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ONE-POT SYNTHESIS OF FULLY SUBSTITUTED OXAZOL-2-AMINES VIA STAUDINGER/AZA-WITTIG/ISOMERIZATION REACTION

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Abstract – Readily available vinyl azide alcohols reacted with triphenylphosphine and aromatic isocyanates via sequential Staudinger reaction and intramolecular aza-Wittig reaction to afford the corresponding isoxazole intermediates, which can isomerize into aromatic oxazol-2-amines in situ without addition of catalyst under 115 ℃. This methodology provided a new and efficient one-pot approach for fully substituted oxazol-2-amines.

Oxazoles, especially aminooxazole derivatives, are one of the most important molecular frameworks in naturally occurring products and pharmaceutically relevant molecules. They have been reported to have antitubercular,[1] HIV-1 inhibitor[2] and diacylglycerol acyltransferase 1 (DGAT1) inhibitors,[3] or inosine monophosphate dehydrogenase (IMPDH) properties.[4]

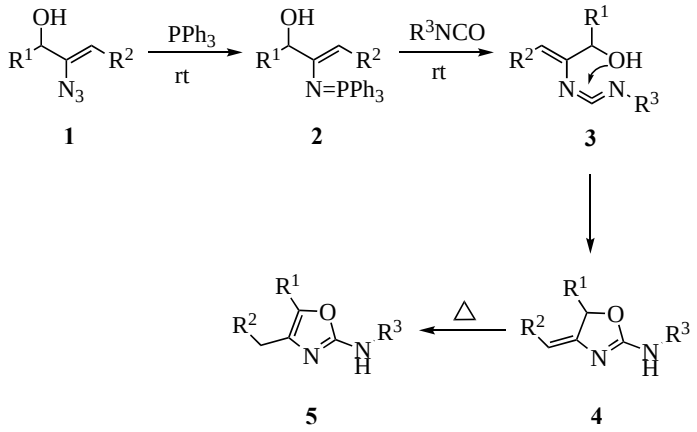
The synthetic methods of oxazole ring have been reported in a large number of literatures,[5] but only a few pathways provided access to oxazol-2-amines. The synthesis of oxazol-2-amines in drug discovery has relied on the PPh_3-mediated annulations of α-azido ketones and isothiocyanates.[6] In this reaction, isocyanates and iminophosphorane reacted by the intermolecular aza-Wittig reaction to produce carbodiimide, which could occur intramolecular cycloaddition reaction successfully in the presence of OH to give an oxazol-2-amine products under very mild conditions. This method plays a more and more important role in the construction of various forms of heterocyclic compounds.[7]

Herein, we described a novel tandem Staudinger/aza-Wittig/isomerization approach to the synthesis of aminooxazole derivatives. Using this procedure we were able to synthesize a fully substituted aminooxazoles with easily available starting materials vinyl azido alcohol, triphenylphosphine and various isocyanates.

Preparation of vinyl azide alcohols **1** was carried out from vinyl azides, which were obtained easily from the condensation of the α-azido ketone with aromatic aldehydes in the presence of piperidinium acetate,

or from the reaction of dibromides with sodium azide according to the literature reports.[8] Subsequently, the vinyl azides were treated with $NaBH_4$ in methanol at 0 ℃ to give vinyl azide alcohols **1**, which was non-stabilized at room temperature due to the existence of enol structure and needed to be stored at 0-5 ℃ for one week.

The Staudinger reaction of vinyl azide alcohols **1** and triphenylphosphine took only a few minutes in dry toluene at room temperature to give iminophosphorane **2** which did not need further separation. Carbodiimide **3** can be obtained by intermolecular aza-Wittig reaction when various isocyanates were added in the reaction mixture. Then, carbodiimide **3** reacted with hydroxyl groups in the molecule to produce isoxazole intermediates **4** without aromatization. Isoxazoles **4** cannot be separated because of instability, but it was observed by thin-layer chromatography. In addition, isoxazoles **4** do not show fluorescence properties at 256 nm or 365 nm. Isoxazoles **4** were isomerized quickly into the aromatized oxazol-2-amines **5** in 2-4 h at reflux. Oxazol-2-amines **5** showed weak fluorescence at 365 nm, this also showed that the aromatic isomerization of isoxazoles **4** produceed an aromatic oxazole rings. It is noteworthy that the reaction proceeds to give various fully substituted oxazol-2-amines **5** under mild conditions, and the overall transformation took place in a simple and efficient one-pot procedure from vinyl azide alcohols **1** in good overall yields.



1 **2** **3** **5** **4**

Scheme 1

Table 1. Preparation of ox azol-2-amines **5**

Comp.	R1	R2	R3	Reaction Time	Yield(%)
5a	Ph	Ph	Ph	3	65
5b	Ph	Ph	4-ClC_6H_4	4	74
5c	Ph	Ph	4-MeC_6H_4	4	67
5d	Ph	4-ClC_6H_4	Ph	4	70

5f	Ph	4-ClC_6H_4	4-ClC_6H_4	4	63
5k	Ph	4-ClC_6H_4	4-MeC_6H_4	4	69

The structures of the oxazol-2-amine derivatives **5** were confirmed from their spectroscopic datas. For example, the ^{1}H NMR spectral data of **5a** show a characteristic singlet at 4.10 ppm due to the hydrogen of CH_2. The signals attributable to the protons of Ar-Hs and N-H are found at 7.01-7.53 ppm as multiplets. The ^{13}C NMR spectrum data in **5a** show the signals of the C-2 carbon of the oxazole at 155.3 ppm. The signals of CH_2 are found at 32.6 ppm. The mass spectrum of **5a** shows a molecular ion peak at *m/z* 325.6 with 100% abundance.

EXPERIMENTAL

All reagents used in the reaction are domestic chemical pure or analytical pure. Toluene (C_6H_5Me) as reaction solvent was dried with anhydrous calcium chloride for 3-5 days, and the common solvents are commercially available analytical purity and can be used directly without purification. Column chromatography purifications were performed under "flash" conditions using 200-300 mesh silica gel, Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F254 plates, which were visualized by exposure to ultraviolet light.

All melting points were determined using a X-4 model apparatus and were uncorrected. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 spectrometer and resonances relative to TMS. MS were measured on a Finnigan Trace MS spectrometer.

General procedure for the synthesis of oxazol-2-amines (**5a-5f**)

A solution of vinyl azide alcohols **4** (5 mmol) and triphenylphosphine (5 mmol) in 20 mL of dried toluene was stirred at ambient temperature, and monitored by TLC until the intermediate iminophosphorane can be completely formed. The resulting iminophosphorane can proceed to the next step without separation, and to the reaction mixture was added aromatic isocyanates (5 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 10 min, the reaction mixture was heated in an oil bath at 115 ℃ for 2-4 h. The solvent was removed in a rotary evaporator at 50 ℃. and the obtained residue was chromatographed on a silica gel column, eluting with petroleum ether (60-90 ℃)/Et_2O (15:1) and then recrystallized from the appropriate solvent to afford aminooxazoles **5a-5f**.

4-Benzyl-N-5-diphenyloxazol-2-amine (5a): White solid. mp 153-155 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.01-7.53 (m, 16H, Ar-H, NH), 4.10 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 155.4, 139.3, 138.8, 138.5, 134.1, 129.1, 128.9, 128.5, 128.2, 126.9, 126.2, 124.0, 121.2, 116.6, 32.6; IR (KBr): ν =3053, 2938, 1653, 1483; MS: *m/z* (%) = 325.6 (100%, M^+), 203(14), 116(24), 77(98).

4-Benzyl-N-(4-chlorophenyl)-5-phenyloxazol-2-amine (5b): White solid. mp 201-203 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.23-7.52 (m, 15H, Ar-H, NH), 4.10 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.4, 138.3, 137.1, 133.3, 129.2, 128.8, 128.6, 128.4, 127.2, 127.1, 126.5, 124.5, 118.5, 32.9; IR (KBr): ν = 3056, 2942, 1649, 1478; MS: *m/z* (%) = 360.1 (100%, M^+), 207(34), 103(74), 77(98).

4-Benzyl-5-phenyl-N-*p*-tolyloxazol-2-amine (5c): White solid. mp 184-186 ℃. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.18 (s, 1H, NH), 7.11-7.53 (m, 14H, Ar-H), 4.06 (s, 2H, CH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 155.6, 138.8, 138.4, 136.9, 134.2, 130.0, 129.6, 129.3, 129.1, 128.6, 128.4, 126.9, 126.2, 124.1, 123.8, 116.8, 116.5, 32.7, 20.4, 20.3; IR (KBr): ν = 3053, 2938, 1645, 1447; MS: *m/z* (%) =340.1 (100%, M^+), 242 (31), 103(21), 77(98).

4-(4-Chlorobenzyl)-N-5-diphenyloxazol-2-amine (5d): White solid. mp 175-176 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.02-7.50 (m, 15H, Ar-H, NH), 4.06 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.9, 140.5, 138.4, 136.9, 133.0, 132.1, 129.7, 129.2, 128.8, 128.6, 127.1, 124.4, 122.4, 117.4, 32.4; IR (KBr): ν = 3045, 2952, 1655, 1452. MS: *m/z* (%) =360.1 (100%, M^+), 209.1(14), 180(26), 77(36).

4-(4-Chlorobenzyl)-N-(4-chlorophenyl)-5-phenyloxazol-2-amine (5e): White solid. mp 194-196 ℃. ^{1}HNMR ($CDCl_3$, 600 MHz) δ 7.25-7.48 (m, 14H, Ar-H, NH), 4.04 (s , 2H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.1, 138.9, 138.2, 137.7, 133.5, 130.9, 130.1, 129.1, 128.8, 128.4, 128.3, 127.1, 124.7, 124.1, 118.1, 33. 0; IR (KBr): ν = 3058, 2937, 1645, 1464; MS: *m/z* (%) = 394.0 (100%, M^+), 238 (27), 109(38), 77(18).

4-(4-Chlorobenzyl)-5-phenyl-N-*p*-tolyloxazol-2-amine (5f): White solid. mp 169-170 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.1-7.48（m, 14H, Ar-H, NH）, 4.04 (s, 2H, CH_2), 2.31 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 155.6, 138.5, 137.8, 136.8, 133.7, 130.9, 130.1, 130.0, 129.3, 129.1, 128.5, 128.4, 126.8, 124.0, 116.7, 116.6, 32.0, 20.3; IR (KBr): ν = 3060, 2940, 1636, 1469. MS: *m/z* (%) = 374.1 (100%, M^+), 242 (31), 112(21), 77(54).

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