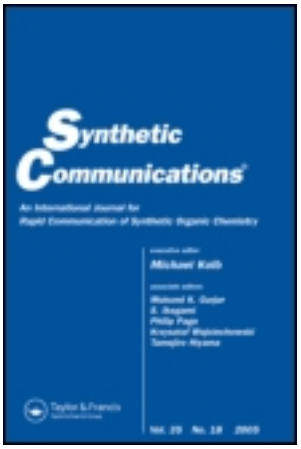


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Highly Efficient Oxidative Dimerization of Thioamides to 3,5-Disubstituted 1,2,4-Thiadiazoles Mediated by DDQ

Dongping Cheng [a], Ruiwen Luo [a], Wen Zheng [a] & Jizhong Yan [a]

[a] College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, China

Accepted author version posted online: 27 Oct 2011.Version of record first published: 26 Mar 2012.

To cite this article: Dongping Cheng , Ruiwen Luo , Wen Zheng & Jizhong Yan (2012): Highly Efficient Oxidative Dimerization of Thioamides to 3,5-Disubstituted 1,2,4-Thiadiazoles Mediated by DDQ, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:13, 2007-2013

To link to this article: http://dx.doi.org/10.1080/00397911.2010.551287

Synthetic Communications®, 42: 2007–2013, 2012

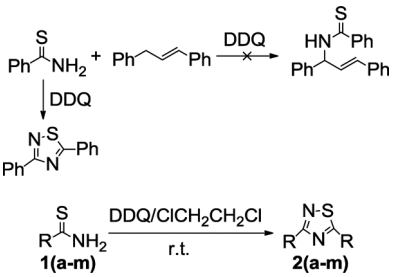
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.551287

Taylor & Francis
Taylor & Francis Group

HIGHLY EFFICIENT OXIDATIVE DIMERIZATION OF THIOAMIDES TO 3,5-DISUBSTITUTED 1,2,4-THIADIAZOLES MEDIATED BY DDQ

Dongping Cheng, Ruiwen Luo, Wen Zheng, and Jizhong Yan
College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, China

GRAPHICAL ABSTRACT



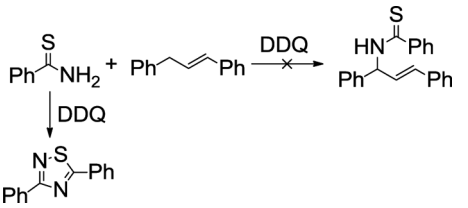
Abstract *A highly efficient oxidative dimerization of thioamides by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is reported. The reaction is carried out in $ClCH_2CH_2Cl$ at room temperature. The corresponding 3,5-disubstituted 1,2,4-thiadiazoles are obtained in good to excellent yields.*

Keywords DDQ; oxidative dimerization; thiadiazoles; thioamides

INTRODUCTION

2,3-Dicyano-5,6-dichloro-1,4-benzoquinone (DDQ) is a well-known oxidant in organic synthesis. It has been mainly used as a dehydrogenating oxidant in the dehydrogenation of steroids and lactones[1] and the aromatization of dihydrobenzene derivatives.[2] Recently, DDQ has been successfully applied in cross-dehydrogenative-coupling (CDC) reactions.[3] For example, Zhang and Li reported first that DDQ mediated the direct CDC reaction between benzyl ethers and simple ketones.[3a] Then, we and others studied a series of oxidative coupling reactions using DDQ.[3b-3i] In our research, 1,3-diarylpropene reacted with some different substances containing active hydrogen, such as active methyenelic compounds, indoles, alcohols, thiols, and oximes. With our interest in the application of DDQ in organic

Received November 26, 2010.
Address correspondence to Jizhong Yan, College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310028, China. E-mail: yjz@zjut.edu.cn



Scheme 1. Synthesis of 1,2,4-thiadiazole mediated by DDQ.

chemistry, more recently we have tried the reaction between 1,3-diphenylpropene and phenylthioamide in CH_2Cl_2 at room temperature. However, in this experiment, we observed that a pale yellow solid (sulfur) precipitated quickly. Unexpectedly, 3,5-diphenyl-1,2,4-thiadiazole was obtained in good yield, not the desired coupling product (Scheme 1).

1,2,4-Thiadiazoles have occupied an important position in chemical and medicial technology as an effective agricultural fungicide, as pesticides, and as intermediates in other processes.[4] Among the existing methods for the preparation of 1,2,4-thiadiazole derivatives, the oxidative dimerization of thioamides is obviously a simpler one.[5] According to the literature, the oxidants used in the dimerization are hypervalent iodine,[5a-5c] dimethyl sulfoxide electrophilic reagent,[5g] polymer-supported diaryl selenoxide and telluroxide,[5f] and organotellurium,[5e] To the best of our knowledge, there are few reports about the self-coupling reaction using DDQ as an oxidant.[6] In 2007, Bose and Idrees reported the synthesis of benzothiazole by intramolecular cyclization of thioformanilides by DDQ.[6a] However, in their research, no example was mentioned of the oxidative dimerization of thioamides, which gives a different product, 1,2,4-thiadiazoles. Herein, we report that DDQ mediates a highly efficient oxidative dimerization of thioamides to 3,5-disubstituted 1,2,4-thiadiazoles at room temperature.

RESULTS AND DISCUSSION

To begin our study, we chose phenylthioamide with DDQ as a model reaction to search for the best reaction conditions (Table 1). Initially, several solvents were screened. The reaction could proceed in all the solvents tested (Table 1, entries 1–6). When the reaction was performed in $ClCH_2CH_2Cl$, it gave the product with 95% yield. Then an analogous quinine oxidant, 1,4-benzoquinone (BQ), was surveyed. The reaction was comparatively sluggish, and the yields were very poor. Obviously, it is not as efficient as DDQ in this dimerization (Table 1, entries 7 and 8). As for the dosage of DDQ, it was found that using the amount of 1 equiv. could also give the product with 95% yield in a few minutes (Table 1, entry 9).

With the optimized reaction conditions established, various thioamides were subjected to oxidative dimerization (Table 2). All the arylthioamides bearing an electron-donating or electron-withdrawing group on the aromatic ring reacted rapidly, and 88–99% yields were obtained (Table 2, entries 1–11). No obvious electronic effect of the substituent on the aromatic ring was observed. Heteroaryl species such as thienyl are also suitable substrates and excellent results was achieved

Table 1. Optimization of the reaction conditions[a]

Entry	Reagent (mol equiv.)	Solvent[b]	Time (min)	Yield (%)[c]
1	DDQ (1.1)	CH_3CN	5	89
2	DDQ (1.1)	$ClCH_2CH_2Cl$	<5	95
3	DDQ (1.1)	CH_2Cl_2	10	87
4	DDQ (1.1)	CH_3NO_2	<5	92
5	DDQ (1.1)	Toluene	10	83
6	DDQ (1.1)	H_2O	30	67
7	BQ (1.1)	$ClCH_2CH_2Cl$	60	33
8	BQ (1.1)	CH_3NO_2	60	27
9	DDQ (1.0)	$ClCH_2CH_2Cl$	<5	95

[a]Reactions were carried out on a 0.5-mmol scale at rt.
[b]1 mL.
[c]Isolated yields.

(Table 2, entry 12). It is worth mentioning that benzylthioamide was compatible with the present procedure, but the product was unstable (Table 2, entry 13).

In summary, we have developed a highly efficient oxidative dimerization of thioamides by DDQ. A series of 3,5-disubstituted 1,2,4-thiadiazoles are synthesized efficiently and concisely. It is a valuable addition to the existing methods available for the oxidative dimerization of thioamides.

General Procedure for the Synthesis of 3,5-Disubstituted-1,2,4-thiadiazoles

DDQ (0.5 mmol) was added at room temperature to a stirred suspension of substrate[7] (0.5 mmol) in 1,2-dichloroethane (1 mL). The mixture was stirred for the time indicated in Table 2. After completion of the reaction, 1,2-dichloroethane was removed under reduced pressure, and the residue obtained was purified through silica gel using petroleum ether/ethyl acetate (10:1) as developer.

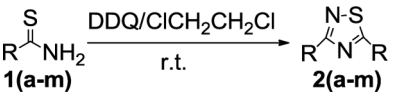
Spectral Data for the 3,5-Disubstituted-1,2,4-thiadiazoles

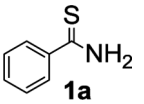
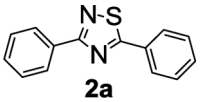
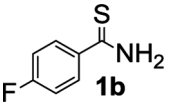
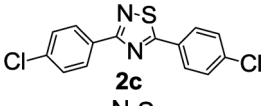
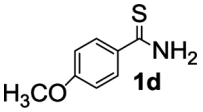
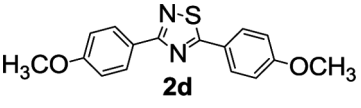
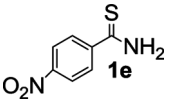
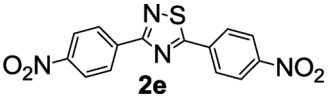
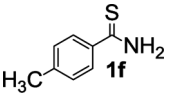
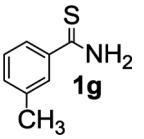
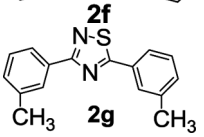
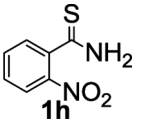
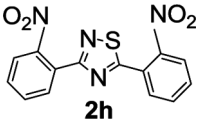
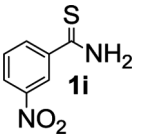
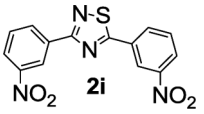
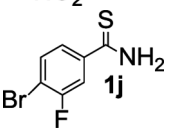
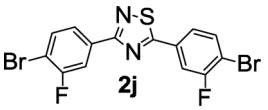
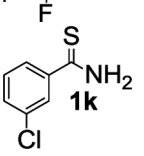
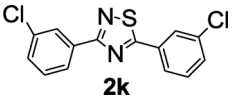
3,5-Diphenyl-1,2,4-thiadiazole (2a). Solid, mp 89–90 °C (lit.[5g] 91–91.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41–8.39 (m, 2H), 8.06–8.05 (m, 2H), 7.55–7.48 (m, 6H) ppm. IR (KBr): 2924, 1510, 1476, 1439, 1330, 760, 707, 682 cm^{-1}.

3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (2b). Solid, mp 185–186 °C (lit.[8a] 185–186). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39–8.36 (m, 2H), 8.07–8.04 (m, 2H), 7.24–7.17 (m, 4H) ppm. IR (KBr): 2963, 1598, 1475, 1410, 1261, 1097, 804, 743 cm^{-1}.

3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole (2c). Solid, mp 161–162 °C (lit.[5g] 161.5–162 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33–8.31 (m, 2H), 8.00–7.97 (m, 2H), 7.52–7.46 (m, 4H) ppm. IR (KBr): 1595, 1468, 1401, 1385, 1091, 828, 739 cm^{-1}.

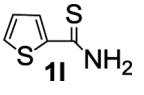
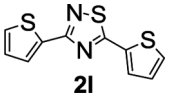
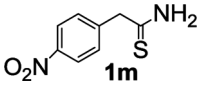
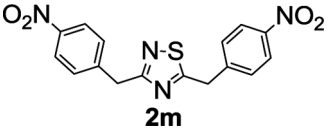
Table 2. Oxidative dimerization of thioamides to 3,5-disubstituted 1,2,4-thiadiazoles[a]



Entry	Substrate (**1**)	Product (**2**)	Time (min)	Yield (%)[b]
1	 **1a**	 **2a**	<5	95
2	 **1b**	 **2b**	<5	93
3	 **1c**	 **2c**	<5	93
4	 **1d**	 **2d**	<5	99
5	 **1e**	 **2e**	<5	90
6	 **1f**	 **2f**	<5	96
7	 **1g**	 **2g**	<5	97
8	 **1h**	 **2h**	<5	88
9	 **1i**	 **2i**	<5	92
10	 **1j**	 **2j**	<5	90
11	 **1k**	 **2k**	<5	94

(*Continued*)

Table 2. Continued

Entry	Substrate (**1**)	Product (**2**)	Time (min)	Yield (%)[b]
12	 **1l**	 **2l**	<5	94
13	 **1m**	 **2m**	<5	77

[a]Reactions were carried out on a 0.5-mmol scale at rt.
[b]Isolated yields.

3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2d). Solid, mp 139–140 °C (lit.[5g] 139–139.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33–8.31 (m, 2H), 8.00–7.98 (m, 2H), 7.02–7.00 (m, 4H), 3.90 (s, 3H), 3.89 (s, 3H) ppm. IR (KBr): 1609, 1477, 1421, 1253, 1169, 1029, 835, 747 cm^{-1}.

3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2e). Solid, mp 198–199 °C (lit.[5a] 200–202 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60–8.58 (m, 2H), 8.43–8.38 (m, 4H), 8.27–8.25 (m, 2H) ppm. IR (KBr): 2924, 2853, 1536, 1470, 1351, 851, 716 cm^{-1}.

3,5-Bis(4-methylphenyl)-1,2,4-thiadiazole (2f). Solid, mp 130–131 °C (lit.[5g] 130.5–131 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, $J = 8.5$ Hz, 2H), 7.94 (d, $J = 8.0$ Hz, 2H) 7.30 (t, $J = 8.3$ Hz, 4H), 2.44 (s, 3H), 2.43 (s, 3H) ppm. IR (KBr): 2923, 1475, 1405, 1321, 815, 737 cm^{-1}.

3,5-Bis(3-methylphenyl)-1,2,4-thiadiazole (2g). Solid, mp 56–58 °C (lit.[8b] 55–57 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 7.88 (s, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.41–7.36 (m, 3H), 7.31 (s, 1H), 2.47 (s, 6H) ppm. IR (KBr): 2918, 1480, 1436, 1309, 800, 731, 686 cm^{-1}.

3,5-Bis(2-nitrophenyl)-1,2,4-thiadiazole (2h). Solid, mp 158–160 °C (lit.[9] 159–160 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.10 (m, 1H), 8.06–8.04 (m, 2H), 7.85–7.83 (m, 1H), 7.81–7.78 (m, 1H), 7.74–7.69 (m, 2H), 7.65–7.61 (m, 1H) ppm. IR (KBr): 1535, 1479, 1372, 779, 700 cm^{-1}.

3,5-Bis(3-nitrophenyl)-1,2,4-thiadiazole (2i). Solid, mp 184–185 °C (lit.[9] 190–191 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (m, 1H), 8.91 (m, 1H), 8.741–8.737 (m, 1H), 8.46–8.36 (m, 3H), 7.79 (t, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, Hz, 1H) ppm. IR (KBr): 3092, 1525, 1493, 1352, 718, 672 cm^{-1}.

3,5-Bis(3-fluoro-4-bromophenyl)-1,2,4-thiadiazole (2j). Solid, mp 180–182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14–8.12 (m, 1H), 8.06–8.04 (m, 1H), 7.85–7.83 (m, 1H), 7.74–7.66 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 186.3, 171.9, 160.5, 160.3, 158.5, 158.3, 134.7, 134.0, 133.65, 133.59, 131.33, 131.27, 124.99, 124.97, 124.2, 124.1, 116.4, 116.2, 115.2, 115.0, 113.6, 113.4, 111.9, 111.7.

IR (KBr): 2926, 1504, 1461, 1433, 1384, 841, 739 cm^{-1}. MS (EI) m/z: 433 ($M^+ + 4$, 11), 431 ($M^+ + 2$, 22), 429 (M^+, 11), 232 (97), 230 (100), 152 (32), 120 (24), 94 (11). Anal. calc. for $C_{14}H_6Br_2F_2N_2S$: C, 38.92; H, 1.40; N, 6.48. Found: C, 38.66; H, 1.66; N, 6.32%.

3,5-Bis(3-chlorophenyl)-1,2,4-thiadiazole (2k). Solid, mp 130–131 °C (lit.[10] 128–128.5 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.28–8.26 (m, 1H), 8.07 (s, 1H), 7.91–7.89 (m, 1H), 7.54–7.52 (m, 1H), 7.49–7.43 (m, 3H) ppm. IR (KBr): 1573, 1473, 1386, 787, 730, 676 cm^{-1}.

3,5-Bis(2-thiophene)-1,2,4-thiadiazole (2l). Solid, mp 94–96 °C (lit.[11] 84–86 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.94–7.93 (m, 1H), 7.71–7.70 (m, 1H), 7.60–7.58 (m, 1H), 7.46–7.45 (m, 1H), 7.18–7.14 (m, 1H) ppm. IR (KBr): 3097, 1540, 1466, 1415, 1312, 840, 710 cm^{-1}.

3,5-Bis(4-nitrobenzyl)-1,2,4-thiadiazole (2m). Solid, mp 73–75 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, $J = 8.5$ Hz, 2H), 8.19 (d, $J = 8.5$ Hz, 2H), 7.52–7.49 (m, 4H), 4.49 (s, 2H), 4.41 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 189.5, 174.2, 147.5, 147.0, 144.3, 143.0, 130.0, 129.97, 124.2, 123.8, 38.9, 37.1 ppm. IR (KBr): 2925, 1524, 1481, 1347, 843, 716 cm^{-1}. MS (EI) m/z: 356 (M^+, 9), 220(12), 194 (100), 164 (25), 148 (43), 89 (24). Anal. calc. for $C_{16}H_{12}N_4O_4S$: C, 53.93; H, 3.39; N, 15.72. Found: C, 53.75; H, 3.48; N, 15.65%.

ACKNOWLEDGMENT

This work was financially supported by the Research Fund of Zhejiang University of Technology (1001116044408).

REFERENCES

1. Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78* (4), 317–361.
2. (a) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67* (2), 153–196; (b) Foster, R.; Foreman, M. In *The Chemistry of the Quinonoid Compounds*; S. Patai (Ed.); John Wiley and Sons: New York, 1974; vol. 1, pp. 257–423.
3. (a) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128* (13), 4242–4243; (b) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45* (12), 1949–1952; (c) Cheng, D. P.; Bao, W. L. *Adv. Synth. Catal.* **2008**, *350* (9), 1263–1266; (d) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, *39*, 5919–5921; (e) Mo, H. J.; Bao, W. L. *Adv. Synth. Catal.* **2009**, *351* (17), 2845–2849; (f) Li, Y.; Bao, W. L. *Adv. Synth. Catal.* **2009**, *351* (6), 865–868; (g) Jin, J.; Li, Y.; Wang, Z. J.; Qian, W. X.; Bao, W. L. *Eur. J. Org. Chem.* **2010**, *7*, 1235–1238; (h) Damub, G. L. V.; Selvam, J. J. P.; Rao, C. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2009**, *50* (45), 6154–6158; (i) Ramesh, D.; Ramulu, U.; Rajaram, S.; Prabhakar, P.; Venkateswarlu, Y. *Tetrahedron Lett.* **2010**, *51* (37), 4898–4903.
4. Kurzer, F. *Adv. Heterocycl. Chem.* **1982**, *32*, 285.
5. (a) Patil, P. C.; Bhalerao, D. S.; Dangate, P. S.; Akamanchi, K. G. *Tetrahedron Lett.* **2009**, *50* (42), 5820–5822; (b) Shah, A. A.; Khan, Z. A.; Choudhary, N.; Lohölter, C.; Schäfer, S.; Marie, G. P. L.; Farooq, U.; Witulski, B.; Wirth, T. *Org. Lett.* **2009**, *11* (16), 3578–3581; (c) Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* **2002**, *32* (14), 2155–2159; (d) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64* (19), 6989–6992; (e) Fukumoto, T.;

Matsuki, T.; Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Chem. Lett.* **1990**, *12*, 2269–2272; (f) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jap.* **1986**, *59* (3), 879–884; (g) Takikawa, Y.; Shimada, K.; Sato, K.; Sato, S.; Takizawa, S. *Bull. Chem. Soc. Jap.* **1985**, *58* (3), 995–999.

6. (a) Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48* (4), 669–672; (b) Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11* (15), 3474–3477; (c) Matheson, J. M.; Musgrave, O. C.; Webster, C. J. *Chem. Commun.* **1965**, *13*, 278–279; (d) Becker, H.-D. *J. Org. Chem.* **1965**, *30* (4), 982–989.
7. Goswami, S.; Maity, A. C.; Das, N. K. *J. Sulf. Chem.* **2007**, *28* (3), 233–237.
8. (a) Rafiqul, I. M. *Heteroatom Chem.* **2004**, *15* (2), 175–186; (b) Komatsu, M. *Bull. Chem. Soc. Jap.* **1983**, *56* (1), 180–183.
9. Broda, W.; Dehmlow, E. V. *Israel J. Chem.* **1985**, *26* (3), 219–221.
10. Yan, M.; Chen, Z.-C.; Zheng, Q.-G. *J. Chem. Res.* **2003**, *10*, 618–619.
11. Machida, M.; Oda, K.; Kanaoka, Y. *Tetrahedron Lett.* **1984**, *25* (4), 409–410.