Deoxygenation of Pyridine *N*-Oxides With Dimethylthiocarbamoyl Chloride

Anthony A. Ponaras,[a]*, Ömer Zaim[b]

[a]Department of Chemistry, The Catholic University of America, Washington, DC 20064(deceased)
[b]Department of Chemistry, Trakya University, Edirne 22030, Turkey
omerzaim@trakya.edu.tr

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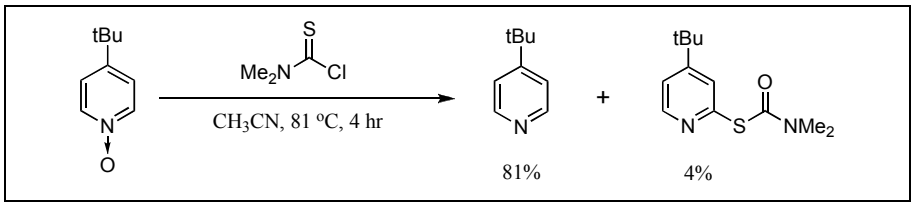

Treatment of pyridine *N*-oxides with dimethylthiocarbamoyl chloride in boiling acetonitrile effects chemoselective deoxygenation to pyridines.

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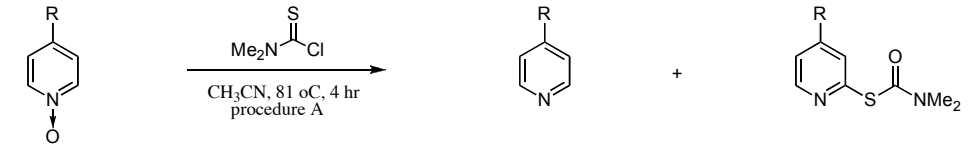
INTRODUCTION

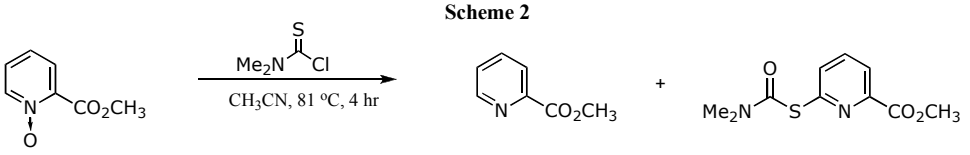
Deoxygenation of pyridine *N*-oxides is an important synthetic transformation [1-4] for which many methods have been reported [5-7]. Of these, the most generally useful are catalytic hydrogenation (especially over nickel catalysts) [8,9], transfer hydrogenation, [10-12] treatment with trivalent phosphorus compounds (especially PCl_3) [13-15] and treatment with metals (especially zinc) [16,17]. These methods, however, are not without drawbacks. We present here a new chemoselective method. When, for example, several 4-substituted pyridine *N*-oxides [18] are treated with commercially-available dimethylthiocarbamoyl chloride (DMTCC) [19] using the general procedure, the parent pyridines, accompanied by 2-dimethylcarbamoylthio pyridines (and very small amounts of 3-dimethylcarbamoylthio pyridines), are produced [20-22] (Scheme 1). The following 2- and 3-substituted and 3,5-disubstituted pyridines behave in similar manner (Scheme 2). Pyridines bearing CHXY groups at C-2 or C-4 exhibit another type of side reaction (Scheme 3).

Scheme 1

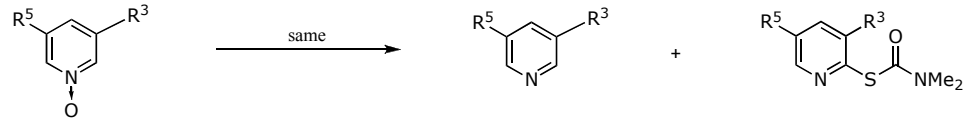


1 (R = tBu)	**2** (81%)	**3** (4%)
4 (R = Ph)	**5** (85%)	**6** (8%)
7 (R = CO_2CH_3)	**8** (35%)	**9** (30%)
10 (R = $COCH_3$)	**11** (20%)	**12** (24%)
13 (R = CN)	**14** (<2%)	**15** (49%)

Scheme 2

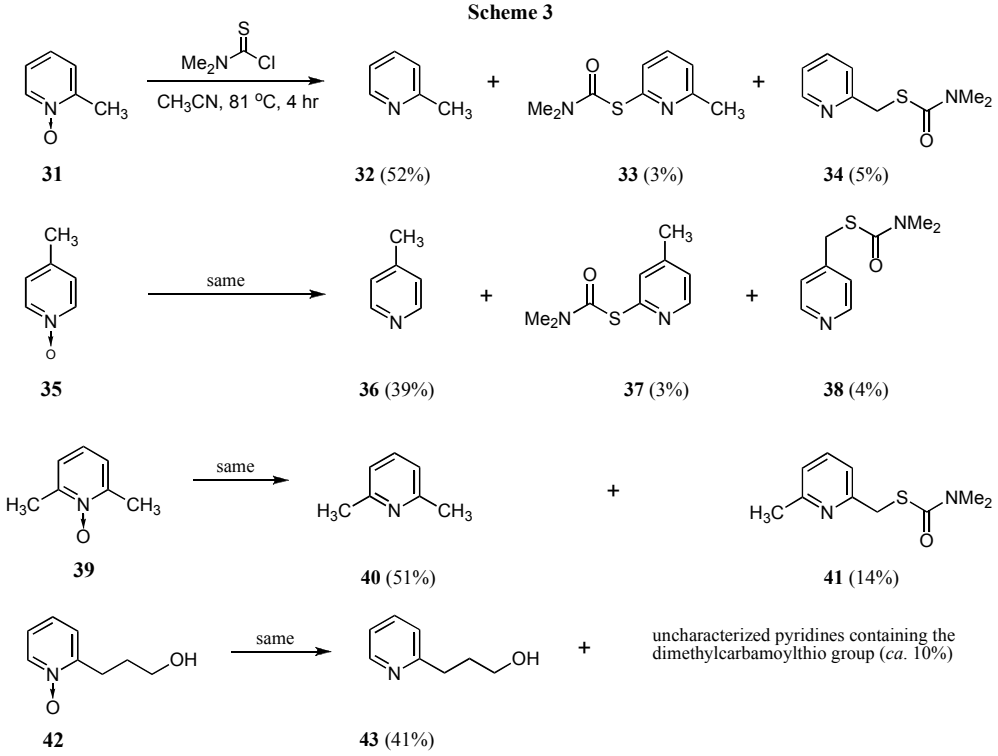


16 **17** (35%) **18** (47%)



19 (R^3 = CH_3, R^5 = CH_3)	**20** (54%)	**21** (3%)
22 (R^3 = CH_2OH, R^5 = H)	**23** (47%)	**24** (9%)[25]
25 (R^3 = CO_2CH_3), R^5 = H)	**26** (36%)	**27** (<10%)[25]
28 (R^3 = Br, R^5 = H)	**29** (41%)	**30** (<5%)[25]

Scheme 3



31 **32** (52%) **33** (3%) **34** (5%)

35 **36** (39%) **37** (3%) **38** (4%)

39 **40** (51%) **41** (14%)

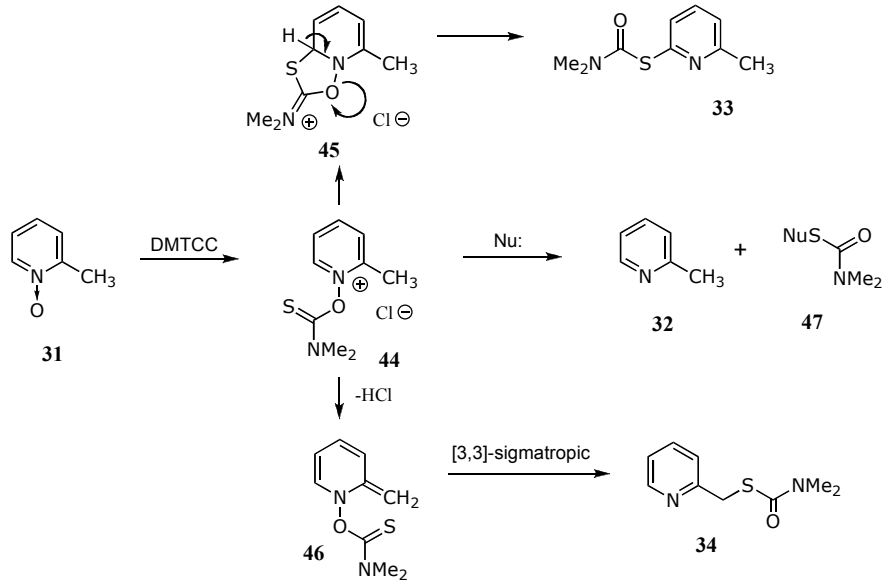
42 **43** (41%)

RESULTS AND DISCUSSION

It is likely that all products originate from *N*-(thioacyl)oxy salts [26]. Using the 2-picoline *N*-oxide example, the production of **33** and **34** may occur as follows; alternative routes can be imagined [27]; 3- and 5-dimethylcarbamoylthio pyridines may arise *via* several processes [27]. The relatively large amounts of α-dimethylcarbamoylthio pyridines produced when there is an electron-withdrawing group at C-2 or C-4 is consistent with internal nucleophilic addition (*cf.* **44** → **45**) (Scheme 4).

We have, at present, little mechanistic understanding of the process(es) leading to deoxygenation. Attack at sulfur by a nucleophile on the initial N-(thioacyl)oxy salt would produce pyridine and a species such as **47**. Indeed, small amounts of bis(dimethylcarbamyl) disulfide [$Me_2N(CO)S\text{-}S(CO)NMe_2$] are found in all reactions.

Scheme 4



31 **44** **45** **46** **32** **33** **34** **47**

Addition of 2 equivalents of iodide ion to the reaction mixture leads to the production of iodine but does not increase the yields of pyridines nor does it accelerate the rate of disappearance of pyridine *N*-oxides. [28] One mole of DMTCC per mole of pyridine oxide is necessary, and dimethylcarbamyl chloride is ineffective at causing deoxygenation of **1**, with or without iodide ion. 3,5-Lutidine *N*-oxide **19** and 2,6-lutidine *N*-oxide **39** are reduced at comparable rates and in comparable yield, suggesting that species analogous to **45** (whose formation in the case of **39** would be sterically disfavored) are not involved in the deoxygenation process [19]. Finally we note that small amounts of tetramethyl thiourea are produced in all reductions

EXPERIMENTAL

General procedure. A 1.48-g (12 mmol) portion of DMTCC is added to a magnetically-stirred solution of 10 mmol pyridine N-oxide in 20 mL of reagent-grade acetonitrile, and the solution is heated at reflux for 4 to 14 hrs until GC shows no further increase in the desired pyridine. Because of the high water-solubility of the products, the following non-aqueous workup is used. The mixture is cooled and treated with 12 mL of a 1 *M* solution of HCl in ether. Solvent is removed on the rotary evaporator and then at the vacuum pump and the residue is triturated with two 20-mL portions of ether; the ether-soluble phase, containing non-basic by-products such as bis(dimethyl-carbamyl) disulfide, is set aside. The ether-insoluble phase is dissolved in hot methylene chloride and treated with 2 mL (18 mmol) *N*,*N*-dimethylethaneamine and the solvent is removed on the rotary evaporator and then at the vacuum pump. The residue is triturated several times with 20-mL portions of ether and the ether-insoluble solid (*N*,*N*-dimethylethaneamine hydrochloride salt) is discarded. The ether-soluble phase is concentrated and distilled or chromatographed on 100 g of silica gel (Davisil grade 643, 200-425 mesh) packed in hexane/ethyl acetate.

This procedure was altered slightly for acid-sensitive compounds by not treating product mixture with acid solution. After removal of solvent on the rotary evaporator and then at the vacuum pump the residue is dissolved in the minimum amount of hot methylene chloride and passed through a short column containing 10 g of basic alumina (CAMAG 5016-A-1, 150 mesh) eluting with hexane/methylene chloride. The eluant is concentrated and the residue is distilled or chromatographed as above.

Acknowledgements. We thank the NSF and the ACS-PRF for their financial support.

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[7] Some recent deoxygenation methods are mentioned in ref [12] below.

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[18] The N-oxides **4, 31, 35,** and **39** are commercially available. Other N-oxides**, 1, 7, 10, 13, 16, 19, 22, 25, 28** and **42** were prepared by treating the corresponding pyridines with 30% aqueous hydrogen peroxide in boiling acetic acid for 5 hours [1] and their properties were compared with the reported data.

[19] A. A. Ponaras and Ö. Zaim, In The Encyclopedia of Reagents for Organic Synthesis, John Wiley; New York: 1993.

[20] All yields given here refer to isolated yields, sometimes by distillation, more often by column chromatography.

[21] All compounds were characterized by IR, NMR and MS.

[22] Authentic samples of **3** and **6** were prepared *via* Newman-Kwart reactions [23,24] on 4-*t*-butyl-2-pyridone and 4-phenyl-2-pyridone, prepared by heating 1 and 4 with trifluoroacetic anhydride at 100 °C in a sealed tube.

[23] M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

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[25] Small amounts (<5%) of substances presumed to be the 6-dimethylcarbamoylthio isomers are also present.

[26] We have prepared crystalline *N*-(dimethylthiocarbamoyloxy) pyridinium chlorides from **1**, **4**, **19** and **39** by mixing the pyridine *N*-oxides and DMTCC at room temperature in methylene chloride and then concentrating the solvent. These salts go on to products when heated in acetonitrile. The salt from pyridine N-oxide and DMTCC has been prepared and characterized but, apparently, has not been subjected to any further transformation: A. N. Pudovic, V. Y. Kovtun, V. K. Khairullin and M. A. Vasyanina, *Zh. Obshch Khim.*, **62**, 269 (1992).

[27] For a discussion of some analogous processes which occur when pyridine *N*-oxides are treated with acylating agents such as acetic anhydride, see: [a] V. J. Traynelis, Mechanisms of Molecular Migrations; B. S. Thyagaragan, Ed.; 1969; Vol. **2**, p 1; [b] S. Tamagaki, S. Kozuka and S. Oae, *Tetrahedron Lett.*, 4765 (1968) and references cited therein.

[28] Our initial work, attempting to exploit a similarity between diosphenols and azaarene *N*-oxides (they are both subject to nucleophilic addition alpha to the oxy group), employed a combination of DMTCC and iodide ion (see ref. 9). It was later found that iodide ion is unnecessary. The deoxygenation of diosphenols with dimethylthio-carbamoyl chloride requires 2-equivalents of iodide ion: A. A. Ponaras,; Ö. Zaim,; Y. Pazo and L. Ohannesian, *J. Org. Chem.*, **53**, 1110 (1988)

[29] We had previously suggested such intermediates (ref [19]).