Molecules **2002**, *7*, 382-385

molecules

ISSN 1420-3049
http://www.mdpi.org

Synthesis of New Active Sulfones in the 5-Nitroimidazole Series

Kamel Benakli , Thierry Terme and Patrice Vanelle*

Laboratoire de Chimie Organique, UMR-CNRS 6517, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cx 5, France. E-mail: patrice.vanelle@pharmacie.univ-mrs.fr

Received: 29 March 2002; in revised form: 30 April 2002 / Accepted: 30 April 2002 / Published: 30 April 2002

Abstract: We describe here the preparation of new 5-nitroimidazoles which are known to have an efficacy against metronidazole-susceptible and -resistant *Giarda*, *Trichomona*s, and *Entamoeba* spp. The multi-step synthesis uses electron transfer methodology.

Keywords: Nitroimidazoles, sulfones, electron transfer.

Introduction

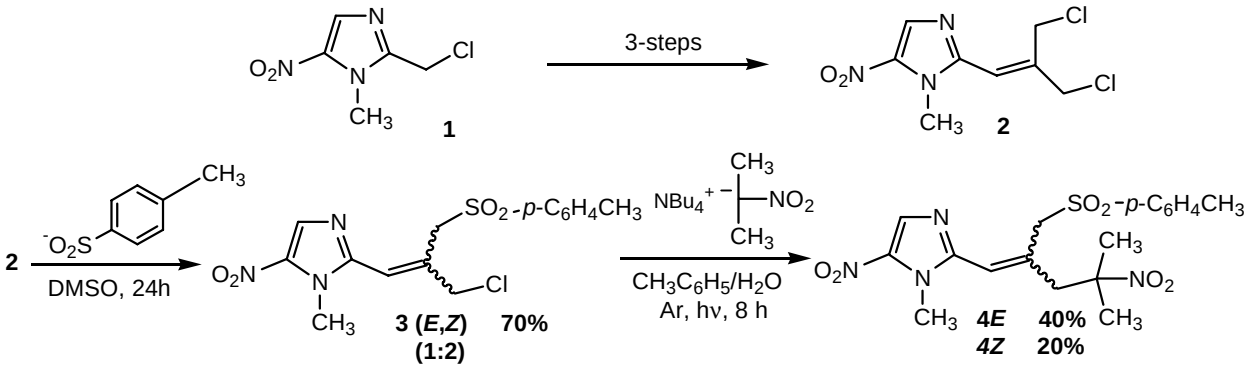
Nitroimidazole drugs have been used for over 20 years, not only as major antimicrobial drugs but also as sensitizers of hypoxic tumors in conjunction with radiotherapy, thus possessing a wider spectrum of useful clinical activity than any other antibiotic. These compounds have various substitutions on the imidazole ring either on the nitrogen at position 1 or on the carbon at position 2. The more common are metronidazole, ornidazole, tinidazole and dimetridazole. Our program directed toward electron transfer reactions in nitroheterocyclic series and in particular the 5-nitroimidazole series led us to synthesize more new active compounds [1]. Among them, we describe in this report the preparation of a series of 5-nitroimidazoles with an allylic-sulfone chain at the 2 position. Moreover, these compounds have shown efficacy against metronidazole-susceptible and -resistant *Giarda*, *Trichomona*s, and *Entamoeba* spp [2].

Results and Discussion

The starting material, 2-(3-chloro-2-chloromethylpropenyl)-1-methyl-5-nitro-*1H*-imidazole (**2**), was obtained in three steps by the previously described procedure starting from 1-methyl-2-chloromethyl-5-

nitro-1*H*-imidazole (**1**) [3, 4]. The reaction of **2** with sodium *p*-toluenesulfinate furnished the allylic-sulfone **3** as an unseparated mixture of *E* and *Z* isomers (1:2) in 70% yield. Under phase-transfer conditions (40% tetrabutylammonium hydroxide in water and toluene as solvent) and under $S_{RN}1$ reaction conditions (inert atmosphere, light catalysis), derivative **3** was treated with 2-nitropropane to give the *C*-alkylation derivative **4** as the sole product. After purification by chromatography, we have obtained the *E* isomer in 40% yield and the *Z* isomer in 20% yield (Scheme 1).

Scheme 1.



The formation of **4** constitutes a new example of the LD $S_{RN}1$ mechanism ($S_{RN}1$ at long distance from the nitro group) in the 5-nitroimidazole series [1]. As the site of metronidazole activation in the anaerobic protozoa is the membrane-localized electron transport pathway [2], the high antiprotozoal activity of **4** may be linked to the side chains that are more hydrophobic than those of metronidazole.

Conclusions

We have reported here a facile route for the formation of new sulfones in the 5-nitroimidazole series by an electron transfer methodology. Moreover, these 5-nitroimidazoles have displayed antiprotozoal activity against metronidazole-susceptible and –resistant species.

Experimental

General

Melting points were determined on Büchi B-540 and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^{1}H- and ^{13}C-NMR spectra were determined on Bruker ARX 200 spectrometer. The ^{1}H chemical shifts were reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the $CDCl_3$solvent peak (76.9 ppm). Silica gel 60 (Merck, 230-400 mesh) was used

for column chromatography. Thin-layer chromatography was performed with silica gel Merck 60F-254 (0.25 mm layer thickness). 2-(3-Chloro-2-chloromethylpropenyl)-1-methyl-5-nitro-1*H*-imidazole (**2**) was prepared as previously described from 2-chloromethyl-1-methyl-5-nitro-1*H*-imidazole (**1**) [3, 4].

Synthesis of 2-[3-chloro-2-(toluene-4-sulfonylmethyl)propenyl]-1-methyl-5-nitro-1H-imidazole (**3**). A solution of sodium 4-methylbenzenesulfinate (0.2 g, 2 mmol) in dimethylsulfoxide (4 mL) was added dropwise to a solution of dichloride **2** (0.5 g, 2 mmol) in dimethylsulfoxide (5 mL) and stirred under inert atmosphere for 12 h. The reaction mixture was poured into cold water and a precipitate was thus formed. After filtration, the crude product was dissolved in dichloromethane (10 mL), washed twice with water (2 x 20 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by chromatography on a silica gel column eluting with dichloromethane-ethyl acetate (95/5) and recrystallization from ethanol gave 0.52 g (70% yield) of 2-[3-chloro-2-(toluene-4-sulfonylmethyl)propenyl]-1-methyl-5-nitro-1*H*-imidazole (**3**) (*E*:*Z*, 1:2): Brown solid, mp 134 °C (ethanol). Anal. Calcd for $C_{15}H_{16}N_3O_4SCl$: C, 48.72; H, 4.36; N, 11.36; Cl, 9.59; S, 8.67; Found : C, 48.71; H, 4.39; N, 11.34; Cl, 9.70; S, 8.60.

E isomer

^{1}H-NMR ($CDCl_3$) δ: 2.49 (s, 3H, CH_3), 3.88 (s, 3H, NCH_3), 4.14 (s, 2H, CH_2Cl), 4.89 (s, 2H, CH_2SO_2), 6.31 (s, 1H, CH=C), 7.41 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.81 (d, 2H, J = 8.2 Hz, CH_{Ar}), 8.02 (s, 1H, CH_{Imid}); ^{13}C-NMR ($CDCl_3$) δ: 22.3 (CH_3), 33.8 (NCH_3), 42.8 (CH_2Cl), 62.0 (CH_2SO_2), 121.1 (CH=C), 129.1 (2 x CH_{Ar}), 130.8 (2 x CH_{Ar}), 133.8 (CH_{Imid}), 136.8 (Cq), 139.0 (Cq), 146.2 (Cq), 146.6 (Cq).

Z isomer

^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.71 (s, 3H, NCH_3), 4.55 (s, 2H, CH_2Cl), 5.05 (s, 2H, CH_2SO_2), 6.54 (s, 1H, CH=C), 7.21 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.63 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.88 (s, 1H, CH_{Imid}). ^{13}C-NMR ($CDCl_3$) δ: 22.1 (CH_3), 33.5 (NCH_3), 48.7 (CH_2Cl), 55.8 (CH_2SO_2), 119.2 (CH=C), 129.1 (2 x CH_{Ar}), 129.7 (2 x CH_{Ar}), 133.2 (CH_{Imid}), 136.2 (Cq), 137.7 (Cq), 145.7 (Cq), 146.8 (Cq).

*$S_{RN}1$ reaction of chloride **3** and 2-nitropropane.* Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (1.6M/water, 3.6 mL, 5.4 mmol) was treated with 2-nitropropane (0.48 g, 5.4 mmol) for 1 h. A solution of chloride **3** (0.5 g, 1.35 mmol) in toluene (10 mL) was added and the mixture was irradiated with a 300W sun lamp for 8 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed twice with water (2 x 30 mL), dried over $MgSO_4$ and removed under reduced pressure. Purification by

chromatography on silica gel eluting with chloroform-ethyl acetate (95/5) and recrystallization from ethanol gave the 3-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-2-(2-methyl-2-nitropropyl)prop-2-ene-1-sulfinic acid *p*-tolyl ester (**4*E***) (0.23 g, 40% yield) and (**4*Z***) (0.12 g, 20% yield).

3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-(2-methyl-2-nitropropyl)prop-2-ene-1-sulfinic acid p-tolyl ester (**4E**): Yellow solid, mp 115 °C (ethanol). ^{1}H-NMR ($CDCl_3$) δ: 1.67 (s, 6H, $(C\underline{H_3})_2CNO_2$), 2.32 (s, 3H, CH_3), 3.17 (s, 2H, $C\underline{H_2}C(CH_3)_2NO_2$), 3.57 (s, 3H, NCH_3), 4.90 (s, 2H, CH_2SO_2), 6.03 (s, 1H, CH=C), 7.16 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.55 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.82 (s, 1H, CH_{Imid}). ^{13}C-NMR ($CDCl_3$) δ: 22.1 (CH_3), 26.8 (2 x CH_3), 33.4 (NCH_3), 47.7 ($\underline{C}H_2C(CH_3)_2NO_2$), 58.9 ($CH_2SO_2$), 89.4 ($\underline{C}(CH_3)_2NO_2$), 121.1 ($\underline{C}H$=C), 129.2 (2 x CH_{Ar}), 129.7 (2 x CH_{Ar}), 133.1 (CH_{Imid}), 135.9 (Cq), 136.5 (Cq), 145.6 (Cq), 147.0 (Cq). Anal. Calcd for $C_{18}H_{22}N_4O_6S$: C, 51.18; H, 5.25; N, 13.26; S, 7.59. Found : C, 51.15; H, 5.21; N, 13.30; S, 7.52.

3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-(2-methyl-2-nitropropyl)prop-2-ene-1-sulfinic acid p-tolyl ester (**4Z**): Yellow solid, mp 118 °C (ethanol). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (s, 6H, $(C\underline{H_3})_2CNO_2$), 2.48 (s, 3H, CH_3), 3.57 (s, 2H, $C\underline{H_2}C(CH_3)_2NO_2$), 3.80 (s, 2H, CH_2SO_2), 3.95 (s, 3H, NCH_3), 6.53 (s, 1H, CH=C), 7.40 (d, 2H, J = 8.2 Hz, CH_{Ar}), 7.78 (d, 2H, J = 8.2 Hz, CH_{Ar}), 8.03 (s, 1H, CH_{Imid}). ^{13}C-NMR ($CDCl_3$) δ: 22.3 (CH_3), 26.6 (2 x CH_3), 33.7 (NCH_3), 41.7 ($\underline{C}H_2C(CH_3)_2NO_2$), 63.5 ($CH_2SO_2$), 89.0 ($\underline{C}(CH_3)_2NO_2$), 122.9 ($\underline{C}H$=C), 129.0 (2 x CH_{Ar}), 130.7 (2 x CH_{Ar}), 133.5 (CH_{Imid}), 136.2 (Cq), 136.4 (Cq), 139.4 (Cq), 146.1 (Cq), 147.4 (Cq). Anal. Calcd for $C_{18}H_{22}N_4O_6S$: C, 51.18; H, 5.25; N, 13.26; S, 7.59. Found : C, 51.15; H, 5.30; N, 13.20; S, 7.80.

References and Notes

1. Vanelle, P.; Crozet, M.P. *Recent Res. Devel. Organic Chem.* **1998**, *2*, 547.
2. Upcroft, J. A.; Campbell, R. W.; Benakli, K.; Upcroft, P.; Vanelle, P. *Antimicrob. Agents Chemother.* **1999**, *43*, 73.
3. Vanelle, P.; Maldonado, J.; Crozet, M. P.; Senouki, K.; Delmas, F.; Gasquet, M.; Timon-David, P.; *Eur. J. Med. Chem.*, **1991**, *26*, 709.
4. Vanelle, P.; Benakli, K.; Maldonado, J.; Roubaud, C.; Crozet, M.P. *Heterocycles*, **1996**, *43*, 731.

Samples Availability: Samples of compounds **4*E*** and **4*Z*** are available from the authors.