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Highly Diastereoselective DABCO-Catalyzed [3 + 3]-Cycloaddition of 1,4-Dithiane-2,5-diol with Azomethine Imines

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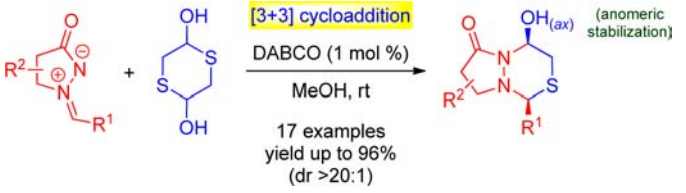
ABSTRACT



An effective diastereoselective [3 + 3] cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines catalyzed by DABCO is described. A variety of highly functionalized six-membered dinitrogen-fused heterocycles can be obtained in good yield with excellent diastereoselectivity, which was controlled by anomeric effect.

Intermolecular cycloaddition is one of the most effective approaches for the facile formation of cyclic compounds from simple starting materials. Heterocycles are privileged structural units that are frequently encountered in biologically active natural products as well as in pharmaceuticals and agrochemicals.[1] In particular, dinitrogen-fused heterocycles, which are typical motifs found in bioactive compounds, have been widely investigated as herbicides, pesticides, and analogues of β-lactam antibiotics such as penicillin and cephalosporin.[2] Azomethine imines, developed by Dorn and Otto in 1968,[3] are easily accessible and stable compounds which have been commonly used as 1,3-dipoles in [3 + 2] cycloadditions for synthesis of pyrazolidines.[4,5] However, these effective 1,3-dipoles have seldom been employed in a single-step construction of six-membered heterocycles to date.[6] In 2006, Hayashi developed a [3 + 3] cycloaddition of azomethine imines with trimethylenemethane catalyzed by $Pd(PPh_3)_4$.[6a] Later on, Scheidt reported a [3 + 3] annulation reaction of

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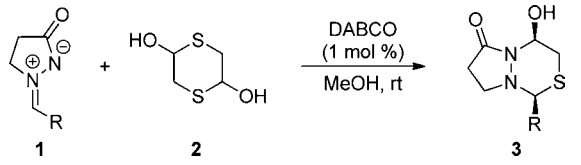
azomethine imines and enals catalyzed by *N*-heterocyclic carbene (NHC).[6b] In 2009, Toste described a [3 + 3] cycloaddition of azomethine imines and propargyl esters catalyzed by $PicAuCl_2$.[6c] Most recently, Doyle reported a [3 + 3] annulation of azomethine imines with enoldiazoacetates catalyzed by $Rh_2(OAc)_4$.[6d] Despite the above achievements, employing azomethine imines as ring-closure partners in the synthesis of six-membered heterocycles is still underdeveloped and highly desirable.

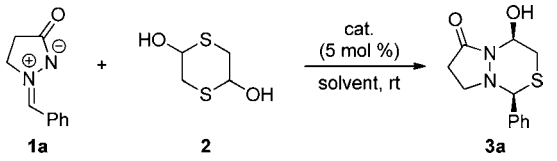
Scheme 1. DABCO-Catalyzed [3 + 3] Cycloaddition of 1,4-Dithiane-2,5-diol with Azomethine Imines



Sulfur-containing compounds exhibit diverse applications in many areas of chemistry and biology.[7] Commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) has proved to be an attractive synthon for the construction of tetrahydrothiophene derivatives through a formal [3 + 2] annulation strategy.[8] However, to our knowledge, cycloaddition reactions of 1,3-dipoles with 1,4-dithiane-2,5-diol have yet to be realized. Herein, we report an unprecedented DABCO-catalyzed [3 + 3] cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines to afford highly functionalized six-membered dinitrogen-containing heterocycles under mild reaction conditions with high efficiency (Scheme 1).

We initiated our investigation by evaluating the reaction of 1,4-dithiane-2,5-diol **2** and azomethine imine **1a** with CH_2Cl_2 as the solvent in the presence of 5 mol % of DABCO at room temperature. To our gratification, this reaction proceeded efficiently to provide an six-membered [3 + 3] cycloadduct **3a** in 86% yield with excellent diastereoselectivity (>20:1 dr) within 40 min (Table 1, entry 1). Encouraged by this promising result, several other bases were screened, and no better results were achieved (entries 2−4).

Table 1. Optimization of the Base-Catalyzed [3 + 3] Cycloaddition of 1,4-Dithiane-2,5-diol **2** with Azomethine Imine **1a**[a]



entry	cat.	solvent	time (h)	yield[b] (%)	dr[c]
1	DABCO	CH_2Cl_2	0.7	86	>20:1
2	Et_3N	CH_2Cl_2	1	82	>20:1
3	DBU	CH_2Cl_2	6	75	>20:1
4	Na_2CO_3	CH_2Cl_2	4	83	>20:1
5	–	CH_2Cl_2	48	34	>20:1
6	DABCO	PhMe	1	83	>20:1
7	DABCO	Et_2O	8	81	>20:1
8	DABCO	THF	0.6	85	>20:1
9	DABCO	EtOAc	0.4	82	>20:1
10	DABCO	MeOH	0.2	92	>20:1
11[d]	DABCO	MeOH	0.2	93	>20:1

[a] Unless otherwise noted, reactions were carried out with 0.2 mmol of **1a** and 0.11 mmol of **2** in 0.5 mL of solvent. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Carried out on a 1.0 mmol scale with 1 mol % of DABCO.

This cycloaddition became much slower in the absence of a base as the catalyst (entry 5). Subsequently, solvent effects were investigated for the reaction (entries 6−10). It was found that this [3 + 3] cycloaddition is highly dependent on the solvent used. Polar and protic solvents such as EtOAc and MeOH were superior to less polar solvents. The reaction became very sluggish when ether was employed as the solvent probably duo to the relatively lower solubility of azomethine imine in Et_2O (entry 7), and MeOH was shown to be the best choice for this transformation in terms of both the reaction rate and the yield, affording the desired product in 92% yield and >20:1 dr in about 10 min (entry 10). In addition, excellent results were obtained even with 1 mol % of DABCO when the reaction was carried out on a larger scale (entry 11). More importantly, we were delighted to observe that the product could be isolated as a white solid by simple filtration, which demonstrates that this method can be easily scaled-up. It is noteworthy that no precautions for the use of inert atmosphere are required since the reactions can be performed in an open flask.

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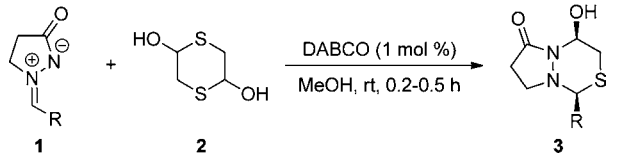
Having established the optimal reaction conditions, the scope of this [3 + 3] cycloaddition reaction was explored with a wide array of azomethine imines **1**. In all cases, the reaction proceeded smoothly to give the expected cycloadducts in good to high yields (75−96%) with excellent diastereoselectivities (> 20:1 dr). As tabulated in Table 2, this cycloaddition is considerably general and tolerates azomethine imines bearing electron-rich and electron-deficient groups at different positions on the aromatic ring. Treating various azomethine imines (**1a**−**i**) with 1,4-dithiane-2,5-diol (**2**) in the presence of 1 mol % of DABCO at room temperature in MeOH for 0.2−0.5 h readily provided the corresponding products **3a**−**i** in 82−93% yields (Table 2, entries 1−9). The azomethine imines containing 2-naphthyl and (*E*)-styryl groups also worked well, giving rise to the anticipated pyrazolidinones as sole diastereomer in high yields (entries 10 and 11). Moreover, heteroaromatic azomethine imines **1l** and **1m** also participated in the reaction well (entries 12 and 13). Remarkably, the less reactive aliphatic aldehyde-derived azomethine imine **1n** was also tolerated in this cycloaddition, affording the expected cycloadduct **3n** in good yield with high level of diastereoselective control (entry 14).

Table 2. Substrate Scope of the DABCO-Catalyzed [3 + 3] Cycloaddition of 1,4-Dithiane-2,5-diol **2** with Azomethine Imines **1**[a]



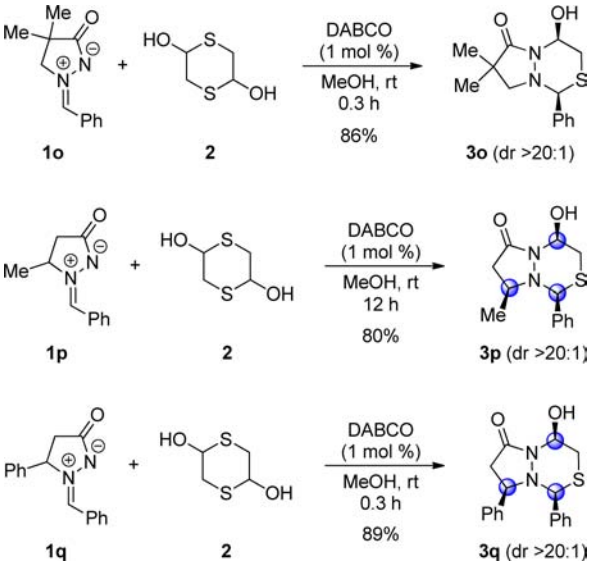
1 **2** **3**

entry	R	product	yield[b] (%)	dr[c]
1	Ph (**1a**)	**3a**	93	>20:1
2	*o*-Me-C_6H_4 (**1b**)	**3b**	83	>20:1
3	*m*-Me-C_6H_4 (**1c**)	**3c**	86	>20:1
4	*p*-Me-C_6H_4 (**1d**)	**3d**	92	>20:1
5	*p*-MeO-C_6H_4 (**1e**)	**3e**	86	>20:1
6	*o*-Cl-C_6H_4 (**1f**)	**3f**	82	>20:1
7	*m*-Cl-C_6H_4 (**1g**)	**3g**	85	>20:1
8	*p*-Br-C_6H_4 (**1h**)	**3h**	87	>20:1
9	*p*-CN-C_6H_4(**1i**)	**3i**	90	>20:1
10	2-naphthyl (**1j**)	**3j**	88	>20:1
11	(*E*)-styryl (**1k**)	**3k**	80	>20:1
12	2-furyl (**1l**)	**3l**	75	>20:1
13	3-pyridyl (**1m**)	**3m**	96	>20:1
14	*n*-pentyl (**1n**)	**3n**	89	>20:1

[a] All reactions were carried out with 1.0 mmol of **1** and 0.55 mmol of **2** in 2.0 mL of MeOH. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Azomethine imines with different substituents on the pyrazolidinone ring can be employed successfully in the current [3 + 3] cycloaddition reaction as well (Scheme 2). For instance, 4,4-dimethyl-substituted 1,3-dipole **1o** furnishes the desired cycloadduct **3o** in 86% yield. Notably, racemic 5-methyl and 5-phenyl-substituted dipoles **1p** and **1q** are converted to the corresponding six-membered heterocycles **3p** and **3q** bearing three tertiary centers in *syn*-configuration with excellent diastereoselective control.

Scheme 2. DABCO-Catalyzed [3 + 3] Cycloaddition of 1,4-Dithiane-2,5-diol **2** with Azomethine Imines **1** Bearing Substituents on the Pyrazolidinone Ring



The relative configuration of the cycloadduct **3q** was unequivocally determined by a single X-ray crystallographic analysis (Figure 1).[9] Notably, the hydroxyl group was preferentially arranged at the axial orientation instead of the less hindered equatorial orientation in the six-membered chairlike configuration due to the stabilization of anomeric effect.[10] The stereochemistry of other cycloadducts **3** was tentatively assumed by analogy.

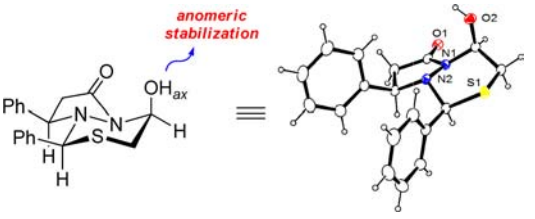


Figure 1. X-ray crystallographic structure of cycloadduct **3q**.

To illustrate the synthetic utility of the present methodology, the reaction of azomethine imine **1a** and 1,4-dithiane-2,5-diol **2** was carried out on a gram scale (Scheme 3). To our delight, in the presence of 0.2 mol % of DABCO, the adduct **3a** was isolated in 95% yield as a

(9) CCDC 944823 (**3q**) contains the supplementary crystallographic data for this paper.

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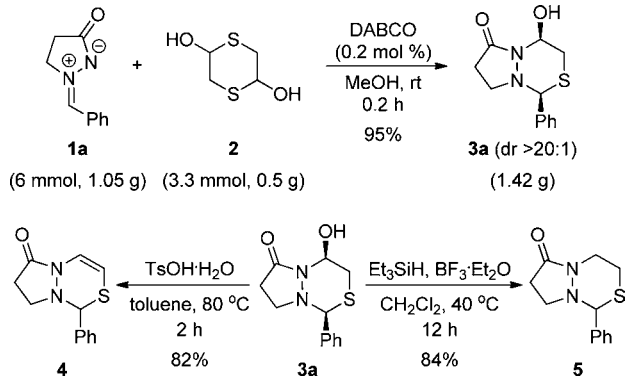
Scheme 3. Scale-up of the Catalytic [3 + 3] Cycloaddition Reaction and Synthetic Transformation of the Cycloadduct **3a**



single diastereomer, and a fast reaction rate was still maintained. Treatment of the cycloadduct **3a** with a catalytic amount of *p*-toluenesulfonic acid monohydrate in toluene at 80 °C delivered the dehydrated product **4** in 82% yield. The hydroxy group of **3a** could be easily removed by reduction with $Et_3SiH/BF_3 \cdot Et_2O$ at 40 °C to give compound **5** in 84% yield.[11]

Based on the above experimental results and activation model reported previously,[8d−f] a plausible catalytic cycle of the current [3 + 3] cycloaddition was proposed, as shown in Scheme 4. We envisioned that the tertiary amine of the catalyst would provide suitable basicity to enhance the nucleophilicity of mercaptoacetaldehyde, which is generated from 1,4-dithiane-2,5-diol **2** under equilibrium conditions. The sulfur nucleophile of the deprotonated mercaptoacetaldehyde is oriented in such way to attack the azomethine imine **1** from the back side with less steric hindrance for the carbon−sulfur bond formation. Subsequent intramolecular cyclization through nucleophilic attack of the negatively charged nitrogen to the aldehyde moiety in excellent diastereoselective fashion, which was efficiently controlled by anomeric effect, then followed by regeneration of the catalyst gives the dinitrogen-fused heterocyclic compounds.

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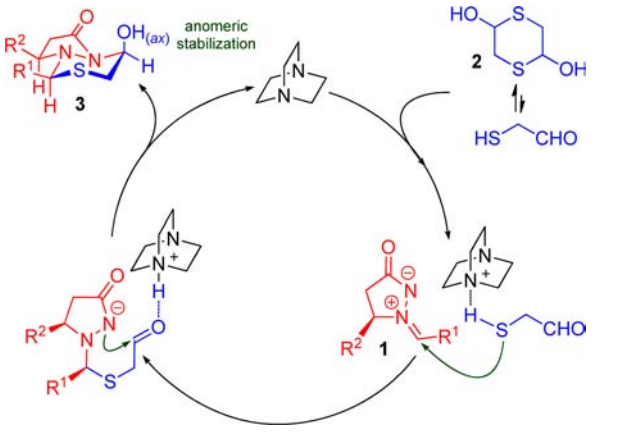
Scheme 4. Proposed Catalytic Cycle for the DABCO-Catalyzed [3 + 3] Cycloaddition of 1,4-Dithiane-2,5-diol with Azomethine Imines



In conclusion, we have successfully developed an effective and unprecedented DABCO-catalyzed [3 + 3] cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines to afford highly functionalized six-membered dinitrogen-fused heterocycles in high yields with excellent diastereoselectivities controlled by anomeric effect. The synthetic utility and practicality of this methodology was demonstrated by a gram-scale synthesis and simple work-up. Further investigations of the development of a catalytic asymmetric variant of this reaction and its application in the synthesis of bioactive molecules are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.