Organic LETTERS

Letter

pubs.acs.org/OrgLett

Room-Temperature Organocatalytic Cycloaddition of Azides with β-Keto Sulfones: Toward Sulfonyl-1,2,3-triazoles

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Supporting Information

ABSTRACT: Organocatalytic enamine−azide [3 + 2] cycloadditions between β-keto sulfones and aryl azides can be performed at room temperature in good to excellent yields of products in the presence of catalytic amounts of pyrrolidine (5 mol %). The proposed organocatalytic methodology was found to be applicable to β-keto arylsulfones containing a range of substituents. A wide variety of aryl azides also work. Basically, this constitutes a remarkably efficient protocol for the synthesis of novel 1,2,3-triazole compounds.

Sulfonyl groups are of considerable importance in synthetic and medicinal chemistry.[1] In particular, β-keto sulfones are versatile organic intermediates that have been employed as precursors in Michael reactions[2] and have been used in chalcone,[3] alkyne,[4] pyrrole,[5] phenanthrene,[6] and chiral cyclic nitrone syntheses.[7] Several molecules containing sulfonyl scaffolds displayed useful biological activities[8] (e.g., antibacterial, antifungal, anticonceptive, anti-inflammatory, and antitumoral). Most importantly, Park and co-workers have synthesized a range of sulfonyl alkenes with therapeutic potential for treating Parkinson's disease (Figure 1).[9] Additionally, the combination of a sulfonyl unit with various types of heterocyclic analogue leads to compounds with promising biological activities.[10]

In the context of heterocyclic compounds, 1,2,3-triazoles comprise an interesting class of nitrogen-based heterocycle widely used in the discovery and modulation of drug candidates and the development of new materials.[11] Several methods for the preparation of these heterocycles have been reported including the 1,3-dipolar cycloaddition of azides with alkynes[12] as well as copper- or ruthenium-catalyzed reactions.[13] In view of the restricted applications of metal-based methodologies in chemical biology,[14] recent studies have been directed toward the development of metal-free methodologies for triazole synthesis.[15] Organocatalytic approaches involving [3 + 2] cycloaddition have been reported for the synthesis of functionalized 1,2,3-triazoles.[16] In these reactions, carbonyl compounds can generate enamines or enolates and act as dipolarophiles in organocatalyzed 1,3-dipolar cycloadditions with organic azides.[16a] On this basis, it is evident that the design of efficient methods that use suitable, environmentally sound, and cheap substrates and reaction conditions to synthesize functionalized 1,2,3-triazoles still remains a challenge in organic synthesis.

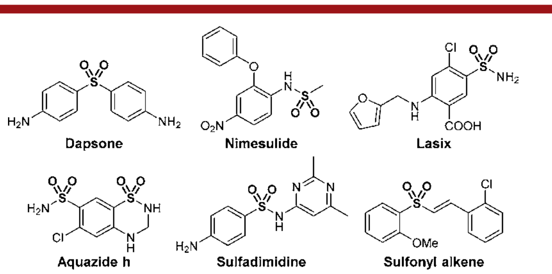
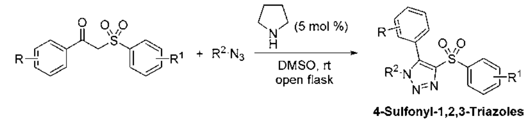


Figure 1. Molecules with biological activity containing sulfonyl moieties in their structure.

Scheme 1. Organocatalytic Synthesis of 4-Sulfonyl-1,2,3-triazoles

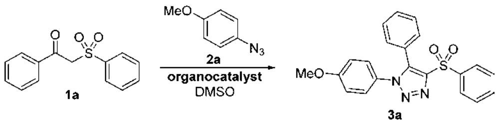


Sulfonyl-containing 1,2,3-triazole compounds are an interesting and still unexplored family of compounds featuring promising and broad biological applications due to the combination of the well-known activity of the sulfonyl group[1] with that of the 1,2,3-triazole core.[11] As an example, a plethora of sulfonyl-1,2,3-triazoles have been synthesized by 1,3-dipolar cycloaddition reactions under ultrasound irradiation and screened for antibacterial, antifungal, and antioxidant activities. The obtained results demonstrated moderated to excellent activities for some of the synthesized compounds.[10c]

Received: November 5, 2015
Published: December 3, 2015

DOI: 10.1021/acs.orglett.5b03196
Org. Lett. 2015, 17, 6206−6209

Table 1. Optimization of Reaction Conditions[a]



entry	organocatalyst (mol %)	time (h)	temp (°C)	yield of **3a**[b] (%)
1	Et_2NH (1)	24	rt	30
2	Et_2NH (5)	24	rt	35
3	Et_2NH (10)	24	rt	60
4	Et_2NH (20)	24	rt	65
5	Et_2NH (10)	4	70	84
6	pyrrolidine (10)	4	70	87
7	pyrrolidine (10)	24	rt	92
8	pyrrolidine (5)	24	rt	92
9	pyrrolidine (5)	4	70	93
10	pyrrolidine (1)	24	rt	45

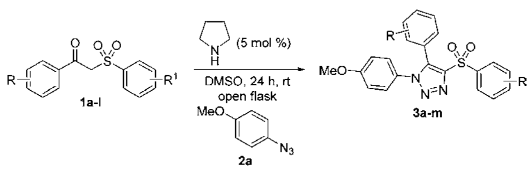
[a]Reaction conditions: 2-benzenesulfonyl-1-phenylethanone **1a** (0.3 mmol) and 4-methoxyphenyl azide **2a** (0.33 mmol) in DMSO (0.6 mL) as solvent in an open flask. [b]Yields are given for isolated products.

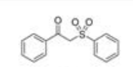
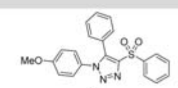
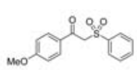
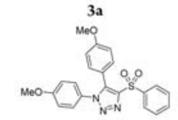
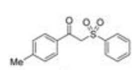
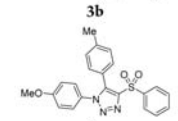
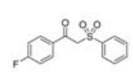
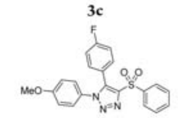
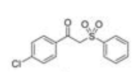
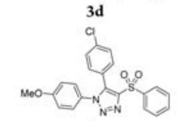
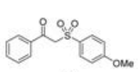
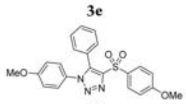
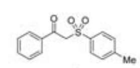
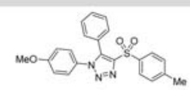
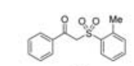
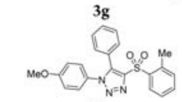
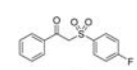
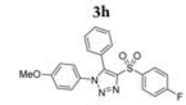
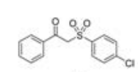
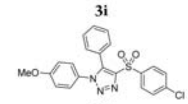
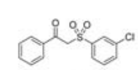
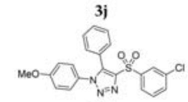
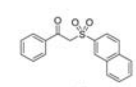
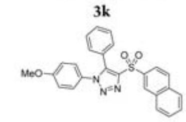
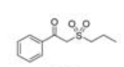
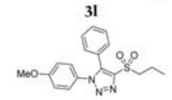
To the best of our knowledge, the direct use of β-keto sulfones to synthesize highly functionalized 1,2,3-triazoles via organocatalytic enamine−azide cycloaddition with organic azides has not been explored to date. In continuation of our research endeavors in the synthesis of functionalized 1,2,3-triazoles, we report herein the organocatalyzed room-temperature synthesis of a range of 1,5-disubstituted 4-(arylsulfonyl)-1*H*-1,2,3-triazoles via enamine-azide [3 + 2] cycloaddition (Scheme 1).

Preliminary experiments to optimize the reaction conditions were performed using β-keto sulfone **1a** and 4-methoxyphenyl azide **2a** as model reaction substrates (Table 1).

On the basis of the conditions described in our previous report,[17] a room-temperature reaction between substrates **1a** (0.3 mmol) and **2a** in DMSO (0.6 mL) using 1 mol % of Et_2NH as organocatalyst provided a poor yield (30%) of the desired product **3a** after 24 h (Table 1, entry 1). The yield of **3a** was observed to increase with an increase in the amount of organocatalyst (1−20 mol %, Table 1, entries 2−4). As expected, a very good yield of product **3a** could be obtained at 70 °C using 10 mol % of Et_2NH (Table 1, entry 5). Similar results were obtained under identical reaction conditions using pyrrolidine as the organocatalyst[18] (10 mol %, Table 1, entry 6). To our delight, a remarkable improvement in chemical yield was achieved when the reaction was carried out at room temperature, however, only after 24 h (Table 1, entries 7 and 8). A decrease in organocatalyst loading (from 10 to 5 mol %) did not seem to influence the reaction yields (Table 1, entries 7 vs 8) Comparatively, the reaction performed in the presence of 1 mol % of pyrrolidine at

Table 2. Scope of the Reaction: Variability of β-Keto Sulfones[a]

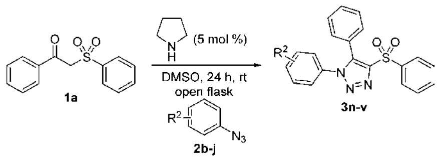


Entry	β-Keto Sulfone 1	Product 3	Yield (%)[b]
1	 **1a**	 **3a**	92
2	 **1b**	 **3b**	84
3	 **1c**	 **3c**	93
4	 **1d**	 **3d**	93
5	 **1e**	 **3e**	95
6	 **1f**	 **3f**	92
7	 **1g**	 **3g**	68
8	 **1h**	 **3h**	96
9	 **1i**	 **3i**	80
10	 **1j**	 **3j**	98
11	 **1k**	 **3k**	86
12	 **1l**	 **3l**	90
13	 **1m**	 **3m**	78

[a]Reactions were performed with β-keto sulfones **1a−m** (0.3 mmol) and 4-methoxyphenyl azide **2a** (0.33 mmol) in DMSO (0.6 mL) as solvent at room temperature in an open flask for 24 h. [b]Yields are given for isolated products.

DOI: 10.1021/acs.orglett.5b03196
Org. Lett. 2015, 17, 6206−6209

Table 3. Scope of the Reaction: Variability of Azide[a]



Entry	Azide 2	Product 3	Yield (%)[b]
1	2b	3n	90
2	2c	3o	90
3	2d	3p	76
4	2e	3q	83
5	2f	3r	96
6	2g	3s	92
7	2h	3t	90
8	2i	3u	83
9	2j	3v	95

[a]Reactions were performed with 2-benzenesulfonyl-1-phenylethanone **1a** (0.3 mmol) and aryl azides **2b–j** (0.33 mmol) in DMSO (0.6 mL) as solvent at room temperature in an open flask for 24 h. [b]Yields are given for isolated products.

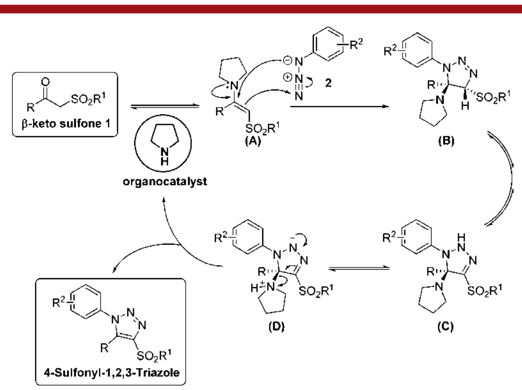


Figure 2. Proposed mechanism.

room temperature gave a poor yield of product **3a** (Table 1, entry 10).

From Table 1, the optimum reaction conditions to obtain 1-(4-methoxyphenyl)-5-phenyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazole **3a** were clearly present in entry 8, using 2-benzenesulfonyl-1-phenylethanone **1a** (0.3 mmol), 4-methoxyphenyl azide **2a** (0.33 mmol), and pyrrolidine (5 mol %) as organocatalyst and DMSO (0.6 mL) as the solvent at room temperature in an open flask.

The scope of the proposed methodology was then extended to a range of *β*-keto sulfones **1** (Table 2) and aryl azides **2** (Table 3) under optimized reaction conditions. 4-Methoxyphenyl azide **2a** reacted efficiently with electron-neutral and different electron-deficient *β*-keto sulfones to give the corresponding 4-sulfonyl-1,2,3-triazoles **3a–m** in good to excellent yields. Interestingly, substituents present in the aryl group vicinal to the ketone (e.g., MeO, Me, F, Cl) did not influence the reactivity, with high yields of products being obtained in all cases (Table 2, entries 2–5, products **3b–e**). Reactions of azide **2a** with *β*-keto sulfones containing electron-donating groups (EDG) **1f–h** and electron-withdrawing (EWG) sustituents **1i–k** at the arylsulfonyl moiety yielded the corresponding products **3f–k** in 68–98% yields (Table 2, entries 6–11). The reaction performed with a *β*-keto sulfone containing a tosyl group (**1g**) gave access to the corresponding triazole **3g** in 68% yield (Table 2, entry 7). Comparably, the reaction with naphthylsulfonyl derivative **1l** as substrate produced the corresponding 4-sulfonyl-1,2,3-triazole **3l** in 90% yield (Table 1, entry 12). Reaction performed with alkyl-substituted sulfone **1m** furnished exclusively the respective product **3m** in 78% yield (Table 1, entry 13).

The reactivity of 2-benzenesulfonyl-1-phenylethanone **1a** with different functionalized aryl azides **2b–j** under otherwise identical reaction conditions was subsequently investigated. In general, the reactions were found not to be sensitive to the electronic conditions in the aryl ring of the azides. Aryl azides containing either an EDG or an EWG on the aromatic ring delivered the expected 4-sulfonyl-1,2,3-triazoles **3o–t** in good isolated yields (Table 3, entries 2–7). However, a decrease in yield was observed when the reaction was performed with aryl azides containing a strongly EWG (NO_2) (e.g., substrate **2e**, Table 3, entry 4). An interesting steric effect was observed when *o*-tolyl azide **2d** was employed, and the desired product **3p** was obtained in 76% yield (Table 3, entry 3). Finally, when the reactions were carried out with 2-azidophenyl phenyl selenide **2i** and 4-azido-7-chloroquinoline **2j**, the corresponding products **3u** and **3v** were obtained in 83 and 95% yield, respectively (Table 3, entries 8 and 9).

On the basis of recently published reports on organocatalytic enamine-azide [3 + 2] cycloadditions employing aryl azides as dipolarophiles,[16,19] it is possible to propose a possible mechanism for this reaction. We believe that the sulfonyl enamine intermediate A is formed first, after condensation of pyrrolidine with the *β*-keto sulfone **1**. A subsequent 1,3-dipolar cycloaddition between the sulfonyl enamine **A** and the aryl azide 2 would give rise to triazoline intermediate **B**, which can undergo a plausible 1,3-hydride shift to generate triazoline intermediate **C**. Finally, the zwitterionic form of C, represented as intermediate **D**, could undergo an elimination reaction to regenerate pyrrolidine to continue the catalytic cycle and produce the desired 4-sulfonyl-1,2,3-triazole (Figure 2).

In summary, a simple, efficient and environmentally friendly room-temperature organocatalytic enamine–azide [3 + 2] cycloaddition between *β*-keto sulfones and aryl azides is

DOI: 10.1021/acs.orglett.5b03196
Org. Lett. 2015, 17, 6206–6209

described herein for the production of a range of 1,5-disubstituted 4-(arylsulfonyl)-1*H*-1,2,3-triazoles. Triazoles could be synthesized in good to excellent yields (65−96%) using catalytic amounts of pyrrolidine. The proposed organocatalytic methodology was compatible with a range of substituents in the β-keto sulfones and/or aryl azides, and this has proven to be an efficient methodology for the synthesis of new 1,2,3-triazole compounds, expected to have promising biological activities which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03196.

General experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the CNPq (Grant Nos. 306430/2013-4, 400150/2014-0, and 447595/2014-8), CAPES, FAPERGS, FAPESP (15/17141-1 and 14/50249-8), and FINEP for the financial support. R.L. graftefully acknowledges support from Ciencia sem Fronteiras Program (2015-2017) as Visiting Scientist to Federal University of Pelotas - UFPel, RS.

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DOI: 10.1021/acs.orglett.5b03196
Org. Lett. 2015, 17, 6206−6209