ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Communication

A Chlorine Gas-Free Synthesis of Dichloroglyoxime

Leah A Wingard, Pablo E Guzman, and Jesse James Sabatini

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.6b00252 • Publication Date (Web): 29 Aug 2016

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Chlorine Gas-Free Synthesis of Dichloroglyoxime

Leah A. Wingard[b], Pablo E. Guzmàn[a], Jesse J. Sabatini*[a]

[a]US Army Research Laboratory, Energetics Technology Branch, Aberdeen Proving Ground, MD 21005, United States

[b]Oak Ridge Associated Universities, Belcamp, MD 21017, United States

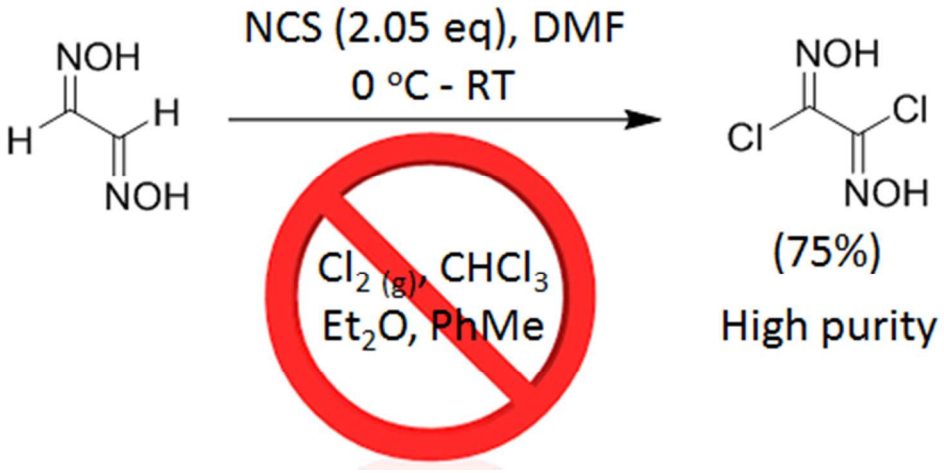


Table of Contents

ABSTRACT

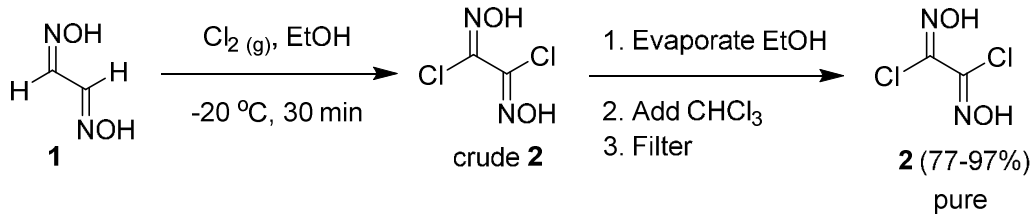
A new procedure for the synthesis and isolation of dichloroglyoxime is discussed. This material has historically been synthesized from glyoxime and elemental chlorine gas. Chlorine gas is difficult to handle and control in the laboratory, and has a high toxicity profile. Our method for making dichloroglyoxime in high purity uses glyoxime and N-chlorosuccinimide in DMF, with a lithium chloride-based work-up. Overall yields are comparable with those obtained using the procedure involving the use of chlorine gas.

KEYWORDS: Dichloroglyoxime, chlorination, lithium chloride, "green" chemistry, energetic materials

INTRODUCTION

Dichloroglyoxime (DCG) is an important building block that has found wide application toward the synthesis of numerous energetic materials. This includes the 5,5'-*bis*-tetrazole-1,1'diol-based materials ABTOX[1] as well as TKX-50[2], and 3,3'dinitramino-4,4'-*bis*-furazan.[3] Further applications of DCG include the synthesis of iridium- and rhenium-based luminescent 3,3'-*bis* isoxazole complexes[4], polynucleating ligand systems, and their complexes of *d*-metals.[5] DCG is most commonly prepared according to Scheme 1.[6] Elemental chlorine gas is bubbled through a stirred suspension of glyoxime in ethanol at -20 ^{o}C for 30 min. After evaporation of EtOH under reduced pressure, chloroform is added to wash the crystals. DCG is then isolated by filtration in 77-97% yield.

Scheme 1. Historical synthesis of dichloroglyoxime.

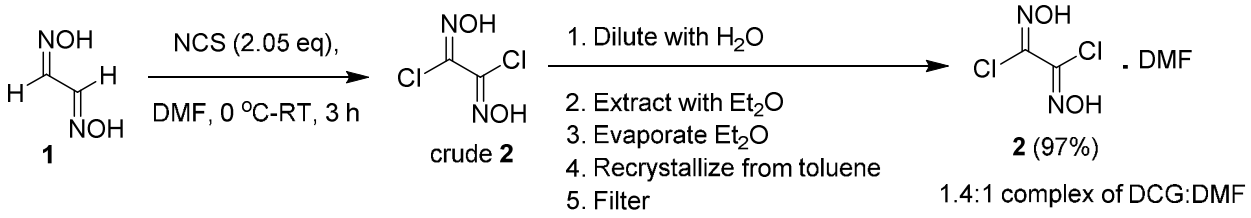


Results and Discussion

The issue with the historical synthesis of DCG centers on the use of chlorine gas. Chlorine gas has a high toxicity profile[7], is a difficult reagent to handle, and its addition is difficult to control. Hydroximoyl chlorides have also been synthesized from aldoximes by using N-chlorosuccinimide (NCS) in DMF[8]. The use of NCS is advantageous over chlorine gas because NCS is an easily-handled solid that is convenient for controlled addition while minimizing the inhalation hazard. As summarized in Scheme 2, a synthetic procedure to make DCG from

glyoxime by the NCS/DMF method was recently reported[4]. According to this procedure, it is reported that pure DCG is obtained in 97% yield. However, despite several attempts to reproduce the procedure, we were unable to obtain a pure product. As per the reported procedure, the reaction mixture is diluted with water when complete, and the product is extracted with Et_2O. After evaporation of the solvent, attempted recrystallization from boiling toluene afforded a white crystalline material in the reported 97% yield. This material, however, is not pure DCG, but is an inseparable complex of DCG and DMF in the molar ratio of 1.4:1 (see supporting information). Thus, the actual yield of DCG by this procedure is only 55%.

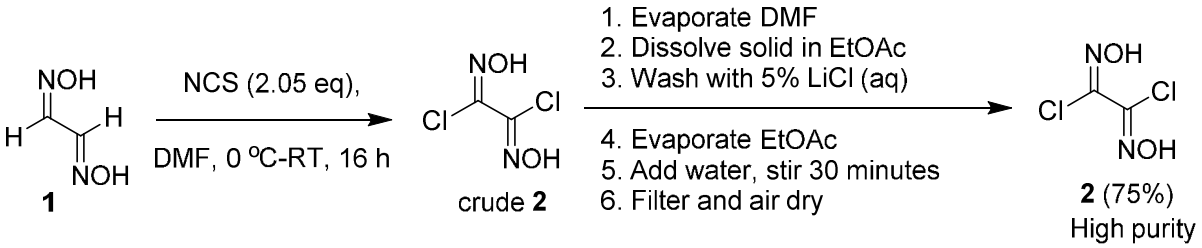
Scheme 2. Initial process of dichloroglyoxime synthesis employing NCS and DMF.



In an effort to obtain DCG in high purity, an alternative work-up was developed (Scheme 3). After the reaction was complete, as much DMF as possible was removed with the aid of a rotary evaporator. The resulting solid was dissolved in EtOAc, and this solution was washed three times with a 5% aqueous LiCl solution[9]. This was sufficient to remove nearly all the residual DMF. EtOAc was removed under pressure to afford a crude white solid. This white solid was suspended in water and stirred vigorously for 30 minutes. During this time, the water turned green. The solid was filtered and air-dried overnight to afford a 75% yield of DCG as a white powder in high purity, as observed by ^{1}H NMR analysis. A sample of DCG prepared by this method was shown by DSC analysis to melt with exothermic decomposition at 203 °C, which is in excellent agreement with the literature (see supporting information)[10]. Our method avoids the

use of halogenated solvents such as chloroform, highly flammable Et_2O, and the need for recrystallization from carcinogenic toluene.

Scheme 3. New process for the synthesis of dichloroglyoxime.



Conclusions

In summary, an improved process for the synthesis of DCG without employing chlorine gas has been developed. The new method provides a product of high purity in 75% yield. Although a previous method to make DCG from glyoxime and NCS was reported, this method involved the use of highly flammable and volatile Et_2O and carcinogenic toluene to afford an inseparable complex of DCG and DMF in the molar ratio of 1.4:1 . The new method involves a LiCl-based work-up to provide DCG in high purity as determined by ^{1}H NMR analysis. This "greener" synthetic method of DCG can be used toward synthesizing numerous materials based on 3,3'-*bis*-isoxazoles, 5,5'-*bis*-tetrazole-1,1'-diol, and 3,3'-diamino-4,4'-*bis*-furazans.

Experimental Section

Chemicals and solvents were used as received from Sigma-Aldrich. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz and 100 MHz instrument, respectively. The chemical shifts quoted in ppm in the text refer to typical standard tetramethylsilane (^{1}H, ^{13}C) in DMSO-d^6 as the solvent. Melting points and decomposition temperatures were measured at a heating rate of 5°C/min using a TA instruments Q10 DSC instrument. Infrared spectra were measured with a Bruker Alpha-P FTIR instrument.

Caution: Though no accidents occurred during our synthesis of dichloroglyoxime, glyoxime should be handled with care due to its reported thermal and shock sensitivity.[11]

Dichloroglyoxime (2)

To a 1000 mL round-bottom flask equipped with a mechanical stir bar was added glyoxime (30.0 g, 0.341 mol, 1.00 eq) and 340 mL of DMF. After the glyoxime dissolved, the solution was cooled to 0 ^{o}C in an ice bath, and *N*-chlorosuccinimide (97.5 g, 0.716 mol, 2.10 eq) was added in eight equal portions over 2 h. After the final portion was added, the reaction mixture was stirred overnight while the ice bath slowly warmed to room temperature. As much DMF as possible was removed under reduced pressure with the aid of a rotary evaporator at 70 ^{o}C. The crude solid was dissolved in 400 mL of EtOAc, and the resulting organic phase was washed with a 5% aqueous solution of LiCl (3 x 333 mL). The organic extract was dried over magnesium sulfate and filtered. EtOAc was removed under reduced pressure with the aid of a rotary evaporator at 40 ^{o}C to afford a crude white solid. The solid was suspended in 700 mL of water, and was stirred vigorously for 30 minutes. During this time, the water color changed from colorless to green. The white solid was filtered with the aid of a fritted funnel, and was left under suction for 1 h. This material was air-dried overnight in a fume hood to yield 40.1 g (75%) of dichloroglyoxime (**2**) as a fine white powder. m.p. (dec.) = 203 ^{o}C; IR: ν_{OH} = 3243 (s) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d^6), δ 13.1 (s, 2H, -NO*H*), ^{13}C NMR (100 MHz, DMSO-d^6), δ 130.7.

Supporting Information

The DSC analysis of glyoxime, the ^{1}H NMR spectra, ^{13}C NMR spectra, IR spectra, and the DSC analysis of dichloroglyoxime, and the ^{1}H NMR spectrum of the 1.4:1 dichloroglyoxime:DMF complex is provided in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

Corresponding Author

*E-mail: jesse.j.sabatini.civ@mail.mil; Phone: 410-278-0235

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

Research sponsored by the Army Research Laboratory was accomplished in part under Cooperative Agreement Number W911NF-12-2-0019. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing official

policies, either expressed or implied, of the Army Research Laboratory or the U.S. Government. The U.S. Government is authorized to reproduce and distribute reprints for Government purposes notwithstanding any copyright notation herein.

ACKNOWLEDGMENT

The authors are indebted to the US Army for financial support in carrying out this work.

ABBREVIATIONS

Cl_2 = chlorine; EtOH = ethanol; $CHCl_3$ = chloroform; NCS = *N*-chlorosuccinimide; DMF = dimethylformamide; Et_2O = diethyl ether; EtOAc = ethyl acetate; DCG = dichloroglyoxime

REFERENCES

1. Klapötke, T. M.; Fischer, N.; Fischer, D.; Piercey, D. G.; Stierstorfer, J.; Reymann, M. *US Patent Number 20140171657 A1*, **2014**.

2. Fischer, N.; Fischer, D.; Klapötke, T. M.; Piercey, D. G.; Stierstorfer, J. *J. Mater. Chem.* **2012,** *22*, 20418-20422.

3. Fischer, D.; Klapötke, T. M.; Reymann, M.; Stierstorfer, J. *Chem. Eur. J.* **2014,** *20*, 6401-6411.

4. Van der Peet, P. L.; Connell, T. U.; Gunawan, C.; White, J. M.; Donnelly, P. S.; Williams, S. J. *J. Org. Chem.* **2013,** *78*, 7298-7304.

5. Voloshin, Y. Z.; Varzatskii, O. A.; Kron, T. E.; Belsky, V. K.; Zavodnik, V. E.; Strizhakova, N. G.; Palchik, A. V. *Inorg. Chem.* **2000,** *39*, 1907-1918.

6. Willer, R. L. *US Patent Number 4539405 A*, **1985**.

7. White, C. W.; Martin, J. G. *Proc. Am. Thorac. Soc.* **2010,** *4,* 257-263.

8. Dash, A. K.; Jaladanki, C. K.; Maiti, D. K.; Singh, D.; Tripathi, A. K.; Gupta, V. K.; Bharatam, P. V.; Mukherjee, D. *ChemSelect*, **2016,** *1,* 567-571.

9. Frontier, A. “Not Voodoo X;” http://chem.chem.rochester.edu/~nvd/pages/workup.php?page=solvent_workup, accessed August 17, 2016. It is well established that DMF can be removed in the work-up by washing with a 5% aqueous solution of LiCl. Other metal chloride salts (i.e. NaCl) were not attempted.

10. Kanno, H.; Yamamoto, H. *US Patent Number 5476967 A*, **1995**.

11. Petree, H. E.; Nabors, Jr. J. B.; Grace, H. C., *US Patent Number 4106927,* August 15, **1978**.