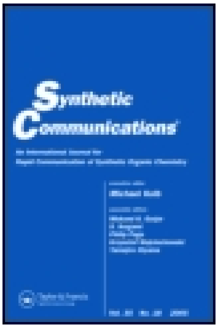

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Brian E. Love [a] & Binh T. Nguyen [a]

[a] Department of Chemistry, East Carolina University, Greenville, NC, 27858

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OXIDATION OF ALCOHOLS BY BROMINE ON ALUMINA

Brian E. Love* and Binh T. Nguyen

Department of Chemistry
East Carolina University, Greenville, NC 27858

Abstract: Bromine adsorbed on neutral alumina is an effective reagent for the oxidation of secondary alcohols to ketones.

Supported reagents have found extensive use in organic synthesis.[1] Reagents have been immobilized on organic polymers,[1b,2] as well as inorganic substances such as silica gel[3] and alumina.[4] Immobilization of a reagent on a solid support not only can facilitate isolation of the desired product of a reaction, but often produces a reagent possessing reactivity which is different from that found for the same reagent in solution. For example, while chromic acid normally oxidizes primary alcohols to carboxylic acids, chromic acid adsorbed on silica gel can be used for the conversion of primary alcohols to aldehydes.[5]

Other chromium based reagents which have been supported on either silica gel or alumina and used to oxidize alcohols include chromium trioxide[6,7,8] and chromyl chloride,[9] as well as a variety of chromate,[10] chlorochromate[11,12] and

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* To whom correspondence should be addressed

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dichromate[10,13] salts. Other reagents such as Oxone®[14], sodium bromite,[15,16] potassium permanganate,[17] and zinc and copper nitrate[18] have also provided useful oxidants for alcohols when supported on either silica gel or alumina. Many of these same oxidants (as well as others) have likewise been immobilized on cationic polymers such as anion exchange resins[19,20,21] and protonated poly(vinyl pyridine).[21,22]

We have found that bromine adsorbed on alumina is also an effective oxidizing agent which is readily prepared and easy to use (see below). The reagent is quite stable and retains its activity after months of storage. This stands in contrast to some other supported oxidants, such as chromic acid on silica gel, which is photosensitive and needs to be used within a week of its preparation.[5] Additionally, toxic chromium salts are not produced as by-products of this reaction.

Bromine adsorbed on alumina has previously been used to effect ring bromination of alkyl benzenes[23] and its reaction with cyclohexene has also been studied.[24] Bromine adsorbed on silica gel has recently been reported as an effective reagent for the oxidation of sulfides to sulfoxides.[25] While the use of bromine (and various co-reactants) to oxidize alcohols is well known in the solution phase,[26] we are unaware of any report of the use of bromine immobilized on a solid support to oxidize alcohols.

Operationally, the reaction is extremely simple. Bromine was added to alumina[27] in the absence of solvent and stirred (or shaken) until uniform in appearance. This reagent was then slowly added to the alcohol, which had also been adsorbed onto alumina (see Experimental section). The bromine color was discharged shortly after addition, and the carbonyl compound was isolated by washing the alumina with methylene chloride, followed by evaporation of solvent.[28] Yields were generally good (see Table 1) and the products were

Table 1

Entry	Alcohol	Ketone	Yield (%)[a]
1	1-phenylethanol	acetophenone	83
2	benzhydrol	benzophenone	84
3	cyclohexanol	cyclohexanone	63
4	2-methylcyclohexanol[b]	2-methylcyclohexanone	80
5	4-methylcyclohexanol[b]	4-methylcyclohexanone	93
6	menthol	menthone	95
7	3-heptanol	3-heptanone	67
8	2-octanol	2-octanone	69

a) isolated yield (see below)
b) mixture of *cis* and *trans* isomers

reasonably pure, though some were contaminated by starting alcohol. Proton NMR spectra of the products were identical with spectra obtained from commercially available samples.

Considerable loss of product was observed when aliphatic ketones were allowed to remain under high vacuum until removal of the CH_2Cl_2 was complete. As a result, these compounds were typically allowed to remain under vacuum only 15-30 min, and consequently were contaminated with CH_2Cl_2. Yields reported in Table 1 for entries 3-8 thus were not based on the total sample weight, but rather were adjusted to reflect only the amount of ketone formed (integration of NMR signals allowed determination of the percentage of CH_2Cl_2 present in these samples). A summary of the purity of samples obtained is provided in Table 2.

Complex mixtures were obtained when 2-(1-hydroxyethyl)furan and 4-phenyl-3-buten-2-ol were used as substrates, presumably due to competing reaction of the bromine with the furan ring and alkene, respectively. Ring

Table 2

Entry	Ketone	Alcohol Present (Mole Percent)[a]	CH_2Cl_2 Present (Mole Percent)[a]
1	acetophenone	0	0
2	benzophenone	5	1
3	cyclohexanone	<3	49
4	2-methylcyclohexanone	<3	26
5	4-methylcyclohexanone	15	12
6	menthone	21	4
7	3-heptanone	0	18
8	2-octanone	<3	35

a) estimated from ^1H NMR spectrum

bromination was not observed for simple aromatic alcohols (see entries 1 and 2 in Table 1).

While secondary alcohols provided ketones in good yield, treatment of primary alcohols with the same reagent produced esters derived from the combination of two molecules of the alcohol (presumably by oxidation of the corresponding hemiacetal) along with unreacted alcohol. Of the primary alcohols investigated, only one (benzyl alcohol) provided the aldehyde as the major reaction product. Benzaldehyde was produced in 72% yield, but was still contaminated with small amounts of benzyl alcohol and benzyl benzoate. Yields of esters derived from 1-butanol, 2-methyl-1-propanol and 1-pentanol were all in the 20-40% range. We have not yet found appropriate conditions to make this transformation synthetically useful. Oxidation of primary alcohols to the corresponding esters has been reported previously using similar reagents, such as chromium trioxide on wet alumina[6] and sodium bromite on alumina,[15] as well as in solution phase using a combination of bromine and potassium bromate.[26h]

Use of between 1.3 and 1.5 equivalents of bromine (relative to alcohol) was found to be optimal. Use of less bromine tended to increase the amount of starting alcohol recovered, while use of larger excesses of bromine often resulted in the formation of small amounts of α-bromoketones. Addition of the bromine on alumina to the alcohol all at once rather than portionwise also tended to increase the amount of impurities slightly. Reagents prepared by adsorbing bromine on both basic and weakly acidic alumina were also investigated as oxidants, but were found to be inferior to the bromine on neutral alumina.

In conclusion, bromine adsorbed on alumina has been found to be a fast, efficient reagent for the conversion of secondary alcohols to ketones. Isolation of the products is simple, and toxic by-products are not produced.

Experimental Section

Preparation of the Reagent: 12.03g (75.2 mmol) of bromine were stirred with 85.23g of neutral alumina[27] to give a reddish brown solid (bromine content: approximately 0.77 mmol/g). The reagent was stored at room temperature in an amber-colored bottle and was found to retain activity for months.

Oxidation of Alcohols: The alcohol was added to neutral alumina[27] in a round-bottom flask (approximately 1 g of alumina per mmol of alcohol). Sufficient CH_2Cl_2 to allow even mixing was added, then removed on a rotary evaporator using aspirator suction to give a free-flowing solid. This mixture was stirred while 1.3 equivalents of the bromine on alumina reagent were added portionwise by means of a powder addition funnel over a period of approximately 20 min. The mixture was stirred for a further 1 h, then packed in a column and rinsed with 100 mL CH_2Cl_2 into a stirred solution of 10% $Na_2S_2O_3$. The organic layer was removed, then washed with 25 mL saturated NaCl. The CH_2Cl_2 was dried ($MgSO_4$) and solvent removed under reduced pressure.

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Doyle, M. P. and Dow, R. L. *Synth. Commun.* **1980,** *10*, 881. (e) DABCO•2 Br_2: Blair, L. K.; Baldwin, J. and Smith, W. C., Jr. *J. Org. Chem.* **1977,** *42*, 1816. (f) Br_2/HMPT: Al Neirabeyeh, M.; Ziegler, J.-C. and Gross, B. *Synthesis* **1976,** 811. (g) $Br_2/(Bu_3Sn)_2O$: Ueno, Y. and Okawara, M. *Tetrahedron Lett.* **1976,** 4597. (h) $Br_2/KBrO_3$: Farkas, L. and Schächter, O. *J. Am. Chem. Soc.* **1949,** *71*, 2827.

27. Brockman Activity I, 80-200 mesh neutral alumina was used. "Activation" of the alumina by heating was not required.

28. Although the bromine color was initially discharged within seconds, reactions were typically allowed to stir for an hour after the addition of the bromine to ensure the reaction had gone to completion.

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