Efficient Microwave-Assisted Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions in 5-Nitroimidazole Series

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Abstract: A new simple, rapid and high yielding synthesis (mean yield = 83%) of various 4-aryl, 4-heteroaryl, and 4-styryl-1,2-dimethyl-5-nitro-1*H*-imidazoles by palladium-catalyzed Suzuki–Miyaura cross-coupling reactions using microwave irradiation is described.

Key words: cross-coupling, 5-nitroimidazoles, palladium, Suzuki reaction, arylations

The 5-nitroimidazole scaffold is well known for exhibiting major anti-infectious activities.[1] Several 5-nitroimidazole-containing active principles are commonly used in medecine such as metronidazole, secnidazole, and ornidazole. These chemotherapeutic agents inhibit the growth of both anaerobic bacteria and some anaerobic protozoa.[2] Nowadays, the most clinically used drug-compound for the treatment of both infections caused by protozoa such as *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia intestinalis*, and infections induced by anaerobic bacteria is metronidazole. However, the 5-nitroimidazoles have been found to possess a high mutagenic activity in prokaryotic microorganisms. A nitroimidazole possessing good pharmacological activities with no mutagenicity[3] would be of great interest, not only from a safety point of view, but would also provide a basis for further investigations on the mechanism involved in their mutagenicity. Moreover, emergence of metronidazole-resistant *Trichomonas vaginalis* results in decreasing the success of current therapies.[4,5] These refractory cases are usually treated with higher doses of metronidazole, which lead to an increase in the occurrence of side effects.[5,6] Thus, alternative curative therapies are needed.

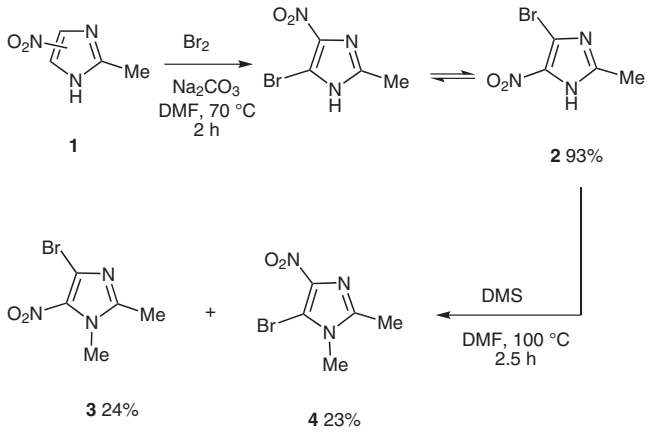
In continuation of our research program on the reactivity of 5-nitroimidazoles and in order to prepare new safe 5-nitroimidazoles as effective drugs against metronidazole-resistant *Trichomonas vaginalis* and *Giardia intestinalis*,[1b,e,7] we were interested in the preparation of new 5-nitroimidazoles bearing an aryl, heteroaryl, or styryl group in the 4-position.

The Suzuki–Miyaura reaction has proved to be extremely versatile and has found extensive use in natural products and heterocyclic synthesis.[8] Only few examples of Suzuki–Miyaura cross-coupling reactions in 2-haloimidazole,[9] 2,4-dihaloimidazole[9a–9c,10] and 4-haloimidazole[10,11] series are reported in the literature. Moreover, no example of Suzuki–Miyaura reaction performed on a nitrated imidazole ring was described to our knowledge.

We have recently reported an efficient microwave-assisted Suzuki cross-coupling reaction of imidazo[1,2-*a*]pyridines.[12] The method, which was tested to carry out cross-coupling reaction, used 10 mol% $Pd(PPh_3)_4$ as a catalyst, 5 equivalents of Na_2CO_3 as the base, 1.3 equivalents of an arylboronic derivative, and 1 equivalent of tetrabutylammonium bromide (TBAB) in water, heating being provided with microwave irradiation.

In continuation of our studies, we focused our research on the interest of microwave heating in Suzuki–Miyaura cross-coupling reaction. The required starting material for the Suzuki cross-coupling reaction is the 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**3**). Unfortunately, it is impossible to obtain the compound **3** in good yield, directly from the nonhalogenated immediate precursor (i.e., dimetridazole or 1,2-dimethyl-5-nitro-1*H*-imidazole).

Indeed, as observed by Sunjic et al.[13] the direct bromination reaction of 1-alkyl-2-methyl-5-nitro-1*H*-imidazole is not possible because of the poor reactivity of the 4-position toward electrophilic substitution reactions. We decided to brominate the 2-methyl-4(5)-nitro-1*H*-imidazole (**1**) as proposed by Bhujanga Rao et al.[14] with elemental bromine (1.1 equiv) in DMF (Scheme 1). Then, the 4(5)-bromo-2-methyl-5(4)-nitro-1*H*-imidazole was methylated by



Scheme 1 Preparation of starting material **3**

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dimethyl sulfate (DMS) following the procedure proposed by Sunjic et al.[13] (Scheme 1).

First attempt of cross-coupling reaction was tested with experimental conditions cited above. Unfortunately, these previous conditions did not work on 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole. Different cross-coupling reaction conditions were therefore examined, in order to study their influence on the reactivity.

All reaction trials were conducted with 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**3**) and phenylboronic acid, in a synthesis multimode microwave oven (ETHOS Synth Lab station) or by classical heating method.

Six reaction parameters were tested (equivalent of arylboronic acid, solvent, base, catalyst, phase transfer agent, heating method). Finally, the best microwave-assisted experimental conditions were defined, permitting the synthesis of 1,2-dimethyl-5-nitro-4-phenyl-1*H*-imidazole (**5**) in 93% yield in one hour. To prepare compound **5**, the 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**3**) and 0.034 equivalent of $Pd(PPh_3)_4$ were dissolved in 1,2-dimethoxyethane (DME) and the mixture stirred for one hour. A solution of phenylboronic acid in ethanol and 3 equivalents of Na_2CO_3 were added. Finally, the mixture was irradiated under microwave (150 W).[15] To evaluate the scope and the limitations of this procedure, we performed coupling reactions with 18 variously substituted boronic acid derivatives. The results show that this coupling reaction is applicable to all aryl, heteroaryl, and styryl boronic acids used in our study (Table 1).

These experimental conditions allowed us to synthesize compounds **20**–**22**, by reaction of **3** with (*E*)-styrylboronic acid, (*E*)-4-(trifluoromethyl)styrylboronic acid, and (*E*)-4-methylstyrylboronic acid, in good to excellent yields (Table 1, entries 16–18), which constitutes an interesting alternative to the Heck reaction. Indeed, there is only one described example, which deals with the Heck reaction on **3**.[16] The reaction was 100% stereoselective. X-ray structure analysis of a crystal of compounds **20** and **21** confirmed the presence of *E*-isomer exclusively (Figures 1 and 2).

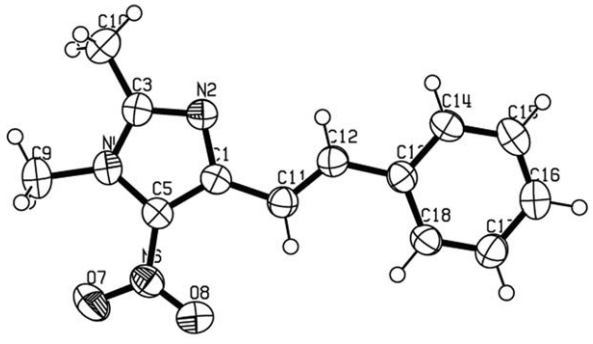
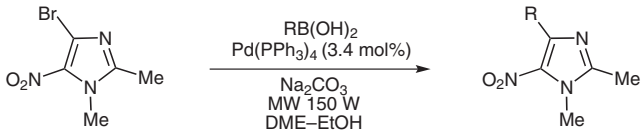


Figure 1 Ortep structure of (*E*)-1,2-dimethyl-5-nitro-4-styryl-1*H*-imidazole (**20**)

Table 1 Microwave-Mediated Suzuki–Miyaura Coupling Reactions of Imidazole **3** with Aryl, Heteroaryl, or Styrylboronic Acids Using $Pd(PPh_3)_4$[a]



3 **5–22**

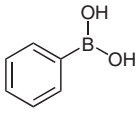
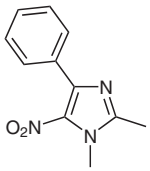
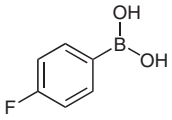
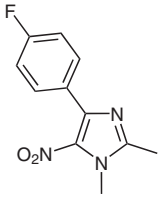
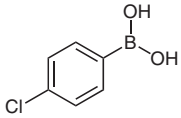
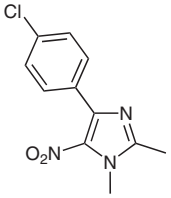
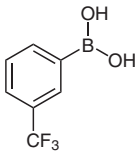
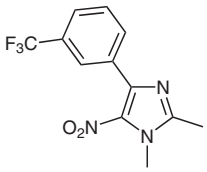
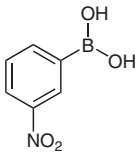
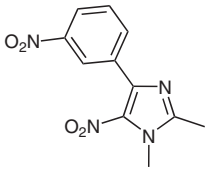
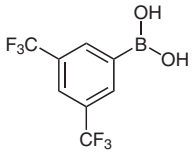
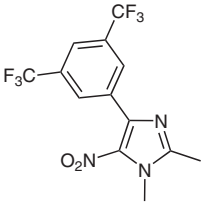
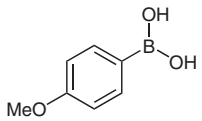
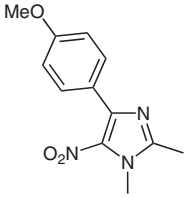
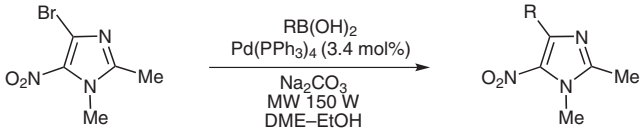
Entry	Boronic acid	Product		Time (h)	Yield (%)
1			**5**	1	93
2			**6**	1	93
3			**7**	1	71
4			**8**	1	68
5			**9**	3	80
6			**10**	2	98
7			**11**	1	89

Table 1 Microwave-Mediated Suzuki–Miyaura Coupling Reactions of Imidazole **3** with Aryl, Heteroaryl, or Styrylboronic Acids Using $Pd(PPh_3)_4$[a] (continued)



3 **5–22**

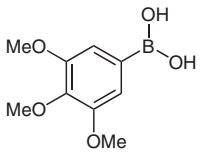
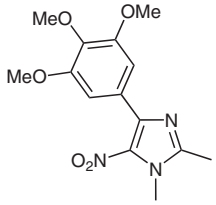
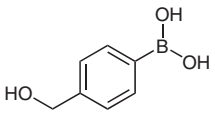
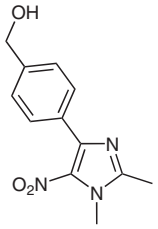
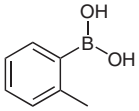
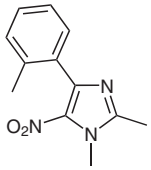
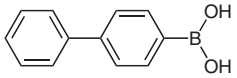
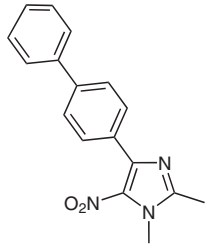
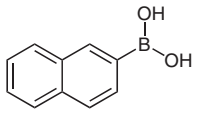
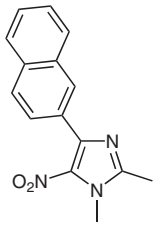
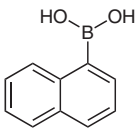
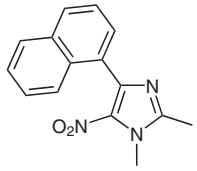
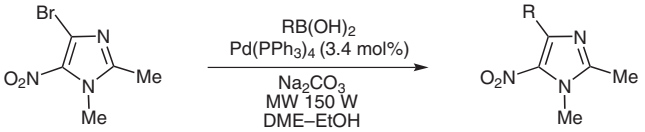
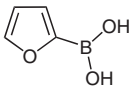
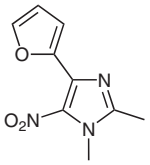
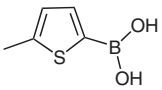
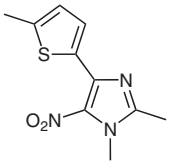
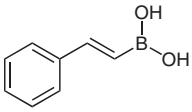
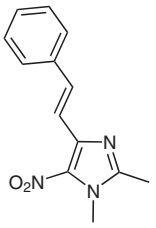
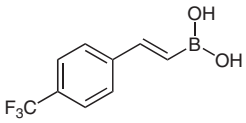
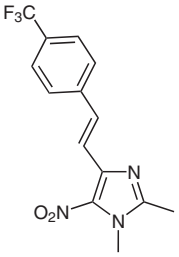
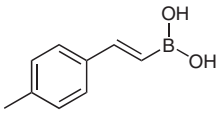
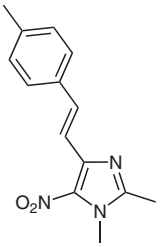
Entry	Boronic acid	Product		Time (h)	Yield (%)
8			**12**	1	91
9			**13**	1	87
10			**14**	1	95
11			**15**	1	78
12			**16**	2	86
13			**17**	2	66

Table 1 Microwave-Mediated Suzuki–Miyaura Coupling Reactions of Imidazole **3** with Aryl, Heteroaryl, or Styrylboronic Acids Using $Pd(PPh_3)_4$[a] (continued)



3 **5–22**

Entry	Boronic acid	Product		Time (h)	Yield (%)
14			**18**	2	87
15			**19**	2	60
16			**20**	1	63
17			**21**	1	95
18			**22**	1	91

[a] Conditions: $Pd(PPh_3)_4$ (3.4 mol%), **3** (1 equiv), arylboronic acid (1.03 equiv) or heteroarylboronic acid (1.03 equiv) or (*E*)-styrylboronic acid (1.03 equiv), Na_2CO_3 (3 equiv), DME–EtOH (6 mL:2 mL). An initial microwave irradiation of 150 W was used, the temperature being ramped from r.t. to 75 °C, then held for the time indicated.

Furthermore, the X-ray structure analysis reveals a static disorder at the level of the CF_3 substituent. The fluorine atoms were refined on several sites with partial occupancies (Figure 2).

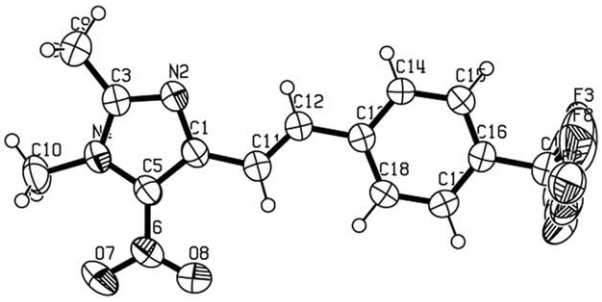


Figure 2 Ortep structure of (*E*)-1,2-dimethyl-5-nitro-4-[4-(trifluoromethyl)styryl]-1*H*-imidazole (**21**)

In summary, we have developed a general operating procedure for the rapid and efficient synthesis of new 4-aryl-, 4-heteroaryl-, or 4-styryl-dimetridazole derivatives from the microwave-assisted palladium-mediated coupling reactions of aryl, heteroaryl, and styryl boronic acids with 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**3**). Finally, a wide array of electron-withdrawing and electron-donating groups has shown to be well tolerated under these microwave-assisted conditions. The extension of this approach to other palladium-catalyzed coupling reactions involving other bioactive compounds is in progress in our laboratory.

Microwave assisted reactions were done in a multimode microwave oven ETHOS Synth Lab Station (Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra were recorded on a Bruker ARX 200 spectrometer in $CDCl_3$ or DMSO-d_6 solution at the Faculté de Pharmacie de Marseille. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to $CHCl_3$ [7.26 ppm (^{1}H) and 76.9 ppm (^{13}C)]. Elemental analyses and X-ray crystal structure analyses were carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme. Silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM) was used for column chromatography. TLC analyses were performed on 5 cm × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluting solvent.

Crystal-Structure Analysis

The X-ray diffraction measurements were carried out on a Bruker-Nonius KappaCCD diffractometer at 293 (2) K. Structures were solved using SIR92 and refinements calculations based on F^2 were performed using SHELXL-97. The compounds **20** and **21** were crystallized by slow evaporation of an *i*-PrOH solution to provide desired single crystals.

Compounds 5–22 via Suzuki Cross-Coupling Reactions; General Procedure

In a 250 mL two-necked flask, 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**3**; 0.91 mmol, 1 equiv) and $Pd(PPh_3)_4$ (0.031 mmol, 0.034 equiv) were dissolved in DME (6 mL), and the solution was stirred under N_2 for 1 h. A solution of the corresponding arylboronic acid or styrylboronic acid (1.03 equiv) in absolute EtOH (2 mL) and aq 1 M Na_2CO_3 (6 mL) was added to the flask. The reaction mixture was heated in a microwave oven and irradiated with 150 W until the disappearance of the starting material as monitored by TLC. Solvents were removed under reduced pressure and the crude residue was dissolved in $CHCl_3$ (50 mL). The organic layer was washed with H_2O (3 × 30 mL) and brine (3 × 30 mL), dried (Na_2SO_4), and concentrated under vacuum. Purification of the residue by column chromatography on silica gel and recrystallization afforded the corresponding 4-aryl-1,2-dimethyl-5-nitro-1*H*-imidazoles **5**–**17**, or 4-heteroaryl-1,2-dimethyl-5-nitro-1*H*-imidazoles **18**,**19**, or 1,2-dimethyl-5-nitro-4-styryl-1*H*-imidazoles **20**–**22**.

1,2-Dimethyl-5-nitro-4-phenyl-1*H*-imidazole (5)

Compound **5** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE–EtOAc, 50:25:25) and recrystallization from cyclohexane; yield: 93%; yellow powder; mp 93 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 7.43–7.46 (m, 3 H, 3 CH), 7.74–7.79 (m, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 34.2, 128.2, 129.6, 129.7, 130.9, 142.7, 148.0.

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 60.82; H, 5.10; N, 19.34. Found: C, 61.09; H, 5.16; N, 19.37.

4-(4-Fluorophenyl)-1,2-dimethyl-5-nitro-1*H*-imidazole (6)

Compound **6** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–EtOAc, 8:2) and recrystallization from butan-2-ol; yield: 93%; yellow powder; mp 161 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 7.07–7.16 (m, 2 H, 2 CH), 7.74–7.81 (m, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.5, 34.5, 115.2 (d, *J* = 22.0 Hz), 127.6 (d, *J* = 3.3 Hz), 131.8 (d, *J* = 8.4 Hz), 142.5, 148.3, 163.6 (d, *J* = 249.9 Hz).

Anal. Calcd for $C_{11}H_{10}FN_3O_2$: C, 56.17; H, 4.29; N, 17.86. Found: C, 56.20; H, 4.42; N, 18.10.

4-(4-Chlorophenyl)-1,2-dimethyl-5-nitro-1*H*-imidazole (7)

Compound **7** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE–EtOAc, 50:25:25) and recrystallization from *i*-PrOH; yield: 71%; pale orange powder; mp 151 °C (Lit.[15] mp 145–147 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 7.40 (d, *J* = 8.7 Hz, 2 H, 2 CH), 7.72 (d, *J* = 8.7 Hz, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.2, 128.4, 130.0, 130.9, 135.6, 142.0, 148.31.

Anal. Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.82; H, 4.15; N, 16.96.

1,2-Dimethyl-5-nitro-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazole (8)

Compound **8** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE–EtOAc, 50:25:25) and recrystallization from cyclohexane; yield: 68%; white cream powder; mp 78 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.95 (s, 3 H, CH_3), 7.52–7.70 (m, 2 H, 2 CH), 7.93–8.03 (m, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 34.0, 123.9 (q, *J* = 272.6 Hz), 125.8 (q, *J* = 3.7 Hz), 126.4 (q, *J* = 4.0 Hz), 128.4, 130.4 (q, *J* = 32.6 Hz), 132.7, 132.8, 134.8, 141.6, 148.5.

Anal. Calcd for $C_{12}H_{10}F_3N_3O_2$: C, 50.53; H, 3.53; N, 14.73. Found: C, 50.24; H, 3.74; N, 14.66.

1,2-Dimethyl-5-nitro-4-(3-nitrophenyl)-1*H*-imidazole (9)

Compound **9** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and recrystallization from *i*-PrOH; yield: 80%; yellow powder; mp 159 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 7.58–7.66 (m, 1 H, CH), 8.08–8.14 (m, 1 H, CH), 8.25–8.31 (m, 1 H, CH), 8.65–8.68 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.4, 124.1, 124.8, 129.0, 133.3, 135.5, 140.5, 147.4, 148.0, 148.6.

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.16; H, 3.85; N, 21.17.

4-[3,5-Bis(trifluoromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole (10)

Compound **10** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and recrystallization from cyclohexane; yield: 98%; white powder; mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 7.92 (s, 1 H, CH), 8.26 (s, 2 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.3, 122.9 (sept, J = 3.7 Hz), 123.2 (q, J = 272.6 Hz), 129.8 (q, J = 2.7 Hz), 137.4 (q, J = 33.4 Hz), 133.9, 135.2, 140.1, 148.8.

Anal. Calcd for $C_{13}H_9F_6N_3O_2$: C, 44.20; H, 2.57; N, 11.90. Found: C, 44.38; H, 2.53; N, 11.89.

4-(4-Methoxyphenyl)-1,2-dimethyl-5-nitro-1*H*-imidazole (11)

Compound **11** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE–EtOAc, 50:25:25) and recrystallization from butan-2-ol; yield: 89%; brown powder; mp 118 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 6.96 (d, J = 8.9 Hz, 2 H, 2 CH), 7.77 (d, J = 8.9 Hz, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 34.2, 55.3, 113.6, 123.6, 131.2, 143.3, 148.2, 160.8.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.40; H, 5.43; N, 17.02.

1,2-Dimethyl-4-(3,4,5-trimethoxyphenyl)-5-nitro-1*H*-imidazole (12)

Compound **12** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–EtOAc, 5:5) and recrystallization from cyclohexane; yield: 91%; yellow powder; mp 115 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 3.91 (s, 6 H, 2 CH_3), 3.93 (s, 3 H, CH_3), 7.11 (s, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.2, 56.2, 60.9, 107.1, 126.7, 134.8, 139.4, 143.0, 148.1, 152.8.

Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 55.14; H, 5.67; N, 13.66.

[4-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]methanol (13)

Compound **13** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–MeCN, 6:4) and recrystallization from toluene; yield: 87%; yellow powder; mp 187 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75 (s, 1 H, OH), 2.52 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 4.74 (s, 2 H, CH_2), 7.42 (d, J = 8.0 Hz, 2 H, 2 CH), 7.75 (d, J = 8.1 Hz, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.1, 65.0, 126.5, 129.7, 131.1, 142.2, 143.3, 148.3.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.25; H, 5.41; N, 16.10.

1,2-Dimethyl-4-(2-methylphenyl)-5-nitro-1*H*-imidazole (14)

Compound **14** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and the solid product obtained was washed with Et_2O (25 mL); yield: 95%; white powder; mp 74 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 7.20–7.33 (m, 4 H, 4 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 19.3, 33.7, 125.1, 128.6, 129.2, 129.6, 132.0, 135.2, 136.9, 143.6, 148.2.

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.26; H, 5.77; N, 18.38.

4-(Biphenyl-4-yl)-1,2-dimethyl-5-nitro-1*H*-imidazole (15)

Compound **15** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–EtOAc, 9:1) and recrystallization from *i*-PrOH; yield: 78%; yellow powder; mp 144 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 7.33–7.56 (m, 3 H, 3 CH), 7.62–7.69 (m, 4 H, 4 CH), 7.87 (d, J = 8.3 Hz, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 34.2, 126.8, 127.2, 127.6, 128.8, 130.0, 130.5, 140.6, 142.2, 143.1, 148.3.

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.47; H, 5.21; N, 14.31.

1,2-Dimethyl-4-(naphthalen-2-yl)-5-nitro-1*H*-imidazole (16)

Compound **16** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and recrystallization from *i*-PrOH; yellow powder; yield: 86%; mp 141 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 7.51–8.02 (m, 6 H, CH), 8.27 (s, 1 H, CH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.9, 34.3, 126.6, 126.8, 127.2, 127.4, 127.7, 128.6, 128.9, 129.6, 132.5, 133.1, 134.9, 142.0, 149.4.

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.49; H, 5.19; N, 15.67.

1,2-Dimethyl-4-(naphthalen-1-yl)-5-nitro-1*H*-imidazole (17)

Compound **17** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and recrystallization from *i*-PrOH; yield: 66%; yellow powder; mp 146 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 3.97 (s, 3 H, CH_3), 7.39–7.71 (m, 5 H, 5 CH), 7.88–7.96 (m, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 34.1, 125.0, 125.9, 126.5, 128.1, 128.5, 129.7, 129.9, 131.3, 133.4, 140.0, 142.7, 148.4.

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.24; H, 4.94; N, 15.64.

4-(Furan-2-yl)-1,2-dimethyl-5-nitro-1*H*-imidazole (18)

Compound **18** was isolated after purification by column chromatography on silica gel (eluent: EtOAc–$CHCl_3$, 8:2) and recrystallization from cyclohexane; yield: 87%; yellow powder; mp 132 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 6.57 (dd, J = 3.6, 1.8 Hz, 1 H, CH), 7.59 (d, J = 3.6 Hz, 1 H, CH), 7.62 (d, J = 1.8 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 34.2, 112.1, 115.7, 134.4, 144.7, 145.6, 149.3.

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.95; H, 5.38; N, 19.95.

1,2-Dimethyl-4-(5-methylthiophen-2-yl)-5-nitro-1*H*-imidazole (19)

Compound **19** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE–EtOAc, 50:25:25) and recrystallization from cyclohexane; yield: 60%; yellow powder; mp 143 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 6.82 (d, *J* = 3.7 Hz, 1 H, CH), 8.01 (d, *J* = 3.7 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.7, 15.4, 34.8, 126.5, 131.5, 138.3, 145.1, 148.8.

Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.56; H, 4.72; N, 17.28.

(*E*)-1,2-Dimethyl-5-nitro-4-styryl-1*H*-imidazole (20)

Compound **20** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–EtOAc, 6:4) and recrystallization from *i*-PrOH; yield: 63%; yellow powder; mp 144 °C (Lit.[17] mp 140 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 7.33–7.45 (m, 3 H, 3 CH), 7.61 (d, *J* = 8.0 Hz, 2 H, 2 CH), 7.77 (s, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.0, 117.5, 127.5, 128.8, 129.0, 136.3, 137.0, 142.1, 149.1.

Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.60; H, 5.50; N, 17.45.

Crystallographic Data[18]

M = 243.26, yellow prisms, crystal dimensions, 0.2 × 0.1 × 0.1 mm. Monoclinic, Space group, $P2_1/c$ (*T* = 293 K) with *a* = 9.6330(2) Å, *b* = 9.9793(2) Å, *c* = 13.0384(3) Å, *α* = 90.00°, *β* = 108.2640(10)°, *γ* = 90.00°, *V* = 1190.25(4) Å^3, *Z* = 4, *μ* = 0.095 mm^{-1}, *F*(000) = 512, index ranges $0 \le h \le 12$, $0 \le k \le 13$, $-17 \le l \le 16$. The *θ* range = 2.23–28.25°, 165 variables and 0 restraints, were refined for 1962 independent reflections with $I \ge 2\ \sigma_I$ to $R = 0.0565$, $wR^2 = 0.1664$, GOF = 1.242.

(*E*)-1,2-Dimethyl-5-nitro-4-[4-(trifluoromethyl)styryl]-1*H*-imidazole (21)

Compound **21** was isolated after purification by column chromatography on silica gel (eluent: EtOAc) and recrystallization from *i*-PrOH; yield: 95%; yellow powder; mp 164 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 7.59–7.88 (m, 6 H, 6 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 34.0, 120.2, 126.8 (q, *J* = 271.9 Hz), 125.7 (q, *J* = 3.7 Hz), 127.5, 130.3 (q, *J* = 32.4 Hz), 134.7, 139.7, 139.8, 141.3, 149.2.

Anal. Calcd for $C_{14}H_{12}F_3N_3O_2$: C, 54.02; H, 3.89; N, 13.50. Found: C, 54.19; H, 4.18; N, 13.56.

Crystallographic Data[18]

M = 311.27, colorless prisms, crystal dimensions, 0.25 × 0.2 × 0.15 mm. Triclinic, Space group, $P\bar{1}$ (*T* = 293 K) with *a* = 6.396 Å, *b* = 10.529 Å, *c* = 11.69 Å, *α* = 110.83°, *β* = 93.69°, *γ* = 106.29°, *V* = 694.3 Å^3, *Z* = 2, *μ* = 0.129 mm^{-1}, *F*(000) = 320, index ranges $0 \le h \le 8$, $-14 \le k \le 13$, $-15 \le l \le 15$. The *θ* range = 1.9–28.73°, 253 variables and 0 restraints, were refined for 2507 independent reflections with $I \ge 2\ \sigma_I$ to $R = 0.0583$, $wR^2 = 0.161$, GOF = 1.135.

(*E*)-1,2-Dimethyl-4-(4-methylstyryl)-5-nitro-1*H*-imidazole (22)

Compound **22** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–EtOAc, 9:1) and recrystallization from *i*-PrOH; yield: 91%; green powder; mp 203–204 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 7.18 (d, *J* = 8.1 Hz, 2 H, 2 CH), 7.51 (d, *J* = 8.1 Hz, 2 H, 2 CH), 7.73 (s, 2 H, 2 CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 21.4, 34.0, 116.5, 127.5, 129.5, 133.5, 137.1, 139.3, 142.4, 149.1.

Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.30 H, 5.94; N, 16.29.

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