A Novel Nickel-Catalyzed Domino Method for the Direct Synthesis of Symmetrical Disulfides Using Potassium 5-Methyl-1,3,4-oxadiazole-2-thiolate as a Sulfurating Reagent

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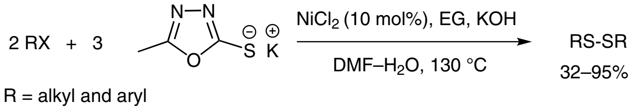

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Abstract A simple, one pot, efficient, and novel protocol has been developed for the direct synthesis of symmetrical organic disulfides using a domino reaction between an aryl/alkyl halide and potassium 5-methyl-1,3,4-oxadiazole-2-thiolate in the presence of $NiCl_2$ as catalyst. A variety of symmetrical aryl/alkyl disulfides can be obtained in moderate to excellent yields (up to 95%).

Key words nickel-catalyzed, disulfides, cross-coupling, 1,3,4-oxadiazole, sulfur-transfer reagents

Nickel catalysis has been increasingly used in cross-coupling chemistry as a reactive and cost-effective alternative to other transition-metal catalysts.[1] Several key properties of nickel, such as its air stability, ease of preparation, and low energy barriers for oxidative addition, have allowed the development of a broad range of innovative reactions.[2] Nickel-catalyzed C–S coupling reactions have been used and investigated for efficient organic disulfide synthesis from thiols.[3]

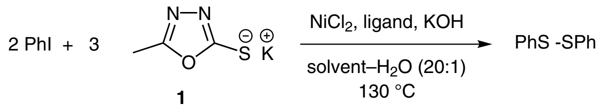
Organic disulfides are important intermediates in various organic transformations.[4] They are used in the sulfenylation of enolates and other anions[5] as well as being essential moieties in biologically active compounds for peptide and protein stabilization.[6] As disulfides are relatively more stable towards oxidation, alkylation, and acylation when compared to their corresponding free thiols, the thiol group can be conveniently protected as a disulfide.[7]

The oxidative coupling of thiols to their corresponding disulfides is the most common method for disulfide formation.[8] Derivatives can be obtained from the copper(I)-catalyzed couplings of aryl/alkyl halides with various types of sulfur-containing substrates involving thioacetamide,[9] di(tri)thiocarbonate,[10] thiourea and thiouronium salts,[11] sulfur/sodium sulfide,[12] and elemental sulfur.[13,14] Although these methods are very effective, they have drawbacks such as the use of highly volatile, toxic, and foul-smelling thiols or large amounts of copper salts as catalyst. To overcome this disadvantage, attention has been directed towards the direct synthesis of symmetrical disulfides in the presence of catalytic amounts of nickel salts. In this regard, potassium 5-methyl-1,3,4-oxadiazole-2-thiolate as a sulfur-transfer reagent was used instead of a free thiol, for the direct synthesis of organic disulfides from an alkyl/aryl halide in the presence of $NiCl_2$.

Our previous work utilized potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**) as a new heterocyclic sulfur donor for the direct synthesis of organic disulfides from aryl/alkyl halides in the presence of a copper catalyst that effectively led to the production of disulfides in high yield.[15] In continuation of our efforts towards the synthesis of organosulfur compounds,[16] we report for the first time a method for the direct synthesis of symmetrical diaryl and dialkyl disulfides from aryl/alkyl halides using nickel catalysis.

In this work, the reaction of iodobenzene with potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**) in the presence of a nickel catalyst and KOH was studied under normal atmospheric conditions in order to optimize the reaction conditions in terms of temperature, amount of reagent, the type of nickel source, ligand and solvent. According to the results shown in Table 1 it was found that the ligand and solvent significantly affected the rate of the reaction. Ethylene glycol (EG) in DMF was the most effective solvent–ligand combination because increasing the amount of EG led to an increased rate of reaction (Table 1, entries 10–14). It seems EG behaves as a cosolvent in addition to acting as a ligand during the reaction. In addition, the reaction yield and reaction rate increased with increases in temperature up to 130 °C. Furthermore, $NiCl_2{\cdot}6H_2O$ provided the best yield when compared to other nickel salts tested in this investigation (Table 2). A large number of symmetrical diaryl/dialkyl disulfides was synthesized in the presence of $NiCl_2{\cdot}6H_2O$ using three equivalents of potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**) at 130 °C under normal atmospheric conditions (Table 3).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Ligand (mol%)	Time (h)	Yield (%)
1	DMF	–	24	20
2	DMF	1,10-phen[b] (20)	24	52
3	DMF	ED[c] (20)	24	trace
4	DMF	L-proline (20)	24	43
5	DMF	glycine (20)	24	48
6	DMF	acac (20)	24	34
7	DMF	glycerol (20)	24	31
8	DMF	glyoxime (20)	24	70
9	DMF	Ph_3P (20)	24	50
10	DMF	EG (20)	24	72
11	DMF	EG (100)	18	85
12	DMF	EG (150)	12	89
13	DMF	EG (200)	4	92
14	DMF	EG (300)	4	95
15	DMSO	EG (200)	4	68
16	toluene	EG (200)	4	N.R
17	1,4-dioxane	EG (200)	4	10
18	MeCN	EG (200)	4	25
19	PEG	EG (200)	4	trace
20	EtOH	EG (200)	4	trace
21	NMP	EG (200)	4	15
22	THF	EG (200)	4	32
23	EG	–	4	trace

[a] Reaction conditions: PhI (2.0 mmol), $NiCl_2{\cdot}6H_2O$(10 mol%), potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**, 3 mmol), KOH (36 mmol), solvent–H_2O (20:1; 2 mL), air.
[b] 1,10-Phenanthroline.
[c] 1,2-Ethylenediamine.

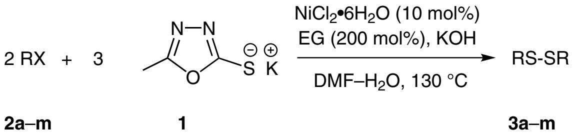
The reaction efficiency for the synthesis of diaryl disulfides from various aryl halides was examined. As can be seen, aryl chlorides were not as reactive as aryl bromides and aryl iodides with yields of 47–95% being obtained (Table 3). Symmetrical diaryl disulfides bearing different functional groups such as Me, OMe, NO_2, and Br were also synthesized in good to excellent yield.

Table 2 Optimization of the Type and Amount of Nickel Source and Temperature[a]

Entry	Temp (°C)	Nickel source (mol%)	Time (h)	Yield (%)
1	25	$NiCl_2{\cdot}6H_2O$ (10)	24	n.r.
2	80	$NiCl_2{\cdot}6H_2O$ (10)	24	trace
3	110	$NiCl_2{\cdot}6H_2O$ (10)	6	54
4	130	$NiCl_2{\cdot}6H_2O$ (10)	4	92
5	130	$NiCl_2{\cdot}6H_2O$ (5)	24	50
6	130	$NiCl_2{\cdot}6H_2O$ (20)	4	94
7	130	$Ni(OAc)_2{\cdot}4H_2O$ (10)	24	trace
8	130	$Ni(SO_4)_2{\cdot}6H_2O$ (10)	24	35
9	130	$Ni(NO_3)_2{\cdot}6H_2O$ (10)	24	58

[a] Reaction conditions: PhI (2.0 mmol), potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**, 3 mmol), EG (200 mol%), KOH (36 mmol), DMF–H_2O (20:1; 2 mL), air.

Table 3 Direct Synthesis of Symmetrical Disulfides from Aryl/Alkyl Halides

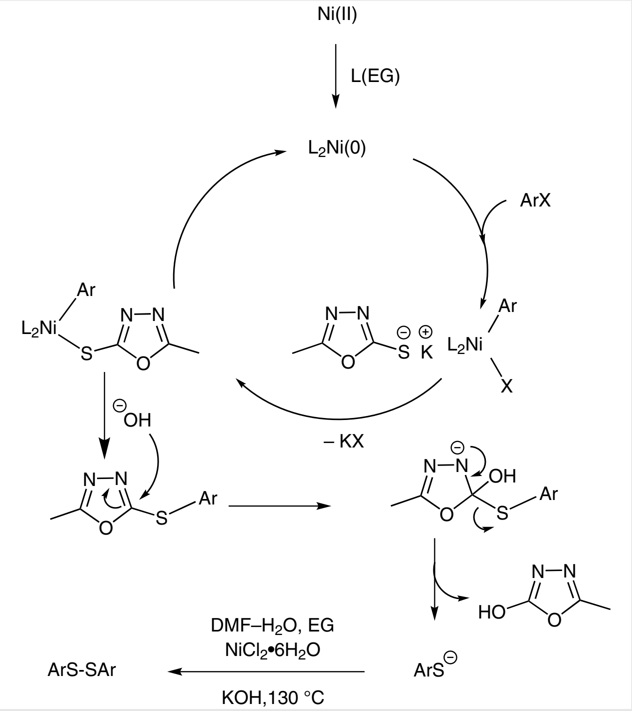


Entry	RX	Product	Time (h)	Yield (%)[a,b]
1	PhI	**3a**	4.0	92[14]
2	PhBr	**3b**	5.0	90[14]
3	$2\text{-}MeC_6H_4I$	**3c**	8.0	70[c,14]
4	1-iodonaphthalene	**3d**	8.0	75[c,14]
5	$4\text{-}BrC_6H_4I$	**3e**	4.5	78[17]
6	2-iodothiophene	**3f**	3.0	89[15]
7	2-bromothiophene	**3f**	3.0	85[15]
8	2-chlorothiophene	**3f**	4.0	82[15]
9	$4\text{-}NO_2C_6H_4Br$	**3g**	1.5	40[14]
10	$2,4\text{-}(NO_2)_2C_6H_3Cl$	**3h**	2.5	32[15]
11	$3\text{-}MeOC_6H_4I$	**3i**	24	47[c,14]
12	$4\text{-}MeOC_6H_4I$	**3j**	24	55[c,14]
13	$PhCH_2Cl$	**3k**	1.5	90[8h]
14	$Ph(CH_2)_2Br$	**3l**	3.5	93[8h]
15	$Ph(CH_2)_3Br$	**3m**	3.0	95[9]

[a] All the products are known compounds and were characterized by comparison of NMR spectroscopic data and melting points with those reported in the literature.
[b] Isolated yield.
[c] Incomplete reaction.

As a general trend, under the optimal conditions determined above, a higher rate of reaction was obtained with aryl substrates possessingelectron-withdrawing groups such as NO_2 (conversion 100%, time 1.5–2.5 h; Table 3, entries 9 and 10) although several products were formed. However, reactions were not complete after 24 hours in the presence of electron-donating groups such as OMe (Table 3, entries 11 and 12). The reaction efficiency for the synthesis of symmetrical dialkyl disulfides was also examined and was found to be as effective as aryl disulfides (Table 3, entries 13–15).

Although we cannot clearly determine the catalytic reaction pathway for the synthesis of diaryl/dialkyl disulfides from aryl/alkyl halides and potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**), the initial conversion of nickel(II) to nickel(0) in the presence of EG is plausible.[1d,e,m,18] The potassium thiolate appears to be generated in the coupling reaction between potassium 5-methyl-1,3,4-oxadiazole-2-thiolate and the aryl/alkyl halide. The potassium thiolate generated is then converted into the corresponding disulfide under the reaction conditions (Scheme 1).[9]



Scheme 1 Proposed mechanism

In conclusion, we have developed a novel, simple and efficient method for the synthesis of diaryl/dialkyl disulfides, that relies on a nickel-catalyzed coupling reaction.[19] The important feature of this method is the use of potassium 5-methyl-1,3,4-oxadiazole-2-thiolate salt as the sulfurating reagent, which is a new, inexpensive, and stable solid and free of foul-smelling thiols. In this work $NiCl_2{\cdot}6H_2O$ (10 mol%) was used as an inexpensive, safe, readily available, and more efficient catalyst. Therefore, this strategy provides a new method for the direct synthesis of symmetrical diaryl and dialkyl disulfides from aryl/alkyl halides, which is more economical and general than previous methods.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380141.

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(19) **Symmetrical Organic Disulfide Synthesis; Typical Experimental Procedure**

A mixture of iodobenzene (2.0 mmol), potassium 5-methyl-1,3,4-oxadiazole-2-thiolate (**1**, 0.462 g, 3.0 mmol), $NiCl_2\cdot 6H_2O$ (10 mol%) and KOH (1.0 g, 18 mmol) were added to a flask containing DMF–H_2O (2 mL, 20:1) and EG (0.11 mL, 2 mmol). The reaction mixture was heated at 130 °C under atmospheric conditions until completion, monitored by TLC. The reaction mixture was then filtered, the filtrate was evaporated under reduced pressure, CH_2Cl_2 (20 mL) was added, and the mixture was washed with H_2O (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to give the crude diaryl/alkyl disulfide, which was purified by preparative TLC (silica gel; *n*-hexane–EtOAc, 20:1).

Compound **3d** was obtained as a creamy yellow solid in 75% yield; mp 94–97 °C. ^1H NMR (400 MHz, $CDCl_3$): $δ$ = 8.41–8.50 (m, 2 H), 7.82–7.95 (m, 4 H), 7.34–7.7 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): $δ$ = 134.1, 132.6, 130.3, 129.9, 128.6, 128.0, 126.8, 126.6, 125.9, 125.1. MS (EI): *m/z* = 318 $[M^+]$.

Compound **3f** was obtained (EtOAc–*n*-hexane, 1:10) as a light green solid in 89% yield; mp 54–55 °C. ^1H NMR (400 MHz, $CDCl_3$): $δ$ = 7.36–7.38 (m, 2 H), 7.22–7.25 (m, 2 H), 6.97–7.00 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): $δ$ = 155.4, 129.7, 120.7, 115.4.

Compound **3j** was obtained (EtOAc–*n*-hexane, 1:5) as a white solid in 55% yield; mp 41–43 °C. ^1H NMR (400 MHz, $CDCl_3$): $δ$ = 7.32 (d, J = 8.8 Hz, 4 H), 6.87 (d, J = 8.8 Hz, 4 H), 3.82 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): $δ$ = 159.0, 132.8, 127.4, 114.7, 55.4.

Compound **3k** was obtained (EtOAc–*n*-hexane, 1:20) as a white solid in 90% yield; mp 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$): $δ$ = 7.28–7.38 (m, 10 H), 3.63 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): $δ$ = 137.4, 129.5, 128.5, 127.5, 43.3.