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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

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To cite this article: N. Iranpoor , H. Firouzabadi & M. A. Zolfigol (1998) Dinitrogen Tetroxide Copper Nitrate Complex $[Cu(NO_3)_2.N_2O_4]$ As a New Nitrosating Agent for Catalytic Coupling of Thiols via Thionitrite, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:2, 367-375, DOI: <u>10.1080/00397919808005729</u>

To link to this article: http://dx.doi.org/10.1080/00397919808005729

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DINITROGEN TETROXIDE COPPER NITRATE COMPLEX [Cu(NO₃)₂.N₂O₄] AS A NEW NITROSATING AGENT FOR CATALYTIC COUPLING OF THIOLS VIA THIONITRITE

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Abstract: A catalytic and efficient oxidative coupling of thiols to disulfides is described using $Cu(NO_3)_2 N_2O_4$ as a new and efficient nitrosating agent in acetone at room temperature. The reaction is shown to occur immediately through the intermediacy of a thionitrite.

Oxidative coupling of thiols to disulfides under neutral and mild conditions is of importance from biological and practical points of view.¹ Thiols are among functional groups which can over oxidised and therefore, extensive studies have

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been carried out for their controlled oxidation.²⁻¹⁸ Although this transformation has been widely studied with different reagents, but as far as we know, there is only one catalytic reaction which was reported by our group with a double salt of Ce(IV) and periodate.¹⁴ Among the reported reagents, gaseous dinitrogen tetroxide (N_2O_4) has been considered as an interesting reagent to convert thiols to disulfides in a non-catalytic reaction through the intermediacy of thionitrites.^{2,3} Incorporation of NO⁺ and the formation of thionitrite as intermediate in the coupling reaction of thiols with clay-supported ferric nitrate or cupric nitrates are also well established.^{8,9,15} Thionitrites are becoming increasingly useful not only as source of thiyl radicals¹⁹ or as nitrosating reagents²⁰ but also as vasodilatory drugs due to their therapeutic use and their remarkable physiological importance.²¹ In a recent study, the effects of copper ions to enhance the rate of formation of disulfides through decomposition of thionitrite intermediate is also reported.¹⁶⁻¹⁸ Considering the reports on the use of dinitrogen tetroxide^{2,3} as a source of NO⁺ for dimerisation of thiols and the catalytic effects of copper ions^{16,18} on the decomposition of thionitrites as intermediate in the formation of disulfides, encouraged us to examine the use of Cu(NO₃)₂.N₂O₄ complex as a source of nitrosating agent for dimerisation of thiols, since both NO⁺ and Cu(II) ion exist together in this stable complex as $NO^{+}[Cu(NO_{3})_{3}]^{-22}$ Indeed, when we used a catalytic amount of this complex for coupling of thiols, we found that the reactions occur immediately in acetone at room temperature with the formation of disulfides in excellent yields (Scheme 1, Table 1).

Scheme 1

$$RSH \qquad \frac{Cu(NO_3)_2 \cdot N_2O_4 \cdot cat}{Acetone, n, immediately} \qquad RSSR$$
(a-i) 89-99%

R = (a) n-C₃H₇- (b) n-C₄H₉- (c) cyclohexyl- (d) Ph- (e) PhCH₂-
(f) 3-CH₃C₆H₄- (g) 4-CH₃C₆H₄- (h) 4-CH₃OC₆H₄- (i)
$$\int_{O}^{O}$$
 CH₂-

Table	1.	Coupling	of	Thiols	with	0.2	Equimolar	of	$Cu(NO_3)_2 N_2O_4$	in	Acetone	at
Room	Tei	mperature	•									

R	Yield * %	M.P(°C) or B.P(°C)/Torr				
		Found	Reported			
a	90	92/760	92/760 ²⁶			
b	91	116-118/19	114-115/18 ⁵			
c	89	127-129	125-130 ²⁶			
d	99	59-60	60 ⁷			
e .	98	71-72	72 ⁶			
f	98	44-45	45 ²⁶			
g	98	45-46	45-46 ⁵			
h	95	44	43-44 ⁶			
i	96	119-121/1	112-115/0.5 ¹⁴			

Reactions occur immediately.
 Vield refers to isolated product.

Although oxidative coupling of thiols has been widely studied with different reagents but due to the ready polymerisation reactions, the reported results on coupling of dithiols are rare.²⁷ We studied the possibility of coupling of 1,3-propanedithiol to 1,2-dithiacyclopentane with Cu(NO₃)₂.N₂O₄ under high dilution conditions.²⁸ The major product from this reaction was found to be some polymeric materials, but 1,2-dithiacyclopentane was also obtained in 20% yield.²⁸ The exact mechanism of this reaction is not clear, but formation of an intense bright red colour in the coupling reaction mixture of thiols with gaseous nitrogen tetroxide or clayfen has been reported as an indication for the formation of thionitrite .^{2,3,8}

In order to show conclusively the intermediacy of thionitrite, the reaction of thiophenol and Cu(NO₃)₂.N₂O₄ was carried out at 0 °C in acetone and quenched immediately by filtration and cooling at -10 °C to avoid coupling to disulfide . UV spectral analysis of the filtrate showed three absorption bands at; λ_{max} (acetone) = 382, 530 and 573 nm with A₃₈₂ / A₅₃₀ / A₅₇₃ = 9.65 / 1 / 1.6; Lit.³ λ_{max} (nhaxane-CCl₄) = 380, 530 and 570 nm; ε_{380} / ε_{530} / ε_{570} = 9.62 / 1 / 1.55 which are characteristics of the formation of the corresponding thionitrite. On the basis of thionitrite intermediacy and the reported catalytic effects of both Cu(I) and Cu(II) on the cleavage and coupling of the thionitrite¹⁶⁻¹⁸ to the corresponding disulfide, the following catalytic mechanism may be proposed.

Conversion of thiols to their corresponding disulfides in the presence of NO⁺ is a known reaction.^{2,3,8,15} This reaction proceeds by the formation of RSNO

Scheme 2

1) RSH + NO⁺[Cu (NO₃)₃]⁻ RSNO + Cu(II) + HNO₃ 2) RSNO NO + [RS·] RSSR 3) NO + Cu(II) NO⁺ + Cu(I) 4) RSH + NO⁺ RSNO + H⁺ 5)RSNO + Cu(I) RS⁻ + NO + Cu(II) 6) RS⁻ + Cu(II) RSSR + Cu(I) 7) Cu(I) + HNO₃ Cu (II) + NO + H₂O

which disintegrates into [RS] and NO species. This disintegration has been reported to be catalysed by copper ions. The catalysis of step (2) by copper ions has been suggested to occur through interaction of copper ions with lone pair electrons of nitrogen in the thionitrite intermediate.^{16,18} This catalysis could explain the great increase in the rate of coupling reaction of thiols which we have observed with N_2O_4 complexed with Cu(II) in comparison with the gaseous N_2O_4 . Interaction of RSNO and Cu(I) in the step (5) followed by coupling of thiolate anion and regeneration of Cu(I) are also well demonstrated.¹⁸ It is important to mention that Cu(II) ion can not alone bring about the catalytic coupling of thiols. Coupling of thiols with copper(II) octanoate required equimolar amount of the reagent and suffer from long reaction times (18 - 22.5h) at 35 - 55 °C.²³ Recent EPR studies has also confirmed the non-catalytic nature of the coupling reaction of thiols by Cu(II) octanoate.²⁴ Regeneration of Cu(II) from unstable Cu(I) ion (step 7) in the presence of HNO₃ which is generated by step 1 is also a well known reaction.25

In conclusion $(Cu(NO_3)_2.N_2O_4)$ which its preparation and handling is easy can act as a stable and efficient reagent as a source for the delivery of nitronium ion under mild conditions. This reagent has also a great potential for catalytic, and rapid conversion of thiols to disulfides in excellent yields at room temperature with easy work-up.

EXPERIMENTAL:

Products were characterized by comparison of their physical data with those of authentic samples. All yields refer to isolated products. IR and UV spectra were recorded on a Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were recorded on a Bruker DPX 250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-14A instrument.

Reaction of n-Butyl Thiol with Cu(NO3)2 . N2O4 . A Typical Procedure.

To a solution of n-butyl thiol (0.18 g, 2 mmol) in acetone (4 mL), Cu(NO₃)₂. N₂O₄ (0.112 g, 0.4 mmol) was added. The resulting mixture was stirred at room temperature for 1 min. To this mixture, CCI₄ (20 ml) was added and the precipitate was filtered. The resulting solution was evaporated and chromatographed on a short column of Silica gel. The pure n-butyl disulfide was obtained as colourless liquid (0.162g, 91%, bp 114-116 / 19 torr, Lit.⁵ bp 116-118/18 torr).

ACKNOWLEDGEMENT:

We are grateful to Shiraz University Research Council for partial support of this work and Mr. N. Maleki for running NMR spectra.

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COUPLING OF THIOLS

(28) The reaction was performed between 1,3 propanedithiol (2 mmol) and Cu(NO₃)₂.N₂O₄ (0.4 mmol) in acetone (200 ml) at room temperature. After 8 h, the product was isolated according to the procedure and identified by its ¹H, ¹³C-NMR and mass spectra data.

(Received in Japan 1 May 1997)

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