# Generation of Alkoxyl Radicals from *N*-Alkoxy-2-pyridones

**Eunae Kim, Chang Ho Cho, and Sunggak Kim[*]**

*Department of Chemistry and Center for Molecular Design & Synthesis, School of Molecular Science (BK21),*
*Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea. [*]E-mail: skim@kaist.ac.kr*
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Alkoxyl radicals have unique characteristic properties such as a facile $\beta$-fragmentation[1] and a hydrogen abstraction[2] due to their high reactivity. Various alkoxyl radical precursors are normally prepared from alcohols and include nitrites,[3] nitrates,[4] hypohalites,[5] sulfenyl ethers,[6] and *N*-alkoxyphthalimides.[7,8] Especially, *N*-alkoxypyridine-2-thiones **3** have attracted a great deal of attention as synthetically useful alkoxyl radical precursors.[9] However, preparations of *N*-alkoxypyridine-2-thiones **3** are problematic due to competing *O*- and *S*-alkylation (eq. 1).[10] Even under carefully controlled conditions, the desired product **3** is normally obtained in poor yields with a significant amount of undesired *S*-alkylated side product **4**. In addition, the radical precursor is also unstable in light. Thus, some improved procedures have been reported, but the chemical yields were not very high.[11] Since radical precursors are needed to be stable for safe handling and better chemical yields, we have been interested in *N*-alkoxy-2-pyridones **5** as new alkoxyl radical precursors.
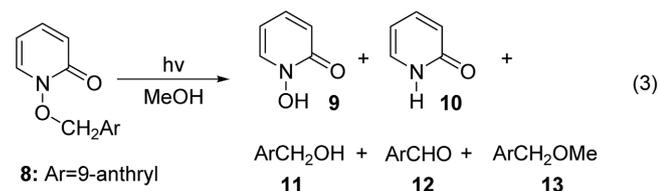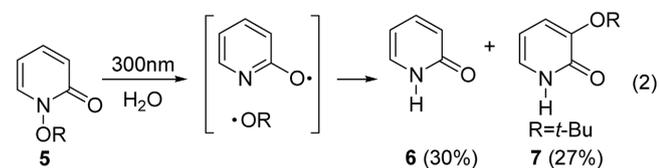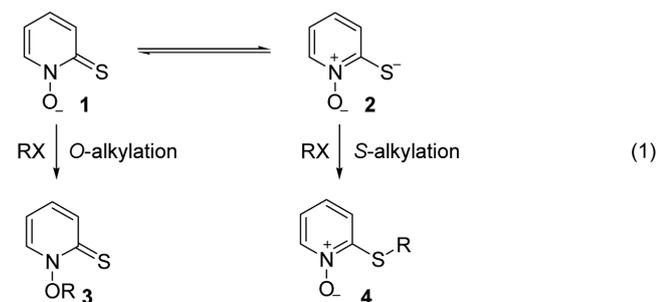


It has been known that *N*-alkoxy-2-pyridones **5** are photochemically decomposed through N-O bond cleavage to give the parent pyridone **6** and the 3-alkoxy-2-pyridone **7**

along with the recovered starting material **5** (30%) (eq. 2).[12] In the case of *N*-arylmethyloxy-2-pyridone **8**, the heterolytic C-O bond cleavage is also observed together with the homolytic N-O bond cleavage (eq. 3).[13] Furthermore, the acyl derivatives of *N*-hydroxy-2-pyridone can be utilized as a source of carbon radicals.[14] We have studied the efficiency and the scope of generation of alkoxyl radicals from *N*-alkoxy-2-pyridones **5** using tributyltin hydride and AIBN.[15]

*N*-Alkoxy-2-pyridones **5** could be conveniently prepared from *N*-hydroxy-2-pyridone (**9**)[16] by routine operations using alkyl halides or alcohols. First, treatment of sodium salt of **9** with alkyl halide **14** in DMF at 60 °C for several hours gave **5** in high yields (method A). Secondly, **5** were conveniently prepared by treatment of alcohols **15** with **9**,

**Table 1**. Preparation of *N*-Alkoxy-2-pyridones and Generation of Alkoxyl Radicals



| R-X (**14** or **15**) | Method | Yield, % **5** | Yield, % R-OH (**15**) |
|---|---|---|---|
| PhO⌒⌒⌒⌒I | A | 88 | 84 |
| Ph⌒⌒OH | B | 81 | 83 |
| TBDPSO⌒⌒⌒⌒X | A (X=Br) / B (X=OH) | 79 / 82 | 86 |
| EtO₂C⌒⌒⌒⌒X | A (X=Br) / B (X=OH) | 83 / 76 | 83 |
| Ph⌒=⌒X | A (X=Br) / B (X=OH) | 71 / 80 | 85 |
| PhCH₂O-C(O)-CH₂Br | A | 83 | 84 |
| Ph⌒⌒⌒X | A (X=Br) / B (X=OH) | 70 / 73 | 73 |
| PhCH₂O-C(O)-CH(CH₃)Br | A | 77 | 74 |
| dioxolane⌒OH | B | 84 | 82 |

**Scheme 1**

diethyl azodicarboxylate, and triphenylphosphine in THF using Mitsunobu method (method B).

Two methods were equally effective and worked well with primary, secondary, allylic, and benzylic substrates. As we expected, *N*-alkoxy-2-pyridones **5** were very stable on silica gel and on heating, and could be kept for several weeks without any decomposition. The experimental results for the preparation of **5** are summarized in Table 1.

As shown in Scheme 1, generation of alkoxyl radical **17** would be initiated by the attack of tributyltin radical onto the carbonyl oxygen and followed by the cleavage of N-O bond to generate the alkoxyl radical **17**. Treatment of **5** with *n*-Bu₃SnH (1.5 equiv.) and AIBN as initiator in refluxing benzene for 6-8 h gave the corresponding alcohols in high yield. Table 1 summarizes experimental results and shows the clean generation of alkoxyl radicals from **5**. It is noteworthy that the reactivity of *N*-alkoxy-2-pyridones **5** toward tributyltin radical was lower than that of aryl bromide group. When the radical reaction was carried out with *N*-(4-bromo-benzyloxy)-2-pyridone (**19**) under the same condition, the bromide group was selectively reduced to yield **20** (71%), whereas benzyl alcohol was obtained in 70% yield using an excess amount of *n*-Bu₃SnH (3.0 equiv.) (eq. 4). Radical reaction of **21** with *n*-Bu₃SnH and AIBN for 5 h gave 2-benzyltetrahydrofuran (**22**) in 75% yield *via* 5-*exo* ring closure of the alkoxyl radical intermediate (eq. 5).
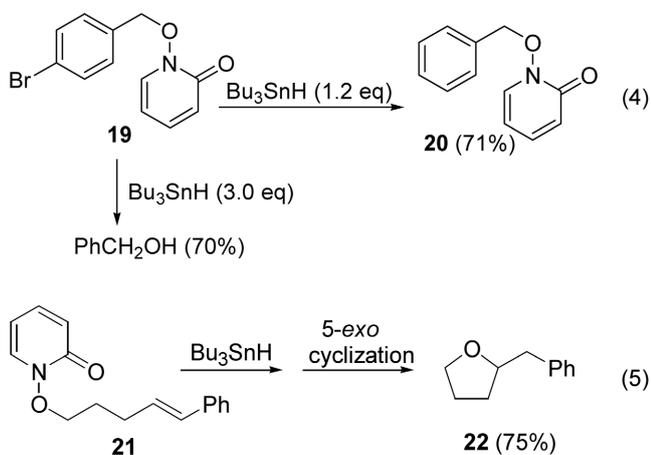




We have studied the efficiency of 1,5-hydrogen transfer from carbon to oxygen using **23**. The radical reaction of **23**



**Scheme 2**
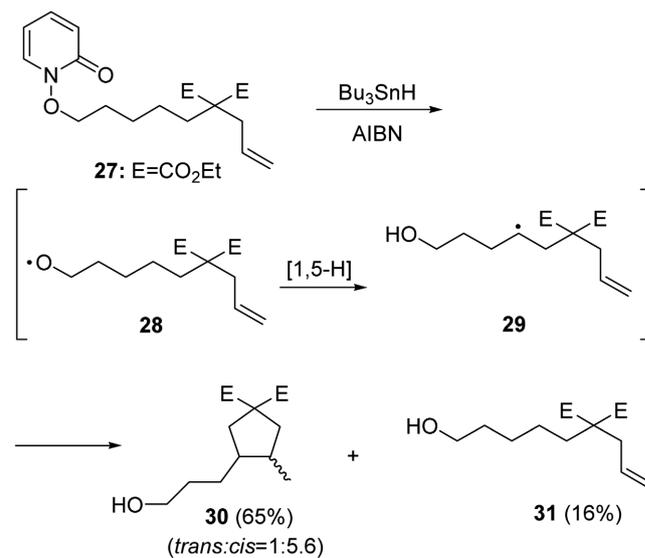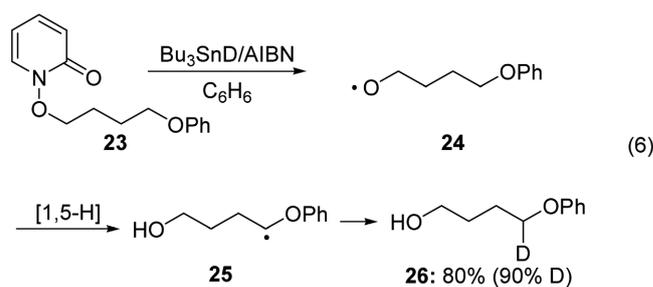
with *n*-Bu₃SnD (1.5 equiv.) and AIBN (0.2 equiv.) in refluxing benzene (0.05 M) under a high dilution afforded **26** in 80% yield with 90% deuterium exchange (eq. 6). As extension of this work, we studied the possibility of a sequential reaction involving 1,5-hydrogen atom transfer and subsequent cyclization. When the radical reaction of **27** was performed under the similar condition, the desired product **30** was isolated in 65% yield along with the direct reduction product **31** in 16% yield (Scheme 2). Evidently, 1,5-hydrogen transfer was followed by the cyclization of an alkyl radical **29** to double bond to provide **30**.

In conclusion, we have shown that readily available and stable *N*-alkoxy-2-pyridones are useful precursors of alkoxyl radicals and can complement the existing methods.

### Experimental Section

**General procedure for the synthesis of *N*-alkoxy-2-pyridones 5. Method A**: To a solution of sodium hydride (26 mg, 0.65 mmol) in dry DMF (1.5 mL) was added *N*-hydroxy-2-pyridone (**9**, 56 mg, 0.5 mmol) at 0 °C, and stirred for 1 h at room temperature. After the addition of 4-phenoxybutyl iodide (189 mg, 0.65 mmol), the mixture was stirred for 12 h at 60 °C and then diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel

*Notes*

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column chromatography (ethyl acetate/*n*-hexane = 1/1) to give *N*-(4-phenoxy-butoxy)-2-pyridone (**5**, RO = PhO(CH$_2$)$_4$O, 114 mg, 88%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.86-2.02 (m, 4H), 4.02 (t, *J* = 5.4 Hz, 2H), 4.32 (t, *J* = 5.4 Hz, 2H), 6.07-6.12 (m, 1H), 6.62-6.67 (m, 1H), 6.86-6.94 (m, 3H), 7.23-7.30 (m, 3H), 7.46-7.49 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.7, 25.6, 67.0, 76.8, 105.0, 114.4, 120.6, 122.9, 129.4, 135.9, 138.5, 158.7, 158.8; IR (ZnSe) 513, 693, 757, 1052, 1249, 1499, 1602 cm$^{-1}$; HRMS (M$^+$) Found: 259.1203, Calcd for C$_{14}$H$_{15}$NO$_2$: 259.1208.

**Method B**: To a solution of *N*-hydroxy-2-pyridone (**9**, 56 mg, 0.5 mmol), 3-phenyl-1-propanol (103 $\mu$L, 0.75 mmol) and triphenylphosphine (144 mg, 0.55 mmol) in THF (1 mL) was added diethyl azodicarboxylate (0.1 mL, 0.55 mmol) in THF (1 mL) at 0 °C under N$_2$. After being stirred for 4 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1/1) to give *N*-(3-phenyl-propoxy)-2-pyridone (**5**, RO=Ph(CH$_2$)$_3$O, 92 mg, 81%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.04 (tt, *J* = 7.8 Hz, 6.5 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 4.22 (t, *J* = 6.5 Hz, 2H), 6.04-6.07 (m, 1H), 6.61-6.65 (m, 1H), 7.16-7.29 (m, 6H), 7.40-7.43 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 29.4, 31.8, 76.4, 105.0, 122.9, 126.0, 128.4, 128.4, 135.8, 138.5, 140.9, 158.7; IR (ZnSe) 703, 754, 1540, 1669, 1965 cm$^{-1}$; HRMS (M$^+$) Found: 229.1111, Calcd for C$_{14}$H$_{15}$NO$_2$: 229.1103.

**General procedure for the generation of alkoxyl radicals from *N*-alkoxy-2-pyridones 5**. A solution of *N*-(3-phenyl-propoxy)-2-pyridone (**5**, RO=Ph(CH$_2$)$_3$O, 34 mg, 0.15 mmol), *n*-Bu$_3$SnH (61 $\mu$L, 0.225 mmol), and AIBN (0.5 mg, 0.03 mmol) in dry benzene (1 mL, 0.15 M) was degassed for 10 min with nitrogen. After being refluxed for 6 h at 80 °C, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column (ethyl acetate/*n*-hexane = 1/2) to give 3-phenyl-1-propanol (**15**, RO=Ph(CH$_2$)$_3$O, 16.9 mg, 83%).

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