Synthesis F. Mathias et al. Paper

# Efficient Access to Original 6-Substituted 5-Nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles

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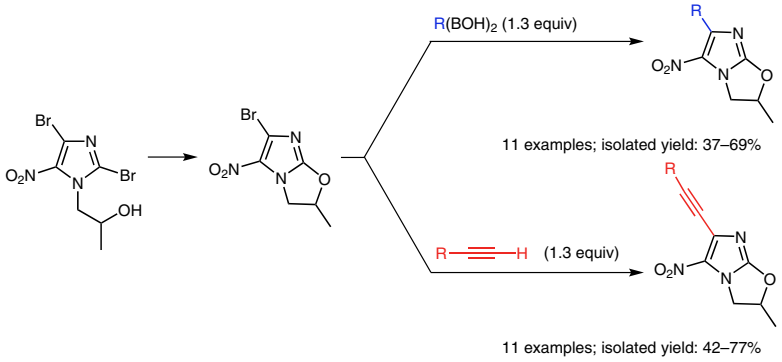


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**Abstract** A one-pot sequential intramolecular cyclization and Suzuki–Miyaura or Sonogashira reaction under microwave irradiation are reported in the 5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole series. The intramolecular cyclization of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol between the hydroxyethyl group and the bromine atom at the 2-position is carried out first, followed by optimization and generalization of the Suzuki–Miyaura and Sonogashira cross-coupling reactions of the bromine atom at the 4-position. The various boronic acids and alkynyl derivatives used to perform these palladium-catalyzed cross-coupling reactions allowed to substitute the 6-position of 5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole compounds.

**Key words** 5-nitroimidazole, Suzuki–Miyaura reaction, Sonogashira reaction, intramolecular cyclization, microwave, palladium

The biological interest of nitroimidazo[2,1-*b*]oxazole derivatives was discovered by Agrawal et al. in 1979. They described a series of compounds with radiosensitizing properties.[1] Thereafter, during a routine screening, Nagarajan et al. showed that some 6-nitroimidazooxazoles had antitubercular activity.[2] Since this discovery, the search for alternative antitubercular molecules with a 6-nitroimidazooxazole scaffold is ongoing.[3] More recently, the Drugs for Neglected Diseases initiative (DNDi) found that this class had antileishmanial properties.[4] Thus, current research is turned toward the synthesis of 6-nitroimidazooxazole compounds, and the 5-nitroimidazooxazole class remains unexplored.

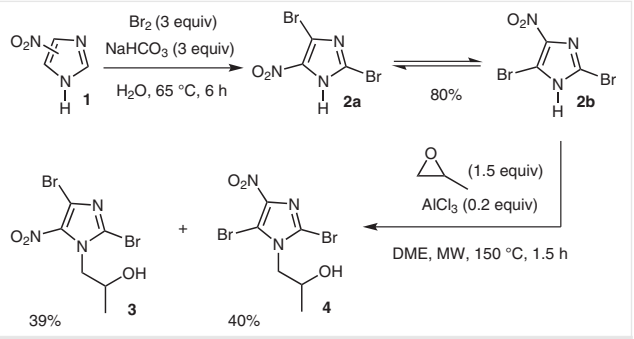
Stable 6-nitroimidazo[2,1-*b*]oxazole can be synthesized by alkylation of 2,4(5)-dinitroimidazole with oxirane to obtain an ethanol chain, which can undergo intramolecular cyclization by the displacement of 2-nitro function on heating.[1a] To improve safety, a new approach was tried using 2-bromo-4-nitroimidazole as the starting compound.[5] The authors showed that cyclization with alcohol could occur in good yields when a halogen, like a bromine, replaced the 2-position of the nitro group. However, this protocol promotes the formation of 6-nitroimidazooxazole, and 5-nitroimidazooxazole is only obtained in minor quantities. We focused our work on the synthesis of 5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole compounds with a bromine in the 6-position able to react under palladium-catalyzed reactions. Suzuki–Miyaura cross-coupling of an organoboron reagent and an organohalide or organosulfonate is the most efficient method of aryl–aryl bond formation, and is widely used in the manufacturing of drug components in the pharmaceutical industry.[6] Sonogashira cross-coupling is a copper and palladium co-catalyzed reaction of terminal alkynes and aryl halides. The resulting compounds are widely used for the synthesis of pharmaceutical compounds.[7]

A few examples of Suzuki–Miyaura and Sonogashira reactions performed on a 4-bromo-5-nitroimidazole were described and showed good reactivity.[8] The nitro group in 5-position increases the electrophilic properties of the C-4, making this position very reactive toward cross-coupling reactions.[9] On the other hand, these palladium-catalyzed cross-coupling were not yet carried out on a 6-bromo-5-nitroimidazooxazole.

We report herein an intramolecular cyclization of the 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol to form the 6-bromo-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole. After undergoing Suzuki–Miyaura or Sonogashira cross-coupling reactions, this allows 6-substituted 5-nitroimidazooxazoles to be obtained in a sequential one-pot process.

The required starting material, compound **3**, was synthesized from the commercial product 4(5)-nitroimidazole (**1**) in two steps as described in Scheme 1. For the first step, we followed Pedada et al.'s methodology,[10] who reported

the dibromination on 4(5)-nitro-1*H*-imidazole. Thus, the reaction was carried out in water using bromine (3 equiv) in the presence of sodium bicarbonate (3 equiv) and led to two tautomeric forms **2a** and **2b** in 80% overall yield. The first study of alkylation employed a mixture of 2,4(5)-dibromo-5(4)-nitroimidazole **2** (**2a** and **2b**), propylene oxide (1.5 equiv), and aluminum chloride as Lewis acid (1.5 equiv) in ethyl acetate, according to the preparation method of secnidazole and ornidazole in a temperature range between 0 and 10 °C for 2.5 hours.[11] However, here we added a short phase of optimization because our starting material **2** was less reactive than 2-methyl-5-nitroimidazole used for the synthesis of secnidazole and ornidazole (probably due to the steric hindrance of the 2-bromine atom as opposed to the methyl group). Based on various approaches developed in our laboratory,[12] we decided to adapt the synthesis using microwave methodology. This enabled us to increase the temperature to 150 °C under microwave irradiation using sealed vessels. These conditions led to the entire consumption of the starting material **2**. Unfortunately, the latter conditions using ethyl acetate as solvent led to the acetylated alcohol of the side chain of compounds **3** and **4**, causing us to change the solvent. DME was tried next, and was found to be very efficient in the synthesis promoted under microwave irradiation.[13] Thus, the reaction was performed with compound **2**, propylene oxide (1.5 equiv), and aluminum chloride as Lewis acid. Furthermore, a short phase of optimization led us to reduce the amount of $AlCl_3$ to 0.2 equivalent to promote the formation of 5-nitro isomer **3** in 39% yield (Table 1, entry 3). The decrease of the amount of $AlCl_3$ to 0.1 equivalent increased the yield of 4-nitro isomer **4** (entry 4), probably due to the low acidity of the medium. The use of acetic acid or phosphoric acid as solvent (entries 5 and 6), found in the protocol of metronidazole synthesis,[14] did not improve the yield of compound **3**. Indeed, the starting compound was in majority and only traces of compounds **3** and **4** were observed in LC/MS. We did not try to operate in basic medium because some publications have shown that these conditions promoted formation of the 4-nitro isomer.[15] Current studies focused on nitroimidazooxazoles are in accordance with our results and have shown that the 4-nitro isomer always predominates after alkylation of 4(5)-nitroimidazole with an epoxide.[3d,16]




**Scheme 1** Synthesis of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**)

**Table 1** Optimization of the Alkylation of Compound **2**

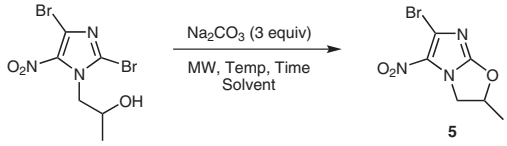
| Entry | Solvent | $AlCl_3$ (equiv) | Temp (°C) | Time (h) | Yield of **3** (%) | Yield of **4** (%) |
|---|---|---|---|---|---|---|
| 1 | DME | 0.5 | MW, 150 | 1.5 | 30 | 46 |
| 2 | DME | 0.3 | MW, 150 | 1.5 | 38 | 42 |
| 3 | DME | 0.2 | MW, 150 | 1.5 | 39 | 40 |
| 4 | DME | 0.1 | MW, 150 | 1.5 | 30 | 49 |
| 5[a] | AcOH | 0.5 | 150 | 72 | – | – |
| 6[a] | $Ac_2O + H_3PO_4$ | – | 150 | 72 | – | – |

[a] Reaction progress was followed by LC/MS.

The structures of **3** and **4** were confirmed on the basis of 2D NMR (HMBC) (see the Supporting Information). A correlation between the carbon (C–$NO_2$) at 137.3 ppm and the hydrogens ($CH_2$) at 4.48 ppm of the alkyl chain of compound **3** was observed, confirming the presence of the nitro group at the 5-position. No correlation was observed between the carbon (C–$NO_2$) at 144.6 ppm and the hydrogens ($CH_2$) of the alkyl chain of compound **4**, confirming the presence of the nitro group at the 4-position.

The 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**) was subjected to intramolecular cyclization and Suzuki–Miyaura cross-coupling with the purpose of identifying reaction conditions, which would allow us to operate in a sequential one-pot process. We started by trying to achieve intramolecular cyclization (Scheme 2) under favorable conditions for Suzuki–Miyaura reaction, as described by Hodgetts et al.[17] Thus, initial trials were performed using 3 equivalents of $Na_2CO_3$ as base, 5 mol% of $Pd(PPh_3)_4$ as catalyst in a DME/$H_2O$ (4:1, v/v) mixture as solvent (Table 2, entry 1). However, in these conditions only 32% yield of compound **5** was obtained because of the formation of side-product following a nucleophilic aromatic substitution with water. Thus, the following attempts were carried out only in dimethoxyethane, which led us to increase the temperature to 110 °C for 1.5 hours (entry 5) to obtain compound **5** in a good yield of 80%. The presence of a catalyst was not found to be essential for the cyclization and compound **5** was obtained in equivalent yield without palladium (entry 1 vs entry 2).

After showing that 6-bromo-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (**5**) could be formed by intramolecular cyclization, our attention was focused on the Suzuki–Miyaura cross-coupling and its optimization at the 6-position with bromine atom in a sequential one-pot two-step process (Scheme 3). First, the cyclization step was performed with $Na_2CO_3$ at 110 °C under microwave irradiation




**Scheme 2** Intramolecular cyclization of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**)

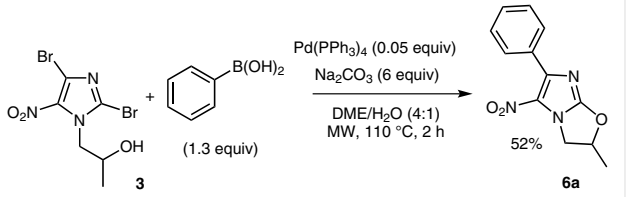
**Table 2** Optimization of the Intramolecular Cyclization Reaction of **3**

| Entry | Solvent | Pd (0.05 equiv) | Temp (°C) | Time (h) | Yield of **5** (%) |
|---|---|---|---|---|---|
| 1 | DME/$H_2O$ | $Pd(PPh_3)_4$ | MW, 100 | 1 | 32 |
| 2 | DME/$H_2O$ | – | MW, 100 | 1 | 30 |
| 3[a] | DME | – | MW, 100 | 1 | 40 |
| 4[a] | DME | – | MW, 110 | 1 | 60 |
| 5 | DME | – | MW, 110 | 1.5 | 80 |

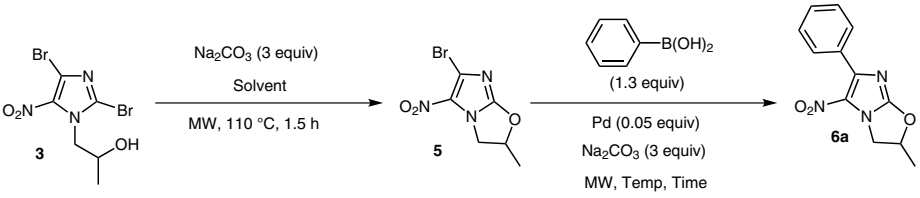
[a] LC/MS ratio.

for 1.5 hours. Total consumption of starting material **3** was monitored by LC-MS in all attempts, before adding the reagents for Suzuki–Miyaura reaction.

The optimization of the Suzuki–Miyaura reaction on 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**5**) was performed with phenylboronic acid by screening palladium sources, ligands, and solvents (Table 3). No side-products were observed. Several solvents were tested with $Pd(PPh_3)_4$ as catalyst (Table 3, entries 1–6) and the best result was obtained with DME/$H_2O$ mixture. When the reaction was carried out in DME, Suzuki–Miyaura cross-coupling did not occur and only the cyclized compound **5** was obtained. Thus, the addition of water during the second step was found to be essential. Then, several sources of palladium were investigated (entries 7–12). From among all the tested catalysts, $Pd(PPh_3)_4$ provided the highest conver-




**Scheme 4** One-pot intramolecular cyclization on **3** and Suzuki–Miyaura reaction with phenylboronic acid

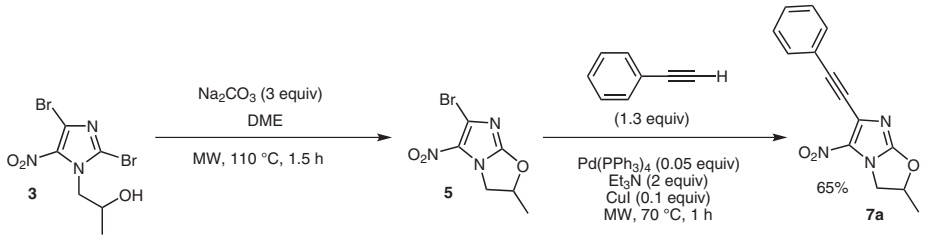



**Scheme 3** One-pot sequential intramolecular cyclization of **3** and Suzuki–Miyaura reaction with phenylboronic acid

**Table 3** Optimization of the Suzuki–Miyaura Reaction of **5**

| Entry | Solvent | Pd/Ligand | Temp (C) | Time (h) | Yield of **6a** (%) |
|---|---|---|---|---|---|
| 1 | DME | $Pd(PPh_3)_4$ | 110 | 1.5 | – |
| 2 | DME/EtOH/$H_2O$ | $Pd(PPh_3)_4$ | 110 | 1.5 | 16 |
| **3** | **DME/$H_2O$** | **$Pd(PPh_3)_4$** | **110** | **1.5** | **69** |
| 4 | DMF/$H_2O$ | $Pd(PPh_3)_4$ | 110 | 1.5 | 11 |
| 5 | 1,4-dioxane/$H_2O$ | $Pd(PPh_3)_4$ | 110 | 1.5 | 42 |
| 6[a] | EtOH/$H_2O$/TBAB | $Pd(PPh_3)_4$ | 110 | 1.5 | – |
| 7 | DME/$H_2O$ | $Pd(PPh_3)_2Cl_2$ | 110 | 1.5 | 55 |
| 8 | DME/$H_2O$ | $Pd(OAc)_2$ | 110 | 1.5 | 40 |
| 9 | DME/$H_2O$ | $Pd(OAc)_2/PPh_3$ | 110 | 1.5 | 27 |
| 10 | DME/$H_2O$ | $Pd(OAc)_2$/Xantphos | 110 | 1.5 | 18 |
| 11 | DME/$H_2O$ | $Pd(OAc)_2$/BINAP | 110 | 1.5 | 27 |
| 12 | DME/$H_2O$ | $Pd(OAc)_2$/JohnPhos | 110 | 1.5 | 13 |

[a] Reaction performed with 1 equiv of tetrabutylammonium bromide (TBAB) as the phase-transfer agent.




**Scheme 5** One-pot intramolecular cyclization and Sonogashira alkynylation of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**)

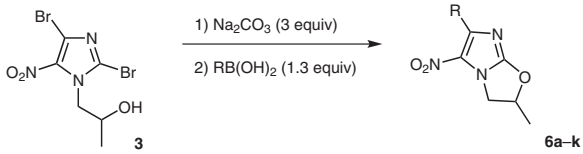
sion into product (entry 3). The addition of ligands to $Pd(OAc)_2$ such as $PPh_3$, Xantphos, JohnPhos, or BINAP led to a considerable decrease in the yield of **6a** (entries 9–12).

Before generalizing this reaction to other boronic acids, the best conditions described in Table 3 (entry 3) were used in an attempt to achieve the cyclization and Suzuki–Miyaura reaction in one step, as shown in Scheme 4. The reaction was carried out with $Na_2CO_3$, $Pd(PPh_3)_4$, and phenylboronic acid (1.3 equiv) at 110 °C for 2 hours. The desired product **6a** was obtained in a lower yield than that observed when the reaction was performed in two steps.

Having determined the best protocol, we tested the scope of the intramolecular cyclization and Suzuki–Miyaura cross-coupling reaction of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**) (Table 4) in two steps. The first step was performed with $Na_2CO_3$ in DME at 110 °C under microwave irradiation for 1.5 hours. In the second step, the reaction was carried out with addition of water, $Pd(PPh_3)_4$ (0.05 equiv), $Na_2CO_3$ (3 equiv), and boronic acid (1.3 equiv) at 110 °C under microwave irradiation for 1.5 hours. A variety of substituted (hetero)arylboronic acids (with electron-donating or electron-withdrawing groups) were used to give the corresponding coupling products **6a–k** in moderate to good yields (37–69%). The yield decreased below 50% when hydroxymethylphenylboronic acid and boronic acids substituted by an electron-withdrawing group such as $NO_2$ was used. The structure of the 5-nitroimidazooxazole derivative was confirmed for compound **6b** with a methoxyphenyl group in the 6-position, on the basis of 2D NMR (NOESY) (see the Supporting Information). No correlation was observed between the protons of the aromatic ring and the protons of the oxazole ring, confirming the presence of the nitro group at the 5-position.

Thereafter, the reaction conditions of the second step were modified to examine the Sonogashira alkynylation of 6-bromo-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (**5**). The first trial was performed with phenylacetylene (Scheme 5) under conditions previously described by our group with the 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole.[8b] The reaction conditions of the first cyclization step described above were used. After cooling, phenylacetylene (1.3 equiv), $Et_3N$ (2 equiv), CuI (0.1 equiv), and $Pd(PPh_3)_4$ were added for the second Sonogashira cross-coupling step. The reaction mixture was stirred for 1 hour at 70 °C under microwave irradiation, yielding 65% of the desired product **7a** (Scheme 5).

**Table 4** Scope of the One-Pot Intramolecular Cyclization and Suzuki–Miyaura Reaction of **3**[a]




| Entry | $RB(OH)_2$ | Product | Yield (%) |
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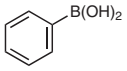
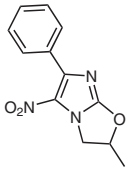
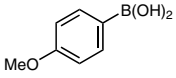
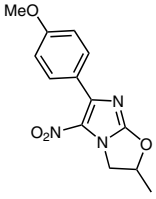
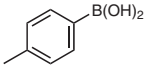
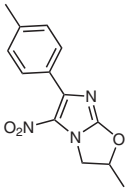
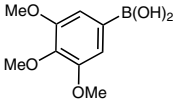
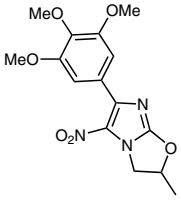
| 1 |  |  | 69 |
| 2 |  |  | 66 |
| 3 |  |  | 60 |
| 4 |  |  | 51 |

| Entry | $RB(OH)_2$ | Product | Yield (%) |
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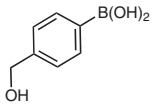
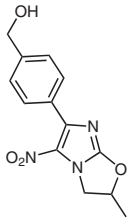
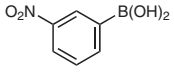
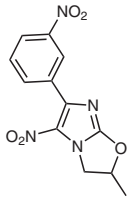
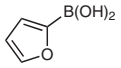
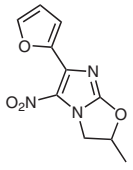
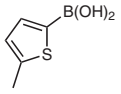
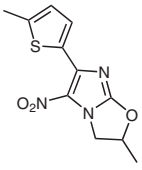
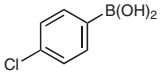
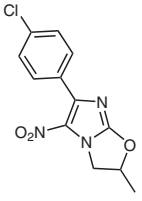
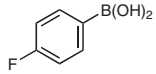
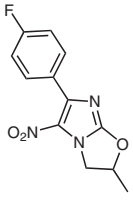
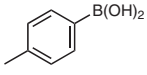
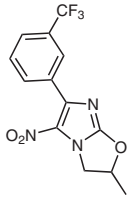
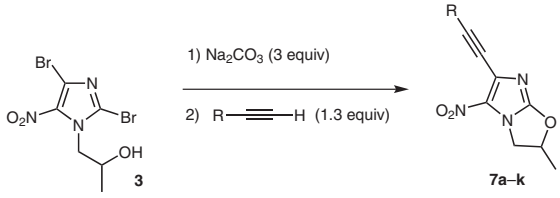
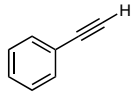
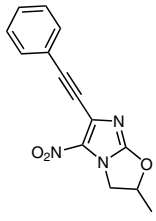
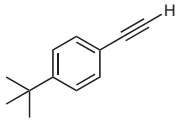
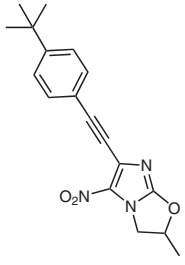
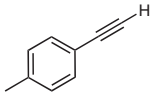
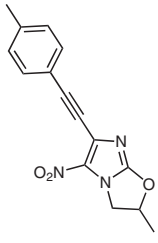
| 5 |  |  | 37 |
| 6 |  |  | 40 |
| 7 |  |  | 57 |
| 8 |  |  | 60 |
| 9 |  |  | 63 |
| 10 |  |  | 63 |
| 11 |  |  | 56 |

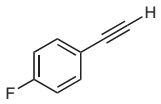
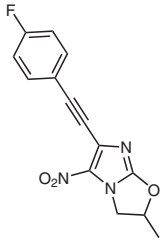
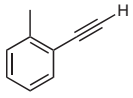
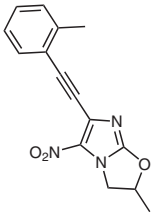
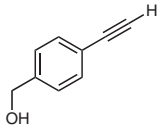
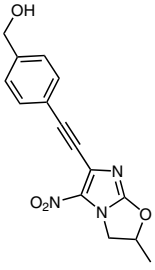
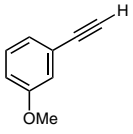
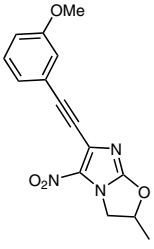
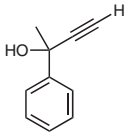
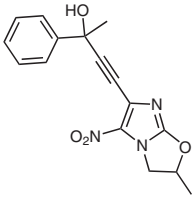
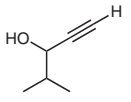
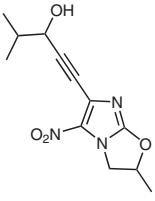
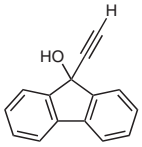
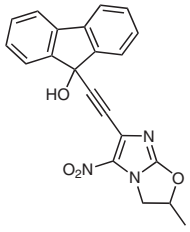
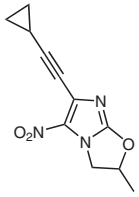
[a] Reaction conditions: Step 1: $Na_2CO_3$ (3 equiv), DME (4 mL), MW, 110 °C, 1.5 h. Step 2: $H_2O$ (0.5 mL), boronic acid (1.3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), $Na_2CO_3$ (3 equiv), MW, 110 °C, 1.5 h.

This protocol was extended to different terminal alkynes (Table 5) to evaluate the scope and limitations of this procedure. A variety of arylacetylenes (Table 5, entries 1–7), acetylenic alcohols (entries 8–10), and cyclopropylacetylene (entry 11) were reacted under this protocol and afforded the corresponding coupled products **7a–k** in moderate to good yields. The best results were obtained with arylacetylenes **7a–g**, in particular when the aryl group carried a fluorine atom at the *para*-position (**7d**, 78%). However, a decrease in yield was observed when the reaction was performed with acetylenic alcohols (compounds **7h–j**).

**Table 5** Scope of the One-Pot Intramolecular Cyclization and Sonogashira Reaction of **3**[a]




| Entry | R—≡—H | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 65 |
| 2 |  |  | 70 |
| 3 |  |  | 67 |

| Entry | R—≡—H | Product | Yield (%) |
|---|---|---|---|
| 4 |  |  | 78 |
| 5 |  |  | 60 |
| 6 |  |  | 67 |
| 7 |  |  | 77 |
| 8 |  |  | 55 |
| 9 |  |  | 42 |
| 10 |  |  | 45 |
| 11 |  |  | 58 |

[a] Reaction conditions: Step 1: $Na_2CO_3$ (3 equiv), DME, MW, 110 °C, 1.5 h. Step 2: alkyne (1.3 equiv), $Pd(PPh_3)_4$ (0.05 equiv), $Et_3N$ (2 equiv), CuI (0.1 equiv), MW, 70 °C, 1 h.

In conclusion, we have developed an efficient method to design 5-nitroimidazooxazole compounds. We optimized a one-pot sequential intramolecular cyclization and Suzuki–Miyaura reaction to form the dihydrooxazole ring and functionalized the 6-position of the heterocycle system with various aryl and heteroaryl groups. Our strategy of choosing a Sonogashira alkynylation to introduce arylacetylenes and acetylenic alcohols in this 5-nitroimidazooxazole scaffold allowed us to form the imidazooxazole cycle and substitute the 6-position with various alkynes in a one-pot process. This method affords easy and rapid access to original 5-nitroimidazooxazole compounds whose biological interest remains to be determined.

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses and HRMS were carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme, Marseille. 250 MHz $^1$H NMR spectra (reference $CDCl_3$ δ = 7.26, DMSO-$d_6$ δ = 2.50) and 62.5 MHz $^{13}$C NMR spectra (reference $CDCl_3$ δ = 77.0, DMSO-$d_6$ δ = 39.7) were recorded at 24 °C on a Bruker ARX 200 spectometer in $CDCl_3$ and DMSO-$d_6$ solvents at the Faculté de Pharmacie de Marseille. Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluent. HRMS spectra were recorded on QStar Elite (Applied Biosystems SCIEX) spectrometer. PEG was the matrix for HRMS.

Microwave reactions were performed with a Biotage® Initiator Microwave oven using 2–5 mL sealed vials; temperatures were measured with an IR-sensor and reaction times are given as hold times.

### 1-(2,4-Dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (3)

*First Step*: To a solution of 4(5)-nitro-1*H*-imidazole (**1**; 10 g, 88.5 mmol) and $NaHCO_3$ (22.3 g, 3 equiv, 265.5 mmol) in $H_2O$ (120 mL) was added $Br_2$ (13.5 mL, 3 equiv, 265.5 mmol) dropwise at 0 °C and

the reaction mixture was heated at 65 °C for 6 h after complete addition of $Br_2$. After cooling, the pH of the reaction mixture was adjusted to 2–3 by adding aq HCl. A yellow precipitate was formed, which was filtered, washed with $H_2O$ (3 × 100 mL), and dried in a vacuum drying oven (desiccator cabinet). Compound 2,4(5)-dibromo-5(4)-nitroimidazole (**2**) was obtained as yellow solid in 80% yield (19.16 g); mp 175 °C.

*Second Step*: To a solution of 2,4(5)-dibromo-5(4)-nitroimidazole (**2**; 0.5 g, 1.9 mmol) and $AlCl_3$ (0.12 g, 0.5 equiv, 0.92 mmol) in DME (5 mL) was added 2-methyloxirane (0.19 mL, 1.5 equiv, 2.78 mmol) at 0 °C under argon and the reaction mixture was heated at 150 °C for 1.5 h under microwave irradiation. After cooling, EtOAc was added and the solution was filtered on Celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, PE/EtOAc, 7:3).

**1-(2,4-Dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (3)**

Yield: 238 mg (39%); yellow oil.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 4.55–4.39 (m, 2 H, $CH_2$), 4.19–4.07 (m, 1 H, CH), 2.09 (s, 1 H, OH), 1.34 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 137.3 ($C_{Ar}$), 126.8 ($C_{Ar}$), 120.0 ($C_{Ar}$), 66.7 (CH), 55.7 ($CH_2$), 21.0 ($CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_6H_7Br_2N_3O_3$: 328.8907; found: 328.8908.

**1-(2,5-Dibromo-4-nitro-1*H*-imidazol-1-yl)propan-2-ol (4)**

Yield: 248 mg (40%); yellow oil.

$^1$H NMR (DMSO-$d_6$, 250 MHz): δ = 5.17 (d, $^3J_{H,H}$ = 4.4 Hz, 1 H, OH), 4.07–3.89 (m, 3 H, CH and $CH_2$), 1.16 (d, $^3J_{H,H}$ = 5.5 Hz, 3 H, $CH_3$).

$^{13}$C NMR (DMSO-$d_6$, 62.5 MHz): δ = 144.6 ($C_{Ar}$), 121.9 ($C_{Ar}$), 109.6 ($C_{Ar}$), 64.5 (CH), 55.0 ($CH_2$), 20.8 ($CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_6H_7Br_2N_3O_3$: 328.8907; found: 328.8907.

**6-Bromo-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (5)**

A mixture of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**; 0.2 g, 0.61 mmol) and $Na_2CO_3$ (0.19 g, 1.82 mmol, 3 equiv) was heated in DME (4 mL) for 1.5 h under microwave irradiation. After cooling, $H_2O$ was added (60 mL) and the aqueous mixture was extracted with $CH_2Cl_2$ (3 × 60 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated under reduced pressure. Flash chromatography (silica gel, PE/EtOAc, 6:4) provided 120 mg (80%) of **5** as a yellow oil.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 5.63–5.50 (m, 1 H, CH), 4.69 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.12 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.9 Hz, 1 H, $CH_2$), 1.70 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 157.7 (C), 121.6 (C), 85.7 (CH), 52.8 ($CH_2$), 20.3 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_6H_6BrN_3O_3$: 247.9665; found: 247.9665.

**One-Pot Sequential Intramolecular Cyclization and Suzuki–Miyaura Reaction of 3 with Boronic Acids; General Procedure**

A solution of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**; 0.15 g, 0.45 mmol) and $Na_2CO_3$ (0.15 g, 1.37 mmol, 3 equiv) in DME (4 mL) was heated at 110 °C under microwave irradiation for 1.5 h. After cooling, the appropriate boronic acid (0.59 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol, 0.05 equiv), $Na_2CO_3$ (0.15 g, 1.37 mmol, 3 equiv), and $H_2O$ (0.5 mL) were introduced under argon and the mixture was heated at 110 °C for 1.5 h under microwave irradiation. After cooling, $H_2O$ (60 mL) was added and the solution was extracted with $CH_2Cl_2$ (3 × 60 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, PE/EtOAc, 7:3 (1:1 for **6d**, **6e**) and recrystallized from *i*-PrOH.

**2-Methyl-5-nitro-6-phenyl-2,3-dihydroimidazo[2,1-*b*]oxazole (6a)**

Yield: 77 mg (69%); yellow solid; mp 66 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.95–7.92 (m, 2 H, ArH), 7.51–7.43 (m, 3 H, ArH), 5.65–5.51 (m, 1 H, CH), 4.75 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.19 (dd, $^2J_{H,H}$ = 10.5 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.73 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.3 ($C_{Ar}$), 147.5 ($C_{Ar}$), 131.2 ($C_{Ar}$), 130.2 ($CH_{Ar}$), 129.8 (2 × $CH_{Ar}$), 128.1 (2 × $CH_{Ar}$), 85.4 (CH), 52.7 ($CH_2$), 20.5 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_3O_3$: 246.0873; found: 246.0872.

**6-(4-Methoxyphenyl)-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6b)**

Yield: 77 mg (66%); yellow solid; mp 118 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.98 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, ArH), 6.96 (d, $^3J_{H-H}$ = 8.9 Hz, 2 H, ArH), 5.60–5.49 (m, 1 H, CH), 4.73 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, $CH_2$), 4.17 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 3.86 (s, 3 H, $OCH_3$), 1.71 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 161.2 ($C_{Ar}$), 158.4 ($C_{Ar}$), 147.9 ($C_{Ar}$), 133.9 ($C_{Ar}$), 131.6 (2 $CH_{Ar}$), 123.7 ($C_{Ar}$), 113.5 (2 $CH_{Ar}$), 85.3 (CH), 55.4 ($OCH_3$), 52.8 ($CH_2$), 20.5 ($CH_3$).

Anal. Calcd for $C_{13}H_{13}N_3O_4$ (275.26): C, 56.72; H, 4.76; N, 15.27. Found: C, 55.70; H, 4.66; N, 14.20.

**2-Methyl-5-nitro-6-*p*-tolyl-2,3-dihydroimidazo[2,1-*b*]oxazole (6c)**

Yield: 71 mg (60%); yellow solid; mp 151 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.85 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.25 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 5.62–5.48 (m, 1 H, CH), 4.73 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 2.40 (s, 3 H, $CH_3$), 1.71 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.4 ($C_{Ar}$), 147.8 ($C_{Ar}$), 140.6 ($C_{Ar}$), 129.7 (2 × $CH_{Ar}$), 129.4 ($C_{Ar}$), 128.8 (2 × $CH_{Ar}$), 128.4 ($C_{Ar}$), 85.4 (CH), 52.7 ($CH_2$), 21.5 ($CH_3$), 20.5 ($CH_3$).

Anal. Calcd for $C_{13}H_{13}N_3O_3$ (259.26): C, 60.22; H, 5.05; N, 16.21. Found: C, 59.47; H, 4.91; N, 15.30.

**2-Methyl-5-nitro-6-(3,4,5-trimethoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (6d)**

Yield: 78 mg (51%); yellow solid; mp 153 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.34 (s, 2 H, ArH), 5.63–5.49 (m, 1 H, CH), 4.74 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 3.90 (s, 9 H, 3 × $OCH_3$), 1.72 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.2 ($C_{Ar}$), 152.6 (2 × $C_{Ar}$), 147.2 ($C_{Ar}$), 139.9 ($C_{Ar}$), 129.6 ($C_{Ar}$), 126.3 ($C_{Ar}$), 107.2 (2 × $CH_{Ar}$), 85.4 (CH), 60.9 ($CH_2$), 56.2 (2 × $OCH_3$), 52.8 ($OCH_3$), 20.5 ($CH_3$).

Anal. Calcd for $C_{15}H_{17}N_3O_6$ (335.31): C, 53.73; H, 5.11; N, 12.53. Found: C, 53.67; H, 4.87; N, 12.22.

**4-(2-Methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazol-6-yl)phenyl]methanol (6e)**

Yield: 46 mg (37%); yellow solid; mp 163 °C.

$^1$H NMR (DMSO-$d_6$, 250 MHz): δ = 7.79 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 7.40 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, ArH), 5.71–5.57 (m, 1 H, CH), 4.69 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, $CH_2$), 4.55 (s, 2 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.59 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR (DMSO-$d_6$, 62.5 MHz): δ = 158.5 ($C_{Ar}$), 146.4 ($C_{Ar}$), 144.7 ($C_{Ar}$), 135.5 ($C_{Ar}$), 130.1 ($C_{Ar}$), 129.5 (2 × $CH_{Ar}$), 126.0 (2 × $CH_{Ar}$), 86.7 (CH), 62.8 ($CH_2$), 52.3 ($CH_2$), 20.0 ($CH_3$).

Anal. Calcd for $C_{13}H_{13}N_3O_4$ (275.26): C, 56.72; H, 4.76; N, 15.27. Found: C, 56.15; H, 4.57, N, 14.62.

**2-Methyl-5-nitro-6-(3-nitrophenyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (6f)**

Yield: 53 mg (40%); yellow solid; mp 113 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 8.83–8.81 (m, 1 H, ArH), 8.31–8.26 (m, 2 H, ArH), 7.62 (t, $^3J_{H,H}$ = 8.1 Hz, 1 H, ArH), 5.69–5.58 (m, 1 H, CH), 4.79 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.23 (dd, $^2J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.75 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.3 ($C_{Ar}$), 148.0 ($C_{Ar}$), 143.9 ($C_{Ar}$), 135.6 ($CH_{Ar}$), 132.8 ($C_{Ar}$), 129.1 ($CH_{Ar}$), 124.9 ($CH_{Ar}$), 124.6 ($CH_{Ar}$), 85.8 (CH), 52.7 ($CH_2$), 20.5 ($CH_3$); C–$NO_2$ was not observed.

Anal. Calcd for $C_{12}H_{10}N_4O_5$ (290.23): C, 49.66; H, 3.47; N, 19.30. Found: C, 49.56; H, 3.30; N, 18.71.

**6-(Furan-2-yl)-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6g)**

Yield: 61 mg (57%); yellow solid; mp 153 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.75 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H, ArH), 7.62 (d, $^3J_{H,H}$ = 1.7 Hz, 1 H, ArH), 6.59 (dd, $^3J_{H,H}$ = 3.6 Hz, $^3J_{H,H}$ = 1.7 Hz, 1 H, ArH), 5.65–5.51 (m, 1 H, CH), 4.74 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.71 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 159.0 ($C_{Ar}$), 145.7 ($C_{Ar}$), 145.2 ($CH_{Ar}$), 137.7 ($C_{Ar}$), 127.9 ($C_{Ar}$), 117.0 ($CH_{Ar}$), 112.4 ($CH_{Ar}$), 85.8 (CH), 52.5 ($CH_2$), 20.4 ($CH_3$).

Anal. Calcd for $C_{10}H_9N_3O_4$ (235.20): C, 51.07; H, 3.86; N, 17.87. Found: C, 51.34; H, 3.68, N, 17.65.

**2-Methyl-6-(5-methylthiophen-2-yl)-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6h)**

Yield: 73 mg (60%); yellow solid; mp 173 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 8.15 (d, $^3J_{H,H}$ = 3.8 Hz, 1 H, ArH), 6.84–6.82 (m, 1 H, ArH), 5.62–5.48 (m, 1 H, CH), 4.72 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.15 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 2.54 (s, 3 H, $CH_3$), 1.70 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.6 ($C_{Ar}$), 146.3 ($C_{Ar}$), 142.5 ($C_{Ar}$), 132.5 ($CH_{Ar}$), 132.1 ($C_{Ar}$), 126.8 ($CH_{Ar}$), 85.6 (CH), 52.6 ($CH_2$), 20.4 ($CH_3$), 15.6 ($CH_3$); C–$NO_2$ was not observed.

Anal. Calcd for $C_{11}H_{11}N_3O_3S$ (265.29): C, 49.80; H, 4.18; N, 15.84. Found: C, 49.37; H, 3.99; N, 15.37.

**6-(4-Chlorophenyl)-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6i)**

Yield: 80 mg (63%); yellow solid; mp 127 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.90 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, ArH), 7.41 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, ArH), 5.64–5.50 (m, 1 H, CH), 4.74 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.72 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.3 ($C_{Ar}$), 146.0 ($C_{Ar}$), 136.2 ($C_{Ar}$), 131.1 (2 × $CH_{Ar}$), 129.6 ($C_{Ar}$), 129.4 ($C_{Ar}$), 128.3 (2 × $CH_{Ar}$), 85.5 (CH), 52.7 ($CH_2$), 20.4 ($CH_3$).

Anal. Calcd for $C_{12}H_{10}ClN_3O_3$ (279.68): C, 51.53; H, 3.60; N, 15.02. Found: C, 51.46; H, 3.44; N, 14.55.

**6-(4-Fluorophenyl)-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (6j)**

Yield: 75 mg (63%); yellow solid; mp 117 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 8.00–7.92 (m, 2 H, ArH), 7.17–7.07 (m, 2 H, ArH), 5.63–5.49 (m, 1 H, CH), 4.73 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.72 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 163.7 (d, $^2J_{C,F}$ = 251.4 Hz, $C_{Ar}$), 158.3 ($C_{Ar}$), 146.4 ($C_{Ar}$), 132.0 (d, $^4J_{C,F}$ = 8.3 Hz, 2 × $CH_{Ar}$), 129.5 ($C_{Ar}$), 127.3 (d, $^5J_{C,F}$ = 3.2 Hz, $C_{Ar}$), 115.2 (d, $^3J_{C,F}$ = 22.1 Hz, 2 × $CH_{Ar}$), 85.5 (CH), 52.7 ($CH_2$), 20.4 ($CH_3$).

Anal. Calcd for $C_{12}H_{10}FN_3O_3$ (263.22): C, 54.75; H, 3.83; N, 15.96. Found: C, 54.83, H, 3.61; N, 15.13.

**2-Methyl-5-nitro-6-[3-(trifluoromethyl)phenyl]-2,3-dihydroimidazo[2,1-*b*]oxazole (6k)**

Yield: 80 mg (56%); yellow oil.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 8.20 (s, 1 H, ArH), 8.12 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, ArH), 7.68 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, ArH), 7.55 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, ArH), 5.64–5.50 (m, 1 H, CH), 4.74 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.18 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.71 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.3 ($C_{Ar}$), 133.0 ($C_{Ar}$), 132.0 ($C_{Ar}$), 130.5 (q, $^3J_{C,F}$ = 32.6 Hz, $C_{Ar}$), 128.5 (2 × $CH_{Ar}$), 126.6 (q, $^4J_{C,F}$ = 3.7 Hz, 2 × $CH_{Ar}$), 123.9 (q, $^2J_{C,F}$ = 272.6 Hz, $C_{Ar}$), 85.7 (CH), 52.6 ($CH_2$), 20.4 ($CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}F_3N_3O_3$: 314.0747; found: 314.0749.

**One-Pot Sequential Intramolecular Cyclization and Sonogashira Reaction of 3 with Terminal Alkynes; General Procedure**

A solution of 1-(2,4-dibromo-5-nitro-1*H*-imidazol-1-yl)propan-2-ol (**3**; 0.15 g, 0.45 mmol) and $Na_2CO_3$ (0.15 g, 1.37 mmol, 3 equiv) in DME (4 mL) was heated at 110 °C under microwave irradiation for 1.5 h. After cooling, the appropriate terminal alkyne (0.59 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol, 0.05 equiv), CuI (9 mg, 0.045 mmol, 0.1 equiv), and $Et_3N$ (0.12 mL, 0.91 mmol, 2 equiv) were introduced under argon and the mixture was heated at 70 °C for 1 h under microwave irradiation. After cooling, $H_2O$ (60 mL) was added and the solution was extracted with $CH_2Cl_2$ (3 × 60 mL). The combined organic layers were washed with $H_2O$ (3 × 100 mL), dried ($Na_2SO_4$), and evaporated. The crude product was purified by column chromatography [silica gel, PE/EtOAc, 7:3 (1:1 for **7f**, **7g**, **7h**, **7i**)] and recrystallized from *i*-PrOH.

**2-Methyl-5-nitro-6-(phenylethynyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (7a)**

Yield: 80 mg (65%); yellow solid; mp 168 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.65–7.61 (m, 2 H, ArH), 7.41–7.35 (m, 3 H, ArH), 5.63–5.49 (m, 1 H, CH), 4.70 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.13 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.9 Hz, 1 H, $CH_2$), 1.71 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.3 ($C_{Ar}$), 148.9 ($C_{Ar}$), 134.2 ($C_{Ar}$), 132.3 (2 × $CH_{Ar}$), 129.7 ($CH_{Ar}$), 128.5 (2 × $CH_{Ar}$), 121.6 ($C_{Ar}$), 98.1 (C), 85.7 (CH), 81.8 (C), 52.1 ($CH_2$), 20.4 ($CH_3$).

Anal. Calcd for $C_{14}H_{11}N_3O_3$ (269.26): C, 62.45; H, 4.12; N, 15.61. Found: C, 62.13; H, 3.93; N, 14.97.

### 6-[(4-*tert*-Butylphenyl)ethynyl]-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (7b)

Yield: 104 mg (70%); yellow solid; mp 156 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.57 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, ArH), 7.39 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, ArH), 5.62–5.49 (m, 1 H, CH), 4.69 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.13 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.71 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$), 1.32 (s, 9 H, 3 × $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.4 ($C_{Ar}$), 153.3 ($C_{Ar}$), 132.1 (2 × $CH_{Ar}$), 128.8 ($C_{Ar}$), 125.5 (2 × $CH_{Ar}$), 118.6 ($C_{Ar}$), 98.7 (C), 85.6 (CH, C), 81.4 (C), 52.1 ($CH_2$), 35.0 ($CH_3$), 31.1 (2 × $CH_3$), 20.4 ($CH_3$); C–$NO_2$ was not observed.

Anal. Calcd for $C_{18}H_{19}N_3O_3$ (325.36): C, 66.45; H, 5.89; N, 12.91. Found: C, 66.13; H, 5.82; N, 12.65.

### 2-Methyl-5-nitro-6-(*p*-tolylethynyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (7c)

Yield: 87 mg (67%); yellow solid; mp 234 °C.

$^1$H NMR (DMSO-$d_6$, 250 MHz): δ = 7.49 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, ArH), 7.29 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, ArH), 5.70–5.57 (m, 1 H, CH), 4.65 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, $CH_2$), 4.14 (dd, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 7.9 Hz, 1 H, $CH_2$), 2.36 (s, 3 H, $CH_3$), 1.58 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR (DMSO-$d_6$, 62.5 MHz): δ = 158.6 ($C_{Ar}$), 140.4 ($C_{Ar}$), 134.7 ($C_{Ar}$), 131.9 (2 × $CH_{Ar}$), 129.9 (2 × $CH_{Ar}$), 126.9 ($C_{Ar}$), 118.0 ($C_{Ar}$), 96.6 (C), 87.1 (CH), 82.3 (C), 51.8 ($CH_2$), 21.4 ($CH_3$), 20.0 ($CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_3$: 284.1030; found: 284.1031.

### 6-[(4-Fluorophenyl)ethynyl]-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (7d)

Yield: 102 mg (78%); yellow solid; mp 199 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.66–7.58 (m, 2 H, ArH), 7.11–7.02 (m, 2 H, ArH), 5.64–5.50 (m, 1 H, CH), 4.70 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.14 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.72 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 163.4 (d, $^2J_{C,F}$ = 252.3 Hz, $C_{Ar}$), 158.3 ($C_{Ar}$), 134.4 (d, $^4J_{C,F}$ = 8.7 Hz, 2 × $CH_{Ar}$), 128.3 ($C_{Ar}$), 117.7 (d, $^5J_{C,F}$ = 3.7 Hz, $C_{Ar}$), 115.9 (d, $^3J_{C,F}$ = 22.5 Hz, 2 × $CH_{Ar}$), 97.0 (C), 85.7 (CH), 81.6 (C), 52.1 ($CH_2$), 20.4 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}FN_3O_3$: 288.0779; found: 288.0780.

### 2-Methyl-5-nitro-6-(*o*-tolylethynyl)-2,3-dihydroimidazo[2,1-*b*]oxazole (7e)

Yield: 78 mg (60%); yellow solid; mp 158 °C.

$^1$H NMR (DMSO-$d_6$, 250 MHz): δ = 7.55 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, ArH), 7.43–7.35 (m, 2 H, ArH), 7.31–7.26 (m, 1 H, ArH), 5.71–5.57 (m, 1 H, CH), 4.66 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.15 (dd, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H, $CH_2$), 2.50 (s, 3 H, $CH_3$), 1.58 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR (DMSO-$d_6$, 62.5 MHz): δ = 158.6 ($C_{Ar}$), 140.9 ($CH_{Ar}$), 134.7 ($C_{Ar}$), 132.4 ($CH_{Ar}$), 130.3 ($C_{Ar}$), 130.1 ($CH_{Ar}$), 126.9 ($C_{Ar}$), 126.4 ($CH_{Ar}$), 120.9 ($C_{Ar}$), 95.4 (C), 87.1 (CH), 86.4 (C), 51.8 ($CH_2$), 20.3 ($CH_3$), 20.0 ($CH_3$).

Anal. Calcd for $C_{15}H_{13}N_3O_3$ (283.28): C, 63.60; H, 4.63; N, 14.83. Found: C, 63.31; H, 4.45; N, 14.53.

### {4-[(2-Methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazol-6-yl)ethynyl]phenyl}methanol (7f)

Yield: 91 mg (67%); yellow solid; mp 206 °C.

$^1$H NMR (DMSO-$d_6$, 250 MHz): δ = 7.56 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, ArH), 7.41 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, ArH), 5.71–5.57 (m, 1 H, CH), 5.35 (t, $^3J_{H,H}$ = 5.4 Hz, 1 H, OH), 4.66 (dd, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, $CH_2$), 4.55 (d, $^3J_{H,H}$ = 5.1 Hz, 2 H, $CH_2$), 4.15 (dd, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.58 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR (DMSO-$d_6$, 62.5 MHz): δ = 158.6 ($C_{Ar}$), 145.2 ($C_{Ar}$), 134.8 ($C_{Ar}$), 131.8 (2 × $CH_{Ar}$), 127.0 (2 × $CH_{Ar}$), 126.8 ($C_{Ar}$), 119.1 ($C_{Ar}$), 96.5 (C), 87.1 (CH), 82.4 (C), 62.6 ($CH_2$), 51.8 ($CH_2$), 19.9 ($CH_3$).

Anal. Calcd for $C_{15}H_{13}N_3O_4$ (299.28): C, 60.20; H, 4.38; N, 14.04. Found: C, 59.62; H, 4.20; N, 13.61.

### 6-[(3-Methoxyphenyl)ethynyl]-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (7g)

Yield: 105 mg (77%); yellow solid; mp 131 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.31–7.21 (m, 2 H, ArH), 7.15–7.14 (m, 1 H, ArH), 6.98–6.93 (m, 1 H, ArH), 5.64–5.50 (m, 1 H, CH), 4.70 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.14 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 3.82 (s, 3 H, $OCH_3$), 1.72 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 159.3 ($C_{Ar}$), 158.3 ($C_{Ar}$), 129.6 ($CH_{Ar}$), 128.4 ($C_{Ar}$), 125.0 ($CH_{Ar}$), 122.5 ($C_{Ar}$), 116.8 ($CH_{Ar}$), 116.6 ($CH_{Ar}$), 98.1 (C), 85.7 (CH), 81.5 (C), 55.4 ($OCH_3$), 52.1 ($CH_2$), 20.4 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_4$: 300.0979; found: 300.0979.

### 4-(2-Methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazol-6-yl)-2-phenylbut-3yn-2-ol (7h)

Yield: 79 mg (55%); brown oil.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.76–7.71 (m, 2 H, ArH), 7.41–7.28 (m, 3 H, ArH), 5.60–5.46 (m, 1 H, CH), 4.64 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.09 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.88 (s, 3 H, $CH_3$), 1.68 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.2 ($C_{Ar}$), 144.5 ($C_{Ar}$), 128.4 (2 × $CH_{Ar}$), 127.9 ($CH_{Ar}$), 125.0 (2 × $CH_{Ar}$), 101.2 ($C_{Ar}$), 85.8 (CH, C), 76.8 (C), 70.4 (C), 52.0 ($CH_2$), 32.8 ($CH_3$), 20.3 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O_4$: 314.1135; found: 314.1136.

### 4-Methyl-1-(2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazol-6-yl)pent-1-yn-3-ol (7i)

Yield: 51 mg (42%); yellow solid; mp 118 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 5.59–5.51 (m, 1 H, CH), 4.70–4.65 (m, 1 H, $CH_2$), 4.44 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, OH), 4.41–4.09 (m, 1 H, $CH_2$), 2.07–1.96 (m, 2 H, 2 × CH), 1.70 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, $CH_3$), 1.09 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, $CH_3$), 1.06 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.2 ($C_{Ar}$), 134.3 ($C_{Ar}$), 127.6 ($C_{Ar}$), 98.4 (C), 85.8 (CH), 77.5 (C), 68.3 (CH), 52.1 ($CH_2$), 34.4 (CH), 20.4 ($CH_3$), 18.0 ($CH_3$), 17.4 ($CH_3$).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_3O_4$: 266.1135; found: 266.1136.

**9-[(2-Methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazol-6-yl)ethynyl]-9*H*-fluoren-9-ol (7j)**

Yield: 77 mg (45%); yellow solid; mp 152 °C.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 7.82–7.79 (m, 2 H, ArH), 7.64–7.61 (m, 2 H, ArH), 7.44–7.32 (m, 4 H, ArH), 5.57–5.43 (m, 1 H, CH), 4.66 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, $CH_2$), 4.62 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H, $CH_2$), 4.07 (dd, $^2J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, $CH_2$), 1.66 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.0 ($C_{Ar}$), 146.0 (2 × $C_{Ar}$), 139.3 (2 × $C_{Ar}$), 129.9 (2 × $CH_{Ar}$), 128.7 (2 × $CH_{Ar}$), 127.2 ($C_{Ar}$), 124.8 (2 × $CH_{Ar}$), 120.2 (2 × $CH_{Ar}$), 98.0 (C), 75.0 (2 C), 85.8 (CH), 52.0 ($CH_2$), 20.3 ($CH_3$); C–$NO_2$ was not observed.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}N_3O_4$: 374.1135; found: 374.1136.

**6-(Cyclopropylethynyl)-2-methyl-5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (7k)**

Yield: 62 mg (58%); yellow oil.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 5.59–5.45 (m, 1 H, CH), 4.64 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, $CH_2$), 4.07 (dd, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.9 Hz, 1 H, $CH_2$), 1.68 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, $CH_3$), 1.59–1.49 (m, 1 H, CH), 0.97–0.94 (m, 4 H, 2 $CH_2$).

$^{13}$C NMR ($CDCl_3$, 62.5 MHz): δ = 158.2 ($C_{Ar}$), 134.1 ($C_{Ar}$), 129.3 ($C_{Ar}$), 104.6 (C), 85.5 (CH), 68.7 (C), 52.0 ($CH_2$), 20.3 ($CH_3$), 9.5 (2 × $CH_2$), 0.7 (CH).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_3O_3$: 234.0873; found: 234.0875.

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## Supporting Information

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