Methyltrioxorhenium Catalyzed Synthesis of Dinitrones from Primary Diamines and Non-Enolizable Aldehydes

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Abstract: Green Chemistry is the design of chemicals and processes that reduce or eliminate the use and generation of hazardous substances, and consequently reduce the risk to human health and the environment. Nitrones have various applications, such as building blocks in the synthesis of natural and biologically active compounds and molecular weight regulators in radical polymerization. In this work, dinitrones were successfully synthesized in a one-pot process from primary diamines and proper aromatic aldehydes employing methyltrioxorhenium (MTO) as catalyst and urea-hydrogen peroxide adduct (UHP) as oxidizing agent. Diamines, such as 1,6-diaminohexane and 1,12-diaminododecane were reacted with benzaldehydes bearing various substituent, such as 4-chloro, 4-nitro, 4-methoxybenzaldehyde, and also furfural. The resulting *N,N'-bis* (benzylidene)-1,6-hexanediamine *N,N'*-dioxides or *N,N'-bis* (benzylidene)-1,12-dodecanediamine *N,N'*-dioxides (or substituted benzylidenes) were separated with 45-60 % yields. The main advantage of the one-pot process is the elimination of need for several separation and purification steps and reduction in consumption of chemicals and waste production. The products selectively were characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR spectroscopies, and elemental analysis (CHNS).

Keywords: Dinitrones, green chemistry, methyltrioxorhenium (MTO), one-pot reaction, urea-hydrogen peroxide (UHP).

INTRODUCTION

During the last few decades, many scientists in different fields have drawn special attention to the nitrones, due to their successful application as building blocks in the synthesis of various natural and biologically active compounds, stable nitroxyl radicals, and other important products [1]. Among those products some are designed for special purposes such as spin traps [2, 3] for the study of radical processes including those that take place in biological systems, sensors and probes for monitoring acid-base, redox, and free radical processes [4], or some used as modifiers and regulators of molecular weight in radical polymerization [5]. The 1,3-dipolar cycloaddition reaction with other proper compounds, is one of the most popular reactions of nitrones, leading to a very versatile range of products [6]. Nitrones have been synthesized using different methods, such as oxidative routes including oxidation of imines, amines, and hydroxylamines [7], or non oxidative methods, including condensation of substituted hydroxyl amines with carbonyls [8], use of oximes [9], nitro [10], and nitroso compounds [11]. For oxidation of imines, reagents such as metachloroperbenzoic acid [12] or potassium peroxymono sulfate [13]. have been used as oxidants. Recently, hydrogen peroxide has been used for the oxidation of chiral imines to access a new series of calix[4]arene derivatives with one or two nitrone groups on the upper rim. The imine intermediates used for this reaction, were prepared *via* amination of the diformyl derivatives of the calix[4]arenes [14].

In another work, aldimines have been photochemically oxidized to nitrones, over TiO_2 particles suspended in acetonitrile in the presence of oxygen [15]. The wavelength of light used in this photooxidation has been 350 nm.

There are few reports that imines have been reduced to secondary amines and afterwards the resulting secondary amines were oxidized to nitrones [16]. The oxidation of secondary amines to nitrones with excellent yields, also has been conducted using methyltrioxorhenium (MTO) - hydrogen peroxide system [17], or polymer supported MTO-H_2O_2 system [18]. The combination of MTO with oxygen has been proved as another technique for oxidation of secondary amines to nitrones [19]. The oxidation of hydroxylamines containing at least one proton on the α- carbon atom, to nitrones has been carried out by different oxidants, such as air, metachloroperbenzoic acid, hydrogen peroxide, and metal oxides (such as PbO_2, MnO_2, HgO) [20]. Among the non-oxidative methods, condensation of the N-benzyl hydroxyl amines with different aldehydes and ketones in the presence of anhydrous magnesium sulfate have resulted in the successful synthesis of the N-benzylnitrones containing chiral and achiral sugars [21]. The same method has been used for preparation of chiral dinitrones by condensation of a C2-symmetrical chiral dihydroxylamine with different aldehydes. The electronic and steric properties of the dinitrones can be modified by changing the aldehyde component [22]. The activity of dinitrones as Lewis base catalysts was examined for the asymmetric allylation of aldehydes with allyltrichlorosilanes. Dinitrones has been also synthesized *via* condensation of N-benzylhydroxylamine with adequate reactants, such as glutaraldehyde. Their intramolecular pinacol coupling reaction induced with Samarium diiodide (SmI_2)

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was carried out, resulting in the formation of cyclic vicinal diamines with good cis-selectivity [23].

N-alkylation of oximes offers a facile non-oxidative method for the preparation of nitrones [9, 24]. Intramolecular cyclization of hydroxylaminoalkynes, depending on the relative position of the hydroxylamino group and acetylenic part results in the formation of the corresponding 5-, to 7-membered cyclic nitrones [25].

More recently, a great tendency has been observed in finding green and sustainable processes, to prevent consumption of large amounts of chemicals as well as production of large volumes of the chemical wastes [26]. A green method for the synthesis of nitrones has been reported in the literature [27]. In this method, under the solvent-free conditions in a ball-mill apparatus, an equimolar mixture of an aldehyde, N-substituted-hydroxylamine hydrochloride, and $NaHCO_3$ were ball-milled for 0.5-2 h to obtain the corresponding nitrones. Using this method, C-aryl and C-alkyl-nitrones were synthesized without any need for excluding air and moisture. The yields of the expected products were so high that there was no need for purification of the products, for example, nitrones such as N-(2-iodobenzylidene) methylamine N-oxide, N-benzylidene-tert-butylamine N-oxide, N-(pyridine-4-ylmethylidene) benzylamine N-oxide, and N-(napht-2-ylmethylidene) benzylamine N-oxide have been obtained almost quantitatively.

In this work, we report a facile one-pot method for the synthesis of the dinitrones. The main advantage of the presented method is that it is one-pot, which avoids several separation and workup steps, and the use of large amounts of solvents. Hence, it is a green method. Using this simple method, several dinitrones were prepared *via* catalytic oxidation of diimines, which have been formed *in situ* by the reaction of primary diamines with different aromatic aldehydes (Scheme **1**). The products were characterized using different spectroscopic methods such as nuclear magnetic resonance (^{1}H-NMR, and ^{13}C-NMR), Fourier Transform Infrared (FT-IR) spectroscopies and elemental analysis (CHNS).

MATERIALS AND METHODS

Methyltrioxorhenium (MTO, containing 71 wt % rhenium), urea-hydrogen peroxide adduct (UHP, 97 %), and 1,12-diaminododecane (97 %) were purchased from Aldrich Chemical Co, and used without any further purification. 1,6-Diaminohexane (99 %, Merck) was sublimated in vacuum at 45 °C. Benzaldehyde (99 %, Merck), 4-methoxybenzaldehyde (98 %, Merck), and furan-2-carboxaldehyde (98 %, Aldrich) were distillated in vacuum shortly before use. 4-Chlorobenzaldehyde (98 %, Merck) and 4-nitrobenzaldehyde (98 %, Merck) were sublimated in vacuum at temperatures slightly higher than their melting temperature (respectively, at 55 °C and 110 °C) [28].

Methanol used as solvent was refluxed over -and distillated over calcium sulfate, and freshly used for the reaction. Ethyl acetate was of high purity grade and distillated before use. High purity grade dichloromethane was refluxed over calcium chloride for 6 h, and then distillated. Petroleum ether was fractionally distillated and the light fraction boiling at 40-60 °C was separated and used as solvent in this work. The melting points of products were measured using a Stuart melting point apparatus from Barloworld Scientific Ltd, UK (SMP3 model).

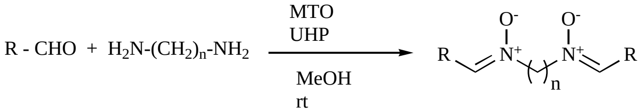
Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) spectra of the compounds were recorded in $CDCl_3$ at 25 °C on a Brucker Avance 400 MHz spectrometer. Chemical shifts were reported in ppm using tetramethylsilane (TMS) as internal standard. Coupling constants were reported in hertz (Hz). Fourier Transform Infrared (FT-IR) spectra of the compounds were recorded as a thin film on KBr disk using a Brucker Tensor 27 spectrometer. The required amounts of the chemicals were weighed to 0.1 mg precision by a balance from AND, Japan, model HR-200. The elemental analysis measurements were carried out using a Vario EL analyzer, from Elementar Analysensysteme GmbH, Germany.

General Procedure for the Preparation of Dinitrones

5 mL methanol, 750 mg of Na_2SO_4, and 1 mmol of desired diamine were weighed into a 10 mL round bottom flask equipped with a magnetic stirrer bar. The content of reaction flask was then stirred on a magnetic stirrer for few minutes. Afterwards, 2.05 mmol of required aldehyde was added to the reaction mixture. Stirring was continued until completion of the reaction, which was monitored by almost complete disappearance of the aldehyde on the TLC plate. The reaction mixture was then cooled to 0 °C and stirred for few minutes. Subsequently, 0.04 mmol (10 mg) of MTO catalyst (2 mol % relative to aldehyde; 4 mol % relative to the diamine) and 566 mg (3 equivalents) of UHP as oxidizing agent were added to the stirred reaction mixture. The reaction was continued for the times mentioned in Table **1**. The reaction mixture was filtered to remove the sodium sulfate, and the filtrate was washed with a few milliliters of methanol. The solvent (methanol) was then removed under reduced pressure. CH_2Cl_2 was added to the resulting residue, and stirred for 5 minutes. The un-dissolved urea was filtered off. Removal of the solvent leaves the crude product which was purified on silica gel TLC plates. The yields of the products, which in most of the cases were white to pale yellow solids, are given in Table **1**.

RESULTS AND DISCUSSION

The results concerning the experiments of the one-pot synthesis of dinitrones from primary diamines and aromatic aldehydes *via* condensation-oxidation reaction using methyltrioxorhenium (MTO) as catalyst (Scheme **1**), are given in the Table **1**.



R = $C_6H_5^-$, *p*-NO_2-C_6H_4-, *p*-Cl-$C_6H_4^-$, *p*-MeO-C_6H_4- or 2-furyl-

n = 6 or 12

Scheme 1.

The experiments carried out here, are very simple, straightforward, and without any need for the special cares, such as removal of oxygen from the reaction medium. The reactants have been mixed at room temperature in a few milliliters of methanol as solvent, which has been known as one of the benign and environmentally friendly solvents. The oxidant used in this study was solid urea hydrogen peroxide (UHP), which nevertheless has a relatively high content of hydrogen peroxide (36.2 %). It is a very safe and stable oxidizing agent compared to the anhydrous hydrogen peroxide [29], and can be stored at room temperature without any decrease in its oxygen content, even for a period of twelve months. The reaction was catalyzed by 2 mol % of MTO relative to aldehyde functional group. To facilitate the reaction between aldehyde and amine, anhydrous sodium sulfate has been added to the reaction medium to absorb the water released during imine formation.

The aldehydes used in this work has been aromatic aldehydes bearing different substitutes on the aromatic ring, together with 1,6–diaminohexane and 1,12–diaminododecane. The experiment carried out using hexanal, an aliphatic aldehyde, which produced a final crude product composed of many by-products that, their separation was practically very difficult. A slight excess of aldehyde was added to the reaction medium to ensure the reaction of both amine groups on each diamine molecule with the aldehyde, and consequently, formation of the nitrone at both ends of the diamine molecule.

The addition of MTO in the reaction medium leads to an instantaneous color change to yellow. This was attributed to the formation of the catalytically active peroxorhenium species [30]. The reaction was checked by TLC until almost complete disappearance of aldehyde. The times required for completion of reaction in each case are given in Table **1**.

In most cases, dinitrones produced by simple mixing of the reactants (one-pot reaction) were obtained with relatively high yields. The one-pot reaction was compared with the two steps reaction, namely, synthesis and separation of the diimine in the first step, and its subsequent oxidation to dinitrone in the second step. Result indicated that, the yield of the two steps reaction is slightly higher than that of one-pot reaction (entry 3, Table **1**). This implies that the presented one-pot reaction offers a very useful method for the synthesis of dinitrones, and in price of only a slight decline in the yield, one can decrease the amount of solvents used for the reaction by almost 50 %. On the other hand, this observation proves that the reaction occurs through the formation of imine by condensation of amine with aldehyde [31]. In the first step, the oxidation of amine to *N*-hydroxylamine, with UHP, is another path mentioned in the literature for the formation of nitrones in one-pot reaction [32]. Then, the subsequent condensation of the *N*-hydroxylamine formed with the aldehyde leads to the formation of the final product, the dinitrone [33]. Here, as the oxidant and the catalyst were added after complete formation of the diimine, it can be concluded that the imine formation pathway has been the main route for the formation of the products.

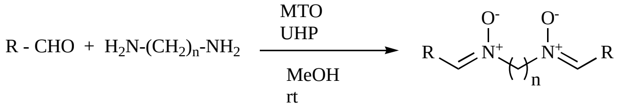
After completion of the reaction, sodium sulfate was filtered off and washed with 2 mL of methanol. The solvent was then removed from the resulting filtrate at reduced pressure using a rotary evaporator. The residue containing the product as well as the urea released from the UHP during the reaction was obtained. It was taken up into 5 mL of dry dichloromethane, and the undissolved urea was filtered off. The spectral characteristics observed for the products are consistent with results from the literature for similar compounds [23, 31]. The spectral data and characterization of each product are given.

Selected Characterization Data of the Products

N,N'-bis benzylidene-1,6-hexanediamine N,N'-dioxide (1a)

Yield: 55 %; m.p. 157-159 °C; FT-IR (film CH_2Cl_2, cm^{-1}): 3065, 2924, 2857, 1633, 1454, 1155, 754, 692; ^1H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.21 (m, 4 H), 7.33–7.44

Table 1. MTO Catalyzed Synthesis of Dinitrones from Non-Enolizable Aldehydes and Diamines



Entry	dinitrone	n	R	Reaction time (h)	Yield (%)
1	**1a**	6	C_6H_5-	12	55
2	**2b**	12	C_6H_5-	16	49
3	**1a**	6	C_6H_5-	-	58(a)
4	**2a**	6	*p*-NO_2-C_6H_4-	10	50
5	**2b**	12	*p*-NO_2-C_6H_4-	13	45
6	**3a**	6	*p*-Cl-C_6H_4-	11	44
7	**3b**	12	*p*-Cl-C_6H_4-	15	52
8	**4a**	6	2-Furyl	12	45
9	**4b**	12	2-Furyl	14	42
10	**5a**	6	*p*-MeO-C_6H_4-	10	60
11	**5b**	12	*p*-MeO-C_6H_4-	12	56

[a] The reaction was done in two steps.

(m, 8 H), 3.93 (t, ^{3}J=7.0 Hz, 4 H, CH_2), 2.01 (m, 4 H, CH_2), 1.32 (m, 4 H, CH_2); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 136.3, 131.1, 128.3, 127.5, 67.9, 28.4, 27.8, 26.5; Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C 74.05; H 7.45; N 8.63. Found: C 73.88; H 7.71; N 8.71; R_f = 0.25 (ethyl acetate 2: methanol 1).

N,N'-bis benzylidene-1,12-dodecanediamine N,N'-dioxide (1b)

Yield: 49 %; m.p. 156-158 °C; FT-IR (film CH_2Cl_2, cm^{-1}): 3055, 2935, 2875, 1625, 1460, 1189, 1100, 915, 754, 692; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.23 (m, 4 H), 7.24–7.44 (m, 8 H), 3.86 (t, ^{3}J=7.0 Hz, 4 H, CH_2), 1.99 (t, ^{3}J=7.0 Hz, 4 H, CH_2), 1.33 (m, 16 H, CH_2); R_f = 0.33 (ethyl acetate 2: methanol 1).

N,N'-bis (4-nitrobenzylidene)-1,6-hexanediamine N,N'-dioxide (2a)

Yield: 50 %; m.p. decomposed at about 130 °C; FT-IR (film, CH_2Cl_2, cm^{-1}): 3050, 2984, 2945, 1635, 1584, 1494, 1456, 1345, 1210, 1160, 1090, 810; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.24 (m, 4 H), 7.63–7.78 (m, 4 H), 7.26 (m, 2 H), 3.65 (t, 4 H, CH_2), 1.57 (m, 4 H, CH_2), 1.26 (m, 4 H, CH_2). ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 132.2, 130.3, 128.7, 127.9, 66.4, 28.4, 26.8, 25.5; Anal. Calcd. for $C_{20}H_{22}O_6N_4$: C 57.97; H 5.35; N 13.52. Found: C 57.81; H 5.88; N 13.41; R_f = 0.26 (ethyl acetate 2: methanol 1).

N,N'-bis (4-nitrobenzylidene)-1,12-dodecanediamine N,N'-dioxide (2b)

Yield: 45 %; m.p. decomposed at about 130 °C; FT-IR (film CH_2Cl_2, cm^{-1}): 3051, 2990, 2948, 1640, 1591, 1492, 1450, 1347, 1204, 1155, 1090, 820; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.22 (m, 4 H), 7.25–7.42 (m, 6 H), 3.91 (t, 4 H, CH_2), 1.97 (m, 4 H, CH_2), 1.31 (m, 16 H, CH_2); R_f = 0.22 (ethyl acetate 2: methanol 1).

N,N'-bis (4-chlorobenzylidene)-1,6-hexanediamine N,N'-dioxide (3a)

Yield: 44 %; FT-IR (film CH_2Cl_2, cm^{-1}): 3043, 2989, 2950, 1640, 1585, 1497, 1430, 1210, 1100, 1065, 835; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.19 (m, 4 H), 7.22–7.47 (m, 6 H), 3.91 (t, ^{3}J=7.1 Hz, 4 H, CH_2), 1.98 (t, ^{3}J=7.0 Hz, 4 H, CH_2), 1.28 (m, 4 H, CH_2); R_f = 0.23 (ethyl acetate 2: methanol 1).

N,N'-bis (4-chlorobenzylidene)-1,12-dodecanediamine N,N'-dioxide (3b)

Yield: 52 %; FT-IR (film CH_2Cl_2, cm^{-1}): 3050, 2995, 2940, 1635, 1592, 1487, 1428, 1211, 1095, 1045, 831; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.21 (m, 4 H), 7.23–7.49 (m, 6 H), 3.88 (t, ^{3}J=7.1 Hz, 4 H, CH_2), 1.96 (m, 4 H, CH_2), 1.25 (m, 16 H, CH_2); Anal. Calcd. for $C_{26}H_{34}O_2N_2Cl_2$: C, 65.40; H 7.17; N 5.86. Found: C 65.01; H 7.08; N 5.78; R_f = 0.26 (ethyl acetate 2: methanol 1).

N,N'-bis (furan-2-ylmethylene)-1,6-hexanediamine N,N'-dioxide (4a)

Yield: 45 %; m.p. 146-148 °C; FT-IR (film CH_2Cl_2, cm^{-1}): 3055, 2930, 2849, 1615, 1607, 1587, 1471, 1270, 1160, 1100, 1010, 935, 830; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.16 (m, 2 H), 7.28–7.41 (m, 6 H), 3.98 (t, 4 H, CH_2), 1.99 (m, 4 H, CH_2), 1.34 (m, 4 H, CH_2); R_f = 0.25 (ethyl acetate 2: methanol 1).

N,N'-bis (furan-2-ylmethylene)-1,12-dodecanediamine N,N'-dioxide (4b)

Yield: 42 %; m.p. 149-151 °C; FT-IR (film CH_2Cl_2, cm^{-1}): 3055, 2919, 2851, 1625, 1610, 1587, 1473, 1274, 1159, 1092, 1013, 938, 836; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.18 (m, 2 H), 7.29–7.45 (m, 6 H), 3.96 (t, 4 H, CH_2), 1.93 (m, 4 H, CH_2), 1.29 (m, 16 H, CH_2); R_f = 0.3 (ethyl acetate 2: methanol 1).

N,N'-bis (4-methoxybenzylidene)-1,6-hexanediamine N,N'-dioxide (5a)

Yield: 60 %; FT-IR (film CH_2Cl_2, cm^{-1}): 3057, 2937, 2865, 1641, 1595, 1475, 1275, 1165, 1100, 948, 628; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.2 (m, 4 H), 7.17–7.44 (m, 4 H), 6.95 (m, 2 H), 3.8-3.96 (m, 4 H, CH_2), 3.81 (s, 6 H), 1.89 (m, 4 H, CH_2), 1.33 (m, 4 H, CH_2); R_f = 0.3 (ethyl acetate 2: methanol 1).

N,N'-bis (4-methoxybenzylidene)-1,12-dodecanediamine N,N'-dioxide (5b)

Yield: 56 %; FT-IR (film CH_2Cl_2, cm^{-1}): 3055, 2927, 2857, 1639, 1587, 1480, 1279, 1159, 1091, 1010, 951, 833; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.2 (m, 4 H), 7.17–7.44 (m, 4 H), 6.95 (m, 2 H), 3.8-3.96 (m, 4 H, CH_2), 3.81 (s, 6 H), 1.89 (m, 4 H, CH_2), 1.33 (m, 4 H, CH_2); R_f = 0.37 (ethyl acetate 2: methanol 1).

CONCLUSIONS

The condensation-oxidation of the aromatic aldehydes with primary diamines was performed successfully using the UHP system as an oxidant, and MTO as a catalyst. This one-pot synthesis produced the corresponding dinitrones in relatively high yields. The method has been proved to be an efficient and useful way to obtain dinitrones. As the reactions were performed in one step, the consumption of large amounts of solvents and chemicals, and the production of large amounts of chemical waste were avoided. Hence, this method is considered as a green method. It was concluded that the reaction proceeded through *in situ* imine formation and its subsequent oxidation to the dinitrones. Dinitrones such as *N,N'-bis* (benzylidene)-1,6-hexanediamine *N,N'*-dioxides or *N,N'-bis* (benzylidene)-1,12-dodecane-diamine *N,N'*-dioxides (or substituted benzylidenes) were prepared with yields of 45-60 %. The structure of the products was confirmed by spectroscopic methods such as ^{1}H-NMR, ^{13}C-NMR, FT-IR spectroscopy and, also elemental analysis (CHNS).

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