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Disulfides as Efficient Thiolating Reagents Enabling Selective Bis-sulfenylation of Aryl Dihalides Under Mild Copper-Catalyzed Conditions

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The selective bis-sulfenylation reactions of aryl dihalides have been achieved by copper-catalyzed C-S coupling reactions under mild conditions of refluxing EtOH (80 °C). Employment of disulfides as thiolating reagents enables the production of various bis(phenylthio)benzenes with excellent selectivity, and no products from mono C-S coupling are isolated.

Introduction

The formation of C-S bonds is one of the fundamental transformations of organic synthesis. Owing to the prevalent presence of C-S bond in biologically relevant compounds, natural products, agrochemicals and organic materials, the researches on the construction of C-S bonds, especially sp²C-S bonds that involving the transformation of inactive sp²C-X (X = halide, H etc) bonds have become an issue of widespread interests.1-7 Presently, transition metal-catalyzed C-S coupling reactions between thiol nucleophiles and aryl/vinyl halides are amongst the most practical approach for the generation of sp²C-S bonds.8-9 Originally, this kind of reaction has been dominantly performed in the presence of a transition metal catalyst and high temperature in polar solvents such as DMSO, DMF or NMP.10-12 Among the different transition metal species which have been used in the C-S cross-coupling reactions, copper catalysts have attracted tremendous attention because of their low cost as well as low toxicity.13-30

While spectacular progress has been witnessed in filed of C-S coupling chemistry during the past decade, interestingly, few attentions have been paid on the chemo-selective C-S coupling reactions of dihalide substrates. These kind of selective reactions providing mono- and bis-sulfenylated aryls, however, are crucial in expanding the application scope of C-S coupling chemistry by affording structurally diverse S-containing products. In 2011, Mao and coworkers reported the ligand-free bis-sulfenylation of diiodoaryl using thiols as S-nucleophiles in the presence of iron/copper mixed catalysts at 140 °C.13 In addition, Bagley and coworkers reported the microwave irradiated, copper-catalyzed protocol which has also been found selectively promote the bis-sulfenylation of dihalobenzenes.29 While these methods rely on the tough reaction conditions to achieve bis-sulfenylation, developing new methodologies enabling selective bis-sulfenylation reactions under milder conditions is highly demanding.

Following our previous work on copper-catalyzed selective mono-sulfenylation (Scheme 1)32 as well as other related copper-catalyzed coupling chemistry,33-37 we report herein the copper-catalyzed selective bis-sulfenylation of dihaloaryl under mild and clean conditions by using disulfides as bis-thiolating agents38 (Scheme 1).

This work: selective bis-sulfenylation of dihalobenzenes

Scheme 1 Tunable mono- and bis-sulfenylation of dihaloaryl

Results and discussion

Since we previously discovered that using thiols in the coupling reactions with diiodobenzenes led to selective mono-sulfenylation,32 in order to achieve the tunable selective bis-sulfenylation, we tentatively chosen disulfides as thiolating reagents in the reactions. Firstly, a class of aryl and alkyl disulfides were synthesized following a simple and clean method developed in our lab.39 The reaction of 1,2-diodobenzene 1a and phenyl disulfide 2a was then employed as model reaction for optimizing investigation. In the presence of CuI, Cs₂CO₃ at 120 °C in DMSO, a series of different ligands were firstly screened. It was found that the bis-sulfenylation could be achieved in the presence of CuI and different types of ligands. Among the examined ligands, including 1,10-phenanthroline (L1), 8-hydroxyquinoline (L2), L-proline (L3), d-glucose (L4) and two enaminone-based ligands (L5 and L6), 2-hydroxyphenyl functionalized enaminone ligand L540 displayed the best effect in assisting the bis-sulfenylation reaction with 93 % yield of product 3a (Fig. 1).
allowed smooth bis-sulfenylation reaction with excellent yield of 3a at reflux and open air conditions (entries 11-14, Table 1). Other low boiling point solvent such as acetonitrile was not able to mediate the reaction effectively (entry 15, Table 1), demonstrating the unique advantage of ethanol in this selective bis-sulfenylation process. Finally, reducing the amount of CuI to 10 mol % loading gave 3a with equally excellent yield (entry 16, Table 1). Further decreasing the catalyst loading, however, was not favored (entry 17, Table 1).

Under the optimal conditions, the application scope of this catalytic method has been investigated by subjecting different diidoaryl and disulfides. As outlined in Table 2, this method has been found with excellent applicability for the synthesis of various bis(phenylthio)benzenes. 4-Substituted phenyl disulfides such as alkyl, halide substituted phenyl disulfides reacted with different diiodobenzenes 2a-2c with generally excellent yields (3a-3f, 3n-3r and 3u-3y, Table 2). Similarly, 2- and 3-substituted phenyl disulfides also displayed excellent tolerance to this synthetic method by providing corresponding products with satisfactory yields (3g-3i, 3s-3t and 3z, Table 2). More importantly, other aryl disulfides such as naphthyl disulfide and heteroaryl disulfides also acted as double thiolating reagents to yield structurally divergent bis-thiobenzilidene bis-3f-3l (Table 2).

Table 2 Application scope of the copper-catalyzed, EtOH mediated bis-sulfenylation of diidoaryl.*

| R | Diodobenzene Product Yield (%) |
|---|-------------------------------|-----------------|
| Ph | 2a | 3a | 94 |
| 4-CH₃C₆H₄ | 2a | 3b | 91 |
| 4-ClC₆H₄ | 2a | 3c | 86 |
| 4-FC₆H₄ | 2a | 3d | 86 |
| 4-ClC₆H₄ | 2a | 3e | 85 |
| 4-BrC₆H₄ | 2a | 3f | 79 |
| 2-ClC₆H₄ | 2a | 3g | 82 |
| 2-CH₃C₆H₄ | 2a | 3h | 83 |
| 3-CH₃C₆H₄ | 2a | 3i | 94 |
| naphthyl | 2a | 3j | 92 |
| pyridine-2-yl | 2a | 3k | 84 |
| benzothiazol-2-yl | 2a | 3l | 81 |
| sec-butyl | 2b | 3m | 72 |
| Ph | 2b | 3n | 91 |
| 4-CH₃C₆H₄ | 2b | 3o | 85 |
| 4-i-PrC₆H₄ | 2b | 3p | 82 |
| 4-FC₆H₄ | 2b | 3q | 82 |
| 4-ClC₆H₄ | 2b | 3r | 86 |
| 2-CH₃C₆H₄ | 2b | 3s | 81 |
| 2-ClC₆H₄ | 2b | 3t | 83 |
| Ph | 2c | 3u | 92 |
| 4-CH₃C₆H₄ | 2c | 3v | 94 |
| 4-i-PrC₆H₄ | 2c | 3w | 86 |
| 4-FC₆H₄ | 2c | 3x | 87 |
| 4-ClC₆H₄ | 2c | 3y | 87 |
| 3-CH₃C₆H₄ | 2c | 3z | 91 |
| 2-NH₂C₆H₄ | - | - | - |
| 2-NO₂C₆H₄ | - | - | - |

General conditions: 1 (0.5 mmol), 2 (0.5 mmol), CuI (0.05 mmol), L₅ (0.1 mmol) and Cs₂CO₃ (1.0 mmol) in alcohol (2 mL), reflux for 15 h.

*Yield of isolated product.
Finally, it is noteworthy that alkyl disulfide was also able to incorporate diiodobenzene to give corresponding bis(alkylthio)benzene 3m, albeit with lower yield than equivalent entries using aryl disulfides. Further attempts on running the bis-sulfenylation with amino and nitro functionalized phenyl disulfides revealed the intolerance of these groups to the present protocol (Table 2).

Based on the known conditions for bis-sulfenylation, the cross bis-sulfenylation using two different disulfides to incorporate 1,2-diodobenzene was attempted. As outlined in Scheme 2, the reaction employing simultaneously tolyl disulfide and p-bromophenyl disulfide led to the production of three mixed products, including the products 3b, 3f from homo-bis-sulfenylation as well as product 3bf from cross bis-sulfenylation.

![Scheme 2 Bis-sulfenylation with 2 different disulfides](image)

Following the good results provided the reactions of diiodobenzenes, the entries using 1,2-dibromobenzene have also been investigated. However, the expect products could only be obtained with low to fair yields from these experiments, although harsher conditions (sealed tube, 110 °C) were employed (Scheme 3).

![Scheme 3 Bis-sulfenylation reactions of 1,2-dibromobenzene](image)

### Conclusions

The selective bis-sulfenylation reactions of aryl dihalides have been achieved with excellent efficiency by employing the disulfides as double thiolating reagent. The present method provided a highly useful methodology for the synthesis of bis(phenylthio)benzenes of type 3. This method also possessed notable advantages such as green reaction medium, mild conditions and full utility of thiolating reagents.

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### Notes and references

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