

Synthesis of *N*-Alkoxy Amines *via* Catalytic Oxidation of Hydrocarbons

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Abstract: Sterically hindered *N*-alkoxy amines **3** are synthesized in good yields by coupling nitroxides **2** with hydrocarbyl radicals generated in situ by *t*-BuOOH hydrogen abstraction from hydrocarbons. The reaction is catalyzed by copper halides as well as by onium iodides.

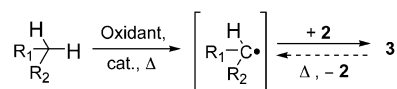
Keywords: *N*-alkoxy amines; *tert*-butyl hydroperoxide; copper; hydrocarbons; nitroxides; oxidation; phase-transfer catalysis; radical reactions; TEMPO

Introduction

Sterically hindered amines (**1**, Scheme 1) are used as additives to prevent photo-oxidation of polyolefins. Their mode of action is believed to involve formation of the nitroxide **2**, a very efficient trap for carbon-centered radicals. The resulting *N*-alkoxy amine **3** in turn may scavenge peroxy radicals to regenerate the nitroxide (Denisov cycle).^[1]

In the past few years, *N*-alkoxy amines have attracted interest as low-basicity analogues of **1** and as polymerization regulators.^[2] A possible way to prepare *N*-alkoxy amines is to generate carbon-centered radicals in presence of nitroxides, e.g., *via* hydrogen atom abstraction from a suitable substrate provided by an oxidant (Scheme 2). Such a process would be extremely attractive both from an economic and ecological point of view. An early process is based on the MoO₃-catalyzed decomposition of *t*-BuOOH, leading to the formation of *t*-BuO• radicals.^[3] The reaction requires relatively high temperatures (up to 100 °C) but allows direct coupling of nitroxides with simple hydrocarbons. However,

the accessibility of *N*-alkoxy amines *via* this process is largely determined by their stability with respect to thermal cleavage (retro-reaction, Scheme 2) and in practice is limited to R¹, R² = H, alkyl. Thus, a process that would allow preparation of *N*-alkoxy amines with lower C–O bond dissociation energy (e.g., R¹ or R² = phenyl, vinyl) was highly desirable.

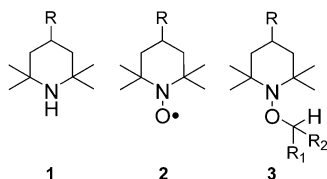


Scheme 2. Formation of *N*-alkoxy amines (**3**) by trapping hydrocarbyl radicals with nitroxides (**2**).

Results and Discussion

Copper Halides as Catalyst^[4]

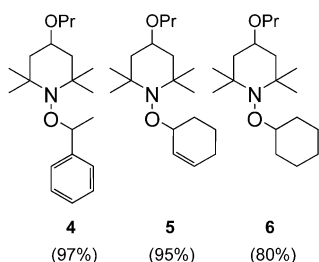
Using a model reaction based on TEMPO (2,2',6,6'-tetramethylpiperidine *N*-oxide **2**, R = H), ethylbenzene and *t*-BuOOH, numerous transition metal salts and oxides have been screened as catalyst. Most of them give only modest yields of **3** (R = H, R¹ = Me, R² = Ph), but copper halides turned out to be highly active. Thus, with as low as 0.05 mol % CuCl₂ and under non-aqueous conditions, high yields (>80%) of *N*-alkoxy amine **3** were obtained at 60 °C. Allylic and non-activated hydrocarbons (e.g., cyclohexene, cyclohexane) were found to work equally well, with 4-propoxy substituents being tolerated (Scheme 3). Running the model reaction at similarly low catalyst loadings (0.05 mol %), but with



Scheme 1. *N*-Oxides (**2**, nitroxides) and *N*-alkoxides (**3**, NOR) of sterically hindered amines (**1**).

Table 1. CuBr₂-catalyzed reaction of TEMPO (**2**, R=H) with ethylbenzene (10 equivs.) at 60 °C using aqueous 70% *t*-BuOOH (3 equivs.); effect of added phase-transfer catalyst (PTC).^[a]

Entry	CuBr ₂ [equivs.]	PTC [equivs.]	Yield [%] ^[b]	Conversion [%] ^[b]
1	0.0005	None	35	48
2	0.0005	Bu ₄ NBr [0.01]	73	92
3	0.0005	Oct ₃ NMeBr [0.01]	78	100
4	0.01	None	83	100

^[a] Results based on 3.2 mmol scale.^[b] Yield of *N*-alkoxy amine **3** (R=H, R¹=Me, R²=Ph) and conversion of TEMPO after 1 h/60 °C, respectively.**Scheme 3.** Synthesis of *N*-alkoxy amines **4** to **6** from nitroxide **2** (R=O-propyl), hydrocarbons and *t*-BuOOH/(cat.) CuCl₂. Conditions (4 mmol scale): nitroxide (1 equiv.), hydrocarbon (11.7 equivs.), *t*-BuOOH (53.4% in decane, 6.9 equivs.), 60 °C, CuCl₂ (1 equiv.), time (**4**: 0.0005 equiv., 60 min; **5**: 0.0005 equiv., 12 min; **6**: 0.0019 equiv., 200 min); yields (crude) given in parenthesis.

aqueous 70% *t*-BuOOH instead, caused the yield to drop to 35% (Table 1, Entry 1) unless some phase-transfer catalyst was added (Table 1, Entry 2). Alternatively, yields could be improved by increasing the copper concentration (Table 1, Entry 4). Thus, 0.05 mol % CuBr₂/1 mol % Bu₄NBr was found to be about equally effective as 1 mol % CuBr₂. The more hydrophobic Oct₃NMeBr did not give much better results compared to Bu₄NBr (Table 1, Entry 3 *versus* 2). Cupric and cuprous ions were found to be similarly effective, but for the reaction to work some halide counter ions (chloride, bromide) from either the copper or the tetraalkylammonium cation need to be present. Thus, CuSO₄ did not work unless some Bu₄NBr was added. Bu₄NHSO₄ on the other hand was not effective as phase-transfer catalyst, the activity of CuBr₂ being largely the same whether or not Bu₄NHSO₄ was added.

Onium Iodides as Catalyst^[5]

Bu₄NBr by itself was found to be active as catalyst. Thus, in the absence of any copper salt and under the conditions shown in Table 1, Bu₄NBr gave about 10% product. Running the reaction without any additive gave no product at all. Surprisingly, however, Bu₄NI exhibited similar catalytic activity as compared to CuBr₂ (Table 2, Entry 4), the order of decreasing activity being I >

> Br ≈ Cl. Fluoride did not catalyze the reaction. Iodo compounds other than Bu₄NI gave significantly lower yields (*ca.* 10% using Bu₄NI₃, NaI, LiI, I₂ or Bu₄NOH/I₂) or no product at all [iodobenzene, Bu₄N (*o*-iodobenzoate), Bu₄NIO₃ or Bu₄NIO₄]. The more hydrophobic Oct₃NMeI exhibited similar activity as compared to Bu₄NI. The catalyst could also conveniently be prepared from, e.g., sodium iodide and a suitable onium salt (e.g., chloride, hydrogen sulfate, etc.) *via in situ* anion exchange. Immobilized onium iodides (e.g., tributylmethylammonium iodide bound to polystyrene) worked also and could be filtered off after the reaction, but the turnover frequency (TOF) was lower due to the heterogeneous nature of the reaction. Non-activated substrates like cyclohexane required higher temperatures (80 °C) for the reaction to work. TOF and yield were generally lower as compared to CuBr₂, the reaction not going to completion even after further addition of *t*-BuOOH (Figure 1). Thus, in the reaction of 4-benzoyloxy-TEMPO (**2**, R=OCOPh) to the *N*-alkoxy amine **3** (R=OCOPh, R¹–R²=pentamethylene), Ph₄PI gave the highest yield (74%; CuBr₂: 82%) and conversion (88%; CuBr₂: 95%) but at low TOF (16/h; CuBr₂: 60/h). Use of polar, inert cosolvents (chlorobenzene and the like) thought to increase the solubility of Ph₄PI did not remarkably improve TOF. Replacing a phenyl group by *i*-propyl, ethyl, hexyl or hexadecyl resulted in lower yield but higher TOF, the effect being partially paralleled by an increase of the *n*-octanol/water partition coefficients (log *K*_{ow}). Thus, maximum TOF and yield did not exceed 36/h and 61%, respectively. Similar values were found for Oct₄PI (37/h, 58%), shortening of the alkyl chains resulting in lower TOF (Bu₄PI: 29/h, 61%) and yield (Et₄PI: 15/h, 46%). A dramatic drop in yield was observed if more than two phenyl groups are replaced by methyl (PhPMe₃I: 16/h, 39%) or if the methyl group is activated (Ph₃PCH₂CO₂MeI: 16/h, 36%). Maximum TOF and yield of tetraalkylammonium iodides (Figure 2) was found to be very similar to the corresponding tetraalkylphosphonium iodides, the values depending on log *K*_{ow} rather than the accessibility (*Q*) of the ammonium cation or the reactivity of the alkyl substituents (benzyl *vs.* alkyl: OctBzI/NMe₂ ≈ Oct₃NMe).^[6] Below some threshold (log *K*_{ow} < 1.7, Bu₄NI: 29/h, 63%) TOF and yield started to decrease (Et₄NI: 14/h, 38%). Trial-

Table 2. Bu₄NHal (0.01 equiv.) catalyzed reaction of TEMPO (**2**, R=H) with ethylbenzene (10 equivs.) at 60 °C using aqueous 70% *t*-BuOOH (3 equivs): effect of halide (absence of copper).^[a]

Entry	Hal	Yield [%] ^[b]	Conversion [%] ^[b]
1	F	—	—
2	Cl	9	2.5
3	Br	10	8
4	I	80	94

^[a] Results based on 3.2 mmol scale.

^[b] Yield of *N*-alkoxy amine **3** (R=H, R¹=Me, R²=Ph) and conversion of TEMPO after 1 h/60 °C, respectively.

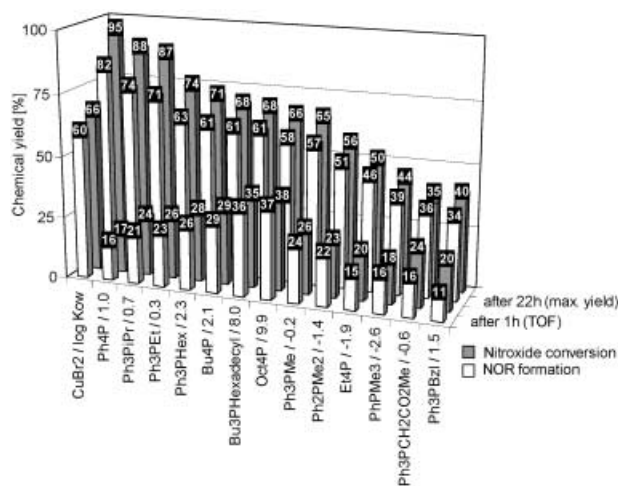


Figure 1. R₄PI (0.01 equiv.) catalyzed reaction of 4-benzoyloxy-TEMPO (**2**, R=OCOPh) with cyclohexane (10 equivs.) at 80 °C using aqueous 70% *t*-BuOOH (3 equivs.): effect of R. Results based on 3 mmol scale; log K_{ow}=*n*-octanol/water partition coefficient (calculated); the reaction with Ph₄PI as catalyst was repeated on a 35 mmol scale to afford after chromatography 63% of *N*-alkoxy amine **3** (R=O₂CPh, R¹=R²=pentamethylene).

kylsulfonium iodides showed the lowest activity (Oct₂SMel: 4/h, 12%). Running the reaction under non-aqueous conditions (*t*-BuOOH 70% in cyclohexane, molecular sieve) was found to increase TOF, but the yield was not affected as demonstrated with Ph₄PI (18/h, 76%; aqueous: 16/h, 74%) and Bu₄NI (52/h, 62%; aqueous: 29/h, 63%). Higher catalyst loadings increased TOF but at the expense of yield.

Comparison of pH Profiles

The redox chemistry of halides being pH dependent it was speculated that the iodide-catalyzed reaction might exhibit a distinctive pH optimum, thus allowing for the reaction to be further optimized. First, the pH and product formation of the Bu₄NI-catalyzed model reaction was

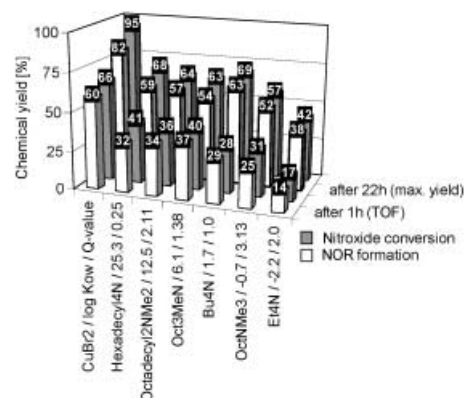


Figure 2. R₄NI (0.01 equiv.) catalyzed reaction of 4-benzoyloxy-TEMPO (**2**, R=OCOPh) with cyclohexane (10 equivs.) at 80 °C using aqueous 70% *t*-BuOOH (3 equivs): effect of R.

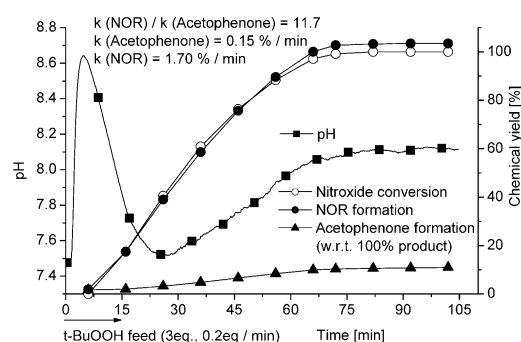


Figure 3. Overlaid plots of pH, *N*-alkoxy amine (NOR) formation, acetophenone formation and nitroxide conversion versus time for the reaction of TEMPO (**2**, R=H, 1 equiv.) and ethylbenzene (10 equivs.) with *t*-BuOOH aq. 70% (3 equivs.)/Bu₄NI (0.01 equivs.) at 60 °C (absence of copper). Results based on 6.4-mmol scale.

monitored and plotted versus time. Results are shown in Figure 3. *t*-BuOOH feed is paralleled by a sharp increase in pH from 7.5 (0% fed) to 8.6 (50% fed), followed by a decrease down again to 7.5 (100% fed). This effect is specific for the iodide/*t*-BuOOH interaction, the pH of 70% aqueous *t*-BuOOH itself being slightly acidic. As the reaction progresses the pH slowly increases from 7.5 to finally 8, presumably due to the slightly basic product. There is clear evidence of an induction period, no product being formed until about 50% of *t*-BuOOH has been introduced. A plot of % product formation versus time is linear between 10% and 80% and the rate was calculated assuming zero-order kinetics to give $k = 1.70\%/min$ (TOF = 102/h, TON = 100). No gap between product formation and TEMPO conversion is seen. The reaction is accompanied by the formation of acetophenone ($k = 0.15\%/min$) as major side product, the total amount at 100% TEMPO conversion being 9% (relative to 100% product). A similar increase and decrease in pH during

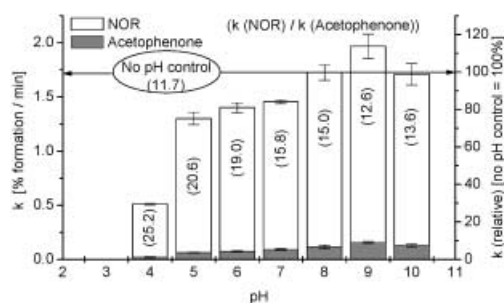


Figure 4. Plot of *N*-alkoxy amine (NOR) and acetophenone formation rates and their ratio as a function of pH for the reaction of TEMPO (**2**, R=H, 1 equiv.) and ethylbenzene (10 equivs.) with *t*-BuOOH aq. 70% (3 equivs.)/Bu₄NI (0.01 equiv.) at 60 °C (absence of copper).

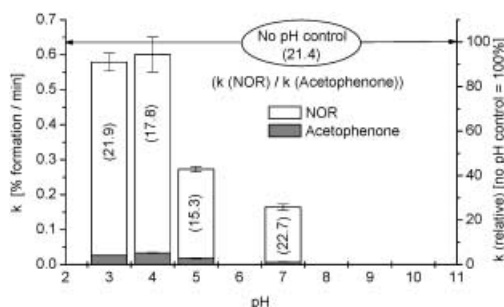


Figure 5. Plot of *N*-alkoxy amine (NOR) and acetophenone formation rates and their ratio as a function of pH for the reaction of TEMPO (**2**, R=H, 1 equiv.) and ethylbenzene (10 equivs.) with *t*-BuOOH aq. 70% (3 equivs.)/CuCl₂ (0.1 molar) at 60 °C.

t-BuOOH feed is seen for the reaction catalyzed by CuCl₂.

To monitor the pH profile, the model reaction was run at different pH values kept constant during addition of *t*-BuOOH and throughout the reaction. Rates were calculated as above assuming zero-order kinetics and then plotted *versus* pH. Results are shown in Figure 4. The pH profile exhibits a flat maximum at pH 9, *k* being 10% higher only as compared to the reaction lacking pH control. As the pH gets more acidic, *k* decreases by about 20% (pH 7) and 70% (pH 4). The ratio of product over acetophenone formation rate is very similar between pH 10 and 7 but gets higher at lower pH.

The CuCl₂ catalyzed model reaction exhibits a complementary pH profile (Figure 5). There is no distinctive maximum, *k* being constant at pH 3 and 4. If the pH is raised to 5, precipitation of the catalyst starts and *k* drops by 60%. This drop is not seen in presence of phase-transfer catalyst (Figure 6). At pH 4, *k* is about four times higher compared to the reaction lacking any phase-transfer catalyst. However, at the same time the acetophenone formation rate is about twenty times higher, resulting in up to 27% acetophenone at the end of the reaction.

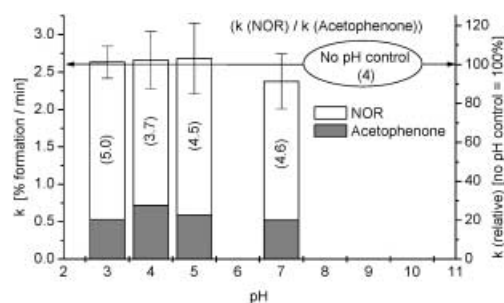


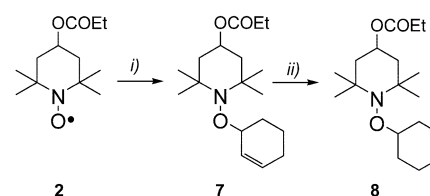
Figure 6. Plot of *N*-alkoxy amine (NOR) and acetophenone formation rates and their ratio as a function of pH for the reaction of TEMPO (**2**, R=H, 1 equiv.) and ethylbenzene (10 equivs.) with *t*-BuOOH aq. 70% (3 equivs.)/CuCl₂ (0.1 molar) at 60 °C: effect of added phase-transfer catalyst (Oct₃NMeCl, 0.01 equiv.).

Stability of *N*-Alkoxy Amines Towards Oxidation

The C–H bonds alpha to the oxygen of the *N*-alkoxy amine group are activated with respect to hydrogen atom abstraction, thus rendering the product more prone towards oxidation compared to the substrate. As long as the substrate is used in large excess, over-oxidation is not an issue. However, as the excess is lowered below some threshold (about 3 equivalents), product oxidation increasingly occurs. This was demonstrated with *N*-alkoxy amine **3** (R=H, R¹=Me, R²=Ph), acetophenone and the amine **1** being formed as main products.

Hydrogenation of *O*-Cycloalkenylhydroxylamines

Taking into account the somewhat lower reactivity of onium iodides compared to copper halides in the coupling of nitroxides with non-activated hydrocarbons, the latter coupling products can also be synthesized *via* hydrogenation of initially formed reaction products with ethylene-type unsaturated hydrocarbons such as *O*-cycloalkenyl hydroxylamines, accessible in good yields *via* onium iodide catalysis. Thus, *O*-cyclohexenyl hydroxylamine **7**, synthesized in good yield using



Scheme 4. Synthesis of *N*-alkoxy amines **7** and **8** from nitroxide **2** (R=OCOEt), cyclohexene and *t*-BuOOH/(cat.) Bu₄NI followed by hydrogenation. Conditions: i) cyclohexene (10 equivs.), *t*-BuOOH aq. 70% (1.5 equivs.), Bu₄NI (0.01 equivs.), 60 °C, 88% (crude); ii) hexane, 10% Pd/C (0.05 equivs.), 25 °C, H₂ (4 bar), 91% (crude).

Bu₄NI as catalyst, was hydrogenated to afford *N*-alkoxy amine **8** (Scheme 4).

Discussion

The *t*-BuOOH/copper halide/Bu₄NBr system has been investigated in detail by Sasson who reported the oxidation of π -activated methylenes such as tetraline (1,2,3,4-tetrahydronaphthalene) affording 1-*t*-butylperoxytetralin as main product.^[7] Although there is no mechanistic evidence presented in the article, it is likely that hydrogen abstraction by *t*-BuO• radicals is the rate-determining step, the formation of *t*-BuO• and *t*-BuOO• radicals from *t*-BuOOH/Cu being well documented.^[8] The efficient formation of *N*-alkoxy amines can be explained by the high trapping rate and concentration of nitroxyl relative to *t*-BuOO• radicals. Indeed, only minor amounts of the corresponding *t*-butyl-(1-methyl-1-benzyl) peroxide could be detected, acetophenone being the main side product. The latter may result from oxidation of initially formed *t*-butyl-(1-methyl-1-benzyl) peroxide or the *N*-alkoxy amine.

The use of aqueous *t*-BuOOH results in the formation of a two-phase system, TEMPO (log $K_{ow} \approx 2$) and *t*-BuOOH (log $K_{ow} \approx 1$) largely being in the organic (ethylbenzene) phase and the copper halide being in the water phase. As expected pH and transport of the catalyst across the phase boundary play important roles. Thus, the results in Table 1 match with the respective pH profiles recorded in absence and presence of phase-transfer catalyst (Figures 5 and 6). At low catalyst loadings (0.05 mol %; Table 1, Entry 1) the pH of the water phase shifts during the reaction from slightly acidic (pH 4.5) to slightly basic (pH 7.5), the shift being paralleled by the precipitation of hydrolyzed catalyst; at higher catalyst loadings (1 mol %; Table 1, Entry 4; [CuBr₂] $\approx$ 0.1 molar at the end of *t*-BuOOH feed) the pH shift is much smaller, i.e., from pH 4 to pH 4.2, the catalyst largely remaining dissolved (Figure 5).

In the presence of a phase-transfer catalyst (Table 1, Entries 2 and 3) the drop in product formation rate, which is observed in the absence of phase-transfer catalyst when going from pH 4 to pH 7, does not occur. Moreover, addition of a phase-transfer catalyst results in a rate increase (fourfold with 1 mol % Oct₃NMeCl at pH 4, Figures 5 and 6). This indicates that *i*) rates primarily depend on the catalyst concentration in the organic phase, *ii*) both CuCl₂ and hydrolyzed CuCl₂ exhibit similar catalytic activity in presence of a phase-transfer catalyst and *iii*) in the absence of a phase-transfer catalyst and compared to CuCl₂, the lower reactivity of hydrolyzed CuCl₂ is due to its lower solubility in the organic phase. It is therefore reasonable to assume that the reaction takes place in the organic phase. This conclusion is supported by the kinetics of the model reaction (Table 1), i.e., in the absence of phase-transfer catalyst the

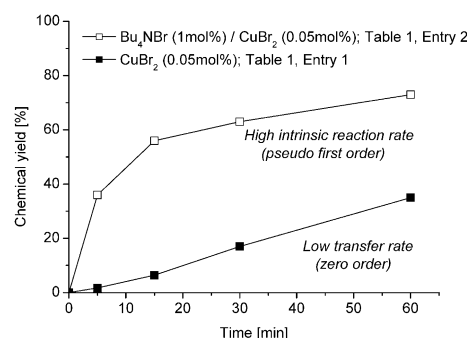
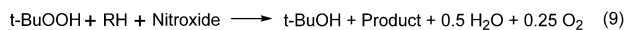
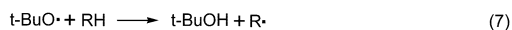
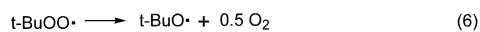
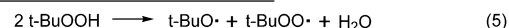
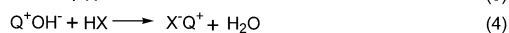
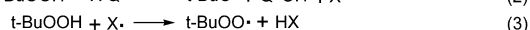
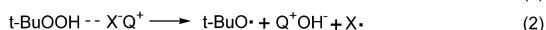
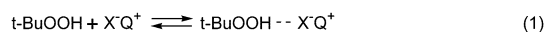


Figure 7. CuBr₂-catalyzed reaction of TEMPO (**2**, R=H) with ethylbenzene (10 equivs.) at 60 °C using aqueous 70% *t*-BuOOH (3 equivs.): effect of added phase-transfer catalyst on the *N*-alkoxy amine formation rate (Table 1, Entries 1 and 2).

transport of Cu catalyst into the organic phase becomes rate determining (Figure 7). It has been shown that Bu₄NBr efficiently extracts metal salts and even metal hydroxides, presumably *via* the formation of hydrogen bond complexes.^[7]

Some years earlier Sasson published a paper describing the decomposition of tetraline hydroperoxide (1,2,3,4-tetrahydronaphthalene 1-hydroperoxide) by tetrahexylammonium halides affording the related alcohol and ketone, respectively.^[9] It was proposed that the O–O bond of the hydroperoxide is cleaved heterolytically *via* an initial hydrogen bond complex formation between the hydroxy group of the hydroperoxide and the anion of the onium catalyst followed by electron transfer to give alkoxy radicals, halide radicals and onium hydroxide. Hydrogen atom abstraction from the peroxide by halide radicals in the presence of the onium hydroxide would then regenerate the onium halide, building up the catalytic cycle shown in Scheme 5 [Eqs. (1)–(5)]. Assuming that the same cycle applies to the formation of *N*-alkoxy amines from nitroxide, hydrocarbon and *t*-BuOOH/onium iodide would imply that the *t*-BuO• radical is the hydrogen atom abstracting species [Scheme 5, Eqs. (6)–(9)]. In fact, ESR spectroscopic analysis of mixtures of *t*-BuOOH and Bu₄NI in ethylbenzene revealed the presence of *t*-BuOO• radicals (Figure 8), from which *t*-BuO• radicals might be formed, a process found to be catalyzed by nitroxides.^[10]

Also, the increase and decrease of pH during *t*-BuOOH feed (Figure 3) would be in line with the appearance of an intermediate basic species as suggested by Sasson's catalytic cycle [Scheme 5, Eq. (2)]. However, there are some open questions that do not exclude that with *t*-BuOOH/onium iodide the mechanism may differ from that shown in Scheme 5. Whereas in Sasson's paper the order of decreasing reactivity is Cl > Br > I, which reflects the strength of the anion hydrogen bond and the hydrogen abstraction capability of the halide radical, the order of decreasing reactivity observed in



Scheme 5. Adaptation of the catalytic cycle published by Sason et al. [Eqs. (1)–(5), X = Br, Cl] to discuss formation [Eqs. (6)–(9)] of *N*-alkoxy amines (**3**) from nitroxide (**2**), hydrocarbon (RH) and *t*-BuOOH/(cat.) onium iodide (Q^+I^- , X = I).

the synthesis of *N*-alkoxy amines is $\text{I} > \text{Br} \approx \text{Cl}$. Hydrogen atom abstraction from hydroperoxides by iodo radicals [Scheme 5, Eq. (3)] being unlikely to occur, iodide must be regenerated by some electron transfer reaction instead or, alternatively, the catalytic cycle consists of other iodo redox couples as in, e.g., the Bray–Liebhafsky reaction.^[11] The low conversions observed in the tetraalkylammonium iodide-catalyzed synthesis of *N*-alkoxy amine **3** ($\text{R} = \text{OCOPh}$, $\text{R}^1\text{--R}^2 = \text{pentamethylene}$) and the reactivity pattern observed for the phosphonium iodides indicate that catalyst deactivation takes place during the reaction. Indeed, once the reaction has stopped (Figure 2, after 22 hours) it can be restarted and brought to higher nitroxide conversions if both additional *t*-BuOOH and onium iodide are added. Catalyst deactivation may be initiated by oxidation of C–H bonds in the vicinity to the quaternary center or by Hofmann elimination induced by a temporary occurring basic species [Scheme 5, Eq. (2)]. Thus, replacement of phenyl groups in PPh_4I by long-chain alkyl groups increases solubility (and TOF), but at the expense of quat stability (and maximum yield).

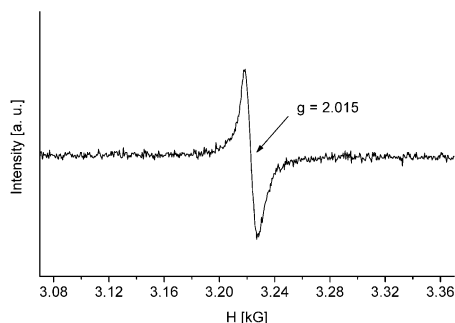


Figure 8. ESR spectrum of a solution of *t*-BuOOH in ethylbenzene after addition of Bu_4NI revealing the presence of *t*-BuOO $\cdot$ radicals ($g = 2.015$).

Conclusion

The present process provides an easy access to *N*-alkoxy amines from nitroxides, hydrocarbons and *t*-BuOOH/(cat.) onium iodide or *t*-BuOOH/(cat.) Cu(I,II)Br,Cl under mild conditions (alkenes 60 °C, alkanes 80 °C). Copper halides under non-aqueous conditions give the highest TOF. With 70% aqueous *t*-BuOOH and activated hydrocarbons (e.g., cyclohexene, ethylbenzene) copper halides are about equally active as Bu_4NI (1 mol % catalyst loadings). For non-activated hydrocarbons (e.g., cyclohexane), TOF and yield depend on the solubility and stability of the onium iodide, respectively. Thus, Ph_4PI gives similar yields but lower TOF compared to CuBr_2 . More hydrophobic long-chain tetraalkylphosphonium or tetraalkylammonium iodides give higher TOF but lower yields.

Experimental Section

General Remarks

Starting materials and catalysts were commercial grade and used as received. Yields and conversions were determined by HPLC, the reaction being run in presence of biphenyl (0.1 equiv.) as internal standard. Quantitative results are based on nitroxide (1 equiv.–0.1 equiv.)/biphenyl and *N*-alkoxy amine (0.1 equiv.–1 equiv.)/biphenyl calibration curves (peak area ratio *versus* amount ratio). Turnover number (TON) refers to number of equivalents product formed/number of equivalents catalyst used, turnover frequency (TOF) to TON/unit of time. ESR spectra were obtained on a Varian E-9 X-band spectrometer.

pH Profiles

The reaction was run in a 20-mL jacketed titration vessel (Metrohm) maintained at 60 °C by a thermostat and equipped with a magnetic stirrer. The temperature and pH were monitored by means of a Pt-1000 sensor (Metrohm) and a pH electrode (Metrohm), respectively. The pH of the aqueous phase was controlled by two (acid and base) motor-driven 1-mL burettes (GP-Titrino 736 and STAT-Titrino 718, Metrohm; smallest increment 1 μL) interfaced to a personal computer, using the Ti-NetTM 2.4 software (Metrohm) for acquisition and control. The titration procedure allowed for automatic (acid or base) set up and hold of a given pH once a desired value had been defined. The electrode was calibrated using standard buffers (pH 4, 7 and 10) at 60 °C, compensating for $\text{d}p\text{H}/\text{d}T$. Aqueous NaOH and H_2SO_4 were used to adjust and maintain the pH. The concentration was chosen so that the volume increase of the aqueous phase was less than 10% at the end of the reaction. *t*-BuOOH was fed by means of a motor-driven 5-mL burette (DOSINO 700, Metrohm) interfaced to a computer (LIQUINO 711, Metrohm). All burette tips were equipped with anti-diffusion valves. In a typical run, the titration vessel was charged with deionized water (6 g), ethylbenzene (6.8 g, 64 mmol), TEMPO (1 g, 6.4 mmol) and biphenyl (98.7 mg, 0.64 mmol).

Stirrer and thermostat were turned on. Stirring was such that the phase boundary of the two-phase system remained horizontal (800 rpm). After the mixture had reached 60 °C, burette tips for titration were introduced into the aqueous phase and the titration procedure started. After the defined pH value had been reached, Bu₄NI (23.6 mg, 0.064 mmol) was added followed by introduction of the burette tip for *t*-BuOOH (70% aqueous) feed into the organic phase. The reaction was started with the addition of *t*-BuOOH (2.64 mL, 19.2 mmol) at a constant rate (0.18 mL, 1.28 mmol/min). During all operations the pH was kept constant. Samples were withdrawn and analyzed by HPLC until conversion of nitroxide reached 100%. For the pH profile of the CuCl₂-catalyzed reaction water (6 g) was replaced by 6 mL of aqueous 0.1 molar CuCl₂ and Oct₃MeNCl as phase-transfer catalyst (25.9 mg, 0.064 mmol).

Preparation of *N*-Alkoxy Amines 7 and 8

A stirred mixture of 7.3 g (32 mmol) propionic acid 2,2,6,6-tetramethylpiperidin-4-yl *N*-oxide ester (**2**, R = OCOC₂H₅), 26.3 g (320 mmol) cyclohexene and 0.12 g (0.32 mmol) Bu₄NI kept at 60 °C was treated with 6.2 g (48 mmol) aqueous *t*-BuOOH (70%) within 25 minutes. The temperature was maintained until the red color of the nitroxide had disappeared (5 min). The reaction mixture was cooled down to 25 °C and stirred with aqueous 10% Na₂SO₃ solution to destroy excess *t*-BuOOH. The aqueous phase was split off and washed with cyclohexane. The combined organic phases were passed through a plug of silica gel and brine-washed, dried over MgSO₄, filtered and the solvent distilled off on a rotary evaporator, affording *O*-cyclohexenyl hydroxylamine **7** as slightly orange oil; yield: 8.7 g (87.9%). Analysis required for C₁₈H₃₁NO₃ (309.45): C 69.87%, H 10.10%, N 4.53%; found: C 69.36%, H 10.03%, N 4.45%; ¹H NMR (400 MHz, CDCl₃): δ = 1.12 (t, *J* = 8 Hz, 3H), 1.20–1.26 (m, 12H), 1.52–1.58 (m, 4H), 1.73–2.1 (m, 6H), 2.29 (q, *J* = 8 Hz, 2H), 4.23 (m, 1H), 5.05 (m, 1H), 5.79–5.82 (m, 1H), 5.90–5.94 (m, 1H).

A mixture of the above product (1 g, 3.19 mmol) and 0.17 g Pd on charcoal (10%) in 30 mL hexane was hydrogenated at 25 °C and 4 bar of hydrogen. Filtration and evaporation of

the solvent afforded *N*-alkoxy amine **8** as slightly yellow oil; yield: 0.9 g (89%). Analysis required for C₁₈H₃₃NO₃ (311.47): C 69.41%, H 10.68%, N 4.50%; found: C 69.20%, H 10.76%, N 4.42%; ¹H NMR (400 MHz, CDCl₃): δ = 1.09 (t, *J* = 8 Hz, 3H), 1.10–1.26 (m, 17H), 1.52–1.57 (m, 3H), 1.74–1.84 (m, 4H), 2.03–2.05 (m, 2H), 2.28 (q, *J* = 8 Hz, 2H), 3.56–3.62 (m, 1H), 4.98–5.06 (m, 1H).

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