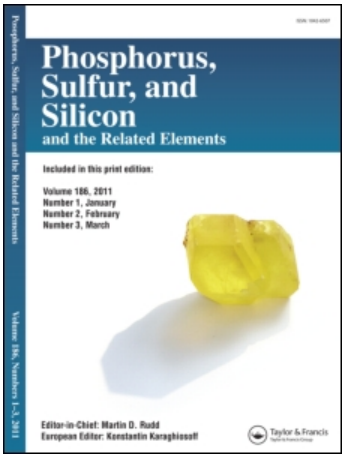

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SELECTIVE AND CONVENIENT OXIDATION OF THIOLS TO DISULFIDES USING *n*-BUTYLTRIPHENYLPHOSPHONIUM DICHROMATE $(Bu^n PPh_3)_2Cr_2O_7$ IN SOLUTION, UNDER SOLVENT-FREE CONDITIONS AND MICROWAVE IRRADIATION

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A variety of aliphatic, aromatic, and heteroaromatic thiols were rapidly and cleanly converted to their corresponding disulfides in excellent yields using n*-butyltriphenylphosphonium dichromate (BTPPDC) in acetonitrile solution under solvent-free conditions and microwave irradiation. Selective oxidation of thiols in the presence of other oxidizable functional groups, such as alcohol and sulfide, is a noteworthy advantage of this method.*

Keywords: Dichromate; disulfides; oxidation; thiols

INTRODUCTION

Selective oxidative conversion of thiols to disulfides is of interest from both a biological and a synthetic point of view.[1,2] Many methods and reagents for the oxidation of thiols to disulfides have been reported in the literature.[3–21] Some of these methods suffer from one or more of the following disadvantages; long reaction times; difficult workup; lack the general applicability to thiol substrates bearing alkyl, aryl, and heterocyclic moieties; and formation of overoxidation products, leading to lower yields, oxidation of other functional groups in the presence of thiol group, and the use of stoichiometric and excess amounts of the reagents for successful oxidation. Thus, there is still a need to develop

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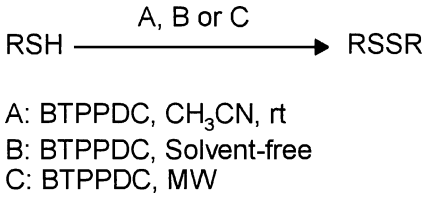
a mild and efficient methodology to synthesize aliphatic, aromatic, and heteroaromatic disulfides. In this respect, we wish to report that *n*-butyltriphenylphosphonium dichromate (BTPPDC) is able to transform different types of thiols to their corresponding disulfides efficiently under different reaction conditions.

RESULTS AND DISCUSSION

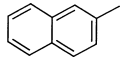
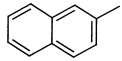
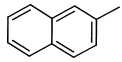
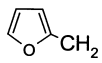
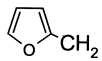
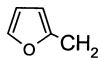
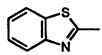
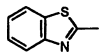
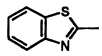
n-Butyltriphenylphosphonium dichromate (BTPPDC) is an inexpensive and easily prepared reagent. Several synthetically useful organic transformations using this reagent have been reported previously.[22,23] In this article the oxidative coupling of thiols with this reagent was investigated in solution under solvent-free conditions and microwave irradiation (Scheme 1).



SCHEME 1

We first examined the oxidative coupling of 2-mercaptopyrimidine (Table I, entries 22–24) as a model substrate in the presence of BTPPDC for 2 min in solution, under solvent-free conditions and microwave irradiation, and the corresponding disulfide was obtained in 10, 15, and 93% yields, respectively. Therefore, to obtain high yields of the products in solution and under solvent-free conditions, longer reaction times are required. The oxidation of 2-mercaptopyrimidine was also investigated in various solvents such as CH_3CN, $CHCl_3$, CH_2Cl_2, Tetrahydrofuran (THF), and *n*-hexane at room temperature for 75 min, and the corresponding disulfide was isolated in 90, 75, 40, 45, and 5% yields, respectively. These results show that CH_3CN can be used as a suitable solvent for oxidation of thiols (method A). As shown in Table I, treatment of a variety of thiols with 0.5 molar equivalent of BTPPDC in acetonitrile at room temperature afforded the corresponding disulfides in 90–95% yields within 30–120 min. Under solvent-free conditions, these reactions proceeded within 6–18 min in the presence of 0.5 molar equivalent of the reagent, and the corresponding disulfides were obtained in 90–95% yields. Finally, the oxidative coupling was carried out

TABLE I Oxidation of Thiols to Disulfides[a] with BTPPDC

Entry	*R*	Method[b]	Time (min)	Yield (%)[c]	M.p. (°C)[9,13,17]
1	Ph	A	45	95	57–58
2	Ph	B	8	95	—
3	Ph	C	1	96	—
4	4-MeC_6H_4	A	30	93	45–47
5	4-MeC_6H_4	B	6	91	—
6	4-MeC_6H_4	C	0.75	95	—
7	4-BrC_6H_4	A	60	94	90–92
8	4-BrC_6H_4	B	10	92	—
9	4-BrC_6H_4	C	1.5	94	—
10	4-ClC_6H_4	A	60	92	74–75
11	4-ClC_6H_4	B	10	92	—
12	4-ClC_6H_4	C	1.5	93	—
13		A	90	92	142–143
14		B	15	91	—
15		C	2	93	—
16		A	45	91	Oil
17		B	8	91	—
18		C	1	93	—
19		A	60	92	54–55
20		B	10	91	—
21		C	1.5	95	—
22		A	75	90	140–143
23		B	12	92	—
24		C	2	93	—
25		A	120	92	181–183
26		B	18	92	—
27		C	3	94	—

(Continued on next page)

TABLE I Oxidation of Thiols to Disulfides[a] with BTPPDC *(Continued)*

Entry	*R*	Method[b]	Time (min)	Yield (%)[c]	M.p. (°C)[9,13,17]
28	$PhCH_2$	A	30	90	69–70
29	$PhCH_2$	B	7	91	—
30	$PhCH_2$	C	1	94	—
31	*c*-C_6H_{11}	A	45	92	Oil
32	*c*-C_6H_{11}	B	9	90	—
33	*c*-C_6H_{11}	C	1.5	90	—
34	*n*-C_8H_{17}	A	80	90	Oil
35	*n*-C_8H_{17}	B	12	91	—
36	*n*-C_8H_{17}	C	2	93	—
37	*n*-C_4H_9	A	40	91	Oil
38	*n*-C_4H_9	B	8	92	—
39	*n*-C_4H_9	C	1.25	94	—
40	$HOCH_2CH_2$	A	40	90	Oil
41	$HOCH_2CH_2$	B	8	93	—
42	$HOCH_2CH_2$	C	1	93	—

[a]All products were characterized by comparison of their spectral and physical data with those of authentic samples.

[b]Method A = Thiol:BTPPDC, 1:0.5, CH_3CN (10 ml per mmol of thiol); Method B = Thiol:BTPPDC, 1:0.5, solvent-free; Method C = Thiol:BTPPDC, 1:0.4, MW.

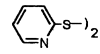
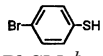
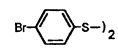
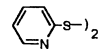
[c]Isolated yields of pure disulfides.

under microwave irradiation in the presence of 0.4 molar equivalent of BTPPDC, with reaction periods ranging between 0.75–3 min, and the pure products were obtained in 90–96% yields. Under microwave irradiation, acetonitrile was used for homogenization of the reaction mixture. The polar character of this solvent also seems to increase the reaction temperature, so the reaction is completed in a short time.[24] The results show that the yields of the products are comparable under the three above mentioned conditions, but the reaction times are considerably shorter under microwave irradiation.

It is important to note that in oxidation of 2-mercaptoethanol (Table I, entries 40–42), only mercaptan functionality was converted to disulfide, and the hydroxy group remained intact in the reaction mixture. Another noteworthy advantage of this reagent is the exclusive oxidation of thiols in the presence of sulfides. When an equimolar mixture of thiol and sulfide was treated with BTPPDC, only the thiol was selectively oxidized to the corresponding disulfide, and sulfide remained unchanged (Table II).

In summary, we have introduced *n*-butyltriphenylphosphonium dichromate as an inexpensive and effective reagent for the oxidation of thiols to disulfides. In addition, high yields of the products, easy

TABLE II Selective Oxidation of Thiols in the Presence of Sulfides with BTPPDC

			Yield%[a] (time/min)		
Entry	Substrate	Product	Solution	Solvent-free	MW
1			91(60)	90(10)	93(1.5)
	$PhSCH_2Ph$[b]	—	—	—	—
2			92(60)	91(10)	92(1.5)
	PhSMe[b]	—	—	—	—
3			91(60)	91(10)	94(1.5)
	n-BuSBu-n[b]	—	—	—	—

[a]Isolated yields of pure disulfides.
[b]Sulfide remained intact in the reaction mixture.

workup, and selective oxidation of thiols in the presence of alcohol and sulfide are noteworthy advantages of this method.

EXPERIMENTAL

General Procedure for the Oxidative Coupling of Thiols in Acetonitrile

In a round-bottomed flask (50 ml), a solution of thiol (2 mmol) in CH_3CN (20 ml) was prepared. *n*-Butyltriphenylphosphonium dichromate (0.854 g, 1 mmol) was added to the solution, and the reaction mixture was stirred at room temperature for 30–120 min. The progress of the reaction was monitored by thin layer chromatography (TLC; eluent: *n*-hexane/ethyl acetate, 4:1). After completion of the reaction, the reaction mixture was filtered and the solid material was washed with CH_3CN (10 ml). Evaporation of the solvent followed by recrystallization or chromatography on silica gel with appropriate eluent afforded the pure disulfides in 90–95% yields (Table I).

General Procedure for the Oxidative Coupling of Thiols under Solvent-Free Conditions

A mixture of thiol (2 mmol) and *n*-butyltriphenylphosphonium dichromate (0.854 g, 1 mmol) in a mortar was ground with a pestle for 6–18 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2. The

solvent was evaporated and the crude product was either recrystallized or subjected to chromatography on silica gel with appropriate eluent to afford the pure products in 90–95% yields (Table I).

General Procedure for the Oxidative Coupling of Thiols under Microwave Irradiation

Thiol (2 mmol) and *n*-butyltriphenylphosphonium dichromate (0.683 g, 0.8 mmol) were mixed and then CH_3CN (2 ml) was added. The mixture was subjected to microwave irradiation at 900 W for 0.75–3 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the resulting crude material was either recrystallized or subjected to chromatography on silica gel with appropriate eluent to afford the pure products in 90–96% yields (Table I).

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