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Dearomative [3 + 2] cycloaddition reaction of nitrobenzothiophenes with nonstabilized azomethine ylides†

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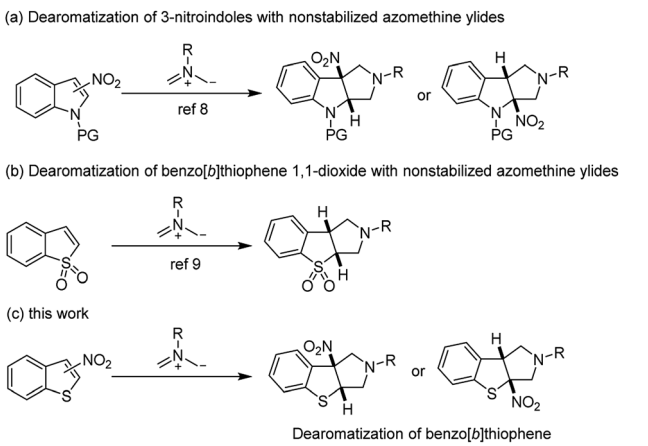
A highly diastereoselective dearomative [3 + 2] 1,3-dipolar cycloaddition reaction of nitrobenzothiophenes with an *in situ*-generated nonstabilized azomethine ylides has been developed. The transformation provides a series of functionalized fused tricyclic benzo[4,5]thieno[2,3-*c*]pyrroles in good yields (up to 92%) under mild reaction conditions. In addition, a gram-scale experiment and the synthetic transformation of the cycloadduct further highlighted the synthetic utility. The relative configurations of the typical products were clearly confirmed by X-ray crystallography.

The dearomative cycloaddition reactions are a powerful synthetic strategy to obtain valuable structural motifs which exist in numerous biologically active natural products, pharmaceutical agents, and also in synthetic and materials building blocks.[1] Among them, indole substrates gained more and more research interest to develop effective methods for the construction of indole-based skeletons and their functionalization *via* dearomative transformation.[2] Because the unique properties of indole ring systems are ubiquitous in biologically active alkaloids,[3] the range of methodologies that have been explored to access dearomatized indole heterocycles is extremely extensive. In contrast to the dearomative reactions of indole substrates, the analogous benzothiophenes derivatives have been less explored.[4] In addition, the benzo[*b*]thiophene derivatives that have found widespread application are frequently found in many bioactive compounds, pharmaceuticals, and as synthetic building blocks.[5] Therefore, the development of efficient synthetic method to realize the dearomatization of benzo[*b*]thiophenes for the construction of diverse functionalized heteroarenes molecules continues to be an important and highly desirable in the organic synthetic community.

On the other hand, 1,3-dipolar cycloaddition of azomethine ylides with electron deficient dipolarophiles that have a wide range of applications in organic synthesis, is a useful and facile synthetic process for five or six membered heterocyclic rings in one step.[6] Especially, nonstabilized azomethine ylides generated *in situ* are highly active intermediates,[7] with electron-deficient benzoheterocycles, including 2-nitroindoles or 3-nitroindoles (Scheme 1a)[8] and benzo[*b*]thiophene 1,1-dioxides (Scheme 1b)[9] as robust electrophiles to construct various polycyclic heterocyclic skeletons *via* the dearomative [3 + 2] 1,3-dipolar cycloaddition reaction in the simple way. However, 3- and 2-nitrobenzothiophenes have been uncovered as electrophiles for the dearomative 1,3-dipolar cycloaddition reactions with nonstabilized azomethine ylides to provide S-containing polyheterocyclic compounds. Enormous efforts have been devoted to the development of ever more efficient synthetic



Scheme 1 Dearomative cycloaddition reaction of electron-deficient heteroarenes with nonstabilized azomethine ylides.

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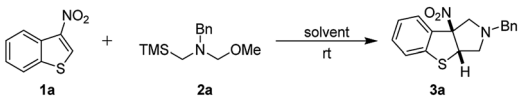
methods for the construction and direct functionalization of these heteroaromatic compounds. Herein, we describe a dearomative [3 + 2] cycloaddition reaction of 3-nitrobenzothiophenes with nonstabilized azomethine ylides without metal catalysts under mild reaction conditions, providing a convenient and efficient access to functionalized fused tricyclic benzo[4,5]thieno[2,3-*c*]pyrroles derivatives bearing two contiguous stereocenters. Additionally, we also successfully extended this new protocol to 2-nitrobenzothiophene and 2-nitrobenzofuran for the corresponding dearomatization products.

Initially, we chosed 3-nitrobenzothiophene **1a** and *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** which generated *in situ* nonstabilized azomethine ylide in the presence of trifluoroacetic acid (TFA) as model substrates to optimize the reaction conditions. As the results are shown in Table 1. To our delight, the cycloaddition reaction proceeded smoothly and the desired [3 + 2] cycloadduct **3a** was obtained in 90% yield with in high diastereoselective CH_2Cl_2 (entry 1). Moreover, the yield could not be further improved when the reaction time was prolonged (entry 2). The yields were decreased (5–81%) when we employed other organic solvents (entries 3–10). In order to further improve the yield, the reaction was performed at 40 °C in CH_2Cl_2. However, the yield of the product decreased to 72% (entry 11), which the possible reason may be that the nonstabilized azomethine ylide was unstable at high temperature that resulted in unexpected side reactions. When the amount of trifluoroacetic acid was loaded to 1.2 equiv., the reaction does not improve the yield of product **3a** (entry 12). Lowering the amount of trifluoroacetic acid led to a decreased yield despite with a prolonged reaction time (entry 13). In addition, the yield of the product **3a** was 64% when the reaction was carried out for 6 h (entry 14) (Table 1).

Table 1 Optimization of reaction conditions[a]

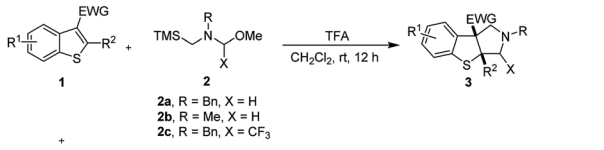


1a 2a 3a

Entry	Solvent	Time	Yield of **3a**[b] (%)
1	CH_2Cl_2	12	90
2	CH_2Cl_2	24	90
3	$CHCl_3$	24	81
4	DCE	24	80
5	EtOAc	24	<5
6	CH_3CN	24	<5
7	Toluene	24	<5
8	THF	24	22
9	Et_2O	24	20
10	Dioxane	24	73
11[c]	CH_2Cl_2	12	72
12[d]	CH_2Cl_2	12	90
13[e]	CH_2Cl_2	24	62
14	CH_2Cl_2	6	64

[a] Unless noted otherwise, reactions were performed with 3-nitrobenzothiophene **1a** (0.1 mmol) and **2a** (0.12 mmol), TFA (0.1 mmol, 1 equiv.) in solvent (1.0 mL) at rt. [b] Yield of the isolated product and dr >20 : 1 by ^{1}H NMR analysis. [c] The reaction was performed at 40 °C. [d] 1.2 equiv. TFA were used. [e] 0.5 equiv. TFA were used.

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



1 2 3

2a, R = Bn, X = H
2b, R = Me, X = H
2c, R = Bn, X = CF_3

Entry	R^1	R^2	Substrate	Yield[b] (%)
1	H	H	**2a**	**3a**, 90
2	5-Me	H	**2a**	**3b**, 92
3	4-Cl	H	**2a**	**3c**, 90
4[c]	5-Cl	H	**2a**	**3d**, 91
5	4-Br	H	**2a**	**3e**, 92
6	5-Br	H	**2a**	**3f**, 88
7	6-Br	H	**2a**	**3g**, 87
8	7-Br	H	**2a**	**3h**, 89
9	H	H	**2b**	**3i**, 84
10	4-Cl	H	**2b**	**3j**, 86
11	5-Cl	H	**2b**	**3k**, 85
12	4-Br	H	**2b**	**3l**, 82
13	5-Br	H	**2b**	**3m**, 83
14	6-Br	H	**2b**	**3n**, 81
15	7-Br	H	**2b**	**3o**, 84
16	H	H	**2c**	**3p**, 0
17[d]	H	H	**2a**	**3q**, 0
18	H	Me	**2a**	**3r**, 0

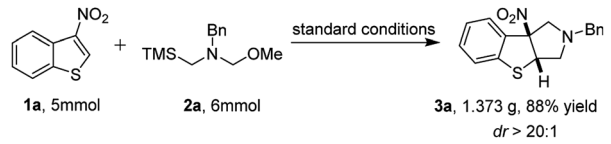
[a] Unless noted otherwise, reactions were performed with 3-nitrobenzothiophene **1** (0.1 mmol), **2** (0.12 mmol), TFA (0.1 mmol, 1 equiv.) in CH_2Cl_2 (1.0 mL) at rt for 12 h, EWG = NO_2. [b] Yield of the isolated product and dr >20 : 1 by ^{1}H NMR analysis. [c] The relative configuration of **3d** was determined by X-ray analysis. The other products were assigned by analogy. [d] EWG = CN.

With the optimized conditions in hand, we set out to investigate the scope and limitation of 3-nitrobenzothiophenes **1** with nonstabilized azomethine ylides *via* dearomative [3 + 2] cycloaddition reaction to provide fused tricyclic benzo[4,5]thieno[2,3-*c*]pyrroles. The representative results are summarized in Table 2. Under the optimized conditions, the dearomative [3 + 2] cycloaddition reactions were tolerated all the screening various 3-nitrobenzothiophenes **1**, regardless of the different positions and electronic properties of substituents into the aryl ring of 3-nitrobenzothiophenes when the 3-

4a, R = Br, X = S
4b, R = H, X = O

5a, 91% yield
5b, 90% yield

Scheme 2 Dearomative cycloaddition reaction of 2-nitrobenzothiophene and 2-nitrobenzofuran with nonstabilized azomethine ylide.

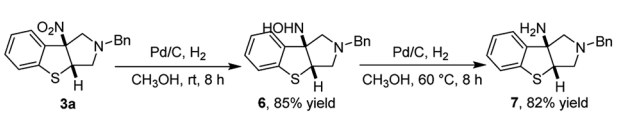


Scheme 3 Scaled-up version of synthesis of fused tricyclic benzo[4,5]thieno[2,3-*c*]pyrrole.

nitrobenzothiophenes **1** reacted smoothly with the precursor of nonstabilized azomethine ylides **2a** or **2b**. The reaction afforded the corresponding products **3** (**3a–o**) in high isolated yields with excellent diastereoselectivities (>20 : 1 dr). In addition, the relative configuration of product **3d** was determined unambiguously as (3*S*,8*S*) or (3*R*,8*R*) *via* single-crystal X-ray diffraction analysis (CCDC 2006826†).[12] For its structural details, see the ESI.†[10] The other products were assigned by analogy. However, when the **2c** substrate reacts with 3-nitrobenzothiophene **1a** and 3-cyanobenzothiophene **1q** reacts with *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** under the standard conditions (entries 16 and 17). These reactions didn't work. These reactions revealed that the compounds **2c** and **1q** had significantly lower reactivity. Subsequently, when we tried the reaction of 3-2-methyl-3-nitrobenzothiophene **1r** with *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** under the standard conditions (entry 18). Unfortunately, it was observed that the reaction did not take place. The possible reason may be due to the increased steric hindrance at the C2-position of the 2-methyl-3-nitrobenzothiophene, inhibiting the cycloaddition reaction.

Having proven the effectiveness of our protocol for dearomative [3 + 2] cycloaddition of 3-nitrobenzothiophenes with nonstabilized azomethine ylides. Then, we next turned our attention to dearomative annulation of other heteroaromatic ring bearing nitro group to confirm the practicability of the methodology (Scheme 2). The results show that the 2-nitrobenzothiophene and 2-nitrobenzofuran proved to be well compatible with the dearomative [3 + 2] cycloaddition reaction and underwent the transformation successfully to provide the expected products in the 91% and 90% yield, respectively.

Moreover, in order to highlight the synthetic utility of our methodology, a gram scale experiment between 5 mmol of 3-nitrobenzothiophene **1a** and 6 mmol of *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2a** proceeded smoothly under the standard conditions and offered compound **3a** (1.373 g) in 88% yield with dr >20 : 1 (Scheme 3). Subsequently, the attempt to reduce the nitro group and remove the benzyl group of **3a** through Pd/C-catalyzed hydrogenation. However, the benzyl group was not removed,[11a] while the nitro group on the quaternary carbon center in **3a** was reduced to give an NHOH intermediate **6** in 85% yield at room temperature.[11b] Next, Pd/C-catalyzed hydrogenation of the NHOH intermediate **6** was successfully conducted at 60 °C to give a free amine **7** in 82% yield (Scheme 4).[11]



Scheme 4 Transformations of product **3a**.

In conclusion, we have successfully developed an efficient dearomative [3 + 2] cycloaddition reaction of nitrobenzothiophenes with nonstabilized azomethine ylides generated *in situ*. The functionalized fused tricyclic benzo[4,5]thieno[2,3-*c*]pyrroles frameworks were efficiently constructed in high yields (up to 92%) with excellent diastereoselectivities (>20 : 1 dr) under mild reaction condition without metal catalyst. 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 polycyclic heterocyclic compounds. The further application of this strategy is presently under bioactive investigation in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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