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[3 + 2] Cycloaddition of Oxazol-5-(4*H*)-ones with Nitrones for Diastereoselective Synthesis of Isoxazolidin-5-ones

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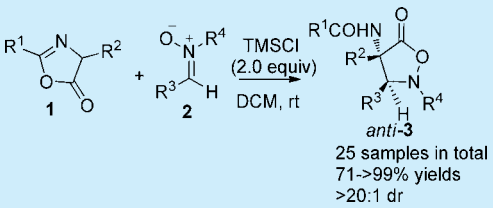
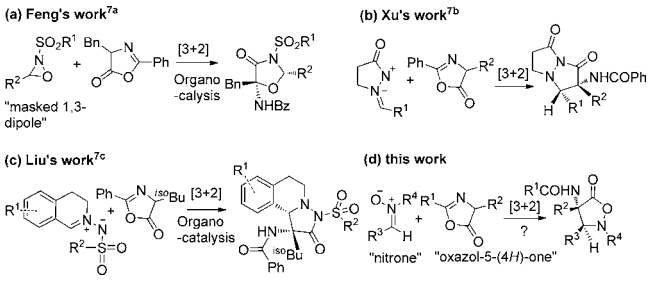
Supporting Information

ABSTRACT: In the presence of TMSCl, the [3 + 2] cycloaddition of oxazol-5-(4*H*)-ones with nitrones proceeded smoothly and furnished the desired isoxazolidin-5-ones with high diastereoselectivities in reasonable chemical yields. The chemical structure of the title compounds was firmly confirmed by X-ray single-crystal structure analysis.



Oxazol-5-(4*H*)-ones represent a class of synthetically robust and versatile building blocks and are widely applied in a variety of cycloaddition reactions.[1] On one hand, by functioning as 1,3-dipoles, oxazol-5-(4*H*)-ones can undergo a wide range of [3 + 2] cycloadditions with structurally diverse dipolarophiles such as olefins,[2] imines,[3] nitriles,[4] and alkynes.[5] Moreover, on the other hand, oxazol-5-(4*H*)-ones can employ their C4 as a nucleophilic site and C5 as an electrophilic site to perform [2 + 2],[6] [3 + 2],[7] [4 + 2],[8] and [8 + 2][9] cycloadditions with an extensive array of chemical entities bearing amphiphilic properties. However, with respect to the cycloaddition between oxazol-5-(4*H*)-ones and 1,3-dipoles, several limited examples have been reported in the literature to date. In 2013, Feng's group envisioned an elegant organocatalytic [3 + 2] cycloaddition of oxazol-5-(4*H*)-ones with oxaziridines as masked 1,3-dipoles for the enantioselective preparation of oxazolin-4-ones (Scheme 1a).[7a] In 2014, Xu and co-workers developed a [3 + 2] cycloaddition of oxazol-5-(4*H*)-ones with azomethine imines as 1,3-dipoles for the synthesis of *N*,*N*-bicyclic heterocycles (Scheme 1b).[7b] Very recently, Liu et al. successfully utilized the organocatalytic inverse-electron-demand 1,3-dipolar cycloaddition of *C*,*N*-cyclic azomethine imines as 1,3-dipoles with oxazol-5-(4*H*)-ones for the enantioselective construction of chiral tricyclic tetrahydroisoquinolines (Scheme 1c).[7c] Even with significant advances in the chemistry of oxazol-5-(4*H*)-ones, it remains highly demanded to develop novel and efficient synthetic methodologies with the involvement of oxazol-5-(4*H*)-ones as reactants.

Scheme 1. Representative Cycloadditions of Oxazol-5-(4*H*)-ones with 1,3-Dipoles



Intrigued by previous works on the chemistry of oxazol-5-(4*H*)-ones, we devised the unknown [3 + 2] cycloaddition of oxazol-5-(4*H*)-ones with synthetically important nitrones[10] as 1,3-dipoles (Scheme 1d), thus furnishing novel isoxazolidin-5-ones bearing the potential bioactivities.[11] We discovered that the designed [3 + 2] cycloaddition proceeded readily and furnished the title compounds in acceptable chemical yields. To the best of our knowledge, such a work has not been reported to date.

Initially, we screened the effects of a variety of additives on the [3 + 2] cycloaddition of oxazol-5-(4*H*)-one **1a** with nitrone **2a** as outlined in Table 1. Obviously, the examined additives remarkably influenced the chemical yield of the [3 + 2] cycloaddition. For example, in the absence of an additive, the [3 + 2] cycloaddition did not take place at all (entry 13). The same negative results were observed with the use of $Yb(OTf)_3$, $Zn(OTf)_2$, TsOH, and DABCO as additives (entries 3, 4, 9, and 11). Compared with the former cases, the [3 + 2] cycloaddition delivered product **3aa** in a trace amount after 20 h in the presence of $Cu(OTf)_2$, $Cu(OAc)_2$, and DIPEA as additives (entries 5, 6, and 12). With the use of TMSOTf, CuI, stearic acid, and TFA as additives, the chemical yield of the [3 + 2] cycloaddition ranged from 10 to 33% (entries 2, 7, 8, and 10). Among all of the tested additives, TMSCl gave product **3aa** in the highest chemical yield of 78% (entry 1).

Subsequently, we investigated the solvent effects on the [3 + 2] cycloaddition of oxazol-5-(4*H*)-one **1a** with nitrone **2a** as shown in Table 2. Indeed, the used solvents drastically affected the chemical yield of the [3 + 2] cycloaddition. In solvents such as

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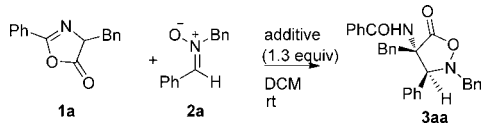
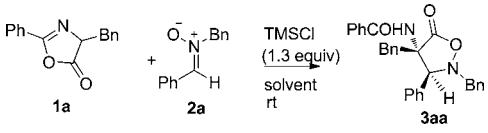
Table 1. Screening of Additives[a]



entry	additive temp	time (h)	yield[b] (%)	dr[d]
1	TMSCl	20	78	>20:1
2	TMSOTf	20	10	>20:1
3	$Yb(OTf)_3$	20	nr[c]	
4	$Zn(OTf)_2$	20	nr[c]	
5	$Cu(OTf)_2$	20	trace	
6	$Cu(OAc)_2$	20	trace	
7	CuI	20	14	>20:1
8	stearic acid	20	33	>20:1
9	TsOH	20	nr[c]	
10	TFA	20	16	>20:1
11	DABCO	20	nr[c]	
12	DIPEA	20	trace	
13		20	nr[c]	

[a]Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), additive (0.13 mmol) in DCM (0.5 mL) at room temperature. [b]Isolated yield. [c]No reaction. [d]Determined by ^{1}H NMR.

Table 2. Screening of Solvents[a]



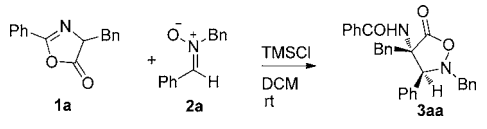
entry	solvent	time (h)	yield[b] (%)	dr[d]
1	DCM	20	78	>20:1
2	1,2-DCE	20	70	>20:1
3	toluene	20	43	>20:1
4	THF	20	35	>20:1
5	Et_2O	20	39	>20:1
6	CH_3CN	20	trace	
7	MeOH	20	55	>20:1
8	TFE	20	nr[c]	
9	HFIP	20	nr[c]	
10	$CHCl_3$	20	65	>20:1

[a]Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), TMSCl (0.13 mmol) in the indicated solvent (0.5 mL) at room temperature. [b]Isolated yield. [c]No reaction. [d]Determined by ^{1}H NMR.

TFE and HFIP, the [3 + 2] cycloaddition did not take place at all after 20 h (entries 8 and 9). In contrast with the former cases, the [3 + 2] cycloaddition furnished product **3aa** in a trace amount by choosing CH_3CN as a solvent (entry 6). When toluene, THF, Et_2O, and MeOH were applied as solvents in the [3 + 2] cycloaddition, the chemical yield of product **3aa** changed from 35 to 55% (entries 3−5 and 7). Moreover, the tremendous increase in the chemical yield of the [3 + 2] cycloaddition was observed with the use of DCM, 1,2-DCE, and $CHCl_3$ as solvents (entries 1, 2, and 10). Among all the solvents examined, DCM proved to be the most suitable solvent, where product **3aa** was achieved in the highest chemical yield of 78% (entry 1).

Simultaneously, we extensively optimized the ratio of **1a**/**2a**/TMSCl in the [3 + 2] cycloaddition of oxazol-5-(4*H*)-one **1a** with nitrone **2a** as summarized in Table 3. Remarkably, we found that the chemical yield of the [3 + 2] cycloaddition was

Table 3. Screening of Ratios of 1a/2a/TMSCl[a]



entry	ratio (**1a**/**2a**/TMSCl)	time (h)	yield[b] (%)	dr[c]
1	1:1:0.1	20	58	>20:1
2	1:1:0.2	20	61	>20:1
3	1:1:0.5	20	65	>20:1
4	1:1:1	20	75	>20:1
5	1:1:1.3	20	78	>20:1
6	1:1:2	10	86	>20:1
7	1:1:2.5	7	87	>20:1
8	1:1:3	7	87	>20:1
9	1.2:1:2	10	90	>20:1
10	1.5:1:2	10	89	>20:1
11	2:1:2	10	90	>20:1
12	1:2:2	10	86	>20:1

[a]Unless otherwise noted, reactions were carried out with **1a**, **2a**, additive in DCM (0.5 mL) at room temperature. [b]Isolated yield. [c]Determined by ^{1}H NMR.

apparently changed with the ratio of **1a**/**2a**/TMSCl. When the ratio of **1a**/**2a**/TMSCl gradually changed from 1:1:0.1 to 1:1:3, the chemical yield of [3 + 2] cycloaddition gradually increased from 58 to 87% (entries 1−8). When the ratio of **1a**/**2a**/TMSCl was set at 1.5:1:2 or 1:2:2 in the [3 + 2] cycloaddition, product **3aa** was obtained in 89 and 86% chemical yields, respectively (entries 10 and 12). The excellent chemical yield of 90% was achieved with the use of a 1.2:1:2 or 2:1:2 ratio of **1a**/**2a**/TMSCl in the [3 + 2] cycloaddition (entries 9 and 11).

Finally, under the optimal reaction conditions, we broadened the reaction scope of the [3 + 2] cycloaddition by varying oxazol-5-(4*H*)-ones **1** with nitrones **2** as shown in Table 4. Obviously, the examined substrates **1** and **2** significantly affected the chemical yield of the [3 + 2] cycloaddition. Generally, regarding the [3 + 2] cycloaddition with substrate **1a**, nitrones **2** with an electron-poor phenyl group as the R^3 substitution tended to furnish products **3** in chemical yields higher than those obtained with nitrones **2** bearing an electron-rich phenyl group at the R^3 position (entries 3−6 vs 7−9). For nitrones **2j**−**2k** using an aromatic heterocycle as the R^3 group, the chemical yields of products **3** were decreased differently in the [3 + 2] cycloaddition with substrate **1a** compared with the former cases (entries 1−9 vs 10 and 11). Meanwhile, in the [3 + 2] cycloaddition with **1a**, nitrones **2** could better endure the existence of a bulky naphthyl group at the R^3 position or a sterically less-hindered methyl group at the R^4 position, thus producing products **3al** in 96% chemical yield and **3am** in 82% chemical yield (entries 12 and 13). Importantly, with regard to the [3 + 2] cycloaddition with **1a**, nitrones **2** completely did not tolerate the introduction of a phenyl group at the R^4 position or an ethyl group at the R^3 position (entries 1 vs 14, 1 vs 15). Interestingly, it was noted that the substitution pattern of the R^3 group of nitrones **2** also drastically affected the chemical yield of the [3 + 2] cycloaddition with **1a** (entries 2 vs 5, 3 vs 4).

Furthermore, we also attempted the [3 + 2] cycloaddition of more reactive nitrone **2a** with a wide range of oxazol-5-(4*H*)-ones **1** containing varying R^1 or R^2 groups (entries 16−21). Normally, in the case of the [3 + 2] cycloaddition with **2a**, the oxazol-5-(4*H*)-ones **1** featuring an electron-rich phenyl group at the R^1 position preferentially delivered products **3** in chemical

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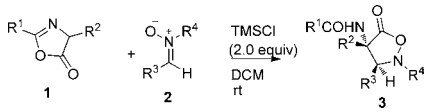
Table 4. Extension of the Reaction Scope[a]



entry	1 (R^1,R^2)	2 (R^3,R^4)	3	time (h)	yield[b] (%)	dr[d]
1	**1a** (Ph, Bn)	**2a** (Ph, Bn)	**3aa**	10	90	>20:1
2	**1a** (Ph, Bn)	**2b** (2-BrC_6H_4, Bn)	**3ab**	10	89	>20:1
3	**1a** (Ph, Bn)	**2c** (3-ClC_6H_4, Bn)	**3ac**	10	99	>20:1
4	**1a** (Ph, Bn)	**2d** (4-ClC_6H_4, Bn)	**3ad**	10	93	>20:1
5	**1a** (Ph, Bn)	**2e** (4-BrC_6H_4, Bn)	**3ae**	10	>99	>20:1
6	**1a** (Ph, Bn)	**2f** (4-$NO_2C_6H_4$, Bn)	**3af**	10	97	>20:1
7	**1a** (Ph, Bn)	**2g** (4-MeC_6H_4, Bn)	**3ag**	18	85	>20:1
8	**1a** (Ph, Bn)	**2h** (4-MeOC_6H_4, Bn)	**3ah**	20	78	>20:1
9	**1a** (Ph, Bn)	**2i** (3,4,5-*tri*-MeOC_6H_2, Bn)	**3ai**	18	89	>20:1
10	**1a** (Ph, Bn)	**2j** (2-furyl, Bn)	**3aj**	24	71	>20:1
11	**1a** (Ph, Bn)	**2k** (2-thienyl, Bn)	**3ak**	24	75	>20:1
12	**1a** (Ph, Bn)	**2l** (2-naphthyl, Bn)	**3al**	12	96	>20:1
13	**1a** (Ph, Bn)	**2m** (Ph,Me)	**3am**	24	82	>20:1
14	**1a** (Ph, Bn)	**2n** (Ph, Ph)	**3an**	24	nr[c]	
15	**1a** (Ph, Bn)	**2o** (Et, Bn)	**3ao**	24	nr[c]	
16	**1b** (2-ClC_6H_4, Bn)	**2a** (Ph, Bn)	**3ba**	24	80	>20:1
17	**1c** (3-ClC_6H_4, Bn)	**2a** (Ph, Bn)	**3ca**	24	78	>20:1
18	**1d** (4-ClC_6H_4, Bn)	**2a** (Ph, Bn)	**3da**	16	85	>20:1
19	**1e** (4-MeC_6H_4, Bn)	**2a** (Ph, Bn)	**3ea**	12	90	>20:1
20	**1f** (Ph, Ph)	**2a** (Ph, Bn)	**3fa**	16	78	>20:1
21	**1g** (Ph, Me)	**2a** (Ph, Bn)	**3ga**	24	75	>20:1
22	**1e** (4-MeC_6H_4, Bn)	**2d** (4-ClC_6H_4, Bn)	**3ed**	10	99	>20:1
23	**1e** (4-MeC_6H_4, Bn)	**2c** (3-ClC_6H_4, Bn)	**3ec**	10	>99	>20:1
24	**1d** (4-ClC_6H_4, Bn)	**2c** (3-ClC_6H_4, Bn)	**3dc**	10	91	>20:1
25	**1d** (4-ClC_6H_4, Bn)	**2e** (4-BrC_6H_4, Bn)	**3de**	12	86	>20:1
26	**1d** (4-ClC_6H_4, Bn)	**2b** (2-BrC_6H_4, Bn)	**3db**	16	72	>20:1
27	**1b** (2-ClC_6H_4, Bn)	**2f** (4-$NO_2C_6H_4$, Bn)	**3bf**	16	83	>20:1

[a]Unless otherwise noted, reactions were carried out with **1** (0.12 mmol), **2** (0.1 mmol), TMSCl (0.20 mmol) in the DCM (0.5 mL) at room temperature. [b]Isolated yield. [c]No reaction. [d]Determined by ^{1}H NMR.

yields higher than those observed with the oxazol-5-(4*H*)-ones **1** using an electron-poor phenyl group as the R^1 substitution (entries 19 vs 16−18). For the oxazol-5-(4*H*)-ones **1** choosing a phenyl or methyl as the R^2 group, the chemical yield of the [3 + 2] cycloaddition with **2a** decreased tremendously in contrast with that obtained with oxazol-5-(4*H*)-one **1a** (entries 1 vs 20 and 21). We found that the [3 + 2] cycloaddition of the oxazol-5-(4*H*)-ones **1** bearing an electron-rich phenyl group as the R^1 substitution with nitrones **2** possessing an electron-poor phenyl as the R^3 group preferred forming products **3** in excellent chemical yields (entries 22 and 23). By comparison, for the [3 + 2] cycloaddition of the oxazol-5-(4*H*)-ones **1** using an electron-poor phenyl group as the R^1 substitution with nitrones **2** having an electron-poor phenyl substitution as the R^3 group, the chemical yield of products **3** changed from 72 to 91% (entries 24−27). Also, we carried out the asymmetric [3 + 2] cycloaddition of oxazol-5-(4*H*)-one **1a** and nitrone **2a** using chiral Lewis acids and organocatalysts, and product **3aa** was generated in 0−31% ee (see details in the Supporting Information).

Meanwhile, the chemical structure of **3ad** was firmly confirmed by single-crystal X-ray analysis, as depicted in Figure 1.[12] The conformational analysis demonstrated that the

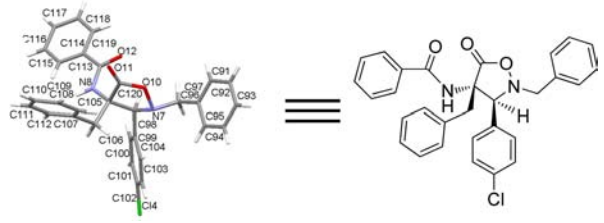
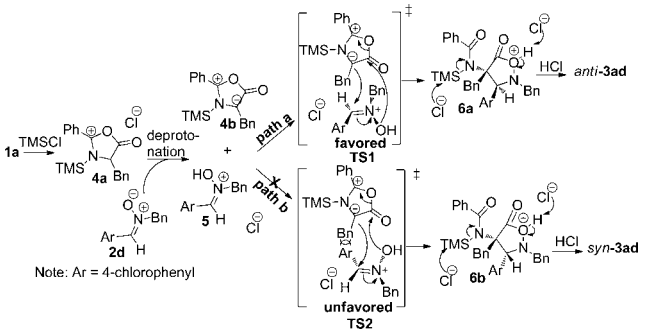


Figure 1. X-ray single-crystal structure of **3ad** (with thermal ellipsoids shown at the 50% probability level).

isoxazolidin-5-one ring moiety of **3ad** features a highly twisted conformation. In addition, we hypothesized the reaction mechanism for the diastereoselective formation of **3ad**, as described in Scheme 2. Initially, treatment of oxazol-5-(4*H*)-one

Scheme 2. Proposed Mechanism for the Formation of 3ad



1a with TMSCl forms **4a**.[3d] Then, the formed **4a** is deprotonated to give **4b** by using **2d** as the base. Finally, the in situ formed **4b** and **5** perform the [3 + 2] cycloaddition via a cascade nucleophilic addition−ring closure process.[13] In this reaction, two possible transition states, **TS1** and **TS2**, are involved: **TS1** delivers intermediate **6a** which is responsible for the formation of *anti*-**3ad**; by comparison, **TS2** affords intermediate **6b** as a precursor for *syn*-**3ad**. With the aid of the molecule model, we found that **TS2** has strong steric repulsion between the Bn group of **4b** and the Ar group of **5**, whereas, regarding the transition state **TS1**, this type of unfavorable interaction is avoided completely. As a consequence, **TS1** reasonably accounts for the diastereoselective generation of *anti*-**3ad**.

In conclusion, the [3 + 2] cycloaddition of oxazol-5-(4*H*)-ones with nitrones was achieved in excellent diastereoselectivities and provided easy access to the novel potentially bioactive isoxazolidin-5-ones in reasonable chemical yields. Furthermore, the exploration of other novel cycloadditions of oxazol-5-(4*H*)-ones with other various dipoles is ongoing in our organic lab and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03206.

Experimental details and NMR spectra for compounds **3** (PDF)

X-ray data for **3ad** (CIF)

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Notes

The authors declare no competing financial interest.

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