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SYNTHESIS AND REACTIVITY OF PHENYL ALKYL AMINO NITROETHENES

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ABSTRACT

1-phenylalkylamino-1-methylthio-2-nitroethenes were prepared from 1,1-bis (methylthio)-2-nitroethene and 1-phenylalkylamines. They were converted into 2-nitro-N-phenylalkylacetamides, 2-(hydroxyimino)-2-phenyl-N-(phenylalkyl) acetamides or 4-methylsulfanyl-2-oxy-4-phenylalkylamino 4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl esters in fair to good yields.

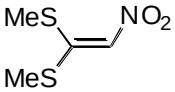
Key words: Phenylalkylmethylthionitroethene / (phenylalkyl) acetamide derivatives / superacidic system / cyclization / oxazine derivatives.

INTRODUCTION

Nitroethene derivatives are known as useful synthon in organic chemistry in the field of heterocyclic synthesis.[1] Particularly they are keen to undergo various condensation reactions[2,3], intramolecular-cyclizations involving nitrile oxides (INOC reactions)[4,5] and are used in the field of drug synthesis[4]. Several compounds having a nitroethene unit in their structures claimed to have insecticidal properties[6,7].

A potential synthon for the preparation of nitroketeneaminals derivatives is 1,1-bis (methylthio)-2-nitroethene **1**. In this compound, both thiomethyl groups are easily substituted by amino groups in mild conditions[8,9]. Reactions with aromatic[10] or non-aromatic amines[11] afford nitroketene S,N-acetals.

Arylaminonitroethene **2** was shown to undergo intramolecular cyclization reactions in superacidic media to form substutedoximes **3**[12].



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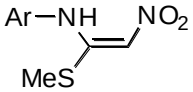

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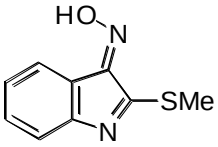

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Recently, we reported the syntheses of hydroxyiminohydroazaazoniabenzocycloalkene derivatives[13] and diazadihydroacenaphthylene derivatives with an isoxazoline ring[14] from cyclization of nitroethene derivatives in trifluoromethanesulfonic acid.

As part of a project to develop the use of nitroethene derivatives in organic chemistry, we report the synthesis of 1-phenylalkylamino-1-methylthio-2-nitroethenes and their conversions into 2-nitro-N-phenylalkylacetamides, 2-(hydroxyimino)-2-phenyl-N-(phenylalkyl)acetamides and 4-methylsulfanyl-2-oxy-4-phenylalkylamino 4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl esters.

EXPERIMENTAL

General remarks

Melting points were determined with a Büchi Melting point B545 apparatus using capillary tubes (temperature rate 2°C/mn) and were not corrected. A Brucker DPX 300 spectrometer, equipped with a low temperature probe, was used for ^{1}H- and ^{13}C- NMR spectra recorded at 300.13 and 75.47 MHz, respectively. NMR spectra were recorded at room temperature and chemical shifts reported relative to Me_4Si. The reproducibility of ^{13}C NMR shift was about ± 0.05 ppm, depending on cell and concentration. Chemical assignments were made using DEPT135 techniques and usual chemical shift assignments rules. Electron-impact ionization (70 eV) mass spectra were obtained with a FinniganIncos 500 Instrument. High Resolution Mass Spectrometry was performed by the "Centre Régional de Mesures Physiques de l'Ouest - Université de Rennes, France". Flash chromatography was achieved on silica gel (20 to 45 μm particle size). Trifluoromethanesulfonic acid was purchased from Acros and 1,1-bis(methylthio)-2-nitroethene from Lancaster and were used without further purification. No attempt was made to optimize the yields.

1-benzylamino-1-methylthio-2-nitroethene (5a): Typical Procedure

1,1-bis (methylthio)-2-nitroethene (2.2 g, 13.32 mmol) and the benzylamine (1.35 mL, 12.36 mmol) were heated together in refluxing 95% ethanol (75 mL) under nitrogen atmosphere and the reaction followed by thin-layer chromatography (CH_2Cl_2). After disappearance of the benzylamine (4 h) and cooling, the mixture was concentrated under reduced pressure. The resulting product was purified by flash chromatography with dichloromethane and then recrystallized from CH_2Cl_2/Petroleum ether to afford **5a** (2.076 g, 75 %) as yellow crystals. M. P. 122.4°C (Dichloromethane/Petroleum ether); ^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 4.61 (d, *J* = 5.93 Hz, 2 H, CH_2), 6.58 (s, 1 H, vinylic H), 7.28-7.31 (m, 2 H, aromatic *o*-H), 7.32-7.36 (m, 2 H, aromatic *m*-H), 7.37-7.38 (m, 1 H, aromatic *p*-H), 10.76 (broad s, NH). ^{13}C NMR ($CDCl_3$): δ = 14.9 (SCH_3), 48.7 (CH_2), 107.1 (= CH-NO_2), 127.8 (2 aromatics CH), 129.5 (2 aromatics CH), 135.9 (*ipso*-C), 165.1 (-NH-C=). HRMS for $C_{10}H_{12}N_2O_2S$ (M^+): calcd. 224.0619, found 224.0621.

1-(Methylthio)-2-nitro-1-(2-phenylethylamino) ethene (5b)

From Phenethylamine (1.5 mL, 12 mmol) and 1,1-bis(methylthio)-2-nitroethene (2.2 g, 13.32 mmol) was obtained **5b** (2.23 g, 78 %) as yellow crystals. M. P. 95.4°C (Absolute Ethanol); ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 2.90 (t, *J* = 7.23 Hz, 2 H, C*H*$_2$-Ph), 3.59 (dd, *J* = 6.99 and 13.00 Hz, 2 H, CH_2-N<), 6.47 (s, 1 H, vinylic H), 7.14-7.23 (m, 3 H, aromatic *o*-H and *p*-H), 7.23-7.28 (m, 2 H, aromatic *m*-H), 10.32 (broad s, NH). ^{13}C NMR ($CDCl_3$): δ = 14.7 (SCH_3), 42.6 (*C*H_2-Ph), 46.4 (CH_2-N<), 106.6 (= CH-NO_2), 127.4 (aromatic CH), 127.7 (2 aromatics CH), 129.2 (2 aromatics CH), 137.8 (*ipso*-C), 165.3 (-NH-C =). HRMS for $C_{11}H_{14}N_2O_2S$ ([M^+]): calcd. 238.0776, found 238.0788.

1-(Methylthio)-2-nitro-1-(3-phenylpropylamino) ethene (5c)

From 3-Phenylpropylamine (1.4 mL, 10 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.98 g , 12 mmol) was obtained **5c** (1.89 g, 75 %) as yellow crystals. – M.P. 84°C (Absolute Ethanol); ^{1}H NMR

($CDCl_3$): δ = 2.02 (dd, *J* = 7.49 and 14.66 Hz, 2 H, CH_2), 2.40 (s, 3 H, CH_3), 2.71 (t, *J* = 7.49 Hz, 2 H, C*H*$_2$-Ph), 3.40 (dd, *J* = 7.49 and 13.11 Hz, 2 H, CH_2-N<), 6.58 (s, 1 H, vinylic H), 7.15-7.23 (m, 3 H, aromatic *o*-H and *p*-H), 7.26-7.33 (m, 2 H, aromatic *m*-H), 10.32 (broad s, NH). ^{13}C NMR ($CDCl_3$): δ = 14.6 (SCH_3), 30.9 (CH_2), 33.1 (*C*H_2-Ph), 44.2 (CH_2-N<), 106.5 (= CH-NO_2), 126.7 (aromatic CH), 128.8 (2 aromatics CH), 129.0 (2 aromatics CH), 140.7 (*ipso*-C), 165.5 (-NH-C=). HRMS for $C_{12}H_{16}N_2O_2S$ (M^+): calcd. 252.0933, found 252.0916.

1-(Methylthio)-2-nitro-1-(4-phenylbutylamino) ethene (5d)

From 4-Phenylbutylamine (1.6 mL, 10 mmol) and 1,1-bis(methylthio)-2-nitroethene (1.98 g, 12 mmol) was obtained **5d** (2.00 g, 75%) as yellow crystals. M. P. 95°C (Absolute Ethanol); ^{1}H NMR ($CDCl_3$): δ = 1.71 (m, 2 H, CH_2), 1.73 (m, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 2.66 (m, 2 H, C*H*$_2$-Ph), 3.42 (dd, *J* = 6.71 and 12.64 Hz, 2 H, CH_2-N<), 6.57 (s, 1 H, vinylic H), 7.15-7.22 (m, 3 H, aromatic *o*-H and *p*-H), 7.25-7.32 (m, 2 H, aromatic *m*-H), 10.54 (broad s, NH). - ^{13}C NMR ($CDCl_3$): δ =14.7 (SCH_3), 28.8 (CH_2), 29.0 (CH_2), 35.7 (*C*H_2-Ph), 44.8 (CH_2-N<), 106.5 (= CH-NO_2), 126.4 (aromatic CH), 128.7 (2 aromatics CH), 128.8 (2 aromatics CH), 142.0 (*ipso*-C), 165.4 (-NH-C =). HRMS for $C_{13}H_{18}N_2O_2S$ (M^+): calcd. 266.1089, found 266.1084.

N-benzyl-2-nitro-acetamide (6a): Typical Procedure

The 1-benzylamino-1-methylthio-2-nitroethene **5a** (1.80 g, 8.03 mmol) and aqueous potassium hydroxide (0.1 N, 100 mL) were heated together at reflux under nitrogen atmosphere for 24 hours while the starting material gradually went into solution. The solution was cooled to room temperature, acidified to pH ~1-2 with HCl (1 N) and the product extracted with a mixture of dichloromethane / methanol (95 : 5). After drying on $MgSO_4$ and evaporation, the crude product was purified by flash chromatography with dichloromethane / methanol (95:5) and then recrystallized from toluene to afford **6a** (0.916 g, 77 %) as white crystals. M. P. 99.4°C (Toluene). ^{1}H NMR ($CDCl_3$): 4.40 (d, *J* = 5.62 Hz, 2 H, CH_2), 5.02 (s, 2 H, CH_2-NO_2), 7.12 (broad s, 1 H, NH). 7.21-7.26 (m, 3 H, aromatic *o*-H and *p*-H), 7.27-7.36 (m, 2 H, aromatic *m*-H). ^{13}C NMR ($CDCl_3$): δ = 44.9 (CH_2), 78.1 (CH_2-NO_2), 129.0 (aromatic CH), 129.1 (2 aromatics CH), 130.1 (2 aromatics CH), 139.4 (*ipso*-C), 163.9 (C=O). HRMS for $C_9H_{10}NO$ ([M – NO_2]$^+$): calcd. 148.0762, found 148.0758.

2-nitro-N-(2-phenylethyl) acetamide (6b)

From 1-(Methylthio)-2-nitro-1-(2-phenylethylamino)ethane **5b** (0.472 g, 2 mmol) and aqueous potassium hydroxide (0.1 N, 30 mL) was obtained **6b** (0.327 g, 79 %) as white crystals. M. P. 102.9 (Toluene). ^{1}H NMR ($CDCl_3$): δ = 2.85 (t, *J* = 6.86 Hz, 2 H, C*H*$_2$-Ph), 3.57 (dd, *J* = 6.86 and 12.79 Hz, 2 H, CH_2-N<), 5.01 (s, 1 H, CH_2-NO_2), 6.66 (broad s, 1 H, NH), 7.16-7.27 (m, 3 H, aromatic *o*-H and *p*-H), 7.28-7.36 (m, 2 H, aromatic *m*-H),. ^{13}C NMR ($CDCl_3$): δ =35.6 (*C*H_2-Ph), 41.7 (CH_2-N<), 78.2 (CH_2-NO_2), 127.2 (aromatic CH), 129.1 (2 aromatics CH), 129.2 (2 aromatics CH), 138.4 (*ipso*-C), 160.5 (C=O). HRMS for $C_{10}H_{12}N_2O_3$ ([M^+]): calcd. 208.0847, found 208.0836.

2-nitro-N-(3-phenylpropyl) acetamide (6c)

From 1-(Methylthio)-2-nitro-1-(3-phenylpropylamino)ethane **5c** (0.75 g, 3 mmol) and aqueous potassium hydroxide (0.1 N, 40 mL) was obtained **6c** (0.638 g, 96%) as white crystals. M. P. x (Toluene). ^{1}H NMR ($CDCl_3$): δ = 1.87 (dd, *J* = 7.49 and 14.82 Hz, 2 H, CH_2), 2.65 (t, *J* = 7.49 Hz, 2 H, C*H*$_2$-Ph), 3.30 (dd, *J* = 6.86 and 12.95 Hz, 2 H, CH_2-N<), 5.06 (s, 1 H, CH_2-NO_2), 6.95 (broad s, 1 H, NH), 7.15-7.22 (m, 3 H, aromatic *o*-H and *p*-H), 7.27-7.30 (m, 2 H, aromatic *m*-H),. ^{13}C NMR ($CDCl_3$): δ = 30.9 (CH_2), 33.4 (*C*H_2-Ph), 40.2 (CH_2-N<), 78.3 (CH_2-NO_2), 126.6 (aromatic CH), 128.7 (2 aromatics CH), 129.0

(2 aromatics CH), 141.4 (*ipso*-C), 161.2 (C=O). HRMS for $C_{11}H_{13}NO$ ($[M\text{-}HNO_2]^+$): calcd. 175.0997, found 175.0985.

2-nitro-N-(4-phenylbutyl) acetamide (6d)

From 1-(Methylthio)-2-nitro-1-(4-phenylbutylamino)ethane **5d** (0.792 g, 3 mmol) and aqueous potassium hydroxide (0.1 N, 40 mL) was obtained **6d** (0.673 g, 95 %) as yellow crystals. M. P. 72.9°C (Toluene). ^{1}H NMR ($CDCl_3$): δ = 1.55 (m, 2 H, CH_2), 1.62 (m, 2 H, CH_2), 2.65 (t, *J* = 7.18 Hz, 2 H, C*H*$_2$-Ph), 3.26 (t, *J* = 6.71 Hz, 2 H, CH_2-N<), 5.04 (s, 1 H, CH_2-NO_2), 7.00 (broad s, 1 H, NH), 7.13-7.20 (m, 3 H, aromatic *o*-H and *p*-H), 7.23-7.30 (m, 2 H, aromatic *m*-H),. - ^{13}C NMR ($CDCl_3$): δ = 28.9 (CH_2), 29.0 (CH_2), 35.8 (*C*H_2-Ph), 40.5 (CH_2-N<), 78.4 (CH_2-NO_2), 126.3 (aromatic CH), 128.8 (4 aromatics CH), 142.3 (*ipso*-C), 161.2 (C=O). HRMS for $C_{12}H_{16}N_2O_3$ ($[M^+]$): calcd. 236.1161, found 236.1175.

(E)-N-benzyl-2-(hydroxyimino)-2-phenylacetamide (8a): Typical Procedure

1-benzylamino-1-methylthio-2-nitroethene **5a** (224 mg, 1 mmol) was dissolved in a mixture of trifluoromethanesulfonic acid (6 mL, 67.5 mmol) and benzene (1 mL, 11.2 mmol) at room temperature (17°C) under nitrogen atmosphere. After disappearance of the starting compound **5a** (8 h), the solution was poured into CH_2Cl_2/MeOH (45 : 5) at -60 to -40°C and let to warm at 0°C then brine (20 mL) and Na_2CO_3 (8.2 g) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography using CH_2Cl_2 / MeOH (99 : 1) to afford **8a** (198 mg, 78%) as white crystals. M. P. 138.7 °C (Dichloromethane/Petroleum ether).^{1}H NMR ($CDCl_3$): δ = 4.52 (d, *J* = 6.08 Hz, 2 H, CH_2), 7.10 (ct, *J* = 6.08 Hz, 1 H, NH), 7.25-7.47 (m, 10 H, aromatic H), 8.39 (broad s, 1 H, O-H).^{13}C NMR ($CDCl_3$): δ = 44.1 (CH_2), 128.1 (aromatic CH), 128.3 (aromatic CH), 128.6 (aromatic CH), 129.2 (aromatic CH), 130.0 (aromatic CH), 138.2 (*ipso*-C), 151.8 (C=O), 163.8 (C=N-OH). HRMS for $C_{15}H_{14}N_2O_2$ ($[M^+]$): calcd. 254.1055, found 254.1046, HRMS for $C_{15}H_{13}N_2O$ ($[M\text{- }OH]^+$): calcd. 237.1028, found 237.1031.

(E)-2-(hydroxyimino)-N-phenethyl-2-phenylacetamide (8b)

From 1-(Methylthio)-2-nitro-1-(2-phenylethylamino) ethane **5b** (238 mg, 1 mmol) was obtained after flash chromatography using (Petroleum ether/ AcOEt 97 : 3) compound **8b (**201.6 mg, 75 %) as white crystals. M. P. 194.8°C (Dichloromethane/ MeOH (9:1)/Petroleum ether).^{1}H NMR ($CDCl_3$): δ = 2.89 (t, *J* = 7.33 Hz, C*H*$_2$-Ph), 3.59 (dd, *J* = 7.33 and 13.57 Hz, CH_2), 7.23 (broad s, 1 H, N-H), 7.25-7.48 (m, 10 H, aromatic H), 11.47 (s, 1 H, OH).^{13}C NMR ($CDCl_3$): δ = 40.8 (CH_2), 45.8 (CH_2), 131.5 (aromatic CH), 132.8 (aromatic CH), 133.7 (aromatic CH), 133.9 (aromatic CH), 134.2 (aromatic CH), 134.7 (aromatic CH), 144.2 (*ipso*-C), 155.5 (C=O), 168.9 (C=N-OH). HRMS for $C_{16}H_{16}N_2O_2$ ($[M^+]$): calcd. 268.1211, found 268.1207. HRMS for $C_{16}H_{15}N_2O$ ($[M\text{- }OH]^+$): calcd. 251.1184, found 251.1184.

(E)-2-(hydroxyimino)-2-phenyl-N-(3-phenylpropyl) acetamide (8c)

From 1-(Methylthio)-2-nitro-1-(3-phenylpropylamino)ethene **5c** (252 mg, 1 mmol) was obtained after flash chromatography using (Petroleum ether/ AcOEt 95 : 5) compound **8c (**182 mg, 65 %) as white crystals. M. P. 122.1°C (Dichloromethane/ MeOH (9 : 1)/Petroleum ether).^{1}H NMR ($CDCl_3$): δ = 1.90 (q, *J* = 7.60 and *J* = 13.57 Hz, 2 H, CH_2), 2.68 (t, *J* = 7.60 Hz, 2 H, C*H*$_2$-Ph), 3.37 (q, *J* = 7.02 and 13.57 Hz, 2 H, C*H*$_2$-N<), 7.10-7.50 (m, 11 H, N-H and aromatic H), 11.43 (s, 1 H, O-H).^{13}C NMR ($CDCl_3$): δ = 31.5 (CH_2), 33.4 (*C*H_2-Ph), 39.3 (CH_2-N<), 126.2 (aromatic CH), 127.9 (aromatic CH), 128.6 (aromatic CH), 128.7 (aromatic CH), 129.3 (aromatic CH), 129.9 (aromatic CH), 141.4 (ipso-C), 150.5 (C=O), 163.8 (C=N-OH). HRMS for $C_{17}H_{18}N_2O_2Na$ ($[M+Na]^+$): calcd. 305.1265, found 305.1255.

(E)-2-(hydroxyimino)-2-phenyl-N-(4-phenylbutyl) acetamide (8d)

From 1-(Methylthio)-2-nitro-1-(4-phenylbutylamino)ethene **5d** (266 mg, 1 mmol) was obtained after flash chromatography using (Petroleum ether/ AcOEt 95:5) compound **8d (**166 mg, 56 %) as white crystals. M. P. 131.9°C (Dichloromethane/Petroleum ether).^{1}H NMR ($CDCl_3$): δ =1.64 (m, 4 H, CH_2), 2.64 (ct, *J* = 7.17 and 7.49 Hz, 2 H, C*H*$_2$-Ph), 3.36 (q, *J* = 6.71 and 13.11 Hz, 2 H, CH_2-N<), 6.78 (ct, *J* = 6.71 Hz, 1 H, NH), 7.15-7.21 (m, 3 H, aromatic *o*-H and *p*-H), 7.25-7.31 (m, 2 H, aromatic *m*-H), 7.38-7.42 (m, 3 H, aromatic *o*-H and *p*-H), 7.42-7.47 (m, 2 H, aromatic *m*-H), 8.30 (broad s, 1 H, OH).^{13}C NMR ($CDCl_3$): δ = 28.6 (CH_2), 29.1 (CH_2), 35.4 (*C*H_2-Ph), 39.5 (CH_2-N<), 125.9 (aromatic CH), 127.9 (aromatic CH), 128.4 (aromatic CH), 128.4 (aromatic CH), 129.5 (aromatic CH), 129.6 (aromatic CH), 142.0 (*ipso*-C), 151.8 (C=O), 163.2 (C=N-OH). HRMS for $C_{18}H_{19}N_2O$ ([M- OH]$^+$): calcd. 279.1497, found 279.1505.

4-benzylamino-4-methylsulfanyl-2-oxy-4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl ester (11a): Typical Procedure

1-benzylamino-1-methylthio-2-nitroethene **5a** (224 mg, 1 mmol) in xylene (1 mL) was mixed with dimethyl acetylene dicarboxylate (0.7 mL, 5.70 mmol). The mixture was exposed to microwave radiation (100 watt) at 120°C for 5 mn. After disappearance of the starting compound **5a** (monitored by TLC using Petroleum ether / AcOEt : 80/20), the crude mixture was directly flash chromatographed with Petroleum ether / AcOEt (95:5) to yield compound **11a** (237 mg, 65%) as viscous oil.^{1}H NMR ($CDCl_3$): δ = 2.19 (s, 3 H, SCH_3), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.56 (s, 2 H, CH_2), 6.70 (s, 1 H, CH=N-), 7.00-7.03 (d, *J* = 6.86 Hz, 2 H, aromatic *o*-H), 7.23-7.32 (m, 3 H, aromatic *p*-H and *m*-H).^{13}C NMR ($CDCl_3$): δ = 20.4 (SCH_3), 49.5 (CH_2), 52.2 (OCH_3), 52.7 (OCH_3), 116.0 (CH), 120.4 (C=C), 126.8 (aromatic CH), 127.1 (*C*-SMe), 127.9 (aromatic CH), 128.0 (aromatic CH), 131.1 (*ipso*-C), 137.6 (=C-O), 162.0 (C=O), 164.8 (C=O). HRMS for $C_{16}H_{17}NO_4S$ ([M-HNO_2]$^+$): calcd. 319.0878, found 319.0899.

4-methylsulfanyl-2-oxy-4-phenethylamino-4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl ester (11b)

From 1-(Methylthio)-2-nitro-1-(2-phenylethylamino)ethane **5b** (238 mg, 1 mmol) was obtained compound **11b** (266 mg, 70 %) as a viscous oil.^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 3 H, SCH_3), 2.97(t, *J* = 7.77 Hz, 2 H, C*H*$_2$-Ph), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.48 (t, *J* = 7.77 Hz, 2 H, CH_2-N<), 6.58 (s, 1 H, CH=N-), 7.15-7.19 (m, 2 H, aromatic *o*-H), 7.21-7.31 (m, 3 H, aromatic *p*-H and *m*-H).^{13}C NMR ($CDCl_3$): δ = 20.1 (SCH_3), 38.1 (CH_2), 48.0 (CH_2), 52.2 (OCH_3), 52.6 (OCH_3), 115.1 (CH), 120.7 (C=C), 125.9 (*C*-SMe), 127.1 (aromatic CH), 129.0(aromaticC), 129.4 (aromatic CH), 130.9 (*ipso*-C), 138.1 (=C-O), 162.0 (C=O), 165.1 (C=O). HRMS for $C_{17}H_{19}NO_4S$ ([M-HNO_2]$^+$): calcd. 333.1035, found 333.1043.

4-methylsulfanyl-2-oxy-4-(3-phenylpropylamino)-4H-[1,2] oxazine-5, 6-dicarboxylic acid dimethyl ester (11c)

From 1-(Methylthio)-2-nitro-1-(3-phenylpropylamino)ethane **5c** (252 mg, 1 mmol) was obtained compound **11c** (301 mg, 77 %) as a viscous oil.^{1}H NMR ($CDCl_3$): δ = 2.03 (q, *J* = 7.77 and 15.64 Hz, 2 H, CH_2), 2.33 (s, 3 H, SCH_3), 2.65 (t, *J* = 7.77 Hz, 2 H, C*H*$_2$-Ph), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.27 (ct, *Japp* = 7.77 Hz, 2 H, CH_2-N<), 6.56 (s, 1 H, CH=N-), 7.16-7.21 (m, 3 H, aromatic *o*-H and *p*-H), 7.26-7.31 (m, 2 H, aromatic *m*-H).^{13}C NMR ($CDCl_3$): δ = 20.0 (SCH_3), 33.1 (CH_2), 33.3 (CH_2), 46.3 (CH_2), 52.1 (OCH_3), 52.6 (OCH_3), 114.9 (CH), 120.5 (C=C), 126.3 (*C*-SMe), 126.5 (aromatic CH), 128.7 (aromaticCH), 128.8 (aromatic CH), 130.6 (*ipso*-C), 141.2 (=C-O), 162.0 (C=O), 165.0 (C=O). HRMS for $C_{18}H_{21}NO_4S$ ([M-HNO_2]$^+$): calcd. 347.1191, found 347.1183.

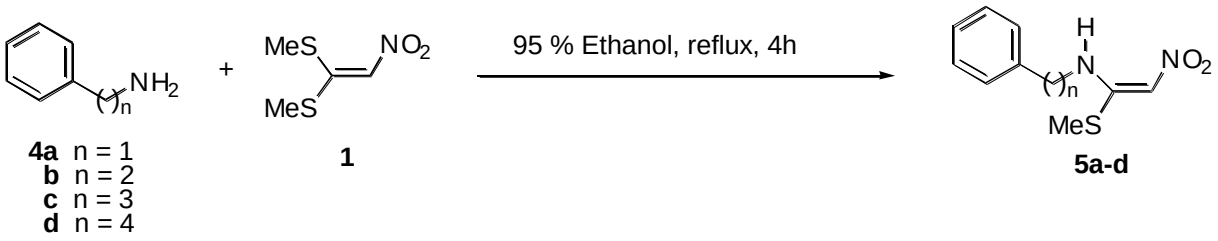
4-methylsulfanyl-2-oxy-4-(4-phenylbutylamino)-4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl ester (11d)

From 1-(Methylthio)-2-nitro-1-(4-phenylbutylamino)ethene **5d** (266 mg, 1 mmol) was obtained compound **11d** (320 mg, 79 %) as a viscous oil.^{1}H NMR ($CDCl_3$): δ = 2.03 (m, 4 H, -CH_2-CH_2-), 2.33 (s, 3 H, SCH_3), 2.62 (t, *J* = 7.02 Hz, 2 H, C*H*$_2$-Ph), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.27 (ct, *J* = 7.02 and 7.64 Hz, 2 H, CH_2-N<), 6.56 (s, 1 H, CH=N-), 7.14-7.19 (m, 3 H, aromatic *o*-H and *p*-H), 7.24-7.29 (m, 2 H, aromatic *m*-H).^{13}C NMR ($CDCl_3$): δ = 20.1 (SCH_3), 28.6 (CH_2), 31.3 (CH_2), 35.7 (CH_2), 46.4 (CH_2), 52.1 (OCH_3), 52.6 (OCH_3), 114.9 (CH), 120.4 (C=C), 126.2 (*C*-SMe), 126.2 (aromatic CH), 128.7 (aromaticCH), 128.8 (aromatic CH), 130.7 (*ipso*-C), 142.2 (=C-O), 162.1 (C=O), 165.0 (C=O). HRMS for $C_{19}H_{23}NO_4S$ ([M-HNO_2]$^+$): calcd. 361.1348, found 361.1353.

RESULTS AND DISCUSSION

Starting material

Starting compounds **5a-d** were prepared from 1.1 mol-equiv. of the corresponding phenylalkylamine **4a-d** with 1,1-bis (methylthio)-2-nitroethene **1** in refluxing 95% ethanol[14] (Scheme 1) in yields varying from 75 to 78 % (Table 1). In all cases, the di-substituted products were formed in a small range.



4a n = 1
b n = 2
c n = 3
d n = 4

1

5a-d

Scheme 1: **Synthesis of 1-phenylalkylamino-1-methylthio-2-nitroethenes derivatives 5a-d**

Table 1: Yields of starting compounds 5a-d

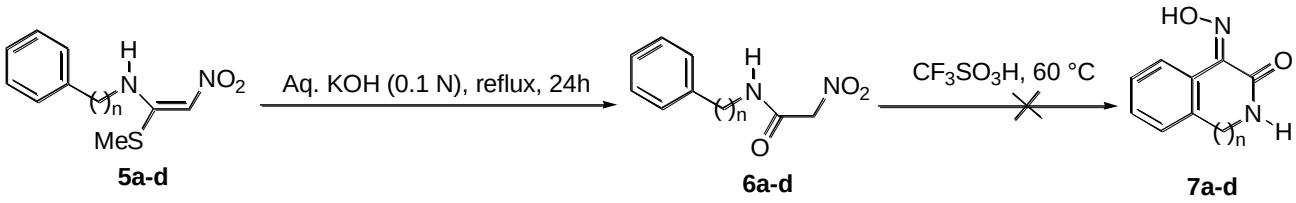
Starting amine	**4a**	**4b**	**4c**	**4d**
Product	**5a**	**5b**	**5c**	**5d**
Yield (%)	75	78	75	75

The products **5** were purified by flash chromatography with dichloromethane, followed by recristallization in appropriate solvents. Their NMR spectra were characterized by: (i) the presence of signals assigned to MeS protons at δ = 2.35-2.41 ppm, vinylic protons at δ = 6.47-6.58 ppm, aromatic protons at δ = 7.14-7.38 ppm and (-NH) protons at δ = 10.32-10.76 ppm in the ^{1}H NMR, (ii) the presence of signals assigned to (=CH-NO_2) at δ = 106.5-107.1 ppm, aromatic carbons at δ = 126.4-142.0 ppm and (-NH-C=) at δ = 165.1-165.6 ppm in the ^{13}C NMR.

In organic solvent, compounds **5a-d** exist as a sole isomer as shown by a single set of signals in the ^{13}C NMR spectra. They are probably all (*E*)-isomers because this conformation allows formation of intramolecular hydrogen bond between the N-H and the –NO_2 groups, as previously reported for the 1-arylamino-1-methylthio-2-nitroethenes **2**[10].

Alkaline hydrolysis reactions

The reactions of 1-phenylalkylamino-1-methylthio-2-nitroethenes **5a-d** in refluxing aqueous potassium hydroxide (0.1 N) under nitrogen atmosphere[10] afforded the corresponding 2-nitro-N-phenylalkylacetamides **6a-d** (Scheme 2). The yields varying from 77 to 96%, globally increased with the length of alkyl chain (Table 2).



Scheme 2: Synthesis of 2-nitro-N-phenylalkylacetamides derivatives 6a-d

Table 2:

Starting substrate	Products (Yield %)		
5a	**6a** (77)	**8a** (78)	**11a** (65)
5b	**6b** (78)	**8b** (75)	**11b** (70)
5c	**6c** (96)	**8c** (65)	**11c** (77)
5d	**6d** (95)	**8d** (56)	**11d** (79)

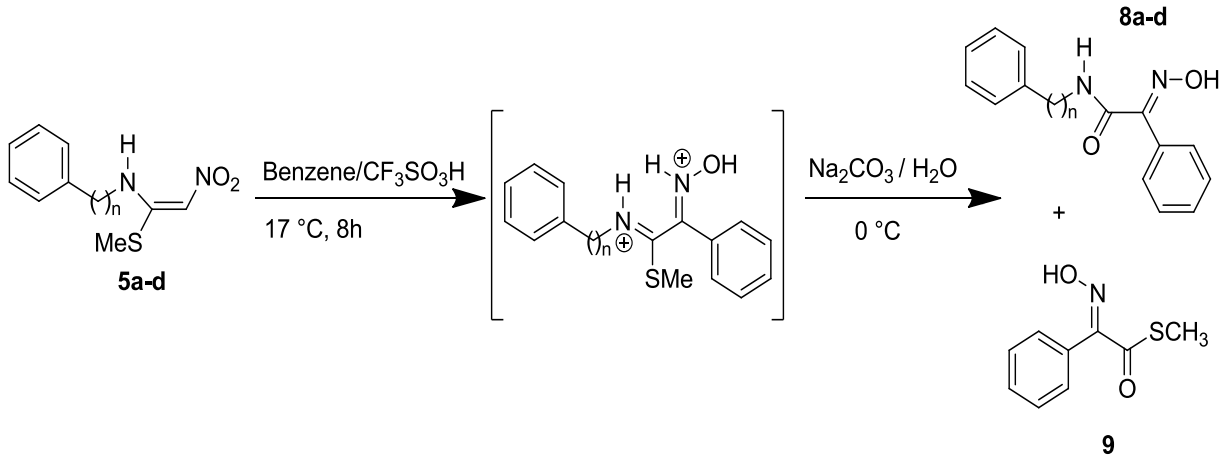
Compounds **6a-d** were purified by flash chromatography using dichloromethane/ethyl acetate (10:1), followed by recrystallization in appropriate solvents.

Their NMR spectra were characterized by the absence of signals corresponding to MeS, vinylic protons and (-NH-C=) carbons and (i) the presence of signals assigned to ($-CH_2-NO_2$) protons at δ = 5.01-5.06 ppm, (-NH) protons at δ = 6.66-7.12 ppm and aromatic protons at δ = 7.13-7.36 ppm in the ^{1}H NMR, (ii) the presence of signals assigned to ($-CH_2-NO_2$) at δ = 78.1-78.4 ppm, aromatic carbons at δ = 126.3-142.3 ppm and (C=O) at δ = 160.5-163.9 ppm in the ^{13}C NMR.

The reactions of **6a-d** in trifluoromethanesulfonic acid, carried out at 0 °C and then 60°C under nitrogen atmosphere, did not afford the expected bicyclic oxime derivatives **7a-d** (Scheme 2).

Trapping of hydroxynitrillium Ions

Nitroethene derivatives have been shown to give stable hydroxynitrillium ions in trifluoromethanesulfonic acid (TFSA) at low temperature.[14] When **5a-d** are dissolved with benzene in TFSA, *in situ* trapping occurred to afford products **8a-d** (Scheme 3) isolated after quenching on the solution CH_2Cl_2/MeOH (45 : 5) at -60 to -40 °C, then brine (20 mL) and Na_2CO_3 at 0° C followed by flash chromatography with CH_2Cl_2 / MeOH (99: 1). The obtained yields, varying from 78 to 56 %, decreased with the length of alkyl chain (Table 2). In these experimental conditions, only **5a** gave by-product **9**[15] with 23%, indicating that the iminium bond is less prone to hydrolysis than the C-SMe bond. Only intermolecular electrophilic aromatic substitution was observed probably because of the rigidity of formed hydroxynitrilium ions preventing cyclization. This could be explained also by the excessively high activation energy of the reaction at this temperature.



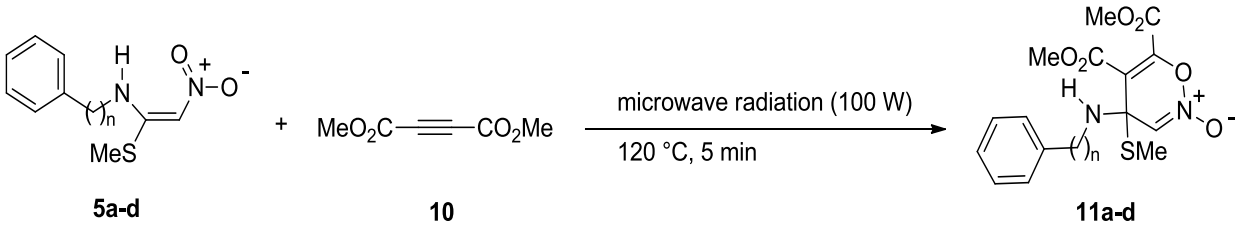
Scheme 3: Synthesis of 2-(hydroxyimino)-2-phenyl-N-(phenylalkyl) acetamides derivatives 8a-d

Compounds **8a-d** were characterized by NMR and HRMS methods. Their NMR spectra were characterized by the absence of signals corresponding to MeS, vinylic protons and (-NH-C=) carbons and (i) the presence of signals assigned to (-NH) protons at δ = 6.78-7.23 ppm, ten aromatic protons at δ = 7.10-7.50 ppm and HO protons at δ = 8.30-11.47 ppm in the ^{1}H NMR, (ii) the presence of signals assigned to (>C=O) at δ = 151.5-151.8 ppm and (>C=N-OH) at δ = 163.2-163.9 ppm in the ^{13}C NMR.

Diels Alder cycloaddition reaction

Diels Alder Cycloaddition[16] is an important method for the preparation of six link cyclic compounds from reaction of a conjugated diene with alkenes or alkynes. The reaction generally occurs in presence of Lewis Acid at room temperature[17], at high temperature[16] or under microwave radiation.[18]

Nitroethene derivatives present in their structure conjugated diene which may allow Diels Alder Cycloaddition. Thus the reactions mixtures of compounds **5a-d** in xylene with dimethyl acetylene-dicarboxylate **10** were exposed to microwave radiation (100 watt) at 120°C for 5 mn. The reaction mixture was directly flash chromatographied using Petroleum ether/AcOEt (95 : 5) to afford the corresponding 4-methylsulfanyl-2-oxy-4-phenylalkylamino 4H-[1, 2] oxazine-5, 6-dicarboxylic acid dimethyl esters **11a-d** (Scheme 4). The yields varying from 65 to 79 %, increased with the length of alkyl chain (Table 2).



Scheme 4: Synthesis of oxazine derivatives 11a-d

Compounds **11a-d** were characterized by NMR and HRMS methods. Their NMR spectra were characterized by (i) the presence of signals assigned to MeS at δ = 2.19-2.33 ppm, MeO protons at δ = 3.75-3.84 ppm, (CH = N<) protons at δ = 6.56-6.70 ppm as a singlet, (-NH) protons at δ = 6.78-7.23 ppm and five aromatic protons at δ = 7.00-7.32 ppm in the ^{1}H NMR, (ii) the presence of signals assigned to (>*C*=C-O) at δ = 120.4-120.7 ppm, (>*C*-SMe) at δ = 125.9-127.1 ppm, (=C-O) at δ = 137.6-142.2 ppm, and two (CO_2) at δ = 162.0-162.1 and 164.8-165.1 ppm in the ^{13}C NMR.

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