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N-Methyl Morpholine Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

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N-Methyl Morpholine Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

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Abstract: Instantaneous generation of *N*-methyl morpholine chlorochromate (NMMCC) is an efficient reagent for oxidation of primary and secondary alcohols to the corresponding carbonyl compounds. The comparison of reaction time and product yield was studied with novel NMMCC and other chlorochromate reagents and shows that the presented method requires less reaction time with good yield at laboratory temperature. The synthesis of reagent, formation of toxic and hazardous chromylchloride have been avoided, and also use of NMMCC under microwave irradiation for oxidation leads to fast reaction time and success of the strategy.

Keywords: Alcohols, carbonyl compounds, microwave irradiation, *N*-methyl morpholine chlorochromate (NMMCC), oxidation

INTRODUCTION

Oxidation of alcohols to aldehydes or ketones is a ubiquitous transformation in organic chemistry. Chromium and chromium trioxide complexes are the mild reagents most extensively used for oxidation in the laboratory.[1–8] Unfortunately, most of them suffer at least from one of the following disadvantages: high cost of preparation, long reaction time, hygroscopisity, high acidity, instability, selectivity, and photosensitivity. Various modifications of the procedure have been developed to minimize

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these problems: (i) the reaction needs to be carried out at higher temperature (reflux temperature), (ii) loss of reagent yield (70–75%) at the reagent synthesis step[9–12] because of high water solubility, and (iii) the formation of chromyl chloride as side product, which is a very toxic and hazardous compound.

Our present work deals with the instantaneous generation of a novel *N*-methyl morpholine chlorochromate (NMMCC) reagent for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds in a single step, and the reaction is carried out at room temperature (25 °C). This reagent is efficient, and the formation of toxic and hazardous chromyl chloride is avoided.

The practicality of microwave irradiation to enhance chemical-reactions by increasing the reaction rates and formation of cleaner products has been recognized. It is clear that synergic applications of microwave-assisted technology allow rapid synthesis of biologically significant molecules on that support.

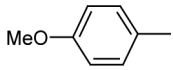
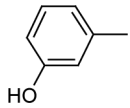
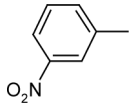
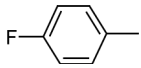
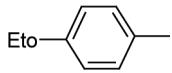
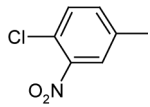
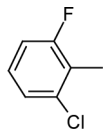
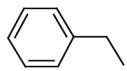
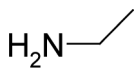
RESULTS AND DISCUSSION

The comparative study of the rate of reaction and the product yield using the conventional method (CM) with known chlorochromate reagents and the present novel reagent (NMMCC) informed us that the proposed reagent is efficient and consumes less time at laboratory temperature with high yield (Table 1). Further, microwave technology shows fast synthesis of the desired products with our new oxidation reagent.

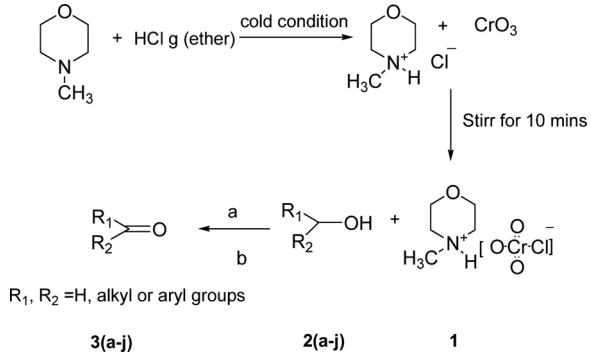
Equimolar ratio of saturated hydrochloric acid in dry ether was added slowly to the cold solution of *N*-methyl morpholine in dry chloroform with constant stirring. The solution was cooled to 0–5 °C, and then chromium trioxide was added portionwise. The reaction mixture was stirred for 10 min at the same temperature, followed by the addition of alcohol. Then the reaction mixture was stirred for 30–50 min at room temperature (Scheme 1). In a similar fashion, the reaction was carried out via microwave irradiation at 65 °C and the reaction completed within 10 min (Table 1). The reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mass was filtered, and the filtrate was evaporated under reduced pressure. The crude residue was purified by a short-length silica-gel column. Finally, the pure product was confirmed by ^{1}H NMR, infra red (IR), and liquid chromatography and mass spectra (LCMS) analysis.

In conclusion, we report a novel and efficient methodology for the oxidation of aliphatic and aromatic alcohols to the corresponding carbonyl compounds. The mild, stable, inexpensive, and straightforward

Table 1. Oxidative comparison of reaction rates of alcohols with the presented reagent (NMMCC) by conventional and microwave methods

			Present method (NMMCC)			
			Time (min)		Yield (%)	
Compounds	R_1	R_2	CM	MW	CM	MW
3a			50	6	96	99
3b		H	45	7	93	98
3c		H	55	7	95	98
3d		H	50	5	90	99
3e		H	50	5	90	96
3f		H	45	6	92	96
3g		H	48	7	91	98
3h		H	45	6	93	98
3i		H	50	6	95	99
3j		H	45	5	90	97

Note. CM = conventional method; MW = microwave method.



Scheme 1. Reaction condition: (a) rt, 30–50 min; (b) MW (65 °C), 5–10 min.

workup makes this method novel. In addition, this method does not require a large amount of the reagent or long reaction time.

EXPERIMENTAL

General

Silica-gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates (Merck F254). IR spectra were recorded using a Jasco FTIR-4100 series instrument. ^{1}H NMR spectra were recorded on a Shimadzu AMX 400-Bruker 400-MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent and TMS as internal standard (chemical shift in δ ppm). Spin multiplets are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Microwave using Biotase Initiator ($TM^{2.0}$) and mass spectra were determined in an ionization energy (EI) at 70 eV ionizing voltage.

Oxidation of benzhydrol to benzophenone (3a)

Equimolar ratio of saturated hydrochloric acid in dry ether (0.5 mL) was added slowly to the cold solution of *N*-methyl morpholine (0.5 mL) in dry chloroform with constant stirring. The solution was cooled to 0–5 °C, and then chromium trioxide (180 mg, 1.5 mmol) was added portionwise. The reaction mixture was stirred for 10 min at the same temperature, and then the reactant benzhydrol (150 mg, 1 mmol) was added and stirred at room temperature for 30–50 min. The same reaction was done through a microwave cavity at 65 °C; the reaction completes in 6 min. The reaction was monitored by thin-layer chromatography (TLC). The resulting crude product was purified by a short-length silica-gel column (60–120 mesh)

using hexane–ethyl acetate (8:2) as an eluent. The reaction time and yield of desired oxidation products are shown in Table 1.

The obtained pure product was in off-white crystalline solid (0.142 g, 96%). ^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.8 (m, 4H, Ar-H), 7.6 (m, 2H, Ar-H), 7.5 (m, 4H, Ar-H). IR (KBr, cm^{-1}): 1651, 1594, 1446, 1318, 1277. MS (ESI + ion): m/z = 183.2.

Oxidation of 4-methoxy benzyl alcohol to 4-methoxy benzaldehyde (3b)

The typical synthetic method described above afforded **3b**; the product obtained was a colorless liquid (0.146 g, 93%) from 4-methoxy benzyl alcohol **2b** (0.16 g, 1.0 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.86 (s, 1H, Ar-CHO), 7.87 (t, 2H, Ar-H, $J = 8$ Hz), 7.12 (t, 2H, Ar-H, $J = 8$ Hz), 3.85 (s, 3H, $-OCH_3$). IR (Nujol, cm^{-1}): 1684, 1599, 1261, 1160, 833. MS (ESI + ion): m/z = 136.7.

Oxidation of 3-hydroxy benzyl alcohol to 3-hydroxy benzaldehyde (3c)

The typical synthetic method described above afforded **3c**; the product obtained was a colorless liquid (0.140 g, 95%), from 3-hydroxy benzyl alcohol **2c** (0.15 g, 1.0 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10 (s, 1H, Ar-CHO), 9.93 (s, 1H, Ar-OH), 7.42 (m, 1H, Ar-H), 7.3 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.1 (m, 1H, Ar-H). IR (Nujol, cm^{-1}): 1669, 1580, 1492, 1284, 1152, 782. MS (ESI − ion): m/z = 120.6.

Oxidation of 3-nitro benzyl alcohol to 3-nitro benzaldehyde (3d)

The typical synthetic method described above afforded **3d**; the product obtained was a pale yellow solid (0.130 g, 90%) from 3-hydroxy benzyl alcohol **2d** (0.15 g, 1.0 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.13 (s, 1H, Ar-CHO), 8.6 (m, 1H, Ar-H), 8.5 (m, 1H, Ar-H), 8.3 (m, 1H, Ar-H), 7.9 (t, 1H, Ar-H, $J = 8.0$ Hz). IR (KBr, cm^{-1}): 1705, 1560, 1350, 1200. MS (ESI + ion): m/z = 151.1.

Oxidation of 4-fluoro benzyl alcohol to 4-fluoro benzaldehyde (3e)

The typical synthetic method described above afforded **3e**; the product obtained was a colorless liquid (0.270 g, 90%) from 4-fluoro benzyl

alcohol **2e** (0.3 g, 1.0 mmol). ^{1}H NMR (DMSO d_6, 400 MHz): δ 9.96 (s, 1H, Ar-CHO), 7.98 (m, 2H, Ar-H), 7.4 (m, 2H, Ar-H). IR (Nujol, cm^{-1}): 1698, 1597, 1506, 1232, 1150, 835, 598. MS (ESI + ion): m/z = 124.0.

Oxidation of 4-ethoxy benzyl alcohol to 4-Ethoxy benzaldehyde (3f)

The typical synthetic method described above afforded **3f**; the product obtained was a colorless liquid (0.184 g, 92%) from 4-ethoxy benzyl alcohol **2f** (0.2 g, 1.0 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.85 (s, 1H, Ar-CHO), 7.84 (d, 2H, Ar-H, $J = 8.0$ z), 7.08 (d, 2H, Ar-H, $J = 8.0$ z), 4.13 (q, 2H, $-OCH_2$), 1.35 (t, 2H, $-CH_3$). IR (Nujol, cm^{-1}): 1692, 1601, 1509, 1259, 1160, 1041, 834, 615. MS (ESI + ion): m/z = 150.7.

Oxidation of 4-chloro-3-nitro benzyl alcohol to 4-chloro-3-nitro benzaldehyde (3g)

The typical synthetic method described above afforded **3g**; the product obtained was a colorless liquid (0.182 g, 91%) from 4-ethoxy benzyl alcohol **2g** (0.2 g, 1.0 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.85 (s, 1H, Ar-CHO), 7.84 (d, 2H, Ar-H, $J = 8.0$ Hz), 7.08 (d, 2H, Ar-H, $J = 8.0$ Hz), 4.13 (q, 2H, $-OCH_2$), 1.35 (t, 2H, $-CH_3$). IR (Nujol, cm^{-1}):): 1692, 1601, 1509, 1259, 1160, 1041, 834, 615. MS (ESI + ion): m/z = 186.7.

Oxidation of 2-chloro-6-fluoro benzyl alcohol to 2-chloro-6-fluoro benzaldehyde (3h)

The typical synthetic method described above afforded **3h**; the product obtained was an off-white crystalline solid (0.186 g, 93%) from 2-chloro-6-fluoro benzyl alcohol **2h** (0.2 g, 1.0 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.3 (s, 1H, Ar-CHO), 7.75 (m, 1H, Ar-H), 7.52 (m, 1H, Ar-H), 7.46 (m, 1H, Ar-H). IR (KBr, cm^{-1}): 1703, 1600, 1454, 1248, 1192, 911, 790. MS (ESI − ion): m/z = 156.7.

Oxidation of benzyl alcohol to benzaldehyde (3i)

The typical synthetic method described above afforded **3i**; the product obtained was a colorless liquid (0.140 g, 95%) from benzyl alcohol **2i** (0.15 g, 1.0 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.94 (s, 1H, Ar-CHO), 8–7.5 (m, 5H, Ar-H). IR (Nujol, cm^{-1}): 1702. MS (ESI + ion): m/z = 107.0.

Oxidation of 2-aminoethanol to 2-aminoacetaldehyde (3j)

The typical synthetic method described above afforded **3j**; the product obtained was a colorless liquid (0.180 g, 90%) from aminoethanol **2j** (0.2 g, 1.0 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.81 (s, 1H, −CHO), 3.5–3.7 (m, 2H, $-CH_2$), 2.9 (s, 2H, $-NH_2$). IR (Nujol, cm^{-1}): 3361, 1722.

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