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Stereospecific Synthesis of 1,5-Disubstituted Tetrazoles from Ketoximes via a Beckmann Rearrangement Facilitated by Diphenyl Phosphorazidate

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ABSTRACT

A novel method for the stereospecific synthesis of 1,5-disubstituted tetrazoles from ketoximes *via* the Beckmann rearrangement was developed using diphenyl phosphorazidate (DPPA) as both the oxime activator and azide source. Various ketoximes were transformed into the corresponding 1,5-disubstituted tetrazoles with exclusive *trans*-group migration and no *E-Z* isomerization of the ketoxime. This method enables the preparation of 1,5-disubstituted tetrazoles without using toxic or explosive azidation reagents.

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Tetrazoles are a significant class of synthetic heterocyclic compounds that have been attracting increasing attention due to their wide range of applications in various scientific fields.[1] Among the tetrazole family, 1,5-disubstituted tetrazoles have been known to exhibit biological activity.[2] For example, cardiazol[3] and cilostazol[4] are 1,5-disubustituted tetrazoles that have been widely used medicinally for treating schizophrenia and intermittent claudication, respectively.

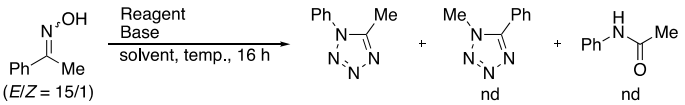
Various methods have been developed for the synthesis of 1,5-disubstituted tetrazoles using a variety of substrates such as amides, thioamides, nitriles, heterocumulenes, amines, ketones, and alkenes.[5] Pioneering studies for the synthesis of 1,5-disubstituted tetrazoles from oxime esters or ketones via the Beckmann[6] or Schmidt rearrangement[7] have also been reported.[8] When using these methods, both the starting materials and end products must be carefully handled because of their inherent toxicities and explosiveness.[9]

Diphenyl phosphorazidate (DPPA)[10] is a less explosive azidation reagent than sodium azide or trifluoromethanesulfonyl azide due to the stabilization of the azide via conjugation with the phosphorus atom. Recently, we have reported the synthesis of 5-substituted 1*H*-tetrazoles from aldoximes using DPPA.[11] This method improved the safety of this azidation operation and utilized DPPA as both the activator and azide source. Therefore, 1,5-disubstituted tetrazoles could be obtained safely from ketoximes if a Beckmann-type rearrangement proceeded by activation and azidation with DPPA.

Initially, we investigated whether the formation of a tetrazole via the Beckmann rearrangement with DPPA was viable using acetophenone oxime **1a** (*E*/*Z*=15/1) as a model substrate. We explored the reaction conditions by investigating various parameters, including temperature, solvent, and base (Table 1).

The reaction performed using DPPA in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in MeCN at room temperature yielded the desired 1,5-disubstituted tetrazole product **2a** with exclusively rearranged phenyl group. However, the yield was low (Table 1, entry 1). To improve yields, the effect of temperature on reactivity was examined (Table 1, entries 2 and 3). The yield improved as the reaction temperature increased, and the desired tetrazole **2a** was obtained in high yield at reflux in MeCN. The use of other solvents decreased the yield relative to MeCN (Table 1, entries 4–8). The effect of base was also investigated; however, the use of triethylamine (Et_3N) or *N*,*N*-diisopropylethylamine (DIPEA) only decreased the yield compared with DBU (Table 1, entries 9 and 10). The use of excess reagent did not improve the yields further (Table 1, entry 11). The tetrazole product **2a** was obtained in moderate yield at room temperature using bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA)[12], which is a more reactive phosphorazidate-type azidation reagent than DPPA. However, the yield decreased when the reaction using *p*-NO_2DPPA was performed at 50 °C (Table 1, entry 13). Notably, the methyl-rearranged **3a** or hydrated products **4a** were not observed as byproducts in any of the tested conditions. Thus, the conditions of entry 3 were the most suitable for our tetrazole formation reaction.

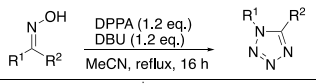
Table 1. Optimization of reaction conditions.



1a **2a** **3a** **4a**

entry	Reagent (eq.)	Base (eq.)	solvent	temp. (°C)	yield (%)
1	DPPA (1.2)	DBU (1.2)	MeCN	rt	11
2	DPPA (1.2)	DBU (1.2)	MeCN	50	63
3	DPPA (1.2)	DBU (1.2)	MeCN	reflux	89
4	DPPA (1.2)	DBU (1.2)	THF	reflux	43
5	DPPA (1.2)	DBU (1.2)	2-MeTHF	reflux	72
6	DPPA (1.2)	DBU (1.2)	CPME	reflux	83
7	DPPA (1.2)	DBU (1.2)	toluene	reflux	80
8	DPPA (1.2)	DBU (1.2)	DMF	110	84
9	DPPA (1.2)	DIPEA (1.2)	MeCN	reflux	48
10	DPPA (1.2)	Et_3N (1.2)	MeCN	reflux	74
11	DPPA (1.5)	DBU (1.5)	MeCN	reflux	91
12	*p*-NO_2DPPA (1.2)	DBU (1.2)	MeCN	rt	69
13	*p*-NO_2DPPA (1.2)	DBU (1.2)	MeCN	50	58

Table 2. Synthesis of various 1,5-disubstituted tetrazoles.

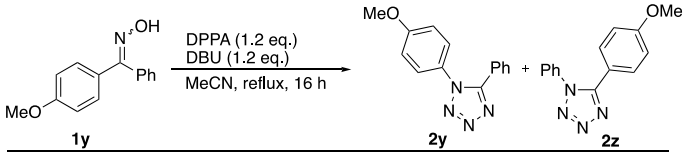


entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	**1a**	**2a**	97	13	**1m**	**2m**	89
2	**1b**	**2b**	97	14	**1n**	**2n**	quant
3	**1c**	**2c**	quant	15	**1o**	**2o**	96
4	**1d**	**2d**	complex mixture	16	**1p**	**2p**	0
5	**1e**	**2e**	complex mixture	17	**1q** (*E*/*Z*=2.8/1)[a]	**2q**	28 (33)[b]
6	**1f**	**2f**	35	18	**1r**	**2r**	61 (68)[b]
7	**1g**	**2g**	87	19	**1s**	**2s**	70 (73)[b]
8	**1h**	**2h**	76	20	**1t**	**2t**	76 (90)[b]
9	**1i**	**2i**	98	21	**1u**	**2u**	70 (81)[b]
10	**1j**	**2j**	16	22	**1v**	**2v**	69 (87)[b]
11	**1k**	**2k**	complex mixture	23	**1w**	**2w**	69 (83)[b]
12	**1l**	**2l**	75	24	**1x**	**2x**	62 (84)[b]

a) Determined by ^{1}H NMR. b) Toluene was used instead of MeCN.

Since tetrazole ring formation via a Beckmann rearrangement proceeded as anticipated, the substrate scope was investigated using various ketoximes, as shown in Table 2. Except for entry 17 in Table 2, all reactions were performed using only the *E* ketoxime isomer. Both aromatic and aliphatic substituted groups rearranged to afford the desired tetrazoles. When a single *E*-isomer of acetophenone oxime **1a** was used, instead of the mixture of isomers used in Table 1, the desired product **2a** was successfully obtained in a high yield (Table 2, entry 1). As expected for the Beckmann rearrangement, electron-rich acetophenone oximes **1c** improved the yield, whereas electron-poor acetophenone oxime starting materials **1d-f** led to lower yields (Table 2, entries 3–6). Halogenated acetophenone oximes **1g** and **1h** afforded the corresponding tetrazoles in reasonable yields under these conditions (Table 2, entries 7 and 8). The substrate bearing a cyano group or a nitro group afforded a complex mixture displaying a plurality of products, so each tetrazole could not be isolated (Table 2, entries 4 and 5). Furthermore, heteroaromatic ketoximes **1j-l** afforded lower yields compared with acetophenone oxime **1a** (Table 2, entries 10–12). Propiophenone **1m** and benzophenone oximes **1n** afforded the corresponding tetrazoles **2m** and **2n** in high yields (Table 2, entries 13 and 14) and vinylic ketoxime **1o** afforded the desired product **2o** in a high yield (Table 2, entry 15). Acetoxime **1p** did not afford the corresponding tetrazole; therefore, we believe the methyl rearrangement is not favorable (Table 2, entry 16). Aliphatic substrates afforded the corresponding tetrazoles in higher yields in toluene than MeCN (Table 2, entries 17–24). Both acyclic and cyclic ketoximes afforded the corresponding desired products. Although the use of benzyl ketoxime **1q** resulted in a low yield (Table 2, entry 17),

Table 3. Tetrazole synthesis using an isomeric mixture of ketoximes.



1y **2y** **2z**

E : *Z* [a]	Yield (%)	ratio [a]
11 : 9	97	11 : 9
1 : 15	99	1 : 15
5 : 1	98	5 : 1

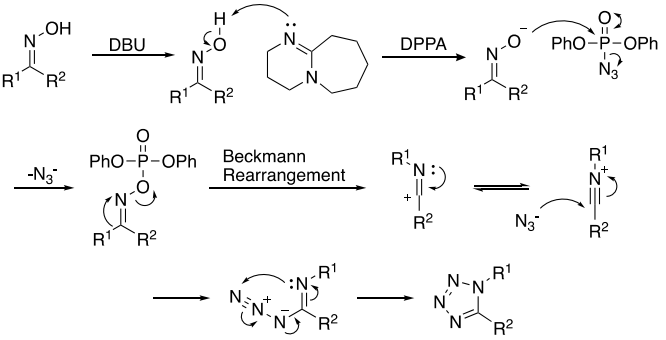
a) Determined by ^{1}H NMR.

sterically hindered ketoximes **1v** and **1x** produced tetrazoles in moderate yields (Table 2, entries 22, and 24). Incidentally, entry 24 displays the synthetic utility of this reaction being able to work with complex natural product-like molecules. In every reaction, only the *trans*-group was exclusively rearranged.

We then applied this tetrazole formation method to bisaryl ketoxime **1y**, which is prone to isomerization. As shown in Table 3, the starting ratio of isomers resulted in the corresponding ratio of products; therefore, isomerization did not take place during our tetrazole formation reaction. These results show that this reaction proceeds stereospecifically.

A plausible reaction mechanism for this reaction is shown in Scheme 1. Initially, the ketoxime is deprotonated by DBU and attacks DPPA to form a phosphate intermediate. Subsequently, the phosphate intermediate undergoes a Beckmann rearrangement to generate a nitrilium ion, followed by attack by the free azide anion and cyclization yields the desired tetrazole.

In summary, we developed a novel method for the synthesis of 1,5-tetrazole from ketoximes *via* a Beckmann rearrangement utilizing DPPA as both the activator and azide source. Various ketoximes were easily converted into the corresponding tetrazoles. No ketoxime isomerization occurred during the reaction and the rearrangement occurred stereospecifically with only the migration of *trans*-group. The advantages of this method include operational simplicity and increased safety as toxic or explosive azide reagents can be avoided.



Scheme 1. Plausible reaction mechanism.

General procedure

DPPA (52 μL, 0.24 mmol) and DBU (36 μL, 0.24 mmol) were added to a solution of the ketoxime (0.20 mmol) in MeCN or toluene (1 mL). After stirring for 16 h at reflux, the mixture was diluted with AcOEt (30 mL). Then, the mixture was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL) and dried over Na_2SO_4. Concentration of the solvent *in vacuo* followed by the purification of the residue on a silica gel column (AcOEt:*n*-Hexane 1:3–3:1) yielded the corresponding 1,5-disubstituted tetrazole.

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Supplementary Material

Supporting information for this article is available online at XXX.

Graphical Abstract

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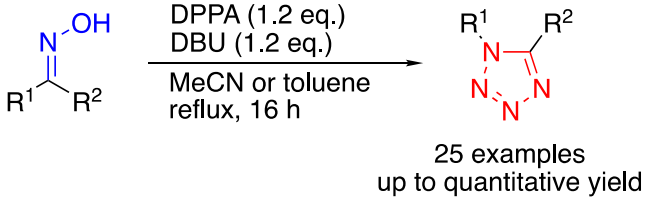

Highlights

- Various ketoximes were easily converted into the corresponding tetrazoles.
- No ketoxime isomerization occurred during the reaction.
- The rearrangement occurred stereospecifically with the migration of *trans* group.
- Tetrazoles can be prepared without using toxic or explosive azidation reagents.