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Rongalite-promoted transition metal-free synthesis of *S*-aryl phosphorothioates

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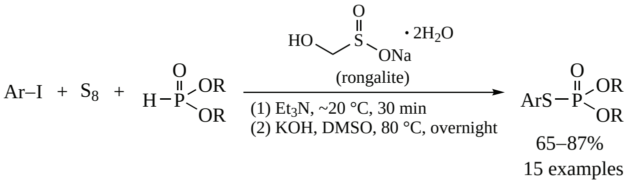
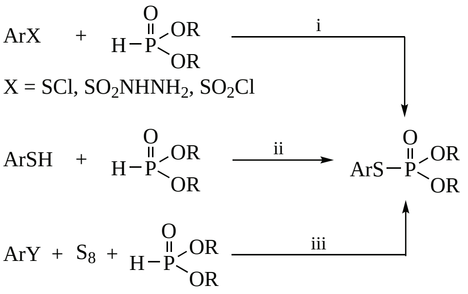
The improved procedure for the synthesis of *S*-aryl phosphorothioates from dialkyl phosphites (*H*-phosphonates), aryl iodides and elemental sulfur deals with the application of rongalite (sodium hydroxymethanesulfinate) as the radical promoter. The reactions proceeded smoothly to give *S*-aryl phosphorothioates in good yields.



Keywords: rongalite, phosphorothioates, arylation, radical process, aryl halides, sulfur.

S-Aryl phosphorothioates and related compounds have found applications in the synthesis of biologically active compounds.[1–7] Traditionally, the synthesis of *S*-aryl phosphorothioates involved the Michaelis−Arbuzov-type reaction[8,9] and phosphorylation of aryl thiols[10,11] (Scheme 1, paths i and ii). These methods, however, suffered from high temperature, toxic reagents, sensitivity of sulfur reagents, and pollution of the environment. Recently, three-component coupling reactions involving Ar–X, sulfur powder, and P(O)H compounds have been developed. Arylboronic acids,[12] aryl diazonium salts[13,14] as well as heteroarenes[15] underwent this transformation successfully to afford a variety of valuable *S*-aryl phosphorothioates. These reactions are efficient and the reaction conditions are mild. Importantly, *O,O*-dialkyl *S*-hydrogen phosphorothioates are generated *in situ* from P(O)H compounds and sulfur powder in the presence of Et_3N, thereby avoiding the use of toxic and odorous sulfur reagents (see Scheme 1, path iii). Just recently, Zhang and co-workers reported a copper-catalyzed multicomponent trifluoromethylphosphorothiolation of alkenes. The coupling of alkenes, P(O)H compounds, sulfur powder, and Togni reagent II successfully provided CF_3-containing *S*-alkyl phosphorothioates.[16]

Aryl radicals are very useful synthetic intermediates in organic chemistry.[17,18] Compared with other methods, generation of aryl radicals from aryl halides is undoubtedly the most suitable way. Much effort has been made to generate aryl radicals *via* halogen abstraction, photo-induced homolytic cleavage of the carbon−halogen bond, transition metal-mediated single-electron transfer (SET) strategy, and base-promoted homolytic aromatic substitution (BHAS).[19–23] Among them, electron-catalysis strategy has attracted much attention in recent years. However, harsh reaction conditions such as high temperature and the use of super-strong base were required in order to generate aryl radicals from aryl halides.

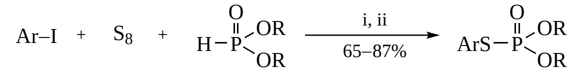


X = SCl, SO_2NHNH_2, SO_2Cl

Y = $B(OH)_2$, N_2BF_4, H

Scheme 1 *Reagents and conditions*: i, MeCN, room temperature, 30 min (ref. 8); ii, KI, TBPB, DMSO, room temperature, 4–8 h (ref. 10); iii, copper catalyst, MeCN, room temperature, overnight (refs. 12 and 13).

Recently, Wang and co-workers reported a rongalite-promoted transition metal-free arylation reaction.[24] Rongalite ($Na^+HOCH_2SO_2^- \cdot 2H_2O$) is a cheap industrial material and it is identified as the precursor of highly reductive sulfoxylate anion ($SO_2^{\cdot -}$). Inspired by their contribution, we herein report a rongalite-promoted transition metal-free synthesis of *S*-aryl phosphorothioates *via* three-component coupling of aryl iodides, sulfur powder, and P(O)H compounds.



1a–l **2a–d** **3a–o**

a Ar = Ph
b Ar = 2-MeC_6H_4
c Ar = 3-MeC_6H_4
d Ar = 4-MeC_6H_4
e Ar = 4-ClC_6H_4
f Ar = 4-FC_6H_4
g Ar = 4-$CF_3C_6H_4$
h Ar = 4-NCC_6H_4
i Ar = 3-$O_2NC_6H_4$
j Ar = 4-$MeC(O)C_6H_4$
k Ar = 4-$EtO_2CC_6H_4$
l Ar = 1-naphthyl

a R = Et
b R = Me
c R = Pr^i
d R = Bn

a Ar = Ph, R = Et
b Ar = 2-MeC_6H_4, R = Et
c Ar = 3-MeC_6H_4, R = Et
d Ar = 4-MeC_6H_4, R = Et
e Ar = 4-ClC_6H_4, R = Et
f Ar = 4-FC_6H_4, R = Et
g Ar = 4-$CF_3C_6H_4$, R = Et
h Ar = 4-NCC_6H_4, R = Et
i Ar = 3-$O_2NC_6H_4$, R = Et
j Ar = 4-$MeC(O)C_6H_4$, R = Et
k Ar = 4-$EtO_2CC_6H_4$, R = Et
l Ar = 1-naphthyl, R = Et
m Ar = Ph, R = Me
n Ar = Ph, R = Pr^i
o Ar = Ph, R = Bn

Scheme 2 *Reagents and optimized conditions*: i, S_8 (0.4 mmol), *H*-phosphonate **2** (0.4 mmol), Et_3N (0.4 mmol), DMSO (1 ml), room temperature, 30 min; ii, ArI **1** (0.2 mmol), rongalite (0.4 mmol), KOH (0.6 mmol), 80 °C, N_2, overnight.

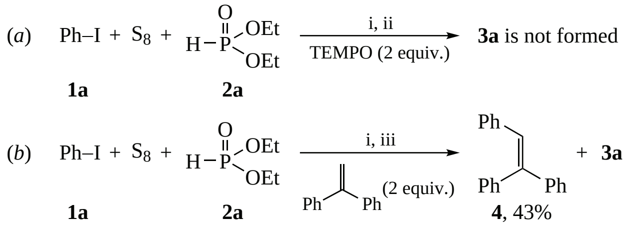
Table 1 Optimization of reaction conditions.[a]

Entry	Base	Solvent	T/°C	Yield of **3a** (%)[b]
1	–	DMSO	80	9
2	DIPEA	DMSO	80	8
3	K_2CO_3	DMSO	80	10
4	KOAc	DMSO	80	14
5	KOH	DMSO	80	77
6	NaOH	DMSO	80	68
7	KOH	DMF	80	12
8	KOH	MeCN	80	17
9	KOH	THF	80	trace
10	KOH	1,4-dioxane	80	trace
11	KOH	MeOH	80	trace
12	KOH	DMSO	60	26
13	KOH	DMSO	100	72
14	KOH	DMSO	80	0[c]
15	KOH	DMSO	80	41[d]
16	KOH	DMSO	80	85[e]

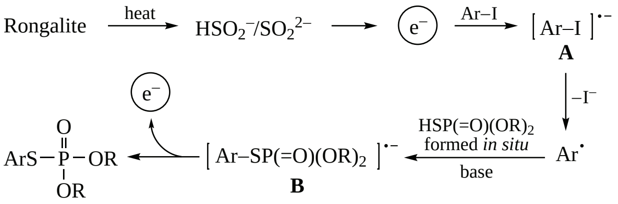
[a] Reaction conditions: S_8 (0.4 mmol), diethyl *H*-phosphonate **2a** (0.4 mmol) and Et_3N (0.4 mmol) in solvent (2 ml) were stirred for 30 min. Then iodobenzene **1a** (0.2 mmol), rongalite (0.4 mmol) and base (0.6 mmol) were added, and the mixture was heated overnight under N_2. [b] Isolated yield. [c] Without rongalite. [d] Reaction under air. [e] Solvent (1 ml).

Reaction conditions were optimized using iodobenzene **1a**, sulfur powder and diethyl *H*-phosphonate **2a** as the model substrates (Scheme 2, Table 1). Initially, a mixture of sulfur powder, diethyl *H*-phosphonate **2a** and Et_3N in DMSO was stirred for 30 min. Then iodobenzene **1a**, rongalite and base were added, and this was heated at 80 °C overnight under N_2. Base nature showed significant influence on the reaction: DIPEA, K_2CO_3 and KOAc gave low yields of product **3a** (entries 1–4). Pleasingly, addition of KOH or NaOH afforded **3a** in 77 and 68% yields, respectively (entries 5 and 6). Reactions in other solvents such as DMF, acetonitrile, THF, 1,4-dioxane and MeOH gave rather poor yields (entries 7–11). Moreover, reaction at 60 °C gave only 26% yield of **3a** and further raising the reaction temperature to 100 °C did not benifit the yield (entries 12 and 13). Control experiment showed that the application of rongalite was crucial, and carrying out the reaction under air decreased the yield to 41% (entries 14 and 15). Finally, diminishing amount of solvent to 1 ml led to 85% yield of **3a** (entry 16).

With the optimized reaction conditions in hand, the scope and generality of the present method were explored (see Scheme 2).[†] Aryl halides containing methyl, halogen, trifluoromethyl, cyano, nitro, keto and ester groups reacted with diethyl *H*-phosphonate **2a** and sulfur powder to give the corresponding products **3a–o** in 65–87% yields, indicating that both electron-rich and electron-deficient aryl halides were compatible. Steric hindrance showed little influence on the reaction. The *ortho*-, *meta*-, and *para*-methyl-substituted iodobenzenes underwent this reaction smoothly to produce compounds **3b–d** in 80–84% yields. Iodobenzenes with strong electron-withdrawing groups provided moderate yields (**3g**,**i**). 1-Iodonaphthalene was also a suitable substrate for the synthesis of **3l** in 80% yield. Other dialkyl *H*-phosphonates **2b–d** also showed good reactivities, generating the corresponding *S*-aryl phosphorothioates **3m–o** in 81–87% yields.



Scheme 3 *Reagents and conditions*: i, S_8, **2a**, Et_3N, DMSO, room temperature, 30 min; ii, **1a**, rongalite, KOH, TEMPO, 80 °C, overnight; iii, **1a**, rongalite, KOH, $Ph_2C=CH_2$, 80 °C, overnight.



Scheme 4

Some control experiments were carried out to gain insight into the reaction. Initially, when 2 equiv. of the radical scavenger, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added, no desired product **3a** was observed (Scheme 3, *a*). Meanwhile, when 1,1-diphenylethylene was added under the standard reaction conditions, product **4** was obtained in 43% yield (Scheme 3, *b*).

On the basis of experimental results and previous reports,[12,13,24] a mechanism is proposed (Scheme 4). Initially, rongalite can release an electron under heating,[25] which is captured by aryl iodide to generate a radical anion **A**. Then, **A** loses an iodine anion to deliver aryl radical. Next, the *in situ* formed $(RO)_2P(O)–SH$[12,13] from $(RO)_2P(O)–H$ and S_8 reacts with aryl radical in the presence of a base to give radical anion **B**. Finally, **B** loses an electron to afford the desired product.

In summary, using aryl iodides as the aryl source and sulfur powder as the sulfur source, we have developed a C(aryl)–S–P bond formation reaction promoted by a rongalite. In this reaction, rongalite was used as a novel precursor of super electron donors to generate aryl radicals from aryl halides. All the starting materials and catalyst are cheap and readily available. A broad scope of aryl halides and *H*-phosphonates survived the reaction conditions to afford *S*-aryl phosphorothioates in good yields.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.033.

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[†] *General procedure for the synthesis of* **3a**–**o**. A sealed tube equipped with a magnetic stirring bar was charged with S_8 (0.4 mmol, 13 mg), *H*-phosphonate **2** (0.4 mmol) and Et_3N (0.4 mmol, 40 mg) in DMSO (1 ml), and this was stirred for 30 min. Then aryl iodide **1** (0.2 mmol), rongalite (0.4 mmol, 47 mg) and KOH (0.6 mmol, 34 mg) were added. The reaction mixture was heated to 80 °C and stirred overnight. Upon reaction completion, the resulting solution was quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (4 : 1, v/v) as eluent to afford products **3a**–**o**.

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