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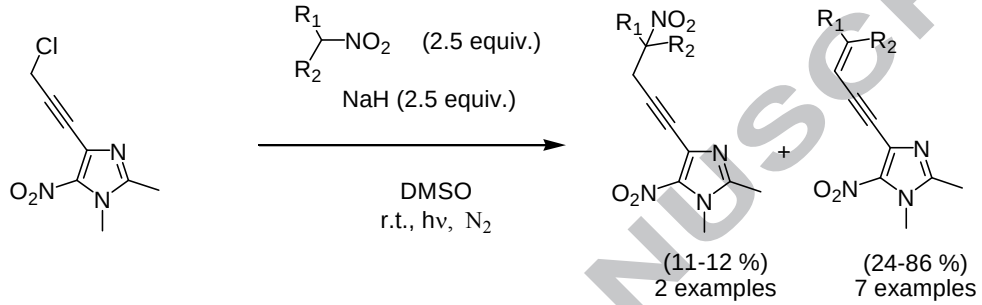

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First Single Electron Transfer Reaction on Propargylic Chloride in 5-Nitroimidazole Series.

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Aix-Marseille Univ, UMR CNRS 7273: Institut de Chimie Radicalaire, Equipe Pharmaco-Chimie Radicalaire (LPCR), Faculté de Pharmacie, 27 Boulevard Jean Moulin, CS 30064, 13385 Marseille cedex 5, France.

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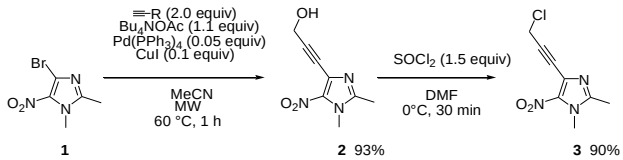
ABSTRACT

We report here the first example of an $S_{RN}1$ reaction on a propargylic chloride in heterocyclic series. The reaction of 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole with nitronate anions led to both the formation of the C-alkylated product through an $S_{RN}1$ mechanism and the predominant enylenic compound resulting from nitrous acid elimination on the C-alkylated product. Interestingly, in contrast to our previous works on $S_{RN}1$ reactivity, no O-alkylated product was observed.

The 5-nitroimidazole scaffold is well known for its major anti-infectious activities.[1] Several 5 nitroimidazole-containing active principles are commonly used in medicine such as metronidazole, secnidazole and ornidazole. These chemotherapeutic agents inhibit the growth of both anaerobic bacteria and some anaerobic protozoa.[2] Nowadays, the leading drug in the nitroimidazole family is metronidazole used extensively for the treatment of infections caused by protozoa such as *Trichomonas vaginalis*, *Entamœba histolytica*, *Giardia intestinalis*, as well as infections induced by anaerobic bacteria. However, the 5-nitroimidazoles have been found to possess a high mutagenic activity in prokaryotic microorganisms. While several hypotheses have been put forward,[3] active research in this area has not yet revealed a comprehensive mechanism for the mutagenic and therapeutic activities of these compounds in eukaryotic cells. Access to a nitroimidazole possessing good pharmacological activities but with no mutagenicity[4] would, therefore, be of great interest not only from a safety point of view but also as a basis for further investigations of the mode of action and mechanism of expression of mutagenicity. Moreover, the emergence of metronidazole-resistant *T. vaginalis* is resulting in decreased success with current therapies.[5,6] These refractory cases are usually treated with higher doses of metronidazole, which leads to an increase in the occurrence of side effects.[6,7] Recently, small nitro-group-containing heterocyclic derivatives, including 5-nitroimidazole series (fexinidazole), have been attracting attention in other biological applications, for instance to treat *Trypasonoma cruzi* (Chagas disease)[8] or *Mycobacterium tuberculosis*.[9] Straightforward access to new derivatives belonging to the biologically relevant 5-nitroimidazole scaffold is therefore likely to be of interest to the scientific community.

Since Kornblum[10] and Russell[11] originally proposed the radical chain mechanism to explain the C-alkylation of nitronate anions by *p*-nitrobenzyl chloride, unimolecular radical nucleophilic substitution[12] ($S_{RN}1$ as per Bunnett[13]) has been found to be a good synthetic pathway for many types of aromatic[14] or heterocyclic substrates.[15] $S_{RN}1$ enables the formation of C-C bonds between an alkyl halide and a nitronate in relatively mild conditions avoiding the use of organometallic species. Moreover, it can give access to tri or tetrasubstituted olefins through nitrous acid elimination from the substitution product. However, the $S_{RN}1$ reaction requires substrates with a suitable leaving group and with an electron-attracting group at an appropriate position. The 5-nitroimidazole moiety was found to be an excellent substrate to perform $S_{RN}1$.[16]



Scheme 1. Preparation of propargylic chloride **3**

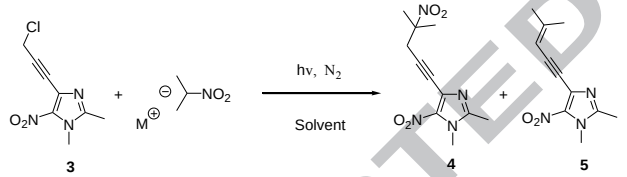
In continuation of our research program centered on the design and synthesis of novel bioactive molecules,[17] this work focused on the 4-position of the 5-nitroimidazole ring because it

* Corresponding author. Tel.: +33-491-835-573; fax: +33-486-136-822; e-mail: patrice.vanelle@univ-amu.fr

had proved to be key modifying in the structure-mutagenicity relationships.[1e,4] Moreover, previous studies had indicated the influence of the planarity of the substrate in $S_{RN}1$ reactions.[16f,18] A lack of planeness greatly influences $S_{RN}1$ reactivity, since the electron withdrawing group effect decreases, which lowers the reducibility of the system. Therefore, the choice of a planar substituent as the propargylic chloride on the 4-position of the imidazole ring met the dual goals of anti-infectious pharmacomodulation and exploring $S_{RN}1$ reactions.

The required starting material for the $S_{RN}1$ reaction is 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole **3** which was prepared in two sequential steps from 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole **1** (scheme 1). The only example of $S_{RN}1$ reaction performed on a triple bond was described by Roche[14f] on the 1-(3-chloroprop-1-ynyl)-4-nitrobenzene. However, the electron transfer is closely connected to the intramolecular electron delocalization toward the nitro group which is very substrate dependent. Thus, an entire $S_{RN}1$ reactivity study of 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole **3** was needed.

First, optimization reactions were performed (Table 1) to identify the best $S_{RN}1$ conditions between **3** and the commercially available 2-nitropropane. The $S_{RN}1$ reaction led to the two expected products, C-alkylated product **4** and ethylenic compound **5** resulting from nitrous acid elimination on C-alkylated product **4** (Scheme 2). The by-product generally observed during studies of $S_{RN}1$ reactivity is a product with aldehyde function resulting from an O-alkylation according to an S_N2 mechanism.[10,11,12] Surprisingly, however, this by-product was never observed in our conditions has monitored by LC/MS. Moreover, contrary to our previous study[14f] on the 1-(3-chloroprop-1-ynyl)-4-nitrobenzene, no trace of the nitrobut-1-enyl derivatives was observed.



Scheme 2. Reactivity of propargylic chloride **3** with the 2-nitropropane anion under $S_{RN}1$ conditions

Under Kornblum conditions[14a-c] (Table 1, entries 1-5), 6 equivalents of 2-nitropropane lithium salt were required to obtain C-alkylated products **4** + **5** in good yields (Table 1, entries 1-3). Moreover, the C-alkylated products formed slowly and poorly in the absence of luminous irradiation (Table 1, entry 4). DMSO proved to be the best solvent to perform the C-alkylation reaction (Table 1, entries 2, 5-7, 11). Trials with DMF led to poorer yields for the same reaction time (Table 1, entries 10-11) while methanol and HMPA did not yield any C-alkylated products **4** + **5**. DMSO should promote solvation of counteranions in 2-nitropropane anion sodium or lithium salt better than DMF, inducing higher base strength in 2-nitropropane anion.[20] Norris transfer phase conditions[21] led mainly to starting chloride **3** with degradation products and with no or poor yield of C-alkylated compounds **4** + **5** (Table 1, entries 8-9). Contrary to benzylic series, the choice of the counter cation of the nitropropane salt proved to be an important parameter (Table 1, entries 2, 10). The best results were defined by *in situ* generation of the 2-nitropropane anion using NaH (Table 1, entries 10-17). Subsequently, reaction time, solvent and number of equivalents of the 2-nitropropane anion were tested (Table 1, entries 10-17) to identify optimal conditions. Thus, the best C-alkylation **4** + **5** yield was obtained using 2.5 equivalents of the 2-nitropropane anion in DMSO after 30 min under light irradiation (Table 1, entry 14).[22]

Under the latter conditions, ethylenic product **5**[23] was formed exclusively. The formation of **4**[24] was favored by shorter reaction times and/or fewer equivalents of the 2-nitropropane anion (Table 1, entries 12, 13, 16) which decreased the overall yield of C-alkylated products.

Table 2 Inhibition of reaction between **3** and 2 nitropropane anion

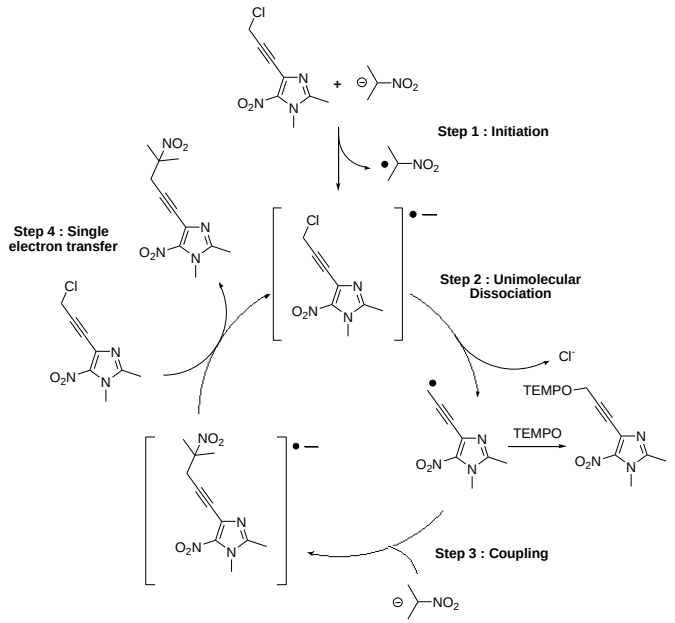
Entry	Scavenger	**4** + **5** (%)
1	None	86
2	TEMPO 0.1 Equiv	13
3	TEMPO 1 Equiv	0
4	O_2 (bubbling)	0
5	*p*-DNB 1 Equiv	39

In order to confirm the single electron transfer mechanism (Scheme 3), inhibition reactions were performed (Table 2) by adding to the optimal reaction conditions (Table 1, entry 14) amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), O_2 or *para*-dinitrobenzene (*p*-DNB), commonly used as inhibitors in the mechanistic study of $S_{RN}1$ reactions.[25] Indeed, these species are well known to act as a radical trap

Table 1 Reactivity study of **3** with 2-nitropropane anion

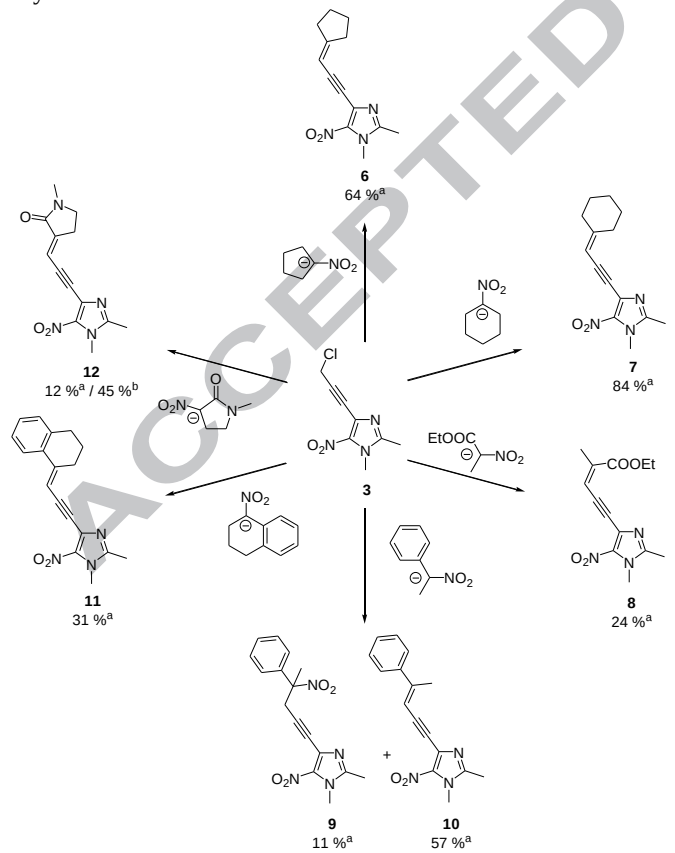
Entry[a]	M	Equiv. of anion	Solvent	Time (h)	Yield **4** (%)	Yield **5** (%)	Yield C-alk **4**+**5** (%)
1	Li	2	DMSO	0.5	0	12	12
2	Li	3	DMSO	0.5	11	21	32
3	Li	6	DMSO	0.5	0	69	69
4[b]	Li	3	DMSO	20	0	19	19
5	Li	3	DMF	2	11	16	28
6	Li	3	HMPA	20	0	0	0
7	Li	3	MeOH	20	0	0	0
8[c]	NBu_4	3	CH_2Cl_2/H_2O	48	0	0	0
9[d]	NBu_4	3	CH_2Cl_2/H_2O	48	2	5	7
10[e]	Na	3	DMSO	0.5	0	86	86
11[e]	Na	3	DMF	0.5	0	58	58
12[e]	Na	1.5	DMSO	0.5	12	40	52
13[e]	Na	2	DMSO	0.5	7	71	78
14[e]	Na	2.5	DMSO	0.5	0	86	86
15[e]	Na	4	DMSO	0.5	0	85	85
16[e]	Na	2.5	DMSO	0.25	10	62	72
17[e]	Na	2.5	DMSO	1	0	84	84

[a] All reactions were performed under nitrogen and irradiation with a 60W fluorescent lamp. All yields refer to chromatographically isolated pure products.
[b] without fluorescent lamp.
[c] Phase transfer conditions with NBu_4Br in water.
[d] Phase transfer conditions with NBu_4OH in water.
[e] 2-nitropropane salt was formed *in situ* using NaH in DMSO or DMF and 2-nitropropane.



Scheme 3. $S_{RN}1$ mechanism of **3** with 2-nitropropane anion

(TEMPO, O_2) or as electron acceptor (*p*-DNB) disrupting the $S_{RN}1$ cyclic mechanism (Scheme 3) by coupling with the propargyl radical (TEMPO, O_2) or by competing with **3** in the electron transfer from the nucleophile during the initiation step (*p*-DNB). Inhibition for the synthesis of C-alkylation products (**4** + **5**) was observed with TEMPO (Table 2, entries 2-3), O_2 (Table 2, entry 4) and *p*-DNB (Table 2, entry 5). The effects of these inhibitors on the reaction between **3** and the 2-nitropropane anion provide good evidence of the $S_{RN}1$ mechanism in the C-alkylation.[12,26]



[a] General conditions: Nitroalkane (2.5 equiv.), NaH (2.5 equiv.); DMSO, r.t., hv, 30 min.
[b] Under Norris phase transfer conditions.

Scheme 4. Reaction of **3** with various nitroalkane anions

Following optimization, the best conditions developed during the study with the 2-nitropropane anion (Table 1, entry 14) were applied to six other nitronate anions (cycloalkane, aromatic, heterocyclic nitronates and nitroester) (Scheme 4). The original C-alkylated products resulting from $S_{RN}1$ reaction were fully characterized.[27] The corresponding nitroalkanes were either commercially available (formation of $S_{RN}1$ product **6**-**8**) or synthesized in one step by oxidation of amine using MCPBA[15d] (formation of $S_{RN}1$ product **9**-**11**) or by nitration of *N*-methypyrrolidone[15d] (formation of $S_{RN}1$ product **12**). As observed with the 2-nitropropane anion, these conditions led almost exclusively to ethylenic products **6**-**8** and **10**-**12**, in 24% to 84% yield of isolated product. Compound **12** with the *N*-methypyrrolidone substituent, which has been shown to enhance antiparasitic activity in 5-nitroimidazole series,[27] reacted poorly with the optimized conditions described above (Table 1, entry 14). However, Norris phase transfer conditions were the best experimental conditions (45% yield) when the 1-methyl-3-nitropyrrolidin-2-one anion was used to synthesize compound **12**. This result could be explained by the poor solubility of the *N*-methypyrrolidone anion in DMSO.[28]

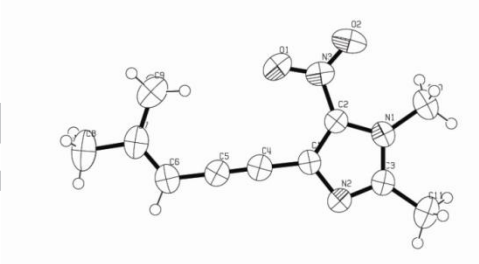


Figure 1. Ortep plot of 1,2-Dimethyl-4-(4-methylpent-3-en-1-ynyl)-5-nitro-1*H*-imidazole **5**

The structure of compound **5** was unambiguously confirmed by X-ray structure analysis (Figure 1).[29] Concerning the stereochemistry of the alkenes **8**, **10**, **11** and **12** resulting from nitrous acid elimination on the C-alkylation product, *E*-stereoisomer was the only isomer observed as confirmed by X-ray analysis of crystal of **10** (Figure 2).[30] The other structures were assigned by analogy and spectral comparison.

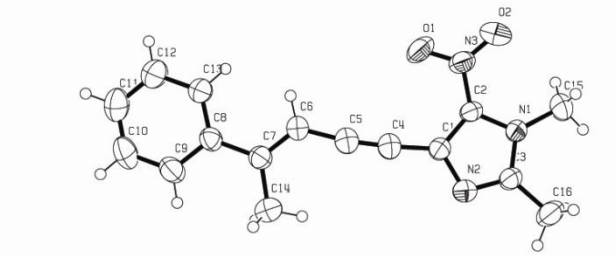


Figure 2. Ortep plot of (*E*)-1,2-Dimethyl-5-nitro-4-(4-phenylpent-3-en-1-ynyl)-1*H*-imidazole **10**

In conclusion, we report here the first example of $S_{RN}1$ on a propargylic chloride in heterocyclic chemistry. After optimization between 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole **3** and the 2-nitropropane anion, $S_{RN}1$ products **4** + **5** were obtained in 86% yield. The methodology was extended to other nitronate anions, notably to substituents possessing features of biological interest. Furthermore, 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole is shown to constitute an outstanding substrate for $S_{RN}1$ reactivity because of the absence of any O-alkylated compound. This substrate could be a good starting material for further single electron transfer studies.

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22. *General procedure for the synthesis of compound* ***4-12*** *via* $S_{RN}1$ *reactions:* In a 100 mL two-necked round flask, to NaH 60% (94 mg, 2.34 mmol; 2.5 equiv.) under N_2 was added nitroalcane (2.34 mmol, 2.5 equiv.) in anhydrous DMSO (4 mL). The reaction mixture was stirred at room temperature for 30 min, then 4-(3-chloroprop-1-ynyl)-1,2-dimethyl-5-nitro-1*H*-imidazole **3** was added in anhydrous DMSO under N_2. The reaction mixture was stirred under light irradiation until disappearance of the starting material as monitored by TLC and LC-MS, diluted in cold water (10 mL) and extracted with EtOAc (6 x 20 mL). The combined organic layers were washed with brine (3 x 100 mL), dried under Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with the corresponding eluent and recrystallized with the corresponding solvent to afford $S_{RN}1$ product **4-12**. Microwave-assisted reactions were performed in a Biotage Initiator Microwave oven using 0.5–2 mL sealed vials; temperatures were measured with an IR-sensor and reaction times are given as hold times.
Methods for the analytical data of compound ***4-12:*** 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 Faculty of Pharmacy of Marseille. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to reference $CHCl_3$ [7.26 ppm (^{1}H) and 77.0 ppm (^{13}C)] and DMSO-d_6 [2.50 ppm (^{1}H) and 39.5 ppm (^{13}C)]. Elemental analyses were carried out at the Spectropole, Faculty of Sciences (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 x 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluting solvent. Visualization was made

with ultraviolet light (234 nm). Purity of synthesized compounds was checked with LC-MS analyses which were realized at the Faculty of Pharmacy of Marseille with a Thermo Scientific Accela High Speed LC System® coupled with a single quadrupole mass spectrometer Thermo MSQ Plus®. The RP-HPLC column used is a Thermo Hypersil Gold® 50 × 2.1 mm (C18 bounded), with particles of 1.9 µm diameter. The volume of sample injected on the column was 1 µL. The chromatographic analysis, total duration of 8 min, is made with the gradient of following solvents: t = 0 min, water/methanol 50/50; 0 < t < 4 min, linear increase in the proportion of water to a ratio water/methanol 95/5; 4 < t < 6 min, water/methanol 95/5; 6 < t < 7 min, linear decrease in the proportion of water to return to a ratio 50/50 water/methanol; 6 < t < 7 min, water/methanol 50/50. The water used was buffered with 5 mM ammonium acetate. The retention times (t_r) of the molecules analyzed are indicated in min.

23. *1,2-Dimethyl-4-(4-methylpent-3-en-1-ynyl)-5-nitro-1H-imidazole **(5)**:* Compound **5** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 8:2) and recrystallization from cyclohexane. Yield: 176 mg (86 %); yellow powder; mp 159 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.88 (s, 3H), 2.06 (s, 3H), 2.45 (s, 3H), 3.88 (s, 3H), 5.53 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 21.7 (CH_3), 25.4 (CH_3), 34.1 (CH_3), 83.9 (C), 96.3 (C), 104.9 (CH), 127.7 (C), 149.3 (C), 154.1 (C). C-NO_2 was not observed in this experiment. LC-MS t_r = 2.20 min; (ESI+) *m/z* 220 $[M+H]^+$, 439 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{11}H_{13}N_3O_2$: 220.1081; found: 220.1082.
24. *1,2-Dimethyl-4-(4-methyl-4-nitropent-1-ynyl)-5-nitro-1H-imidazole **(4)**:* Compound **4** was isolated after purification by column chromatography on silica gel (eluent: $CHCl_3$–PE, 8:2 then 1:0) and recrystallization from cyclohexane. Yield: 28 mg (12%); beige solid; mp 132 °C.^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.77 (s, 6H), 2.45 (s, 3H), 3.16 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (CH_3), 25.7 (2 x CH_3), 31.9 (CH_2), 34.2 (CH_3), 76.1 (C), 86.9 (C), 92.2 (C), 125.9 (C), 149.1 (C). LC-MS t_r = 1.21 min; (ESI+) *m/z* 267 $[M+H]^+$, 533 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{11}H_{14}N_4O_4$: 267.1088; found: 267.1087.
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27. *4-(3-Cyclopentylideneprop-1-ynyl)-1,2-dimethyl-5-nitro-1H-imidazole **(6)**:* Compound **6** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 8:2) and recrystallization from cyclohexane. Yield: 148 mg (64%); yellow powder; mp 136 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (m, 4H), 2.46 (m, 2+3H), 2.63 (m, 2H), 3.89 (s, 3H), 5.66 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 26.2 (CH_2), 26.7 (CH_2), 33.0 (CH_2), 34.1 (CH_3), 34.5 (CH_2), 84.4 (C), 96.8 (C), 99.8 (CH), 127.9 (C), 138.4 (C), 149.3 (C), 166.9 (C). LC-MS t_r = 3.24 min; (ESI+) *m/z* 246 $[M+H]^+$, 491 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+Na]^+$ calcd. for $C_{13}H_{16}N_3O_2$: 246.1237; found: 246.1236.

    *4-(3-Cyclohexylideneprop-1-ynyl)-1,2-dimethyl-5-nitro-1H-imidazole **(7)**:* Compound **7** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 8:2) and recrystallization from cyclohexane. Yield: 205 mg (84%); yellow powder; mp 111 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60 (s, 6H), 2.24 (m, 2H), 2.45 (s, 3H), 2.59 (m, 2H), 3.89 (s, 3H), 5.50 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 26.3 (CH_2), 27.8 (CH_2), 28.4 (CH_2), 32.2 (CH_2), 34.1 (CH_3), 36.4 (CH_2), 83.7 (C), 96.2 (C), 101.4 (CH), 127.7 (C), 138.4 (C), 149.3 (C), 161.5 (C). LC-MS t_r = 3.65 min; (ESI+) *m/z* 260 $[M+H]^+$, 519 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{18}N_3O_2$: 260.1394; found: 260.1390. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C,64.75; H,6.73; N, 15.84.

    *(E)-Ethyl 5-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)-2-methylpent-2-en-4-ynoate **(8)**:* Compound **8** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2) and recrystallization from cyclohexane. Yield: 63 mg (24%); yellow powder; mp 98 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3H), 2.23 (d, *J* = 1.4 Hz, 3H), 2.51 (s, 3H), 3.93 (s, 3H),4.26 (q, *J* = 7.1 Hz, 2H), 6.86 (q, *J* = 1.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.3 (CH_3), 15.9 (CH_3), 34.2 (CH_3), 61.4 (CH_2), 92.0 (C), 93.1 (C), 118.1 (CH), 125.9 (C), 142.5 (C), 149.5 (C), 166.8 (C). C-NO_2 was not observed in this experiment. LC-MS t_r = 2.53 min; (ESI+) *m/z* 278 $[M+H]^+$, 555 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{15}N_3O_4$: 278.1135; found: 278.1140.

    *1,2-Dimethyl-5-nitro-4-(4-nitro-4-phenylpent-1-ynyl)-1H-imidazole **(9)**:* Compound **9** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 95:05) and recrystallization from cyclohexane. Yield: 34 mg (11%); beige powder; mp 139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3H), 2.43 (s, 3H), 3.58 (dd, J_1 = 51.5Hz , J_2 = 17.2Hz, 2H), 3.85 (s, 3H), 7.36-7.49 (m, 5H). LC-MS t_r = 2.58 min; (ESI+) *m/z* 329 $[M+H]^+$, 657 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{16}N_4O_4$: 329.1244; found: 329.1242.

    *(E)-1,2-Dimethyl-5-nitro-4-(4-phenylpent-3-en-1-ynyl)-1H-imidazole **(10)**:* Compound **10** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 8:2) and recrystallization from cyclohexane. Yield: 120 mg (57%); yellow powder; mp 154 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (m, 6H), 3.92 (s, 3H), 6.17 (s, 1H), 7.34-7.53 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (CH_3), 19.1 (CH_3), 34.2 (CH_3), 87.3 (C), 96.5 (C), 105.8 (CH), 125.8 (2 x CH), 127.4 (C), 128.6 (2xCH), 128.8 (CH), 140.5 (C), 149.5 (C), 152.6 (C). C-NO_2 was not observed in this experiment. LC-MS t_r = 3.65 min; (ESI+) *m/z* 282 $[M+H]^+$, 563 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}N_3O_2$: 282.1237; Found: 282.1242. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C,68.05; H,5.41; N, 14.68.

    *(E)-4-[3-(3,4-Dihydronaphthalen-1(2H)-ylidene)prop-1-ynyl]-1,2-dimethyl-5-nitro-1H-imidazole **(11)**:* Compound **11** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–PE, 6:4) and recrystallization from cyclohexane. Yield: 103 mg (31%); yellow powder; mp 163 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.92 (qt, *J* = 6.3Hz, 2H), 2.52 (s, 3H), 2.84 (t, *J* = 6.2Hz, 2H), 2.99 (t, *J* = 6.3Hz, 2H), 3.93 (s, 3H), 6.32 (s, 1H), 7.12-7.26 (m, 3H), 7.63-7.67 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 23.0 (CH_2), 30.0 (CH_2), 30.7 (CH_2), 34.2 (CH_3), 88.4 (C), 97.0 (C), 101.5 (CH), 124.0 (CH), 126.4 (CH), 127.6 (C), 129.1 (CH), 129.5 (CH), 133.9 (C), 138.9 (C), 149.5 (C), 152.5 (C). C-NO_2 was not observed in this experiment. LC-MS t_r = 4.15 min; (ESI+) *m/z* 308 $[M+H]^+$, 615 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{18}H_{17}N_3O_2$: 308.1394; found: 308.1394.

    *(E)-3-[3-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)prop-2-ynylidene]-1-methylpyrrolidin-2-one **(12)**:* Compound **12** was isolated after purification by column chromatography on silica gel (eluent: CH_2Cl_2–MeOH, 98:2) and recrystallization from cyclohexane. Yield: 90 mg (35%); yellow powder; mp 216 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.51 (s, 3H), 2.98 (s, 3H), 3.05 (td, J_1 = 6.1Hz , J_2 = 3.1Hz, 2H), 3.48 (t, J = 6.1Hz, 2H), 3.93 (s, 3H), 6.56 (t, *J* = 3.1Hz, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 14.3 (CH_3), 24.5 (CH_2), 30.5 (CH_3), 34.3 (CH_3), 46.7 (CH_2), 89.5 (C), 96.2 (C), 108.6 (CH), 126.1 (C), 147.5 (C), 149.5 (C), 166.9 (C). C-NO_2 was not observed in this experiment. LC-MS t_r = 0.78 min; (ESI+) *m/z* 275 $[M+H]^+$, 549 $[2M+H]^+$. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{15}N_4O_3$: 275.1139; found: 275.1141.
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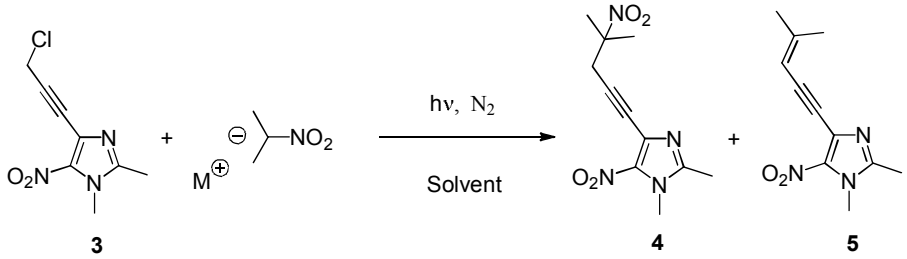
29. CCDC 980833 contains the supplementary crystallographicdata of compound **5** for this paper. These data can be obtained free of charge from The CambridgeCrystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
30. CCDC 980834 contains the supplementary crystallographicdata of compound **10** for this paper. These data can be obtained free of charge from The CambridgeCrystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.



3 **4** **5**

Scheme 2