Oxazole Synthesis from Isocyanides

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Abstract: A new synthetic path toward oxazoles starting from isocyanides is presented. This two-step oxazole preparation involves a bromination–cyclization followed by a Suzuki cross-coupling.

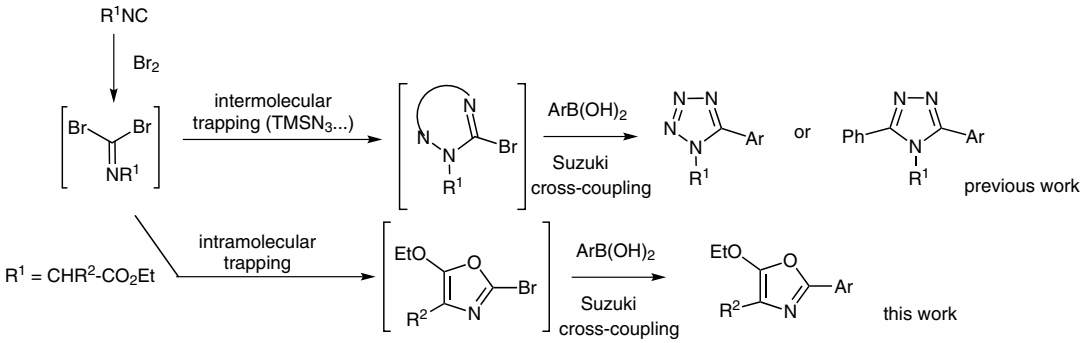
Key words: oxazoles, Suzuki, palladium, isocyanides, dihalogenoisocyanides

Due to their carbenic nature, isocyanides are versatile reagents, which have been widely used in heterocyclic chemistry. Their success is mainly associated with the Ugi reaction,[1] considered as the most powerful four-component coupling. Aside these applications, they are excellent ligands for transition metals, as attested by the impressive bibliography available in inorganic chemistry. However, due to this high affinity, few metal-catalyzed processes have been reported[2] as they are often limited to the use of bulky isocyanides.[3] To circumvent such difficulties, the isocyanides may be transformed into dihalogenoisocyanides, intermediates which have proven their interest in a few palladium-catalyzed processes.[4,5] More recently, we used this strategy in a one-pot tetrazole and 1,2,4-triazole synthesis starting from isocyanides (Scheme 1).[6] We wish to report herein a new oxazole synthesis involving *gem*-dihalogenoisocyanoester derivatives (Scheme 1).[7]

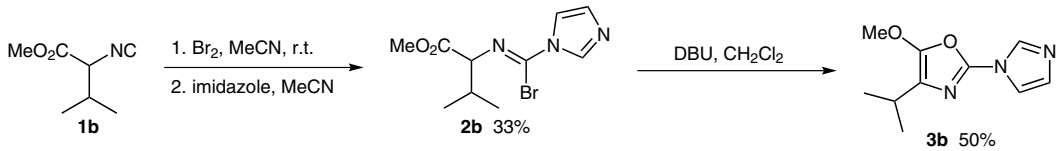
To test the feasibility of the process, isocyano glycinate **1a** was treated with one equivalent of bromine. As previously observed, the bromination could be perfomed in various solvents at room temperature, such as dichloromethane or acetonitrile. Decoloration of the solution occurred within a few minutes giving quantitative formation of the desired *gem*-dibromo isocyanoester intermediate, which is then treated under basic conditions. Different bases have been tested in acetonitrile. Potassium phosphate, potassium carbonate, and triethylamine failed to give any product even at reflux, and in all the cases, the starting isocyanide was recovered up to 60%. When treated with one equivalent of DBU at 0 °C, the desired bomooxazole was isolated in 11% yield, but it turned to be quite unstable.

Due to the instability of this intermediate, the sequence was repeated with substituted isocyano glycinates derived from valine **1b** and phenylalanine **1c**. Similar trials failed to give any cyclized adducts. Surprisingly, when treated with two equivalents of imidazole, the *gem*-dibromoisocyano valinate gave 33% of the corresponding bromoamidine **2b**, which can be cyclized under DBU treatment to afford the imidazolo oxazole **3b** in 50% yield (Scheme 2).

Ethyl α-phenyl-α-isocyanoacetate **1d** gave, after sequential treatment with bromine and DBU at 0 °C, the desired



Scheme 1 Cascades involving dibromoisocyanides



Scheme 2 Attempted oxazole formation in the presence of imidazole

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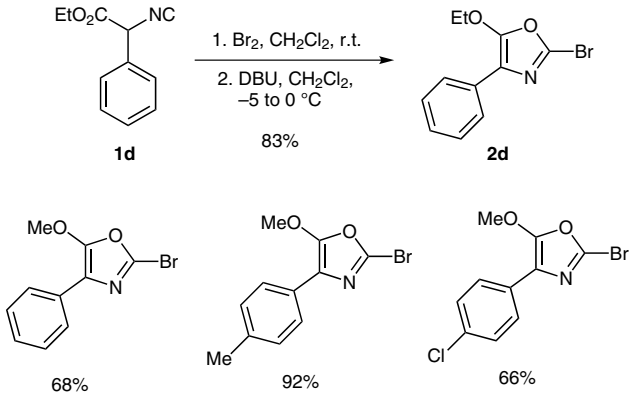
bromooxazole **2d** in 83% yield. The same behavior was observed with other aromatic derivatives as bromooxazole were isolated in good yields with a methyl or a chloro as substituent (Scheme 3).

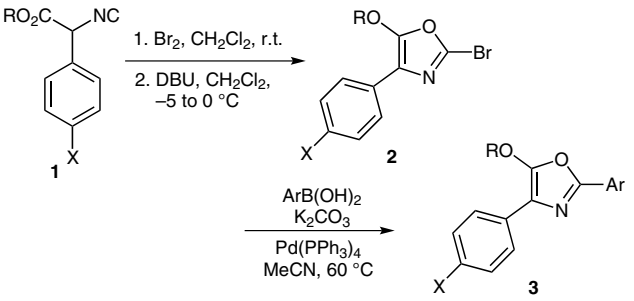


Scheme 3 2-Bromooxazole synthesis from isocyanides

To circumvent the instability of the bromooxazole, which rapidly decomposed after 24 hours at room temperature, we decided to test if its formation could be combined with the subsequent Suzuki–Miyaura cross-coupling. For this purpose, acetonitrile was chosen as solvent, and the tolyl boronic acid, potassium carbonate, and a catalytic amount of Pd(0) were added to the reaction mixture containing both bromooxazole and DBU hydrobromide salt. Unfortunately, no traces of cross-coupling could be detected under these conditions. However, after rapid filtration of the mixture to eliminate the amine salt, the bromooxazole **2d** was successfully transformed into the corresponding aryl oxazole **3d**. Due to the necessity of this intermediate filtration, the more volatile dichloromethane was selected instead of acetonitrile for the first step. The Suzuki coupling was performed using two equivalents of tolyl boronic acid, 10 mol% of tetrakistriphenyl phosphine palladium, and a slight excess of potassium carbonate in acetonitrile, under stirring for 16 hours at 60 °C. The resulting aryl-substituted oxazole was isolated in 59% (Table 1, entry 1). All attempts to improve the yields varying the solvent (toluene instead of acetonitrile) and the temperature (60 °C to reflux) failed to improve the reaction outcome. Under these conditions, different arylated oxazoles have been synthesized using various boronic acids (Table 1). The reactions proceed smoothly with electron-donating groups and halogens on the boronic acid. However, electron-withdrawing groups such as acetyl (Table 1, entry 14) or cyano (Table 1, entry 8) inhibit the reaction. For low efficient couplings, the reduced oxazole was isolated as a side product: for instance, the 4-(4-chlorophenyl)-5-methoxyoxazole (Table 1, entry 14; Figure 1) was isolated as the major compound instead of the corresponding coupled product.

Considering the three-component aminooxazole formation reported by Zhu et al.,[8] we thought that a similar sequence could be performed starting with the corresponding isocyano amides (pyrrolidino and morpholino derivatives). Unfortunately, the corresponding dibromo isocyanide decomposed spontaneously, and no trace of product could even be detected.

Table 1 Synthesis of Aryl Oxazoles **3**



Entry	R	X	Ar	Yield (%)
1	Et	H	4-MeC_6H_4	59
2	Et	H	4-*t*-BuC_6H_4	33
3	Et	H	4-MeOC_6H_4	49
4	Et	H	2-MeOC_6H_4	30
5	Et	H	Ph	23
6	Me	H	4-EtC_6H_4	33
7	Me	H	4-*t*-BuC_6H_4	53
8	Me	H	4-NCC_6H_4	–
9	Me	H	2-MeC_6H_4	19
10	Me	H	4-ClC_6H_4	18
11	Me	Me	4-MeOC_6H_4	18
12	Me	Me	2-MeOC_6H_4	54
13	Me	Me	4-MeC_6H_4	29
14	Me	Cl	4-MeCOC_6H_4	–[a]
15	Me	Cl	4-MeOC_6H_4	45
16	Me	Cl	4-MeC_6H_4	58
17	Me	Cl	4-*t*-BuC_6H_4	49

[a] The reduced oxazole (Figure [1]) was isolated in 62% yield.

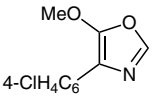


Figure 1

To conclude, a new synthetic path to trisubstituted oxazoles was developed based on isocyanide chemistry. Oxazoles are found in a large number of natural compounds isolated from various marine sources as well as numerous bacteria.[9] Beside the interest for the synthesis of natural products, the preparation of oxazoles has been the object

of a sustained interest due to their lower aromatic stabilization and their use as synthetic intermediates towards various heterocycles and aliphatic compounds.[10]

2-Bromo-5-ethoxy-4-phenyloxazole (2d)
To a solution of ethyl 2-isocyano-2-phenylacetate (**1d**, 500 mg, 2.65 mmol) in CH_2Cl_2 (5 mL) was added bromine (0.127 mL, 2.65 mmol), and the mixture was stirred for 2 min at r.t. The resulting mixture was then cooled at 0 °C before dropwise addition of DBU (1.0 mL, 6.62 mmol) and stirred at –5 °C to 0 °C for an additional 10 min. After completion of the reaction (checked by TLC analysis), CH_2Cl_2 was evaporated. The crude residue was purified by flash chromatography on silica gel using a 1:9 mixture of Et_2O–PE as eluant. Evaporation of the solvent under reduced pressure at 25–30 °C gave **2d** (590 mg, 83%) as a pale yellow liquid.

IR (thin film): 1739, 1683, 1595, 1456, 1270, 1207, 1176 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (dd, 2 H, *J* = 1.2, 7.4 Hz), 7.39 (t, 2 H, *J* = 7.4 Hz), 7.28–7.22 (m, 1 H), 4.36 (q, 2 H, *J* = 7.1 Hz), 1.47 (t, 3 H, *J* = 7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 155.7, 130.2, 128.5, 127.0, 124.9, 122.8, 119.1, 70.7, 15.1. HRMS: *m/z* calcd for $C_{11}H_{10}BrNO_2$: 266.9895; found: 266.9885.

5-Ethoxy-4-phenyl-2-(*p*-tolyl)oxazole (3d)
To a well-stirred solution of 2-bromo-5-ethoxy-4-phenyloxazole (220 mg, 0.82 mmol) in MeCN (0.2 M) under argon atmosphere were successively added K_2CO_3 (340 mg, 2.46 mmol), *p*-tolyl boronic acid (223 mg, 1.64 mmol), and $Pd(PPh_3)_4$ (47.5 mg, 5 mol%). The resulting mixture was stirred under argon atmosphere at 55–60 °C for 16 h. It was then cooled to r.t., filtered off, and the volatiles were evaporated. The crude residue was purified by flash chromatography on silica gel (Et_2O–PE) to afford **3d** (135 mg, 59%) as a pale yellow solid.

IR (thin film): 1738, 1686, 1499, 174, 1384, 1277, 1200, 1179, 1016 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.77 (m, 4 H), 7.30 (t, 2 H, *J* = 7.8 Hz), 7.17–7.12 (m, 3 H), 4.32 (q, 2 H, *J* = 7.1 Hz), 2.30 (s, 3 H), 1.40 (t, 3 H, *J* = 7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 153.6, 152.2, 139.8, 131.5, 129.4, 128.4, 126.3, 125.5, 125.0, 124.9, 116.7, 69.8, 21.5, 15.2. HRMS: *m/z* calcd for $C_{18}H_{17}NO_2$: 279.1259; found: 279.1252.

Acknowledgment

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