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Organocatalytic Synthesis of Fused Bicyclic 2,3-Dihydro-1,3,4-oxadiazoles through an Intramolecular Cascade Cyclization

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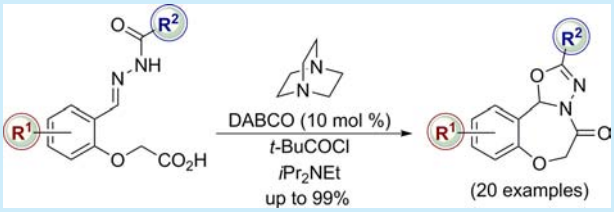
Supporting Information

ABSTRACT: Hydrazone-carboxylic acids undergo intramolecular cyclization in the presence of pivaloyl chloride, iPr$_2$NEt, and catalytic DABCO to form a range of substituted fused tricyclic 2,3-dihydro-1,3,4-oxadiazoles in high yields.

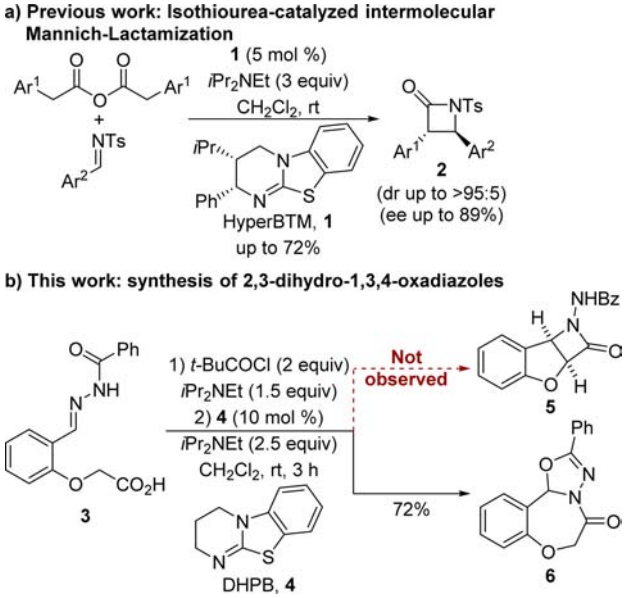


Heterocyclic motifs are ubiquitous throughout medicinal and synthetic organic chemistry, with novel methods for the synthesis of heterocyclic cores under constant development.[1] The organocatalytic synthesis of functionalized heterocycles from readily available carboxylic acid starting materials has received widespread attention since the seminal contribution of Romo and co-workers on the nucleophile-catalyzed aldol-lactonization reaction.[2,3] For example, previous work from this laboratory has demonstrated that ammonium enolates generated from the reaction of carboxylic acids and isothiourea-based organocatalysts are versatile intermediates in a variety of inter- and intramolecular processes for the syntheses of heterocycles.[4−6]

We have previously applied this strategy to the stereoselective synthesis of β-lactams **2** through HyperBTM **1** catalyzed intermolecular Mannich addition−lactamization of homoanhydrides and *N*-sulfonyl aldimines (Scheme 1a).[7] Given the biological and synthetic importance of β-lactam motifs,[8] attempts were made to develop an intramolecular version of this Mannich-lactamization process for the synthesis of fused bicyclic β-lactams from bench stable hydrazone-carboxylic acids such as **3**. The envisaged reactivity involves generation of an ammonium enolate through reaction of an isothiourea catalyst with an activated carboxylic acid, followed by intramolecular cyclization onto the pendent hydrazone and subsequent lactamization.[9,10] The reaction of **3** with pivaloyl chloride (2 equiv) and iPr$_2$NEt (1.5 equiv) in CH_2Cl_2 to form a mixed anhydride *in situ*, followed by addition of catalytic DHPB **4** (10 mol %), showed no formation of the expected bicyclic β-lactam **5**. However, crude ^{1}H NMR analysis showed complete consumption of **3** into a single major product isolated in 72% yield, with further characterization revealing its structure to be a unique 2,3-dihydro-1,3,4-oxadiazole containing a fused seven-membered oxazepine ring **6** (Scheme 1b).

Various substituted 2,3-dihydro-1,3,4-oxadiazoles have previously been shown to possess a range of biological activities including anticancer,[11a,b,e] antibacterial,[11c] monoamine oxidase (MAO) B inhibition (**7**),[11d] immunosuppressive activity,[11f] and antiviral properties (Figure 1).[11g] Current syntheses of 2,3-dihydro-1,3,4-oxadiazoles typically rely on the intermolecular cyclization of hydrazones by heating at reflux in acetic anhydride, with corresponding methods for intramolecular cyclization reactions to form fused bicyclic systems largely unknown.[12] Various fused oxazepine derivatives also display biological activities,[13] including the antidepressant Sintamil and tricyclic compounds such as **8** that showed inhibition against telomerase.[13d] Considering the unprecedented nature of the

Scheme 1. Previous and Current Work



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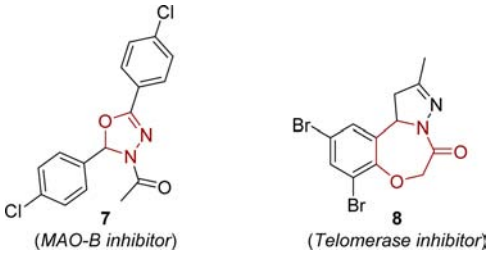
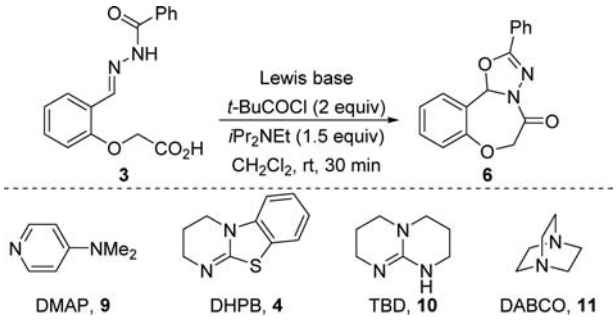


Figure 1. Examples of a biologically active 2,3-dihydro-1,3,4-oxadiazole and a fused oxazepine.

intramolecular cascade cyclization of hydrazone **3**, further efforts explored the utility of this process.

First, a catalyst screen was performed on the cyclization of hydrazone **3** into 2,3-dihydro-1,3,4-oxadiazole **6** (Table 1). The

Table 1. Catalyst Screen[a]



entry	Lewis base	mol %	yield (%)[b]
1	–	–	46[c]
2	DMAP, **9**	10	39
3	DHPB, **4**	10	24
4	TBD, **10**	10	53
5	DABCO, **11**	10	97[c]
6	DABCO, **11**	5	89
7	DABCO, **11**	1	60
8[d]	DABCO, **11**	10	70[c]

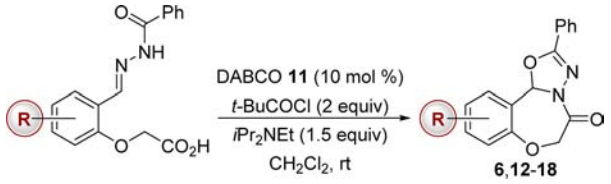
[a]Reactions performed on a 0.25 mmol scale. [b]Determined by ^{1}H NMR using 1,4-dinitrophenol as an internal standard. [c]Isolated yield. [d]Reaction performed on a 3.75 mmol (1.12 g of **3**) scale.

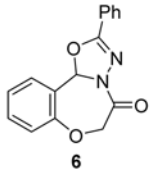
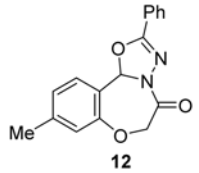
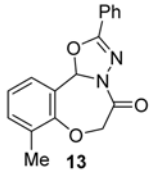
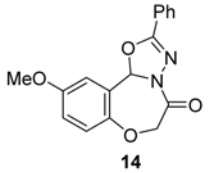
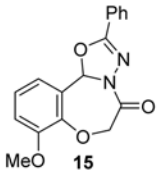
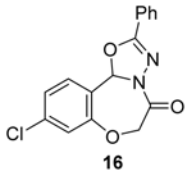
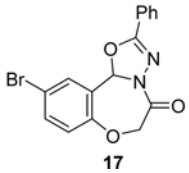
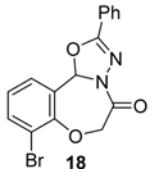
reaction occurs in the presence of only pivaloyl chloride (2 equiv) and iPr$_2$NEt (1.5 equiv) with the addition of Lewis bases such as DMAP **9**, DHPB **4**, and TBD **10** having little effect on the yield (Table 1, entries 1–4).[14,15]

However, adding DABCO **11** (10 mol %) significantly increased the rate of reaction, allowing **6** to be isolated in 97% yield after only 30 min at room temperature (Table 1, entry 5). The yield of **6** reduced in line with decreased catalyst loadings (Table 1, entries 6 and 7). The reaction could be performed on a preparative scale (3.75 mmol of **3**), forming 737 mg of **6** (70%) under the optimized reaction conditions (Table 1, entry 8).

The scope of this process was then explored through incorporation of substituents within the benzenoid ring. A range of substituted hydrazones was synthesized in three steps from the corresponding salicylaldehyde derivatives and treated under the previously optimized reaction conditions (Table 2).[16] Electron-donating Me– and MeO– groups were tolerated in various positions around the ring, forming products **12**–**15** in excellent yield. Incorporation of a 9-Cl substituent also worked

Table 2. Reaction Scope[a]



product	yield (%)	product	yield (%)
 **6**	97	 **12**	76
 **13**	90	 **14**	80
 **15**	99	 **16**	84
 **17**	54[a]	 **18**	58

[a]Reaction performed at 40 °C using 20 mol % **11**.

well, forming 2,3-dihydro-1,3,4-oxadiazole **16** in 84% yield. The presence of a 10-Br substituent required an elevated temperature of 40 °C and a higher catalyst loading to form product **17** in 54% yield. A slight reduction in reactivity was also observed with the introduction of an 8-Br substituent, but product **18** could still be isolated in 58% yield after 1 h at room temperature.

Next, the scope and limitations with regard to the hydrazone substituent were examined (Table 3). Both electron-donating and electron-withdrawing substituents were well tolerated, forming 2,3-dihydro-1,3,4-oxadiazoles **19**–**21** in high yields. Introduction of halogen substituents generally led to reduced reactivity, for example 2′-F-**22** was formed in 52% yield while elevated temperatures were required to form 4′-Cl-**23** and 4′-Br-**24** in 64% and 23% yield, respectively. Notably, the cyclization of hydrazones bearing halogen substituents did not proceed at all in the absence of DABCO **11**, even after extended reaction times. Heteroaromatic 2-furyl and 3-pyridyl substitution was also possible, forming functionalized products **25** and **26** in good yields, respectively. The cyclization did not proceed as smoothly in the presence of an NH-indole substituent, forming **27** in only low 33% yield. Alkyl-substituted hydrazones could be utilized, forming cyclized products **28** and **29** albeit in slightly reduced yields. Alkenyl substitution was not possible under the previously optimized reaction conditions, with only a trace amount of a cinnamyl substituted product formed even at higher temperatures.[16] The extent to which the

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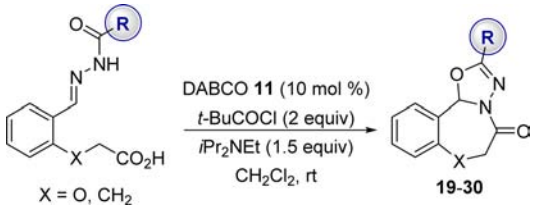
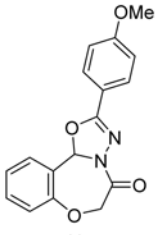
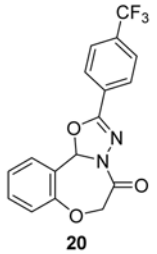
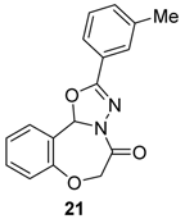
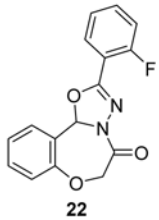
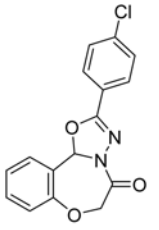
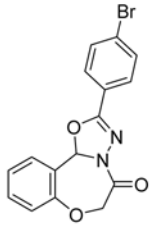
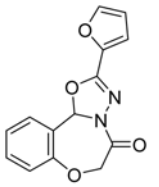
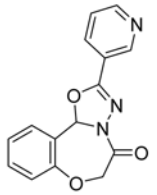
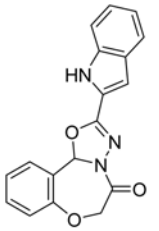
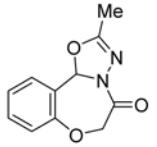
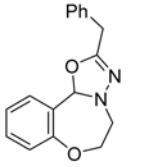
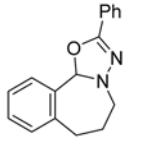
Table 3. Reaction Scope



product	yield (%)	product	yield (%)
 **19**	97	 **20**	71
 **21**	99	 **22**	52[a]
 **23**	64[a,b]	 **24**	23[a]
 **25**	61	 **26**	54[a]
 **27**	33	 **28**	53[a,b]
 **29**	38	 **30**	<5

[a]Reaction performed at 40 °C. [b]20 mol % **11**.

phenolic linker within the hydrazone aids the cyclization to form the 2,3-dihydro-1,3,4-oxadiazole ring was investigated through synthesis of a carbon analogue (X = CH_2). However, reaction under the previously optimized conditions led to only a trace amount of product **30**, indicating that the oxygen atom is essential for this process.

Single-crystal X-ray analysis of 2,3-dihydro-1,3,4-oxadiazole **20** confirmed the structural assignment and revealed the conformation of the fused-tricyclic products in the solid state (Figure 2).[17] A particularly striking feature is the angle of 113.84° (C11−O12−C13) between the plane of the benzenoid ring and the fused seven-membered oxazepanone ring.

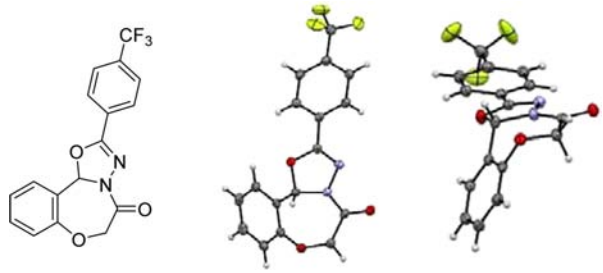
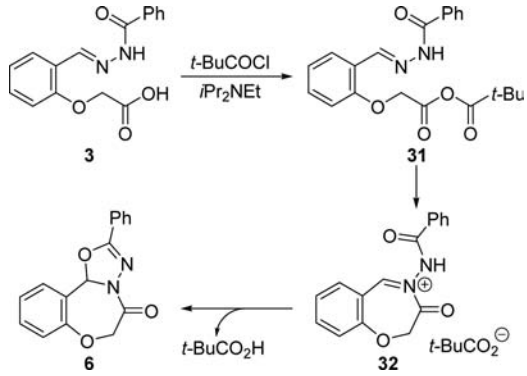


Figure 2. Representation of the single-crystal X-ray structure of 2,3-dihydro-1,3,4-oxadiazole **20**.

The proposed mechanism begins with acylation of carboxylic acid **3** using pivaloyl chloride and iPr_2NEt to form mixed anhydride **31** (Scheme 2). Intramolecular cyclization of the

Scheme 2. Proposed Mechanism



hydrazone onto the mixed anhydride forms oxazepinium intermediate **32**, which undergoes a second intramolecular cyclization to form 2,3-dihydro-1,3,4-oxadiazole **6**. As the phenolic oxygen atom is essential for the reaction to proceed, it is possible that conjugation of the oxygen atom in **32** is necessary to allow the second cyclization to occur. The mechanism by which catalytic DABCO **11** significantly accelerates the rate of this process is unclear. One possibility is that the DABCO **11** undergoes *N*-acylation through reaction with mixed anhydride **31** to form an activated *N*-acyl ammonium that is more susceptible to cyclization. However, more traditional *N*-acylating agents such as DMAP **9** and DHPB **4** did not accelerate this process (see Table 1). Therefore, an alternative possibility is that DABCO **11** acts as a proton-transfer agent and helps to promote the cyclization of **32** into **6**.

In conclusion, hydrazone-acid starting materials underwent efficient intramolecular cyclization in the presence of catalytic DABCO **11** to form oxazepine fused 2,3-dihydro-1,3,4-

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oxadiazoles. A wide range of substituents was tolerated on both the benzenoid ring and the hydrazone moiety, forming the functionalized fused tricyclic products in high yields under mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02997.

Experimental procedures, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for all novel compounds (PDF)

Crystallographic data for **20** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Leaving the uncatalyzed reaction for 3 h allows **6** to be isolated in 79% yield.

(15) Reaction with the enantiomerically pure isothiourea HyperBTM **1** led to formation of racemic **6**.

(16) See the Supporting Information for details.

(17) CCDC 1430692 contains the supplementary crystallographic data for 2,3-dihydro-1,3,4-oxadiazole **20**.

(18) The data underpinning this research can be found at DOI: http://dx.doi.org/10.17630/9c704848-8ca9-4e41-8811-2f2fea2e5f6c.

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