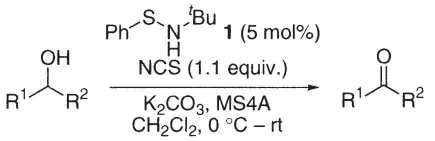
Sulfenamide-catalyzed Oxidation of Primary and Secondary Alcohols with Molecular Bromine

Jun-ichi Matsuo, Asahi Kawana, Hiroyuki Yamanaka, and Teruaki Mukaiyama
The Kitasato Institute, Center for Basic Research, TCI, 6-15-5, Toshima, Kita-ku, Tokyo 114-0003

(Received November 19, 2002; CL-020986)

Primary and secondary alcohols were smoothly oxidized to the corresponding aldehydes and ketones in high yields at room temperature with 1.1 equiv. of molecular bromine by using a catalytic amount of *N-t*-butyl-2-nitrobenzenesulfenamide in the coexistence of potassium carbonate and molecular sieves 4A.

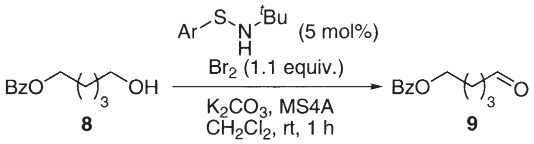
A new method for catalytic oxidation of alcohols to carbonyl compounds was recently reported from our laboratory: that is, various primary and secondary alcohols were smoothly oxidized to the corresponding aldehydes and ketones under mild conditions by using a stoichiometric amount of *N*-chlorosuccinimide (NCS) in the coexistence of a catalytic amount of *N-tert*-butylbenzenesulfenamide (**1**), potassium carbonate, and molecular sieves 4A (Eq 1).[1] In order to establish an improved method, it was recommended to use a simple halogenating agent instead of the NCS mentioned above. Molecular bromine (Br_2)[2–7] was then chosen because it was readily available, and also, hydrogen bromide formed during the oxidation was easily captured by bases. In this communication, we would like to report on *N-tert*-butyl-2-nitrobenzenesulfenamide (**5**)-catalyzed oxidation of primary and secondary alcohols with Br_2.

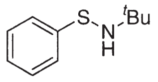
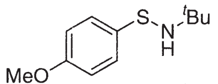
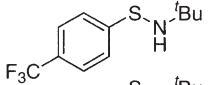
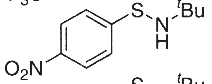
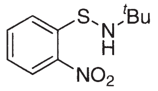
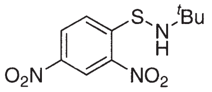
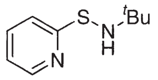

(Eq. 1)

Oxidation of 5-hydroxypentyl benzoate (**8**) to the corresponding aldehyde **9** was chosen as a model reaction, and catalytic oxidation of **8** with 1.1 equiv. of Br_2 was first tried by using 5 mol% of the catalyst **1** in the coexistence of potassium carbonate and molecular sieves 4A (MS4A). Contrary to our expectation, the desired aldehyde **9** was then obtained only in 36% yield (Table 1, entry 1), which was much lower than that of aforementioned sulfenamide **1**-catalyzed oxidation of alcohols with NCS. Since the above yield was not improved even after screening of the reaction conditions, the catalyst **1** was thought to decompose by cleavage of S–N bond of **1** with Br_2 or with hydrogen bromide formed during the oxidation. Therefore, experiments using several *N-tert*-butylarenesulfenamides were tried so as to search for clues to an appropriate catalyst for catalytic oxidation with Br_2.

As shown in Table 1, the results of sulfenamides having electron-withdrawing groups on their benzene rings were better than those having electron-releasing groups. Supposedly, the electron-withdrawing groups enhanced the stability of sulfenamides to tolerate the present oxidation conditions.[8] Among electron-withdrawing groups, a nitro group excelled a trifluoromethyl group, and an *ortho*-nitro group turned out still superior to a *para*-nitro group (entries 3–5). 2,4-Dinitro-substituted sulfenamide (**6**) gave aldehyde **9** in only 20% yield probably because the formation of its key intermediate, sulfinimidoyl bromide, took place very slowly (entry 6). Also, the yield of aldehyde **9** was only 34% when 2-nitrophenyl moiety of **5** was replaced with 2-pyridyl moiety (entry 7). Then, it became clear that *N-tert*-butyl-2-nitrobenzenesulfenamide (**5**)[9] catalyzed the oxidation of alcohol **8** with Br_2 most efficiently. As oxidation of **8** with Br_2 did not proceed in the absence of catalyst **5**, it was evidently shown that catalyst **5** promoted the present oxidation.

Table 1. Effect of sulfenamide catalysts[a]

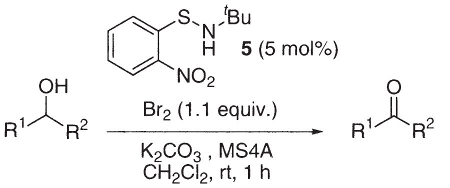


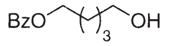
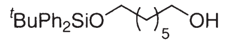
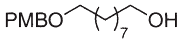
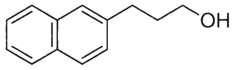
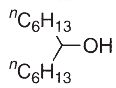
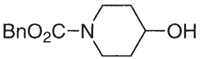
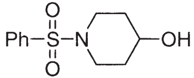
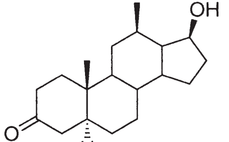
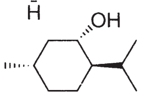
Entry	Sulfenamide		Yield/%[b]
1		**1**	36
2		**2**	30
3		**3**	45
4		**4**	76
5		**5**	90
6		**6**	20
7		**7**	34

[a] K_2CO_3 (20 equiv.) and MS4A (1.0 g/mmol) were used, and Br_2 was slowly added within 10 min. [b] Isolated yield.

Next, sulfenamide **5**-catalyzed oxidation of various primary and secondary alcohols with Br_2 was tried (Table 2). In the case of primary alcohols, Br_2 was added slowly for 30–60 min since rapid addition caused esters to yield in considerable amounts. It is probably because of oxidation of hemiacetals produced from alcohols and initially formed aldehydes.[6] On the other hand, slow addition of Br_2 was not necessary in the oxidation of secondary alcohols, and the corresponding ketones were afforded in high yields by usual experimental procedures. It was noted that menthol, a sterically hindered secondary alcohol, was also smoothly oxidized to menthone while the same oxidation by the combination of catalyst **1** and NCS proceeded very slowly (entry 12).[10] When the oxidation of 4-phenylcyclohexanol with Br_2 was

Table 2. Catalytic oxidation of alcohols with Br_2[a]



Entry	Alcohol	Br_2 addition/min	Yield/%[b]
1		10	90
2		30	86
3[c]		60	80
4		30	91
5		60	80
6		60	84
7		60	95
8		10	98
9		10	98
10		10	92
11[c]		60	96
12[c,d]		10	90[e]

[a] K_2CO_3 (20 equiv.) and MS4A (1.0 g/mmol) were used. [b] Isolated yield. [c] The catalyst **5** (10 mol%) was used. [d] Reaction time was 2 h. [e] Determined by GC-analysis.

carried out in the absence of catalyst **5**, 4-phenylcyclohexanone was obtained in only 55% yield along with various by-products. This result clearly indicated that sulfenamide **5** efficiently catalyzed the oxidation of secondary alcohols with Br_2 to afford ketones in high yields. When alcohols having double bonds within the same molecule were oxidized under the present conditions, however, bromination of double bonds proceeded in the first place and oxidation of a hydroxy group took place in turn. On the other hand, *p*-methoxybenzyl, *tert*-butyldimethylsilyloxy, and benzylcarbamoyl groups were not damaged in the present oxidation.

Thus, it was noted that both primary and secondary alcohols were oxidized with Br_2 by using a catalytic amount of sulfenamide **5**, and the corresponding aldehydes and ketones were easily isolated in good to high yields.

Typical experimental procedure is as follows (Table 2, entry 1): To a stirred suspension of potassium carbonate (829 mg, 6.00 mmol), molecular sieves 4A (300 mg), 5-hydroxypentyl benzoate (**8**) (62.5 mg, 0.30 mmol), and sulfenamide **5** (3.5 mg, 15 µmol) in dichloromethane (4.0 mL) was added dropwise a solution of Br_2 (52.7 mg, 0.33 mmol) in dichloromethane (1.0 mL) at room temperature for 10 min. After the reaction mixture was stirred for 50 min, the reaction was quenched by adding 10% aqueous $Na_2S_2O_3$ solution (1.0 mL). The mixture was filtered through Celite pad, and the filtrate was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by preparative thin-layer chromatography (hexanes - ethyl acetate = 3:1) to give 4-formylbutyl benzoate (**9**) (55.6 mg, 90%) as a colorless oil.

The present work was partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

1 T. Mukaiyama, J. Matsuo, D. Iida, and H. Kitagawa, *Chem. Lett.*, **2001**, 846.
2 M. A. Neirabeyeh, J.-C. Ziegler, and B. Gross, *Synthesis*, **1976**, 811.
3 a) K. Saigo, A. Morikawa, and T. Mukaiyama, *Chem. Lett.*, **1975**, 145. b) K. Saigo, A. Morikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 1656 (1976). c) Y. Ueno and M. Okawara, *Tetrahedron Lett.*, **1976**, 4597.
4 L. K. Blair, J. Baldwin, and W. C. Smith, Jr., *J. Org. Chem.*, **42**, 1816 (1977).
5 a) M. P. Doyle and R. L. Dow, *Synth. Commun.*, **10**, 881 (1980). b) M. P. Doyle and V. Bagheri, *J. Org. Chem.*, **46**, 4806 (1981).
6 D. R. Williams, F. D. Klingler, E. E. Allen, and F. W. Lichtenthaler, *Tetrahedron Lett.*, **29**, 5087 (1988).
7 For oxidation of alcohols to carbonyl compounds with Cl_2, see: a) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972). b) E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, **14**, 919 (1973). c) J. Wicha and A. Zarecki, *Tetrahedron Lett.*, **15**, 3059 (1974).
8 Amino groups are protected with *o*-nitrobenzenesulfenyl group. See: T. W. Greene and P. G. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, New York (1999).
9 *N-tert*-Butyl-2-nitrobenzenesulfenamide (**5**) was prepared by the reaction of 2-nitrobenzenesulfenyl chloride and *tert*-butylamine. See also: R. Schubart, U. Eholzer, and T. Kempermann, Eur. Pat. Appl. 301376 (1989).
10 Catalytic oxidation of menthol by using **1** (10 mol%), NCS (1.1 equiv.), K_2CO_3 (10 equiv.), and MS4A (1 g/mmol) in CH_2Cl_2 at room temperature for 2 h gave menthone in 18% yield.