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One-pot synthesis of vinylisoxazolidines from simple hydroxylamines and conjugated carbonyls

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ABSTRACT

Herein is reported the highly chemo- and regioselective synthesis of 3-vinyl-4-formyl and 3-vinyl-5-formylisoxazolidines from enals, hydroxylamines and dipolarophiles under thermal conditions. The reaction works in high yields for a large array of substituted enals and a variety of dipolarophiles. The reaction provides the respective isoxazolidines with high chemoselectivity, stereospecificity and diastereoselectivity without significant purification. The substitution pattern on the dipolarophile directs the regioselectivity of the reaction to provide either 3,4- or 3,5-substituted isoxazolidine isomers. This method provides access to a wide variety of highly substituted, stereochemically dense isoxazolidine scaffolds from the selective reaction of the three proposed components.

Isoxazolidines are predominant scaffolds among several natural products and commercial drugs.[1] Thus, efficient methods for their synthesis have received increased interest over the last 50 years.[2]

Similarly, this scaffold has played a substantial role in drug discovery, mimicking a wide range of natural building blocks and being found to exhibit diverse biological activities.[3] Therefore, the development of novel methods for the systematic synthesis of highly functionalized substituted isoxazolidines remains an important goal in the field of organic chemistry.

The 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated aldehydes has been one of the most successful reactions for the construction of substituted isoxazolidines.[4] Despite the high energetic demand required for this reaction to be productive,[5] Lewis acid catalysis has been used to enhance reaction rates, conversion, scope, regio-, diastero- and enantioselectivities.[6]

Despite the large number of methods for the synthesis of these scaffolds, there are not clear trends that provide evidence for predictable regio- and diastereoselectivities.[7] Computational efforts have shown that there is an electronic bias for the 3,5-isoxazolidine with carbonyls and cyano groups on the dipolarophile, and selectivity for the 3,4-isoxazolidine with other electron-withdrawing groups.[8] Moreover, similar calculations have demonstrated a clear preference for the *endo* product (Scheme 1). Similar efforts also predict that thermal or Lewis acid (LA) promoted nitrone dipolar cycloadditions have the same regioselective tendencies.[9] On the other hand, there are no reported efforts that rationalize the steric effects or the nitrone electronic effects on this reaction's selectivities.

Substituted nitrones as suitable dipoles for cycloadditions can be obtained from a variety of methods depending upon the added functionality around the nitrone.[10] Vinyl nitrones from the condensation of conjugated carbonyls and hydroxylamines are ideal substrates to introduce key synthetic handles for the synthesis of highly complex heterocycles.[11] Thus, the cycloaddition of vinyl nitrones with α,β-unsaturated carbonyl dipolarophiles would produce highly functionalized isoxazolidines.

Multicomponent reactions take advantage of the chemoselectivity of multiple chemical scaffolds to efficiently produce highly complex moieties.[12] Thus, we envisioned studying the reaction of hydroxylamines, substituted α,β-unsaturated carbonyls and terminal α,β-unsaturated carbonyl dipolarophiles to predictably produce 3-vinyl-4-formyl- or 3-vinyl-5-formylisoxazolidines (3,4-VFI vs 3,5-VFI). To the best of our knowledge, this is the first report for the selective synthesis of such scaffolds (Scheme 1).

The Moura-Letts laboratory is focused on developing novel methods for the synthesis of novel, highly functionalized heterocyclic scaffolds.[13] These efforts led to the discovery that α,β-unsaturated carbonyls undergo selective condensation to provide vinylnitrones with complete conversion and without elaborated purifications.

This condensation reaction proved to work with very high conversions in the presence of a variety of Lewis acids and/or solvents for a wide range of enals and enones. One of these experiments

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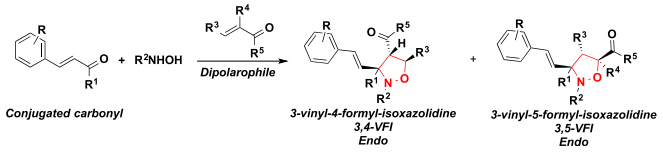
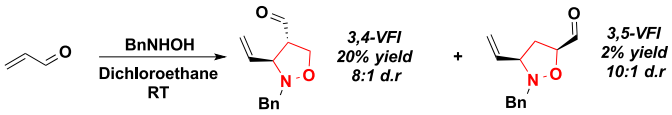


Scheme 1. Proposed method for the synthesis of 3-vinyl-4-formyl and 3-vinyl-5-formyl isoxazolidines.

showed that in excess of acrolein in dichloroethane (DCE), 20% conversion to the corresponding 3,4-VFI scaffold was observed instead (Scheme 2). The other regioisomer in this reaction was also produced in isolatable amounts (3,5-VFI in 2% yield).[14] This result was comparable to reported cycloaddition outcomes for unsubstituted nitrones and simple dipolarophiles.[15]

Thus, we rationalized that in the presence of a second enal the initially obtained vinylnitrone would undergo selective dipolar cycloaddition with the more reactive dipolarophile. Therefore providing either of the proposed isoxazolidine scaffolds as seen in Table 1.

The follow-up experiment (enal is allowed to react with hydroxylamine and then exposed to dipolarophile) showed that with a bulky enal (*p*-methoxycinnamaldehyde) the background reaction for **A** is not synthetically significant under the same reaction conditions, but we still observed formation of **E** and **F** as the predominant products (Table 1, Entry 2). Furthermore, the product



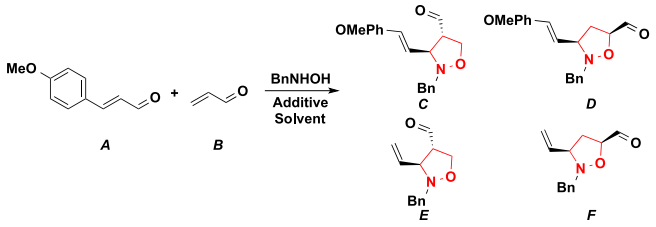
Scheme 2. Reaction discovery.

distribution did not display a significant change when enal **B** was in excess (Entry 3). Enal **A** clear lack of reactivity as a dipolarophile was further demonstrated when reacted with enal **B** and hydroxylamine at RT to provide the expected product in an encouraging 44% yield as a 10:1 mixture of regioisomers (Entry 4). More importantly, the main isomer **C** was isolated in a 10:1 d.r and only small amounts of isoxazolidine **D** were found (4%). The first variable to change towards improving the conversion of this reaction was temperature. Several reports have demonstrated high temperature to efficiently promote dipolar cycloadditions of similar substrates without erosion in the chemo-, regio- or stereoselectivity.[16]

Consequently, at 40 °C and 60 °C we did observe a significant increase in reaction productivity, without erosion of the reaction regioselectivity but with a surprising increase of diastereoselectivity (Entries 5 and 6). Moreover, we observed that at 80 °C the desired 3,4-VFI (**C**) was obtained in 88% yield and as a 15:1 mixture of diastereomers (Entry 7). These results are in agreement with analogous reports that clearly display a preference for the observed *endo* product. Higher temperatures proved to provide the product with similar conversions but significantly lower regioselectivities (Entry 8). Another important variable in these types of cycloadditions are the solvent effects. We observed that similar polar aprotic solvents (dioxane, acetonitrile and DMF) provided the respective 3,4-VFI in similar regioselectivities, but lower conversions (Entries 9–11).

Next we turned our attention to transition metal Lewis acids. We initially found that in the presence of 20 mol% of $Cu(OTf)_2$ there was significant acceleration of the reaction rate with very high conversion, but the product was found to be a mixture of **C** and **D** in a 64:28 ratio (Entry 12). Despite the poor regioselectivity, product **C** was isolated in a 20:1 diastereomeric ratio. Moreover, $Cu(OAc)_2$ provided the product with significantly lower regioselectivities, clearly indicating that triflates play a significant role in

Table 1
3-Vinyl-4-formyl-isoxazolidine reaction optimization.



Entry[1]	Enal	Dipolarophile	Additive[2]	Solvent	Time	Temperature	% Yield of C:D:E:F[3]	d.r[4]
1	B	B	None	DCE	48 h	rt	0:0:20:2	8:1
2	B[5]	B	None	DCE	48 h	rt	5:1:10:2	8:1
3	B	A	None	DCE	48 h	rt	8:2:6:2	6:1
4	A	A	None	DCE	48 h	rt	40:4:0:0	10:1
5	A	B	None	DCE	48 h	40 °C	53:6:0:0	15:1
6	A	B	None	DCE	16 h	60 °C	64:9:0:0	15:1
7	A	B	None	DCE	16 h	80 °C	88:4:0:0	15:1
8	A	B	None	DCE	18 h	90 °C	80:16:0:0	10:1
9	A	B	None	Dioxane	16 h	80 °C	80:4:0:0	15:1
10	A	B	None	Acetonitrile	16 h	80 °C	73:8:0:0	15:1
11	A	B	None	DMF	16 h	80 °C	64:12:0:0	15:1
12	A	B	$Cu(OTf)_2$	DCE	6 h	rt	64:28:0:0	20:1
13	A	B	$Cu(OAc)_2$	DCE	6 h	rt	35:24:0:0	20:1
14	A	B	AgOTf	DCE	6 h	rt	53:22:0:0	20:1
15	A	B	AuOTf	DCE	6 h	rt	48:20:0:0	15:1
16	A	B	$Fe(OTf)_3$	DCE	6 h	rt	46:32:0:0	15:1

[1] Ratio of enal:dipolarophile:hydroxylamine, 1:2:1.
[2] Lewis acid was added in 20 mol%.
[3] Isolated yields.
[4] Ratio for the major isomer, measured by ^1H NMR.
[5] 1:1 ratio of enal:dipolarophile.