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N,*N*′-Dichloro bis(2,4,6-trichlorophenyl)urea (CC-2): an efficient reagent for the synthesis of α-chloro-nitroso compounds

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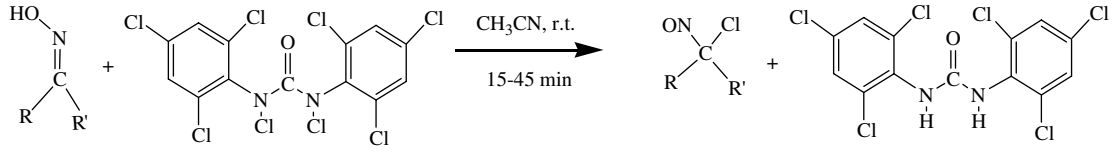
Abstract—A simple, efficient, rapid, and mild method for the synthesis of α-chloro-nitroso compounds is described using bis(2,4,6-trichlorophenyl)urea (CC-2).

α-Chloro-nitroso compounds are versatile intermediates for the synthesis of various organic compounds, and differences in their chemical and biological properties is governed by reactions in which either one or more of the functional groups take part in the reactions.[1–5] Several methods have been developed to prepare aliphatic and cyclic α-halo-nitroso compounds from their corresponding oximes, by using various halogenating agents such as elemental chlorine,[6] aqueous hypochlorous acids,[6] nitrosyl chloride,[7] alkylhypochlorites,[8] *N*-bromosuccinimide,[9] and *N*-bromoacetamide.[10] These methods often result in the formation of undesired side products such as over-oxidized nitro- and/or keto-derivatives,[11,12] mixtures of *gem*-dichloro alkanes and dimerized products of α-chloro-nitroso compounds. Since the reaction of ketoximes with elemental chlorine is reversible, continuous removal of HCl is necessary to drive the reaction to completion. On the other hand, the reactions of ketoximes with other halogenating agents need to be controlled at the α-chloro-nitroso stage only to avoid the formation of over-oxidized products. Control of the reaction could either be governed by manipulating the reaction conditions or by using selective reagents. Quenching the reaction at the α-chloro-nitroso stage would entail a study of the kinetic profile of the reaction. The use of selective reagents has also been reported but many of them have drawbacks such as the use of hazardous solvents, long reaction times, involve tedious work-ups and result in poor to moderate yields.[12,13] Due to these limitations, there is a need to develop efficient reagents and synthetic methods that would afford better yields in shorter reaction times.

The use of recyclable reagents in organic synthesis has received considerable attention due to stringent environmental rules.[14] We have investigated the possibility of



1 **2** **3** **4**

Scheme 1.

Keywords: *N*,*N*′-Dichloro bis(2,4,6-trichlorophenyl)urea; CC-2; Bis-(2,4,6-trichlorophenyl)urea; α-Chloro-nitroso alkanes; Oximes; *tert*-Butyl hypochlorite.
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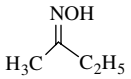
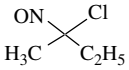
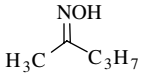
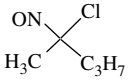
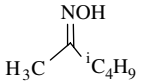
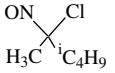
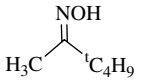
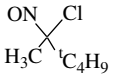
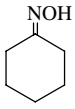
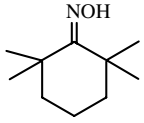
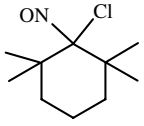
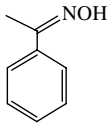
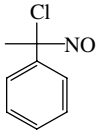
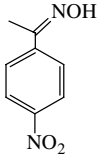
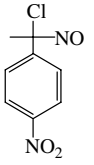
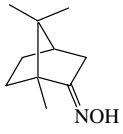
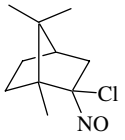
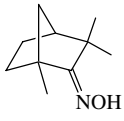
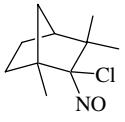
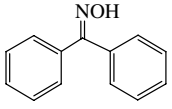
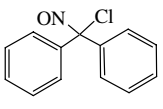
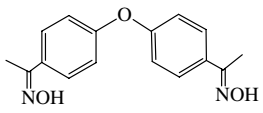
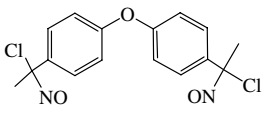
Table 1. Preparation of α-chloro-nitroso compounds from ketoximes using CC-2

Entry	Substrate	Product[a]	Time (min)	Yield[b]
1			15	96
2			15	94
3			20	95
4			30	96
5			15	92
6			20	94
7			30	89
8			35	85
9			25	88
10			30	89
11			45	82
12			40	80
13			45	80

[a] All the products were compared with authentic sample and gave satisfactory IR, NMR, and MS data.
[b] Isolated yields.

using a stable, nontoxic, and efficient chlorine releasing reagent namely, *N*,*N*′-dichloro bis(2,4,6-trichlorophenyl)urea (CC-2) **2**.[15] CC-2 has been incorporated as a reactive ingredient in a formulation developed in our laboratory to decontaminate bis-(2-chloroethyl)sulfide (sulfur mustard), a cytotoxic, alkylating vesicant chemical warfare agent.[16] Having established a commercially viable synthetic procedure for CC-2, we explored its application in the synthesis of dialkyl chloro phosphate from dialkyl phosphates.[17] In continuation of this work, we have explored the use of CC-2 as an alternative reagent for the conversion of ketoximes to α-chloro-nitroso compounds. Herein, we describe a convenient, rapid, economic, environmentally friendly, and scaleable method for the synthesis of α-chloro-nitroso compounds from their corresponding ketoximes at room temperature.[18] This method has allowed us to obtain excellent yields of the products in reduced reaction times. The general synthetic method is given in Scheme 1.

To demonstrate the versatility of this reagent, a variety of ketoximes were chlorinated (Table 1). It is evident from Table 1, that changing the alkyl chain length does not influence significantly the reaction time (entries 1–4). Aliphatic/alicyclic ketoximes reacted a little faster than aromatic ketoximes, while aromatic and bicyclic ketoximes required longer times which could be attributed to steric hindrance. We also examined the role of other factors such as temperature and solvents and found that these also influenced the course of the reaction to some extent. Although the reactions were exothermic, external cooling was not necessary. Amongst various solvents, dichloromethane and acetonitrile were found to be the most suitable in terms of reaction time, yield and work-up. One of the unique features of this method is convenient isolation of the reaction products. The by-product, bis-(2,4,6-trichlorophenyl)urea (**4**) was insoluble and hence could be removed by filtration.

Both aliphatic and aromatic α-chloro-nitroso compounds were stable for several days if stored below 5 °C. Tertiary nitroso compounds, on the other hand, were quite stable.

Caution: *gem*-Chloro-nitroso compounds are thermally unstable. Great caution should be exercised especially when distilling them, if the pressure is allowed to rise, explosion may occur.[6]

In conclusion, we have reported a highly efficient method for the preparation of aliphatic as well as aromatic α-chloro-nitroso compounds in excellent yields. This method has advantages over earlier reported methods in terms of versatility, easy work-up, recyclability of the reagent (**4** was collected after filtration, re-chlorinated and used for further reactions) and reaction time.

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References and notes

1. (a) Cecherelli, P.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **1998**, *39*, 4385; (b) Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* **1993**, *58*, 1939.
2. (a) Sabuni, M.; Kresz, G.; Braun, H. *Tetrahedron Lett.* **1984**, *25*, 5377; (b) Walters, T. R.; Zajac, W., Jr.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 316.
3. Yamamoto, M.; Momiyama, N. *Chem. Commun.* **2005**, 3514.
4. Martynov, I. V.; Chepakova, L. A.; Brel, V. K.; Sokolov, V. B. *Zh. Obshch. Khim.* **1986**, *56*, 2020.
5. (a) Kruglyak, Yu. L.; Landau, M. A.; Leibovskaya, G. A.; Martynov, I. V.; Saltykova, L. I. *Zh. Obshch. Khim.* **1971**, *41*, 2338; (b) Kayen, A. H. M.; De Boer, Th. *Recl. Trav. Chim. Phys. Bas.* **1977**, *96*, 8.
6. (a) Archibald, T. G.; Garver, L. G.; Baum, K.; Cohen, M. C. *J. Org. Chem.* **1989**, *54*, 2869; (b) Labaziewicz, H. L.; Riddell, F. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2926; (c) Diekmann, H.; Luttke, W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 388; (d) Barnes, M. W.; Patterson, J. M. *J. Org. Chem.* **1976**, *41*, 733.
7. (a) Kugelman, M.; Mallams, A. K.; Vernay, H. F. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1113; (b) Bozzi, E. G.; Shiue, Ch. Y.; Clapp, L. B. *J. Org. Chem.* **1973**, *38*, 56.
8. (a) Diekmann, H.; Luttke, W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 387; (b) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1117; (c) Felber, H.; Kresze, G.; Brau, H.; Vasella, A. *Tetrahedron Lett.* **1984**, *25*, 5381.
9. Bull, J. R.; Jones, E. R. H.; Meakins, G. D. *J. Chem. Soc.* **1965**, 2601.
10. Iffland, D. C.; Fu-Yen, T. *J. Am. Chem. Soc.* **1954**, *76*, 4083.
11. Wichterle, O.; Hudlicky, M. *Collect. Czech. Chem. Commun.* **1947**, *12*, 661.
12. (a) Cuthbertson, F.; Musgrave, W. K. R. *J. Appl. Chem.* **1957**, *7*, 99; (b) Doering, W. Von.; Henderson, W. A., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 5274; (c) Orazi, O. O.; Corral, R. A.; Schuttenberg, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2087; (d) Olah, G. A.; Welch, J. *Synthesis* **1974**, 2087; (e) Seyferth, D.; Murphy, G. J.; Mauze, B. *J. Am. Chem. Soc.* **1977**, *99*, 5317; (f) Villieras, J.; Perriot, P.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1977**, 765; (g) Kruglova, N. V.; Freidline, R. K. *Bull. Acad. Sci. USSR, Engl. Trans.* **1984**, 346; (h) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281.
13. Migrdiechian, V. *Organic Synthesis*. In *Open Chain Saturated Compounds*; Chapman and Hall: London, 1960; Vol. 1, p 702.
14. Laszlo, P. *Organic Reactions: Simplicity and Logic*; Wiley: New York, 1995.
15. Dubey, D. K.; Malhotra, R. C.; Vaidyanathaswamy, R.; Vijayraghavan, R. *J. Org. Chem.* **1993**, *64*, 8301.
16. Vijayraghavan, R.; Praveen Kumar; Dubey, D. K.; Ram Singh *Biomed. Enviro. Sci.* **2002**, *15*, 25.
17. Shakya, P. D.; Dubey, D. K.; Pardasani, D.; Palit, M.; Gupta, A. K. *J. Chem. Res.* **2005**, 821–823.
18. (a) *Typical experimental procedure*: A solution of 2,2,6,6-tetramethylcyclohexanone oxime, (8.45 g, 0.05 mol) in 50 mL dry acetonitrile was added slowly to a suspension of CC-2, (12.2 g, 0.025 mol) in 25 mL acetonitrile with stirring at room temperature. A blue color appeared after mixing the reactants which indicated formation of the product. The flask was wrapped with black carbon paper to avoid photochemical reactions. Progress of the reaction was monitored by TLC and GC analysis. The reaction mixture was filtered under suction and washed with acetonitrile (3 × 10 mL). The solvent was evaporated and

the residue was crystallized from acetonitrile–hexane (70:30 by volume) mixture to afford α-chloro-nitroso-2,2,6,6-tetramethylcyclohexane as blue crystals; yield: 9.06 g (89%), mp 115–116 °C (Table 1, entry 7). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.75$ (m, 2H), 2.40 (m, 1H), 2.18 (m, 1H), 1.86 (m, 2H), 1.21 (s, 6H), 0.28 (s, 6H). ^{13}C NMR (100.62 MHz, $CDCl_3$): 136.51, 42.15, 40.25, 27.56, 20.06. MS; *m*/*z* (%) = 168 (8), 158 (14), 145 (15), 143 (48), 137 (54), 131 (13), 123 (26), 107 (17), 105 (20), 107 (18), 97 (16), 91 (14), 95 (42), 83 (25), 81 (38), 79 (19), 69 (100), 67 (38), 57 (36), 55 (46), 43 (24), 41 (73). IR (KBr): 2961, 2925, 2875, 1592, 1478, 1381, 1367, 1212, 638 cm^{-1}. (b) *Preparation of N,N′-dichloro bis(2,4,6-trichlorophenyl)urea (CC-2)*: Bis(diphenyl)urea (25 g, 0.117 mol) was dissolved in 200 mL of acetic acid and 20 mL of pyridine was added followed by stirring at 70 °C. Chlorine gas was bubbled into the reaction for 4 h with stirring. Absorption of chlorine ceased with complete precipitation of bis(2,4,6-trichlorophenyl)urea. The mixture was cooled to 10 °C in an ice bath, and solid NaOH (7 g) was added in portions to bring the pH of the mixture to almost neutral. Chlorine gas was passed through until all the organic matter had re-dissolved. The mixture was poured into water to precipitate the CC-2, which was washed with water, filtered and re-crystallized from toluene. After drying, the yield was 56 g, 98%, mp 179–180 °C. The chlorine content of CC-2 was checked by standard iodometric titration and was found to be 14.51% (theoretical value 14.54%).