



Na-promoted aerobic oxidation of alcohols to ketones

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ABSTRACT

Aerobic oxidation of a number of diaryl and arylalkyl carbinols to ketones was promoted by Na in THF at room temperature with up to 99% yield. This new oxidation method is also selective with good efficiency for the oxidation of benzylic secondary alcohols but not for a primary alcohol or nonbenzylic secondary alcohols. Under nitrogen, a catalytic amount of Ni or transition metal halides such as CoCl₃, FeCl₃, and NiCl₂ in combination with Na was also found to conduct a dehydrogenation of a secondary alcohol to the corresponding ketone in high yield at room temperature.

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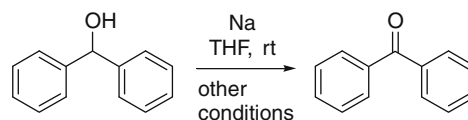
Oxidation of alcohols is one of the most fundamental reactions in organic chemistry. A great variety of metal and non-metal-based stoichiometric reagents have been developed to oxidize primary and secondary alcohols to the corresponding aldehydes, ketones, and carboxylic acids.^{1–3} These processes generally produce significant amount of inorganic or organic wastes that are of environmental concern. Aerobic^{4–7} and anaerobic⁸ oxidations of alcohols in the presence of transition metal catalysts and/or other catalysts have also been investigated extensively. Although these processes are more environmentally benign, they often need expensive metals and/or other reagents. Thus, the search for environmentally friendly as well as economical oxidation processes continues. Recently, Wang and coworkers reported a practically useful oxidation of secondary alcohols to ketones catalyzed by NaH under nitrogen.⁹ Herein, we report our finding of an aerobic oxidation of secondary alcohols to ketones promoted by the commercially cheaper Na at room temperature.

We first studied the conversion of diphenylmethanol to benzophenone (Scheme 1). The results for the screening experiments are summarized in Table 1. No oxidation of the alcohol under nitrogen in the presence of Na (10 mg, 2 equiv) in THF was observed (entry 1). However, addition of a catalytic amount of the transition metal salts such as CoCl₃, FeCl₃, and NiCl₂ in combination with Na (2 equiv) led to high conversions of the alcohol to the ketone (entries 2–4). Using a catalytic amount of Na in combination with the transition metal salts led to incomplete conversions (entries 5–7).

We also found that the transition metal salts alone could not catalyze the oxidation of the alcohol under nitrogen (entries 8–10). The combination of Na (2 equiv) with a small amount of Ni also led to complete conversion of the alcohol to ketone (entry 11) but the combination of Na with Fe did not oxidize the alcohol (entry 12). Using Ni alone under nitrogen only led to 10% conversion of the alcohol to the ketone over 40 h (entry 13) and Fe could not promote this reaction (entry 14). Finally, when the reaction was conducted in the presence of Na (2 equiv) and air in THF at room temperature without any transition metal additive, a complete conversion of the alcohol to the ketone was observed (entry 15).

The above-mentioned screening experiments demonstrate that (1) in the presence of air, Na can promote an efficient oxidation of the alcohol; (2) without air, Na cannot promote the oxidation; and (3) without air, a catalytic amount of transition metal salts or Ni combined with Na can promote the oxidation of the alcohol. These observations present intriguing questions that remain to be answered for the mechanisms of these oxidation processes.

Encouraged by the high conversion and mild reaction conditions for the Na-promoted aerobic oxidation of diphenylmethanol, we have applied this method for the oxidation of a number of alcohols. The results are summarized in Table 2. These oxidations



Scheme 1. Oxidation of diphenylmethanol to benzophenone.

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Table 1
Oxidation of diphenylmethanol to benzophenone in THF at room temperature^a

Entry	Metal reagents	N ₂ or air	Time (h)	Conversion to ketone ^b
1	Na (2 equiv)	N ₂	16	None
			40	None
2	Na (2 equiv) + CoCl ₃ (0.03 equiv)	N ₂	16	6
			40	100
3	Na (2 equiv) + FeCl ₃ (0.03 equiv)	N ₂	16	15
			40	78
4	Na(2 equiv) + NiCl ₂ (0.04 equiv)	N ₂	16	20
			40	92
5	Na (0.4 equiv) + CoCl ₃ (0.03 equiv)	N ₂	40	18
6	Na (0.4 equiv) + FeCl ₃ (0.03 equiv)	N ₂	40	0
7	Na (0.4 equiv) + NiCl ₂ (0.04 equiv)	N ₂	40	40
8	CoCl ₃ (0.03 equiv)	N ₂	40	None
9	FeCl ₃ (0.03 equiv)	N ₂	40	None
10	NiCl ₂ (0.04 equiv)	N ₂	40	None
11	Na (2 equiv) + Ni (0.085 equiv)	N ₂	40	100
12	Na (2 equiv) + Fe (0.09 equiv)	N ₂	16	None
			40	None
13	Ni (0.085 equiv)	N ₂	40	10%
14	Fe (0.09 equiv)	N ₂	40	None
15	Na (2 equiv)	Air	16	67
			40	100

^a Conditions: Diphenylmethanol (36.8 mg, 0.2 mmol), THF (3 mL), rt.







































^b Estimated by using ¹H NMR spectroscopy.

were conducted by first stirring an alcohol with 1 equiv Na in THF in air for 4 h at room temperature. Then second equivalent of Na was added to continue the reaction. As shown in Table 2, good yields are obtained for the oxidation of a variety of diaryl and arylalkyl carbinols. This reaction tolerates functional groups such as thiophenyl, methoxy, bromo, and nitrile. Lower yields were observed for the oxidation of several sterically hindered alcohols (entries 11–13). Oxidation of a primary alcohol, *p*-phenylbenzylic alcohol, was also tested which gave only ~1% conversion to the corresponding aldehyde after 16–40 h (entry 17). Thus, this method is highly selective for the oxidation of the secondary alcohols. Inactivity of nonbenzylic secondary alcohols was also observed under the reaction conditions (entries 18 and 19). This Na-promoted oxidation could potentially be used to selectively oxidize the benzylic secondary alcohols in the presence of these inactive alcohols.

The general experimental procedure for the Na-promoted aerobic oxidation is given here. To a flame-dried round-bottomed flask were added an alcohol (0.2 mmol) and THF (dry, 3 mL). Sodium (0.2 mmol, 1.0 equiv) was cut into small pieces under nitrogen and added to the alcohol solution. The reaction mixture exposed to air through a drying tube (anhydrous CaSO₄) was stirred at room temperature for 4 h. Additional sodium (0.2 mmol, 1.0 equiv) was added and the stirring continued. [Note: Slow stirring was necessary to allow the Na chips to be always covered by the solvent.] The reaction was monitored with TLC. The solvent was then evaporated and a 5% HCl solution was added until pH 7. The solution was extracted with EtOAc, and the combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel eluted with EtOAc/hexane (1:6) to give the desired ketone product.

In summary, we have discovered a Na-promoted aerobic oxidation of a number of diaryl and arylalkyl carbinols at room temperature. The simple and mild reaction conditions and the easily available reagent make this new method synthetically useful. This method is also selective with good efficiency for the oxidation of benzylic secondary alcohols but not for a primary alcohol or nonbenzylic secondary alcohols. In the absence of air, a catalytic amount of Ni or transition metal halides in combination with Na can also convert a secondary alcohol to the corresponding ketone. These

Table 2
Aerobic oxidation of various alcohols to ketones promoted by Na in THF at room temperature

Entry	Alcohol	Ketone	Time ^a (h)	Isolated yield (%)
1			20	95
2			48	92
3			46	72
4			46	99
5			44	90
6			23	79
7			10	69
8			36	82
9			16	65
10			20	61
11			20	46
12			20	41
13			24	38
14			24	71
15			18	62
16			20	70
17			16–40	~1 ^b
18			20	None ^b
19			20	None ^b

^a The total reaction time for the oxidation promoted by the first and second equivalents of Na.

^b Observed by using ¹H NMR spectroscopy.

findings present interesting mechanistic questions that require further investigation.

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