

Aerobic Oxidation of Benzylic Alcohols with Nitric Acid/Copper Bromide(II) in Ionic Liquid

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Oxidation of benzylic alcohols to the corresponding carbonyl compounds is an important and fundamental transformation in organic synthesis.¹ Amongst others, nitric acid can be considered as a valuable oxidant due to its ready availability and low price. Nitric acid has been successfully utilized for the oxidation of benzylic alcohols to the corresponding carbonyl compounds in dichloromethane.² However, in this protocol, the required use of an excess of nitric acid (up to three-fold) was disadvantage in consideration of its corrosive nature and detrimental environmental effects of nitrous oxide by product. Recently, a number of nitric acid induced aerobic oxidation of benzyl alcohols with sub-stoichiometric amounts of nitric acid have been reported. For examples, these methods utilized catalytic nitric acid together with activators like NaNO₂/amberlyst-15,³ strong acid⁴ or carbon based materials.⁵ However, the drawbacks associated with harsh reaction conditions, low product yields and use of exotic reagents limits their further applications.

Copper(II) bromide is an attractive safe, cheap and readily available reagent that has proven to be very effective for α -bromination reactions of various carbonyl compounds.^{6,7} The reagent is also suitable to the bromination of variety of functional groups such as alkenes,⁸ alkynes,⁹ benzylic alcohols,¹⁰ and aromatic compounds.¹¹ In the oxidation reactions of alcohols and amines, much attention has been focused on the utilization of reagent combination of copper(II) bromide and strongly basic lithium *tert*-butoxides.^{12,13} However, to the best of our knowledge, there has been no reports on the efficient and practically useful oxidation method utilizing copper(II) bromide as an activator in nitric acid mediated catalytic oxidation reactions.

During the last decade, ionic liquids has been received much attention as alternative solvents in various important organic reactions due to their advantageous properties such as high polarity, low flammability, high viscosities and sufficient solubility for the catalyst complexes.¹⁴

As part of our program to the study of organic synthesis in ionic liquids, we required a convenient method for the aerobic oxidation of benzylic alcohols with nitric acid. Now we report new nitric acid induced catalytic oxidation of benzylic alcohols with copper(II) bromide in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄). Thus, treatment of benzylic alcohols with 65% nitric acid (0.5 equiv) and copper(II) bromide (0.5 equiv) in 1.0 mL of

[bmim]BF₄ at 60 °C under air atmosphere led to the corresponding carbonyl compounds in high yields. In general, most of cases investigated in this study completed in the reaction times of less than 4 h. A variety of benzylic alcohols were subjected to oxidation by this protocol to provide the corresponding carbonyl compounds in high yields. The results are summarized in Table 1. As shown in the Table 1, the primary and secondary benzylic alcohols were oxidized equally well. Aromatic nuclear bromination has not been observed for all substrates examined at the present reaction conditions. We also found that the oxidation of a benzylic alcohol with powerful electron-withdrawing nitro substituent, the corresponding carbonyl compounds obtained in excellent yields (entries **5** and **6**) after prolonged reaction times of 16 h. In other reported conventional methods, the yields for the oxidation of benzylic alcohols with nitro substituents usually provided much lower yields.^{15,16} In the cases of aliphatic alcohols, the desired products obtained in somewhat lowered yields (entries **15** and **16**) due to the formation of α -bromin-

Table 1. HNO₃/CuBr₂ promoted oxidation of benzylic alcohols

| Entry | Substrate | Product | Yield (%) ^a |
|-----------|---|--|------------------------|
| 1 | PhCH ₂ OH | PhCHO (1a) | 81 |
| 2 | 4-MeC ₆ H ₄ CH ₂ OH | 4-MeC ₆ H ₄ CHO (2a) | 91 |
| 3 | 4-BrC ₆ H ₄ CH ₂ OH | 4-BrC ₆ H ₄ CHO (3a) | 82 |
| 4 | 4-ClC ₆ H ₄ CH ₂ OH | 4-ClC ₆ H ₄ CHO (4a) | 85 |
| 5 | 3-NO ₂ C ₆ H ₄ CH ₂ OH | 3-NO ₂ C ₆ H ₄ CHO (5a) | 92 |
| 6 | 4-NO ₂ C ₆ H ₄ CH ₂ OH | 4-NO ₂ C ₆ H ₄ CHO (6a) | 95 |
| 7 | PhCH(OH)CH ₃ | PhCOCH ₃ (7a) | 87 |
| 8 | 4-MeC ₆ H ₄ CH(OH)CH ₃ | 4-MeC ₆ H ₄ COCH ₃ (8a) | 90 |
| 9 | 4-BrC ₆ H ₄ CH(OH)CH ₃ | 4-BrC ₆ H ₄ COCH ₃ (9a) | 81 |
| 10 | 4-ClC ₆ H ₄ CH(OH)CH ₃ | 4-ClC ₆ H ₄ COCH ₃ (10a) | 85 |
| 11 | C ₆ H ₅ CH(OH)CH ₂ CH ₃ | C ₆ H ₅ COCH ₂ CH ₃ (11a) | 91 |
| 12 | PhCH(OH)Ph | PhCOPh (12a) | 93 |
| 13 | 9-Hydroxyfluorene | 9-Fluorenone (13a) | 92 |
| 14 | α -Tetralol | α -Tetralone (14a) | 94 |
| 15 | Octan-2-ol | 2-Octanone (15a) | 45 |
| 16 | Cyclohexanol | Cyclohexenone (16a) | 35 |

^aAll yields refer to pure isolated products.

ated by-products. Attempted oxidation of allylic alcohols, crotyl alcohol and cinnamyl alcohol, was unsuccessful at the present reaction conditions. Replacing of [bmim]BF₄ ionic liquid reaction medium with dichloromethane provided much lowered yields at the present reaction system. Attempts to replacement of the copper(II) bromide with other various Lewis acid such as copper(II) chloride, ferric chloride, magnesium bromide, or magnesium chloride gave invariably gave products yields less than 50% in most cases. Substitution of nitric acid/copper(II) bromide by Cu(NO₃)₂ provided unchanged starting benzylic alcohols at the present reaction conditions. It is presumed the reaction occurred *via* the activation of nitric acid with copper(II) bromide in analogous to the reported sonochemical oxidation of alcohols with HNO₃ in the presence of FeCl₃.¹⁷

In summary, the combination of substoichiometric amounts of nitric acid and copper(II) bromide in [bmim]BF₄ ionic liquid provides an efficient process for the oxidation of benzylic alcohols into the corresponding carbonyl compounds.

Experimental Section

In this study 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) and the benzylic alcohols were purchased from Aldrich and used as received. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. All products were known and characterized by comparing their ¹H NMR spectra with those of reported literature data. ¹H NMR spectra were recorded on a Varian Gemini 2000 (300 MHz) using CDCl₃ and TMS as solvent and respectively. Mass spectra were recorded with a Micromass Autospec spectrometer. All products were known and characterized by comparing their ¹H NMR spectra with those of reported literature data.

General Procedure. To a stirred solution of a benzylic alcohol (1.0 mmol) in 1 mL [bmim]BF₄ was added 65% nitric acid (0.5 mmol) and copper(II) bromide (0.5 mmol). The reaction mixture was stirred in the air at 60 °C for 4 h and the reaction monitored by TLC for the complete consumption of the benzylic alcohol. The solution was cooled to room temperature and the product is extracted into ethyl acetate (2 × 20 mL), washed with water and dried over MgSO₄. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (ethyl acetate/*n*-hexane = 1:5, v/v) to yield the desired carbonyl compound.

Benzaldehyde (1a)¹⁸: ¹H NMR (300 MHz, CDCl₃) δ 11.02 (s, 1H), 8.87 (m, 2H), 8.74-8.40 (m, 3H); MS; *m/z* calcd for C₇H₆O [M]⁺: 106.04, found 106.17.

4-Methylbenzaldehyde (2a)¹⁸: ¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 7.76 (d, *J* = 8.1, 2H), 7.32 (d, *J* = 8.1, 2H), 2.42 (s, 3H). MS; *m/z* calcd for C₈H₈O [M]⁺: 120.06, found 120.24.

4-Bromobenzaldehyde (3a)¹⁹: ¹H NMR (300 MHz, CDCl₃) δ 9.97 (s, 1H), 7.75 (d, *J* = 8.5, 2H), 7.67 (d, *J* = 8.5, 2H). MS; *m/z* calcd for C₇H₅BrO [M]⁺: 183.95, found 183.09.

4-Chlorobenzaldehyde (4a)²⁰: ¹H NMR (300 MHz, CDCl₃)

δ 9.99 (s, 1H), 7.83 (d, *J* = 8.7, 2H), 7.51 (d, *J* = 8.3, 2H). MS; *m/z* calcd for C₇H₅ClO [M]⁺: 140.00, found 140.21.

3-Nitrobenzaldehyde (5a)²¹: ¹H NMR (300 MHz, CDCl₃) δ 10.14 (s, 1H), 8.86-8.65 (m, 1H), 8.63-8.39 (m, 1H), 8.37-8.15 (m, 1H), 7.80 (t, *J* = 7.9, 1H). MS; *m/z* calcd for C₇H₅NO₃ [M]⁺: 151.03, found 151.21.

4-Nitrobenzaldehyde (6a)¹⁸: ¹H NMR (300 MHz, CDCl₃) δ 10.17 (s, 1H), 8.41 (d, *J* = 8.6, 2H), 8.09 (d, *J* = 8.9, 2H). MS; *m/z* calcd for C₇H₅NO₃ [M]⁺: 151.03, found 151.21.

Acetophenone (7a)¹⁸: ¹H NMR (300 MHz, CDCl₃) δ 7.99-7.91 (m, 2H), 7.60-7.39 (m, 3H), 2.60 (s, 3H). MS; *m/z* calcd for C₈H₈O [M]⁺: 120.06, found 120.29.

1-*p*-Tolylethanone (8a)²²: ¹H NMR (300 MHz, CDCl₃) δ 7.84 (d, *J* = 8.1, 2H), 7.24 (d, *J* = 8.1, 2H), 2.56 (s, 3H), 2.39 (s, 3H). MS; *m/z* calcd for C₉H₁₀O [M]⁺: 134.07, found 134.25.

1-(4-Bromophenyl)ethanone (9a)²⁰: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, *J* = 8.7, 2H), 7.45 (d, *J* = 8.7, 2H), 2.46 (s, 3H). MS; *m/z* calcd for C₈H₇BrO [M]⁺: 197.97, found 198.15.

1-(4-Chlorophenyl)ethanone (10a)²³: ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 8.8, 2H), 7.42 (d, *J* = 8.8, 2H), 2.59 (s, 3H). MS; *m/z* calcd for C₈H₇ClO [M]⁺: 154.02, found 154.20.

Propiophenone (11a)²⁴: ¹H NMR (300 MHz, CDCl₃) δ 7.95 (m, 2H), 7.64-7.28 (m, 3H), 2.97 (q, *J* = 7.2, 2H), 1.21 (t, *J* = 7.2, 3H). MS; *m/z* calcd for C₉H₁₀O [M]⁺: 134.07, found 134.27.

Benzophenone (12a)¹⁸: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 4H), 7.51-7.40 (m, 2H), 7.39-7.29 (m, 4H). MS; *m/z* calcd for C₁₃H₁₀O [M]⁺: 182.07, found 182.25.

9-Fluorenone (13a)²⁴: ¹H NMR (300 MHz, CDCl₃) δ 7.65 (m, 2H), 7.53-7.42 (m, 4H), 7.32-7.20 (m, 2H). MS; *m/z* calcd for C₁₃H₈O [M]⁺: 180.06, found 180.26.

α-Tetralone (14a)²⁵: ¹H NMR (300 MHz, CDCl₃) δ 8.03 (m, 1H), 7.46 (m, 1H), 7.37-7.19 (m, 2H), 3.09-2.88 (m, 2H), 2.77-2.55 (m, 2H), 2.13 (m, 2H). MS; *m/z* calcd for C₁₀H₁₀O [M]⁺: 146.07, found 146.25.

2-Octanone (15a)²⁵: ¹H NMR (300 MHz, CDCl₃) δ 2.42 (t, *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 1.52-1.62 (m, 2H), 1.27-1.31 (m, 6H), 0.88 (t, *J* = 7.5 Hz, 3H). MS; *m/z* calcd for C₈H₁₆O [M]⁺: 128.12, found 128.35.

Cyclohexanone (16a)²⁵: ¹H NMR (300 MHz, CDCl₃) δ 2.34 (t, *J* = 6.6 Hz, 4H), 1.87 (m, 4H), 1.42-1.72 (m, 2H). MS; *m/z* calcd for C₆H₁₀O [M]⁺: 98.07, found 99.99.

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