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Iodine-promoted ring-opening methylation of benzothiazoles with dimethyl sulfite†

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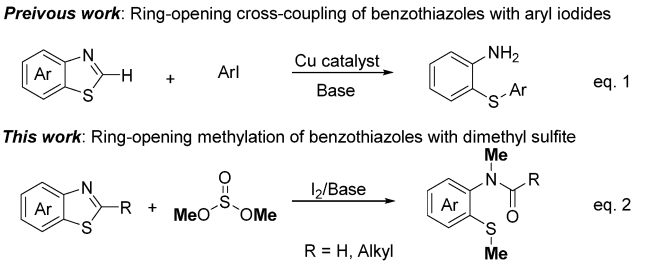
A halogen-bond promoted ring-opening methylation of benzothiazoles has been developed using dimethyl sulphite as a methylating reagent in the presence of a base. This approach represents a simple and efficient synthesis of *N*-methyl-*N*-(*o*-methylthio)phenyl amides, and features direct construction of both N–Me and S–Me bonds in a one-pot reaction through the decomposition of easily prepared benzothiazoles.

As the smallest alkyl group in organic molecules, the methyl group plays a very important role in organic synthesis, biochemistry, and medicinal chemistry.[1] The introduction of a methyl group into organic compounds can increase their hydrophobic character and modulate their biological activities and physical properties. For example, the installation of a methyl group can dramatically improve IC50 values in the development of drugs.[2] Therefore, the methylation reaction is one of the most crucial functionalizations in organic synthesis to realize the key chemical transformation of a methyl group from a methylating reagent.[3] Traditionally, dimethyl sulfate, methyl iodide and diazomethane are widely used as a methylating reagent in the formation of methyl ether or ester, although the toxicity or/and explosive nature limit their broad applications.[4] Dimethyl carbonate,[5] methanol,[6] peroxide,[7] and *N*,*N*-dimethylformamide[8] are also reported in some special methylation reactions. Dimethyl sulfite is a cheaper, lower toxicity and readily available chemical reagent, which was earlier used in the preparation of methyl ether from metal enolates[9] and phenols[10] or alcohols[11] under harsh reaction conditions. To the best of our knowledge, dimethyl sulphite has never been used in the methylation of amines and thiols.

Benzothiazoles are easily prepared heterocycles and have been widely used in organic synthesis, especially for the copper catalyzed ring-opening reactions under basic reaction conditions.[12] For example, the Xu and Han groups independently reported the ring-opening cross-coupling reaction of benzothiazoles with aryl iodides for the synthesis of *o*-sulfanylaniline derivatives which have a broad range of applications in medicinal chemistry and materials science.[13] During the course of our recent research on the synthesis of thioethers,[14] we serendipitously found that the benzothiazoles could undergo the ring-opening coupling reaction with dimethyl sulfite with the assistance of halogen-bond coordination (eqn (2), Scheme 1). Herein, we report an iodine-promoted ring-opening methylation of benzothiazoles using dimethyl sulfite as a safe and cheap methylating reagent for the facile synthesis of *N*-methyl-*N*-(*o*-methylthio)phenyl amides.

The reaction of benzo[*d*]thiazole **1a** with dimethyl sulfite **2a** was selected as a model reaction for the optimization of the reaction conditions as shown in Table 1. Firstly, treatment of substrate **1a** with 10 equiv. of dimethyl sulfite, 0.5 equiv. KI and 3.0 equiv. of triethylamine in MeCN (2 mL) afforded the product **3a** in 47% yield (entry 1). Subsequently, a variety of iodine sources were tested (entries 1–5), including tetrabutylammonium iodide (TBAI), elemental iodine, *N*-iodosuccinimide (NIS) and ICl, and I_2 was demonstrated to be the optimal promoter and the product **3a** was isolated in 53% yield (entry 5). However, the reaction did not work completely in the absence of iodine (entry 6). During the investigation of a base, EtONa was found to be more efficient than Et_3N, $(n\text{-Bu})_3N$,



Scheme 1 Ring-opening cross-coupling of benzothiazoles.

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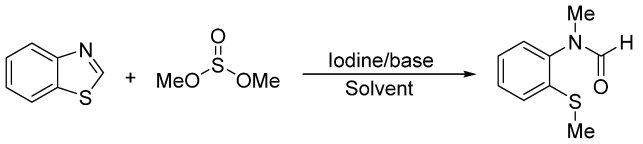
Table 1 Screening conditions[a]



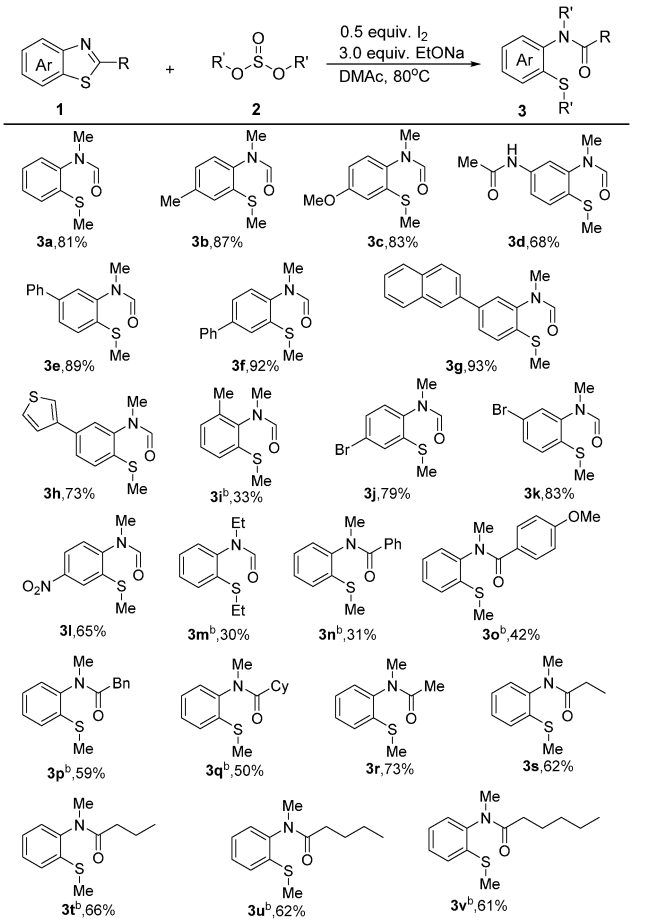
Entry	I source	Base	Solvent	Yield (%)
1	KI	Et_3N	CH_3CN	47
2	TBAI	Et_3N	CH_3CN	27
3	I_2	Et_3N	CH_3CN	53
4	NIS	Et_3N	CH_3CN	49
5	ICl	Et_3N	CH_3CN	50
6	—	Et_3N	CH_3CN	NR
7	I_2	$(n\text{-}Bu)_3N$	CH_3CN	29
8	I_2	DBU	CH_3CN	49
9	I_2	Na_2CO_3	CH_3CN	34
10	I_2	K_3PO_4	CH_3CN	35
11	I_2	*t*-BuOK	CH_3CN	42
12	I_2	EtONa	CH_3CN	65
13	I_2	—	CH_3CN	Trace
14	I_2	EtONa	DMF	60
15	I_2	EtONa	DMAC	81
16	I_2	EtONa	NMP	70
17	I_2	EtONa	DMSO	NR
18	I_2	EtONa	DMAc	48[b], 63[c], 50[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mmol), I source (50 mol%), EtONa (3.0 equiv.), DMAc (2.0 mL) at 80 °C for 24 h, isolated yield. [b] I source (0.4 equiv.). [c] Base (2.0 equiv.). [d] At 60 °C.

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Na_2CO_3, K_3PO_4 and *t*-BuOK, and a 65% reaction yield was observed (entries 7–12). Only trace amount of product was detected in the absence of base (entry 13). The solvent effect was further investigated by switching to DMF, DMAc, NMP and DMSO (entries 14–17), and we were pleased to find that the product **3a** was obtained in 81% yield when the reaction was carried out in DMAc (entry 15). Lower yields were observed when the loading of I_2 and base was reduced or when the reactions were carried out at 60 °C (entry 18).

With the optimal reaction conditions in hand, we investigated the substrate scope of the ring-opening methylation. As shown in Table 2, a variety of benzo[*d*]thiazoles were tested in the reaction with dimethyl sulfite **2a**, and the results demonstrated that both electron-rich and electron-poor substituents are compatible with this transformation. Methyl, methoxyl and acetamido substituted benzothiazoles afforded the corresponding acetanilide **3b–3d** in 68–87% yields. 5- and 6-phenyl benzothiazoles gave the products **3e** and **3f** in 89% and 92% yields, respectively. Moreover, polycyclic 5-naphthyl and heterocyclic 5-thienylbenzothiazoles also afforded the products **3g** and **3h** in 93% and 73% yields. The steric effect was observed when 5-methyl benzothiazole was used as a coupling partner with dimethyl sulfite, and the *ortho*-methyl substituted acetanilide **3i** was obtained only in 33% yield even when the reaction temperature was enhanced to 100 °C. The bromide benzothiazoles also gave the products **3j** and **3k** bearing an active bromo group in 79% and 83% yields, which might serve as a potential handle for further transformations. It is noteworthy that benzothiazole with a strong electron-withdrawing nitro group underwent the reaction smoothly to furnish the product **3l** in 65% yield. Subsequently,

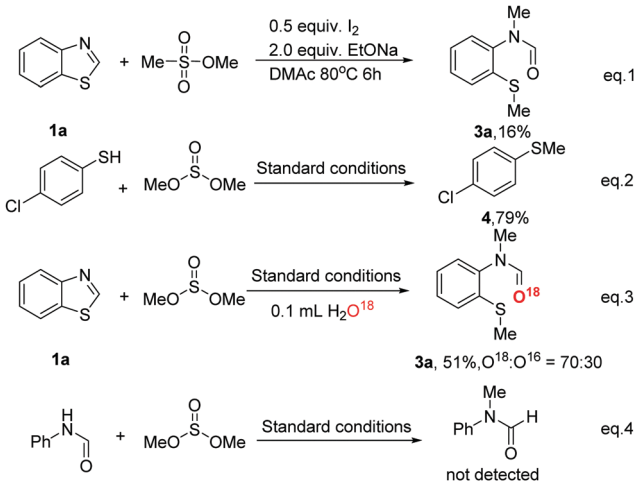
Table 2 Scope of benzothiazoles and dialkylsulfites[ab]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mmol), I_2 (0.1 mmol), EtONa (3.0 equiv.), DMAc (2.0 mL) at 80 °C for 24 h, isolated yield. [b] 100 °C.

various alkyl sulfites were investigated with benzothiazole **1a** under standard reaction conditions. Unfortunately, only diethyl sulfite was performed successfully to give ethylated product **3m** in 30% yield. During the examination of 2-site substituents, various aryl and alkyl groups were found to be suitable for this reaction. Interestingly, moderate yields were obtained for phenyl and 4-methoxyphenyl, while alkyl groups delivered products **3p–3v** in 50–73% yields.

To further understand this ring-opening methylation, some control experiments were conducted as shown in Scheme 2. In consideration of the effect of a leaving group, methyl methanesulfonate[15] was firstly used as a methylating reagent instead of dimethyl sulfite, and a 16% yield was obtained after 6 hour. These results indicated that methyl methanesulfonate might be the key intermediate, which was generated *in situ* from the rearrangement of dimethyl sulfite in the presence of a base.[16] 4-Chlorothiophenol was next performed under standard conditions to give methylated product 4-chlorothioanisole in 79% yield, suggesting that methylation of the phenylthio anion occurred in the ring-opening reaction of benzothiazole. The reaction of benzothiazole was conducted with 0.1 mL H_2O^{18} under standard conditions (eqn (3)). A mixture of the products O^{18}-**3a** and O^{16}-**3a** was isolated in 51% yield with a 70 : 30 ratio

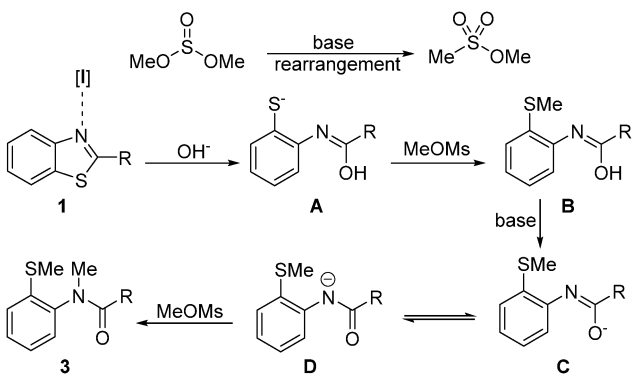


Scheme 2 Control experiments.

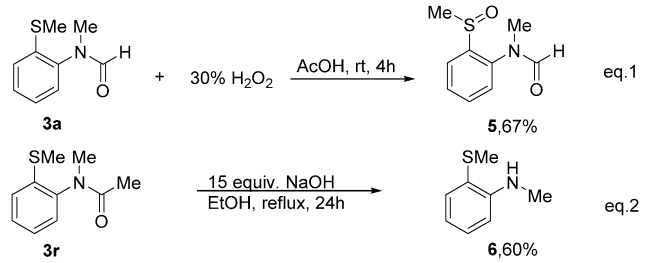
(detected by GC-MS), which demonstrated that the hydrolysis of the intermediate from the ring-opening reaction with water in the solvent provided the amide moiety. The methylation of *N*-phenylformamide did not work under standard conditions (eqn (4)), implying that the products were not from the direct N–H methylation of amides.

On the basis of the obtained results and previous literature reports,[13a,b] a possible mechanism is proposed as outlined in Scheme 3. The rearrangement of dimethyl sulfite in the presence of a base produces methyl methanesulfonate *in situ* in which an $-OSO_2Me$ group has better leaving ability.[15,16] The halogen bond between iodine and a nitrogen atom promotes the decomposition of benzothiazole.[17] Firstly, the ring-opening reaction of benzothiazole with a base provides benzenethiolate anion **A**. The following nucleophilic substitution of anion **A** with methyl methanesulfonate affords methylated enol intermediate **B**. Then, the deprotonation of intermediate **B** under basic conditions gives enol anion **C** and its tautomer **D**. The final nucleophilic substitution of amide anion **D** with methyl methanesulfonate furnishes the products **3**.

Methyl sulfoxide derivatives show a wide range of biological and pharmacological activities.[18] To demonstrate the applicability of this transformation in the organic synthesis, further transformations of



Scheme 3 Possible mechanism.



Scheme 4 Further transformation of product **3a** and **3r**.

the obtained *N*-methyl-*N*-(*o*-methylthio)phenyl amides were explored as outlined in Scheme 4. Treatment of product **3a** with 30% H_2O_2 in acetic acid at room temperature afforded methyl sulfoxide **5** in 67% yield.[19] The hydrolysis of amide **3r** with sodium hydroxide also proceeded smoothly in methanol to give *N*-methyl-2-(methylthio) aniline **6** in 60% yield.[20]

In summary, a halogen bond promoted ring-opening methylation of benzothiazoles has been developed for the efficient synthesis of *N*-methyl-*N*-(*o*-methylthio)phenyl amides. This process utilizes dimethyl sulfite as a safe and cheap methylating reagent to accomplish the direct S- and N-atom methylation of a range of benzothiazoles under mild reaction conditions. The present iodine-promoted transformation provides an alternative route for the synthesis of methyl thioethers and amides, and may find promising applications in other important methylations.

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Conflicts of interest

There are no conflicts to declare.

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