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N-Phenyltriazolinedione as an efficient, selective, and reusable reagent for the oxidation of thiols to disulfides

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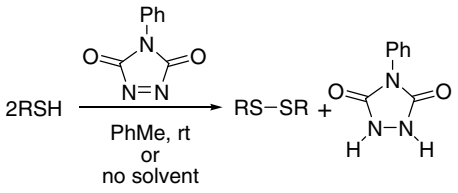
Abstract—*N*-Phenyltriazolinedione is an efficient and chemoselective reagent for the oxidation of thiols to their corresponding symmetrical disulfides. The method is applicable to aromatic, aliphatic, and bi-functional thiols. The one-pot reaction takes a few minutes (in most cases studied) for completion and after a simple work-up affords the corresponding symmetrical disulfides in very good to excellent yields. Furthermore, the reaction could be performed with the same results in the absence of solvent for liquid thiols.

Oxidative coupling of thiols to disulfides under neutral and mild conditions is of practical importance in synthetic chemistry[1] and biochemistry.[2] Disulfides have found industrial applications as vulcanizing agents[3] and are important synthetic intermediates with many applications in organic synthesis.[4] Various reagents and oxidants have been employed for the conversion of thiols to disulfides, under a range of experimental conditions.[5] We report here a new, very simple, one-pot, oxidation of a variety of thiols to their corresponding symmetrical disulfides with good to excellent isolated yields, after a simple work-up. In the case of liquid thiols no solvent was necessary leading to the same results.

We have been involved in the chemistry of ene[6] reactions of triazolinediones (TADs)[7] with alkenes.[8] TADs are powerful electrophiles and have been used in addition reactions to various alkenes with synthetic importance,[9] and have been extensively used in the synthesis of polyureas.[10] In addition, they are known for their dehydrogenating properties,[11] for their oxidation of alcohols to aldehydes and ketones,[12] and have been used for the oxidation–aromatization of pyrazolines to pyrazoles.[13] During an ongoing study in our laboratory dealing with new synthetic applications of triazolinediones, we found that a red solution of *N*-phenyltriazolinedione (PhTAD) in toluene was decolorized almost instantaneously in the presence of benzenethiol. Filtration of the white solid product floating at the top of the solution, afforded quantitatively, the parent *N*-phenylurazole, which was identified by GC–MS ($m/z = 178$ amu). In addition, diphenyl disulfide was isolated from the filtrate, and identified spectroscopically. We decided then to further test the applicability of disulfide formation with a variety of thiols.

The procedure is based on the addition of solid PhTAD to a solution of the corresponding thiol (twice the stoichiometric ratio with regard to PhTAD) in dry toluene at rt (Scheme 1). After decolorization of the red solution (indication of completion of the reaction), the resulting mixture was washed twice with 10% NaOH solution, then with brine and the organic phase was dried over Na_2SO_4. Removal of the volatile compounds and solvent afforded solidified disulfides of a high purity, which gave correct ^1H and ^{13}C NMR spectroscopic, and FAB MS spectrometric data.[14] No further purification of the 'crude' product was needed except for recrystallization from *n*-hexanes/EtOAc solvent mixtures (Table 1).



Scheme 1. Synthesis of symmetrical disulfides, from the reaction of *N*-phenyltriazolinedione with thiols.

Keywords: *N*-Phenyltriazolinedione; Oxidation; Thiols; Disulfides.
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Table 1. Synthesis of symmetrical disulfides from the reaction of PhTAD with thiols[a]

Entry	Substrate (thiol)	Time (min)	Product (disulfide)	Yield (%)
1	PhSH	5	$(PhS)_2$	~100
		5		~100[b]
2	$PhCH_2SH$	5	$(PhCH_2S)_2$	~100
		5		~100[b]
3	*p*-MeC_6H_4SH	10	(*p*-$MeC_6H_4S)_2$	~100
		10		~100[b]
4	PhC(=O)SH	5	$[PhC(=O)S]_2$	72
5	$HO(CH_2)_2SH$	30	$[HO(CH_2)_2S]_2$	~100[c]
6	$HO(CH_2)_{11}SH$	[d]	$[HO(CH_2)_{11}S]_2$	61[c]
7	*p*-HOC_6H_4SH	10	(*p*-$HOC_6H_4S)_2$	~100[c]
8	$CH_3(CH_2)_{15}SH$	10	$[CH_3(CH_2)_{15}S]_2$	~100
9	$CH_3(CH_2)_{17}SH$	[d]	$[CH_3(CH_2)_{17}S]_2$	82

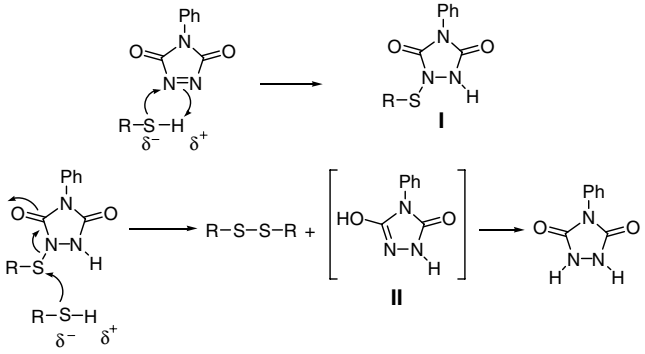
[a] In toluene at rt, unless otherwise stated.
[b] Reaction performed without solvent.
[c] Work-up: filtration through a pad of Celite (no extraction with basic solution), and removal of the volatile compounds.
[d] Left overnight, until decolorization of the solution.

From Table 1 it can be seen that the present method is of general applicability to aromatic (entries 1–3) and aliphatic thiols (entries 8 and 9), and also showed high efficiency and chemoselectivity in the case of bi-functional thiols. As can be seen from entries 4–7, hydroxyl- and carbonyl functionalities can be present in the substrate thiols and remain intact during the formation of the product disulfides. The observed inertness of the acidic hydroxyl–hydrogen (entries 5–7) is consistent with the higher acidity of S–H over O–H.[15]

The present work on the oxidation of thiols to disulfides is the first involving a cis-locked diazo-compound as the oxidant. Thiol additions to diethyl azodicarboxylate (DEAD) are known.[16] It is well documented that when a 2:1 molar ratio of thiol/DEAD is used, the first addition of one thiol molecule to DEAD results in the formation of a diethyl *N*-alkylsulfenyl hydrazodicarboxylate derivative (1:1 adduct), which undergoes a subsequent nucleophilic displacement by a second thiol molecule, resulting in the formation of the hydrazine derivative (diethyl hydrazodicarboxylate) together with the respective disulfide.[15,16a,b] If a stoichiometric amount of thiol/DEAD (1:1) is used, the sulfenyl hydrazide derivative is formed. This sequence has been used for the preparation of unsymmetrical disulfides.[16c,d]

Taking into account the above information, we propose an analogous two step sequence for the dimerization–oxidation of thiols with PhTAD.[14] In the first step a thiol molecule is added to the diazene double bond ('displacement' of an electron pair) to yield a sulfenyl urazole derivative **I**. In a subsequent step, a second thiol molecule attacks, as a nucleophile, the sulfur atom of **I**, to yield a disulfide and the parent *N*-phenylurazole, after tautomerization through intermediate **II** (Scheme 2).

In summary, we report a new, simple, and efficient method for the oxidation of thiols to symmetrical disulfides in good to excellent yields, utilizing the cis-locked azo-compound *N*-triazolinedione as the oxidant. Furthermore, this method allows for the isolation of the parent *N*-phenylurazole, by simple filtration from the reaction mixture, which can be re-used in the regeneration of PhTAD by known oxidation procedures.[17]



Scheme 2. A possible two step mechanism for the synthesis of disulfides.

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14. *Selected spectral data for representative disulfides*. (p-$MeC_6H_4S)_2$ (entry 3, Table 1): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.34 (s, 6H), 7.12 (d, $J = 7.50$ Hz, 4H), 7.42 (d, $J = 7.50$ Hz, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 21.0, 128.5, 129.8, 133.9, 137.4; FT IR (KBr, ν cm^{-1}): 2914, 1487, 1397, 1303, 1209, 1182, 1116, 1076, 1041, 801, 480; ESI MS: $[M]^+ = 246$ (25); $[M+Na]^+ = 269$ (100). $[HO(CH_2)_2S]_2$ (entry 5, Table 1): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.59 (s, 2H, OH), 2.87 (t, $J = 6.25$ Hz, 4H), 3.89 (t, $J = 5.00$ Hz, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 41.2, 60.4; ESI MS: $[M+K]^+ = 193$ (100).
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