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作品名稱 **Reactions of Bis(oxy)enamines with
O-Nucleophiles in the Presence of Metal
Salts**

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Reactions of Bis(oxy)enamines with O-Nucleophiles in the Presence of Metal Salts

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Abstract

NO donors are an emerging class of pharmaceutical compounds, with many important functions in the cardiovascular, nervous and immune systems. With great therapeutic potential, the development of new NO donor compounds would be of great medicinal value, potentially opening a whole class of drugs to be used to treat various ailments.

This project studies a specific class of compounds, substituted cyclic oxime ethers, which have proven to be useful intermediates in fields such as medicine and biochemistry. The cyclic structure along with a determinable substitutable group at the C₃ position is highly valuable, as it allows the oxime ether to act as a convenient precursor for a variety of useful products, playing key components in many drugs. And with a substituted nitrate group, which is an O-nucleophile, the oxime ether has the potential to become an NO-donor, and hence become a possible intermediate in a wide array of NO donor drugs.

Co(NO)₃ was used in the synthesis of the cyclic oxime ether, directly from a phenyl substituted bis(oxy)enamine intermediate, producing an entirely new compound: α -hydroxyoxime nitrates, the oxime ether being substituted with a nitrate group. This new reaction of the synthesis of α -hydroxyoxime nitrates was further studied for optimization purposes, in order to open a new class of NO donor precursors. In addition, other nucleophiles were also explored in this class of reactions, forming important bonds such as C-N and C-S bonds, with key structures for other types of synthesis intermediates and precursors. Different metal nitrates, or various other nucleophiles in place of the nitrates, were used in reaction with bis(oxy)enamine, and the yield and structure of the final products were determined by NMR spectra.

Successful optimization of the synthesis of α -hydroxyoxime nitrates has been achieved, where the conditions for optimum synthesis involve using Cr(NO₃)₃•9H₂O which achieved a high yield of 76%, dissolved in THF with the bis(oxy)enamine starting compound. It has been determined that the metal in the salt affects the reaction pathway, as the nature of the metal cation affects its efficiency to cleave the N-O bond in the starting compound (with d-block elements being the best performing), and H⁺ ions can promote the reaction as well. Also, the reaction proceeds with different types of bis(oxy)enamines, meaning the substrate scope can be expanded to give a variety of products. The reaction can also proceed to form other products with different nucleophiles other than the nitrate group, where the C-N and C-S bonds were successfully formed in the reactions from bis(oxy)enamine to oxime ether.

Thus, this class of reaction in converting the bis(oxy)enamine to a cyclic oxime ether has potentially opened a new class of NO donor compounds, and further possesses the potential to form a wide variety of products to be used in other important synthesis procedures.

Reactions of Bis(oxy)enamines with O-Nucleophiles in the Presence of Metal Salts

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Introduction

NO donors are an emerging class of pharmaceutical compounds. The free radical NO is an important messenger molecule involved in many pathological and physiological processes within the mammalian body, such as vasodilation, making exogenous NO sources a powerful way to supplement NO, when the body is not able to generate enough for normal biological functions^{1,2}. NO donors have several important therapeutic indications, regarding cardiovascular diseases, pain and inflammation, osteoporosis, urinary incontinence, Alzheimer's disease and respiratory disorders^{3,4}. However, no new NO donors have substantially impacted the market since the discovery of NO as a crucial cardiovascular mediator in the 1980s⁵. Thus, the development of new NO donor compounds would be of great medicinal value, potentially opening a whole class of drugs to be used therapeutically to treat various ailments^{6,7,8}.

As such, a class of compounds was selected to be studied in greater detail, to investigate their potential to be NO donors. Substituted cyclic oxime ethers have proven to be useful intermediates in fields such as medicine and biochemistry. The cyclic structure along with a determinable substitutable group at the C₃ position are highly valuable, as they allow the oxime ethers to act as convenient precursors for a variety of useful products, such as proline derivatives and substituted pyrrolidine⁹. Previously, substituted cyclic oxime ethers could only be prepared through [4+2] cycloaddition of conjugated nitrosoalkenes with electron-rich alkenes, which was problematic synthesis-wise^{10,11}. Improved synthesis was then made possible, where bis(oxy)enamine intermediates are firstly synthesized by the known procedure from cyclic nitronates, followed by silylation to obtain the cyclic oxime ethers¹².

Research regarding the silylation had been done and the reaction was optimized by replacing the silicon Lewis acid ((CH₃)₃SiBr) with CoBr₂, since Co is a stronger Lewis acid, and would shift the equilibrium further towards the product side, hence giving a higher yield. Yields of this reaction ranged from 70% - 95%¹³.

Given the high yield CoBr₂ achieved in the synthesis of 3-bromomethyl substituted cyclic oxime ethers and its successful role as a catalyst, investigations have been conducted into the nature of metal salts as catalysts, with other Co salts being used to give rise to different substitutable groups, conducted by Sukhorukov and Buckland. It was found that Co(NO₃)₂ used in the synthesis of the cyclic oxime ether directly from a phenyl substituted bis(oxy)enamine intermediate (Compound 1), produced an entirely new compound: α-hydroxyoxime nitrates (Compound 2), the oxime ether being substituted a nitrate group (*see Fig. 1*) (*see Table 1 Exp. 12*).

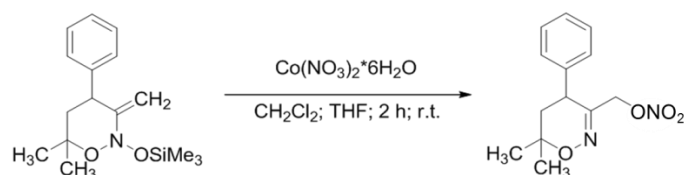


Figure 1: Reaction of Compound 1 with Co(NO₃)₂ to form desired product Compound 2

The presence of the nitrate group renders this compound as a potential NO-donor. With NO being a crucial biological mediator, the discovery of the compound by MCL-NJC has opened a new class of NO donor precursors. It is thus crucial to optimize and further study this class of reactions involving the synthesis of α-hydroxyoxime nitrates.

Also, the synthesis of this new type of C-O bond in the α -hydroxyoxime nitrate, gives rise to the possibility of other important bonds being newly formed, such as C-C bonds and C-S bonds in organic compounds.

Therefore, this project studies reactions of bis(oxy)enamines with O-nucleophiles in the presence of metal salts, aiming to develop a general procedure for the synthesis of α -hydroxyoxime nitrate by studying the effect of varying metal nitrates and substrate scope on the reaction, whilst studying similar reactions of bis(oxy)enamines with nucleophiles other than the nitrate group to produce a new range of useful organic synthesis precursors.

Hypothesis

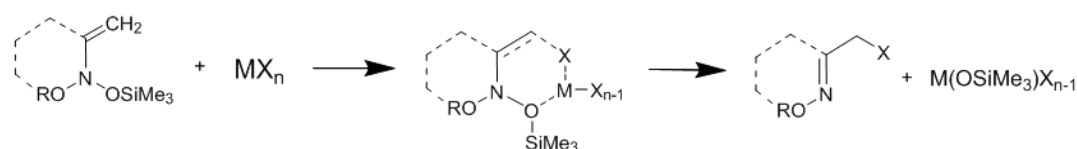


Figure 2: General reaction scheme of bis(oxy)enamine intermediate with variable metal salts to form substitutable oxime ethers

Different metal nitrates are able to promote the addition of the nitrate ion to the bis(oxy)enamine to synthesise the potential NO donor α -hydroxyoxime nitrate, but the nature of the metal will influence the direction of the reaction (see Fig. 2), while the catalytic effect of the metal salt will allow for the reaction to proceed with other nucleophiles.

Methodology

For all reactions, including the novel reaction to synthesis the α -hydroxyoxime nitrate for the first time, a standard molar equivalence between Compound 1: MX_n of 1:2 is used, with the metal salt in excess as a precaution, and actual equivalence needed was determined with UV-Vis titration. The standard amount of Compound 1 used was 0.125mmol, added into a small flask with the corresponding amount of dissolved metal salt. Solvents used were tetrahydrofuran (THF) or dimethylformamide (DMF), depending on which the metal salt is soluble in. The reaction is left to stir with a magnetic stirring bar for 2 hours. Then, in order to isolate the organic product, aqueous workup is conducted. with a separating funnel. After undergoing rotary evaporation and vacuum drying, the remaining compound is prepared for NMR sampling. Yields of the final compound were determined by NMR, with structure confirmed by the spectra. Additional products were also identified by characteristic peaks in the NMR spectra, such as the isomer of Compound 1.

Results & Discussion

Varying Metal Nitrates

#	$M(NO_3)_n$	Position of M in Periodic Table	Solvent	Yield of Compound 2 (%)
1	$LiNO_3$	s	THF	17
2	$Mg(NO_3)_2 \cdot 6H_2O$	s	THF	42
3	$Ca(NO_3)_2 \cdot 4H_2O$	s	THF	34
4	$Ba(NO_3)_2$	s	DMF	36
5	$Al(NO_3)_3 \cdot 9H_2O$	p	DMF	51
6	$Ga(NO_3)_3 \cdot 6H_2O$	p	THF	61
7	$Pb(NO_3)_2$	p	DMF	40

8	Bi(NO ₃) ₃ •5H ₂ O	p	DMF	10
9	Cr(NO ₃) ₃ •9H ₂ O	d	THF	76
10	Mn(NO ₃) ₂ •H ₂ O	d	THF	44
11	Fe(NO ₃) ₃ •9H ₂ O	d	THF	39
12	Co(NO ₃) ₂ •6H ₂ O	d	THF	66
13	Co(NO ₃) ₂	d	THF	53
14	Ni(NO ₃) ₂ •6H ₂ O	d	THF	75
15	Cu(NO ₃) ₂ •3H ₂ O	d	THF	57
16	Zn(NO ₃) ₂ •6H ₂ O	d	THF	67
17	Y(NO ₃) ₃ •6H ₂ O	d	THF	30
18	AgNO ₃	d	DMF	18
19	Cd(NO ₃) ₂	d	THF	49
20	La(NO ₃) ₃ •6H ₂ O	f	THF	16
21	Eu(NO ₃) ₃ •6H ₂ O	f	THF	27
22	Ho(NO ₃) ₃ •5H ₂ O	f	THF	35
23	NH ₄ NO ₃	-	DMF	47
24	HNO ₃	-	THF	61

Table 1: Yield of Compound 2 in experiments employing different metal nitrates in reaction with Compound 1

In the general reaction of synthesizing Compound 2 from Compound 1, the yields achieved by the different metal nitrates show certain trends in correspondence with the location of the metal cations in the periodic table. (see Table 1)

D-block (transition) metals performed the best, achieving the highest yield of Compound 2 with an average yield of 52%. The different yields of the different metal nitrates obtained prove that the nature of the metal does affect the pathway the reaction takes and thus its subsequent yield. The yield of desired product of the reaction would depend on the metal cation's efficiency to bind to O in the OSi(CH₃)₃ group and activate the N-O bond. This means that the orbital energies of the d-block elements correspond to the energy of binding to N-O bonds, explaining why only d-block elements give high yields instead of an increasing trend down the periodic table. Also, the yield of the desired product would depend on the efficiency of the metal to bind to the nitrate group, meaning the more electronegative the cation, the less likely the nitrate group can bind to the cyclic intermediate. This could explain why s-block metals and p-block metals generally behave poorer in comparison to d- and f-block metals.

In addition to the above reactions, in order to further examine this reaction, several constants were changed to determine their effect on the reaction to synthesize Compound 2, while keeping the metal nitrate constant. Cr(NO₃)₃•9H₂O (exp. 9) was used as it was the highest performing metal nitrate with a yield of Compound 2 of 76%. Firstly, Compound 1 was changed, by replacing it with a bis(oxy)enamine with a methoxyphenyl group instead of a phenyl group, giving a yield of 72%, and a chlorophenyl group, which gave a yield of approximately 46%. The fact that these reactions proceeded to give similar oxime ethers with a nitrate group proves that the substrate scope of these reactions can be expanded.

Secondly, the solvent was changed. Since $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ can dissolve in both THF and DMF, the reaction was run twice under similar reaction conditions. It was found that the reaction with DMF had a decreased yield of 43%. This means that in the event of choosing a solvent for similar reactions, THF would be a more suitable option.

Lastly, instead of metal nitrates, NH_4NO_3 and HNO_3 were used, giving respective yields of 47% and 61%. This suggests the H^+ ions present in both reactions promote the addition of the nitrate ion to bis(oxy)enamine, with high yield as well. This means that hydrated metal nitrates could also make use of H^+ as catalysts, and that metal cations are not necessary for the reaction to proceed, as H^+ ions work similarly.

Varying Nucleophiles

N_3 -methyl-substituted and Et.COS₂-methyl -substituted oxime ethers were successfully synthesized with relatively high yields. However in when using C-nucleophiles, other products were preferentially formed, instead of the formation of the desired C-C bond. This means that only a C-N bond and C-S bond were successfully formed, whereas other reaction pathways were preferred over the formation of a C-C bond.

Conclusion

Successful optimization of the synthesis of α -hydroxyoxime nitrates was achieved, where it has been determined that the metal in the metal salt affects the reaction pathway, as the nature of the metal cation affects the efficiency of the metal ion to activate the N-O bond in the starting compound as well as dissociate from its nitronate group. H^+ ions can promote the reaction as well. In order to achieve the highest yields, conditions include:

- d-block metal cations, which in metal nitrates give the highest yield, especially $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$
- THF to be used as solvent

The reaction proceeds with different types of bis(oxy)enamines, meaning the expanded substrate scope can give a variety of products, and thus a variety of organic precursors to be used in other procedures. This proves the versatility of this type of reaction, and the potential for the structure to be altered whilst having the NO group for pharmaceutical purposes.

Furthermore, the reaction can proceed to form other products with different nucleophiles other than the nitrate group, meaning the oxime ether can be substituted with different groups, hence the ability to form a wide variety of products to be used in other procedures. Thus, this type of reaction in converting the bis(oxy)enamine to a cyclic oxime ether possesses the potential to form a wide variety of products to be used in other important synthesis procedures.

Future work entails working with a wider substrate scope to test the versatility of this reaction of bis(oxy)enamines with metal nitrates, in order to incorporate the NO group into different structures used in different drugs. The efficiency of the desired compound to donate NO must also be tested. Work also includes further study into the usage of different metal nitrates in the formation of α -hydroxyoxime nitrates, to determine the catalytic nature of the metal cations and their correlation with H^+ ions. This would provide an understanding of the optimum metal catalysts to use in not only this type of reaction, but other similar ones as well. Future study should also be conducted on the effect of substrate scope, and solvent on the reaction, to optimize the procedure. Other nucleophiles such as azides, xanthates and acetylides, can also be employed in reaction with the bis(oxy)enamine to form new products (such as those that form a new type of C-C bond), which can produce a whole new class of organic precursors for useful synthesis procedures.

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The project focuses on synthesis of cycle oxime other by different metal salt. Successful results were obtained for the symethesis of there major products. The careful characteristic in a HNMR, IR atc are impressive. It demonstrated potential NO donor, x-hydroxyoxime nitrates, can be synthesized with good yield. Product characterization will be more compete if HRMS or elemental analysis are carried out. The current result is applicable to other related cycle oxime other compounds.