Facile Generation of Alkoxy Radicals from *N*-Alkoxyphthalimides

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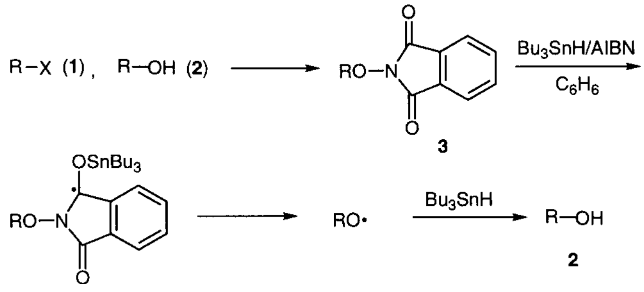
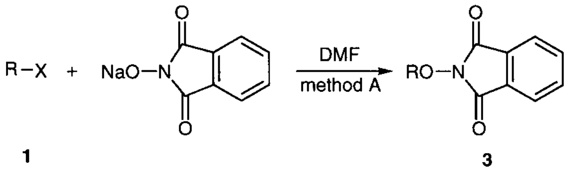
Abstract: *N*-Alkoxyphthalimides, stable and readily accessible from alcohols and alkyl halides, are found to be very efficient alkoxy radical precursors.

Alkoxy radicals have unique characteristic properties such as β-fragmentation[1] and hydrogen atom abstraction[2] due to their high reactivity, as compared with alkyl and aminyl radicals. Various precursors for the generation of alkoxy radicals are normally prepared from alcohols and include nitrites,[3] nitrates,[4] hypohalites,[5] and sulfenyl ethers,[6] in which nitrates and certain sulfenyl ethers[7] are relatively stable to be isolated. However, their preparations often require acidic conditions and/or reactive reagents which can not be compatible with other labile functional groups in the molecule. *N*-Alkoxypyridine-2-thiones have been developed as stable alkoxy radical precursors.[8] However, the selective *O*-alkylation of the sodium salt of 2-mercaptopyridine-*N*-oxide with alkyl halides is still a problem due to competing *S*-alkylation.[9] Although a new procedure for the preparation of *N*-alkoxypyridine-2-thiones has appeared recently,[10] the yields are not generally high.

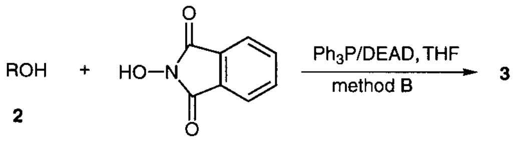
During our studies on the functionalization of unactivated C-H bonds via 1,5-hydrogen transfer from carbon to oxygen, a stable and efficient alkoxy radical precursor was needed.[11] Thus, we turned our attention to the possibility of using *N*-alkoxyphthalimides as possible alkoxy radical precursors because *N*-alkoxyphthalimides are very stable and easily accessible from alkyl halides and alcohols (Figure 1). *N*-Acyloxyphthalimides are known to generate alkyl radicals both under photolysis[12] and under the standard radical conditions using Bu_3SnH/AIBN.[13]

N-Alkoxyphthalimides were readily prepared from alkyl halides and alcohols in high yield by routine operations. Experimental results for the preparation of **3** and for the generation of alkoxy radicals from **3** are shown in Table 1. Firstly, treatment of alkyl halide **1** with the sodium salt of *N*-hydroxyphthalimide in DMF gave *N*-alkoxyphthalimide **3** in high yields (method A) (eq 1).[14] The reaction normally was complete within 10 h at room temperature and the reaction time could be considerably shortened by performing the reaction at 70 °C. Secondly, *N*-alkoxyphthalimides were prepared by treatment of alcohol **2** with *N*-hydroxyphthalimide, diethyl azodicarboxylate, and triphenylphosphine using the well-known Misunob procedure (method B) (eq 2).[15,16] Two procedures were equally effective and worked well with primary and secondary alkyl halide **1** and alcohol **2**. As we expected, *N*-alkoxyphthalimides were very stable and could be kept for several weeks without any decomposition.





(1)



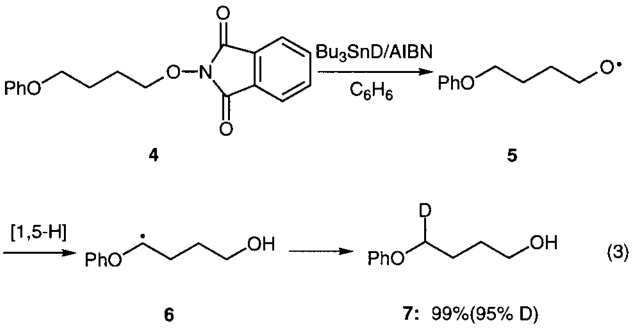
(2)

Table 1. Preparation of *N*-Alkoxyphthalimides and Generation of Alkoxy Radicals[a]

RX (**1**), ROH (**2**)	method	time,h[b]	yield,%[b] (**3**)	yield,%[c] ROH (**2**)
$PhCH_2Br$	A	10	86	95
$PhCH_2OH$	B	18	92	
$Ph(CH_2)_3Br$	A	5	63	95
$Ph(CH_2)_3OH$	B	18	84	
$Ph(CH_2)_5Br$	A	18 (3)	80 (87)	95
$PhO(CH_2)_4Br$	A	10	87	99
$PhO(CH_2)_4I$	A	7	92	
$NC(CH_2)_4Br$	A	16 (2)	81 (82)	91
trans-$PhCH{=}CHCH_2Br$	A	10	81	90
trans-$PhCH{=}CHCH_2Br$	B	18	91	
trans-$PhCH{=}CHCHOHCH_3$	B	18	75	91
$CH_3CHBrCO_2CH_2Ph$	A	6	91	92
$Ph(CH_2)_2CHBrCH_2CH_3$	A	(6)	(62)	93
$Ph(CH_2)_2CHOHCH_2CH_3$	B	20	26	
$Ph(CH_2)_2CHICH_3$	A	(2)	(78)	91
$HO(CH_2)_6Br$	A	14	65	93

[a] The yield refers to the isolated yield. [b] The numbers in the parentheses indicate the reaction time and the yield at 70 °C. Otherwise, the reaction was carried out at room temperature. [c] The reaction was complete within 2 h

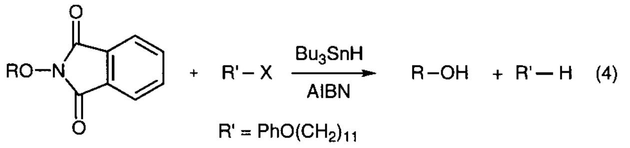
We began our studies with *N*-alkoxyphthalimide **4**. Radical reaction of **4** with Bu_3SnD/AIBN in refluxing benzene under a high dilution afforded **7** in 99% yield (95% deuterium exchange), resulting from the generation of alkoxy radical **5** and the subsequent 1,5-hydrogen transfer from carbon to oxygen (eq 3). Encouraged by this result, we carried out several experiments to examine the reactivity of *N*-alkoxyphthalimides relative to other radical precursors toward tributyltin radical. Treatment of an equimolar amount of *N*-alkoxyphthalimide **8** and alkyl bromide **9a** with Bu_3SnH/AIBN afforded alcohol **10** (9%) and reduction product **11** (88%) (eq 4), indicating that **8** was much less reactive than bromide **9a**. However, **8** was more reactive than phenylselenide **9b.** Table 1 summarizes experimental results and shows the clean generation of alkoxy radicals from the corresponding *N*-alkoxyphthalimides under the standard conditions (Bu_3SnH/ AIBN).[17] The reaction was complete within 2 h in refluxing benzene and the yields were consistently high. Radical cyclization of an alkoxy radical onto the double bond was successfully carried out with **12** to afford 2-benzyltetrahydrofuran (**13**) in 93% yield (eq 5). We also found that *tris*(trimethylsilyl)silane[18] was equally effective for the generation of alkoxy radicals from *N*-alkoxyphthalimides (eq 6).



4 **5**

6 **7**: 99%(95% D)

(3)

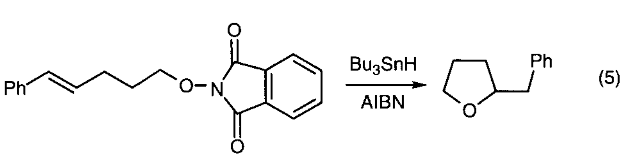


(4)

R' = $PhO(CH_2)_{11}$

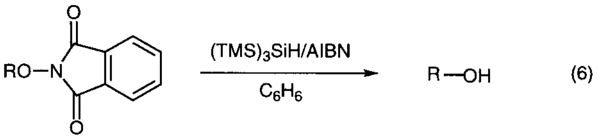
8: R = $Ph(CH_2)_5$ **9a**: X = Br **10** (9%) **11** (88%)

9b: X = SePh (90%) (10%)



(5)

12 **13** (93%)



(6)

8: R = $Ph(CH_2)_5$ **10** (85 %)

14: R = $CN(CH_2)_4$ **15** (90 %)

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(14) Method A: To a solution of *N*-hydroxyphthalimide (200 mg, 1.2 mmol) and sodium hydride (64 mg, 1.6 mmol) in DMF (4 ml) was added 5-bromovaleronitrile (195 μl, 1.6 mmol) at 25 °C under N_2. After being stirred for 16 h at room temperature, the reaction mixture was diluted with water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by passing through a column of silica gel using an eluent (2:1, n-hexane-ethyl acetate) to give *N*-alkoxy phthalimide **3** ($RO=NC(CH_2)_4O$, 242 mg, 81 %). ^1H-NMR (200 MHz, $CDCl_3$) δ 1.86-1.93 (m, 4H), 2.49 (t, J=6.9 Hz, 2H), 4.20 (t, J=5.6 Hz, 2H), 7.69-7.81 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.6, 21.8, 26.8, 76.9, 119.4, 123.4, 128.6, 134.5, 163.4; IR (KBr) 3098, 2952, 2239, 1789, 1727, 1462, 1130, 700 cm^{-1}.

(15) Method B: To a solution of *N*-hydroxyphthalimide (40 mg, 0.26 mmol), benzyl alcohol (38 μl, 0.38 mmol) and triphenyl-phosphine (74 mg, 0.28 mmol) in THF (1.5 ml) was added diethyl azodicarboxylate (45 μl, 0.28 mmol) in THF (0.6 ml) at 25 °C under N_2. After being stirred for 18 h at room temperature, the reaction mixture was diluted with water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by passing through a column of silica gel using an eluent (2:1, n-hexane-ethyl acetate) to give *N*-alkoxyphthalimide **3** ($RO=PhCH_2O$, 58 mg, 92 %). ^1H-NMR (200 MHz, $CDCl_3$) δ 5.19 (s, 2H), 7.34-7.77 (m, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 79.8, 123.4, 128.5, 128.8, 129.3, 129.8, 133.6, 134.3, 163.4; IR (KBr) 3076, 2954, 1789, 1730, 1382, 1131, 976, 698 cm^{-1}.

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(17) General procedure for the generation of alkoxy radicals from *N*-alkoxyphthalimides **3**. To a solution of *N*-alkoxyphthalimide **3** ($RO=PhCH_2O$, 60 mg, 0.24 mmol) and AIBN (6 mg) in benzene (4.8 ml, 0.05 M) was added Bu_3SnH (72 μl, 0.26 mmol). The reaction mixture was degassed for 20 min with nitrogen. After being refluxed in refluxing benzene for 2 h, the reaction mixture was concentrated and purified by silica gel column chromatography to give benzyl alcohol (24.6 mg, 95 %).

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