Dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate) as a new S-donor for direct synthesis of symmetrical disulfides

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In this research, a simple, efficient and novel protocol is developed for the direct synthesis of symmetrical disulfides using dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate) as a new, low toxicity, inexpensive, stable solid and free of foul-smelling thiols for synthesize symmetric diaryl/dialkyl disulfides from aryl and alkyl halides in presence of MOF-199 and CuO nanoparticles. Significantly, using this method results in obtaining a variety of symmetrical disulfides in moderate to excellent yields (up to 98%).

Disulfides which are used in many organic procedures play a very important role as vulcanizing agents and linkages for controlled drug delivery. Furthermore, this compound has received significant attention because of being indispensable in many important synthetic chemistry, biochemistry and industrial applications1-5. Due to the importance of these compounds, various methods have been developed in order to prepare such compounds. The use of oxidative coupling of thiols with stoichiometric oxidation or catalytic oxidation has become a classical protocol for the synthesis of disulfides. In this sense, reagents such as 4,4'-azopyridine6, N-phenyltriazolinedione7, Fe(NO3)3, 9H2O/Fe(HSO4)38, DDQ9, tributylammonium halochromates/silica gel10, Burgess reagent11, CAN12, bromate13 and N2O4/PVP14 have been used as stoichiometric oxidants. Although these methods are used for synthesis of disulfides, they have some specific disadvantages, i.e. long reaction time, difficult work-up, use of toxic or costly reagents, low yield of product due to over oxidation, etc. It is worth mentioning that some of the proposed methods have been devised with various sulfur-transfer agents, such as sulfonyl chlorides15, carbon disulfide16, 1,3-thiazolidinedione17, thiourea18 and sulfur19. In this regard, thiols have been used in most methods designed to synthesize organosulfurs. In addition, thiols are malodor, volatile, and toxic compounds. Thus, in order to overcome these problems, other sources and transporters of sulfur which are solid, stable and odorless have been introduced. Significantly, sulfur transporters play an effective role in the formation of carbon–sulfur (C-S) bonds.

Herein, in continuation of our researches, regarding the synthesis of organosulfur compounds20-22, a new method is reported for the synthesis of symmetric diaryl and dialkyl disulfides from aryl and alkyl halides using dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate) as an excellent sulfur source in presence of CuO and MOF-199 nanoparticles (Fig. 1).

MOF-199 is a unique class of metal–organic frameworks which are known for their applications in various fields such as drug delivery, gas storage, semiconductors and catalysis23,24. Metal–organic frameworks (MOFs) due to their unique properties such as their exceptional porosity and high surface area have been wildly used as catalyst and, accordingly, have shown good potential in producing heterogeneous catalysis.

In this research we also used CuO nanoparticles as catalyst for the synthesis of diaryl and dialkyl disulfides. Nano-crystalline metal oxides with advantages such as high surface area and reactive morphologies can be exceptionally applied as catalysts for various organic transformations25,26.

After synthesizing MOF-199 and CuO nanoparticles, FT-IR, SEM, EDX and XRD analyses were used in order to characterize these nanoparticles.

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Results and discussion
The FT-IR spectrum of MOF-199 indicated three peaks at 3440 cm\(^{-1}\), 1642 cm\(^{-1}\) and 1446 cm\(^{-1}\) which belong to H\(_2\)O, EtOH molecules in the cavities of the matter, carbonyl group of the benzene tricarboxylic acid and the double bond of the benzene ring, respectively (Fig. 2). Regarding the FT-IR of CuO nanoparticles, the stretching vibrations at 477 cm\(^{-1}\), 522 cm\(^{-1}\) and 603 cm\(^{-1}\) can be related to the Cu–O band (Fig. 3).

The morphology and size of MOF-199 and CuO nanoparticles are determined, using scanning electron microscopy technique. Moreover, SEM images show that the particle size of MOF-199 and CuO NPs are 30–40 nm (Figs. 4, 5).

One of the best approaches to determine of elements present in nanoparticles and the purity of nanoparticles is energy-dispersive X-ray spectroscopy (EDS). The EDX spectra of the MOF-199 and CuO NPs approve the presence of Cu and O elements in the structure of the catalysts and also confirm the fact that the nanoparticles have been successfully synthesized (Figs. 6, 7).
X-ray diffraction (XRD) was used in order to investigate the structure of MOF-199 and CuO NPs. Regarding the XRD pattern of MOF-199, the biggest peak (222) is at 2θ = 11.76°. Considering the peaks observed in the region of 2θ = 10°–20° indicate the crystal structure of the MOF-199 metal–organic framework, which is consistent with the pattern presented in previous studies. (Fig. 8). Moreover, it is worth mentioning that 2θ = 34.45°, 37.30° for the CuO NPs confirms the structure of the catalyst (Fig. 9).

After the synthesis and characterization of MOF-199 and CuO NPs, the sulfur-transfer of 1,3,4-thiadiazole-2,5-bis(thiolate) was investigated in the synthesis of disulfides. In order to reach optimum conditions, iodo-benzene and 1,3,4-thiadiazole-2,5-bis(thiolate) were used as a sulfur source in presence of different parameters including solvent, temperature and amounts of MOF-199 (method a) and CuO (method b). Based on the results of Table 1, the best results were obtained in dimethylformamide as a solvent using 4 mg MOF-199 and 5 mg CuO at 100 °C.

After obtaining the optimum conditions, a large number of symmetrical diaryl (alkyl) disulfides (1a–1l) was synthesized using 1,3,4-thiadiazole-2,5-bis(thiolate) in presence of MOF-199 and CuO NPs, the results of which are shown in Table 2. As can be seen, aryl iodides were more reactive than aryl bromides. Also based on
results in Table 2, both catalysts have a good to excellent yields, but MOF-199 has more activity and efficiency for the synthesis of diaryl and dialkyldisulfides. In most cases, the yield of the reactions was higher with shorter reaction times in the presence of MOF-199.

The possible mechanism for the synthesis of disulfides is shown in Fig. 10. The mechanism of this reaction is similar to Ullmann's reaction. The first step is the oxidative addition of copper to the aryl halide, which the organocopper intermediate (I) is formed. Consequently, it reacts with 1,3,4-thiadiazole-2,5-bis(thiolate) and finally converts to intermediate (II). Afterwards, intermediate (III) is produced using CuO extraction.
Subsequently, when hydroxide attacks intermediate (III), compound (IV) is produced. In the following, by exit of compound (V), the corresponding disulfide is synthesized under the reaction conditions.

Experimental section

Synthesis of MOF-199. Considering the synthesis of MOF-199, a mixture of benzene-1,3,5-tricarboxylic acid (2.38 mmol) and Cu(OAc)₂·H₂O (4.31 mmol) was added to the EtOH/H₂O/DMF (1:1:1). Afterwards, Et₃N (0.5 mmol) was added to the reaction mixture and, then, stirred for the 24 h at room temperature. After completion, the product was separated by filtration, washed with DMF for several times and, finally, dried at 150 °C in oven.

Synthesis of CuO nanoparticles. In order to synthesize CuO NPs, the solution of NaOH (100 ml, 0.1 M) was added dropwise to the 50 ml of Cu(OAc)₂·2H₂O (0.05 M) and, then, sonicated at 60 °C for the 45 min. Subsequently, 10 g PEG was solved in 10 ml distillated water and, then, it was added to the reaction mixture dropwise and sonicated for 1 h. Finally, the product was separated using centrifugation process and, then, dried at 45 °C in oven.

Synthesis of dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate). In order to synthesize dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate), a mixture of hydrazine hydrate (0.02 mmol), carbon disulfide (0.02 mmol) and pyridine (50 ml) was added to EtOH at room temperature for thirty minutes. Afterwards, the reaction mixture was stirred for the 5 h at 60 °C. After completion of the reaction, HCl (5 ml) was added to the reaction mixture and, then, the product (1,3,4-thiadiazole-2,5-dithiol) was separated by filtration, washed with EtOH for the several times and dried at 80 °C in oven. In the next step, a mixture of 1,3,4-thiadiazole-2,5-dithiol (10 mmol)

| Entry | Sulfur Source (mmol) | Temp (°C) | Solvent (ml) | Cat (mg) | Time (h) | Yield (%) |
|-------|----------------------|-----------|--------------|----------|----------|-----------|
| 1     | 1.5                  | 100       | PEG, DMF     | a 4 b 5  | 7 8:30   | 85 82     |
| 2     | 2                    | 100       | PEG, DMF     | a 5 b 5  | 5 5 98   | 98 98     |
| 3     | 2.5                  | 100       | PEG, DMF     | a 5 b 5  | 6 6 90   | 87 87     |
| 4     | 2                    | 100       | PEG, DMF     | a 6 b 5  | 9 85 87  | 87 87     |
| 5     | 2                    | 100       | PEG, DMF     | a 7 5 8  | 87 94    |           |
| 6     | 2                    | 100       | H₂O, H₂O     | a 4 5    | 24 24 45 | 45 30     |
| 7     | 2                    | 100       | PEG, PEG     | a 5 b 4  | 8 58 65  |           |
| 8     | 2                    | 100       | PEG, DMF     | a 5 b 6  | 5 87 99  |           |
| 9     | 2                    | reflux    | EtOH, EtOH   | a 4 5    | 10 9 80  | 85 85     |
| 10    | 2                    | reflux    | EtOH, DMF    | a 4 4    | 5 – 88   |           |
| 11    | 2                    | 45        | PEG, DMF     | a 4 4    | 6 5 66   | 60 60     |
| 12    | 2                    | 75        | PEG, DMF     | a 4 4    | 5 70 65  |           |
| 13    | 120                  | 120       | PEG, DMF     | a 4 4    | 5 90 87  |           |

Table 1. Optimization of the reaction conditions*. a: Reaction conditions: iodobenzene (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate), Temp (°C), 2 ml solvent, MOF-199. b: Reaction conditions: iodobenzene (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate), Temp (°C), 2 ml solvent, CuO NPs.

Figure 9. XRD of CuO nanoparticles.
and KOH (20 mmol) was added to EtOH (15 ml) for 3 h at 40 °C. After completion of the reaction, the product was separated by filtration, washed with EtOH for the several times and dried at 50 °C in oven.

**General procedure for the synthesis of disulfides using MOF-199.** A mixture of aryl or alkyl halide (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate) (2 mmol) and MOF-199 (4 mg) in DMF (2 ml) was stirred at 100 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and, then, the product was separated using H2O and EtOAc.

**General procedure for the synthesis of disulfides using CuO NPs.** A mixture of aryl or alkyl halide (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate) (2 mmol) and CuO (5 mg) in PEG (2 ml) was stirred at 100 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and, then, the product was separated using H2O and EtOAc.

**Table 2. Synthesis of disulfidesa.** a: Reaction conditions: aryl or alkyl halide (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate) (2 mmol), MOF-199 (4 mg) 100 °C, DMF b: Reaction conditions: aryl or alkyl halide (1 mmol), 1,3,4-thiadiazole-2,5-bis(thiolate) (2 mmol), CuO (5 mg), 100 °C, PEG.

| Entry | Aryl/Alkyl halide          | Time (h) | Yield (%) | m.p (°C) | Ref  |
|-------|---------------------------|----------|-----------|----------|------|
| 1     | Iodobenzene (1a)          | 4        | 98        | 98       | 57–60 |
| 2     | Bromobenzene (1a)         | 7        | 80        | 90       | 58–61 |
| 3     | Chlorobenzene (1a)        | 8        | 85        | 83       | 86–91 |
| 4     | 1-Iodo-2-methoxybenzene (1b) | 9:30   | 85        | 90       | 119–120 |
| 5     | 1-Iodo-4-methoxybenzene (1c) | 8        | 85        | 83       | 60–62 |
| 6     | 1-Bromo-4-iodobenzene (1d) | 8        | 80        | 75       | 92–96 |
| 7     | 1-Bromo-4-nitrobenzene (1e) | 8        | 75        | 83       | 173–175 |
| 8     | 1-Iodonaphthalene (1f)    | 6        | 92        | 90       | 93–94 |
| 9     | 1-Bromonaphthalene (1f)   | 8        | 85        | 83       | 92–94 |
| 10    | 2-Iodothiophene (1g)      | 7        | 92        | 90       | 52–54 |
| 11    | 2-Bromothiophene (1g)     | 8:30     | 85        | 80       | 53–55 |
| 12    | Benzyl chloride (1h)      | 2:30     | 90        | 87       | 69–71 |
| 13    | 2-Phenylethyl bromide (1i) | 1        | 95        | 92       | Oil |
| 14    | (3-bromopropyl) benzene (1j) | 1        | 98        | 95       | Oil |
| 15    | 4-Iodoaniline (1k)        | 9        | 87        | 80       | 73–76 |
| 16    | 1-Iodo-2-methylbenzene (1l) | 3        | 98        | 88       | 38–40 |

**Conclusion**
In conclusion, an effective method was reported for the synthesis of symmetric diaryl (dialkyl) disulfides from aryl and alkyl halides. The salient features of the present protocol include: being more economic, comprehensive and environmentally friendly than previous methods. Moreover, dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate) was introduced as a new sulfur source for the synthesis of symmetric disulfides from aryl and alkyl halides in presence of MOF-199 and CuO nanoparticles. Dipotassium 1,3,4-thiadiazole-2,5-bis(thiolate) has great potential as a sulfur-transfer reagent and possesses some specific advantages such as: low toxicity, water-solubility,
stability and being odorless. Therefore, this strategy provides a new method for the direct synthesis of symmetrical disulfides.

Data availability
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Figure 10. A possible mechanism for the synthesis of disulfides.
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Author contributions
M.S.-B. supervised the research project, made interpretation of data and corrections to the text and is the corresponding author of the manuscript. M.A. K. and H.K. collected the data, and wrote the main manuscript text. Z.A made the experiments, collected the data.

Competing interests
The authors declare no competing interests.

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