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Facile Barton–McCombie Deoxygenation of Alcohols with Tetrabutylammonium Peroxydisulfate and Formate Ion

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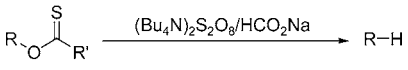
ABSTRACT



R = alkanes, R' = OMe, OPh, or imidazolyl

A new method for efficient radical deoxygenation of alcohols is described for preparing bulk chemicals avoiding scale-up problems. Treatment of various thiocarbonyl derivatives with $(Bu_4N)_2S_2O_8$ and HCO_2Na in DMF afforded the corresponding deoxygenated products in excellent yields. The deoxygenation appears to be initiated by the transfer of a single electron to thiocarbonyl derivatives from $CO_2^{\bullet -}$ rather than from $SO4^{\bullet -}$.

Radical deoxygenation of aliphatic alcohols is useful and important in organic synthesis. One of the most well-known methods is described by Barton and co-workers.[1] It utilizes the combination of the radicophilic nature of the thiocarbonyl group of thionocarbonates and xanthates and Bu_3SnH.[2] Although Bu_3SnH is the reagent most commonly used for effecting this reduction, it has some drawbacks related to the toxic organotin compounds.[3]

Considerable efforts have been made to devise more acceptable replacements such as silanes,[4] dialkyl phosphates,[5] and hypophosphorous acid and its salts[5] instead of the tin hydride. Despite these efforts and in consideration of the prices of reagents, the control in radical reactions, and the simplicity of product separation, new methods for efficient and cost-effective deoxygenation processes are still in demand especially for preparing bulk chemicals avoiding scale-up problems.

Among the known deoxygenation reactions, suitable hydrogen atom sources are inevitably used in combination with proper radical initiators such as AIBN and peroxides. The explosive property of AIBN and peroxides is another drawback of this kind of radical reaction. Thus the reaction control is also difficult in large-scale synthesis.[6]

It is reported that ethyl carbon radical generated from Et_3B−air interacts with the thiocarbonyl group in xanthate and drives the deoxygenation, although yields are somewhat low.[7a] Additionally, undecyl carbon radicals arising from the thermolysis of the lauroyl peroxide were used for the same reaction.[7b] Formation of carbon dioxide radical anion ($CO_2^{\bullet -}$) is reported by the reaction of the one-electron oxidant ammonium peroxydisulfate and HCO_2Na.[8]

In our earlier work, tetrabutylammonium peroxydisulfate ($(Bu_4N)_2S_2O_8$) was readily prepared by mixing 2 equiv of tetrabutylammonium hydrogen sulfate and potassium per-

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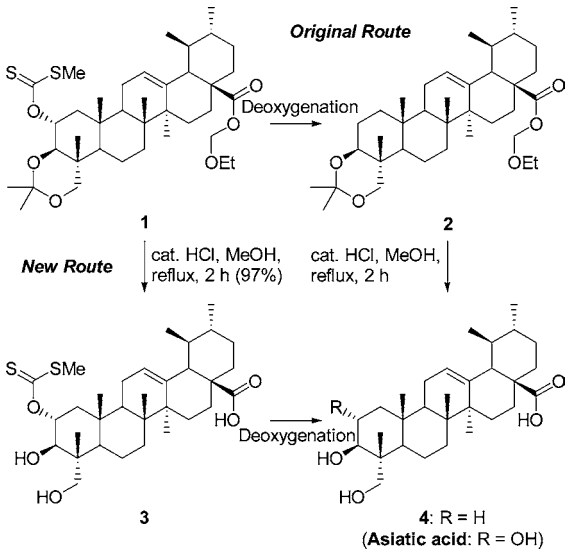
sulfate in water followed by extraction with methylene dichloride.[9] In contrast to metal or ammonium peroxydisulfate, $(Bu_4N)_2S_2O_8$ is readily soluble in organic solvents such as acetonitrile, DMF, acetone, CH_2Cl_2, $CHCl_3$, and ethyl ether. Radicophilic cleavage of thiocarbonyl derivatives has been examined using $(Bu_4N)_2S_2O_8$ and HCO_2Na as a new alkyl radical generator.

Compound **4** is regarded to be a candidate as a therapeutic Alzheimer's disease drug that protects neurons from Ab toxicity and is in the preclinical stage as a hepatoprotective drug.[10] In our new alternative process for improving the purification step, a key step in the synthesis of **4** involved the conversion of **3** to **4** (Scheme 1).

Scheme 1. Deoxygenation of Asiatic Acid



Barton−McCombie deoxygenation of **3** with Bu_3SnH in toluene at 110 °C gives **4** in 76% yields. Purification steps have been needed to remove residual toxic organotin byproducts in order to meet regulatory stipulations. This procedure affects product isolation.

Furthermore the reaction of **1** using another method,[11] using less toxic diphenylsilane and AIBN in toluene at 110 °C, gave **4** in 70% yields after a deprotection reaction with catalytic HCl in methanol.

Substrate **3** was reacted with $(Bu_4N)_2S_2O_8/HCO_2Na$ (3 equiv/6 equiv) in DMF at 50 °C for 4 h to afford **4** in excellent yield of 95%. In the absence of HCO_2Na or $(Bu_4N)_2S_2O_8$, no product **4** was obtained: starting material **3** was recovered. This result indicates that both $(Bu_4N)_2S_2O_8$ and HCO_2Na are necessary for this deoxygenation.

In connection with these results, various alcohols were subjected to this optimized deoxygenation protocol. The results obtained are shown in Table 1. As shown, several different primary, secondary, and tertiary alcohols were successively deoxygenated in high to excellent yields.

Table 1. Deoxygenation of Primary, Secondary, and Tertiary Alcohols with $(Bu_4N)_2S_2O_8$ (3 equiv)/HCO_2Na (6 equiv) in DMF

entry	substrate	temp (°C)	time (min)	product	yield (%)[a]
1	**5a**	50	30	**5b**	100
2	**6a**	65	15	**6b**	86
3	**7a**	40	60	**7b**	96
4	**8a**	75	30	**8b**	100
5	**9b**	65	15	**9c**	95
6	**10b**	65	15	**10e**	75
7	**10b**	65	15	**10e**	98[b]
8	**10c**	65	20	**10e**	90[b]
9	**10d**	65	15	**10e**	97[b]
10	**11b**	65	15	**11c**	65
11	**11b**	65	15	**11c**	75[b]
12	**12b**	65	15	**12d**	65[b]
13	**12b**	65	15	**12d**	73[c]
14	**12c**	65	15	**12d**	75[c]
15	**13**	60	60	**14**	95
16	**15a**	65	120	**16a**	95[d]
17	**15a**	80	20	**16a**	95[e]
18	**15a**	80	10	**16a**	95
19	**15b**	65	15	**16b**	90
20	**17**	65	60	**18**	86[b]

[a] Isolated yields obtained by silica gel column chromatography. [b] 8 equiv Na_2CO_3 was added. [c] 8 equiv Et_3N was added. [d] DMSO. [e] 3 equiv $(HCO_2)_2Cu$.

The *S*-methyl xanthate **9b** was prepared from **9a**,[12] which was obtained from the reduction of 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine[13] using DIBAL-H. As an opioid derivative, **9c**[14] was obtained in excellent yield. Substrates **10b**,[15] **10c**,[16] and **10d**[17] were prepared from glucofuranose derivative **10a**. Compounds **11b** and **12b** were prepared from **11a**[18] and **12a**,[19] respectively. Their 3-deoxy sugar derivatives **10e**[15] and **11c**[18] and 5-deoxy sugar derivative **12d**[20] obtained are useful intermediates in pharmaceutical synthesis.

Of special note, **12d** was obtained by the indirect deoxygenation of **12b**. Because cyclic 3,5-*O*-thionocarbonate **12c**

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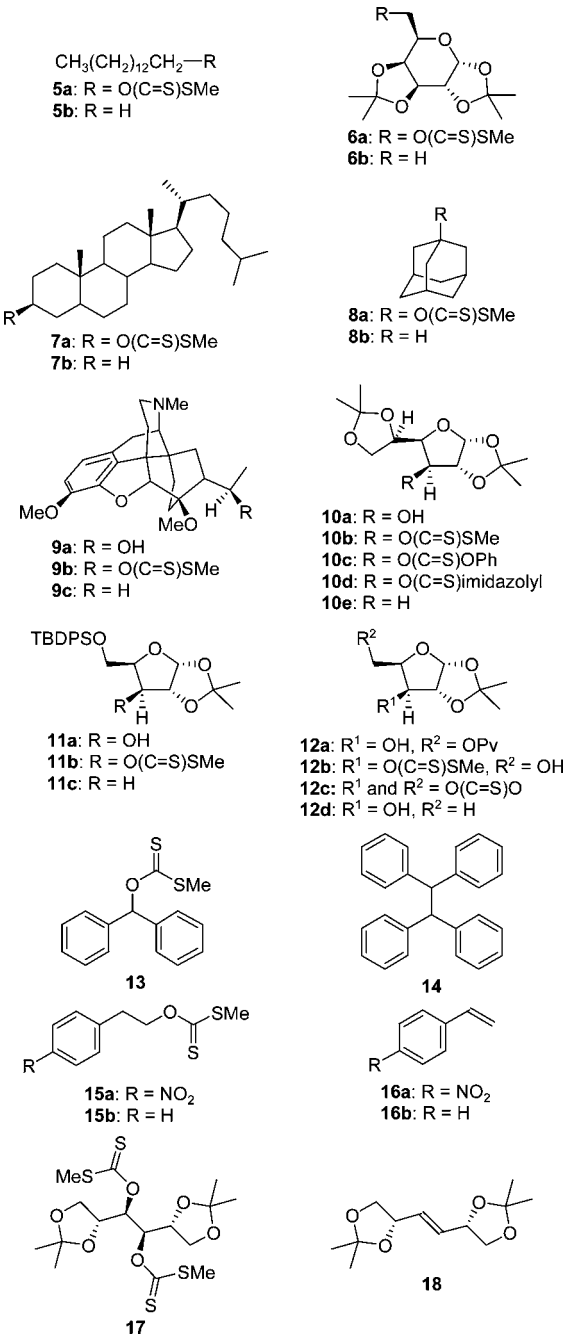
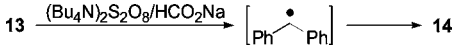


was deoxygenated also to give **12d** (entry 14), it can be concluded that the reaction of **12b** goes through the cyclic thionocarbonate intermediate **12c**. Since deoxygenation of a primary alcohol is somewhat difficult, it can be an alternative deoxygenation method for primary alcohols. In these conversions, triethylamine or sodium carbonate was used as a base additive for diminishing the deprotection of products and reactants.

It is noteworthy that deoxygenation of **13**[21] gave the coupled product **14**[22] (entry 15). The diphenylmethyl radicals arising from the radical-induced C−O bond cleavage events may be too stabilized to abstract a hydrogen atom from the formate ion (or other possible sources) and end up dimerizing (Scheme 2). The diphenylmethyl radicals do not provide

Scheme 2. Radical−Radical Combination Reaction



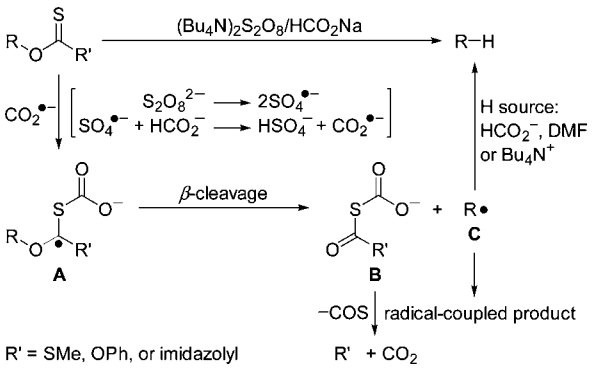
sufficient steric inhibition to radical−radical combination reactions, which is required for persistence.[23]

Deoxygenation of **15a** and **15b**,[21] which possess labile benzylic hydrogens, gave styrene derivatives **16a**[24] and **16b**,[25] respectively. Furthermore, bis-xanthate **17**[4b] was deoxygenated to give the dideoxygenated product **18**[4b] having a carbon−carbon double bond.

Besides sodium formate as a hydrogen source, copper formate and ammonium formate were tested with **10b**. The reactions were monitored by TLC analysis. A copper formate system did not give any deoxygenated product **10e**: starting material was recovered. The system of ammonium formate gave a low yield of **10e** (8%).

It can be postulated that alkyl radical **C** (Scheme 3) abstracts a hydrogen atom from formate ion, tetrabutylam-

Scheme 3. Plausible Mechanism for Deoxygenation of Alcohols with $(Bu_4N)_2S_2O_8$ and HCO_2Na



monium ion, or solvent to form the deoxygenated product. To investigate the hydrogen source of products, **19** (Table 2) was synthesized by a conventional method[15] using CD_3I instead of CH_3I.

The deoxygenation of **10b**, **10c**, and **19** has been examined in the presence of DCO_2Na or HCO_2Na in various solvents (Table 2). The amount of atom % deuterium incorporation of **20** was fully characterized by ^1H NMR.[26] None of the

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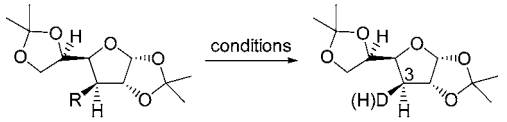
Table 2. Deoxygenation of **10b**, **10c**, and **19** with $(Bu_4N)_2S_2O_8$ (3 equiv), HCO_2Na or DCO_2Na (6 equiv), and Na_2CO_3 (8 equiv) in 0.05 M Solvent at 65 °C for 15 min



10b: R = O(C=S)SMe
10c: R = O(C=S)OPh
19: R = O(C=S)SCD$_3$

20: mixture of βD and βH

entry	substrate	conditions	ratio of βD/βH in **20**[a]	yield (%)[b]
1	**10b**	DCO_2Na, DMF	22/78	98
2	**10b**	DCO_2Na, DMF-d_7	20/80	98
3	**10b**	DCO_2Na, DMSO	17/83	97
4	**10c**	DCO_2Na, DMF	47/53	98
5	**10c**	DCO_2Na, DMSO	91/9	90[c]
6	**19**	HCO_2Na, DMF	0/100	98

[a] Determined by ^{1}H NMR. [b] Isolated yields after silica gel column chromatography. [c] The reaction time was 30 min.

substrates (**10b**, **10c**, and **19**) give any 3α-deuterated product under the reaction conditions. Thus deuteration occurred at the 3-position in a β-face selective manner.

When **10b** reacted with $(Bu_4N)_2S_2O_8/DCO_2Na$ in DMF and DMF-d_7, the atom % D incorporation of **20** reached 22% and 20%, respectively (entries 1 and 2). In the case of **10c** the atom % D incorporation of **20** was 47% in DMF. Interestingly, when DMSO was used as a solvent the deuteration using $(Bu_4N)_2S_2O_8/DCO_2Na$ occurred with 91 atom % D incorporation at the selective position. This result can be applied to obtain the deuterated 3-deoxy furanose derivatives.[27] Since an undeuterated $(Bu_4N)_2S_2O_8/HCO_2Na$ system did not give deuterated product **20** and quantitative yield of **10e** (98%, entry 6) was obtained, one of the hydrogen sources must be the hydrogen of HCO_2Na.

A plausible mechanism can be suggested from previously known results of tin hydride reduction.[7a] The deoxygenation appears to be initiated by the transfer of a single electron to thiocarbonyl derivatives from $CO_2^{\bullet -}$ rather than from $SO_4^{\bullet -}$. The combination of the radicophilic nature of thiocarbonyl derivatives and $CO_2^{\bullet -}$ might be utilized to form alkyl radical **C** (Scheme 3).

In summary, an efficient and versatile deoxygenation method has been developed via the thiocarbonyl derivatives of alcohols such as xanthates, phenyl thionocarbonates, and thiocarbonylimidazolides. This new process may be generally available in the deoxygenation of alcohols bearing acid-sensitive functionalities. Of particular note, in the case of **10c** (phenyl thionocarbonate) the $(Bu_4N)_2S_2O_8/DCO_2Na$ deoxygenation system in DMSO can provide the deuterated furanose derivatives at C3 position.

Supporting Information Available: General procedures, experimental procedures, characterization data, and copies of ^{1}H and/or ^{13}C NMR spectra for compounds **1**, **3**, **4**, **5a,b**, **6a,b**, **7a,b**, **8a,b**, **9a−c**, **10b−e**, **11b,c**, **12b−d**, and **13−20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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