One-Pot Synthesis of (3-Phenylisoxazol-5-yl)methanol Derivatives Under Ultrasound

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Abstract: An ultrasonic-assisted, one-pot, efficient, convenient procedure for the synthesis of (3-phenylisoxazol-5-yl)methanol derivatives has been developed. (3-Phenylisoxazol-5-yl)-methanol derivatives with biological and pharmaceutical property have been synthesized in moderate to excellent yields. The synthetic methods possess the advantages of high yield, facile operation process and shorter reaction time, and so on.

Keywords: Ultrasound, aldoximes, 1,3-dipolar cycloaddition, nitrile oxide, isoxazole, one-pot synthesis.

INTRODUCTION

Isoxazole derivatives are widely used intermediates for the synthesis of a variety of complex natural products [1, 2] and important pharmacophores in medicinal chemistry [3, 4], such as treating diseases of Alzheimer [5] and cardiovascular [6], sterilization [7], herbicide [8] and so on. Therefore, an effective method for preparation of isoxazole derivatives is of great interest in organic synthesis. Isoxazole derivatives were usually synthesized by reaction of 1,3-dicarbonyl compounds with hydroxylamine, followed by dehydration and cyclization of the intermediate monoxime [9]. The synthetic and mechanistic aspects of 1,3-dipolar cycloadditions using nitrile oxides to give all kinds of heterocyclic compounds have been investigated in 1963 and 1984 [10, 11]. The synthesis of isoxazole derivatives *via* the cycloaddition of nitrile oxide to unsaturated dipolarophiles is one of successful examples [12]. In the previous reports, the aldoximes have been used as starting materials [13]. The widespread procedure to form the nitrile oxides is halogenated by an active halogen compound and subsequently dehydrohalogenation in a basic condition. Then, the formation of isoxazoles by 1,3-dipolar cycloadditions between nitrile oxides and alkynes. The synthetic mothods possess the disadvantages of lower yield, complex operation process, long reaction time and so on.

It is known that ultrasound technology has recently attracted more and more attention from synthetic organic chemists due to the many advantages ultrasound irradiation affords over conventional heating in chemical transformations, particularly the enormous acceleration of the reaction rate, significant energy savings, as well as high chemical yields and cleaner reactions [14-17]. In the report, our group has been interested in projecting new methodologies for the synthesis of isoxazole derivatives (3-phenylisoxazol-5-yl)methanols from aldoximes in one-pot synthesis under ultrasound. One-pot synthesis is a strategy to improve the efficiency of 1,3-dipolar cycloadditions whereby the aldoximes are subjected to successive chemical reactions in just one reactor, which can avoid a lengthy separation process and purification of oxime halides, save time and resources while increasing chemical yield. Overall, compared with the traditional methods [18], as a results, the synthesis of (3-phenylisoxazol-5-yl)methanol derivatives from aldoximes can surely shorten reaction time and enhance product yield in one-pot synthesis under ultrasound.

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RESULTS AND DISCUSSION

The reaction for synthesizing (3-phenylisoxazol-5-yl)methanol derivatives by one-pot method under ultrasound and traditional method were illustrated by Scheme **1** and Scheme **2**, respectively. The traditional method was operated by two process, which lead to the lower yields of products and ineffective. To investigate the effect to synthesizing (3-phenylisoxazol-5-yl)methanol derivatives in one pot under ultrasound, compared the experiment results of in one pot method to that of traditional method were summarized in Table **1**. As shown Table **1**, various (3-phenylisoxazol-5-yl)methanol derivatives were synthesized under irradiation of ultrasound in one-pot synthesis to give the corresponding (3-phenylisoxazol-5-yl)methanol derivatives by 45-87% yield in 1.5-4.5h, however, the yields of products were only 5-73% in 3-6h in traditional method. Therefore, the entire process was dramatically accelerated by ultrasound irradiation in one pot, the reaction times were shorten over an hour while the yields of the products were enhanced 14 - 40% comparable to those obtained previously.

It is noteworthy that the electron-rich substituting groups on the aromatic ring have a higher yield than the electron–poor ones. This can be observed in the following syntheses. When the substituent is a nitro group (entry 8, 9), the yield is very low between the traditional method and the ultrasonic method. While the substituents are electron-donating groups, the yields of compounds are above 70% under ultrasonic conditions, because hydroxy group possess high electron-donating characteristic, the yield of the product is the highest in the reactions (87%). However, when it is the same substituted with electron-donating groups on ortho position

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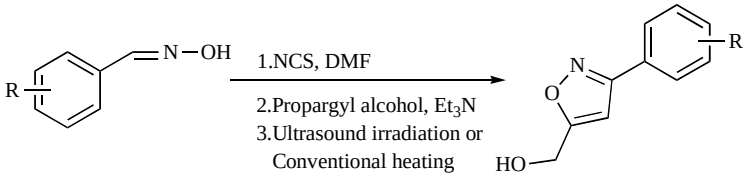
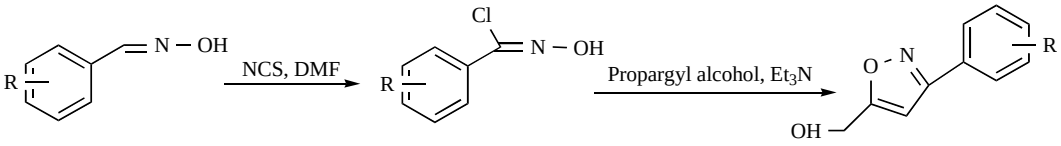


Scheme 1.



Scheme 2.

Table 1. Comparison Between Ultrasound and Conventional Method

entry	ArCH=NOH	Total time		Isolated yield [a] (%)		Mp (°C)
		Classical(h)	U.S.(h)	Classical	U.S.	
1	benzaldehyde oxime	3.0	1.5	27	70	49–50
2	2-chlorobenzaldehyde oxime	5.0	4.0	10	79	66-67
3	4-chlorobenzaldehyde oxime	5.0	4.0	45	74	93-94
4	2-methoxybenzaldehyde oxime	4.0	2.5	73	83	liquid
5	4-methoxybenzaldehyde oxime	4.0	2.5	58	75	82-83
6	4-hydroxybenzaldehyde oxime	5.0	3.0	20	87	136-138
7	4-*tert*-butylbenzaldehyde oxime	3.2	2.0	67	74	48-50
8	3-nitrobenzaldehyde oxime	4.0	2.2	5	59	90-92
9	4-nitrobenzaldehyde oxime	6.0	4.5	7	45	117-119

[a]Yield refers to be purified by recrystallization after column chromatography.

of aromatic ring (such as -OCH_3, -Cl), the yield is higher than on para position, which may be because electron-donating groups at ortho position of aromatic ring would better benefit activity. Moreover, when the substituted is *tert*-butyl group, the yield is lower than other electron-donating groups, because *tert*-butyl group has larger steric restriction.

EXPERIMENTAL SECTION

Materials and Analysis

Et_3N, DMF, propargyl alcohol and NCS (N-chloro succinimide) were all reagent grade and used without further purification. Aldoximes were generated from oximation of aldehydes according to the reported procedure [19]. All melting points were determined on a XT-4 melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were measured with Bruker AM-300 or a Bruker AVANCE-500 NMR spectrometer using DMSO or $CDCl_3$ as solvent and with TMS as an internal standard. MS spectra were measured with a Q-trapspectrometer. Sonication was performed in a Shanghai Branson–CQX ultrasonic cleaner with a frequency of 25 kHz and a nominal power 250 W. The reaction flask was located at the maximum energy area in the cleaner and the temperature of the water bath was controlled by automatic temperature control system.

General Procedure

Ultrasonic method: To a solution of aldoximes (10 mmol) in DMF (10 ml), NCS (10 mmol) was added at room temperature. After ultrasonic irradiation for about 30 min, the reaction mixture was cooled with ice. When the temperature was about 0 °C, the Et_3N (2.73 ml) was dropped into the reaction solution followed by propargyl alcohol (2 ml). The reaction process was monitored by TLC. After complete reaction, the reaction mixture was washed with water and extracted with a mixture of ethyl acetate and petrolrum ether through multiple extraction. The combined organic layers were washed with deionized water (10 ml), brine (10 ml), dried (Na_2SO_4) and evaporated under a vacuum to give a crude product which was purified by recrystallization after column chromatography (silica gel, 200-300 mesh) to furnish the product.

Traditional method: compared the synthetic methods of one-pot method under ultrasond to that of traditional method, there existed employing ultrasound technology with the

function of heating, stirring and accelerating the reaction rate, While magnetic stirring was used in traditional method.

Characterization of Products

(3-phenylisoxazol-5-yl)methanol

Entry **1** (1.22g, yield 70%) mp: 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm, 7.78 (d, J = 3.7 Hz, 2H), 7.44 (d, J = 2.5 Hz, 3H), 6.56 (s, 1H), 4.81 (s, 2H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 171.94, 162.50, 130.12, 128.96, 128.78, 126.81, 100.06, 56.57. MS m/z: Calc. for $C_{10}H_9NO_2$ 175.1. Found: 175.1 $[M]^+$, 176.1 $[M+H]^+$.

(3-(2-chlorophenyl)isoxazol-5-yl)methanol

Entry **2** (1.65g, yield 79%) mp: 66-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.73 (dd, J = 7.1, 2.2 Hz, 1H), 7.48 (s, 1H), 7.41 – 7.34 (m, 2H), 6.73 (s, 1H), 4.86 (s, 2H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 171.09, 161.13, 132.95, 130.97, 130.45, 128.18, 127.15, 103.37, 56.59. MS m/z: Calc. for $C_{10}H_8ClNO_2$ 209.0. Found: 209.9$[M]^+$, 210.9 $[M+1]^+$, 211.9 $[M+2]^+$.

(3-(4-chlorophenyl)isoxazol-5-yl)methanol

Entry **3** (1.54g, yield 74%) mp: 93-94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.74 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 6.54 (s, 1H), 4.83 (s, 2H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 172.30, 161.56, 136.21, 129.27, 128.10, 127.29, 99.96, 56.53. MS m/z: Calc. for $C_{10}H_8ClNO_2$ 209.0. Found: 209.9 $[M]^+$, 210.9 $[M+1]^+$, 211.9 $[M+2]^+$.

(3-(2-methoxyphenyl)isoxazol-5-yl)methanol

Entry **4** (1.70g, yield 83%) liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.80 (dd, J = 7.7, 1.8 Hz, 1H), 7.38 (dd, J = 4.6, 3.7 Hz, 1H), 7.06 – 6.91 (m, 2H), 6.71 (s, 1H), 4.76 (d, J = 0.6 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 170.12, 159.10, 156.17, 130.29, 128.31, 119.81, 116.56, 110.47, 102.35, 55.13, 54.41. MS m/z: Calc. for $C_{11}H_{11}NO_3$ 205.0. Found: 205.9 $[M+1]^+$, 206.9 $[M+2]^+$, 227.9 $[M+Na]^+$.

(3-(4-methoxyphenyl)isoxazol-5-yl)methanol

Entry **5** (1.53g, yield 75%) mp: 82-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.73 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.50 (s, 1H), 4.80 (d, J = 0.7 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 172.29, 162.51, 161.47, 128.61, 121.63, 114.76, 100.22, 56.86, 55.75. MS m/z: Calc. for $C_{11}H_{11}NO_3$ 205.0. Found: 205.9$[M+1]^+$, 206.9 $[M+2]^+$, 227.9 $[M+Na]^+$.

(3-(4-hydroxylphenyl)isoxazol-5-yl)methanol

Entry **6** (1.66g, yield 87%) mp: 136-138 °C; ^{1}H NMR (300 MHz, DMSO) δ ppm 9.85 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 6.88 (s, 1H), 6.85 (s, 1H), 6.77 (d, J = 0.6 Hz, 1H), 5.64 (s, 1H), 4.58 (d, J = 5.9 Hz, 2H). ^{13}C NMR (125.5 MHz, DMSO) δ ppm 173.65, 161.95, 159.59, 128.59, 119.98, 116.27, 99.94, 55.33. MS m/z: Calc. for $C_{10}H_9NO_3$ 191.0. Found: 192.0 $[M+1]^+$, 193.0 $[M+2]^+$.

(3-(4-tert-butylphenyl)isoxazol-5-yl)methanol

Entry **7** (1.71g, yield 74%) mp: 48-50°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.73 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.55 (s, 1H), 4.82 (d, J = 0.5 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (125.5 MHz, $CDCl_3$) δ ppm 172.63, 162.80, 153.87, 126.98, 126.33, 100.43, 56.77, 35.23, 31.59. MS m/z: Calc. for $C_{14}H_{17}NO_2$ 231.1. Found: 232.0 $[M+1]^+$, 233.0 $[M+2]^+$, 254.0 $[M+Na]^+$.

(3-(3-nitrophenyl)isoxazol-5-yl)methanol

Entry **8** (1.30g, yield 59%) mp: 90-92°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.62 (s, 1H), 8.46 – 8.22 (m, 1H), 8.22 – 8.05 (m, 1H), 7.66 (s, 1H), 6.67 (s, 1H), 4.87 (d, J = 0.8 Hz, 2H). ^{13}C NMR (125.5 MHz, DMSO) δ ppm 173.97, 159.59, 147.73, 132.27, 130.16, 129.68, 124.01, 120.31, 99.53, 54.27. MS m/z: Calc. for $C_{10}H_8N2O_4$ 220.0. Found: 221.0 $[M+1]^+$, 222.0 $[M+2]^+$.

(3-(4-nitrophenyl)isoxazol-5-yl)methanol

Entry **9** (0.99g, yield 45%) mp: 117-119°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.37 (dd, J = 28.8, 12.2 Hz, 4H), 6.65 (s, 1H), 4.87 (s, 2H). ^{13}C NMR (125.5 MHz, DMSO) δ ppm 175.19, 160.75, 135.22, 128.35, 124.77, 100.83, 55.33. MS m/z: Calc. for $C_{10}H_8N_2O_4$ 220.0. Found: 220.9 $[M+1]^+$, 221.8 $[M+2]^+$.

CONCLUSION

In conclusion, an efficient, ultrasonic-assisted, one-pot procedure for the direct conversion of aldoxime to (3-phenylisoxazol-5-yl) methanol derivatives has been developed. The desired isoxazole derivatives have been obtained in moderate to excellent overall yields. This approach provides an ideal synthetic approach for the similar synthesis of an isoxazole derivatives library. However, we believe that the operational facility of this method makes it attractive for preparative applications as well as for the synthesis of other interesting heterocycles which were applied in biology and material field, *etc*, is currently in progressing in our laboratory.

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