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Cu(I)-mediated deoxygenation of *N*-oxides to amines☆

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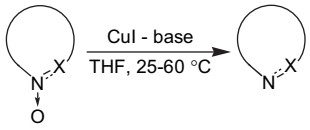
Abstract—A mild and highly efficient deoxygenation of variety of *N*-oxides using an inexpensive CuX, or a CuX–Zn or CuX–Al couple is described.

1. Introduction

Organic *N*-oxides are important species in chemical as well as biological studies. While many chemical transformations essentially require *N*-oxide intermediates,[1] often they are formed as unwanted side products. These species are also formed during biochemical oxidation of nitrogen containing drug substances[2a] and serve as a major source of drug metabolism studies.[2b] Search for suitable deoxygenating agents for various *N*-oxides continued for many years. The first generation reagents for this purpose include Pd–C combinations,[3] H_2SO_3,[4] Ni–Al alloy,[5] metals,[6] alkali metal hydrides,[7] NaHTe,[8] phosphorus compounds,[9] S and Se compounds,[10] aluminium halides,[11] $TiCl_3$,[12] silanes,[13] $CrCl_2$,[14] R_3N–SO_2 complex[15] and acetic formic anhydride.[16] But, most of these reagents and reaction conditions are harsh, and affect other sensitive groups in the substrate to yield unwanted products. Therefore, milder and specific reagents such as Zn–NH_4Cl,[17a] Zn–HCO_2NH_4,[17b] $TiCl_4$–$SnCl_2$,[18a] $TiCl_4$–Zn,[18b] $TiCl_4$–Mg,[18c] $TiCl_4$–NaI,[18d] $TiCl_4$–$NaBH_4$ complex,[18e] bis-(cyclopentadienyl)titanium(IV)dichloride–In,[18f] titanocene methylidene complex,[18g] tributyltinhydride,[19] SmI_2[20] and tetrathiomolybdate[21] have been developed in recent years to overcome the above problems. Very recently, more specific and environmentally benign reagents such as $ZrCl_4$–$NaBH_4$,[22a] LiCl–$NaBH_4$,[22b] $InCl_3$ (X=Cl, Br),[23a] In–NH_4Cl,[23b] polymethylhydrosiloxane (PMHS),[24] Ph_3P–oxorhenium(V) catalyst,[25] NaOEt,[26] $MoO_2Cl_2(dmf)_2$,[27] $RuCl_3 \cdot xH_2O$,[28] $Mo(CO)_6$,[29] Zn/Cu–triflates[30] and $CoCl_2 \cdot 6H_2O$–In[31] have been investigated for the purpose. But, most of these reagents are costly, partially selective, unknown to the environment and require special preparation. The deoxygenation of *N*-oxides is also catalyzed by microbes,[32a] haem moiety of cytochrome P-450[32b] and rat liver preparations[32c] at ambient temperature. But, they are highly expensive for large scale conversions. Thus, there still remains a need for developing simple, cheap and environment friendly reagents for the exclusive deoxygenation of various amine *N*-oxides to corresponding amines.

2. Results and discussion

Apart from several other uses, cuprous iodide is known to be a prime component of C–C and C–N bond formation reactions.[33] During the development of a drug candidate in our laboratory, an extremely safe reagent was desired for the deoxygenation of its *N*-oxide intermediate to afford an impurity-free active pharmaceutical ingredient (API) under mild reaction conditions. We experimented with many of the reported reagents, and found a novel use of cuprous iodide (CuI) as a highly effective reagent for the deoxygenation of *N*-oxide. To the best of our knowledge, there is no report on such kind of use of this reagent in the literature. In an extensive study, this reagent was able to reduce a variety of aliphatic and aromatic *N*-oxides to corresponding free amines in high yield with excellent chemoselectivity (Scheme 1, Table 1). Hence, in this report, we describe the experimental conditions, which led to the identification of CuX (Cl, I), CuX–Zn and CuX–Al as highly effective deoxygenating agents for various *N*-oxides.



Scheme 1.

The reaction conditions were optimized by varying the solvent, temperature, base and cuprous salt using a representative aliphatic *N*-oxide (entry **12**). Among the solvents, THF, MeCN and Me_2SO were found to be suitable to favour the reaction at room temperature. Other solvents required high

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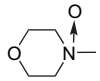
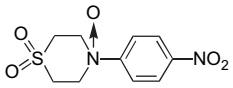
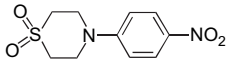
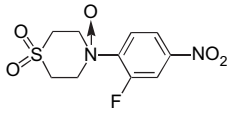
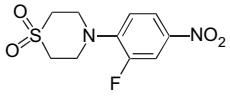
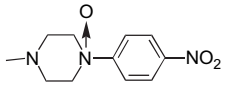
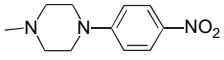
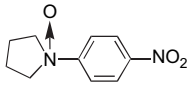
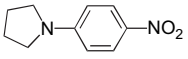
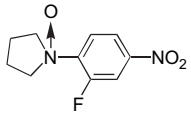
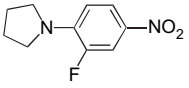
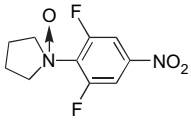
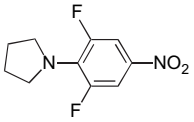
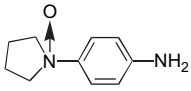
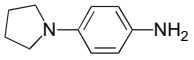
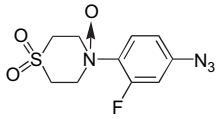
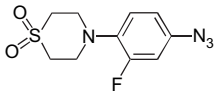
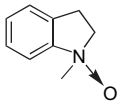
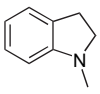
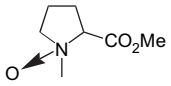
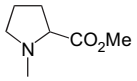
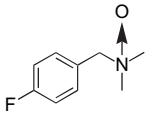
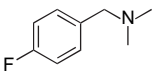
Table 1. Deoxygenation of amine *N*-oxides[a]

Entry	Substrate	Base	Temp (°C)	Time (h)	Yield (%)	Product
1	$(Et)_3N \rightarrow O$	[b]	25–30	1.5	95	$(Et)_3N$
2		[b]	25–30	1.5	95	
3		[d]	25–30	1.0	98	
4		[d]	25–30	1.0	98	
5		[d]	25–30	2.0	97	
6		[d]	35–40	3.0	96	
7		[d]	35–40	3.0	97	
8		[c]	25–30	2.0	95	
9		[d]	35–40	3.0	96	
10		[c]	35–40	3.0	95	
11		[d]	25–30	2.0	97	
12		[d]	35–40	2.0	95	
13		[c]	35–40	3.0	97	

[a] All the reactions were carried out in THF using CuI.
[b] Without base.
[c] Triethylamine (1.0 equiv).
[d] *N*,*N*′-diisopropylethylamine (1.0 equiv).

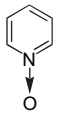
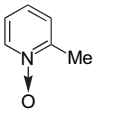
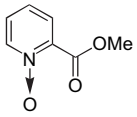
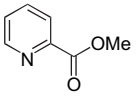
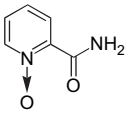
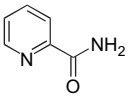
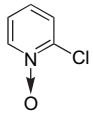
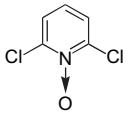
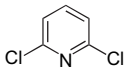
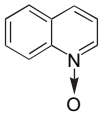
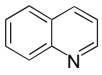
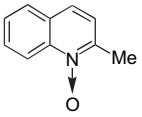
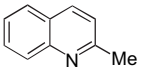
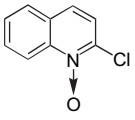
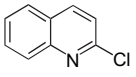
temperature and afforded only partially deoxygenated product even after extended duration. Addition of organic base such as triethylamine or *N*,*N*′-diisopropylethylamine further reduced the reaction time from 2–3 h to 0.5–1.0 h, and this reaction when heated to 50–60 °C, was over within 30 min. Other cuprous salts, viz. CuBr, CuCl, CuCN and Cu_2O were also tried. While CuCl was found to be as effective as CuI and worked at room temperature, CuBr required higher temperature for completion. Only 60–70% conversion was observed in case of CuCN and Cu_2O even after heating overnight.

While simple warming (30–50 °C) of aliphatic and aromatic *N*-oxides with CuI in above solvents afforded quantitative yields of corresponding amines (Table 1), the deoxygenation of nitrone **14**[30,34a] and azoxybenzene **16**[30,34b] essentially required one of the above bases and heating at higher temperature for long time. But, this set of conditions failed to deoxygenate heteroarene *N*-oxide (entry **18**). Different solvents such as MeCN, DMF and DMSO, bases (triethylamine or *N*,*N*′-diisopropylethylamine) and elevated temperatures (50–100 °C) also did not lead to better conversion. Even benzyl alcohol, a recently reported

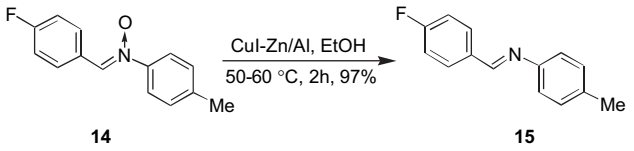
reaction medium,[35] could not assist the CuI mediated deoxygenation.

Presumably, the CuX mediated deoxygenation process is a simple reduction–oxidation reaction where lower valent Cu(I) reduces the *N*-oxides, and itself gets oxidized to higher valent Cu(II) salt. Though few metals and their alloys have been used along with suitable reagents for similar conversion, there was no report of pure metals, viz. Zn and Al being used for the purpose in neutral medium. We selected these metals because they are known to have high affinity for oxygen. Pyridine *N*-oxide (entry **18**) and the aliphatic *N*-oxide (entry **12**) when refluxed in ethanol, alone with these metals (in 1:1 molar proportion), were partially reduced (10–15%) to the corresponding amines after 10–12 h. However, the CuI–Zn and CuI–Al combinations turned out to be extremely efficient, and caused the deoxygenation of these substrates within 2 h. Many heteroarene *N*-oxides (entries **18–26**, Table 2), nitrone **14**[30] (Scheme 2), azoxybenzene **16**[30] (Scheme 3), aliphatic and aromatic *N*-oxides (entries **1–13**, Table 1) were deoxygenated by these two reagents in quantitative yields, but no deoxygenation of heteroarene *N*-oxides was observed on changing the solvent from ethanol to THF, MeCN or DMSO even after addition of above bases.

Table 2. Deoxygenation of heteroarene *N*-oxides[a]

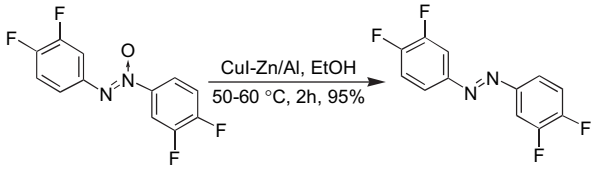
Entry	Substrate	Time (h)	Yield (%)	Product
18		2.0	96	
19		1.5	96	
20		1.5	95	
21		2.5	95	
22		3.0	70[b]	
23		3.0	75[b]	
24		2.0	96	
25		2.0	95	
26		3.0	95	

[a] All the reactions were performed using representative condition.
[b] Partial de-chlorination (10–15%) was observed.



14 15

Scheme 2.



16 17

Scheme 3.

Since most of the *N*-oxides were prepared from corresponding amines,[36] the progress of reaction was monitored on TLC to cross-match the reaction mixture with authentic samples. The starting materials (generated by standard methods) and products were characterized by spectroscopic methods where an upward chemical shift (~1 ppm) for all the protons in their ^{1}H NMR spectra was observed on conversion of *N*-oxides to corresponding amines.

Under the described reaction conditions, while the potential sensitive functional groups such as nitro, amino, azide, ester, amide, sulfone, fluoro and methyl remained unaffected, a minor de-chlorinated product (10–15%) was observed during the deoxygenation of 2-chloro and 2,6-dichloropyridine *N*-oxides (entries **22–23**, Table 2). However, surprisingly, there was no such incidence observed in the case of 2-chloroquinoline *N*-oxide (entry **26**, Table 2).

3. Conclusion

In conclusion, we have described use of inexpensive CuX (X=Cl, I), CuX–Zn and CuX–Al in deoxygenation of various *N*-oxides. The protocol offers an attractive alternative to currently used reagents. Though CuX alone effectively deoxygenates the aliphatic and aromatic *N*-oxides in aprotic solvents at lower temperature (30–50 °C), the CuX–Zn and CuX–Al systems require refluxing the substrates, viz. nitrone, azoxybenzene and heteroarene *N*-oxides in ethanol at 50–60 °C. The reagents are mild, efficient, safe to delicated groups, environmentally benign, and do not involve any prior preparation.

4. Experimental

4.1. General

Solvents and reagents (LR grade) were used in the reactions without distillation/purification. Reactions were monitored

by thin-layer chromatography (TLC) using silica gel plates (60 F_{254}; Merck), visualizing with ultraviolet light or iodine spray. The yields are un-optimized. IR spectra were recorded on Perkin–Elmer FT-IR 1650 spectrometer. ^{1}H NMR experiments were performed at Varian Gemini 200 spectrometer and their chemical shifts are reported in δ units with respect to TMS as an internal standard. Mass spectra were recorded on HP-5989A spectrometer. All the analyses were performed at Analytical Research Division of Discovery-Research, Dr. Reddy's Laboratories Ltd.

4.1.1. 4-(4-Nitrophenyl) thiomorpholine 1,1-dioxide[36a] (representative procedure for the deoxygenation of aliphatic and aromatic *N*-oxides, Table 1). 4-(4-Nitrophenyl) thiomorpholine 1,1,4-trioxide (entry **3**, 500 mg, 1.83 mmol), dissolved in THF (5 mL), was added with CuI (350 mg, 1.83 mmol) and *N*,*N*-diisopropylethylamine (237 mg, 1.83 mmol), and the reaction mixture was stirred at 25–30 °C for 1 h. The reaction mixture was filtered and washed with THF (3 mL). The filtrate was concentrated and the gummy mass was stirred with a mixture of ice-water and ammonia (1:1; 2.0 mL) for 0.5 h. The content was extracted with ethyl acetate and the combined organic layers were washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford a viscous mass, which on trituration with a minimum quantity of dichloromethane and petroleum ether (1:1) afforded pure 4-(4-nitrophenyl) thiomorpholine 1,1-dioxide (423 mg, 90%). IR (KBr) 2955, 1518, 1468, 1367, 1334, 1305 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (d, J=8.4 Hz, 2H, Ar), 7.18 (d, J=8.4 Hz, 2H, Ar), 4.05–3.85 (m, 4H), 3.00–2.80 (m, 4H). MS (CI method) 257 (M+H)$^+$, 238, 185, 141.

4.1.2. 4-(2-Fluoro-4-nitrophenyl) thiomorpholine 1,1-dioxide.[36b] Product obtained in entry **4**. IR (KBr) 3102, 3012, 2952, 1539, 1470, 1368, 1330, 1298 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06–7.95 (m, 2H, Ar), 7.02 (t, J=9.0 Hz, 1H, Ar), 3.82 (t, J=5.6 Hz, 2H), 3.22 (t, J=5.6 Hz, 2H). MS (CI method) 275 (M+H)$^+$, 259, 245, 209, 163.

4.1.3. 1-(2-Fluoro-4-nitrophenyl) pyrrolidine.[36b] Product obtained in entry **7**. IR (KBr) 2955, 1517, 1458, 1347, 1308 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (t, J=8.8 Hz, 1H, Ar), 7.45–7.40 (m, 1H), 6.95–6.90 (m, 1H), 2.89–2.75 (m, 4H), 1.98–1.72 (m, 4H). MS (CI method) 211 (M+H)$^+$, 178, 139.

4.1.4. 1-(2,6-Difluoro-4-nitrophenyl) pyrrolidine.[36b] Product obtained in entry **8**. IR (Neat) 2978, 2855, 1603, 1515, 1335 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (t, J=8.6 Hz, 1H, Ar), 6.95 (t, J=8.8 Hz, 1H, Ar), 3.30 (m, 4H), 1.85–1.60 (m, 4H). MS (CI method) 229 (M+H)$^+$, 219, 208, 177, 167, 137.

4.1.5. 4-(4-Azido-2-fluorophenyl) thiomorpholine 1,1-dioxide.[36c] Product obtained in entry **10**. IR (Neat) 2933, 2851, 2116, 1575, 1508, 1305 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, J=8.6 Hz, 1H, Ar), 6.79–6.75 (m, 2H, Ar), 3.57 (t, J=5.2 Hz, 2H), 3.20 (t, J=5.2 Hz, 2H). MS (CI method) 271 (M+H)$^+$, 245, 242.

4.1.6. CAS nos. of the product. CAS nos. of the product obtained in: (a) entry **5** [16155-03-6], (b) entry **6** [10220-22-1], (c) entry **9** [2632-65-7], (d) entry **11** [824-21-5], (e) entry **12** [933-94-8], (f) entry **13** [702-11-4].

4.1.7. Representative procedure for the deoxygenation of nitrones, azoxybenzenes and heteroarene *N*-oxides (Table 2 and Schemes 2 and 3). Quinaldine *N*-oxide (entry **25**; 500 mg, 3.14 mmol), dissolved in absolute ethanol (5 ml), was added with CuI (597 mg, 3.14 mmol) and Zn-powder (204 mg, 3.14 mmol), and the reaction mixture was refluxed at 55–60 °C for 2 h. After completion, the reaction was brought to room temperature and the content was filtered. The filtrate was poured over ice-water, stirred with aqueous ammonia and extracted with ethyl acetate. The combined organic layers were washed with water, dried (anhydrous Na_2SO_4) and evaporated to afford a viscous mass, which on trituration with minimum quantity of petroleum ether afforded pure quinaldine (427 mg, 95%). Similar results were obtained when the same molar proportion of aluminium was used in the reaction. All the products were confirmed by spectroscopic analyses (IR, ^{1}H NMR and MS) and by comparing the data available in the literature.[36]

4.1.8. (4-Fluoro-benzylidene)-*p*-tolyl-amine 15.[30] IR (Neat) 3015, 2141, 1565, 1503, 1317 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.35–7.24 (m, 4H, Ar), 7.02 (d, J=7.6 Hz, 2H, Ar), 6.78 (d, J=7.6 Hz, 2H), 2.16 (s, 3H). MS (CI method) 214 (M+H)$^+$, 105.

4.1.9. Bis-(3,4-difluorophenyl) diazene 17.[30] IR (KBr) 2945, 2125, 1548, 1402, 1343 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.50 (m, 4H, Ar), 7.15–7.05 (m, 2H, Ar). MS (CI method) 255 (M+H)$^+$, 128.

4.1.10. CAS nos. of the products. CAS nos. of the product obtained in: (a) entry **19** [109-06-8], (b) entry **20** [2459-07-6], (c) entry **21** [1452-77-3], (d) entry **22** [109-09-1], (e) entry **23** [2402-78-0], (f) entry **24** [91-22-5], (g) entry **25** [91-63-4], (h) entry **26** [612-62-4].

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