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Diisopropylamine as a single catalyst in the synthesis of aryl disulfides

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Abstract: The search for less time-consuming and inexpensive methods for the synthesis of disulfides continues to be a hot subject of research. Herein, we report that diisopropylamine (*i*Pr_2NH) can act as a very effective catalyst for this process. The oxidative coupling of aryl thiols was carried out in the presence of catalytic amount of *i*Pr_2NH in air (room temperature) in acetonitrile, without metal catalyst, additives, or external activators. This procedure opens a low-cost, green, and industrially applicable synthetic pathway to obtain aryl disulfides.

Keywords: amines; base catalysis; disulfides; oxidative coupling; thiols.

1 Introduction

The oxidative coupling of thiols, despite its long history, is still the subject of interest for many chemists. It might be said that almost everything has been done in this area. The obtained products-disulfides-accompany us everywhere in our daily lives, such as in biochemistry [1–4], in vulcanization [5], and oil refinery [6] applications. Numerous procedures employing sulfur-sulfur bond in the organic processes have also been reported [7–13].

Thiols can be relatively easily oxidized to disulfides by various agents. Many procedures have been developed in this field [14–22]. Hence, the main interest in developing methods leading to the formation of S-S bond is oriented towards mild, simple, and inexpensive protocols. Moreover, alkylamines, along with other bases, can accelerate the air oxidation rate of thiols [23, 24]. Oswald and co-workers have published very important results in this field [25]. Moreover, triethylamine (Et_3N) has often been used as an additive or co-catalyst. Nolan demonstrated the dehydrogenative coupling of thiols catalyzed by ruthenium complex in the presence of Et_3N (0.25 eq.) at 60°C (1–3.5 h) [26]. Rosenthal et al. [27] have reported the synthesis of disulfide polymers in the presence of hydrogen peroxide and Et_3N (1.25 eq.). Ruano et al. [28] have reported a very efficient synthesis of disulfides by air oxidation of thiols under sonication in basic conditions. At the beginning, they studied the behavior of thiols and Et_3N (1 eq.) in dimethylformamide (DMF) as a solvent (in air, at 80°C). Disulfides were obtained in high yields after 24–48 h. The lengthy reaction and the need of high temperatures prompted them to explore the external activation for acceleration of this reaction. They revealed that, under sonication conditions, the complete conversion of thiols to the corresponding disulfides is significantly less time-consuming. In the abovementioned articles, the final list of requirements for the synthesis of the S-S bond always include the use of triethylamine and some external stimulations, such as another catalyst, sonication, and/or heating. Additionally, the molar ratio between thiols and Et_3N is relatively high (it is not a catalytic amount), which implies the incurrence of higher costs.

Recently, our group has reported protocols describing the use of metal triflates [29–32] (*S*-germylation, oxidative coupling of thiols and hydrothiolation reactions) as the catalysts in many organic procedures.

During our work on *S*-functionalisation reactions [29–31, 33] we noticed trace amounts of disulfides as by-products. We tested inter alia *N,N*-dimethylallylamine (1 eq.) in the hydrothiolation reaction (benzenethiol, 1.1 eq.) mediated by scandium(III) triflate. In this test, we observed a total conversion (99%, measured by GC) of benzenethiol to diphenyl disulfide (rt, 30 min.). The purpose of our further research was to check the influence of various amines on the oxidative coupling of thiols.

In the current work, we present our results concerning the extremely mild (rt) and improved procedure to obtain aryl disulfides. The proposed procedure is inexpensive because it requires a low amount of the catalyst and a shorter reaction time, and uses only atmospheric air as the oxidant. Diisopropylamine was used as the lone catalyst without any other catalysts, additives or external activators. Last but not least, the amount of the amine was significantly reduced (only 0.1 eq.). The presented work fits squarely into postulates of green chemistry [34].

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2 Materials and methods

2.1 Materials and general methods

Thiols used for experiments were purchased from Sigma-Aldrich Co. (Poznan, Poland) and used without further purification. Amines were purchased from Sigma-Aldrich Co. Acetonitrile (ACN, 99.8%) was purchased from J.T. Baker Company (Gliwice, Poland). All spectra of the synthesized products were collected in the supporting information file (Supplemental material). ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Bruker Avance III HD NanoBay (Bruker, Poznan, Poland) (600 MHz) spectrometer using $CDCl_3$ as solvent (99.8 atom % D). Deuterated NMR solvent was purchased from Sigma-Aldrich Co. GC analyses were performed on a Varian 3400 with a Megabore column (30 m) and TCD (Varian, Walnut Creek, CA, USA). Mass spectra of the products were determined by GC-MS analysis on a Varian Saturn 2100T, equipped with a BD-5 capillary column (30 m) and Finnigan Mat 800 ion trap detector (Finnigan, San Jose, CA, USA).

2.2 General procedure for the synthesis of disulfides

To the 25 ml one-necked round-bottom flask, 0.9 mmol of thiol, 0.009 mmol of iPr$_2$NH, and 1 ml of ACN were added. Next the reaction mixture was stirred at room temperature for 1.5–2 h. Next, the solvent and the catalyst were evaporated and the products were purified by column chromatography on silica gel eluting diethyl ether to give the expected products (Table 3, 1–8) with 92%–98% yield.

3 Results and discussion

3.1 Optimization of the reaction conditions

We initially focused on choosing and testing various amines and solvents. As the starting point, the oxidative coupling of benzenethiol in various conditions was considered. All experiments were carried out in vials (capacity = 10 ml) equipped with magnetic stirring bars and stoppers. Results are summarized in Table 1. The aprotic polar solvents accelerate the oxidation of thiols in the presence of oxygen [35]. By using the measurements reported by Christian Reichardt [36], we decided to check the following polar aprotic solvents (relative polarity): acetonitrile (0.460), tetrahydrofuran (0.207), and diethyl ether (0.117). DMF (0.386) was not considered as the solvent in our tests, because of the results (95% conversion of thiols but after 24 h at rt) obtained by Ruano and co-workers [28]. Dimethylformamide, despite its relatively high polarity, is also known as toxic aprotic solvent. In addition, its boiling point is 153°C, which poses serious problems on distillation. Subsequently, various amines were tested as catalysts in the oxidative coupling of benzenethiol. The addition of these reagents permits the formation of thiolate species from thiols. In this connection, the basicity of amines is the major factor in these transformations. By using basicity measurements [37, 38] and considering the costs of nitrogen-containing reagents (www.abcr.de), we decided to check the following amines: diethylamine (Et_2NH, 2.5 l ~ 35 EUR), triethylamine (Et_3N, 2.5 l ~ 45 EUR), diisopropylamine (iPr$_2$NH, 2.5 l ~ 40 EUR). Secondary and tertiary alkyl amines were selected and tested in the reaction; aromatic ones were not chosen because of their lower basicity and high toxicity compared with aliphatic derivatives [39].

Table 1: The oxidative coupling of benzenethiol in various solvents catalyzed by selected amines.[a]

Entry	Solvent[b]	Amine (eq.)	Time (h)	Conversion (%)[c]
1	ACN	–	24	20
2	ACN	Et_3N (0.03)	3	82
3	ACN	Et_3N (0.10)	3	95
4	ACN	Et_2NH (0.03)	3	86
5	ACN	Et_2NH (0.10)	3	96
6	ACN	iPr$_2$NH (0.03)	3	89
7	ACN	iPr$_2$NH (0.10)	3	99
8	Et_2O	–	24	5
9	Et_2O	Et_3N (0.10)	20	20
10	Et_2O	Et_2NH (0.10)	20	20
11	Et_2O	iPr$_2$NH (0.10)	20	25
12	THF	–	24	10
13	THF	Et_3N (0.10)	20	30
14	THF	Et_2NH (0.10)	20	30
15	THF	iPr$_2$NH (0.10)	20	35

[a]Reaction conditions: thiol (1 eq., 0.05 g, 0.45 mmol), solvent (2 ml), stirring rate (900 rpm), air atmosphere, closed system, room temperature; [b]ACN (Acetonitrile); [c]measured by GC.

Results showed that the acceleration of thiol oxidation caused by polar aprotic solvents was substantiated. The best results were consistently obtained for the mixture of reagents in acetonitrile. As mentioned, ACN demonstrated the highest polarity among the solvents tested. More interesting was the selection of the most suitable amine. By considering several factors, such as boiling points, relative toxicity, time of thiols' conversion, and costs of reagents, diisopropylamine was selected to further work (Table 1, entry 7). In order to optimize the conditions of this reaction, we also studied the influence of the vessel capacity and solvent's volume. The results are shown in Table 2.

Additional increase in the vessel capacity was found to have a positive influence on the time of conversion. As expected, larger capacity levels led to higher amounts of oxygen, which decisively decrease the time of the reaction (Table 2, entries 1–3). The amount of solvent can also be reduced to 1 ml. Finally, we decided to check

Table 2: The further optimization of the oxidative coupling of benzenethiol catalyzed by diisopropylamine in acetonitrile solution.[a]

Entry	Solvent (ml)	Vessel capacity (ml)	Time (h)	Conversion (%)[b]
1	2	10	2	88
2	2	25	2	98
3	2	50	2	99
4	1	25	2	98
5[c]	2	25	1.75	99
6[c]	1	25	1.75	99

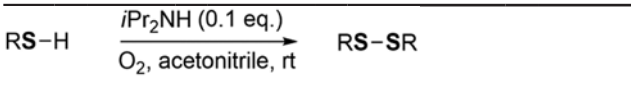
[a]Reactions conditions: thiol (1 eq., 0.05 g, 0.45 mmol), iPr$_2$NH (0.1 eq., 0.0046 g, 0.045 mmol), acetonitrile, stirring rate (900 rpm), air atmosphere, closed system, room temperature; [b]measured by GC; [c]stirring rate (1200 rpm).

the rate of stirring. When the stirring rate was increased to 1200 rpm (Table 2, entries 5 and 6), we observed our best results (Table 2, entry 6). The possibility of the over-oxidation product formation was investigated, and the findings proved that our method can be controlled to stop at the disulfide stage, without the over-oxidation of any by-product.

3.2 Synthesis of various disulfides catalyzed by diisopropylamine

With the chosen catalyst in hand, we next investigated various types of thiols under the optimized conditions. Aryl (Table 3, entries 1–8), alkyl, and heterocyclic thiols were used in this process. Results are summarized in Table 3.

Table 3: The oxidative coupling of aryl thiols in the presence of diisopropylamine.[a]



R = aryl

Entry	R	Time (min)	Product	Yield (%)[b]
1	Ph	105	Ph_2S_2 (**1**)	98
2	2-MePh	105	$(2\text{-MePh})_2S_2$ (**2**)	93
3	3-MePh	105	$(3\text{-MePh})_2S_2$ (**3**)	93
4	4-MePh	105	$(4\text{-MePh})_2S_2$ (**4**)	95
5	4-FPh	80	$(4\text{-FPh})_2S_2$ (**5**)	95
6	2-FPh	90	$(2\text{-FPh})_2S_2$ (**6**)	93
7	4-ClPh	90	$(4\text{-ClPh})_2S_2$ (**7**)	95
8	3-MeOPh	90	$(3\text{-MeOPh})_2S_2$ (**8**)	92

[a]Reactions conditions: thiol (1 eq., 0.9 mmol), solvent (2 ml), stirring rate (1200 rpm), flask capacity (25 ml), air atmosphere, closed system, room temperature; [b]isolated yields.

Aryl thiols were reactive in this process, and all of them gave the expected disulfides with excellent yields (92%–98%). The nature of substituents attached to phenyl ring in aryl mercaptans demonstrated a minor effect on the time of reaction. The presence of electron withdrawing groups (Table 3, entries 5–8) slightly shortens the thiols' conversion. These groups considerably facilitate the formation of thiolate species. The selectivity of the proposed reaction was also excellent, which was proven by the absence of product over-oxidation. However, in some cases, we observed trace amounts of diaryl sulfides (<2%). Alkyl thiols are extensively used in nanotechnology [40], but they are less reactive than aryl derivatives due to their higher pK_a. Unfortunately, we observed the same dependence in the oxidative coupling catalyzed by diisopropylamine. When we used 0.1 eq. of the catalyst, we observed unsatisfying results (conversion <40%/6 h). The same feedback was also attained for heterocyclic thiols (conversion <60%/3 h) when we increased the amine amount (0.3 eq.).

4 Conclusion

In summary, we propose an upgraded method for the synthesis of diaryl disulfides in a green manner, by using atmospheric air as an oxidant and inexpensive diisopropylamine (0.1 eq.) as a single catalyst in acetonitrile (1 ml) at room temperature. In previous reports, the amount of amine was always stoichiometric. We have demonstrated the possibility to reduce by 10-fold the amount of amine required. The simplicity of our experimental techniques, the mild conditions, high selectivity, and yields are the advantages of this method. Our further work will focus on *S*-functionalization of various organic compounds by using disulfides as reagents in these transformations.

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Supplemental Material: The online version of this article (DOI: 10.1515/gps-2016-0205) offers supplemental material (full NMR data and spectra).

Bionotes

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