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Arylation of benzazoles at the 4 positions by activation of their 2-methylsulfinyl groups

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Treatment of 2-methylsulfinylbenzazoles with triflic anhydride in the presence of phenols yields the corresponding 4-(*p*-hydroxyphenyl)-2-methylsulfanylbenzazoles. This regioselective dehydrative C–H/C–H coupling arylation represents a rare example of functionalizations on the benzene rings of benzo-fused azoles.

Benzo-fused azoles are often found in bioactive molecules[1] and organic electronics materials,[2] providing platforms of various useful functions. It is therefore important to synthesize multi-substituted benzazoles with high efficiency. As benzazoles are conventionally synthesized from *ortho*-functionalized anilines such as *o*-hydroxy, *o*-amino, and *o*-mercapto through condensation reactions with carbonyl compounds, 2-substituted benzazoles are easy to prepare (Fig. 1A).[3] However, the synthesis of benzazoles having a substituent on the benzene ring is troublesome because it should start with trisubstituted anilines that are not readily available. Conceivable late-stage functionalizations on the benzene rings of benzazoles are difficult (Fig. 1B) because the electron density of the benzene π orbital is rather low and reluctant to undergo electrophilic substitution.[4] For example, there are a handful of electrophilic substitutions of benzazoles, most of which are nitration and halogenation at the 6 position or non-selective complete multi-halogenation under harsh conditions.[5,6] Therefore, there is a strong need for methods to directly and selectively functionalize the benzene rings of benzazoles.

Our group has been interested in the development of methods for functionalizing unsaturated sulfoxides through activation with anhydrides.[7,8] During the course of our study, we have developed arylation reactions of aryl sulfoxides with phenols (Fig. 1C).[9] The arylation involves the activation of the sulfoxide with reactive anhydride, nucleophilic attack of the phenol at the cationic sulfur center, [3,3] sigmatropic rearrangement (stepwise in some case), and global rearomatization. The reaction represents a metal-free dehydrative C–H/C–H coupling for the synthesis of biaryls.

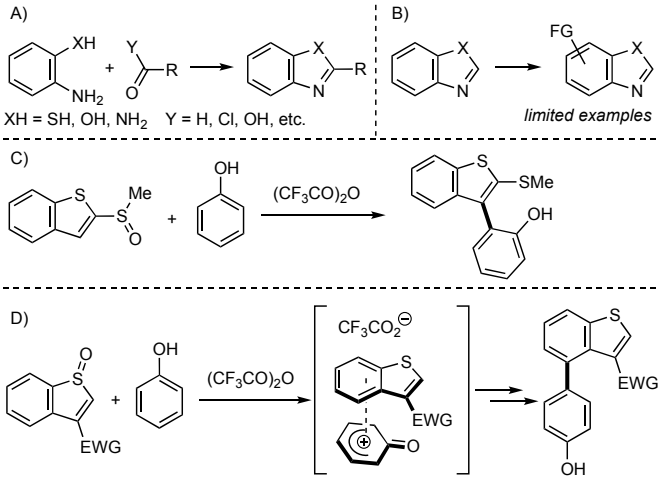

Fig 1. Background. A) Conventional synthesis of benzazoles. B) Difficult functionalizations of the benzene ring in benzazoles. C) Our arylation of benzothiophene at the 3 position by activation of its 2-methylsulfinyl group. D) Procter's arylation of benzothiophene at the 4 position by activation of its *S*-oxide.

Recently, sulfonium-mediated [5,5] sigmatropic rearrangement has attracted increasing attention for the *para* functionalizations of aryl sulfoxides.[10] Very recently, Procter, Paton, and co-workers have reported an interesting remote functionalization starting from benzothiophene *S*-oxides and phenols (Fig. 1D).[11] The arylation takes place at the 4 position of the benzothiophene core and was calculated to proceed via a stepwise mechanism, i.e., formal [5,5] rearrangement. We thus envisioned [5,5] rearrangement by using 2-methylsulfinylbenzazoles as substrates wherein conceivable

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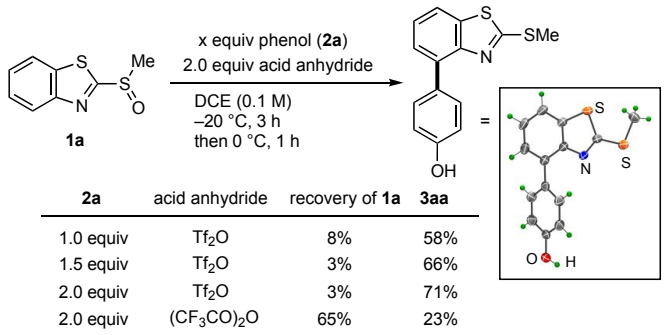
[3,3] rearrangement would be inhibited by the nitrogen. Here we report such remote arylation of benzazoles on the benzene rings.

Treatment of a mixture of 2-methylsulfinylbenzothiazole (**1a**) and phenol (**2a**) with triflic anhydride (Tf_2O) in 1,2-dichloroethane (DCE) at –20 ˚C for 3 h then at 0 ˚C for an additional 1 h provided the corresponding coupling product **3aa** in 58% yield (Fig. 2). The coupling took place exclusively between the 4 position of **1a** and the *para* position of **2a**. None of the conceivable *N*-arylated products were observed. The use of larger amounts of **2a** improved the yield of **3aa**. Notably, trifluoroacetic anhydride, which was uniquely the best activator in the previous arylation,[9] was found to be ineffective, yielding **3aa** in only 23% yield with 65% recovery of **1a**.

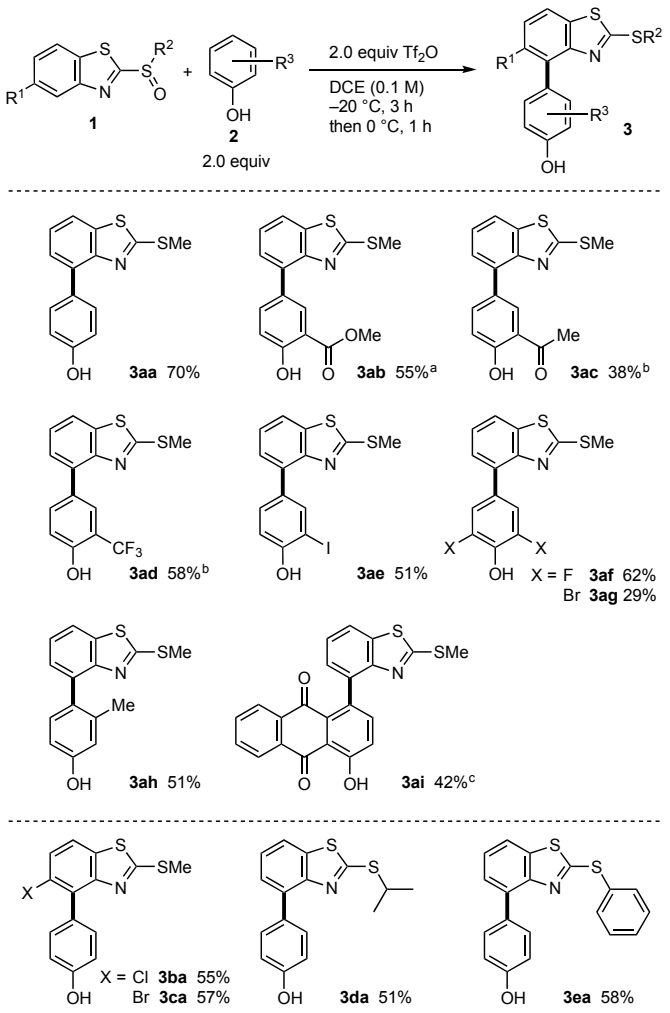


2a	acid anhydride	recovery of 1a	3aa
1.0 equiv	Tf_2O	8%	58%
1.5 equiv	Tf_2O	3%	66%
2.0 equiv	Tf_2O	3%	71%
2.0 equiv	$(CF_3CO)_2O$	65%	23%

Fig. 2. Arylation of **1a** with **2a**. Yields were determined by ^{1}H NMR with mesitylene as an internal standard. The X-ray structure of **3aa** is shown in an inset at 50% probability.

A series of phenols were examined (Scheme 1). Under acidic conditions, the methyl ester of **2b** and the acetyl group of **2c** were compatible to yield **3ab** and **3ac**, respectively. An *ortho*-trifluoromethyl group in **2d** and an iodo group in **2e** did not retard the reaction. This coupling reaction also accommodates *ortho*-disubstituted phenols **2f** and **2g** to give **3af** and **3ag**, respectively. A methyl group at the *meta* position did not hamper the reaction to yield **3ah**. It is worth mentioning that no regioisomers were identified and that the reaction is not sensitive to steric factors. A π-extended phenol **1i** was also applicable to give **3ai** in 42% yield. Due to the limited accessibility to benzothiazole derivatives other than 2-substituted ones, 5-halobenzothiazoles (X = Cl, Br) were employed to prepare sulfoxides **1b** and **1c**, and the 4-arylation smoothly proceeded to give the corresponding biaryls **3ba** and **3ca**, respectively. Sterically hindered isopropylsulfinylbenzothiazole **1d** also participated in the coupling to afford **3da**. Although arylation on the phenyl moiety of **1e** via [3,3] sigmatropic rearrangement[9] was concerned, the arylation reaction exclusively proceeded at the 4-position of benzothiazole moiety to yield **3ea**.

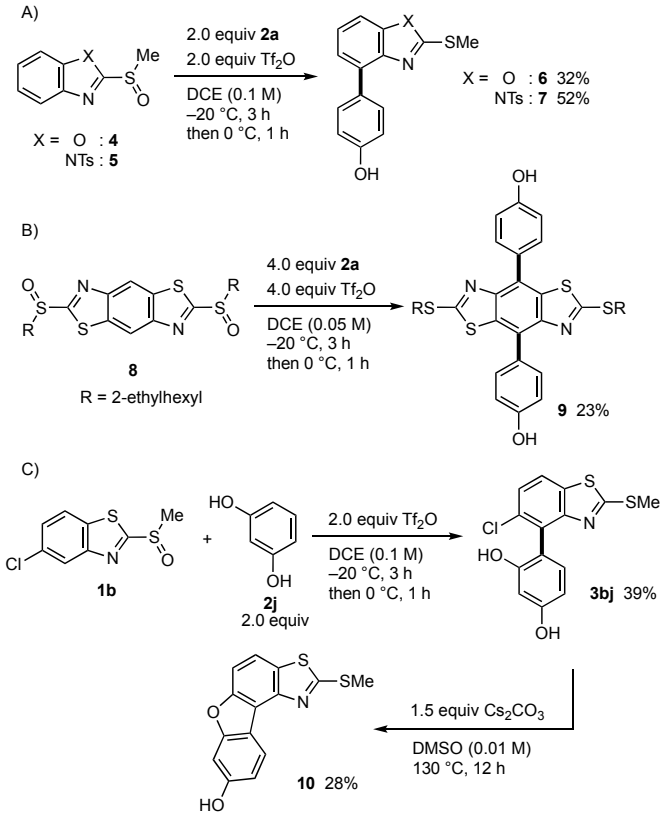
Not only benzothiazoles **1** but benzoxazole **4** and *N*-tosylbenzimidazole **5** participated in the arylation with phenol (**2a**) (Scheme 2A). The arylation is powerful to convert benzobisthiazole **8** through two-fold arylation for the synthesis of **9**. This diarylation would be useful for the synthesis of new benzobisthiazole-based materials[12] for organic electronics (Scheme 2B). Chlorobenzothiazole **1b** reacted with resorcinol (**2j**) to yield the corresponding product **3bj**, which underwent Cs_2CO_3-mediated S_NAr cyclization to yield tetracyclic aromatic system **10** (Scheme 2C).



Scheme 1. Scope with respect to sulfinylbenzothiazoles **1** and phenols **2**. (a) –20 ˚C, 3 h, then rt, 1 h. (b) –20 ˚C, 3 h, then rt, 2 h. (c) rt, 5 h.

To understand the mechanism of the coupling reaction, especially of the regioselective C–C-bond-forming step, DFT calculations were performed (Fig. 3). From the phenoxy-substituted sulfonium ion **A**, there are two possible pathways for the observed C–C bond formation, i.e., a concerted sigmatropic rearrangement[7,8] and a stepwise rearrangement[11,13] via a π complex. After our extensive efforts, we could not find any transition states for the [5,5] sigmatropic rearrangement, probably due to the structural constraint. Instead, we found a π complex intermediate **B** consisting of 2-methylsulfanylbenzothiazole and phenoxonium ion. Intermediate **B** is higher in free energy by only 4.44 kcal/mol than **A**, and the activation barrier to **B** was calculated to be as low as 5.53 kcal/mol (**TSi**). The transition state **TSii** of the C–C bond formation from **B** was located at 8.05 kcal/mol to give dearomatized coupling intermediate **C**. While intermediates **A** and **C** are comparable in energy, the subsequent aromatization of **C** into the product should drive the reaction irreversibly

forward. Akin to our previous study on the stepwise C–C bond formation for [3,3] rearrangement,[13b] conceivable N–C bond formation between the 3 position of the methylsulfanylbenzothiazole moiety and the *ortho* position of the phenoxonium ion from **B** was also considered. The corresponding transition state was located at 9.93 kcal/mol, which is slightly higher in free energy by 1.88 kcal/mol than that of the 4-arylation **TSii** (Fig. S1). The difference in activation free energy is sufficiently large to realize selective [5,5] rearrangement.



Scheme 2. Arylation of benzazoles: A) Arylation of benzoxazole and benzimidazole. B) Two-fold arylation of benzobisthiazole. C) Construction of tetracyclic aromatic system **10**.

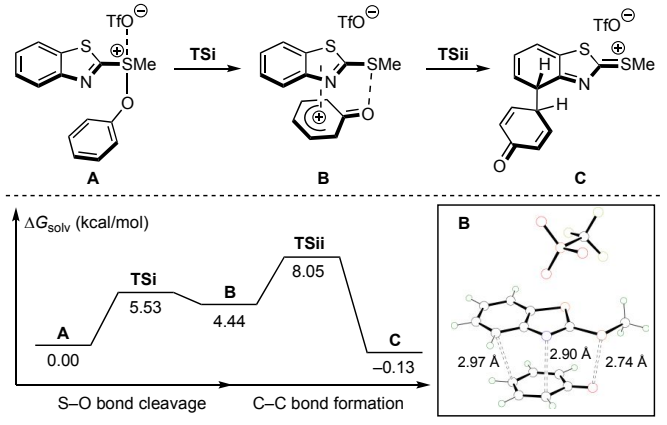
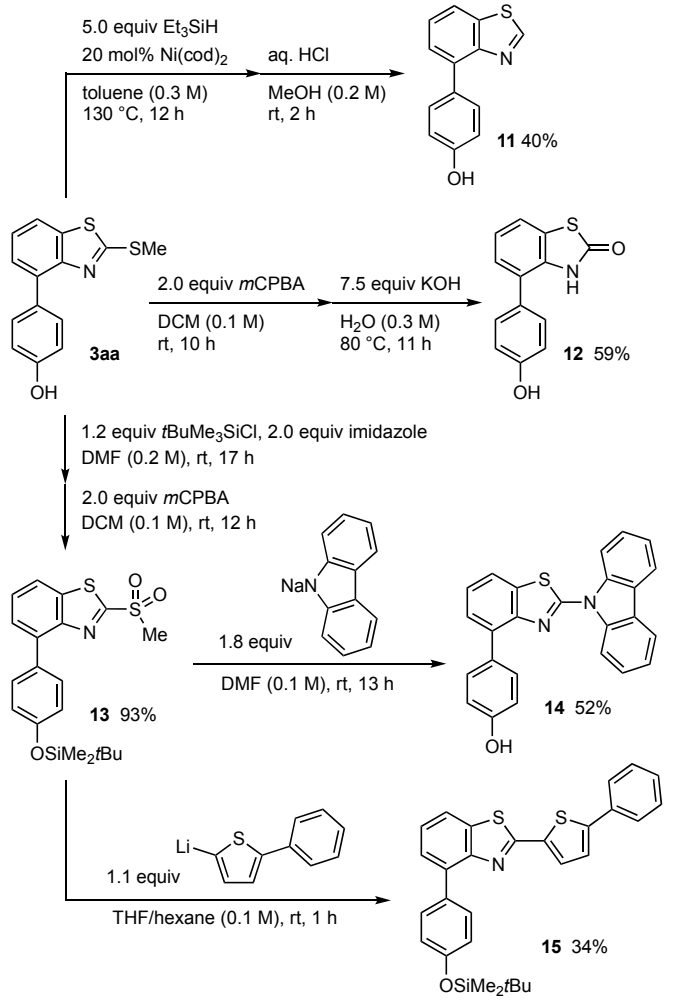


Fig 3. Stepwise rearrangement from **A** to **C** via **B**, calculated at the B3LYP-D3(BJ)/6-31+G(d,p) level of theory using the SMD model (dichloromethane).

Several transformations were explored to convert the remaining methylsulfanyl group in **3aa**. Reductive removal was achieved by using Et_3SiH under nickel catalysis,[14] furnishing **11** after acidic desilylation at the phenolic hydroxy group that was triethylsilylated *in situ* during the reduction. Treatment of **3a** with *m*CPBA followed by hydrolysis via nucleophilic substitution in aqueous KOH yielded 2-benzothiazolinone **12**. Sodium carbazolide and thienyllithium also participated in nucleophilic substitution reaction of TBS-protected **13** to yield **14** (desilylated *in situ*) and **15**, respectively. Notably, **15** contains a thienyl-benzothiazolyl hybrid motif that is often found in organic semiconductors.[12] Our protocol that is composed of arylation/oxidation/transition metal-free thienylation provides a new route to this valuable skeleton.



Scheme 3. Derivatizations of **3aa**.

A new method has been developed to achieve a selective functionalization of the benzene ring of benzazoles. Dehydrative metal-free C–H/C–H coupling of 2-methylsulfinylbenzazoles with phenols proceeds with the aid of triflic anhydride to yield the corresponding 4-(p-hydroxyphenyl)-2-methylsulfanylbenzazoles. Due to its mechanistic uniqueness, the coupling reaction enables selective

and direct arylation at the 4 position on the fused benzene ring. Computational investigations have revealed the stepwise nature of the C–C-bond-forming step. The products serve as valuable synthetic intermediates by using their residual methylsulfanyl groups for further functionalizations.

Conflicts of interest

There are no conflicts to declare.

Author Contributions

S.W. and H.Y. conceived the project. R.W. and S.W. performed the experiments. T.K. performed X-ray crystallography and DFT calculations. T.K. and H.Y. directed the research. All authors composed the manuscript and the ESI section and contributed to the editing.

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