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Efficient [4+3] Cycloaddition Reaction of aza-*o*-Quinodimethanes with *C,N*-cyclic Azomethine Imines: Stereoselective Synthesis of 1,2,4-Triazepines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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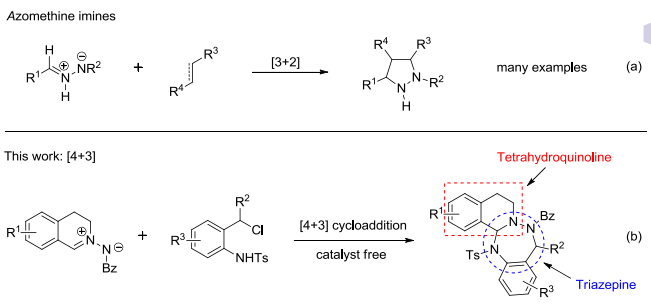
An efficient [4+3] cycloaddition reaction of in situ generated aza-*o*-quinodimethanes with *C,N*-cyclic azomethine imines has been developed. A wide range of 1,2,4-triazepine derivatives were synthesized in high yields (81-99%).

The biological activity of natural products has not only stimulated the development of efficient strategies for the assembly of complex structures, but also inspired the design of unnatural molecules with diverse structures and pharmaceutical applications.[1] Particularly intriguing are nitrogen-containing heterocyclic compounds. For example, seven-membered heterocycles are key subunits found in a large number of complex molecules with significant biological activities.[2] Among the wide variety of synthetic approaches to access these heterocycles, the 1,3-dipolar cycloaddition reaction, extensively studied by Huisgen,[3] has emerged as a particularly useful strategy, because of their bond-forming efficiency, atom economy, excellent stereoselectivity, product structure diversity/complexity, etc.[4] Recently, 1,3-dipolar cycloaddition reaction of alkynes or electron-deficient alkenes with azomethine imines (Scheme 1a), a less common but yet functionally valuable class of 1,3-dipoles, has recently attracted more attention.[5]

Azomethine imines were for a long time restricted to acyclic structures, whose generation requires a high activation energy,[6] or special pyrazolidinone-derived *N,N'*-cyclic forms.[7] Novel *C,N*-cyclic *N'*-acyl azomethine imines were then discovered by Tamura[8] and more recently developed by Maruoka and co-workers,[9] thus opening the field to an unexplored class of dipoles. From then on, normal- and inverse-electron-demand 1,3-cycloaddition reaction with these substrates was realized, first with enals via Ti–binolate catalysis[9] and second with vinyl ethers or acrolein-derived vinylogous azaenamines catalyzed by a chiral dicarboxylic acid.[10] Furthermore, these *C,N*-cyclic azomethine imine substrates were recently used in thermal 1,3-cycloaddition reaction with *N*-aryl maleimides,[11] allenoates,[12] and seleno- or thioaldehydes,[13] phosphine-catalyzed [3 + 2] and [4 + 3] annulation reactions with allenoates,[14] and catalyst free [5 + 1] cycloaddition with isocyanides.[15] Finally, several recent reports concern a variety of metal-catalyzed cycloaddition reactions of azomethine imines,[16] including an enantioselective Ni-catalyzed cycloaddition with alkylidene malonates.[17] More recently, our group reported the asymmetric [3+2] cycloaddition of *C,N*-cyclic azomethine imines with α,β-unsaturated aldehydes and aldehydes.[18] As a part of our continuing interests in this area,[19] herein, we report the first example regarding an efficient catalyst-free [4+3] 1,3-dipolar cycloaddition reaction of *C,N*-cyclic azomethine imines with in situ generated aza-oquinodimethanes, which generated 1,2,4-triazepine derivatives in high yields and excellent stereo-control (Scheme 1b).



Scheme 1. Strategies for the reaction of azomethine imines..

We started our study with the model reaction of *N*-(2-(chloromethyl) phenyl)-4-methylbenzenesulfonamide **1a** (1.0 equiv) and *C,N*-cyclic azomethine imine **2a** (1.1 equiv) in the presence of Na_2CO_3 (1.1 equiv). **1a** and **2a** were carried out in DMSO at room temperature for 1h. Pleasingly, thin-layer chromatography (TLC) indicated that **1a** showed an excellent conversion. NMR analysis revealed that the desired 1,2,4-triazepine **3aa** was generated in 79% (Table 1, entry 1). To further improve the chemical yield, several bases were screened (Table 1, entry2-6). Notably, inorganic bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, KOH, and $NaHCO_3$) gave good yields (Table 1, entries 1-5), while the use of organic base, Et_3N led to a huge decrease in chemical yield (Table 1, entry 6). In addition, solvent was found to be a critical impact on the reaction efficiency

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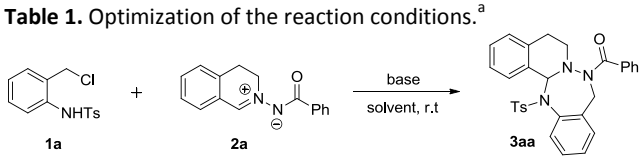
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

(Table 1, entries 7-11). As the result indicated in Table 1, THF were identified as an ideal medium for the generation of **3aa** (entry 11, 99%). Reducing the reaction time to 0.5 h (Table 1, entry 12), the chemical yield was slightly diminished to 89%.

With the optimized conditions in hands (Table 1, entry 11; **1a** (1.0 equiv), **2a** (1.1 equiv), Na_2CO_3 (1.1 equiv), THF as solvent, room temperature), we next investigated the substrate scope by employing a variety of *N*-(*ortho*-chloromethyl)aryl amides and *C,N*-cyclic azomethine imines (Table 2). The scope of *N*-(*ortho*-chloromethyl)aryl amides was examined firstly (Table 2, entries 1-11). *N*-(*ortho*-chloromethyl)aryl amides bearing electron-neutral (Table 2, entry 1) or electron-rich (Table 2, entries 2-4) substituents afforded high yields of the cycloadducts **3aa-3da**. When *N*-(*ortho*-chloromethyl)aryl amides bearing electron-deficient substituents, the corresponding products **3ea-3ia** were obtained in high to excellent yields (Table 2, entries 5-9). Furthermore, incorporation of methyl or chloro substituents at the *ortho*, *meta*, or *para*- positions of the NHTs group did not retard the reaction, thus demonstrating that steric effects in the *N*-(*ortho*-chloromethyl)aryl amides did not alter the reaction efficiency (Table 2, entries 2, 3, 5 and 6). In addition, disubstituted *N*-(*ortho*-chloromethyl)aryl amide **1j** with electron-donating substituent (R^3 = 3,4-Me_2) was efficiently formed cycloadduct **3ja** in 96% yield (Table 2, entry 10). Disubstituted *N*-(*ortho*-chloromethyl)aryl amide **1k** with electron-withdrawing group (R^4 = 5-Cl) resulted in a slightly lower yield (Table 2, entry 11). Moreover, substrates with substituents (**1l**: R^4 = 2-ClC_6H_4, **1m**: R^4 = Me) at the benzylic position also underwent the transformation to produce the corresponding products in excellent yields (Table 2, entries 12 and 13, 90% and 87%, respectively).

Table 1. Optimization of the reaction conditions.[a]

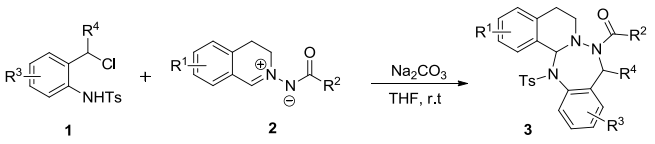


Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	Na_2CO_3	DMSO	1	79
2	K_2CO_3	DMSO	1	74
3	KOH	DMSO	1	58
4	Cs_2CO_3	DMSO	1	65
5	$NaHCO_3$	DMSO	1	68
6	Et_3N	DMSO	1	27
7	Na_2CO_3	CH_2Cl_2	1	80
8	Na_2CO_3	CH_3OH	1	83
9	Na_2CO_3	CH_3CN	1	67
10	Na_2CO_3	Et_2O	1	74
11	**Na_2CO_3**	**THF**	**1**	**99**
12	Na_2CO_3	THF	0.5	89

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.11 mmol), base (0.11 mmol) in the solvent (2.0 mL) at r.t. [b] Isolated yield.

We next turned our attention to *C,N*-cyclic azomethine imines (Table 2, entries 14-24). It was found that both 7-Br and 7-Me substituted *C,N*-cyclic azomethine imines **2b** and **2c** reacted with *N*-(*ortho*-chloromethyl)aryl amides to give the corresponding products in good yields (Table 2, entries 14-15 and 19-21, 86-92%). Notably, azomethine imine with a simple acetyl group (**2f** and **2c**, R^2 = Ac) on the nitrogen also underwent the desired cyclization smoothly to give the desired cycloadduct **3af** and **3bc** in 90% and 89%, respectively (Table 2, entries 18 and 24). The relative configuration of the analogues was assigned based on single-crystal X-ray analysis of **3aa**.[20]

Table 2. Substrate scope of the reaction.[a]

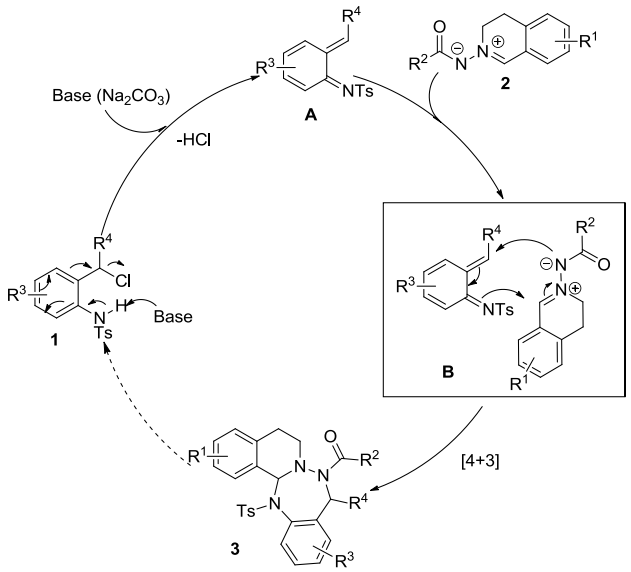


Entry	R^3, R^4 (**1**)	R^1, R^2 (**2**)	Product	Yield (%)[b]
1	H, H (**1a**)	H, Ph (**2a**)	**3aa**	99
2	3-Me, H (**1b**)	H, Ph (**2a**)	**3ba**	98
3	5-Me, H (**1c**)	H, Ph (**2a**)	**3ca**	98
4	5-MeO, H (**1d**)	H, Ph (**2a**)	**3da**	91
5	4-Cl, H (**1e**)	H, Ph (**2a**)	**3ea**	90
6	5-Cl, H (**1f**)	H, Ph (**2a**)	**3fa**	89
7	4-F, H (**1g**)	H, Ph (**2a**)	**3ga**	89
8	4-NO_2, H (**1h**)	H, Ph (**2a**)	**3ha**	81
9	5-Br, H (**1i**)	H, Ph (**2a**)	**3ia**	88
10	3,4-Me_2, H (**1j**)	H, Ph (**2a**)	**3ja**	96
11	3-Me/5-Cl, H (**1k**)	H, Ph (**2a**)	**3ka**	85
12	5-Cl, 2-ClC_6H_4 (**1l**)	H, Ph (**2a**)	**3la**	90
13	H, Me (**1m**)	H, Ph (**2a**)	**3ma**	87
14	H, H (**1a**)	7-Br, Ph (**2b**)	**3ab**	86
15	H, H (**1a**)	7-Me, Ph (**2c**)	**3ac**	88
16	H, H (**1a**)	H, 4-ClC_6H_4 (**2d**)	**3ad**	93
17	H, H (**1a**)	H, 4-MeC_6H_4 (**2e**)	**3ae**	95
18	H, H (**1a**)	H, Me (**2f**)	**3af**	90
19	5-Me, H (**1c**)	7-Br, Ph (**2b**)	**3cb**	92
20	5-MeO, H (**1g**)	7-Br, Ph (**2b**)	**3gb**	89
21	H, Me (**1m**)	7-Br, Ph (**2b**)	**3mb**	87
22	5-MeO, H (**1g**)	H, 4-ClC_6H_4 (**2d**)	**3gd**	95
23	H, Me (**1m**)	H, 4-MeC_6H_4 (**2e**)	**3me**	90
24	3-Me, H (**1b**)	Me, Ph (**2c**)	**3bc**	89

[a] Unless otherwise noted, reactions were carried out with **1** (0.1 mmol), **2** (0.11 mmol), Na_2CO_3 (0.11 mmol) in THF (2.0 mL) at r.t. for 1-2 h. [b] Isolated yield.

As shown in Scheme 2, we proposed a plausible reaction pathway to explain the reaction mechanism. First, *N*-(*ortho*-chloromethyl)aryl amide **1** reacts with 1.1equivalent of Na_2CO_3 to form the *in situ* generated aza-*o*-quinodimethane intermediate **A**. Intermediate **A** then reacts with the *C,N*-cyclic azomethine **2** to

generate the desired product **3** through a thermal [4+3] cycloaddition (**B**).



Scheme 2. Plausible mechanism.

Conclusions

In summary, we have developed an efficient method for the [4+3] cycloaddition reaction of in situ generated aza-*o*-quinodimethanes with *C,N*-cyclic azomethine imines. The reaction generated 1,2,4-triazepine derivatives in high yields. Considering the large variety and the operational simplicity, a convenient, practical and highly yield of synthesis has been developed.

Acknowledgments

We thank the financial support from the National Natural Science Foundation of China (21272043), the Science and Technology Planning Project of Guangdong Province (2007A020300007-10, 2011B090400573) and the Guangdong Natural Science Foundation (S2011010004967).

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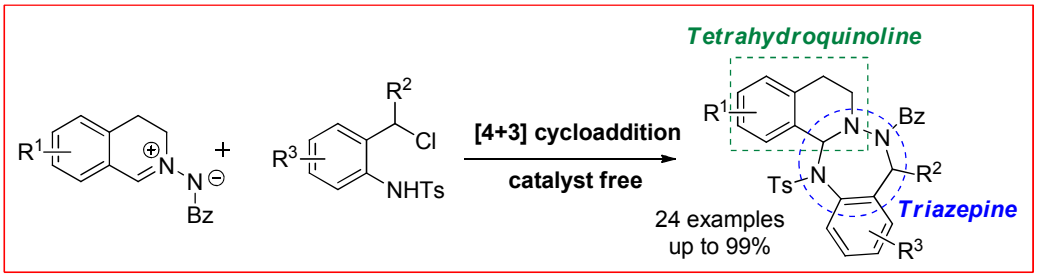
20 CCDC 1415310 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



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