ORGANIC LETTERS

2010
Vol. 12, No. 23
5570−5572

Synthesis of Sulfur−Sulfur Bond Formation from Thioamides Promoted by 2,3-Dichloro-5,6-dicyanobenzoquinone

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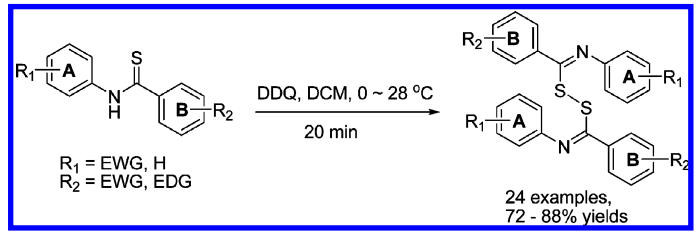
Received October 11, 2010

ABSTRACT



A mild and efficient synthesis of sulfur−sulfur bond formation from thioformanilides with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is described. Functionality on the aromatic ring plays a key role in the formation of a sulfur−sulfur bond.

Molecules containing a disulfide moiety play a vital role in chemistry and biochemistry.[1] In particular, disulfide-containing molecules appeared in a variety of biologically active target molecules such as anticancer activity.[2] A number of synthetic strategies have been discovered and reported on sulfur−sulfur bond formation.[3−5] Among them, oxidation of thiols with halogens[6] and H_2O_2[7] is the most common. Recently, we reported an efficient synthesis and biological evaluation of 2-phenylbenzothiazole derivatives **4** as photosensitizing agents.[8] The results showed that most of **4**, under UVA light exposure, induced basal cell carcinoma (BCC) all apoptosis. These results encouraged us to design and synthesize a larger diversity of 2-phenylbenzothiazoles **4**. Our initial attempt was to synthesize benzothiazole scaffolds from thioformanilides with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) for SAR studies. Surprisingly, the dimerized products with "−S−S−" bond linkage resulted instead of the expected benzothiazoles **4** (Scheme 1). These results showed the difference in reactivity followed by outcome of the products as compared to the reaction pattern observed by Bose.[9−11] Presumably, this might be the substituent effect on both the rings A and B of thioformanilides **2**. We then switched our attention to sulfur−sulfur bond formation from thioformanilides bearing different substituent groups on aromatic rings. S−S bond formation

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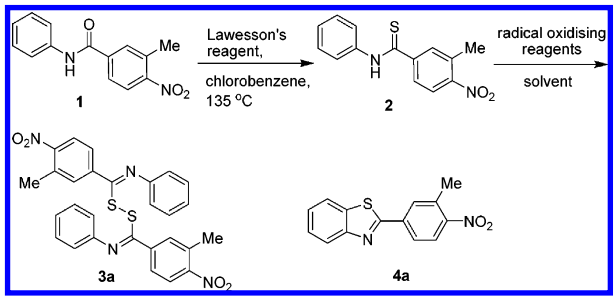
10.1021/ol102455x
Published on Web 11/10/2010

Scheme 1. Optimization of Reaction Conditions to Synthesize Disulfides **3**



reactions may be of interest to chemists working in the field of dynamic combinatorial chemistry.[12]

Furthermore, we also explored the dimerization activity with a variety of oxidative reagents[13] viz., DDQ, cerium(IV) ammonium nitrate (CAN), Dess−Martin periodinane (DMP), phenyliodine(III) bis(trifluoroacetate) (PIFA), and potassium ferricyanide $K_3Fe(CN)_6$. Herein, we describe our studies by general investigations of the sulfur−sulfur bond formation of thioformanilides **2**.

Initially, a reaction of *N*-(phenyl)-3-methyl-4-nitrothiobenzamide **2a**, generated by sulfonation of the corresponding benzamides with Lawesson's reagent,[8] was examined. These results are summarized in Table 1. The reaction of **2a** and benzothiazole **4a** (entry 3, Table 1), whereas reaction in methanol gave **3a** in 57% and **4a** in 33% yield (entry 4, Table 1). Since hypervalent iodo reagents such as DMP[16] and PIFA[17] are notable oxidants, we then examined their dimerization ability on **2a**. Interestingly, benzothiazole **4a** was obtained as a major product (entries 5−8). Treatment of substrate **2a** with $K_3Fe(CN)_6$[8,18] in acetonitrile at 0 °C for 2 h gave exclusively benzothiazole **4a** in 72% yield (entry 9, Table 1). Increasing the solvent polarity and reaction temperature with $K_3Fe(CN)_6$, no reaction was observed, and the starting material was recovered (entry 10). The structure of **3a** was confirmed by single-crystal X-ray crystallographic analysis (Figure 1).

Table 1. Optimization of S−S Bond Formation with Various Oxidizing Reagents

entry	reagent	equiv	solvent	temp (°C)	time (min)	yield **3a** (%)	yield **4a** (%)
1	DDQ	1.2	CH_2Cl_2	0−28	20	88	0
2	DDQ	1.2	MeOH	0−28	20	62	31
3	CAN	4.2	CH_3CN	0	30	43	55
4	CAN	4.2	MeOH	0	30	57	33
5	DMP	1.2	CH_2Cl_2	0	40	42	46
6	DMP	2.2	MeOH	0	30	12	54
7	PIFA	1.2	CH_2Cl_2	28	30	17	58
8	PIFA	2.2	CH_3CN	0	90	14	64
9	$K_3Fe(CN)_6$	4	CH_3CN	0	120	0	72
10	$K_3Fe(CN)_6$	4	EtOH	reflux	90	0	0

the commercially available DDQ (1.2 equiv) was first conducted in dichloromethane at 0 °C.[14] The reaction was performed at room temperature for 20 min to furnish dimerized compound **3a** with 88% yield (entry 1, Table 1). However, reaction in methanol solvent furnished **3a** in 62% yield along with intramolecular cyclization product **4a** in 31% yield (entry 2, Table 1).

By using 4.2 equiv of CAN[15] in acetonitrile at 0 °C for 30 min, the reaction produced almost a 1:1 ratio of dimer **3a** and

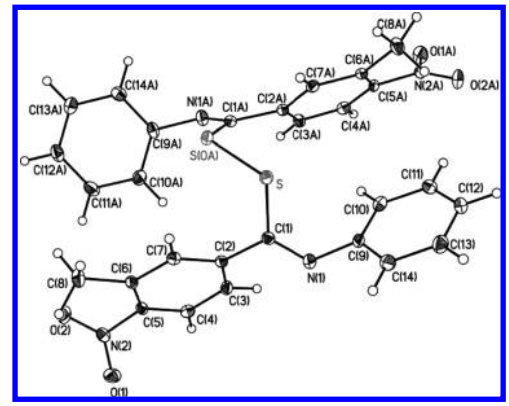


Figure 1. ORTEP diagram of **3a**.

With optimized conditions in hand (Table 1, entry 1), we explored the scope and limitations of this process. We designed and synthesized various substituents on ring A and ring B of thioformanilides with an electron-donating group (EDG), with an electron-withdrawing group, (EWG) and without any substituent (Table 2). Aromatic ring A without substituent and ring B bearing strong EWG ($-NO_2$) of compound **2a** was smoothly converted to **3a** in high yield (entry 1, Table 2), while ring A with strong EWG ($-NO_2$) and ring B with strong EDG ($-OMe$) could also be dimerized in good yields (entries 2 and 3). Ring A bearing relatively less EWG (Cl or CF_3) and ring B with strong EWG ($-NO_2$) were generated to disulfide compound in 74−82% yield (entries 4−7, Table 2). Having a strong electron-withdrawing nitro group on ring A and less electron-withdrawing halide or trifluoromethyl gave desired product in good to high yields (entries 8−15). When the nitro group was on the para or meta position of ring A, the corresponding products were obtained in good to high yields (entries 16−24, Table 2).

Benzothiazole formation occurred without substituent on ring A and with EDG on ring B in 76% yield. Functionality

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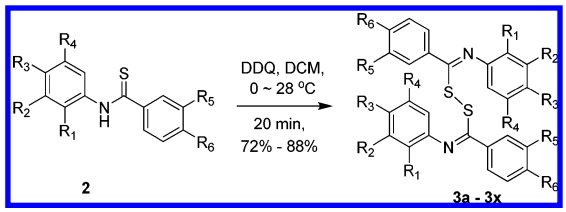
Table 2. Reaction of Various Thioformanilides **2** with DDQ to Form Dimerized Products **3**



entry	**3**	R_1	R_2	R_3	R_4	R_5	R_6	yield (%)
1	**3a**	H	H	H	H	Me	NO_2	88
2	**3b**	H	H	NO_2	H	OMe	H	74
3	**3c**	Me	H	NO_2	H	OMe	H	74
4	**3d**	H	H	CF_3	H	H	NO_2	76
5	**3e**	H	H	Cl	H	H	NO_2	74
6	**3f**	H	H	CF_3	H	Me	NO_2	82
7	**3g**	H	H	Cl	H	Me	NO_2	77
8	**3h**	H	H	NO_2	H	H	CF_3	75
9	**3i**	H	H	NO_2	H	H	F	76
10	**3j**	H	H	NO_2	H	H	Cl	72
11	**3k**	H	H	NO_2	H	H	Br	72
12	**3l**	Me	H	NO_2	H	H	CF_3	81
13	**3m**	Me	H	NO_2	H	H	F	79
14	**3n**	Me	H	NO_2	H	H	Cl	83
15	**3o**	Me	H	NO_2	H	H	Br	71
16	**3p**	H	NO_2	Cl	H	H	CF_3	72
17	**3q**	H	NO_2	Me	H	H	CF_3	72
18	**3r**	Me	NO_2	H	H	H	F	83
19	**3s**	Me	NO_2	H	H	H	Cl	74
20	**3t**	Me	H	H	NO_2	H	CF_3	86
21	**3u**	Me	H	H	NO_2	H	F	84
22	**3v**	Me	H	H	NO_2	H	Cl	81
23	**3w**	H	NO_2	F	H	H	CF_3	78
24	**3x**	Me	NO_2	H	H	H	CF_3	82

on aromatic ring plays a key role in the formation of sulfur−sulfur bonds. Compound **3l** was selected by the U.S. National Cancer Institute for evaluation in the in vitro preclinical antitumor screening program against 60 human tumor cell lines derived from nine cancer cell[19] types. The selected biological evaluation results for the dimerization compound are presented in Table 3. The mean GI_{50} value for dimerization of **3l** was 0.372 μM, indicating that this agent has the potential for use as a highly potent broad-spectrum anticancer compound to inhibit the growth of a variety of cancer cell lines.

A plausible mechanism for the synthesis of disulfides by DDQ is depicted in Scheme 2. Arylthioformanilide **2** can form as thioiminol **5**, which reacts with DDQ to generate thiyl radical intermediate **6**. If EWG is present on ring A or ring A with hydrogen and ring B bearing EWG, the dimerization reaction is predominant rather than cyclization. The presence of EDG on ring A would stabilize the radical

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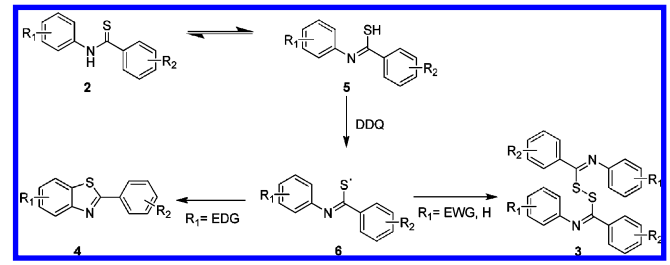
Table 3. In Vitro Cytotoxicity of Compound **3l** in Selected Cancer Cell Lines[a]

cell line	GI_{50} (μM)
Non-Small Cell Lung Cancer	
HOP−92	0.175
NCI-H226	0.427
Colon Cancer	
HCT−15	0.388
CNS Cancer	
SNB−75	0.141
Melanoma	
LOX MVI	0.304
MALME-3M	0.252
SK-MEL-5	0.262
Ovarian Cancer	
IGROV1	0.217
Breast Cancer	
T-47D	0.221
Mean	0.372

[a] Data obtained from NCI's in vitro disease-oriented tumor cells screen.

Scheme 2. Plausible Mechanism for the DDQ-Mediated Dimer Formation with Disulfide Bond



intermediate that leads to the formation of the cyclized product **4**. In contrast, the stability of the radical intermediate by the substituents on the ring system directs the formation of either cyclized product or dimerized product.

In summary, we have developed a mild and efficient synthetic route for sulfur−sulfur bond formation reactions with DDQ in high yields. This methodology may be applicable for other sulfur−sulfur bond formations of different thio substituent molecules and various analogues. Further biological activities of these compounds are under investigation.

Acknowledgment. We thank the National Science Council of the Republic of China and KMU Center of Excellence for Environmental Medicine for financial support.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102455X