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Bonds Activation and C-S Bond Formation

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ARTICLE



The Thiolation of Pentafluorobenzene with Disulfides by C–H, C–F teo bisarylthiolation derivatives along with tetrafluoroaryloxthines under a similar reation condition (Scheme 1, Reaction c).9 In 2016, Hoover and co-workers¹⁰ reported the synthesis of dithiolated compounds from pentafluorobenzoic acid and thiophenol catalyzed by Cul in the presence of O₂ (Scheme 1, 24 H

Scheme 1 Synthetic methods for diaryl thioether compounds

K-CO

The synthetic methods mentioned above share some drawbacks which limits further applications of these reactions: 1) employment of expensive transition metal catalysts; 2)

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A metal-free thiolation reaction between pentafluorobenzene and disulfides through C–H, C–F bond activation and C-S bond formation is reported. Bisthiolated tetrafluorobenzene derivatives would be prepared in moderate to good yield from pentafluorobenzene and disulfides under mild condition. A possible mechanism for the reaction was given.

1) RhH(PPh₃)₄ (1

dppe (2 mol% PPh₃ (0.5 eq.) THF, refl., 2 h

a)4 (2.5 mol%)

pher t-Bu

DDQ DMSO

60 1

CuBr. t-BuOL

L, DMSO

2) C₆F_{6 (2} eq.)

dppe (5 C₆H₅Cl

Reaction d).

Reaction

Reaction d

Introduction

Hetero atoms such as fluorine or sulfur possess some crucial differences from carbon and hydrogen (e.g. covalent radius and electronegativity). Thus, the chemical and physicochemical properties of an organic compound may be changed dramatically by introduction of hetero atoms or heteroatom containing groups.¹ Fluorinated organic compounds could enhance lipophilicity, metabolic stability and membrane permeability,^{1f, 2} which made fluorine containing drug have a wide range of applications³. Sulfur-containing compounds usually have specific physiological activities,1d-f which made them useful in pharmaceuticals and agrochemicals.⁴ For compounds containing both fluorine and sulfur atoms, their potential properties are equally attractive. For example, the introduction of fluorine into polysulfide imide can improve the solubility and optical transparency of polymers, which can be widely applied in optical waveguide materials.⁵

Synthesis of fluorinated thioether derivatives have been reported by some groups. In 2008, Yamaguchi and co-workers⁶ reported the synthesis of multiple thioether compounds from hexafluorobenzene and disulfides catalyzed by RhH(PPh₃)₄ and 1,2-bis(diphenylphosphino)benzene (dppBz) (Scheme 1. Reaction a). Thioesters, which was synthesized by acid fluorides and disulfides, could also be applied in the preparation of thioether compounds (Scheme 1, Reaction b).⁷ In 2012, Shi and co-workers8 developed a CuBr catalyzed synthesis of bisarylthiolation derivatives from pentafluorobenzene and diaryl disulfides in the presence of O2. They also found that aryl thiols could be used instead of diaryl disulfides to yield

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employment of excess of malodorous thiols or thiophenol; 3) relatively high reaction temperature; 3) generation of byproducts.⁶⁻¹⁰ This paper developed an environment-friendly and effective synthetic method for the preparation of fluorinated sulphides under mild condition.

Results and discussion

ARTICLE

Initially, attempts on the reaction of pentafluorobenzene (2, 0.5 mmol) and dimethyl disulfide (1a, 0.5 mmol) in the presence of *t*-BuOK (1 mmol) gave 1,4-bis(methylmercapto)-tetrafluorobenzene (3a) (Scheme 2).



Scheme 2 The reaction of pentafluorobenzene and dimethyl disulfide

Table 1 Optimization of the reaction condition. ^a

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	~ ^S ~S′ +	F F F 25 1 , 10 h		~s
	1a	2	3a	
Entry	1a : 2	Base (equiv.) ^b	Solvent	Yield (%) ^c
1	1:1	<i>t</i> -BuOK (2.0)	DMF	50
2	1:2	<i>t</i> -BuOK (2.0) ^d	DMF	35 ^d
3	2:1	<i>t</i> -BuOK (2.0)	DMF	57
4	2:1	<i>t</i> -BuOK (0.5)	DMF	20
5	2:1	<i>t</i> -BuOK (1.0)	DMF	38
6	2:1	<i>t</i> -BuOK (3.0)	DMF	18
7	2:1	<i>t</i> -BuOLi (2.0)	DMF	63
8	2:1	<i>t</i> -BuONa (2.0)	DMF	40
9	2:1	LiOH (2.0)	DMF	Trace
10	2:1	NaOH (2.0)	DMF	73
11	2:1	KOH (2.0)	DMF	97
12	2:1	Ca(OH) ₂ (2.0)	DMF	n.d. ^e
13	2:1	NEt₃ (2.0)	DMF	n.d. ^e
14	2:1	KOH (2.0)	THF	Trace
15	2:1	KOH (2.0)	DME	14
16	2:1	KOH (2.0)	MeCN	20
17	2:1	KOH (2.0)	CH_2CI_2	n.d. ^e

 a All reaction temperature was 25 $^\circ \rm C.$ b Equivalent was based on 2. c Yield was based on 2 and determined by GC, using dodecane as an internal standard substance. d Equivalent was based on 1a. e n.d. = no detection.

This reaction was chosen as the model reaction and different conditions were screened. These results are shown in Table 1. Initially, different ratio of **1a** and **2** was investigated in the presence of excess *t*-BuOK. The desired product **3a** could be obtained in relatively high yield while the ratio of **1a** to **2** was 2 : 1 (Table 1, entries $1 \approx 3$). Then different amount of base was investigated. Based on the amount of **2**, it was found that 2 equivalent of *t*-BuOK gave the highest yield of **3a** (Table 1, entries $3 \approx 6$). Employment of excess base led to the formation of multi-substituted products, thus reducing the yield of the

target product **3a** (Table 1, entry 6). Various bases, such as ite BuOLi, *t*-BuONa, *t*-BuOK, LiOH, NaOH, KOH, Ca(OH), PN(EO) were investigated. The addition of KOH gave the highest yield of **3a** (Table 1, entries 7 ~ 13). Later, different solvents were screened and DMF performed best (Table 1, entries 14 ~ 17). In general, DMF has a better solubility for inorganic substances than other solvents, indicating that solvent solubility of inorganic bases has a significant effect in this reaction. In summary, the optimal reaction conditions for the thiolation of pentafluorobenzene with disulfides were released: the ratio of disulfides, pentafluorobenzene and KOH was 2 : 1 : 2, DMF as solvent, 25 °C, 10 h.

Table 2 Scope of thiolation for disulfides and pentafluorobenzene. a, b





With the above optimal conditions in hand, we explored scope of this reaction (Table 2). As given in Table 2, most linear alkyl disulfides could react with **2** smoothly to give high to excellent yields of the corresponding products (Table 2, **3a-3c**, yield: 90%~97%). However, the yield of bis(butylthio)-2,3,5,6-tetrafluorobenzene (**3d**) decreased obviously compare to that of **3a** ~ **3c** when dibutyl disulphide (**1d**) was used in this reaction.

Entry

1

2

3

6

8

R

н

н

 \mathbb{R}^1

CH₃

n-Pr

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Benzyl disulfide (1e) and dithenyl disufide (1f) could also be employed in this reaction to give corresponding products 1,4bis(benzylthio)-2,3,5,6-tetrafluorobenzene (3e, 44% yield) and 1,4-bis(furfurylthio)-2,3,5,6-tetrafluorobenzene (3f, 46% yield). In the series reactions of diaryl disulfides, diphenyl disulfide (1g) could react with 2 under optimal conditions to give corresponding product 3g in 63% yield. Aryl disulfides substituted with electron-donating groups gave corresponding products in relatively high yields (Table 2, 3h ~ 3j). However, employment of aryl disulfides substituted with electronwithdrawing groups gave corresponding products in moderate to good yields. (Table 2, 3m, 3n). In particularly, bis(4nitrophenyl) disulfide (1k) and bis(3-nitrophenyl) disulfide (1l) reacted with 2 only gave (4-nitrophenyl)(2,3,5,6tetrafluorophenyl)sulfane (3k) and (3-nitrophenyl)(2,3,5,6tetrafluorophenyl)-sulfane (3I) in low yields. Heterocyclic substituted products (3o, 3p and 3q) could be prepared in moderate yields from disulfides 2,2'-dipyridyl disulfide (10), 2,2'-dithienyl disulfide (1p) and bis(2-methyl-3-furyl)disulphide (1q) via this reaction.



^a Reaction conditions: 4 (0.8 mmol, 2 equiv.), 2 (0.4 mmol, 1 equiv.), KOH (0.8 mmol, 2 equiv.), DMF (2 mL). ^b NMR yields determined by ¹⁹F NMR, using benzotrifluoride as an internal standard substance.



Table 4 The reaction of arylsulfane tetrafluorobenzene and disulfides. ^a



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Scheme 4 The reaction of sodium thiophenolate and pentafluorobenzene.



Reactions of asymmetric disulfides (4) and 2 were also conducted (Table 3). Methyl propyl disulphide (4a) could react with 2 to generate 3a (10%), 3c (31%) and methyl(2,3,5,6-

8 (74%)

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Producte (yield) le Online

5b (40%

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tetrafluoro-4-propylthiophenyl)sulfane (**5a**, 38%). When 2-((4chlorophenyl)disulfanyl)pyridine (**4b**) was applied in this reaction, only **3I** was received in 43% yield. Methyl 2-methyl-3furyl disulphide (**4c**) could react with **2** under the optimal conditions, generating **3a** in 21% yield and **3f** in 36% yield.

Several experiments were conducted to investigate the mechanism of this process. 1). A DMF solution of sodium thiophenolate (6a) or 4-methylbenzenethiol sodium (6b) and 2 (1:1) were stirred overnight, generating 1-phenylthio-2,3,5,6tetrafluorobenzene (7a, 65% yield) or 2,3,5,6-tetrafluoro-1-(ptolylthio)benzene (7b, 40% yield) as the major product (Scheme 3); 2). 7 could react with various disulfides under the optimal condition, giving corresponding products 5 in moderate yields (Table 4). As shown in Table 4, 7a could react with series of 1 (1a, 1c, 1h and 1o) to yield 5b (40%), 5c (34%), 5d (56%) and 5e (57%) in the presence of KOH (Table 4, entries 1 ~ 4). Similarly, 5f (39%), 5g (32%), 5d (52%) and 5h (51%) could be prepared from 7b and corresponding disulfides (1a, 1c, 1g and 1o) under the optimal conditions; 3). Employment of excess 4 with 2 only gave product 1,2,4-tris(phenylthio)-3,6-difluorobenzene (8) in 74% yield (Scheme 4); 4). As mentioned above, the reaction of 1k, 1l and 2 only gave 3k and 3l in low yields. These results indicated that sulfhydryl anion could substitute the fluorine atom at the C-4 position of 2, and the hydrogen of 2 could be extracted by KOH. However, the shedding of fluorine at the C-4 position of 2 was also easier than that hydrogen.

Based on the above preliminary results, a plausible mechanism was proposed in Scheme 4. As reported by Kisliuk, Taddei and other people, base could help activating the disulfide via homolytic cleavage.¹¹ Initially, reactive sulfhydryl ion intermediates were generated from disulfides in the presence of base. The reactive sulfhydryl ion then reacted with the C-F bond at C-4 position of 2 to provide intermediate A. Then the C-H bond would be broken in the presence of base, followed by reaction with reactive sulfhydryl ion intermediates B or other disulfides to give corresponding products C or D. However, employment of excess base would destroy more disulfides at the beginning of the reaction, thus leading to the break of more C-F bonds of pentafluorobenzene in the first step and the formation of multi-substituted products. This would limit the second step, resulting in a decrease in the yield of desired products.

Conclusions

In conclusion, the thiolation of pentafluorobenzene with disulfides by C–H, C–F bonds activation and C-S bond formation was demonstrated. This is a new and environment-friendly methodology of thiolation reaction. The reaction proceeds under mild and metal-free conditions, and the corresponding products were obtained in moderate to good yields. A possible mechanism for the reaction was given through some experiments.

Conflicts of interest

There are no conflicts to declare.

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