TMEDA: Efficient and Mild Catalyst for the Acylation of Alcohols, Phenols and Thiols under Solvent-free Condition

Santosh T. Kadam, Hanbin Lee, and Sung Soo Kim*

*Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: sungsoo@inha.ac.kr*
Received January 31, 2009, Accepted March 20, 2009

N,N,N′,N′-tetramethylethylenediamine (TMEDA) acts as a simple, mild and efficient catalyst for the acylation of alcohols, phenols and thiols at room temperature under solvent-free condition. Acylation reaction with acetic anhydride and benzoic anhydride proceeds with good to excellent yield in the presence of TMEDA as the catalyst.

Key Words: Acylation, TMEDA, Alcohols, Thiols, Solvent-free

Introduction

Ester and thioester are ubiquitous functional groups in natural and synthetic chemistry. Accordingly esterification and thioesterification are among the most fundamental and important reactions in organic chemistry.[1] Acylation is usually carried out by treating alcohols or thiols with acetic anhydride or acetyl chloride in the presence of acid or base catalyst in suitable organic solvent. Acetic anhydride is most commonly used due to low toxicity.[1] The most efficient base catalyst for acylation of alcohols are 4-(dimethylamino) pyridine (DMAP)[2a] and phosphines.[2b] Various acidic catalysts employed include $CoCl_2$,[2c] $RuCl_3$,[2d] nitrobenzenboronic acid,[2e] $Sc(OTf)_3$,[2f] $Al(OTf)_3$,[2g] $Cu(OTf)_2$,[2h] $LiClO_4$,[2i] $Cu(ClO_4)_2$,[2j] and N-heterocyclic carbene.[2k] Apart from some operational disadvantages such as moisture-sensitivity and high cost of catalyst, numerous methods employ perchlorates which are explosive[3] or toxic metal derivatives for the catalyst. Most of the work takes advantage of chlorinated hydrocarbon as solvent. Accordingly simple, mild and efficient catalytic method without help of metal and solvent is desirable.

N,N,N′,N′-tetramethylethylenediamine (TMEDA) can be classified as an organic base like amines and amidines that are regarded as the strong base[4] due to the resonance stability of their conjugate acid.[5] Recently Zhang *et al.* have reported that TMEDA promotes the synthesis of thiourea and its derivatives.[6] TMEDA was also used as an effective catalyst in combination with $CoCl_2$ for hydrosilylation of acrylonitrile.[7] Nishiyama *et al.* have shown that TMEDA acts as a powerful ligand for the hydrosilylation of ketones.[8] TMEDA also promotes regioselective ring opening of aziridines with trimethylsilylated nucleophiles.[9] Sano *et al.*[10] demonstrated that TMEDA could induce the acylation of alcohol with benzoyl chloride.

Experimental

In all cases the ^{1}H NMR (200 MHz) spectra were recorded with Varian Gemini 200. Chemical shifts were reported in ppm in $CDCl_3$ with TMS as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 400 (100 MHz). Some compounds were also identified by HRMS (EI) with Jeol DMX 303 and GCMS (EI 70eV). Data were collected through 1200L Single Quadrupole GC/MS system with 3800GC/Varian.

Acylation of Alcohols, Phenols and Thiols. TMEDA (45 μL, 0.3 mmol) was added to the mixture of alcohol (phenol and thiol) (1.0 mmol) and Ac_2O (2.0 mmol). The reaction mixture was stirred at room temperature for the appropriate time (Table 2). The reaction was monitored by TLC. Water was added after completion of reaction that was extracted with EtOAc (3×20 mL). The organic phase was dried over Na_2SO_4 and concentrated for purification by column chromatography with silica gel.

Benzyl Acetate (Table 2, entry 1): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.00 (s, 3H), 5.01 (s, 2H), 7.32-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$,100 MHz): δ 20.94, 66.19, 128.04, 128.06, 128.14, 128.36, 135.76, 170.58. HRMS (EI+): *m/z* $[M+H]^+$ Calcd for $C_9H_{10}O_2$: 150.0684; found: 150.0680. GCMS (EI, 70 eV): M+ *m/z* (%) = 149.90 (100).

4-Methoxybenzyl Acetate (Table 2, entry 2): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s, 3H), 4.15(s, 3H), 5.39 (s, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.67(d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.78, 55.96, 114.23, 127.21, 127.78, 128.12, 13.47, 17.32.

4-Methylbenzyl Acetate (Table 2, entry 3): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.10 (s, 3 H), 2.37 (s, 3 H), 5.09 (s, 2 H), 7.20 (d, *J* = 10 Hz, 2H), 7.26 (d, *J* = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$,100 MHz): δ 20.87, 65.96, 128.10, 128.89, 132.70, 137.65, 170.39. HRMS (EI+): m/z [M + H] calcd for $C_{10}H_{12}O$: 164.0837; found: 164.0837.

4-Nitrobenzyl Acetate (Table 2, entry 4): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.34 (s, 3H), 5.24 (s, 2H), 7.28-7.30 (m, 2H), 8.23-8.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.98, 109.25, 118.01, 122.24, 132.59, 152.65, 169.29.

4-Fluorubenzyl Acetate (Table 2, entry 5): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.37 (s, 3H), 5.28 (s, 2H), 7.42 (d, *J* = 7 Hz, 2H), 7.30 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.87, 65.43, 115.16, 115.37, 130.10, 131.63, 163.61, 170.51.

4-Bromobenzyl Acetate (Table 2, entry 6): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.17 (s, 3H), 5.08 (s, 2H), 7.12 (d, *J* = 6.9 Hz, 2h), 7.72 (d, *J* = 6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.92, 65.33, 122.48, 128.56, 129.45, 133.63, 170.51.

3-Aminobenzyl Acetate (Table 2, entry 7): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.17 (s, 3H), 3.90 (bs, 2H), 5.04 (s, 2H), 7.06 (d, 4Hz, 1H), 7.27 (t, *J* = 8 Hz, 1H), 7.45 (d, *J* = 4 Hz, 1H), 7.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.91, 66.07, 119.71, 123.77, 136.69, 138.45, 169.32.

(E)-3-Phenylprop-2-enyl Acetate (Table 2, entry 8): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.98 (s, 3H), 4.60 (t, *J* = 6.2 Hz, 2H), 6.20-6.22 (m, 1H), 6.54 (d, *J* = 1.7 Hz, 1H), 7.17-7.30

(m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.95, 64.97, 123.77, 126.42, 127.88, 128.42, 133.99, 136.01, 170.55.

4-Methoxyphenethyl Acetate (Table 2, entry 9): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.03 (s, 3H), 2.87 (t, *J* = 8 Hz, 2H), 3.78 (s, 3H), 4.23 (t, *J* = 8 Hz, 2H), 6.83 (d, *J* = 4 Hz, 2H), 7.14 (d, *J* = 4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.75, 34.03, 55.00, 64.98, 113.75, 129.66, 129.68, 158.17, 170.78.

1-(4-Chlorophenyl)ethyl Acetate (Table 2, enry 10): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (d, *J* = 4 Hz, 3H), 2.06 (s, 3H), 5.84 (q, *J* = 10 Hz, 1H), 7.25 (d, *J* = 4 Hz), 7.29 (d, J = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.17, 22.07, 71.52, 127.51, 128.64, 138.45, 140.25, 170.05.

Benzhydral Acetate (Table 2, entry 11): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.48 (s, 3H), 6.98 (s, 1H), 7.66-7.70 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.17, 76.72, 126.88, 127.68, 128.28, 140.00, 169.66.

Cyclopropyl(phenyl)methyl Acetate (Table 2, entry 12): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.37-0.40 (m, 2H), 0.53-0.59 (m, 2H), 1.32 (m, 1H), 2.08 (s, 3H), 5.22 (d, *J* = 4Hz), 7.27-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 2.97, 4.04, 16.48, 21.19, 79.57, 126.51, 127.75, 128.27, 140.28, 170.28.

Pyridine-2-methyl Acetate (Table 2, entry 13): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.13, (s, 3H), 5.19 (s, 2H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.95, 64.97, 123.00, 126.43, 127.88, 128.42, 133.99, 136.01, 170.55.

Furan-2-ylmethyl Acetate (Table 2, entry 14): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.06 (s, 3H), 5.04 (s, 2H), 6.35 (d, *J* = 10 Hz, 2H), 7.41 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.73, 57.99, 97.29, 110.50, 143.19, 150.53, 175.95.

1-3-Dioxoisoindolin-2yl-Acetate (Table 2, entry 15): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.38 (s, 3H), 7.77 (d, *J* = 4 Hz, 2H), 7.87(d, *J* = 4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.52, 123.92,134.55, 161.82, 166.50.

1-1′-Binaphthyl-2-2′-diyl Diacetate (Table 2, entry 16): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.98 (s, 6H), 7.15 (m, 2H), 7.28 (m, 2H), 7.43 (m, 2H), 7.47 (m, 2H), 7.94 (m, 2H), 8.00 (M, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.56, 121.91,123.46. 125.73, 126.20,126.75, 128.04, 129.52, 131.54, 133.39, 146.81, 169.35.

Bicyclo-(2, 2, 1) hept-5-ene-2, 3-diylbis(methylene) Diacetate (Table 2, entry 17): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30, 1.50 (d,d, *J* = 4, 4 Hz, 2H), 2.01 (m, 2H), 2.03 (s, 6H), 2.48-2.51 (m, 2H), 2.88 (s, 2H), 3.74 (t, *J* = 10 Hz, 2H), 3.87 (t, *J* = 10 Hz, 2H), 6.1 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.86, 40.56, 45.46, 48.92, 64.44, 135.33, 170.72.

Undecyl Acetate (Table 2, entry 18): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6 Hz, 3H), 1.19-1.29 (m, 17H), 1.59 (t, *J* = 6 Hz, 2H) 20.02 (s, 3H), 4.03 (t, *J* = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.02, 20.89, 22.63, 25.87, 28.58, 29.25, 26.58, 31.86, 64.60, 175.98.

Decan-2-yl Acetate (Table 2, entry 19): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.84 (t, *J* = 10 Hz, 3H), 1.14-1.21 (m, 5H), 1.30-1.52 (m, 12H), 1.97 (s, 3H), 3.74 (q, *J* = 4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.99, 19.85, 21.25, 22.58, 25.33, 29.17, 29.39, 31.79, 35.87, 70.97, 175.95.

(E)-3,7-Dimethylocta-2,6-dienyl Acetate (Table 2, entry 20): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.59 (s, 3H), 1.68 (s, 6H), 2.02 (s, 3H), 2.06-2.09 (m, 4H), 4.55 (d, *J* = 4 Hz, 2H) 5.07 (t, *J* = 6 Hz, 1H), 5.32 (t, *J* = 6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.41, 17.63, 20.99, 25.61, 26.82, 39.50, 61.36, 118.27, 123.73, 131.78, 142.19, 171.04.

Cyclohex-3-enylmethyl Acetate (Table 2, entry 21): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.56 (s, 3H), 1.27-1.37 (m, 2H), 1.60-1.79 (m, 4H), 2.05 (s, 3H), 3.97 (t, *J* = 10 Hz, 2H), 5.64-5.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.79, 24.28, 25.18, 28.03, 32.87, 68.66, 125.37, 126.97, 171.10.

3,5,5-Trimethylcyclohex-2-enylacetate (Table 2, entry 22): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.28 (m, 6H), 1.71-1.76 (m, 4H), 1.89-1.91 (m, 1H), 2.01 (s, 3H), 3.91 (q, *J* = 6 Hz, 1H), 5.62 (t, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.81, 24.30, 25.19, 28.03, 32.88, 68.67, 125.38, 126.93, 171.11.

2-Isopropyl-5-methylcyclohexyl Acetate (Table 2, entry 23): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.74-0.76 (s, 3H), 0.81-0.89 (m, 6H), 1.31-1.48 (m, 4H), 1.62-1.69 (m, 3H), 1.83-1.87 (m, 1H), 2.02 (s, 3H), 4.66 (q, *J* = 12 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.68, 21.26, 21.96, 23.46, 26.28, 31.32, 34.22, 40.89, 46.96, 74.10, 170.62.

5,6,7,8-Tetrahydronaphthalen-yl Acetate (Table 2, entry 24): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.76-1.79 (m, 4H), 2.30 (s, 3H), 2.56-2.78 (m, 4H),6.82 (d, *J* = 4H), 6.95 (d, *J* = 4 Hz, 1H), 7.09 (d, *J* = 4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.77, 22.47, 22.66, 23.25, 29.42, 118.89, 125.88, 126.92, 129.38, 139.20, 149.12, 169.32.

Phenyl Acetate (Table 2, entry 25): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.49 (s, 3H), 7.21 (d, *J* = 7 Hz, 2H), 7.58 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.95, 122.77, 129.23, 130.93, 148.92, 168.88.

4-Isopropylphenyl Acetate (Table 2, entry 26): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (d, *J* = 7.6 Hz, 6H), 2.25 (s, 3H), 2.86-2.88 (m, H), 6.96 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.07, 24.00, 33.60, 121.21, 127.30, 146.29, 148.63, 170.14. GCMS: *m/z*: 178 [$M^{+\cdot}$], 136, 121.

4-Nitrophenyl Acetate (Table 2, entry 27): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.34 (s, 3H), 7.28-7.30 (m, 2H), 8.23-8.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.98, 109.25, 118.01, 122.24, 132.59, 152.65, 169.29.

4-Cyanophenyl Acetate (Table 2, entry 28): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.33 (s, 3H), 7.21-7.28 (m, 2H), 7.6-67.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.98, 109.12, 118.42, 122.53, 133.39, 153.63, 170.18. HRMS (EI+): *m/z* $[M+H]^+$ Calcd for $C_9H_7NO_2$: 161.0477, found: 161.0487.

3-Methoxyphenyl Acetate (Table 2, entry 29): ^{1}H NMR ($CDCl_3$, 200 MHz): 2.25 (s, 3H), 3.76 (s, 3H), 6.65-6.69 (m, 3H), 7.22-7.28 (m,1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.77, 22.47, 22.66, 23.25, 29.42, 118.89, 125.88, 126.92, 129.38, 139.20, 149.12, 169.32.

2-Formylphenyl Acetate (Table 2. Entry 31): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.21 (s, 3H), 7.48 (d, *J* = 6 Hz, 1H), 7.71 (d, *J* = 6 Hz,1H), 7.87 (d, *J* = 6 Hz, 1H), 7.92 (d, *J* = 6 Hz, 1H), 10.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.95, 122.32, 123.98, 126.12, 131.28, 134.77, 135.30, 151.24, 169.70, 188.87.

Phenyl Ethanethioate (Table 2, entry 32): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 3H), 7.32-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.13, 127.90, 129.14, 129.37, 134.39, 193.95. HRMS (EI+): m/z [M + H] calcd for C_8H_8OS : 152.0296; found: 152.0284.

4-Chlorophenyl Ethanethiol (Table 2, entry 33): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 3H), 7.12 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.53, 127.48, 129.21, 129.77, 133.89, 193.75.

4-Chlorobenzyl Ethanethiol (Table 2, entry 34): ^{1}H NMR

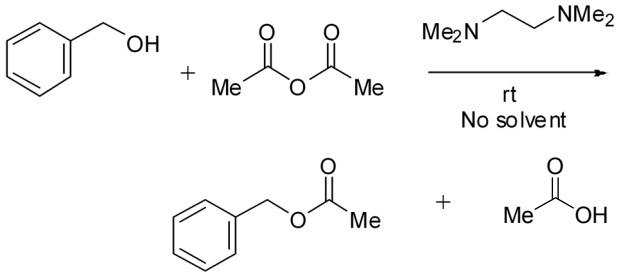
($CDCl_3$, 200 MHz): δ 2.39 (s, 3H), 4.11 (s, 2H), 7.24-7.29 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.18, 32.62, 128.63, 128.73, 130.05, 130.15, 193.45.

4-Methoxybenzyl Ethanethiol (Table 2, entry 35): ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40 (s, 3H), 3.84 (s, 3H), 4.14 (s, 2H), 6.87 (d, J = 10 Hz, 2H), 7.27 (d, J = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.31, 32.94, 55.23, 114.02, 129.57, 129.93, 158.82, 193.55.

Result and Discussion

In light of our success in developing several catalytic systems for the synthesis of chiral and achiral cyanosilyl ether,[11] we extend them to the acylation of alcohol.[12] Herein we wish to report the acylation of alcohols, phenols and thiols with acetic anhydride in the presence of TMEDA at room temperature under solvent-free condition (Scheme 1). In order to establish the optimized reaction condition, we have performed study using benzyl alcohol as a model substrate in the presence of various amount of TMEDA (Table 1). Initially 0.20 equiv of TMEDA and acetic anhydride give only 55% of product within 30 min, while 0.30 equiv of TMEDA yields 98 % in 6 min reaction time. Neither increasing TMEDA amount from 0.30 to 0.40 equiv nor decreasing the reaction temperature to 0 °C affects the catalyst performance. Use of 1.0 equiv of acetic anhydride gives somewhat lower yield of 70% in quite longer reaction time (50 min). Accordingly, the catalyst loading of 0.30 equiv with 2.0 equiv of acetic anhydride at room temperature can be regarded as optimal condition for the acylation (Table 1, entry 3).

A wide range of structurally diverse and functionalized alcohols, phenols and thiols underwent the acylation in excellent yield in most cases. The results are shown in Table 2. A large-scale (10.0 g) acylation of benzyl alcohol is carried out with the same amount of catalyst and the reaction proceeded rapidly in high yield (entry 1). Various benzyl alcohols having electron-donating and electron-withdrawing substituent undergo acylation in quite high yield (entries 2-6). Halogenated benzyl alcohols such as *p*-flouro and *p*-bromobenzyl alcohol produce acylated products (entries 5 and 6). This indicates that electronic effect of halogen atom may have little influence on the acylation. *m*-Aminobenzyl alcohol gives poor yield of 68% product within 13 min reaction time (entry 7). Cinnamyl alcohol and *p*-methoxyhydrocinnamyl alcohol are able to produce 90 and 95% yield of the acetates in 20 and 10 min reaction time, respectively (entries 8 and 9). This procedure is also applicable to several secondary aromatic alcohols with "relatively" longer reaction time of 24-32 min (entries 10-12). Heterocyclic furfuryl alcohol and 2-pyridinecarbinol give corresponding acetates with excellent yield (entries 13 and 14). This may suggest that adjacent heterocyclic ring have no influence at all on the reactions. The same procedure is also equally useful for the *N*-hydroxyphthalimide, which produces acetate with excellent yield in short reaction time (6 min, entry 15). In addition to the aromatic alcohols this catalyst is effective for the variety of aliphatic alcohols (entries 17-23). Long chain aliphatic secondary alcohol requires longer reaction time (2 h) relative to primary one (20 min). The longer reaction time could be due to the steric effect exerted by long straight chain. Acid sensitive molecule like geraniol consumes 30 min for 88% yield. However, 3, 5, 5-trimethyl-2-cyclohexene-ol demands increased catalyst amount of 1 equiv for the 96% yield within 25 min (entry 22). Menthol also underwent smooth acylation and gives 85% yield in 46 min reaction time (entry 23).



Scheme 1. TMEDA Catalyzed Acylation of Benzyl Alcohol.

Interestingly, phenols too undergo acylation smoothly under the same reaction condition. Phenols with activating and deactivating groups altogether undergo acylation rapidly with very high yield except for one case (entry 31). Strongly electron-withdrawing groups of cyano and nitro substituent produces 98 and 95% yield in 6 and 4 min reaction time, respectively (entries 27 and 28). *p*-Methoxyphenol needs 4 min to give 94% of product while *m*-methoxy phenol takes "relatively" quite longer reaction time with slightly lower yield (20 min and 91%, entries 29 and 30). Here again electronic effect exerts insignificant influence on the reaction. Salicylaldehyde produces 60% acylated product in 20 min reaction time which could be counted as poor yield (entry 31).

The same catalytic system also able to catalyze the thioesterification of thiols (entries 32-35). Benzenethiol gives corresponding acetate with 92% yield within 5 min reaction time. Benzylmercaptan having chloro and methoxy substituents on benzene ring produce corresponding acylated product with considerably high yield in short reaction time (entries 34 and 35). Although all the reactions are carried out

Table 1. Optimization of the Reaction Condition for Acylation of Benzyl Alcohol with Acetic Anhydride.

Entry	Acetic Anhydride (equiv)	Catalyst (mmol)	Temp (°C)	Time (Min)	Yield[a] (%)
1	2.0	0.10	rt	No reaction	No reaction
2	2.0	0.20	rt	30	55
3	2.0	0.30	rt	6	98
4	2.0	0.30	0	6	97
5	2.0	0.40	rt	6	97
6	1.0	0.30	rt	50	70

[a]Isolated yield.

Table 2. Acylation of Alcohols, Phenols and Thiols with Acetic Anhydride Catalyzed by TMEDA[a]

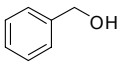
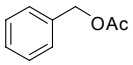
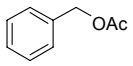
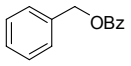
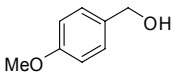
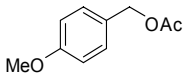
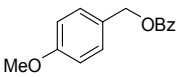
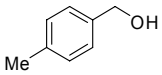
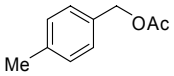
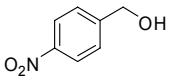
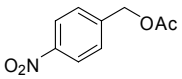
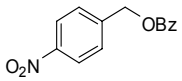
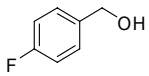
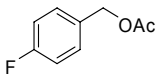
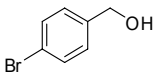
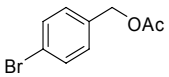
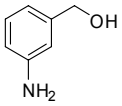
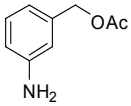
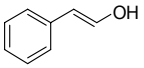
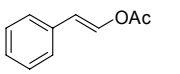
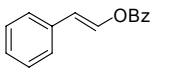
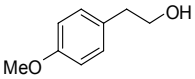
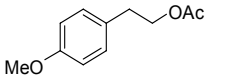
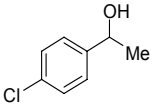
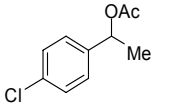
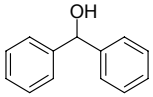
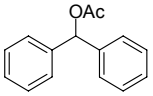
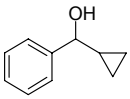
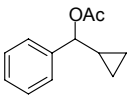
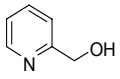
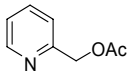
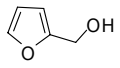
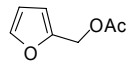
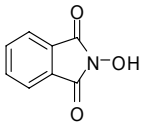
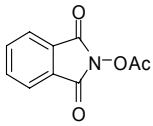
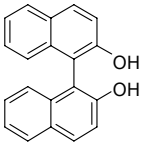
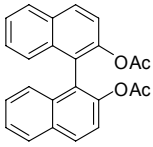
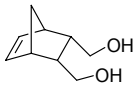
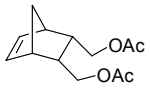
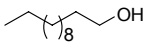
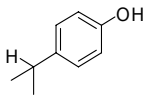
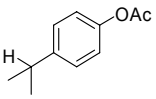
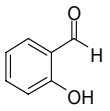
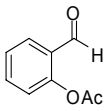
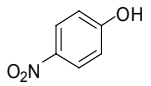
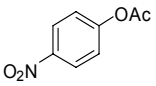
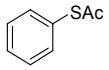
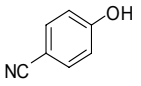
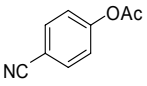
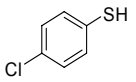
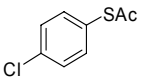
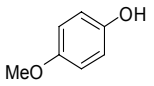
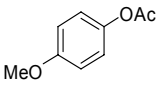
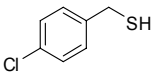
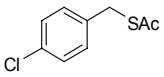
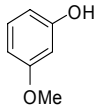
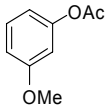
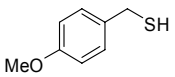
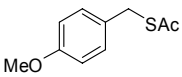
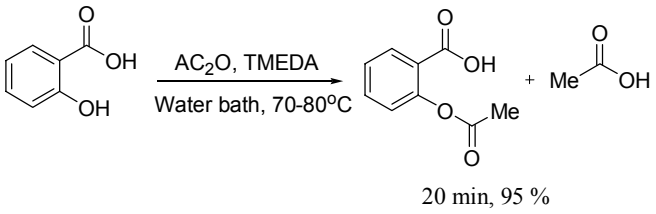
Entry	Substrate	Product	Time (min)	Yield (%)[b]
1			6	97
			10	94[c]
			30	94[d]
2			15	94
			20	92[d]
3			16	93
4			7	97
			30	77[d]
5			10	90
6			7	87
7			13	68
8			20	90
			35	83[d]
9			10	95
10			32	85
11			25	71
12			24	92
13			7	98
14			15	94
15			6	97
16			13	93
17			18	84
18			20	80
19			2 h	77
20			30	88
21			6	92
22			25	96[e]
23			46	85
24			23	85
25			8	93

Table 2. Continued

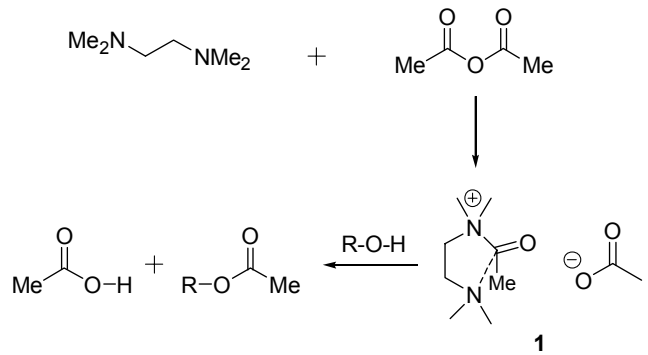
Entry	Substrate	Product	Time (min)	Yield (%)[b]	Entry	Substrate	Product	Time (min)	Yield (%)[b]
26			4	98	31			20	60
27			4	95	32			5	92
28			6	98	33			5	90
29			4	94	34			15	98
30			20	91	35			5	94

[a]Reagent and Condition: Alcohol (1 equiv), Ac_2O (2 equiv), TMEDA (0.3 equiv), room temperature. All products were characterised by ^1H and ^{13}C NMR and compared with the liturature.[12,17] [b]Isolated yield. [c]Large scale reaction employes 10.0 mmol of benzyl alcohol. [d]Benzoylation with 1.0 mmol of Benzoic Anhydride. [e]1.0 mmol TMEDA used.

with acetic anhydride, other anhydride such as benzoic anhydride is also equally effective for acylation of benzyl alcohol (Table 2, entries 1, 2, 4 and 8). Benzoylation with benzoic anhydride takes relatively longer reaction time compared to the reactions with acetic anhydride. The acylation of salicylic acid (asprin synthesis) turns out to give 95% yield within 20 min at "elevated" temperature (80 °C) (Scheme 2). The industrial production of asprin normally employs mineral acid or Lewis acid at high temperature too. The proposed reaction path has been shown in Scheme 3. The formation of acyl-TMEDA



Scheme 2. Synthesis of Asprin.



Scheme 3. Plausible Reaction Path for Acylation of Alcohol.

cation, **1** through reaction of TMEDA with acetic anhydride and then alcohol reacts with acylated TMDA in second step to form the ester product.[10,18]

Nitrobenzenboronic acid (2.5 mol%)[2e] catalyzes the acylation of furfuryl alcohol (92%) and 4-nitrophenol (90%) in 10 h and 8 h reaction time, respectively. The present reaction condition however needs only 0.3 equiv of TMEDA within 15 and 4 min for 94 and 95% yield (entry 14 and 27). Methylbenzensulphonimide as catalyst needs 0.05-0.3 equiv to give acylated product (90-97%) within 1-17 h reaction time using dichloromethane as solvent.[13] Trichloroisocyanuric acid (0.05 equiv) is required for 75-95% yield of acylated product within 1-20 h in dichloromethane.[14] Five mol% of $ErCl_3$ is consumed for 99% yield of acetate at over 50 °C within 1-3 h reaction time.[15] In comparison with our results, $CoCl_2$ [2c] claims 5 mol % for 90-98% yield within 2-6 h reaction time at 25-80 °C and 5 mol% of CBr_4 requests 6 h reaction time for 96% yield at 60 °C,[16] whereas present method give similar yield within shorter reaction time (6-40 min) at room temperature. The same reaction demands 1 mol% of $Mg(ClO_4)_2$ for 85-98% yield within 30 min to 3 h reaction time.[17] Oriyama *et al.* has reported that acylation of alcohol with benzoyl chloride required 0.6 equiv of TMEDA with molecular sieves 4Å (MS) as an additive at -78 °C in dichloromethane.[10] In contrast to these results it is clear that present catalytic method needs relatively less amount of TMEDA (0.3 mmol) without any additive at room temperature under solvent-free condition in comparatively shorter reaction time.

Conclusion

TMEDA is found to be efficient and mild catalyst for acylation of alcohols, phenols and thiols within comparatively short reaction time. This method constitutes an excellent

way of acylation reaction, which avoids the use of hazardous acid, expensive Lewis acid and metal salts. This method is able to catalyze the acylation of benzyl alcohol with benzoic anhydride. The present catalytic method is suitable of large-scale acylation for industrial application. The solvent and metal free conditions are environmentally friendly.

Acknowledgments. Authors thank the Centre for Biological Modulators for the financial support. BK21 has been provided from Korea Research Council.

References

1. (a) For general reviews, see Larock, R. C. *Comprehensive Organic Transformation*, 2nd ed.; Wiley-VCH: New York, 1996; 1999; p 1955. (b) *Comprehensive Organic Synthesis*; Torst, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1992; Vol. 6. (c) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Syntheis*, 2nd ed.; Wiely-VCH: New York, 1991; Chapter 7 and 3rd ed.; 1999; pp 150-160.
2. (a) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Eng.* **1978**, *17*, 569. (b) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (c) Iqbal, J.; Srivastava, R. R. *J. Org. Chem*. **1992**, *57*, 2001. And references cited therein. (d) Dey, S. K. *Tetrahedron Lett.* **2003**, *45*, 2919. (e) Tale, R. H.; Adude, R. N. *Tetrahedron Lett.* **2006**, *47*, 7263. (f) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem*. **1996**, *61,* 4560. (g) Kamal, A.; Khan, M. A.; Reddy, S. Y.; Srikant, V. V.; Krishnaji, T. *Tetrahedron Lett.* **2007**, *48*, 3813. (h) Saravanan, P.; Singh, V. *Tetrahedron Lett.* **1999**, *40*, 2611. (i) Nakae, Y.; Kusaki, I.; Sato, T. S*ynlett* **2001**, 1584. (j) Kondasamy, J. K.; Chaand, D. K. *J. Mol Catal. A: Chem.* **2006**, *255*, 275. (k) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4,* 3583.
3. Schumacher J. C. *Perchlorates-Their Properties, Manufacture and use* in *ACS Monograph Searies*; Reinhold: New York, 1996.
4. (a) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc. Perkin Trans 1*, **1998**, 1541. (b) Kovacevic, B.; Maksic, Z. B. *Org. Lett.* **2001**, *3*, 1523.
5. Yamamota, Y.; Kojima, S. In *The Chemistry of Amidines and Imidates*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, p 485.
6. Wei, T. B.; Lin, Q.; Zhang, Y. M.; Wang, H. *Synth. Commun.* **2004**, *34*, 2205.
7. Chauhan, M.; Boudjouk, P. *Can. J. Chem.* **2000**, *78*, 1396.
8. Nishiyama, H.; Furuta, A. *Chem. Commun*. **2007**, 760.
9. Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509.
10. Sano, T.; Ohashi, K.; Oriyama, T. *Synthesis* **1999**, 1141.
11. (a) Kim, S. S.; Song, D. H. *Eur. J. Org. Chem.* **2005**, 1777. (b) Kim, S. S.; Lee, S. H. *Synth. Commun.* **2005**, *35*, 751. (c) Kim, S. S.; Lee, S. H. Kwak, J. M. *Tetrahedron Asymmetry* **2006**, *17*, 1165. (d) Kim, S. S.; Kwak, J. M. *Tetrahedron* **2006**, *62*, 49. (e) Kim, S. S.; Rajagopal, G.; Song, D. H. *J. Organomet. Chem.* **2004**, *689*, 1734. (f) Kim. S. S.; Kim, D. W.; Rajagopal, G. *Synthesis* **2004**, 213. (g) Kim, S. S.; Rajagopal, G.; Kim, D. W.; Song, D. H. *Synth. Commun.* **2004**, *34*, 2973. (h) Kim, S. S.; Rajagopal, G. *Synthesis* **2007**, 215. (i) Kim, S. S.; Kadam, S. T. *Bull. Korean Chem. Soc.* **2008**, *29*, 1320. (j) Kim, S. S.; Kadam, S. T. *Catal. Commun*. **2008**, *9*, 1342.
12. (a) Kadam, S. T.; Kim, S. S. *Synthesis* **2008**, 267. (b) Kadam, S. T.; Kim, S. S. *Synthesis* **2008**, *20*, 3307.
13. Khazaei, A.; Rostami, A.; Tanbakouchian, Z.; Zinati, Z. *Catal. Commun.* **2006**, *7*, 214.
14. Zolfigol, M. A.; Khazaei, A.; Cjoghamarani, A. G.; Rostami, A.; Hajjami, M. *Catal. Commun*. **2006**, *7*, 399.
15. Dalpozzo, R.; Nino, A. D.; Maiulo, L.; Oliverio, M.; Procopio, A.; Russo, B.; Tocci, A. *Aus. J. Chem.* **2007**, *60*, 75.
16. Zhag, L.; Luo, Y.; Fan, Renhua, F.; Wu, J. *Green Chem*. **2007**, *9*, 1022.
17. Chakraborti, A. K.; Sharma, L.; Gilhane, R.; Shivani. *Tetrahedron* **2003**, *59*, 7661.
18. Shangjie, Xu.; Ingmar, H.; Bernhard, K.; Herbert, M.; Wolfgang, S.; Hendrik, Z. *Chem. Eur. J.* **2005**, *11*, 4751.