Organic & Supramolecular Chemistry

Cesium Carbonate Catalyzed Oxa-Michael Addition of Oximes to Acrylonitrile

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We report the O-alkylation of oximes with Michael acceptors using Cs_2CO_3 as the catalyst. The transformation proceeds stereospecifically with retention of the oxime configuration. Irradiation with visible light in the presence of diphenyl anthracene and cerium complexes affects the *E* to *Z* configuration ratio of the oxime ether products, but a complete stereocontrol was not achieved. The operationally simple protocol allows the synthesis of various O-alkylated oxime products that are useful precursors for further chemical transformations.

Introduction

Oxime ethers and their respective ester derivatives are essential structural elements in organic chemistry. They are present in natural products, in anti-bacterial or anti-inflammatory drugs or cancer therapeutics.[1] Heterocyclic oxime ethers such as Oxicanazole are important antifungal drugs that are used in the treatment of mycosis.[2] Respective structure motifs are shown in Figure 1.

Different strategies were reported for the synthesis of oxime derivatives *via* oxa-Michael addition.[3] The Buchwald group functionalized the hydroxyl moiety of an oxime *via* palladium-catalyzed cross-coupling with aryl halides yielding the respective aryl-substituted oximes (see Scheme 1a).[4] Leonori *et al.* developed photocatalytic strategies for the generation of nitrogen centered radicals based on hydroxylamine derivatives. They were able to generate nitrogen radicals of various polarities and reactivities by incorporating redox-active substituents on the oxime group.[5] The group of Xiao performed an enantioselective addition of aldoximes to β-CF_3-β-disubstituted nitro alkenes (see Scheme 1b).[6] By adding chiral alkaloid organo-catalysts, they were able to induce a new stereo centre enantioselectively on the β-carbon atom of the alkene. Narayanan *et al.* demonstrated that oxime ethers could also be prepared by Michael addition to the hydroxyl group of the oxime (see Scheme 1c).[7] Applying PPh_3 as the catalyst they

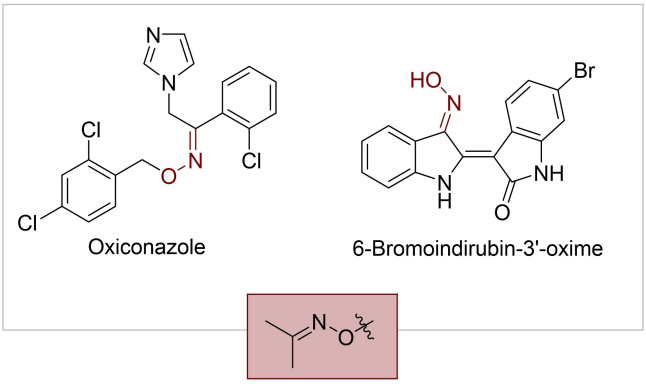

Figure 1. Oxime based drugs.

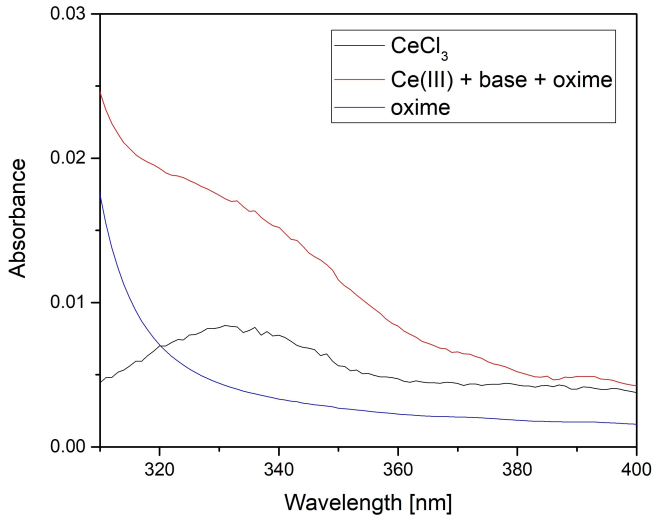

Figure 2. Absorbance (arbitrary units) of $CeCl_3$ (black) oxime **1** (blue) and a mixture of cerium salt, base and oxime (red); all spectra at (0.1 M) in CH_3CN.

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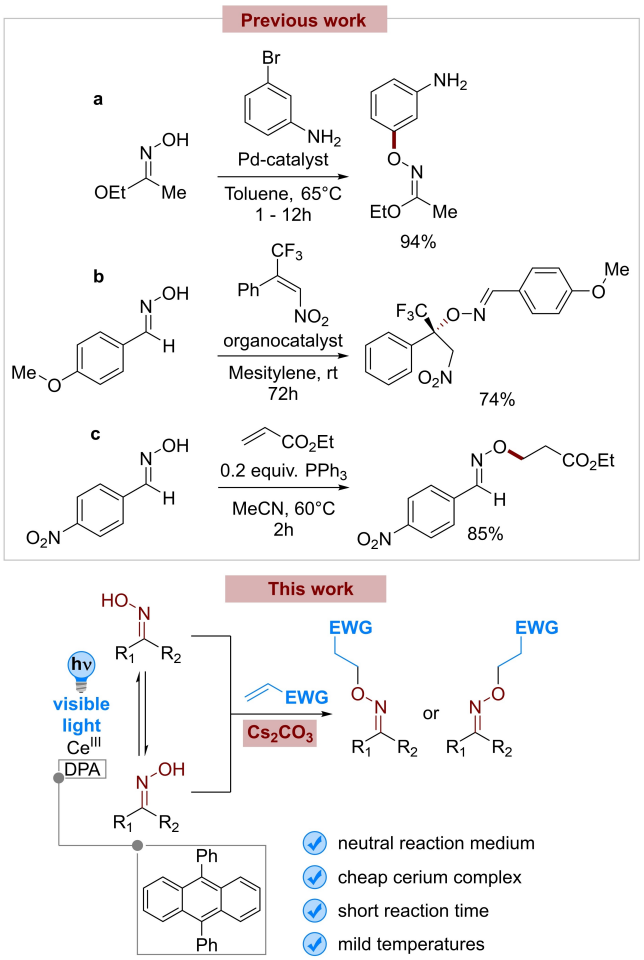
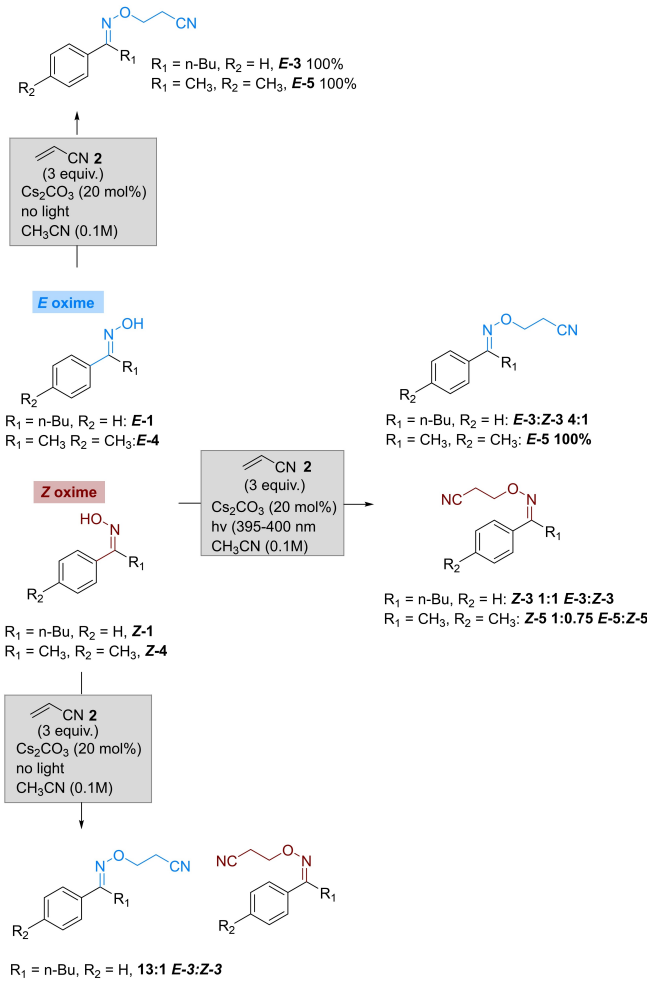


Scheme 1. Oxime O-functionalizations in literature.



Scheme 2. Oxa-Michael addition of *E*- and *Z* configured oximes in presence or absence of light.

were able to synthesize various ethers by addition of malonate derivatives.[7] However, PPh_3 can readily be oxidized by atmospheric oxygen to triphenyl phosphine oxide that needs to be removed by recrystallization or precipitation.[8]

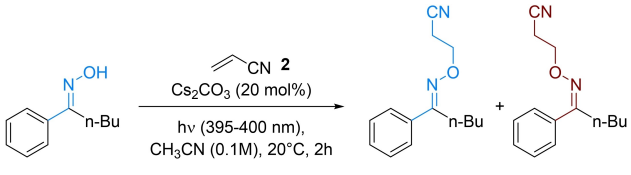
Interestingly, none of the reported synthesis strategies considered the possibility to control the product outcome exploiting the photochemical *E-Z* isomerization of the oximes. The geometric isomerization of oximes is a well-known photoreaction of this substance class.[9] By direct UV B irradiation, sensitization or by acid catalysis the *E* and *Z* isomers can be interconverted.[10] *E* to *Z* isomerization of oximes and their derivatives has been investigated by several research groups.[11] The unstructured absorption spectra of typical *E* and *Z* configured oximes differ only slightly in the UV B range, which makes a selective excitation and high photostationary states challenging with conventional light sources. In 2004, O'Brien *et al.* reported the acid-catalyzed isomerization of *E*- and *Z*-*p*-methoxy benzaldehyde oximes that proceeds through hydrolysis *via* formation of a tetrahedral intermediate. They also observe a bathochromic shift of the oxime absorption when the neutral oxime was protonated.[11a] Olsen *et al.* developed the sensitized isomerization of cinnamic acid oxime derivatives around the carbon-carbon or carbon-nitrogen bond. They propose that the isomerization behavior of the respective *E,E* or *E,Z*-derivative can be tuned by sensitization using triplet sensitizers of different energies.[10b]

Herein, we propose an effective method for the O-alkylation of oximes using Cs_2CO_3 as a cheap, non-toxic and air-stable reagent for the activation of the oxime hydroxyl group. The reaction shows nearly quantitative yield after 2 h with retention of the oxime stereochemistry in the oxime ether if performed in the dark. However, under irradiation in the presence of a cerium Lewis acid and diphenyl anthracene (DPA) as the photosensitizer the *E* / *Z* ratio changes from the oxime to the oxime ether.

Results and Discussion

Inorganic salts are widely used in organic synthesis as bases, acids or neutral salts, but also as electrolytes and Lewis acids due to their availability, low costs and effectivity.[12] Especially, cesium salts have gained considerable attention due to their unique characteristics. The cesium cation possesses a larger

Table 1. Screening for carbonate bases.

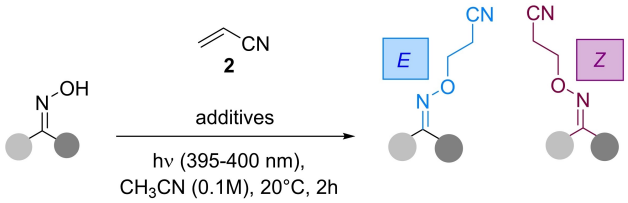


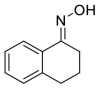
***E*-1** (E> 90%) ***E*-3** ***Z*-3**

[a]Entry	Deviation from standard condition	Irradiation	[b]Conversion [%]	Product ratio ***E*-3**:***Z*-3** [%]
a	None	yes	93	80:20
b	None	no	94	100:0
c	CsBr (20 mol%)	yes	0	–
d	CsI (20 mol%)	yes	0	–
e	CsF (20 mol%)	yes	0	–
f	CsOAc (20 mol%)	yes	0	–
g	$Cs_2C_2O_4$ (20 mol%)	yes	0	–
h	$MgCO_3$ (20 mol%)	yes	0	-
i	Na_2CO_3 (20 mol%)	yes	0	–
j	K_2CO_3 (20 mol%)	yes	57	80:20

[a]Reactions were performed using ***E*-1** (0.1 mmol, 1 equiv.), acrylonitrile **2** (0.3 mmol, 3 equiv.) and an inorganic base (20 mol%, 0.02 equiv.) in acetonitrile (0.1 M) under irradiation with 395–400 nm at 20 °C for 2 h.[b] Conversion and product ratio were determined using naphthalene as internal standard for GC FID.

Table 2. Survey of parameters controlling the stereochemistry of the products.



Entry	Oxime starting material[a]	Deviation from standard condition	Product ratio *E*:*Z* [%][b]
a	*E*-1	none	80:20
b	*E*-1	Ce(III)DOTA (10 mol%)	67:33
c	*E*-4	none	83:17
d	*E*-4	Ce(III)DOTA (10 mol%)	75:25
e	 ***E*-7**	none	67:37
f	*E*-7	Ce(III)DOTA (10 mol%)	42:58
g	*E*-1	Diphenyl anthracene (20 mol%)	75:25
h	*Z*-1	Diphenyl anthracene (20 mol%), no light	93:7
i	*E*-1	Diphenyl anthracene (20 mol%), no light	100:0
j	*E*-1	Diphenyl anthracene (20 mol%), $ZnCl_2$ as Lewis acid (10 mol%)	–[c]
k	*E*-1	Diphenyl anthracene (20 mol%), $CeCl_3$ as Lewis acid (10 mol%)	> 9:1
l	*E*-1	Diphenyl anthracene (20 mol%), BF_3 as Lewis acid (10 mol%)	26:74

[a]Reactions were performed using the *E* or *Z*-oxime (0.1 mmol, 1 equiv.), acrylonitrile (**2**) (0.3 mmol, 3 equiv.) and Cs_2CO_3 (20 mol%, 0.02 equiv.) in acetonitrile (0.1 M) [b]Product ratios were determined by GC FID using naphthalene as internal standard. [c] no O-alkylation product detected.

atom radius compared to other alkali metal ions and it is fully solvated in various polar aprotic organic solvents (e.g DMSO and DMF).[13] This property, along with the limited solvation of the counterion in the same environment, is the principal cause of the "cesium effect".[14] Additionally, cesium salts have a perfectly balanced acid-base character that allows for selective deprotonations.[15]

In an early state of our research, we recognized that we obtain two stereoisomers of the same O-alkylated oxime. This product ratio was dependent on the light-driven isomerization of the oxime starting material around the carbon-nitrogen double bond.

We started our investigations by converting different *E* and *Z* oximes in an oxa-Michael reaction using acrylonitrile (**2**) as electron-deficient coupling reagent (Scheme 2).[16] We added Cs_2CO_3 to our reaction mixture to increase the nucleophilicity of the oxime.[17,18] The reaction of oxime ***E*-1** or ***E*-4** under 400 nm irradiation gave the respective products ***E*-3** and ***E*-5** as confirmed by NMR; in the case of ***E*-3** some isomerization to ***Z*-3** was observed. When the same reaction under 400 nm irradiation was performed starting with the pure *Z* configured oximes ***Z*-1** and ***Z*-4**, we detected by NMR a 1:1 ratio for ***E*-3**:***Z*-3** and 1:0.75 for ***E*-5**:***Z*-5**.

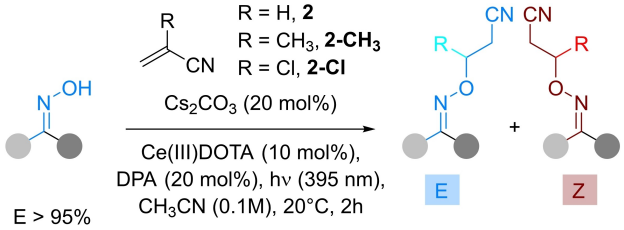
The reactions of ***E*-1** or ***E*-4** were repeated in the dark and isomerically pure ***E*-3** and ***E*-5** were formed, respectively. Performing the reaction with ***Z*-1** in the absence of light a ratio of 13:1 for ***E*-3**:***Z*-3** was achieved, indicating that only under irradiation with visible light the respective *Z*-configured alkylation product can be formed in larger amounts.

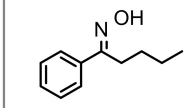
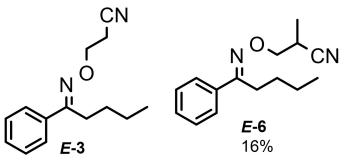
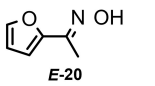
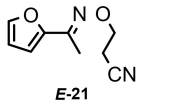
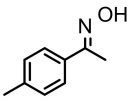
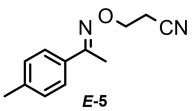
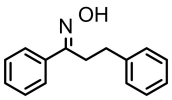
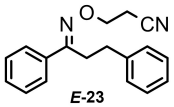
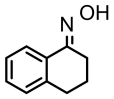
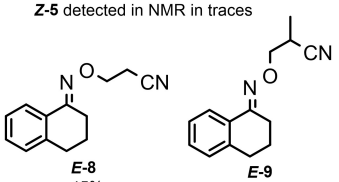
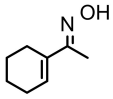
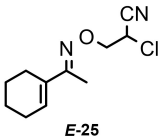
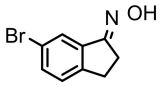
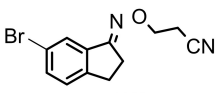
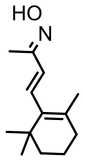
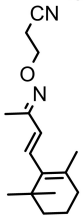
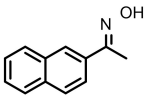
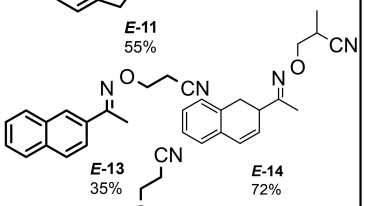
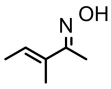
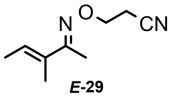
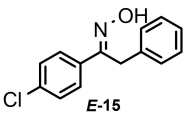
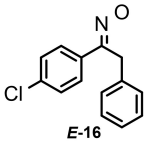
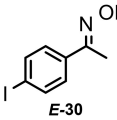
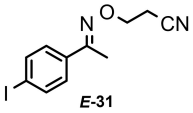
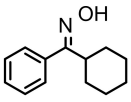
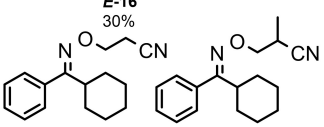
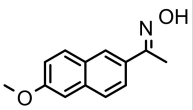
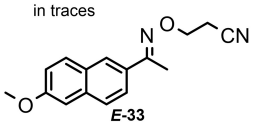
The complete separation of the oxime starting material by column chromatography turned out to be challenging and even short exposition to daylight led to the formation of the sterically and electronically favoured *E*-Oxime from the *Z*-Oxime.[19]

As Cs_2CO_3 was necessary for the formation of the O-alkylated product, we investigated the reaction using oxime **1**, acrylonitrile (**2**) and different inorganic bases.

Again, two products ***E*-3** and ***Z*-3** were observed in the gas chromatographic analysis of the reaction mixture, showing that the product ratio is highly dependent on irradiation (Table 1, entries a and b). Without irradiation, the tendency of *E*-*Z* isomerization of the oxime starting material was negligible, leading to the exclusive formation of product ***E*-3** (entry b). Adding Cs_2CO_3 in 20 mol%, nearly quantitative conversion of the oxime starting material was achieved and the products were formed in a ratio of 80:20 (entry a). In order to screen for the best reaction conditions, different cesium and carbonate salts were tested. In addition to cesium carbonate only K_2CO_3 catalyzes the reaction leading to the same product ratio observed in entry a, but with a lower conversion (entry j). In the

Table 3. Synthesis of oxime ethers.



Oxime[a]	Product trapping reagent[b]	Oxime[a]	Product trapping reagent[b]
 *E*-1	 *E*-3 65%; *Z*-3 detected in NMR in traces; *E*-6 16%; *Z*-6 detected in NMR in traces	 *E*-20	 *E*-21 42%
 *E*-4	 *E*-5 42%; *Z*-5 detected in NMR in traces	 *E*-22	 *E*-23 35%
 *E*-7	 *E*-8 45%; *E*-9 18%	 *E*-24	 *E*-25 15%
 *E*-10	 *E*-11 55%	 *E*-26	 *E*-27 20%
 *E*-12	 *E*-13 35%; *E*-14 72%	 *E*-28	 *E*-29 41%
 *E*-15	 *E*-16 30%	 *E*-30	 *E*-31 35%; *Z*-32 detected in NMR in traces
 *E*-17	 *E*-18 45% *Z*-18 4%; *E*-19 15%	 *E*-32	 *E*-33 65%

[a]Reactions were performed using the respective oxime (*E* > 90%). [b]All given yields are isolated yields if not otherwise stated.

case of other cesium or carbonate salts, no conversion to O-alkylated products was observed. Cesium carbonate is therefore the optimal base for the alkylation of the O–H of the oxime.[15][20]

Next, we investigated several additives to enhance the effect of irradiation on the stereochemistry of the reaction (Table 2). The presence of a cerium complex changes for some oximes the product ratio of the photochemical reaction to a

higher amount of the *Z* product in the reaction mixture compared to reactions without lanthanide salt (Table 2, entries b, d, f). To ensure a defined interaction between the Lewis acidic cerium complex and the oxime we used a cerium (III) 1,4,7-10-tetraazacyclododecan-1,4,7,10-tetraacetic acid (DOTA)[19,21] complex. Mixing the oxime and the cerium complex in presence of the base results in a slight yellow colour (Figure 2). The assembly of interacting compounds has a significant absorption around 340 nm tailing into the visible region of the spectrum. The UV Vis spectrum of the oxime or the cerium salts in acetonitrile show only slight absorption above 350 nm. The results of the UV vis study are highlighted in Figure 2.

Diphenyl anthracene is known as photosensitizer for the *E*/*Z*-isomerisation of the oxime starting material. Reactions in the presence of diphenyl anthracene and in combinations of the cerium complex and diphenyl anthracene show that the isomeric products ***E*-3** and ***Z*-3** are formed in a ratio of 75:25% (entry g). This value differs only slightly from the product ratio that was achieved from the entries with Cs_2CO_3 and acrylonitrile (**2**) (entry a). Reactions of ***Z*-1** in the dark show thermal back isomerization to the E isomer (entry h), while the ***E*-1** isomer retains its configuration (entry i). $ZnCl_2$ as Lewis acids (entry j) did not provide the O-alkylated product of the oxime, while BF_3 and diphenyl anthracene isomerization (entry l) gave the largest ratio of Z-configured oxime ether.

More oximes were converted into their respective oxime ethers (Table 3). With the intention to achieve a more significant control of the product stereochemistry the reactions were performed in the presence of cerium and diphenyl anthracene and irradiation. However, the alkylation product resulting from the *Z* oxime was only formed in small amounts and we were not always able to isolate it. Different acrylonitrile derivatives (**2**, **2-CH$_3$** and **2-Cl**) were used as alkylation reagents and the respective products were isolated. Acyclic and cyclic alkylated oximes were obtained from the respective oxime.

Conclusions

In summary, we prepared O-alkyl oxime ethers from oximes *via* an oxa-Michael reaction.[22] The cheap and non-toxic cesium carbonate proved to be the best base for the reaction. Alkylation of configurationally defined oxime isomers proceeds under retention of the carbon-nitrogen double bond configuration in the absence of light. The oxime double bond configuration can in part be controlled by photoisomerization. The addition of Lewis acids and diphenyl anthracene as sensitizer increases the amount of Z configured oxime ether, but the major stereoisomer of the obtained O-alkyl oxime ethers remains the *E*-configured compound.

Supporting Information Summary

Supporting information includes the experimental procedure, characterization data and NMR spectra (^{1}H, ^{13}C) of all the synthesized compounds, UV Vis spectra of the reaction mixture, the photocatalyst diphenyl anthracene and an exemplary oxime in its *E* and *Z* configuration as well as calculations regarding the stability of *E* and *Z* oximes.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cesium carbonate catalyst · Lewis acids · Oxa-Michael addition · Photochemistry · Stereoisomers

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