Pergamon

Tetrahedron Letters 43 (2002) 4127–4129

TETRAHEDRON LETTERS

A new synthetic approach for novel 4-substituted-5-nitroimidazoles†

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Received 17 April 2002; accepted 19 April 2002

Abstract—A new synthetic approach, involving an $S_{RN}1$ reaction of the anion of 1-methyl-4-phenylsulfonyl-methyl-5-nitro-1*H*-imidazole with 2,2-dinitropropane and a radical anion or a concerted radical reductive elimination of sulfonyl and nitro groups affords an original 5-nitroimidazole bearing a trisubstituted ethylenic double bond at 4-position.

The $S_{RN}1$ reaction of 1-methyl-2-chloromethyl-5-nitro-1*H*-imidazole with the lithium salt of a secondary nitroalkane followed by nitrous acid elimination has been shown to be a good method for the preparation of various 1-methyl-5-nitro-1*H*-imidazoles bearing a trisubstituted double bond in the 2 position.[1] By this method, very active compounds against anaerobic bacteria have been prepared.[2] Because, 1-methyl-4-chloromethyl-5-nitro-1*H*-imidazole is unknown and its precursor, 1-methyl-4-hydroxymethyl-5-nitro-1*H*-imidazole, is relatively difficult to synthesize,[3] another approach was necessary to prepare various 1-methyl-5-nitro-1*H*-imidazoles bearing a trisubstituted double bond in 4-position in order to compare their biological activities with the 2-substituted isomers. The vicarious nucleophilic substitution of hydrogen (VNS) in nitroarenes with carbanions bearing leaving groups X at the anion center is a process of general character and significant practical value for organic synthesis. In 1-methyl-5-nitro-1*H*-imidazole series, Makosza et al. have been prepared by VNS reaction, 1-methyl-4-phenylsulfonylmethyl-5-nitro-1*H*-imidazole **2** in 63% yield from chloromethyl phenyl sulfone and the easily available 1-methyl-5-nitro-1*H*-imidazole **1**.[4]

Then, the VNS reaction is a powerful method to prepare a phenylsulfone bearing 1-methyl-4-substituted-5-nitro-1*H*-imidazole, which after removal of a proton by a strong base to give the stabilized carbanion $\mathbf{2}^-$ could be used as nucleophile for $S_{RN}1$ reactions with various nitro electrophiles. Indeed, Ono et al. have shown that carbanions bearing a sulfonyl group and an electron-withdrawing group (cyano, ethyl ester) are able to react by $S_{RN}1$ reaction with *gem*-dinitroalkanes.[5]

On the other hand, α-nitrosulfones are useful synthetic intermediates. For example, the lithium or sodium salts of (phenylsulfonyl)nitromethane gave predominant *C*-alkylation when treated with methyl iodide, primary alkyl iodides, and benzylic bromides or iodides.[6] This is in sharp contrast to typical nitronates which give predominant *O*-alkylation under these conditions. So, the study of the reactivity in $S_{RN}1$ reaction of a carbanion bearing a phenylsulfonyl group and a nitroheterocyclic group with a *gem*-dinitroalkane to give **3** became an interesting problem concerning scope and limitations of $S_{RN}1$ reaction. Finally, to complete the synthesis of 1-methyl-5-nitro-1*H*-imidazoles bearing a trisubstituted double bond, it was of interest to examine the ease with which the secondary sulfonyl group and the tertiary nitro group could be eliminated in a radical anion[7] or a concerted radical reductive elimination[8] from the β-nitrosulfone **3**. In this paper, we would like to report that the stabilized carbanion $\mathbf{2}^-$ is able to react by the $S_{RN}1$ mechanism with different nitro electrophiles[9] and that 1-methyl-5-nitro-1*H*-imidazole bearing a trisubstituted double bond in 4 position as **4** can be prepared according to the following scheme:

Keywords: $S_{RN}1$ reaction; sulfonyl carbanion; *C*-alkylation; desulfonylation; 5-nitroimidazole.

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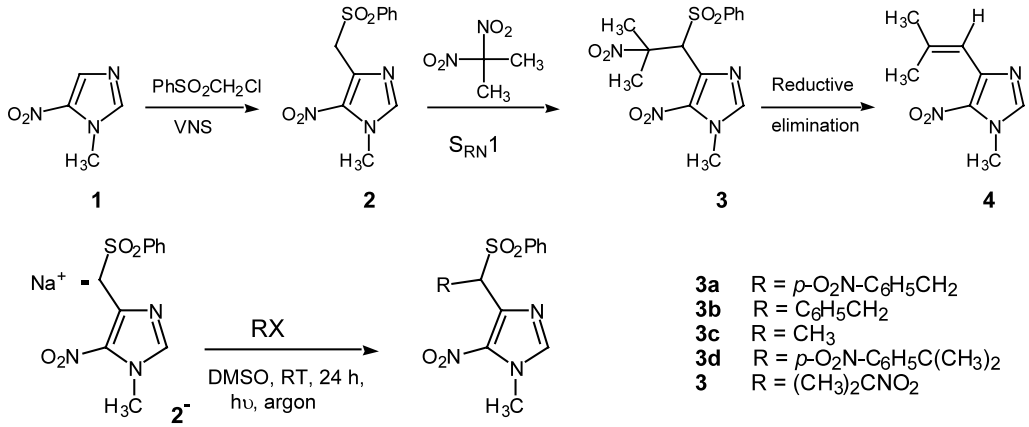
† This paper is dedicated to the late Professor Jean-Marie Surzur. Deceased on January 24, 2002.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00767-0



First and foremost, it has been shown that the sodium salt of **2** reacted with *p*-nitrobenzyl chloride, the classical nitro electrophile to study a substitution reaction which proceeds via radical anion intermediates,[10] and that the stabilized carbanion **2**$^-$ reacted with *p*-nitrobenzyl chloride either by the S_N2 mechanism, the $S_{RN}1$ mechanism or by the two mechanisms.

The sodium salt of **2** has been prepared from **2** in DMSO under argon at room temperature by reaction of sodium hydride (60% dispersion in mineral oil) and reacted with *p*-nitrobenzyl chloride during 24 h under photostimulation. After work-up and purification, the product **3a** has been obtained in 70% yield. The same reaction in presence of *p*-dinitrobenzene[11] (5% molar) gave **3a** in 75% yield showing no inhibition. To confirm that **2**$^-$ is able to react by S_N2 mechanism with different primary alkyl halides, the *C*-alkylation of **2**$^-$ has been studied under the same experimental conditions with benzyl bromide and methyl iodide. The corresponding secondary sulfones **3b** and **3c** have been obtained in, respectively, 81% and 84% yields. The same yields of **3a**–**c** are approximately obtained under spontaneous initiation.

Under photostimulation, α,*p*-dinitrocumene gave traces of **3d** and *p*,*p*′-dinitrobicumyl[12] in 22% yield. By addition of *p*-dinitrobenzene (5% molar), the formation of **3d** significantly increased (12% yield) showing that the $S_{RN}1$ *C*-alkylation of **2**$^-$ by a nitro electrophile at a tertiary carbon atom is possible and *p*-dinitrobenzene with a relatively slow electron-transfer chain reaction speeds up the reaction.[12]

Under the experimental conditions (sodium salt, DMSO, photostimulation, RT, argon, 24 h), 2,2-dinitropropane (1 equiv.) gave after column chromatography (silica gel, ethyl acetate) the desired compound **3** in 27% yield and a mixture of **2** and **3**′ resulting from nitrous acid elimination from **3**. With a small excess (1.1 equiv.) of 2,2-dinitropropane or 2-bromo-2-nitropropane and entrainment[10] by the lithium salt of 2-nitropropane, **3** was obtained in 38% yield with a mixture of 40% of **2** and 15% of **3**′ as calculated from ^{1}H NMR spectra. To prepare the alkene **4**, first the experimental conditions for reductive elimination reaction induced by a reducing agent such as Na_2S were used. The β-nitrosulfone **3** was treated with Na_2S, 9 H_2O (1.5 equiv.) in DMF at room temperature under argon with photostimulation to give after purification by column chromatography (silica gel, ethyl acetate) **4** in 28% yield and **3**′ in 16% yield. A higher yield in **4** (55%) after column chromatography (silica gel, $CHCl_3$/Et_2O: 6/4) was obtained with modification of the experimental conditions described[8] for reductive elimination induced by tin radical (Bu_3SnH, 2.5 equiv., AIBN, 0.9 equiv., 22 h).

In conclusion, a new synthetic approach, involving an $S_{RN}1$ reaction of the stabilized anion formed from 1-methyl-4-phenylsulfonyl-methyl-5-nitro-1*H*-imidazole with 2,2-dinitropropane and a radical anion or a concerted radical reductive elimination of sulfonyl and nitro groups affords an original 5-nitroimidazole bearing a trisubstituted ethylenic double bond at 4-position. The extension of this direct and rapid radical approach to new 4-substituted-5-nitroimidazoles to more complex nitro electrophiles and other nitroheterocyclic sulfones is in progress in our laboratories.

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9. 4-[1-Benzenesulfonyl-2-(4-nitrophenyl)-ethyl]-1-methyl-5-nitro-1*H*-imidazole **3a**: Yellow solid, mp 175°C (ethanol), ^{1}H NMR 300 MHz ($CDCl_3$) δ 3.63 (dd, $J=3.6$ Hz, $J=13.8$ Hz, 1H); 3.80–4.00 (m, 4H); 5.60 (dd, $J=3.8$ Hz, $J=11.7$ Hz, 1H); 7.24–8.04 (m, 10H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 32.4 (CH_2); 36.1 (CH_3); 63.9 (CH); 123.8 (CH); 128.9 (CH); 129.1 (CH); 129.9 (CH); 134.3 (CH); 135.8 (C); 137.1 (C); 139.9 (CH); 144.1 (C); 146.9 (C). Anal. Calcd for $C_{18}H_{16}N_4O_6S$ (416.41): C, 51.92; H, 3.87; N, 13.45. Found: C, 52.12; H, 3.88; N, 13.50. 4-[1-Benzenesulfonyl-2-phenyl-ethyl]-1-methyl-5-nitro-1*H*-imidazole **3b**: White solid, mp 163°C (ethanol). ^{1}H NMR 300 MHz ($CDCl_3$) δ 3.52 (dd, $J=3.6$ Hz, $J=13.6$ Hz, 1H); 3.66–3.76 (m, 1H); 3.82 (s, 3H); 5.62 (dd, $J=3.6$ Hz, $J=11.7$ Hz, 1H); 7.02–7.83 (m, 11H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 33.14 (CH_2); 36.4 (CH_3); 64.9 (CH); 127.2 (CH); 128.9 (CH); 129.3 (CH); 129.4 (CH); 134.5 (CH); 136.7 (C); 137.1 (C); 138.0 (C); 138.2 (C); 140.4 (CH). Anal. Calcd for $C_{18}H_{17}N_3O_4S$ (371.41): C, 58.21; H, 4.61; N, 11.31. Found: C, 57.91; H, 4.59; N, 11.35. 4-[1-Benzenesulfonyl-ethyl]-1-methyl-5-nitro-1*H*-imidazole **3c**: White solid, mp 156°C (ethanol). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.72 (d, $J=7.0$ Hz, 3H); 3.91 (s, 3H); 5.34 (q, $J=7.0$ Hz, 1H); 7.46–7.80 (m, 6H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 12.8 (CH_3); 36.0 (CH_3); 58.4 (CH); 128.9 (CH); 133.9 (CH); 137.3 (C); 138.1 (C); 140.0 (CH). Anal. Calcd for $C_{12}H_{13}N_3O_4S$ (295.32): C, 48.80; H, 4.44; N, 14.23. Found: C, 48.88; H, 4.44; N, 14.14. 4-[1-Benzenesulfonyl-2-methyl-2-(4-nitro-phenyl)-propyl]-1-methyl-5-nitro-1*H*-imidazole **3d**: Yellow solid, mp 225°C (ethanol), ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.67 (s, 3H); 2.07 (s, 3H); 3.77 (s, 3H); 5.95 (s, 1H); 7.30–8.04 (m, 10H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 26.3 (CH_3); 27.6 (CH_3); 36.1 (CH_3); 43.7 (C); 69.7 (CH); 123.2 (CH); 127.2 (CH); 127.8 (CH); 128.7 (CH); 133.5 (CH); 137.6 (C); 139.8 (CH); 140.0 (C); 146.4 (C); 154.2 (C). Anal. Calcd for $C_{20}H_{20}N_4O_6S$ (444.46): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.03; H, 4.58; N, 12.43. 4-(1-Benzenesulfonyl-2-methyl-2-nitro-propyl)-1-methyl-5-nitro-1*H*-imidazole **3**: White solid, mp 189–191°C (acetone/petroleum spirit 60–80: 3/5). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.67 (s, 3 H); 2.34 (s, 3 H); 3.88 (s, 3 H); 6.56 (s, 1 H); 7.42–7.66 (m, 6H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 23.9 (CH_3); 27.1 (CH_3); 36.2 (NCH_3); 65.9 (CH); 89.5 (C); 128.3 (2CH); 129.2 (2CH); 133.8 (C); 134.5 (CH); 138.3 (C); 140.1 (CH); (C-NO_2 not observed under the conditions of this experiment). Anal. Calcd for $C_{14}H_{16}N_4O_6S$ (368.37): C, 45.65; H, 4.38; N, 15.21. Found: C, 45.38; H, 4.38; N, 15.38. The structure of **3** was further confirmed by single crystal X-ray diffraction. Crozet, M. D. Thesis, University of Aix-Marseille, in preparation. 4-(1-Benzenesulfonyl-2-methyl-propenyl)-1-methyl-5-nitro-1*H*-imidazole **3′**: Pale yellow solid, mp 135–136°C (ethanol). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.74 (s, 3H); 2.21 (s, 3H); 4.00 (s, 3H); 7.44–7.60 (m, 4H); 7.88–8.00 (m, 2H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 21.6 (CH_3); 25.2 (CH_3); 35.9 (NCH_3); 127.5 (CH); 128.8 (CH); 131.0 (C); 132.9 (CH); 137.0 (C); 137.8 (C); 139.9 (CH); 142.4 (C); 155.7 (CH). Anal. Calcd for $C_{14}H_{15}N_3O_4S$ (321.35): C, 52.33; H, 4.70; N, 13.08. Found: C, 52.27; H, 4.71; N, 13.08. 4-(2-Methylpropenyl)-1-methyl-5-nitro-1*H*-imidazole **4**: Yellow solid, mp 106–107°C (hexane). ^{1}H NMR 300 MHz ($CDCl_3$) δ 2.00 (s, 3H); 2.19 (s, 3H); 3.96 (s, 3H); 6.77 (s, 1H); 7.46 (s, 1H). ^{13}C NMR 75 MHz ($CDCl_3$) δ 20.7 (CH_3); 27.9 (CH_3); 35.9 (NCH_3); 115.0 (CH); 139.9 (CH); 144.3 (C); 146.9 (C); (C-NO_2 not observed under the conditions of this experiment). Anal. Calcd for $C_8H_{11}N_3O_2$ (181.19): C, 53.03; H, 6.12; N, 23.19. Found: C, 53.07; H, 6.06; N, 22.84.

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