Michael addition of Fisher's base to (E)- β -nitrostyrenes

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University of Oslo, Department of Chemistry, Blindern, N-0315 Oslo, Norway Michael's addition reaction of 1,3,3-trimethyl-2-methylene-2,3-dihydro-1*H*-indole (Fisher's base) with (*E*)- β -nitrostyrenes afforded (*E*)-2-[2-(phenyl)-3-nitropropylidene]-1,3,3-trimethyl-2,3-dihydro-1*H*-indoles as a major product. The geometry of (*E*)-2-[2-(4-methoxyphenyl)-3-nitropropylidene]-1,3,3-trimethyl-2,3-dihydro-1*H*-indole was established by single crystal X-ray analysis.

Key words: Fisher's base, (E)-β-nitrostyrene, Michael addition, X-ray crystal structure

INTRODUCTION

trans-\beta-Nitrostyrenes are particularly versatile intermediates in organic synthesis and can be used as starting materials for the synthesis of many classes of compounds [1-6]. They easily participate in the carbon-carbon bond forming reactions with various electrophiles, and a nitro group may be transformed into a wide range of functionalities. trans-\beta-Nitrostyrenes found their application in the functionalization of various heterocycles, including indoles, the nucleus of which is present in many practically important compounds. 1H-indole possesses an electron-rich site at C-3 of the endocyclic enamine moiety and easily takes part in Michael addition reaction with conjugated electrophiles. The functionalization of 1*H*-indoles with trans- β -nitrostyrene derivatives was used for the preparation of tryptamine [7] and tryptophan analogues [8]. Michael addition of the 1H-indole C-3 atom to the polarized double carbon-carbon bond of trans-β-nitrostyrenes is usually performed in the presence of such catalysts, as iodine [9], sulfamic acid [10], silica-supported sodium sulfonate [11] and sodium hydrogen sulfate [12], chiral bis-sulfamide [7] and various Lewis acids [13], including chiral complexes of copper triflate [8, 14].

1,3,3-trimethyl-2-methylene-2,3-dihydro-1*H*-indole, the Fisher's base, is widely used in the preparation of various cyanine dyes [15]. It possesses an electron-rich site at exocyclic β -carbon atom of the enamine moiety, which was employed in the carbon–carbon bond forming with such electrophiles as methyl and ethyl iodides [16], 2-iodoacetamide [17], acrylamide [18] and nitro-olefins [19]. Suprisingly, its reaction with trans- β -nitrostyrenes still remains unexplored.

RESULTS AND DISCUSSION

In the present work we investigated the reaction of Fisher's base 1 with three trans- β -nitrostyrenes: (E)-1-(4-methoxyphenyl)-, (E)-1-(4-chlorophenyl)- and (E)-1-(4-bromophenyl)-2-nitroethenes (2a-c). The starting compounds 2a-c were prepared in good yields by a reaction of 4-substituted benzaldehydes with nitromethane in acetic acid in the presence of ammonium acetate [20].

The reaction of Fisher's base **1** with (*E*)-1-(4-methoxyphenyl)-2-nitroethene (**2a**) was carried out in boiling ethanol without a catalyst. The ¹H NMR spectrum of the crude product revealed the presence of doublets 4.38 (J = 10.8 Hz) and 4.23 ppm (J = 9.6 Hz), which can be attributed to the C=CH group proton of Michael adducts **3a**, **4a** (the ratio of isomers is 20 : 1). The major product **3a** was obtained from organic solvents by crystallization, characterized by single crystal X-ray crystallography and the suggested *E*-configuration of the molecule (Figure, Table). The C(10)–C(11) bond length of **3a** is 1.3470(12) Å and corresponds to the double character. The minor product (*Z*)-**4a** was not isolated in pure state, since its presence in the mixture of the products was negligible.

The reactions of Fisher's base **1** with (*E*)-1-(4-chlorophenyl)and (*E*)-1-(4-bromophenyl)-2-nitroethenes (**2b**, **c**) proceeded in a similar way with high selectivity to give Michael adducts **3b** and **c** as major products. The ¹³C NMR spectra of compounds **3b** and **c** contained the characteristic signal of enamine β -carbon

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0(2)

in the area of 90 ppm. The IR spectra of 3c revealed absorption bands at 1654 and 1540 cm⁻¹, characteristic of enamine and nitro groups, respectively.

0(1)

Table. Selected bond lengths	(Ì	I)	and an	gles	(deg) for	com	pound	3a
	•				· · · ·				

N(1)–C(1)	1.5028(12)	N(1)-C(1)-C(2)	111.79(7)
N(2)–C(11)	1.4036(10)	C(10)–C(2)–C(1)	106.46(7)
N(2)–C(15)	1.5362(13)	C(10)–C(2)–C(3)	110.33(7)
N(2)–C(16)	1.3875(11)	C(11)-C(10)-C(2)	127.04(7)
C(1)–C(2)	1.5362(13)	C(3)–C(2)–C(1)	113.88(7)
C(2)–C(10)	1.5126(12)	C(10)–C(2)–H(2)	110.4(8)
C(2)–C(3)	1.5273(12)	C(2)-C(10)-H(10)	114.6(9)
C(10)–C(11)	1.3470(12)	C(11)–C(10)–H(10)	118.4(9)

EXPERIMENTAL

¹H NMR spectra were recorded with a Bruker DPX-300 instrument (300 MHz). ¹³C NMR spectra were obtained on a Bruker DPX-300 instrument (75 MHz). Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer (KBr pellets). Pre-coated TLC plates (silica gel 60 F254, Merck) were used for thin-layer chromatographic (TLC) analyses.

(*E*)-2-[2-(4-Methoxyphenyl)-3-nitropropylidene]-1,3,3trimethyl-2,3-dihydro-1*H*-indole (3a). A solution of 1,3,3trimethyl-2-methylene-2,3-dihydro-1*H*-indole (Fisher's base)

Figure. ORTEP drawing of compound 3a. The thermal elipsoids are shown at 50% probability

(1.73 g, 10 mmol) and (E)-1-(4-methoxyphenyl)-2-nitroethene (1.79 g, 10 mmol) in ethanol (20 ml) was boiled for 4 h. Then the reaction mixture was allowed to reach room temperature and left at 5 °C for 48 h. The obtained crystalline material was filtered off and recrystallized from ethanol to yield 2.11 g (67%) of adduct 3a with melting point 115-116 °C. IR (KBr): 1650 (enamine C=CH), 1540 (NO₂) cm⁻¹; ¹H NMR (300 MHz, CDCl₂): δ 1.41 (3H, s, 3-CH₂); 1.59 (3H, s, 3-CH₂); 3.00 (3H, s, NCH₂); 3,78 (3H, s, OCH₃); 4.38 (1H, d, J 10.8 Hz, C=CH); 4.49 (1H, d. d, ²J 11.1 Hz, ³J 7.8 Hz, ¹/₂ CH₂); 4.65 (1H, d. d, ²J 11.1 Hz, ³J 7.8 Hz, ½ CH₂); 4.75 (1H, d. t., ³J 10.8 and 7.8 Hz, CH); 6.48 (1H, d, J 8.1 Hz, 7-H); 6.71-6.76 (1H, m, 5-H); 6.86-6.89 (2H, m, Ar-H_{phenyl}); 7.04 (1H, d. d ²J 7.4; ³J 0.9 Hz, 4-H); 7.08–7.12 (1H, d. t, m, 6-H); 7.25–7.28 (2H, m, Ar-H_{phenyl}). ¹³C NMR (DMSO-d₆): δ 27.85; 28.04; 28.83 (3-CH₃, 3-CH₃, CH₂, CH); 40.82 (NCH₃); 44.56 (C-3); 55.12 (OCH₃); 81.38 (CH₂); 91.01 (C=CH); 104.84 (CH); 114.32 (CH); 118.43 (CH); 121.32 (CH); 127.68 (CH); 128.13 (CH); 128.33 (CH); 133.16 (C); 137.79 (C); 145.72 (C); 156.02 (C-2); 158.72 (C). Calculated for C₂₁H₂₄N₂O₃: C, 71.57; H, 6.86; N, 7.95%. Found: C, 71.28; H, 6.55; N, 7.92%.

(*E*)-2-[2-(4-Chlorophenyl)-3-nitropropylidene]-1,3,3-trimethyl-2,3-dihydro-1*H*-indole (3b) was obtained in a similar method as described for 3a. Yield 31%, melting point 87–88 °C (from acetone). ¹H NMR (300 MHz, CDCl₃): δ 1.38 (3H, s, 3-CH₃); 1.58 (3H, s, 3-CH₃); 3.00 (3H, s, NCH₃); 4.32 (1H, d, *J* 10.5 Hz, C=CH); 4.50 (1H, d. d, ²*J* 11.4 Hz, ³*J* 7.8 Hz, ¹⁄₂ CH₂); 4.65 (1H, d. d, ${}^{2}J$ 11.4 Hz, ${}^{3}J$ 7.8 Hz, ${}^{1}_{2}$ CH₂); 4.75 (1H, d. t., ${}^{3}J$ 10.5 and 7.8 Hz, CH); 6.49 (1H, d, J 7.5 Hz, 7-H); 6.75 (1H, m, 5-H); 7.04 (1H, d. d, ${}^{2}J$ 7.2; ${}^{3}J$ 0.9 Hz, 4-H); 7.10 (1H, d. t, ${}^{2}J$ 7.5; ${}^{3}J$ 1.2 Hz, 6-H); 7.24–7.33 (4H, m, Ar-H_{phenyl}). 13 C NMR (DMSO-d₆): δ 27.87; 28.09; 28.92 (3-CH₃, 3-CH₃, CH₂CH); 41.00 (NCH₃); 44.70 (C-3); 82.01 (CH₂); 90.01 (C=*CH*); 105.11 (CH); 118.70 (CH); 121.41 (CH); 127.81 (CH); 128.58 (2 × CH); 129.22 (2 × CH); 133.15 (C); 137.68 (C); 139.81 (C); 145.65 (C); 156.70 (C-2). Calculated for C₂₀H₂₁ClN₂O₂: C, 67.32; H, 5.93; N 7.85%. Found: C, 67.33; H, 5.66; N, 7.71%.

(E)-2-[2-(4-Bromophenyl)-3-nitropropylidene]-1,3,3-trimethyl-2,3-dihydro-1H-indole (3c) was synthesized in a similar method as described for 3a. Yield 60%, melting point. 124-125 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.39 (3H, s, 3-CH₃); 1.58 (3H, s, 3-CH₂); 3.00 (3H, s, NCH₂); 4.32 (1H, d, *J* 10.8 Hz, C=CH); 4.50 (1H, d. d, ²J 11.5 Hz, ³J 7.7 Hz, ¹/₂ CH₂); 4.64 (1H, d. d, ²J 11.5 Hz, ³J 7.7 Hz, ¹/₂ CH₂); 4.75 (1H, d. t., ³J 10.8 and 7.7 Hz, CH); 6.49 (1H, d, J 7.8 Hz, 7-H); 6.75 (1H, d. t, ²J 7.4; ³J 0.9 Hz, 5-H); 7.03 (1H, d. d, ²*J*7.4; ³*J*0.9 Hz, 4-H); 7.09 (1H, d. t, ²*J*7.7; ³*J*1.3 Hz, 6-H); 7.21–7.25 (2H, m, Ar-H_{phenyl}); 7.45–7.48 (2H, m, Ar-H_{phenyl}). ^{13}C NMR (DMSO-d₆): δ 27.84; 28.08; 28.90 (3-CH₃, 3-CH₃, CH₂, CH); 41.04 (NCH₃); 44.68 (C-3); 81.90 (CH₂); 89.89 (C=CH); 105.11 (CH); 118.70 (CH); 121.20 (C); 121.39 (CH); 127.97 (CH); 128.92 (2 × CH); 132.16 (2 × CH); 137.16 (C); 140.32 (C); 145.61 (C); 156.72 (C-2). Calculated for C₂₀H₂₁BrN₂O₂: C, 59.86; H, 5.27; N 6.98%. Found: C, 59.66; H, 5.17; N, 6.82%.

X-ray crystal data and structure determination of 3a.

C₂₁H₂₄N₂O₃, *M*r 352.42, triclinic, space group P-1, *a* = 8.1908(7) Å, *b* = 9.3399(8) Å, *c* = 12.8752(11) Å, α = 76.949(4)°, β = 73.607(3)°, β = 86.527(4)°, V 920.52(3) Å³, Z = 2, D_{calc} = 1.271 mg mm⁻³, absorption coefficient 0.085 mm⁻¹, F(000) = 376, $\lambda = 0.71073$ Å. Data were collected using a crystal size of 0.55 × 0.35 × 0.15 mm on a Siemens SMART CCD diffractometer. A total of 16693 reflections (unique 6522) were collected for 10.26 < θ < 33.14° and -12 < = *h* < = 12, -13 < = *k* < = 14, -19 < = *l* < = 19. The completeness to θ = 33.14 was 92.8%. Full-matrix least-squares on *F*² were used as a refinement method, and data / restraints / parameters were 6522 / 0 / 331, respectively. The final *R* indices were [*I* > 2.00 σ(*I*)] *R*₁ = 0.0457, *wR*₂ = 0.1279, and (all data) *R* = 0.0618, *wR*₂ = 0.1400. The goodness-of-fit on *F*² was 1.051 and the largest difference peak and hole were 0.384 and -0.260 e A⁻³.

CONCLUSION

Michael addition reaction of Fisher's base with (E)- β -nitrostyrenes proceeds with high selectivity and gives (E)-2-[2-(phenyl)-3-nitropropylidene]-1,3,3-trimethyl-2,3-dihydro-1*H*-indoles as a major product.

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FIŠERIO BAZĖS PRIJUNGIMAS PRIE (Ε)-β-NITROSTIRENŲ PAGAL MICHAELĮ

Santrauka

1,3,3-Trimetil-2-metilen-2,3-dihidro-1*H*-indolą (Fišerio bazę) prijungiant prie (*E*)-β-nitrostirenų pagal Michaelį kaip pagrindinis produktas susidaro (*E*)-2-[2-(fenil)-3-nitropropiliden]-1,3,3-trimetil-2,3-dihidro-1*H*-indolai. (*E*)-2-[2-(4-metoksifenil)-3-nitropropiliden]-1,3,3-trimetil-2,3-dihidro-1*H*-indolo geometrija buvo nustatyta ištyrus jo kristalą rentgeno spindulių analizės metodais.