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Graphical Abstract

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Dithioates of Meldrum's acid, dimedone, and barbituric acid, novel sulfur transfer reagents for the one-pot copper-catalyzed conversion of aryl iodides into diaryl disulfides

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ABSTRACT

Article history: Received Received in revised form Accepted Available online We report herein the first application of CH-acid dithioates as sulfur transfer reagents. A new route for the synthesis of diaryldisulfides using the copper-catalyzed conversion of aryl iodides in the presence of Melderum's acid, dimedone or barbituric acid dithioates is discussed.

Keywords: copper-catalyzed conversion sulfur transfer reagent diaryl disulfide dithioates

Disulfide compounds have significant industrial and biological applications 1-6 and are utilized in the synthesis of natural products and medicinal compounds,^{7,8} as well as in the preparation of organic reagents such as sulfenyls and sulfinyls.9,10 They also play an important role in protein and peptide synthesis, as vulcanizing agents, in the preparation of dynamic combinatorial libraries, catenanes and macrocycles, carceplexes, dendrimers, rotaxanes and micelles.¹¹ Due to their widespread usage, the development of new synthetic methods for these compounds is still of interest. The most common methods for preparing disulfides such as the oxidation of thiols, reductive coupling of sulfonyl chlorides, reaction of activated aromatic compounds, alkynes and alkenes with sulfur monochloride (S₂Cl₂), and radical cyclization of substituted aminothiourea derivatives have been reviewed in detail by Witt.¹² Recently, sulfur transfer reagents such as thiourea, potassium thiocyanate, thiosemicarbazide, sodium sulfide, 5-methyl-1,3,4-oxadiazole-2thiolate, thioacetamide and morpholin-4-ium morpholine-4carbodithioate have also been used for the synthesis of sulfides and disulfides from alkyl or aryl halides.¹³ More recently, the dithioate of morpholine has been used as a sulfur transfer reagent for the synthesis of aryl and alkyl disulfides.¹

Furthermore, active methylene compounds have received widespread attention in the synthesis of organic compounds.¹⁵⁻²¹ Meldrum's acid, dimedone, barbituric acid and their derivatives have been widely used for the preparation of biologically active compounds, intermediates, heterocycles and in multistep drug synthesis.²²⁻²⁴ We recently developed a concise and effective synthesis for a series of novel ketene dithioacetals by the condensation of active methylene compounds with carbon

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disulfide in the presence of acetylenedicarboxylates. ^{25, 26} In a continuation of our work on copper-catalyzed reactions, ²⁷ we were interested in the copper-catalyzed conversion of aryl iodides into the corresponding diaryldisulfides using dithioates of Melderum's acid, dimedone, and barbituric acid as sulfur transfer reagents (Scheme 1).²⁸

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$$X = CH_2, O, NH$$

Scheme 1. Copper-catalyzed conversion of aryl iodides into diaryl disulfides using dithioates.

According to the previously reported work by Yavari and coworkers regarding the *S*-arylation of the malononitrile- CS_2 adduct, ²⁹ initially we had decided to apply the same reaction for *S*-arylation of dithioates of Melderum's acid, dimedone, and barbituric acid. However, in all examined cases a diaryldisulfide was obtained as the only product, indicating that dithioates of the mentioned CH-acids acted as good sulfur transfer reagents.

The required dithioates were readily prepared by the reaction of CS_2 with the enolate anion of the above CH-acids in the presence of Et_3N . To optimize the reaction conditions, iodobenzene was chosen as a model substrate and different parameters such as catalyst, base, solvent and temperature were investigated. Optimization of the reaction conditions for

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dithioates of dimedone, Meldrum's acid, and barbituric acid are compiled in Tables 1, 2 and 3, respectively. In all three cases, we observed that when the reaction was performed in air, the desired product was not formed and no reaction occurred in the absence of a copper catalyst (Tables 1-3, entry 4). The greatest activity was found at 100 °C for Meldrum's acid and barbituric acid dithioates (Tables 2 and 3, entry 3), and at 60 °C for dimedone dithioate (Table 1, entry 2). Different Cu sources were tested using CS₂ in DMF (Tables 1-3, entries 5-9) and the best conversion was observed with CuCl. The reaction was also examined with different catalyst loadings showing that 10 mol% of CuCl (relative to the aryl iodide) was optimal. At lower catalyst loadings the reaction was not complete and increased catalyst loadings did not have a significant impact on the efficiency of the reaction (Table 1-3, entries 10 and 11). A solvent effect was observed and DMF was the best solvent for the reaction of dimedone and Meldrum's acid dithioates with iodobenzene while in the case of the barbituric acid dithioate, DMSO was the best solvent (Tables 1-3, entries 12-15). Next, we investigated the effect of the base on the reaction. No improvement was shown using bases other than Et₃N in the cases of Meldrum's acid and dimedone dithioates, however, the addition of a mineral base increased the yield when using barbituric acid dithioate (Table 3, entries 16-18).

Therefore our most general optimal reaction conditions for the conversion of iodobenzene into the titled product using dithioates of Meldrum's acid, dimedone and barbituric acid as sulfur transfer reagents are as follows; for dimedone dithioate: 10 mol% CuCl as catalyst, DMF as solvent and the reaction carried out at 60 °C under an N₂ atmosphere. For Meldrum's acid dithioate: 10 mol% CuCl as catalyst, DMF as solvent and the reaction carried out at 100 °C under an N₂ atmosphere, and for barbituric acid dithioate: 10 mol% CuCl as catalyst, Cs₂CO₃ as the second base, DMSO as the solvent and the reaction was carried out at 100 °C under an N₂ atmosphere.

Next, we investigated the scope of the reaction with respect to aryl iodides (Table 4). Most of the aryl iodides examined under the optimized reaction conditions gave good yields. Table 4 shows that the dithioate of Meldrum's acid was the best sulfur donor and barbituric acid dithioate was better than dimedone dithioate. Sterically hindered aryl iodides gave the corresponding diaryl disulfides in good yields (Table 4, entries 2, 3, 8 and 9). Aryl iodides with nitro substituents such as 1-iodo-4nitrobenzene, 1-iodo-2-nitrobenzene and 1-iodo-2,4dinitronenzene were also examined under optimized reaction conditions but no desired product was obtained.

On the basis of previously reported findings in the literature, the proposed mechanism for the copper-promoted conversion of an aryl halide into a diaryldisulfide using a sulfur donor may involve two main steps.^{13, 14, 30} In the first step, aryl thiolate is generated in the coupling reaction between the sulfur donor and aryl halide via an Ullman-type mechanism. Then, the generated thiolate is converted into the corresponding disulfide by an oxidative coupling. It is obvious that the oxidative coupling of the arylthiolate must use a stoichiometric copper salt or oxygen as the oxidant. However, in our case, when the reaction was performed in air, the desired product was not formed. Moreover, in order to check the presence of the phenyl thiolate as the intermediate, the synthesis of diphenyl disulfide from thiophenol was studied under optimal reaction conditions, but no product was found in this case. Therefore, it is possible that this reaction proceeds through the activation of the aryl iodide via a Cu(I)/ Cu(II) redox couple SET (Single Electron Transfer) mechanism followed by in situ generation of a thiolate radical via an S_{RN}1 (Unimolecular Radical Nucleophilic Substitution) mechanism thiolate radical and finally, coupling to form the diaryldisulfide.13g, 33

Table 1. Optimization of reaction conditions for the dithioate of dimedone ^a

$$O + Ph-I \xrightarrow{Cu cat.} S-S'$$

solvent Ph
2a

	S ² S			2a		
Entry	Catalyst	Solvent	T (°C)	t (h)	2a (%)	
1	CuCl	DMF	25	24	10	
2	CuCl	DMF	60	4	72	
3	CuCl	DMF	100	4	72	
4	-	DMF	60	4	-	
5	CuI	DMF	60	4	62	
6	CuO	DMF	60	4	20	
7	CuO ^b	DMF	60	4	70	
8	$CuSO_4$	DMF	60	4	47	
9	Cu(OAc) ₂	DMF	60	4	55	
10	CuCl ^c	DMF	60	4	40	
11	CuCl ^d	DMF	60	4	74	
12	CuCl	DMSO	60	4	66	
13	CuCl	H_2O	60	4	-	
14	CuCl	1,4-Dioxane	60	4	25	
15	CuCl	Toluene	60	4	40	

^aModel reaction conditions: PhI (1.0 mmol), CuCl (0.1 mmol), DMF (2 mL), dimedone dithioate solution in DMF contains dimedone (1 mmol), CS₂ (1 mmol) and Et₃N (2 mmol), under a N_2 atmosphere.

 $^{\mathrm{b}}\mathrm{CuO}$ nanoparticles. (CuO nanoparticles were synthesized as described in the literature). 31

°CuCl (0.05 mmol).

^dCuCl (0.2 mmol).

Table 2.	Optimiza	ation of rea	action cond	litions for t	the dithioate
of Meldr	um's acid	l ^a			

Dh

	or single statements and statements	O + Ph-I	Cu cat. T (°C) solvent	S-S' Ph' 2a	11
Entry	Catalyst	Solvent	T (°C)	t (h)	2a (%)
1	CuCl	DMF	25	24	Trace
2	CuCl	DMF	60	4	55
3	CuCl	DMF	100	4	94
4	-	DMF	60	4	-
5	CuI	DMF	60	4	85
6	CuO	DMF	60	4	50
7	CuO ^b	DMF	60	4	94
8	$CuSO_4$	DMF	60	4	66
9	Cu(OAc) ₂	DMF	60	4	80
10	CuCl ^c	DMF	60	4	64
11	CuCl ^d	DMF	60	4	95
12	CuCl	DMSO	60	4	88
13	CuCl	H_2O	60	4	-
14	CuCl	1,4-Dioxane	60	4	20
15	CuCl	Toluene	60	4	60

Model reaction conditions: PhI (1.0 mmol), CuCl (0.1 mmol), DMF (2 mL), Meldrum's acid dithioate solution in DMF contains Meldrum's acid (1 mmol), CS_2 (1 mmol) and Et_3N (2 mmol), under a N_2 atmosphere.

^bCuO nanoparticles.

^cCuCl (0.05 mmol).

^dCuCl (0.2 mmol).

Table 3. Optimization of reaction conditions for the dithioate of barbituric acid ^a



ł	Entry	Catalyst	Solvent	Base	T (°C)	t (h)	2a (%)
	1	CuCl	DMF	-	25	24	Trace
	2	CuCl	DMF	-	60	4	25
	3	CuCl	DMF	-	100	4	64
	4	-	DMF	-	100	4	-
	5	CuI	DMF	-	100	4	55
	6	CuO	DMF	-	100	4	30
	7	CuO ^b	DMF	-	100	4	64
	8	$CuSO_4$	DMF	-	100	4	46
	9	Cu(OAc) ₂	DMF	-	100	4	50
	10	CuCl ^c	DMF	-	100	4	44
	11	CuCl ^d	DMF	-	100	4	65
	12	CuCl	DMSO	-	100	4	68
	13	CuCl	H_2O	-	100	4	-
	14	CuCl	1,4-Dioxane	-	100	4	-
	15	CuCl	Toluene	-	100	4	40
	16	CuCl	DMSO	K_2CO_3	100	4	74
	17	CuCl	DMSO	Cs ₂ CO ₃	100	4	85
	18	CuCl	DMSO	K_3PO_4	100	4	75

^aModel reaction conditions: PhI (1.0 mmol), CuCl (0.1 mmol), DMSO (2 mL), barbituric acid dithioate solution in DMSO contains barbituric acid (1 mmol), CS_2 (1 mmol) and Et_3N (2 mmol), under a N_2 atmosphere.

^bCuO nanoparticles ^cCuCl (0.05 mmol).

 $^{\rm d}$ CuCl (0.05 mmol).

In conclusion, we have reported for the first time, a new route for the synthesis of diaryldisulfides by the copper-catalyzed conversion of aryl iodides using dithioates of Melderum's acid, dimedone, and barbituric acid as effective sulfur transfer reagents. This method offers several advantages including operational simplicity, good yields, and easy work-up procedures. **Table 4.** Copper-catalyzed conversion of aryliodides to symmetrical diaryldisulfide by dithioates



Entry		ArI	ArSSAr	Yield	l (%) ^a ,	X =	
			AISSAI		CH_2	NH	
1	1a	I	2a ^{32a}	94	72	85	
2	1b		2b ^{32b}	80	58	71	
3	1c		3c ^{32c}	83	61	74	
4	1d	Br	2d ^{13k}	88	66	79	
5	1e	Me	2e ^{32d}	78	56	69	
6	1f	Me	2f ^{32e}	83	61	74	
7	1g		2g ^{32f}	80	58	71	
8	1h		2h ^{32g}	74	52	65	
9	1i		2i ¹³¹	91	69	82	
10	1j	MeO	2j ^{32h}	77	55	68	
11	1k		2k ³²ⁱ	69	47	60	
12	11	F	21 ^{32j}	74	52	65	
13	1m	Cl F I	2m	62	45	55	

^aIsolated yield

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