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A Novel and Efficient Zinc-catalyzed Thioetherification of Aryl Halides

Amrutha P Thankachan,[a] K S Sindhu,[a] K Keerthi Krishnan [a] and Gopinathan Anilkumar [a]*

X = I/ Br/ Cl
R^1 = -OMe, $-NO_2$, -CN,$-COCH_3$
R^2 = Aryl/ Alkyl

The first Zn-catalyzed protocol for C-S cross-coupling reactions for the synthesis of substituted aryl and alkyl sulfides with good yields under mild reaction is described.

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ARTICLE TYPE

A Novel and Efficient Zinc-catalyzed Thioetherification of Aryl Halides

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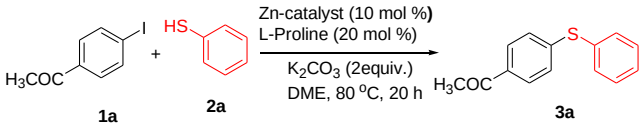
The first zinc-catalyzed protocol for the C-S cross-coupling reactions is reported. Zinc catalysis has an undeniable significance over other catalytic systems due to its non-toxic, easily available, cheap and environmentally benign properties. This novel, efficient, palladium- and triphenylphosphine-free protocol yielded a variety of aryl and alkyl sulfides having moderate to excellent yields.

Aryl Sulfides and their derivatives are very important reactive intermediates in synthetic organic chemistry due to their biological and pharmacological activity.[1] Over the last few years significant growth has been realized in the field of transition metal catalyzed carbon-heteroatom bond formation. In this context, numerous protocols have been reported for carbon-nitrogen and carbon-oxygen bond forming reactions while that for carbon-sulfur bond formation is moderate.[2] This is due to the deactivation of the metal catalyst by organosulfur reactant because of the strong coordination capacity of sulfur with the metal catalysts. The usual methods for carbon-sulfur bond formation reactions are highly inefficient due to the pre-requisite of extremely harsh reaction conditions such as elevated temperature, extensive reaction time, use of more polar solvents and multistep reactions. One of the major challenges associated with the transition metal-catalyzed Carbon-Sulfur bond formation is its greater tendency for oxidative S-S coupling. A large number of fine reports are available for palladium,[3] copper,[4] cobalt,[5] nickel,[6] iron,[7] indium[8] and rhodium[9] catalyzed C-S cross-coupling reactions. The first report on C-S cross-coupling reaction was published by Migita *et al*. in 1978 using catalytic amount of tetrakis(triphenylphophine)palladium.[10]

To the best of our knowledge, no Zn-catalyzed C-S bond forming reaction is reported so far. There are a few reports on zinc-mediated transition metal-catalyzed C-S coupling reactions where zinc is used either as a reducing agent[11] or as an electrophilic buffer[12] to protect the transition metal catalyst. The bio-catalytic ability of zinc is well established and there exist a large number of reports in which zinc is used as a catalyst in organic synthesis.[13] This prompted the idea of using zinc as a catalyst in carbon-heteroatom bond formation reactions. Even though Zinc-catalysts used in carbon-carbon coupling reactions showed great tolerance towards many functional groups,[14] to our surprise, zinc-based catalytic systems have not been used for C-S cross-coupling reactions. In our study we used zinc catalyst along with L-proline as ligand for the C-S cross-coupling reaction in a perspective manner that it may perform chemical transformations similar to that of enzymatic catalysis. Compared to the traditionally used phosphine-based ligands, L-proline is very cheap, non-toxic and readily available.

We herein report a novel and efficient zinc-catalyzed C-S cross-coupling reaction between aryl halides and thiophenols. At first the reaction involving 4-iodoacetophenone and thiophenol was chosen as a model reaction. The reactions are conducted in a previously dried sealed tube in the presence of K_2CO_3 in DME at 80 ^oC under nitrogen atmosphere (Scheme 1).



Scheme 1. Zn-catalyzed C-S cross-coupling of 4-iodoacetophenone and thiophenol.

Screening of different zinc sources revealed that only Et_2Zn along with L-proline showed catalytic ability (Table 1, entry 4). The structure of the product **3a** was assigned based on nuclear magnetic resonance and mass spectrometric analyses. Having obtained the product in moderate yield, we decided to perform the optimization studies in detail.

Table 1. Screening of different zinc-sources for the C-S cross-coupling reaction.[a)]

Entry	Catalyst	Yield[b)]
1	Zn-granules	nd[c)]
2	Zn-powder	nd
3	$Zn(OAc)_2$	nd
4	$ZnEt_2$	54

[a)] Reaction conditions: aryliodide (1mmol), thiophenol (1.1 mmol), K_2CO_3 (2 equiv.), Zn-source (10 mol %), L-proline (20 mol %), DME (3 ml), 80 ^oC, 20 h. [b)] isolated yield. [c)] not detected

First, we tried to find out the influence of the quantity of Et_2Zn catalyst for the C-S cross-coupling reaction. The results revealed that the amount of catalyst loading has great control over the yield, and the optimum catalyst loading was found to be 8 mol % (Table 2**,** entry 2**)**. Further decrease in catalyst loading reduced

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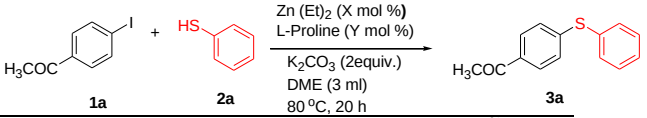
the yield.

Table 2. Effect of the amount of Et_2Zn catalyst for the C-S cross-coupling reaction.[a)]



1a 2a 3a

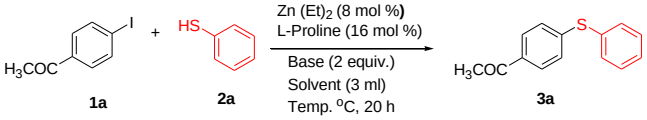
Entry	Zn $(Et)_2$ (mol %)	L-proline (mol %)	Yield[b)]
1	10	20	54
2	**8**	**16**	**53**
3	6	12	35
4	4	8	19
5	2	4	10

[a)] Reaction conditions: aryliodide (1mmol), thiophenol (1.1 mmol), K_2CO_3 (2 equiv.), DME (3 ml), 80 °C, 20 h. [b)] isolated yield

Next we examined the influence of solvents, bases and temperature on Zn-catalyzed thioetherification. The solvent effect analysis revealed that the preferred solvents are DME (Table 3, entries 1, 9, 10, 11) and acetonitrile (Table 3, entries 3, 14, 16, 17). Lower conversions were observed when THF (Table 3, entry 2) and *t*-BuOH were used as solvents (Table 3, entry 5). The base optimization studies on thiolation showed that inorganic bases such as K_2CO_3, Cs_2CO_3, NaO^tBu, KO^tBu and NaH are better compared to triethylamine. The dependence of the amount of bases on C-S cross-coupling indicated that on decreasing the amount of base there is considerable decrease in the amount of product formation (Table 3, entry 21). Studies on the influence of temperature on thioetherification revealed that no reaction took place at 0 °C and at room temperature (Table 3, entries 18, 19). But at 80 °C the product could be isolated. On further increasing the temperature to 125 °C, the yield of the coupled product decreased presumably due to the decomposition of the product at the elevated temperature (Table 3, entry 20).

As part of control experiment, the reaction was performed at optimized conditions in the absence of base, ligand and catalyst. In the absence of base no product could be detected (Table 3, entry 23). In the absence of catalyst and ligand only trace amounts of the product were detected (Table 3, entries 22, 24). Carrying out the reaction in the absence of inert atmosphere afforded the diphenyldisulfide as the major product along with a trace amount of the desired C-S coupling product (Table 3, entry 25). The optimization studies revealed that the yield was vastly dependent upon the base, solvent, reaction temperature and the amount of catalyst. The optimum reaction condition for the desired zinc-catalyzed C-S cross-coupling reaction was found to be 8 mol % of Et_2Zn, 16 mol % of L-proline and 2 equivalents of NaO^tBu at 80 °C in acetonitrile to obtain 95 % of 1-(4-phenylsulfanyl-phenyl)-ethanone (Table 3, entry 17).

Table 3. Optimization of reaction conditions for Zn-catalyzed thioetherification.[a)]



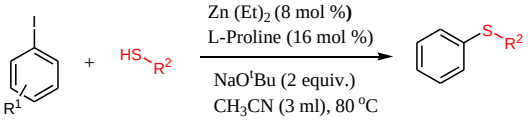
1a 2a 3a

Entry	Base (2 equiv.)	Solvent (3 ml)	Tempereture (°C)	Yield[b)] (%)
1	K_2CO_3	DME	80	54
2	K_2CO_3	THF	80	34
3	K_2CO_3	CH_3CN	80	81
4	K_2CO_3	DMF	80	nd[c)]
5	K_2CO_3	^tBuOH	80	34
6	K_2CO_3	DMSO	80	nd
7	K_2CO_3	Toluene	80	nd
8	K_2CO_3	1,4-dioxane	80	nd
9	Cs_2CO_3	DME	80	75
10	NaO^tBu	DME	80	64
11	NaH	DME	80	62
12	Et_3N	DME	80	nd
13	K_3PO_4	DME	80	14
14	KO^tBu	CH_3CN	80	75
15	NaH	CH_3CN	80	20
16	Cs_2CO_3	CH_3CN	80	85
17	**NaO^tBu**	**CH_3CN**	**80**	**95**
18	NaO^tBu	CH_3CN	0	nd
19	NaO^tBu	CH_3CN	rt	nd
20	NaO^tBu	CH_3CN	125	54
21[d)]	NaO^tBu	CH_3CN	80	43
22[e)]	NaO^tBu	CH_3CN	80	traces
23	-	CH_3CN	80	nd
24[f)]	NaO^tBu	CH_3CN	80	traces
25[g)]	NaO^tBu	CH_3CN	80	traces

[a)]Reaction conditions: aryliodide (1mmol), thiophenol (1.1 mmol), Base (2 equiv.), Et_2Zn (8 mol %), L-proline (16 mol %), Solvent (3 ml), Temp. (°C), 20 h. [b)]isolated yield. [c)]not detected. [d)]1.5 equiv. of NaO^tBu. [e)]Absence of Et_2Zn. [f)]Absence of L-proline. [g)]Absence of inert atmosphere.

To explore the scope of the reaction, we carried out the thiolation reaction of electronically and structurally diverse aryl iodides and thiols with Zn-proline catalytic system at 80 °C in acetonitrile. A variety of substrates are transformed to their corresponding diarylsulfides in good to excellent yields under the optimized reaction conditions. It is observed that electron withdrawing substituents in the aryl iodides increased the yield of the desired product compared to electron releasing substituents (Table 4, entries 4, 6). Attempts to extend the catalytic system to alkyl thiols were successful, and under the optimized reaction conditions both benzyl and butyl thiols reacted with various aryl iodides affording the products in good yields (Table 4, entry 16, 17, 18).

Table 4. Substrate scope of Zn-catalyzed C-S cross-coupling reactions.[a)]



R^1 = -CN, $-OCH_3$, $-NO_2$, $-COCH_3$
R^2 = aryl/alkyl

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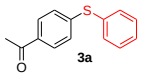
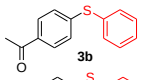
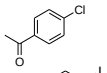
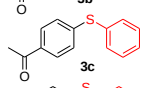
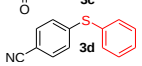
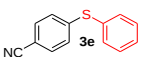
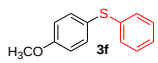
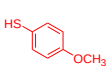
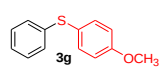
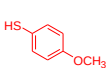
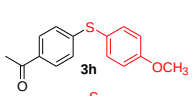
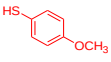
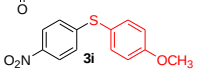
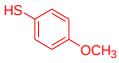
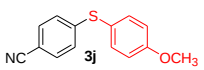
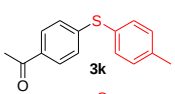
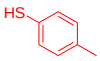
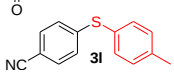
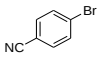
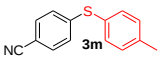
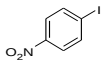
Entry	Aryl halide	Thiol	Product	Yield[b] (%)
1				95
2				58
3				33
4				97
5				60
6				61
7				70
8				86
9				70
10				86
11				53
12				65
13				47
14				82
15				85
16				90
17				70
18				59

[a] Reaction conditions: aryliodide (1mmol), thiophenol (1.1 mmol), Na^{t}Bu (2 equiv.), Et_2Zn (8 mol %), L-proline (16 mol %), CH_3CN (3 ml), 80 ^oC), 20 h. [b] isolated yield

To extend the scope of the reaction further, the Zn-proline catalytic system was then applied to aryl bromides and chlorides. As expected, the new catalytic system was found to be compatible with aryl bromides and chlorides and yielded the products *albeit* in low yields (Table 4, entries 2, 3, 5, 13). The coupling reaction of thiophenol with 4-iodoacetophenone, 4-bromoacetophenone and 4-chloroacetophenone demonstrates the higher reactivity of aryl iodides over bromides and chlorides affording the coupling products in 95 %, 58 % and 33 % yield respectively (Table 4, entries 1, 2, 3).

In conclusion we have developed the first Zn-catalyzed C-S cross-coupling reactions of aryl halides with thiophenols under mild conditions using *in situ* generated Et_2Zn-proline in CH_3CN in the presence of NaO^{t}Bu at 80 ^oC. The Et_2Zn-proline catalytic system showed moderate to excellent yield on a variety of electronically diverse aryl halides for the C-S cross-coupling reactions. The newly developed Zn-proline catalytic system is an efficient and successful combination for the production of aryl sulfides in high yields with 8 mol % of catalyst loading, and shows high functional group tolerance. We hope that the new procedure will finely substitute the existing methodologies for the C-S cross-coupling of aryl halides with both aryl and alkyl thiols. Further studies of this zinc-catalyzed reaction of C-S coupling are in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Typical Experimental Procedure for the Synthesis of 1-(4-phenylsulfanyl-phenyl)-ethanone (**3a**)**:** A dry sealed tube was charged with 1mmol (246 mg) of 4-iodoacetophenone, 16 mol% of L-proline (18 mg) and 2 equiv. of NaOtBu (192 mg) under nitrogen. To the above mixture was added 8 mol % of Et_2Zn (1M in hexane, 0.08 ml) and 3 ml of acetonitrile followed by the addition of 1.1 mmol of thiophenol (0.11 ml) under nitrogen. The sealed tube was heated in an oil bath which was preheated to 80 ^oC and the reaction mixture was stirred under the same conditions for 20 hours. The reaction mixture was then cooled and extracted with ethyl acetate (3 x 15 ml) and the ethyl acetate layer was washed with saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure in a rotary evaporator. The crude residue was purified by column chromatography using EtOAc-hexane as the eluent to get 217 mg (95 %) of the product as a colourless solid. M. P: 67 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83(d, J = 8.4 Hz, 2H), 7.51-7.48 (m, 2H), 7.41-7.39 (m, 3H), 7.22 (d, J = 8.4 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.10, 144.92, 134.55, 133.87, 132.16, 129.69, 128.91, 128.79, 127.52, 26.46; IR (neat): 3060, 1669, 1555, 1182, 819, 616 cm^{-1}; HRMS (QToF): $[M+H]^+$ calculated for $C_{14}H_{12}OS$ is 229.0687; found 229.0675

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