hydrotrope solution as a safer medium for microwave enhanced hantzsch dihydropyridine ester synthesis. *Tetrahedron Lett*. **1995**, *36*, 8083–8086.
10. Cho, C.S.; Kim, J.H.; Shim, S.C. Ruthenium-catalyzed synthesis of indoles from anilines and trialkanolammonium chlorides in an aqueous medium. *Tetrahedron Lett*. **2000**, *41*, 1811–1814.
11. Totlani, V.M.; Peterson, D.G. Reactivity of epicatechin in aqueous glycine and glucose maillard reaction models: Quenching of C_2, C_3, and C_4 sugar fragments. *J. Agric. Food Chem.* **2005**, *53*, 4130–4135.
12. Wnorowski, A.; Yaylayan, V.A. Influence of pyrolytic and aqueous-phase reactions on the mechanism of formation of maillard products. *J. Agric. Food Chem.* **2000**, *48*, 3549–3554.
13. Bose, D.S.; Fatima, L.; Mereyala, H.B. Green chemistry approaches to the synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones by a three-component coupling of one-pot condensation reaction: Comparison of ethanol, water, and solvent-free conditions. *J. Org. Chem*. **2003**, *68*, 587–590.
14. Shi, D.Q.; Chen, J.; Zhuang, Q.Y.; Hu, H.W. Three-component processes for the synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin in aqueous media. *J. Chem. Res.* **2003**, *2003*, 674–675.
15. Jin, T.S.; Zhang, J.S.; Guo, T.T.; Wang, A.Q. One-pot clean synthesis of 1,8-dioxo-decahydro-acridines catalyzed by p-dodecylbenzesulfonic acid in aqueous media. *Synthesis* **2004**, *2004*, 2001–2005.
16. Wender, P.A.; Verma, V.A.; Paxton, T.J.; Pillow, T.H. Function-oriented synthesis, step economy, and drug design. *Acc. Chem. Res*. **2008**, *41*, 40–49.
17. Conti, P.; Amici, M.D.; Grazioso, G.; Roda, G.; Pinto, A.; Hansen, K.B.; Nielsen, B.; Madsen, U.; Bräuner-Osborne, H.; Egebjerg, J.; Vestri, V.; Pellegrini-Giampietro, D.E.; Sibille, P.; Acher, F.C.; Micheli, C.D. Synthesis, binding affinity at glutamic acid receptors, neuroprtective effects, and molecular modeling investigation of novel dihydroisoxazole amino acids. *J. Med. Chem*. **2005**, *48*, 6315–6325.
18. Srirastara, S.; Bajpai, L.K.; Batra, S.; Bhaduri, A.P.; Maikhuri, J.P.; Gupta, G.; Dhar, J.D. In search of new chemical entities with spermicidal and anti-HIV activities. *Bioorg. Med. Chem.* **1999**, *7*, 2607–2613.

19. Lin, Y.; Lang, S.A. New synthesis of isoxazoles and isothiazoles. A convenient synthesis of thioenaminones from enaminones. *J. Org. Chem*. **1980**, *45*, 4857–4860.
20. Nakamura, T.; Sato, M.; Kakinuma, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Koda, A.; Kameo, K. Pyrazole and isoxazole derivatives as new, potent, and selective 20-hydroxy-5,8,11,14-eicosatetraenoic acid synthase inhibitors. *J. Med. Chem*. **2003**, *46*, 5416–5427.
21. Shi, D.Q.; Niu, L.H.; Yao, H.; Jiang, H. An efficient synthesis of pyrimido[4,5-*b*]quinoline derivatives via three-component reaction ia aqueous media. *J. Heterocycl. Chem*. **2009**, *46*, 237–242.
22. Shi, D.Q.; Shi, J.W.; Rong, S.F. An efficient and clean synthesis of pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives in aqueous media. *J. Heterocycl. Chem*. **2009**, *46*, 1331–1334.
23. Shi, D.Q.; Yao, H. Clean synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives in aqueous media. *J. Heterocycl. Chem.* **2009**, *46*, 1335–1338.
24. Li, Y.L.; Chen, H.; Shi, C.L.; Shi, D.Q.; Ji, S.J. Efficient one-pot synthesis of spirooxindole derivatives catalyzed by L-proline in aqueous media. *J. Comb. Chem*. **2010**, *12*, 231–237.
25. Chen, H.; Shi, D.Q. Efficient one-pot synthesis of novel spirooxindole derivatives via three-component reaction in aqueous medium. *J. Comb. Chem.* **2010**, *12*, 571–576.
26. Shi, D.Q.; Shi, J.W.; Rong, S.F. A facile and clean synthesis of pyrimidine derivatives via three-component reaction in aqueous media. *Chin. J. Chem*. **2010**, *28*, 791–796.
27. Dou, G.L.; Zhong, X.X.; Wang, D.M.; Shi, D.Q. An efficient synthesis of *N*-substituted-3-aryl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propanamides by four-component reaction in aqueous medium. *Chin. J. Chem.* **2011**, *29*, 2368–2372.
28. Shi, D.Q.; Li, Y.; Wang, H.Y. Synthesis of indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine derivatives and their recognition properties as new type anion receptors. *J. Heterocycl. Chem*. **2012**, *49*, 1086–1090.
29. Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. Asymmetric catalytic Strecker reaction of *N*-phosphonyl imines with Et_2AlCN using amino alcohols and BINOLs as catalysts. *Chem. Commun*. **2010**, *46*, 4330–4332.
30. Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. Asymmetric catalytic *N*-phosphonyl imine chemistry: The use of primary free amino acids and Et_2AlCN for asymmetric catalytic Strecker reaction. *J. Org. Chem.* **2010**, *75*, 5144–5150.
31. Kaur, P.; Wever, W.; Pindi, S.; Milles, R.; Gu, P.; Shi, M.; Li, G. The GAP chemistry for chiral *N*-phosphonyl imine-based Strecker reaction. *Green Chem*. **2011**, *13*, 1288–1292.
32. Jyoti, S.; Vidya, D.; Santosh, T. Domino primary alcohol oxidation—Wittig reaction: Total synthesis of ABT-418 and (E)-4-oxonon-2-enoic acid. *Synthesis* **2004**, *2004*, 1859–1863.
33. Umaprasanna, B. B-Diketones in ring formation. III. *J. Indian Chem. Soc.* **1931**, *8*, 119–128.
34. Choji, K.; Akira, K.; Yuko, Y.; Yoshimori, O. Ring transformation reaction of 1,4,6-trisubstituted 2(1*H*)-pyrimidinones and –thiones with hydroxylamine. *Chem. Pharma. Bull*. **1981**, *29*, 2516–2519.

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