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Long distance-$S_{RN}1$ in nitroimidazole series favored by temperature

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ABSTRACT

New reductive alkylating agents in 4- and 5-nitroimidazole series produce exclusively O-alkylation with nitronate anions under classical $S_{RN}1$ conditions at room temperature. Electron-transfer C-alkylation is observed under microwave irradiation or under conventional heating. Furthermore, X-ray spectroscopy shows that the dihedral angles between the phenyl and imidazole rings for the two series are different, which could greatly influence reactivity in 4- and 5-nitroimidazole series.

5-nitroimidazole scaffold is known to display major anti-infectious activities.[1] Several 5-nitroimidazole-containing active principles are commonly used in medicine. These chemotherapeutic agents inhibit the growth of anaerobic bacteria and of some anaerobic protozoa.[2] Nowadays, 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol (metronidazole) is the drug compound most frequently used clinically for the treatment of infections caused both by protozoa such as *Trichomonas vaginalis*, *Entamœba histolytica*, *Giardia intestinalis*, and by anaerobic bacteria.

However, 5-nitroimidazoles have been found to possess high mutagenic activity in prokaryotic micro-organisms.[3] Moreover, the emergence of metronidazole-resistant *T. vaginalis* is currently affecting therapeutic success.[4,5] These refractory cases are usually treated with higher doses of metronidazole, which leads to increased side effects.[5,6] A nitroimidazole offering good pharmacological activities against metronidazole-resistant *T. vaginalis* and *G. intestinalis*, with no mutagenicity, would be of great interest.[1b,e,7,8]

Unimolecular radical nucleophilic substitution ($S_{RN}1$) has been found to be an excellent synthetic pathway for many types of aromatic, heterocyclic, or aliphatic substrates with suitable leaving groups,[9] requiring substrates substituted with an electron-attracting group at the appropriate position.

Since Kornblum[10] and Russell[11] originally proposed the radical chain mechanism to explain the C-alkylation of nitronate anions by *p*-nitrobenzyl chloride, later designated as $S_{RN}1$ (unimolecular radical nucleophilic substitution) by Bunnett,[12] the extensions of this reaction at sp^3 carbon have been studied extensively.[13] These studies showed that ambident nitronate anion reacted by O-alkylation with benzylic halides. For example, benzyl chloride led to benzaldehyde only by O-alkylation with the 2-nitropropane anion from an S_N2 mechanism. In contrast, *p*-nitrobenzyle chloride reacted by C-alkylation with the 2-nitropropane anion, leading to the C-alkylated product.

Our previous study investigated a new $S_{RN}1$ reaction on (*E*)-2-[4-(chloromethyl)styryl]-1-methyl-5-nitro-1*H*-imidazole, involving a long distance (10 bonds) between the electron-withdrawing and leaving groups (LD-$S_{RN}1$). Unfortunately, when the chloride reacted with 2-nitropropane anion under various suitable conditions for the $S_{RN}1$ reaction (inert atmosphere, light), it only led to the aldehyde derivative through an S_N2 process (Scheme 1).[14]

These reactions are usually performed in DMSO at room temperature under inert atmosphere and photostimulation in order to initiate the $S_{RN}1$, but the influence of temperature on the competition between S_N2 and $S_{RN}1$ has never been evaluated.

Moreover, Geske showed in 1964 that the planarity of the nitrobenzyl group has an influence on this competition.[15] Indeed, *o*-nitrobenzyl chloride was more difficult to reduce than *p*-nitrobenzyl chloride, and provided 52% of *o*-nitrobenzaldehyde by O-alkylation. This has been established via the steric hindrance between the nitro group and the chloromethyl group on the phenyl ring in the *ortho* isomer, which decreased the coplanarity in the molecule. The system became less reducible by tending electronically to isolate the nitro group from the ring.

To further our work on $S_{RN}1$ (LD-$S_{RN}1$) reactivity and its limits in 5-nitroimidazole series and as part of a program aimed at the preparation of new and potentially safer nitroimidazoles, we

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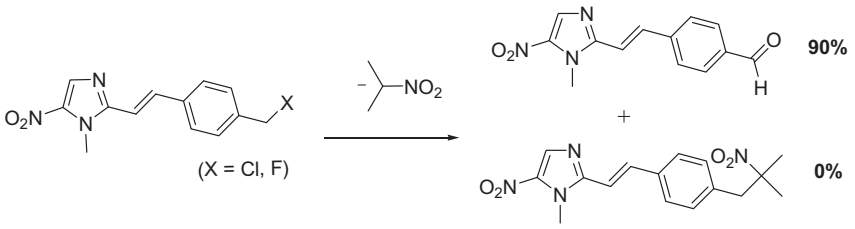
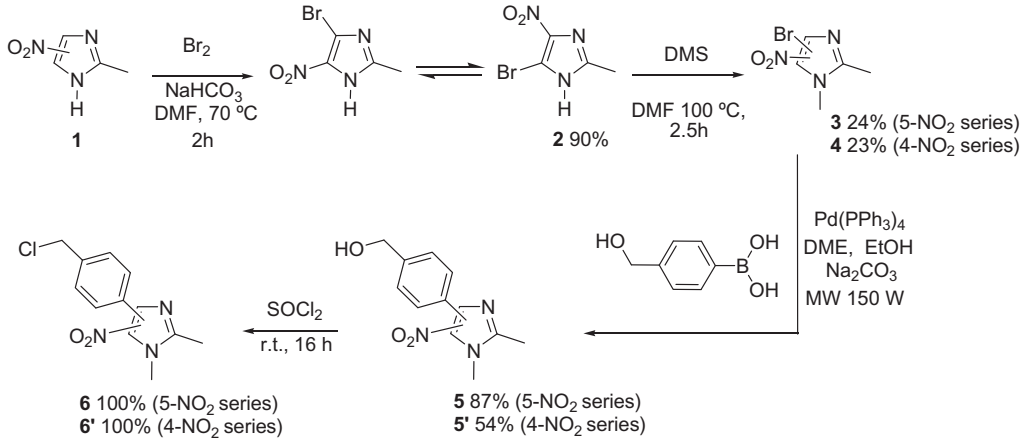


Scheme 1. (*E*)-2-[4-(Chloromethyl)styryl]-1-methyl-5-nitro-1*H*-imidazole reactivity with 2-nitropropane anion.

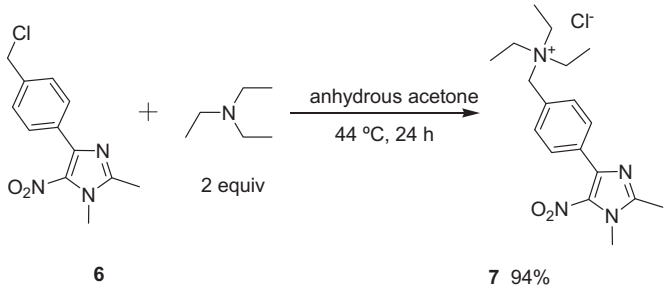


Scheme 2. Preparation of LD-$S_{RN}1$ precursors **6** and **6′**.

prepared 4(5)-[4-(chloromethyl)phenyl]-1,2-dimethyl-5(4)-nitro-1*H*-imidazoles and studied their reactivities with different nucleophiles, under $S_{RN}1$ experimental conditions (LD-$S_{RN}1$), in order to determine the reactivity of both isomers.

The starting material was obtained by the bromination of commercial 2-methyl-4(5)-nitro-1*H*-imidazole **1** with elemental bromine in DMF, methylation of **2** by dimethylsulfate to obtain **3**, which was then subjected to a Suzuki–Miyaura cross-coupling reaction to synthesize [4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)phenyl]methanol **5**.[16] Chlorination of **5** with thionyl chloride provided 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **6**,[17] which appeared to be a good candidate to investigate LD-$S_{RN}1$ (six bonds) (Scheme 2).

Furthermore, as alkylammonium chlorides are known to be poor leaving groups in S_N2 reactions,[9] we decided to synthesize and study the reactivity of *N*-[4-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)benzyl]-*N,N*-diethylethanaminium chloride **7**. *N,N,N*-Triethylethanaminium chloride derivative **7** was prepared in 94% yield from **6** with triethylamine (2 equiv) in anhydrous acetone at 44 °C for 24 h (Scheme 3).



Scheme 3. Preparation of **7**.

The first result in Table 1 shows that **6** reacts with the 2-nitropropane anion to give exclusively **10**[18] (entries 2, 6) resulting from an S_N2 O-alkylation with good yields under the usual $S_{RN}1$ conditions described by Kornblum (65% in DMSO–72% in DMF) at room temperature. Different $S_{RN}1$ reaction conditions were therefore examined, in order to study their influence on reactivity. Under conventional heating (oil-bath heating) in DMSO at 170 °C, a mixture of the expected C-alkylated products **8** (36%) and **9** (43%) resulting from the consecutive $S_{RN}1$ C-alkylation and base-promoted nitrous acid elimination were obtained (entry 8) without aldehyde **10**. In DMF at 140 °C, the reaction gave **8** (57%) and **10** (12%) (entry 4), but no trace of compound **9**. DMSO should solvate counterion in 2-nitropropane anion sodium salt better than DMF, inducing higher base strength in 2-nitropropane anion.[19]

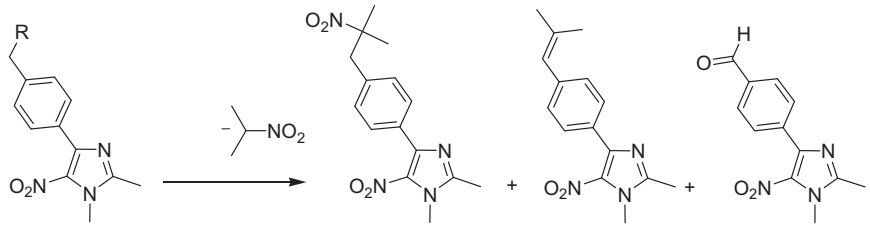
With these encouraging results and on the basis of our previous studies,[20] we decided to evaluate the influence of microwave irradiation on the LD-$S_{RN}1$ reaction. The best microwave-assisted experimental conditions were defined, yielding in DMF a mixture of **8**[21] (60%), **10** (22%), and the appearance of **9**[21] (10%) (Table 1, entry 5). In DMSO, these conditions allowed the formation of **9** in 60% yields (entry 9).

Thus, no 'specific effect' (non-thermal effect)[22] from microwave irradiation was found and thermal effect alone appears sufficient to affect the main reaction from S_N2 to $S_{RN}1$.

As shown in entry 11 (Table 1), the use of the best experimental conditions cited above (Table 1, entry 5) with compound **7** gave a mixture of expected products **8** (44%) and **9** (32%). Moreover, no trace of aldehyde derivative was observed. These results suggest that both substrates **6** and **7** formed C-alkylated product by LD-$S_{RN}1$.

In order to confirm the single-electron transfer mechanism, inhibition reactions were performed (Table 2) by adding to the reaction mixture catalytic amounts (10 mol %) of cupric chloride ($CuCl_2$) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which

Table 1
Reactivity study of **6** and **7** through LD-$S_{RN}1$



6 R = Cl
7 R = $(Et)_3N^+Cl^-$

8 **9** **10**

Entry	Substrate	Equiv anion	Solvent	Time (h)	Conditions	**8** (%)	**9** (%)	**10** (%)
1	6	6	DMF	0.5	N_2, dark, rt	—	—	73
2	6	6	DMF	0.5	N_2, hν, rt	—	—	72
3	6	6	DMF	0.5	N_2, dark, 140 °C	56	—	—
4	6	6	DMF	0.5	140 °C	57	—	12
5	6	6	DMF	0.5	MW 140 °C	60	10	22
6	6	3	DMSO	0.5	N_2, hν, rt	—	—	62
7	6	6	DMSO	0.5	N_2, dark, 170 °C	28	33	Traces
8	6	6	DMSO	0.5	170 °C	36	43	—
9	6	6	DMSO	0.5	MW 170 °C	—	60	—
10	7	3	DMSO	48	N_2, hν, rt	—	—	22
11	7	6	DMF	0.5	MW 140 °C	44	32	—

Table 2
Inhibition reactions with 2-nitropropane anion[a]

Entry	Inhibitor (0.1 equiv)	**8** (%)	**9** (%)	**10** (%)
1	—	60	10	22
2	$CuCl_2$	25	14	22
3	TEMPO	8	10	27

[a] All reactions performed using 1 equiv of **6**, 6 equiv of 2-nitropropane anion in DMF under microwave irradiation, at 140 °C, for 0.5 h.

are commonly employed inhibitors used to provide mechanistic study of $S_{RN}1$ reactions.[9h,13a] The reaction times were identical for the inhibition study and corresponded to the conditions in Table 1, entry 5 without an inhibitor.

Inhibition for the production of **8** was observed with TEMPO and $CuCl_2$. The effects of classical inhibitors[13a] on the reaction of **6** with the 2-nitropropane anion leading to **8** and **9** provide good evidence for assigning the $S_{RN}1$ mechanism for the C-alkylation.

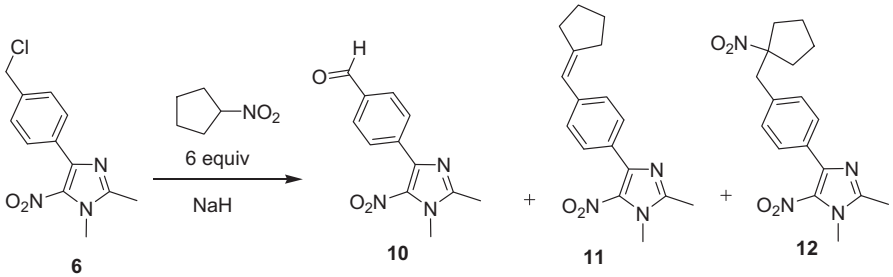
The reactivity of **6** was investigated with the nitrocyclopentane anion. As a result, formation of the expected C-alkylation products was observed under microwave heating in 19–22% overall yield (Table 3, entries 4 and 5). Under $S_{RN}1$ classical conditions, aldehyde **10** was formed with up to 98% yield (Table 3, entry 3).

The nature of the nucleophile is crucial for $S_{RN}1$ reactions and necessitates an understanding of the relationship between the nucleophile and the substrate in single-electron transfer reactions.[13b]

In order to extend the reaction to a variety of nucleophiles, the study next explored the *S*-centered anion (Scheme 4).[23] The reaction between 4-methylbenzenesulfinic acid sodium salt and **6** in DMSO at 100 °C under microwave irradiation gave the required S-alkylated product **13**[24] in good yield (79%).

To identify the main mechanism of the reaction, the reactivity of this latter reaction was studied by adding an inhibitor (Table 4, entries 2 and 3). The reaction rate decrease is less significant than with 2-nitropropane anion, indicating that the reaction could possibly result from a combination of S_N2 and $S_{RN}1$ mechanisms.

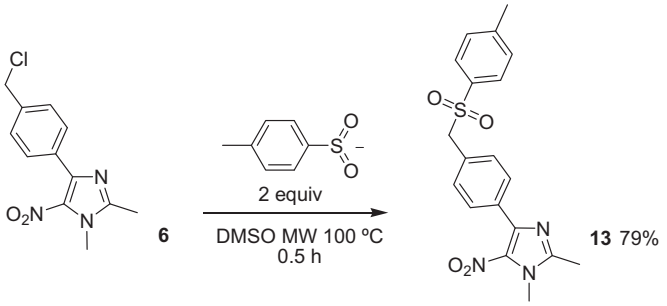
Table 3
Reactivity of **6** with the nitrocyclopentane anion



6 **10** **11** **12**

Entry	Solvent	Conditions	Time (h)	**10** (%)	**11** (%)	**12** (%)
1	DMF	N_2, hν, rt	3	65	—	—
2	DMF[b]	N_2, hν, rt	24	50	—	—
3[a]	DMSO	N_2, hν, rt	0.3	98	—	—
4	DMSO	MW 170 °C	0.2	—	22	—
5	DMF	MW 140 °C	0.5	43	4	15

[a] The reaction was induced by adding a catalytic amount of nitropropane anion.
[b] DMF distilled.



Scheme 4. Reactivity of **6** with 4-methylbenzenesulfinic acid sodium salt.

Table 4
Inhibition reactions with 4-methylbenzenesulfinic acid sodium salt [a]

Entry	Inhibitor (0.1 equiv)	**13** (%)
1	—	79
2	$CuCl_2$	55
3	TEMPO	46

[a] All reactions performed using 1 equiv of **6**, 2 equiv of 4-methylbenzenesulfinic acid sodium salt, in DMSO under microwave irradiation, at 100 °C, for 0.5 h.

In order to compare the influence of the 4- versus 5-position of the nitro group on the imidazole ring through LD-$S_{RN}1$, the 5-[4-(chloromethyl)phenyl]-1,2-dimethyl-4-nitro-1*H*-imidazole **6′** was synthesized through the same synthesis pathway as **6** from **4** and the reactivity with *C*-centered and *S*-centered anions was studied[24] (Table 5).

The reaction of **6′** with 2-nitropropane anion under experimental conditions as defined in Table 1 (entry 5) provides the expected product **9′** in 49% yield. However, the C-alkylation products in 5-nitroimidazole series were obtained in 70% overall yield. Although, thermal effect was required to observe an $S_{RN}1$ reactivity, yields obtained in 4-nitroimidazole series were generally lower than in 5-nitroimidazole series. This surprising result encouraged us to study the structure by X-ray analysis of a crystal of **6**[25] and **6′**.[26] We observed that the dihedral angles between the two planes formed by the phenyl and imidazole rings (N_1–C_1–C_6–C_{11}) were, respectively 39.8° (**6**) and 55.2° (**6′**) (Fig. 1 and 2). These different dihedral angle values may greatly affect reactivity in 4- and 5-nitroimidazole series.

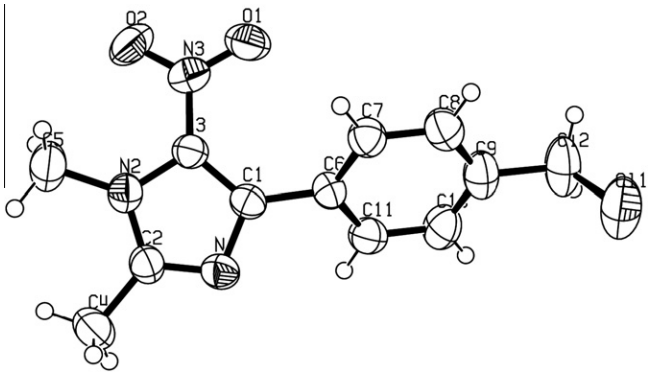


Figure 1. Ortep plot of 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **6**.

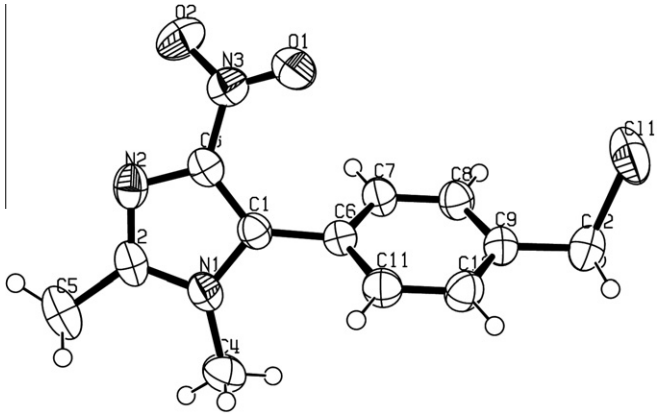
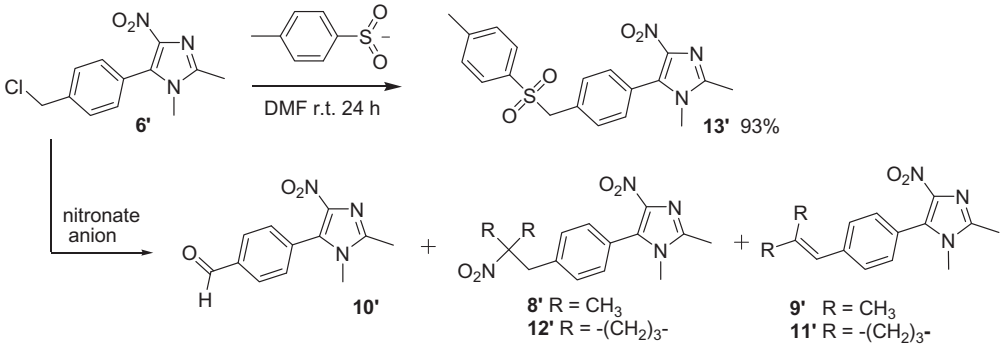


Figure 2. Ortep plot of 5-[4-(chloromethyl)phenyl]-1,2-dimethyl-4-nitro-1*H*-imidazole **6′**.

Table 5
Reactivity of **6′** through LD-$S_{RN}1$



Entry	Anion 6 equiv	Conditions	Time (h)	**8′** (%)	**9′** (%)	**10′** (%)	**11′** (%)	**12′** (%)
1	2-Nitropropane[a]	N_2, hν, rt	48	—	—	98	—	—
2		140 °C	0.5	17	—	18	—	—
3		MW 140 °C	0.5	—	49	—	—	—
4[c]	Nitrocyclopentane[b]	N_2, hν, rt	3	—	—	98	—	—
5		MW 170 °C	0.2	—	—	—	Traces	—

[a] 2-Nitropropane anion was dissolved in DMF.
[b] Nitrocyclopentane anion was formed in situ using NaH in DMSO.
[c] The reaction was induced by adding a catalytic amount of 2-nitropropane anion.

The different yields observed could be explained by a lower electronic conjugated system between the phenyl and imidazole rings. Indeed, it has been established that a lack of planeness greatly influences $S_{RN}1$ reactivity,[15] since the electron-withdrawing group does not function properly, which lowers the reducibility of the system.

In conclusion, we have shown in this Letter that 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole **6** and 5-[4-(chloromethyl)phenyl]-1,2-dimethyl-4-nitro-1*H*-imidazole **6′** react with various carbon- and sulfur-centered anions by substitution at the chloromethyl group. The reaction with *C*-centered nucleophiles is very probably mediated by the $S_{RN}1$ mechanism and is greatly influenced by thermal effect. Heating leads to a major inversion of rate between S_N2 and $S_{RN}1$ processes. These results constitute the first example of a specific LD-$S_{RN}1$ reactivity promoted by the thermal effect. Investigations with other nitronate anions and antiparasitic evaluation of synthesized compounds are currently in progress.

Acknowledgments

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18. *General procedure of classical conditions:* 2-Nitropropane anion (6 equiv) was added to a solution of **6** or **6′** (1 equiv) in DMF or DMSO (25 mL) in a nitrogen-flushed flask. The mixture was irradiated with a 60 W tungsten lamp and stirred for 0.5 h. Then, the mixture was poured into cold H_2O. The aqueous solution was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The product was purified by chromatography column on SiO_2 (ethyl acetate). *4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)benzaldehyde (**10**):* Yellow crystals, mp 190 °C (toluene). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.94 (s, 3H), 7.93 (s, 4H), 10.06 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 34.2 (CH_3), 129.3 (2×CH), 130.1 (2×CH), 136.5 (C), 137.6 (C), 141.6 (C), 148.5 (C), 191.78 (CHO). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 59.34; H, 4.70; N, 16.90.
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21. *General procedure of conventional heating:* 2-Nitropropane anion (6 equiv) was added to a solution of **6** or **6′** (1 equiv) in DMF or DMSO (25 mL) in a nitrogen-flushed flask. The mixture is placed in an oil-bath previously heated to 140 °C (DMF) or (170 °C) and stirred for 0.5 h. After cooling, the mixture was poured into cold H_2O. The aqueous solution was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The product was purified by chromatography column on SiO_2 (ethyl acetate/chloroform mixtures). *General procedure of microwave experimental conditions:* 2-nitropropane anion (6 equiv) was added to a solution of **6** or **6′** (1 equiv) in DMF or DMSO (25 mL) and then heated to 140 °C (DMF) or 170 °C (DMSO) for 0.5 h under microwave irradiation (200 W). After cooling, the mixture was poured into cold H_2O. The aqueous solution was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The product was purified by chromatography column on SiO_2. Microwave-assisted reactions were performed in a multimode ETHOS Synth Lab station and MicroSYNTH Lab terminal 1024 (Ethos start, Milestone Inc.) ovens. *1,2-Dimethyl-4-[4-(2-methyl-2-nitropropyl)phenyl]-5-nitro-1H-imidazole (**8**):* Brown oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58 (s, 6H), 2.53 (s, 3H), 3.25 (s, 2H), 3.91 (s, 3H), 7.17 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (CH_3), 25.6 (2×CH_3), 34.3 (CH_3), 46.4 (CH_2), 88.5 (C), 129.7 (2×CH), 129.9 (2×CH), 130.3 (C), 136.6 (C), 142.2 (C), 148.2 (C). HRMS calcd for $C_{15}H_{18}N_4O_4$ [M+H]$^+$: 319.1401, found: 319.1400. *1,2-Dimethyl-4-[4-(2-methylprop-1-enyl)phenyl]-5-nitro-1H-imidazole (**9**):* Yellow crystal, mp 108 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89 (d, J = 1.2 Hz, 3H), 1.90 (d, J = 1.2 Hz, 3H), 2.52 (s, 3H), 3.90 (s, 3H), 6.29 (br s, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 19.5 (CH_3), 27.0 (CH_3), 34.1 (CH_3), 124.8 (CH), 128.4 (2×CH), 128.8 (C), 129.2 (2×CH), 136.7 (C), 140.0 (C), 143.4 (C), 148.2 (C). HRMS calcd for $C_{15}H_{17}N_3O_2$ [M+H]$^+$: 272.1394, found: 272.1400.
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24. *1,2-Dimethyl-5-nitro-4-[4-(tosylmethyl)phenyl]-1H-imidazole (**13**)*: Yellow neddle, mp 198 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 s, 3H), 2.52 (s, 3H), 3.90 (s, 3H), 4.33 (s, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.6 (CH_3), 34.2 (CH_3), 62.8 (CH_2), 128.7 (2×CH), 129.6 (2×CH), 129.7 (2×CH), 130.5 (2×CH), 131.8 (C), 134.8 (2×C), 142.1 (C), 144.8 (2×C), 148.2 (C). Anal. Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.25; H, 5.03; N, 10.98; S, 8.35. *1,2-Dimethyl-5-[4-(2-methylprop-1-enyl)phenyl]-4-nitro-1H-imidazole (**9′**)*: Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.92 (d, J = 1.0 Hz, 3H), 1.94 (d, J = 1.0 Hz, 3H), 2.50 (s, 3H), 3.41 (s, 3H), 6.30 (br s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.6 (CH_3), 27.1 (CH_3), 31.9 (CH_3), 124.3 (CH), 124.3 (C), 129.0 (2×CH), 129.9 (2×CH), 132.9 (C), 137.5 (C), 140.5 (C), 143.8 (C). HRMS calcd for $C_{15}H_{17}N_3O_2$ [M+H]$^+$: 272.1394, found: 272.1395. *4-(1,2-Dimethyl-4-nitro-1H-imidazol-5-yl)benzaldehyde (**10′**)*: White powder, mp 163 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.42 (s, 3H), 7.57 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.2 Hz, 2H), 10.10 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4 (CH_3), 31.9 (CH_3), 127.0 (C), 129.8 (2×CH), 131.0 (2×CH), 133.1 (C), 136.9 (C), 143.0 (C), 144.6 (C), 191.3 (CHO). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.64; N, 16.87. *1,2-Dimethyl-4-nitro-5-[4-(tosylmethyl)phenyl]-1H-imidazole (**13′**)*: Yellow neddle, mp 224 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.51 (s, 3H), 3.40 (s, 3H), 4.35 (s, 2H), 7.30 (s, 6H), 7.56 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5 (CH_3), 21.6 (CH_3), 31.9 (CH_3), 62.6 (CH_2), 127.8 (C), 128.5 (2×CH), 129.7 (2×CH), 130.3 (C), 130.3 (2×CH), 131.3 (2×CH), 131.8 (C), 134.8 (C), 143.0 (C), 144.1 (C), 145.1 (C). Anal. Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.36; H, 5.08; N, 10.84; S, 8.30.

25. *Crystal data for compound* **6**: $C_{12}H_{12}ClN_3O_2$, yellow prisms ($0.22 \times 0.14 \times 0.12$ mm^3), MW = 265.70, orthorhombic, space group, $P2(1)2(1)2(1)$ (T = 293 K), a = 7.4952(2) Å, b = 12.8330(3) Å, c = 13.1171(5) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; V = 1261.68(7) Å^3, Z = 4, D_{calc} = 13.99 g cm^{-1}, μ = 0.3 mm^{-1}, $F(000)$ = 552, index ranges $0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 17$, $0 \leqslant l \leqslant 17$; θ range = 3.13–28.73°, 163 variables and 0 restraints, were refined for 1310 reflections with $I \geqslant 2\sigma I$ to R_1 = 0.0702, wR_2 = 0.1656, GooF = 1.077. CCDC 825743 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif of from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; email: deposit@ccdc.cam.ac.uk.

26. *Crystal Data for compound* **6′**: $C_{12}H_{12}ClN_3O_2$, brown prisms, ($0.22 \times 0.18 \times 0.1$ mm^3), MW = 265.70, orthorhombic, space group, $P2(1)2(1)2(1)$ (T = 293 K) a = 7.7310(2) Å, b = 10.1625(2) Å, c = 15.9718(5) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; V = 1254.85(6) Å^3, Z = 4, D_{calc} = 14.06 g cm^{-1}, μ = 0.302 mm^{-1}, $F(000)$ = 552, index ranges $0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 13$, $0 \leqslant l \leqslant 21$; θ range = 2.38–28.71°, 165 variables and 0 restraints, were refined for 1388 reflections with $I \geqslant 2\sigma I$ to R_1 = 0.0589, wR_2 = 0.1898, GooF = 1.155. CCDC 825744 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif of from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; email: deposit@ccdc.cam.ac.uk.