ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 14606

Received 24th October 2019,
Accepted 5th November 2019

DOI: 10.1039/c9cc08326j

rsc.li/chemcomm

Pyridinium 1,4-zwitterionic thiolates as a useful class of sulfur-containing synthons: application to the synthesis of 2,5-dihydro-1,4,5-thiadiazepines†

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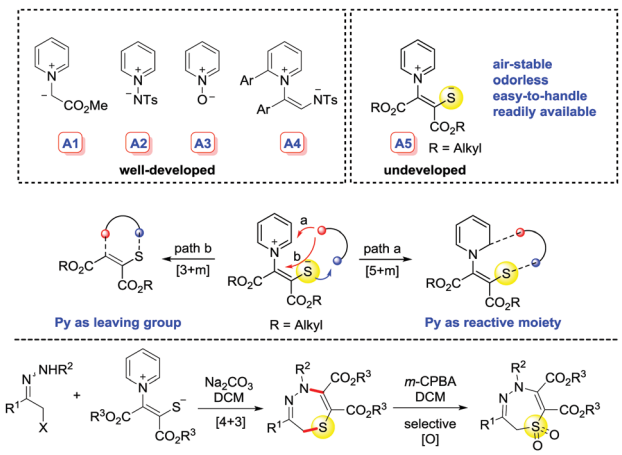
A novel [4+3] cascade cyclization reaction of pyridinium 1,4-zwitterionic thiolates with azoalkenes derived from α-halo hydrazones *in situ* has been developed. This reaction was found to allow expedient access to an array of 2,5-dihydro-1,4,5-thiadiazepines. Libraries of highly functionalized sulfoxide and sulfone analogues of 2,5-dihydro-1,4,5-thiadiazepines were also obtained *via* selective oxidation with *m*-CPBA.

Sulfur is a chemical element closely involved in various aspects of human life, as it is ubiquitous in natural products,[1] pharmaceutical molecules,[2] functional materials[3] and almost all living organisms.[4] Organosulfur compounds are found in a variety of forms (*e.g.*, thioethers, sulfoxides, and sulfones, among others) that serve various functions in agrochemistry, medicinal chemistry, material chemistry and food chemistry. Thus, many efficient methods have been developed to introduce sulfur atoms into target molecules.[5] Thiols and thioethers have traditionally been used as the sulfur-containing synthons, and sulfur powder, inorganic metal sulfides and sulfur-containing small organic molecules have also been developed as sulfuration agents. However, the use of these synthons to incorporate sulfur into organic molecules does have some drawbacks, such as the unpleasant odor of thiols and thioethers, and the need to involve transition-metal catalysts.[1c,6] Thus, developing air-stable, odorless, easy- to -handle, and readily available sulfur-containing synthons is highly desired.

Pyridinium zwitterions have been long used as a class of powerful and flexible organic synthons, and great advances in this field have been made during the past decades by organic chemists.[7] The commonly used pyridinium zwitterions mainly include **A1–A3** and their analogues (Scheme 1), one of the important applications of which was using them as 1,3-dipoles to produce diversified heterocyclic compounds, where the pyridine moiety was retained in the target molecules. Recently, Yoo reported the pyridinium 1,4-zwitterionic compounds **A4** (Scheme 1) and successfully applied them to a series of cycloaddition reactions (*e.g.*, [5+2], [5+3]) to access unusual medium-sized heterocycles, where the pyridine part of **A4** was also incorporated into the target products.[8] In 2011, Bazgir reported an efficient and simple synthesis of pyridinium 1,4-zwitterionic thiolates **A5** (Scheme 1) from dialkyl acetylenedicarboxylates, elemental sulfur, and pyridine.[9] However, 1,4-zwitterionic thiolates of this class have not yet been recognized as useful and versatile synthons to the best of our knowledge. In this context, intrigued by their unique structures, we envisaged that the reactive intermediates could be used to prepare sulfur-containing heterocycles *via* two reaction modes: [5+*m*, path a], with pyridine as a reactive moiety, and [3+*m*, path b], with pyridine as a leaving group (Scheme 1). Thus, we embarked on a program to explore and understand their properties and reactivities comprehensively.



Scheme 1 Commonly used pyridinium zwitterions and our design of pyridinium 1,4-zwitterionic thiolates.

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† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra and HRMS data. CCDC 1885455 (**3a**) and 1887981 (**4l**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc08326j

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Here, we describe our preliminary results on their cascade cyclization reactions with azoalkenes to access 2,5-dihydro-1,4,5-thiadiazepines *via* path b. In addition, libraries of highly functionalized sulfoxide and sulfone analogues of 2,5-dihydro-1,4,5-thiadiazepines were obtained *via* selective oxidation with *m*-CPBA.

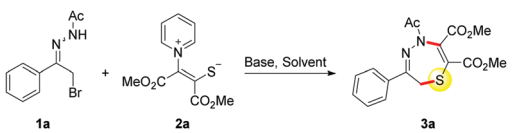
According to the literature,[10] azoalkenes could be readily prepared *in situ* from α-halo hydrazones. Thus, α-bromo *N*-Ac hydrazone **1a** and pyridinium 1,4-zwitterionic thiolate **2a** were adopted as the model substrates to probe the cyclization reaction. To our delight, the reaction proceeded cleanly with Na_2CO_3 as the base in dichloromethane (DCM) at room temperature under air, affording 2,5-dihydro-1,4,5-thiadiazepine **3a**, an intriguing seven-membered sulfur-containing diazaheterocycle, in 79% yield (Table 1, entry 1).[11] The exact structure of **3a** was unambiguously established using X-ray diffraction analysis.[12] It was evident that **3a** was generated along the [4+3] pathway (Scheme 1, path b) with **2a** as a three-atom reactant. It should be pointed out that there have been no reports on the reactions of pyridiniums **A1–A3** with azoalkenes in the literature, although some other 1,3-dipoles (*e.g.*, nitrones, azomethines) could react with azoalkenes to form seven-membered heterocycles.[10a–f] Encouraged by this initial success, we then screened a series of reaction conditions including the equivalents of the reactants (entries 1–4), bases (entries 5 and 6), and solvents (entries 7–9), and a 98% yield of **3a** was obtained under the optimal reaction conditions (**1a** : **2a** : Na_2CO_3 = 1 : 1.5 : 2, DCM, room temperature, under air, Table 1, entry 2).

With the optimal reaction conditions in hand, we started to scrutinize the generality and scope of this [4+3] cascade cyclization reaction. As shown in Table 2, we first studied the aryl-substituted *N*-Ac hydrazones. The electronic properties of the substituents on the phenyl group had no obvious influence on the cyclization efficiency, as all of them worked well and afforded an array of seven-membered S/N-heterocycles (**3a–i**) in 81% to 98% yields. The 2-furyl-substituted substrate was also tolerated and gave the corresponding product (**3g**) in 55% yield. Then, alkyl and alkenyl-substituted *N*-Ac hydrazones were examined, and found to be suitable substrates as well, furnishing the cyclization products (**3h** and **3i**) in 91% and 64% yields, respectively. Ethyl ester-derived 1,4-zwitterionic thiolate was equally efficient and delivered **3j** in 89% yield. The reaction of α-bromo *N*-Boc hydrazones showed a similar situation as the α-bromo *N*-Ac ones and gave a library of analogues of seven-membered sulfur-containing heterocycles (**3k–t**). As exemplified by **3f**, **3h**, **3p** and **3r**, α-chloro hydrazones were amenable to this cascade transformation. Interestingly, *N*-Ac hydrazones showed higher yields than did *N*-Boc hydrazones for some substrates (*e.g.*, **3h** *vs.* **3r**) and lower yields for other substrates (*e.g.*, **3g** *vs.* **3q**). In addition, this [4+3] cascade cyclization reaction could be performed on the gram scale with only a slight decrease in yield (see, **3a**).

With the library of seven-membered sulfur-containing heterocycles established above, we next turned our attention to accessing their sulfone and sulfoxide analogues *via* selective oxidation. Thioethers can be transformed to and from sulfoxides or sulfones. More importantly, their different oxidative states could exhibit diverse bioactivities.[13] Fortunately, when *m*-CPBA (1.0 equiv.) was adopted as the oxidant, sulfoxides (**4a–j**, Table 3) were obtained as the major products with satisfying yields. Moreover, when 3 equiv. of *m*-CPBA was used, representative sulfone analogues (**4k–o**) comprising phenyl, 2-furyl, *t*-butyl, and (*E*)-styrenyl groups were smoothly produced as the sole products.[12] Of note, both of the *N*-Ac and *N*-Boc substrates and various functional groups were compatible with these selective oxidation conditions. Thus, a library of seven-membered sulfur-containing diazaheterocycles with three distinct oxidation states (thioether, sulfoxide and sulfone) was successfully established, and is expected to have great potential and value for structure–activity relationship (SAR) studies.

Based on the previous reports,[14] we proposed a plausible reaction mechanism for the [4+3] cascade cyclization reaction (Scheme 2). Here azoalkenes, formed *in situ* from α-halo hydrazones under basic conditions, react with 1,4-zwitterionic thiolates *via* a cascade process including S-Michael addition, N-Michael addition and retro-Michael addition/Py extrusion to afford 2,5-dihydro-1,4,5-thiadiazepines. An alternative pathway

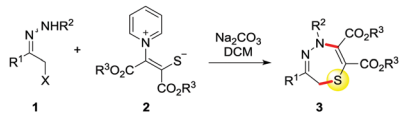
Table 1 Optimization of the reaction conditions[a]



Entry	**1a** : **2a**	Base (equiv.)	Solvent	Yield (%)
1	1 : 1.5	Na_2CO_3 (1.5)	DCM	79
2	***1 : 1.5***	***Na_2CO_3 (2.0)***	***DCM***	***98***
3	1 : 2.0	Na_2CO_3 (2.0)	DCM	93
4	1 : 1.1	Na_2CO_3 (2.0)	DCM	81
5	1 : 1.5	K_2CO_3 (2.0)	DCM	78
6	1 : 1.5	Cs_2CO_3 (2.0)	DCM	97
7	1 : 1.5	Na_2CO_3 (2.0)	THF	41
8	1 : 1.5	Na_2CO_3 (2.0)	MeCN	90
9	1 : 1.5	Na_2CO_3 (2.0)	DCE	78

[a] Reaction conditions: **1a** (0.3 mmol), **2a**, base, solvent (3 mL), r.t. (25 °C), under air. Isolated yield.

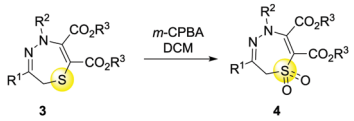
Table 2 [4+3] cascade cyclization reaction[a]



Entry	R^1	R^3	X	Yield (%) R^2 = Ac	Yield (%) R^2 = Boc
1	C_6H_5	Me	Br	**3a**, 98 (91)[b]	**3k**, 93
2	4-MeO-C_6H_4	Me	Br	**3b**, 89	**3l**, 62
3	4-Me-C_6H_4	Me	Br	**3c**, 86	**3m**, 83
4	4-NO_2-C_6H_4	Me	Br	**3d**, 81	**3n**, 97
5	4-CF_3-C_6H_4	Me	Br	**3e**, 91	**3o**, 95
6	4-F-C_6H_4	Me	Cl	**3f**, 92	**3p**, 92
7	2-Furyl	Me	Br	**3g**, 55	**3q**, 84
8	*t*-Bu	Me	Cl	**3h**, 91	**3r**, 51
9	(*E*)-Styrenyl	Me	Br	**3i**, 64	**3s**, 52
10	C_6H_5	Et	Br	**3j**, 89	**3t**, 92

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv.), Na_2CO_3 (0.6 mmol, 2.0 equiv.), solvent (3 mL), 25 °C, in air. Isolated yield. [b] The reaction was conducted on the gram scale.

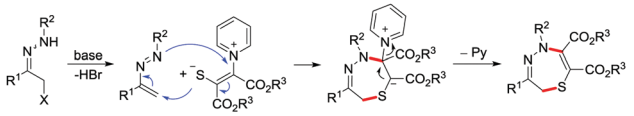
Table 3 Oxidation of **3** to sulfoxides or sulfones with *m*-CPBA[a]



3 **4**

Entry	R^1	R^3	Yield (%) Sulfoxide	Sulfone
1	C_6H_5	Me	**4a**, 72 **4b**, 74[b]	**4k**, 70 **4l**, 66[b]
2	4-MeO-C_6H_4	Me	**4c**, 69	
3	4-Me-C_6H_4	Me	**4d**, 62	
4	4-CF_3-C_6H_4	Me	**4e**, 71	
5	4-F-C_6H_4	Me	**4f**, 72	
6	2-Furyl	Me	**4g**, 78	**4m**, 69
7	*t*-Bu	Me	**4h**, 78	**4n**, 68
8	(*E*)-Styrenyl	Me	**4i**, 74	**4o**, 71
9	C_6H_5	Et	**4j**, 69	

[a] For sulfoxides, reaction conditions: **3** (0.3 mmol), *m*-CPBA (1.0 equiv.), CH_2Cl_2 (3 mL), 25 °C, R^2 = Boc unless otherwise noted. For sulfones, reaction conditions: **3** (0.3 mmol), *m*-CPBA (3.0 equiv.), CH_2Cl_2 (3 mL), 25 °C. Isolated yield. [b] R^2 = Ac.



Scheme 2 Proposed mechanism for the [4+3] cascade cyclization reaction of α-halo hydrazones and pyridinium 1,4-zwitterionic thiolates.

involving S-nucleophilic substitution reaction of halides followed by N-Michael addition and retro-Michael addition/Py extrusion could not be excluded.[15]

In summary, a new reaction mode of pyridinium 1,4-zwitterionic thiolates has been developed, and was found to allow expedient access to 2,5-dihydro-1,4,5-thiadiazepines *via* a [4+3] cascade cyclization reaction under mild conditions. Selective oxidations of 2,5-dihydro-1,4,5-thiadiazepines with *m*-CPBA were successfully achieved, affording libraries of highly functionalized sulfoxide and sulfone analogues. The other performances and reaction modes of pyridinium 1,4-zwitterionic thiolates will be reported in due course.

We thank the NSFC (21971092, 21472072, 21871018, 21732001, and 2167201), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT_15R28) and FRFCU (lzujbky-2019-50, lzujbky-2017-90). We also thank Dr Hanwei Hu for assistance in polishing the manuscript.

Conflicts of interest

There are no conflicts to declare.

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