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Oxidative Azo–Ene Cyclization

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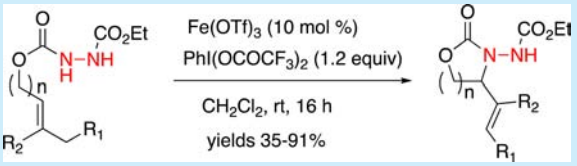
Supporting Information

ABSTRACT: An expedient procedure for catalytic oxidative azo–ene cyclization of allylic and homoallylic 1,2-hydrazinedicarboxylates is reported. The reaction produced a wide range of cyclic carbamate derivatives featuring an appended alkene fragment ready for further functionalization.



Oxazolidinones are highly valued motifs in the synthesis of biologicaly active compounds.[1] Several drugs bearing this core have entered the global pharmaceutical market, e.g., the antibiotic linezolid (**1**), used against pneumonia and skin/soft tissue infections,[2] and zolmitriptan (**2**), a selective serotonin receptor antagonist used for the treatment of migraines[3] (Figure 1).

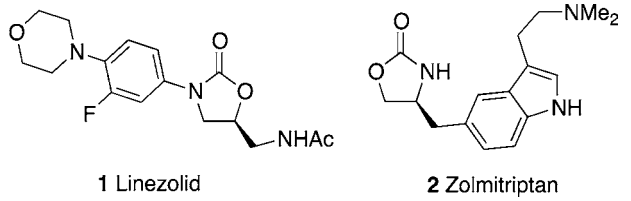
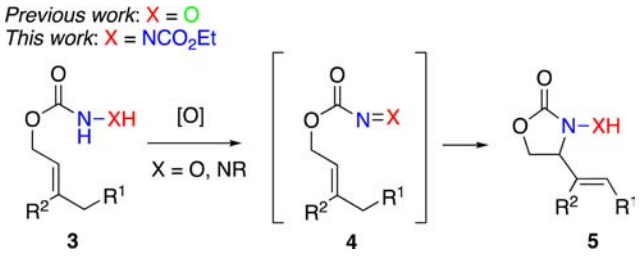


Figure 1. Pharmaceuticals with an oxazolidinone core.

Among the variety of methods for constructing the oxazolidinone core,[4] hetero–ene reactions,[5−7] where the role of the enophile is fulfilled by azo or nitroso derivatives, are particularly appealing since they provide direct C–N bond formation complemented by a pendant alkene fragment amenable to further functionalization. Recently, the group of Read de Alaniz[8] and our group[9] independently reported catalytic oxidation protocols to effect cyclization of hydroxycarbamates **3** (Scheme 1, X = O) into the respective oxazolidinones **5** in a single step. The reaction was also applied to form the respective six-membered heterocycles. The issues of inherent instability of the intermediate carbamoylnitroso derivatives **4** (X = O) were overcome by employing mild oxidizing reagents, thus avoiding overoxidation of the short-lived nitroso intermediates **4**. However, despite some success, in a wider context the intramolecular nitroso–ene reaction was found to be limited to relatively reactive, sterically unbiased alkenes. In contrast to the acylnitroso compounds, the respective azo derivatives **4** (X = NR) are significantly more stable and therefore could serve as suitable alternatives for the hetero–ene reaction. However, to date only a few examples of intramolecular azo–ene reactions leading to lactams have been reported.[7] Herein we present an expedient method for catalytic oxidative azo–ene cyclization of 1,2-hydrazinedicarboxylates to afford cyclic derivatives of 1,2- and 1,3-amino alcohols.

Scheme 1. Hetero–Ene Reactions



Initial studies involved screening of the cyclization conditions (Table 1). Dicarboxylate **6a**, which is readily synthesized in a single step from prenyl alcohol (see the Supporting Information for details), was employed as a model substrate; various combinations of oxidants and metal catalysts were examined. Representative examples of the optimization studies are shown in Table 1. Following the pioneering work by Vedejs on the cyclization of acyl hydrazides into lactams,[7a] MnO_2 as a stoichiometric oxidant was tested first (entry 1). However, only traces of the product were observed after 16 h. Sodium periodate on its own was inactive, but when used in combination with $FeCl_3$ as a catalyst, it led to 14% conversion (entry 2). The catalytic systems based on H_2O_2 and either $FeCl_3$ or $CuCl_2$, which were successfully used in the oxidation of hydroxycarbamates to nitroso derivatives,[9,10] both exhibited low efficiency (entries 3 and 4). Equally unsuccessful at promoting the cyclization was aerobic oxidation of **6a** mediated by $CuCl_2$ in acetonitrile (entry 5).[8,11] Following the recent report by Taniguchi and co-workers[12] on a catalytic aerobic oxidation of arylhydrazinecarboxylates to their azo derivatives using iron(phthalocyanine) (Fe(Pc)) complexes, the method

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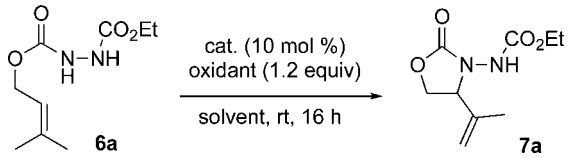
Table 1. Optimization of the Cyclization Conditions[a]



6a 7a

entry	catalyst	oxidant	solvent	conv. (%)[b]
1	–	MnO_2	CH_2Cl_2	4
2	$FeCl_3$	$NaIO_4$	CH_2Cl_2	14
3	$FeCl_3$	H_2O_2	MeCN	10
4	$CuCl_2$	H_2O_2	MeCN	30
5	$CuCl_2$	O_2	MeCN	SM
6[c]	Fe(Pc)	O_2	THF	30
7	–	PIDA	CH_2Cl_2	76
8	$Cu(OTf)_2$	PIFA	CH_2Cl_2	94
9	$FeCl_3$	PIDA	CH_2Cl_2	82
10	$Fe(OTf)_3$	PIDA	CH_2Cl_2	97
11	–	PIFA	CH_2Cl_2	89
12	$Cu(OTf)_2$	PIFA	CH_2Cl_2	94
13	$FeCl_3$	PIFA	CH_2Cl_2	88
14	$Fe(OTf)_3$	PIFA	CH_2Cl_2	98

[a]General conditions: substrate (0.35–1 mmol), catalyst (10 mol %), oxidant (1.2 equiv), and dry solvent (10 mL). The reactions were performed under a nitrogen atmosphere at rt for 16 h, unless stated otherwise. [b]Determined by ^{1}H NMR analysis. [c]The reaction was carried out at 65 °C.

was evaluated with our principal substrate **6a**. There was no reaction at room temperature, but at 65 °C a promising 30% conversion to **7a** was observed (entry 6). However, no further improvement could be achieved by increasing the catalyst loading or varying the solvent (CH_2Cl_2, toluene).

Iodosobenzene diacetate (PIDA) is another potent oxidant that has proved to be successful in promoting oxidative acylnitroso–ene cyclization[13] and oxidizing hydrazines to their azo derivatives in Mitsunobu reactions.[14] When PIDA was applied to our model reaction in the absence of a metal catalyst, 76% conversion to the cyclized product **7a** was observed (entry 7). However, the reaction was cleaner and more efficient when PIDA was used in combination with a metal salt (entries 8–10): $Cu(OTf)_2$, $FeCl_3$, and $Fe(OTf)_3$ gave 94%, 82%, and 97% conversion, respectively. Phenyliodine bis(trifluoroacetate) (PIFA), an oxidant with a related structure, was also evaluated. Using PIFA on its own resulted in 89% conversion (entry 11). Again, the conversion and the reaction rate improved in the presence of metal catalysts (entries 12–14). Nearly quantitative conversion (98%) was achieved with $Fe(OTf)_3$ and PIFA in CH_2Cl_2 (entry 14). The latter conditions were taken as optimal. The use of anhydrous solvents is of particular importance, as trace water may lead to formation of the Prins-type byproduct.[15]

A brief kinetic analysis of the reaction using PIFA as the oxidant with and without catalytic $Fe(OTf)_3$ was carried out using ^{1}H NMR spectroscopy by taking aliquots at regular intervals. The catalyzed reaction was found to be complete after 30 min, with 72% conversion achieved after only 5 min. The noncatalyzed reaction was considerably slower, and 95% conversion was reached after 3 h. To examine whether Brønsted acid was released during the oxidation with PIDA or PIFA and influenced the reaction rate, iodosobenzene (PhI=O) was tested as the oxidant. No significant changes in the conversion rates were observed under both metal-catalyzed and metal-free conditions. It might be possible that the metal facilitates oxidation of the N–N bond, which is the slowest reaction step. However, a more detailed mechanistic investigation of the process is required before any meaningful conclusions can be drawn.

Having established the optimal conditions for the oxidative cyclization (Table 1, entry 14), the reaction scope was next investigated. The results are displayed in Figure 2. For

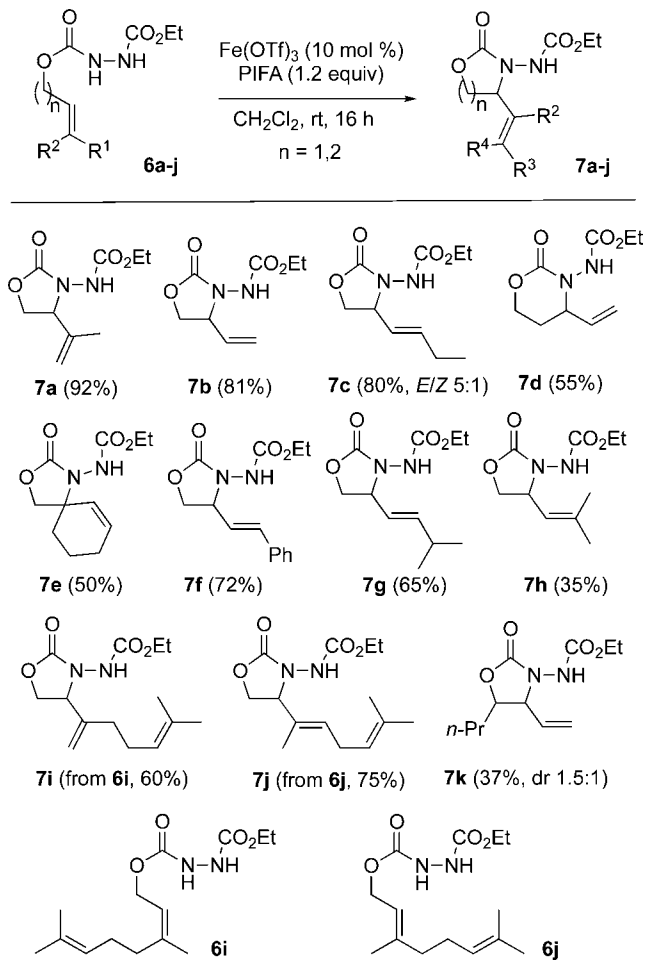


Figure 2. Oxidative cyclization scope. General conditions: substrate (0.35–1 mmol), $Fe(OTf)_3$ (10 mol %), PIFA (1.2 equiv), and dry solvent (10 mL). The reactions were performed at rt for 16 h. Yields of the isolated compounds are given.

substrates **6a–c**, the reactivity trend was similar to that of the related nitroso–ene cyclization.[9] Derivatives of prenyl (**6a**) and crotyl (**6b**) alcohol proved most reactive, affording the respective products **7a** and **7b** in 92% and 81% yield. Substrate **6c** with a longer alkyl chain furnished **7c** (80%) as a 5:1 *E*/*Z* mixture, mirroring the result obtained with the nitroso analogue (64%, 6:1 *E*/*Z*).[9] Formation of a six-membered ring turned out to be less facile compared to the five-membered counterpart. Thus, oxazinanone **7d** was obtained in a reduced 55% yield. A lower reaction rate was also observed in the formation of the sterically more challenging spiro compound **7e** (50%).

The role of steric factors influencing removal of the allylic hydrogen during the ene cyclization was assessed by comparing the reactivity of **6c** (R_1 = *n*-Pr; R_2 = H) with those of bulkier analogues **6f–h** (R_1 = Bn, *i*Bu, *i*Pr, respectively; R_2 = H). The rate of the cyclization dropped in the order *n*-Pr > Bn ≈ *i*Bu >

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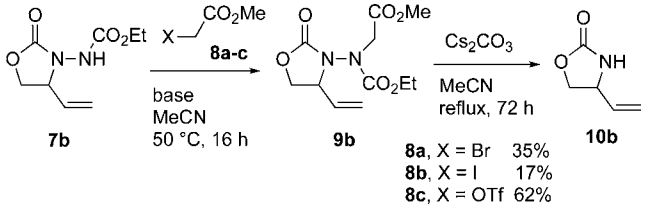
*i*Pr, reflecting the increased steric congestion around the allylic C−H bond. Thus, hydrazides **6f** and **6g** afforded the respective oxazolidinones **7f** and **7g** in 72% and 65% yield, whereas more sterically hindered **7h** was formed in a lower yield of 35%. However, it is pertinent to highlight the increased stability of the azo derivatives relative to their nitroso counterparts, which is critical in allowing the reaction to follow along the desired manifold. Thus, in the nitroso series, the analogue of **7f** was isolated in just 10% yield, whereas the hydroxylamine congener of **7h** was not formed at all because of decomposition of the short-lived nitroso species.

The other two substrates that failed to produce the cyclized products in the nitroso−ene series but were successful in the azo−ene cyclization are **6i** and **6j** derived from nerol and geraniol, respectively.[16] They furnished the respective oxazolidinones **7i** (60%) and **7j** (75%) in respectable yields. The additional double bond did not interfere with the reaction. Substrates **6i** and **6j** also served to illustrate the stereochemistry of the removal of the allylic hydrogen: in both instances the proton was abstracted from the *trans* alkyl position, mirroring the trend observed in the nitroso series.[8,9]

On the other hand, oxidative cyclization of 1,2-hydrazinedicarboxylate **6k** derived from a secondary allylic alcohol reacted sluggishly to give a 1.5:1 mixture of *syn* and *anti* isomers in a reduced 37% yield. The stereochemistry of the more abundant isomer has not been rigorously established but was assumed to be *syn* in analogy with the nitroso series.[9]

Next, cleavage of the N−N bond was investigated employing hydrazide **7b** as a model substrate (Scheme 2). The traditional

Scheme 2. Cleavage of the N−N Bond in 7

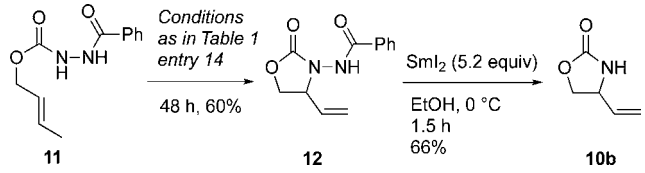


reduction methods (Raney Ni, H_2 with Pd/C) could not be used if the double bond was to be retained. Literature examples of the reduction of N−N bonds employ Li or Na in liquid ammonia[7d] or SmI_2 in EtOH.[17] These proved unsuccessful, returning the unreacted starting material. Eventually, cleavage of the N−N bond was achieved by modifying a procedure reported by Magnus.[18] According to the original protocol, **7b** was first alkylated at the NH with methyl bromoacetate (**8a**) to give **9b**, which was then heated at reflux in the presence of base to trigger fragmentation leading to the desired **10b** (Scheme 2).

Our attempts to carry out the process stepwise were met with limited success, as the first methylation step resulted in a complex mixture containing **9b**, **10b**, and unidentified byproducts. Therefore, the reaction was performed as a single-pot operation. With bromoacetate **8a** as the alkylating reagent, oxazolidinone **10b** was obtained in 35% yield. More reactive methyl iodoacetate (**8b**) failed to offer any improvement (17%). The problem was resolved by employing the triflate derivative **8c**, synthesized from the corresponding methyl hydroxyacetate. Slow addition of this compound to **7b** followed by heating at reflux for 72 h afforded the target compound **10b** in 62% yield. This deprotection was carried out on scales of up to 5 mmol with no effect on the yield. It is worth noting that compound **10b** has previously served as an important building block in a number of synthetic routes toward natural products.[19]

Successful cleavage of the N−N bond in cyclic *N*-benzoyl hydrazides with SmI_2 in EtOH as reported by Chi[17] prompted us to revisit this method (Scheme 3). The respective precursor

Scheme 3. Cleavage of the N−N Bond in 12



11 was synthesized from *N*-benzoyl hydrazine and crotyl alcohol and subjected to the optimized cyclization conditions to afford oxazolidinone **12** (60%). It is noteworthy that **11**, in comparison with the analogue **6b**, proved markedly less reactive, requiring 48 h for completion. Deprotection of **12** with 5.2 equiv of SmI_2 furnished **10b** in 66% yield. Overall, *N*-benzoyl hydrazides can be used as alternative starting substrates to the carbamoyl hydrazides, though the cyclization step would require further optimization. This method also carries the drawback of requiring a large excess of SmI_2 for deprotection.

In conclusion, an expedient procedure for catalytic oxidative azo−ene cyclization of allylic and homoallylic 1,2-hydrazinedicarboxylates has been developed. The reaction employs a hypervalent iodine reagent (PIFA) as a stoichiometric oxidant and proceeds at ambient temperature. The use of a catalytic amount of $Fe(OTf)_3$ facilitates the process, making the reactions cleaner and faster. Importantly, allylic azo compounds derived from 1,2-hydrazinedicarboxylates demonstrated a clear advantage over the respective nitroso analogues in terms of stability and, as a result, offer a wider application scope in the synthesis of substituted 1,3-oxazolidin-2-ones and 1,3-oxazinan-2-ones. Work in our laboratories is ongoing to develop an asymmetric variant of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03525.

Experimental procedures and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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(15) Trace water was found to be less of an issue in the case of **6a−j**, giving only minute quantities of the Prins-type byproducts. In contrast, cyclization of **11** in wet CH_2Cl_2 afforded the Prins alcohol in up to 25% yield. See the Supporting Information for details.

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