Article

Highly Efficient and Diastereoselective Construction of Substituted Pyrrolidines Bearing A Quaternary Carbon Center via 1,3-Dipolar [3 + 2] Cycloaddition

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Abstract: A general approach to substituted pyrrolidines via [3 + 2] 1,3-dipolar cycloaddition between nonstabilized azomethine ylides and cyanosulfones was developed. The efficient method provides a series of substituted pyrrolidines bearing a quaternary carbon center in high yields (up to 98%) excellent diastereoselectivities (up to >25:1 *dr*) under ambient reaction conditions.

Keywords: Pyrrolidines; 1,3-dipolar cycloaddition; azomethine ylides; cyanosulfones

1. Introduction

The pyrrolidine ring is attractive five-membered nitrogen-containing heterocycle and appear as an important structural skeleton in a variety of natural products, biologically active alkaloids, organocatalysts and pharmaceuticals [1-3]. In fact, about 400 bioactive natural products are comprised of pyrrolizidine framework [4]. Especially, lots of drugs and bioactivated compounds include pyrrolidine motifs exhibit remarkable pharmacological activities when the pyrrolidine ring bearing a quaternary carbon at C3 position. For example, some representative examples of pyrrolidines containing quaternary stereocenter always exhibit a broad range of important biological activities (Figure 1), such as antibacterial agent [5], anthelmintic activity (Cucurbitine) [6,7], anticholesteremic and immunomodulattor (SkandF 103811) [8], RORγt inverse agonists [9] and so on. Therefore, the development of efficient and novel synthetic methods for functionalized pyrrolidine scaffolds bearing a quaternary carbon center at C3 position has become an attractive objective.

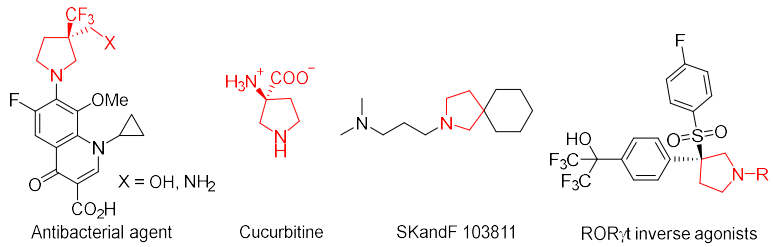

Figure 1. Representative examples of biologically active nature products and pharmaceuticals containing pyrrolidine units.

To the best of our knowledge, the [3 + 2] 1,3-dipolar cycloaddition reaction of azomethine ylides with activated alkenes was proved to be one of the most effective and

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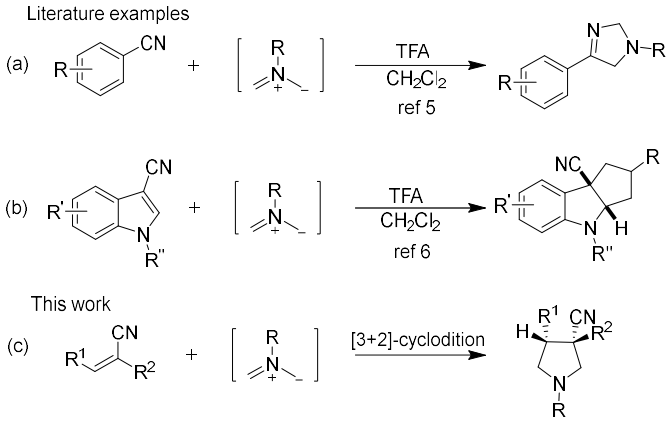
well-established methods for the chemo- and stereoselective construction of polyfunctional pyrrolidines in a single step [10-14]. In particular, azomethine ylides of non-stabilized type generated in situ from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-alkyl-amine are highly reactive intermediates [15], which reached with a diverse range of dipolarophiles to afford various nitrogen compounds via [3 + 2] [16-24] or [3 + 3] [25,26] cycloaddition reactions. Moreover, the non-stabilized azomethine ylides could take place the C≡N bond of some containing cyano-group compounds (Scheme 1a) [27]. The dearomative cycloadditions between non-stabilized azomethine ylides and 3-cyanoindoles or benzofuran also had been develop to afford the corresponding cyano-group compounds bearing a quaternary carbon centre at the ring junction (scheme 1b) [28]. on the other hand, the cyano [29-32] and sulfonyl group [33-36] is a valuable functional group in organic synthesis and has shown interesting application potential in drug design and synthesis. Inspired by these previous studies, we developed that a general approach to access functionalized pyrrolidines from α,β-unsaturated α,α-disubstituted aryl cyanosulfones [37,38] with non-stabilized azomethine ylides via [3 + 2] dipolar cycloaddition (scheme 1c). Our strategy leads to the pyrrolidines derivatives bearing a quaternary carbon center at C3 position with two functional groups (the cyano and sulfonyl group substituted) important for medicinal chemistry.



Scheme 1. [3+2]-Dipolar cycloaddition reaction of involving cyano-group compounds with non-stabilized azomethine ylides.

2. Results

Our investigation commenced with α-*p*-toluenesulfonyl-cinnamonitrile **1a** and non-stabilized azomethine ylide generated in situ from *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** in the presence of trifluoroacetic acid (TFA) as the model substrates to optimize the reaction conditions. As the results are summarized in Table 1. To our delight, It was found that the [3 + 2] cycloaddition reaction proceeded smoothly and the desired cyclization product **3a** was obtained in 90% yield with in high diastereoselective (*dr* > 25;1) using CH_2Cl_2 as solvent for 6 h (Table 1, entry 1). In order to enhance the conversion, the time of the reaction was prolonged to 12 h, providing the cycloadduct **3a** in 98% yield (entry 2). In addition, the yield could not change when the reaction time went on prolonging to 18 h (entry 3). Subsequently, the solvent effect was investigated (entries 4-11). From among the tested solvents, the CH_2Cl_2 proved to be the best choice with respect to efficiency. When using the $CHCl_3$, DCE or CH_3CN as the solvent, the reaction gave the product in higher yield (entries 4-5 and 7). Other the solvent, such as toluene, EtOAc, Et2O, THF or dioxane, affording the product in medium yield (entries 6 and 8-11). Reducing the loading of TFA to 50 mol% resulted in some loss of yield (entry 12).

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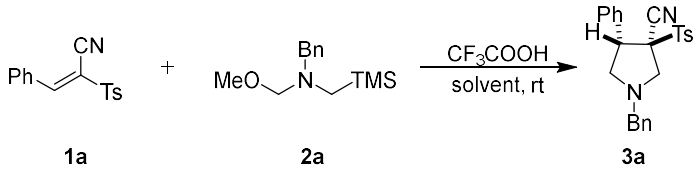
Table 1. Optimization of reaction conditions. [a]



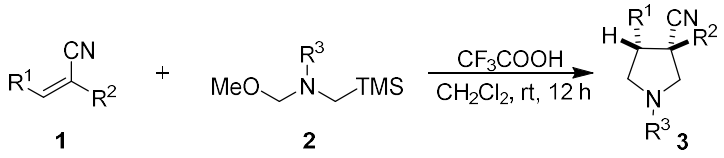
1a 2a 3a

Entry	Solvent	Time	Yield (%)[b]
1	CH_2Cl_2	6	90
2	CH_2Cl_2	12	98
3	CH_2Cl_2	18	98
4	$CHCl_3$	24	95
5	DCE	24	91
6	Toluene	24	72
7	CH_3CN	24	90
8	EtOAc	24	76
9	THF	24	61
10	Et_2O	24	55
11	dioxane	24	58
12[c]	CH_2Cl_2	24	85

[a]Unless noted otherwise, reactions were performed with α-*p*-toluenesulfonyl-cinnamonitrile **1a** (0.1 mmol) and *N*-(methoxymethyl)-*N*-(trimethyl silylmethyl)-benzyl-amine **2a** (0.12 mmol), TFA (0.12 mmol, 1 equiv.) in solvent (1.0 mL) at rt. [b]Yield of the isolated product and *dr* >25:1 by ^{1}H NMR analysis. [c]0.5 equiv.TFA were used.

3. Discussion

Table 2. Substrate scope and limitations of the [3 + 2] cycloaddition.[a]



1 2 3

Entry	R^1	R^2	R^3	Yield (%)[b]
1	Ph	Ts	Bn	**3a**, 98
2	4-MeC_6H_4-	Ts	Bn	**3b**, 94
3	4-$MeOC_6H_4$-	Ts	Bn	**3c**, 95
4	4-BuC_6H_4-	Ts	Bn	**3d**, 94
5	4-FC_6H_4-	Ts	Bn	**3e**, 97
6	4-ClC_6H_4-	Ts	Bn	**3f**, 96
7	2-BrC_6H_4-	Ts	Bn	**3g**, 98
8[c]	3-BrC_6H_4-	Ts	Bn	**3h**, 97
9	4-BrC_6H_4-	Ts	Bn	**3i**, 98
10	4-CF_3C6H_4-	Ts	Bn	**3j**,95
11	3,5-$Cl_2C_6H_3$-	Ts	Bn	**3k**, 95
12	2-Furyl	Ts	Bn	**3l**, 92
13	3-Thienyl	Ts	Bn	**3m**, 93
14	1-Naphthyl	Ts	Bn	**3n**, 96
15	2-Naphthyl	Ts	Bn	**3o**, 96
16	Ph	Ts	Me	**3p**, 92
17	Ph	$C_6H_5SO_2$-	Bn	**3q**, 95
18	Ph	4-$ClC_6H_4SO_2$-	Bn	**3r**, 96
19[d]	Ph	CN	Bn	**3s**, 92
20[d]	Ph	COOEt	Bn	**3t**, 93
21	Ph	Ac	Bn	**3u**, mess

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22	Ph	Bz	Bn	**3v**, mess
23	Cy	Ts	Bn	**3w**, mess

[a]Unless noted otherwise, reactions were performed with α,β-unsaturated α,α-disubstituted aryl cyanosulfones **1** (0.1 mmol), *N*-(methoxymethyl)-*N*-(trimethyl silylmethyl)-alkyl-amine **2** (0.12 mmol), TFA (0.12 mmol, 1 equiv.) in CH_2Cl_2 (1.0 mL) at rt for 12 h. [b]Yield of the isolated product and *dr* >25:1 by ^1H NMR analysis. [c]The relative configuration of **3h** was determined by X-ray analysis. The other products were assigned by analogy. [d]The reaction was performed for 24 h.

Having the optimized conditions in hand, we set out to investigate the scope and limitation of a range of conjugated arylcyanosulfones **1** for the [3 + 2] 1,3-dipolar cycloaddition reaction with non-stabilized azomethine ylides to provide substituted pyrrolidines. Under the optimized conditions, we were pleased to find that they all exhibited good reactivity. The results of the experiments starting from methyl-, methoxy-, tertiary butyl-, halogen-, trifluoromethyl-, substituted cyanosulfones (**1b**-**k**) and other analogues (**1l**-**o**, R^1 = 2-furyl, 3-thienyl, 1-naphthyl, 1-naphthyl) are presented in Table 2. The [3 + 2] cycloaddition reactions were tolerated all the screening various conjugated arylcyanosulfones **1** without any detrimental effects on the reactivity or stereoselectivity, regardless of the different positions and electronic properties of substituents and steric hindrance substituents into the aryl ring of arylcyanosulfones when the arylcyanosulfones **1** reacted smoothly with the precursor of non-stabilized azomethine ylides **2a** (entries 1-15) or **2b** (entry 16). The reaction afforded the corresponding products **3** (**3a**–**p**) in high isolated yields (92-98%) with excellent diastereoselectivities (>25:1 *dr*). Additionally, the effect of the sulfonyl group of cyanosulfone **1q** [39-40] and **1r** [41-45] was studied to give the corresponding products **3q** and **3r** in 95% and 95% yields, respectively. It's worth noting that the cycloaddition reaction was also amenable to the present system, and a similar degree of diastereoselectivities was observed when the cyano group or ester group instead of the sulfonyl group (entries 19-20). However, when the substrate **1u** and **1v** [46]of the acetyl group or benzoyl group instead of the sulfonyl group and the alkylsulfonyl-substituted cyanosulfone substrate **1w** were treated with the [3 + 2] cycloaddition reaction under the standard condition, the reaction was disordered and offered inseparable mixture.

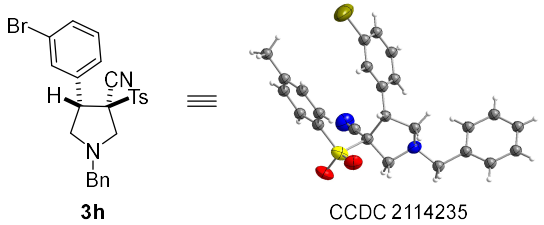
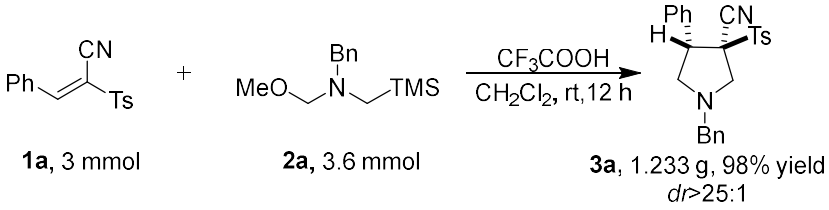


Figure 2. X-ray crystal structure of compound **3h**.

The structure and relative configuration of product **3h** (CCDC 2114235) (see Figures S4 Supplementary Material) was unequivocally established by X-ray crystallographic analysis (Figure 2). For its structural details, see the Supporting information. The other products were assigned by analogy.



Scheme 2. Scaled-up version of synthesis of substituted pyrrolidine **3a**.

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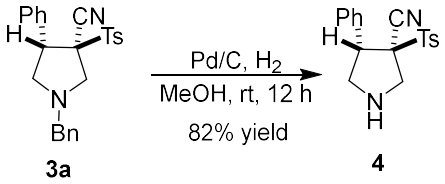

Scheme 3. Transformations of product **3a**.

Finally, in order to show the broad synthetic utility of pyrrolidines for the preparation of pharmaceutically relevant molecules their gram scale experiment and subsequent transformations were studied. Firstly, 3 mmol of α-*p*-toluenesulfonyl-cinnamonitrile **1a** and 3.6 mmol of *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** proceeded smoothly under the standard conditions and offered compound **3a** (1.233 g) in 98% yield with *dr*>25:1 (Scheme 2). Next, we studied the reactivity of the obtained cycloadducts for further modification of the substituted pyrrolidine motif. Cleavage of *N*-benzyl group and remove the benzyl group by hydrogenolysis of **3a** at room temperature using 10% Pd/C as a catalyst afforded the target product **4** in 82% yield (Scheme 3).

4. Materials and Methods

NMR data were obtained for ^{1}H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. Column chromatography was performed on silica gel (200-300 mesh) eluting with ethyl acetate/petroleum ether. TLC was performed on glass-backed silica plates. UV light, I_2, and solution of potassium permanganate were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted. Petroleum ether and ethyl acetate were distilled. THF was freshly distilled from sodium/benzophenone. Unless otherwise noted, experiments involving moisture and/or air sensitive components were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes.

α,β-unsaturated α,α-disubstituted aryl cyanosulfones **1a-r** [37] and benzylidenemalononitrile **1s** [39,40] and ethyl α-cyanocinnamate **1t** [42-44] and α-Cyano-α,β-unsaturated ketones **1u-v** [45] were prepared according to the literature procedures. The α,β-unsaturated α,α-disubstituted aryl cyanosulfones **1** (0.1 mmol), *N*-(methoxymethyl)-*N*-(trimethyl silylmethyl)alkylamine **2** (0.12 mmol), and the TFA (0.12 mmol) were dissolved in CH_2Cl_2 (1.0 mL). Then the solution was stirred at rt for 12 h. After completion, the mixture was directly purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1 to 5:1) to afford the product **3**.

5. Conclusions

In summary, we have successfully shown that α,β-unsaturated α,α-disubstituted aryl cyanosulfones behave as C=C dipolarophiles when reacted with a non-stabilized azomethine ylides generated in situ as electron-rich enriched 1,3-dipoles. The transformation features excellent diastereoselectivities, broad substrate scope, low cost of reagents, and convenient operation. The [3 + 2] cycloaddition provides an efficient protocol for affording novel and substituted pyrrolidines bearing a quaternary centre from easily available substrates in high yields (up to 98%) with excellent diastereoselectivities (>25:1 *dr*) without any metal catalysts. The potential synthetic utility and practicality of the approach were also highlighted by the gram-scale experiment and the synthetic transformation of the product into other heterocyclic compounds. The further application of this strategy is presently under bioactive investigation in our laboratory.

Supplementary Materials: The following are available online. Figure S1: Some new substrates of α,β-unsaturated α,α-disubstituted aryl cyanosulfones, Figure S2: General procedure for [3+2] dipolar cycloaddition, Figure S3: Transformations of product **3a**. Figure S4: X-ray crystal structure of compound **3h**. Figure S5: NMR spectra.

Author Contributions: K.K. Wang, Y.L. Li and Y.C. Zhao participated in the synthesis, purification and characterization of the new compound. R.X. Chen and A.L. Sun participated in the interpretation of spectroscopy of new compounds and the review of the manuscript. R.X. Chen and Z.Y. Wang participated in the interpretation of the results, writing, revision and correspondence to the journal of molecules until the manuscript was accepted. All authors have read and agreed to the published version of the manuscript.

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Sample Availability: Samples of the compounds are available from the authors.

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