Remarkably Fast Acylation of Alcohols with Benzoyl Chloride Promoted by TMEDA

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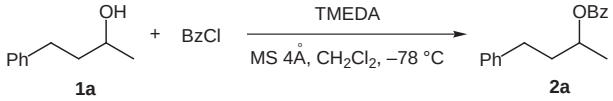
Received 13 January 1999

Abstract: Reaction of alcohols with benzoyl chloride in the presence of TMEDA at –78°C resulted in very fast acylation to afford the corresponding benzoates in excellent yields.

Key Words: TMEDA, benzoyl chloride, benzoylation of alcohols, chemoselectivity



Scheme 1

Acylation of alcohols is a very important functional group transformation in synthetic organic chemistry. Acylations in general take place by the treatment of alcohols with acid anhydride or acid halide under the influence of a base such as triethylamine, pyridine etc.[1,2] For example, the benzoylation of alcohols with benzoyl chloride usually proceeds in the presence of pyridine at above 0°C. Several other procedures for the benzoylation of alcohols at –40°C or upper have been reported.[3] However, to the best of our knowledge, only Koreeda et al.[4] have reported that benzoylation with benzoyl triflate in the presence of pyridine can be carried out smoothly even at –78°C.

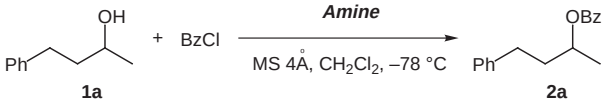
Our previous reports have documented the utility of chiral 1,2-diamines derived from (*S*)-proline as efficient catalysts capable of catalyzing an asymmetric acylation of racemic secondary alcohols[5] and *meso*-1,2-diols[6] with achiral benzoyl chloride. The use of only 0.5 mol% of chiral 1,2-diamine to the substrate combined with a stoichiometric amount of achiral triethylamine at –78°C gave the corresponding benzoate with good to excellent ee in good yields.

Now we wish to report an expedient method for the remarkably fast acylation of alcohols at –78°C with benzoyl chloride promoted by the 1,2-diamine, TMEDA (*N*,*N*,*N'*,*N'*-tetramethylethylenediamine)[7]. In the first place, we undertook to examine the acylation of 4-phenylbutan-2-ol (**1a**) as a model substrate with benzoyl chloride in the presence of TMEDA and molecular sieves 4Å (MS) at –78°C in dichloromethane (Scheme 1, Table 1). When the reaction was performed with 1.2 equivalents of benzoyl chloride in the presence of 1.0 equivalent of TMEDA for 5 minutes, the corresponding benzoate **2a** was obtained in 96% yield (Entry 1). On the other hand, the reaction proceeded in the absence of MS 4Å somewhat slower than in its presence (Entry 2). When the amount of TMEDA was decreased to 0.6 equivalent, a similar fast acylation was completed in 20 minutes to give the benzoate **2a** in 97% yield (Entry 4). In EtCN the starting alcohol **1a** still remained after 20 minutes (Entry 5).

Table 1 Acylation of 4-Phenylbutan-2-ol (**1a**) with Benzoyl Chloride (BzCl) in the Presence of TMEDA

Entry	BzCl (equiv)	TMEDA (equiv)	Time (min)	Yield of **2a** (%)[a]	Recovery of **1a** (%)[a]
1	1.2	1.0	5	96	0
2	1.2	1.0[b]	5	72	21
3	1.1	0.6	5	96	trace
4	1.1	0.6	20	97	0
5	1.1	0.6[c]	20	87	7

[a] Isolated yield of purified product.
[b] Carried out without MS 4Å.
[c] Performed in EtCN instead of CH_2Cl_2.

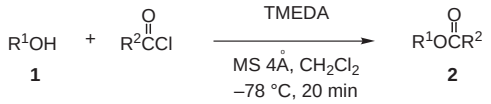


Scheme 2

Table 2 The Effect of Various Amines on the Acylation of 4-Phenylbutan-2-ol (**1a**) with Benzoyl Chloride (BzCl)

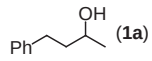
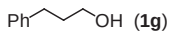
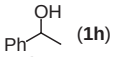
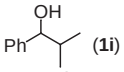
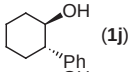
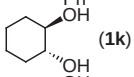
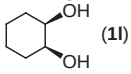
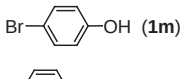
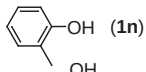
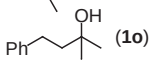
Entry	Amine (equiv)	BzCl (equiv)	Time	Yield of **2a** (%)[a]
1	TMEDA (0.6)	1.1	20 min	97
2	none	1.5	3 h	0
3	Et_3N (1.1)	1.5	3 h	2
4	Py (1.0)	1.5	5 h	48
5	$Me_2NCH_2NMe_2$ (0.6)	1.1	3 h	2[b]
6	DMPRA[c] (1.1)	1.5	3 h	26
7	DABCO[d] (1.1)	1.6	3 h	88
8	$Me_2N(CH_2)_3NMe_2$ (0.6)	1.1	3 h	22
9	$Me_2N(CH_2)_4NMe_2$ (0.6)	1.1	3 h	16

[a] Isolated yield of purified product.
[b] *N*,*N*-Dimethylbenzamide was obtained in 85% from BzCl.
[c] DMPRA = 1,4-dimethylpiperazine.
[d] DABCO = 1,4-diazabicyclo[2.2.2]octane.



Scheme 3

Table 3 Acylation of Various Alcohols with Acyl Chlorides in the Presence of TMEDA[a]

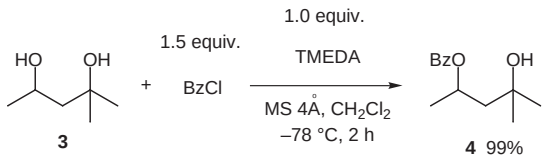
Entry	R^1OH	R^2	Product	Yield (%)[b]
1	 (**1a**)	Ph	**2a**	97
2		4-$NO_2C_6H_4$	**2b**	99
3		4-$MeOC_6H_4$	**2c**	95
4		4-MeC_6H_4	**2d**	96
5[c]		2-MeC_6H_4	**2e**	95
6[d]		Me	**2f**	33
7	 (**1g**)	Ph	**2g**	97
8	 (**1h**)	Ph	**2h**	97
9[d]	 (**1i**)	Ph	**2i**	94
10	 (**1j**)	Ph	**2j**	96
11[e]	 (**1k**)	Ph	**2k**	96[f]
12[e]	 (**1l**)	Ph	**2l**	95[f]
13	 (**1m**)	Ph	**2m**	95
14	 (**1n**)	Ph	**2n**	96
15[g]	 (**1o**)	Ph	**2o**	0

[a] R^2COCl (1.1 equiv), TMEDA (0.6 equiv).
[b] Isolated yield of purified product.
[c] Reaction was carried out for 2 h.
[d] Reaction was carried out for 6 h.
[e] 1.2 equivalents of TMEDA and 2.2 equivalents of BzCl were used.
[f] Corresponding dibenzoate.
[g] Reaction was carried out for 3 h.

The effect of various amines was then examined (Scheme 2, Table 2). No acylation of **1a** with benzoyl chloride in the presence of only MS 4Å took place at –78°C (Entry 2). A stoichiometric amount of triethylamine and pyridine gave rise to acylation of **1** at –78°C to afford the benzoylated product **2** even after 3–5 hours in only 2 and 48% yield, respectively (Entries 3 and 4). The 1,1-diamine, *N*,*N*,*N*',*N*'-tetramethylmethanediamine also hardly gave the benzoate **2a** because it reacted with benzoyl chloride to afford *N*,*N*-dimethylbenzamide (Entry 5). 1,2-Diamines such as DMPRA (1,4-dimethylpiperazine) and DABCO (1,4-diazabicyclo[2.2.2]octane), 1,3-diamine such as *N*,*N*,*N*',*N*'-tetramethylpropane-1,3-diamine, and 1,4-diamine such as *N*,*N*,*N*',*N*'-tetramethylbutane-1,4-diamine were not effective compared with TMEDA (Entries 6–9). These results showed that TMEDA was the most effective amine for the acylation with benzoyl chloride at –78°C. Acylation of **1a** occurred very smoothly at –78°C for 20 minutes to give the benzoate **2a** in 97% yield (Entry 1).

The acylation was conducted with a variety of alcohols and the results are represented in Table 3 (Scheme 3). Similar fast acylations with substituted benzoyl chloride having nitro, methoxyl, and methyl groups were also successful as shown in Entries 2–5. On the other hand, acylation with acetyl chloride proceeded slowly under the same reaction conditions to give the acetate even after 6 hours in only 33% yield (Entry 6). Various alcohols including primary and secondary alcohols and, acyclic and cyclic alcohols were benzoylated facilely to the corresponding benzoates in excellent yields (Entries 7–10). Diols also gave the corresponding dibenzoates in excellent yields (Entries 11 and 12). Phenolic hydroxyl groups were also acylated readily with benzoyl chloride in the presence of TMEDA (Entries 13 and 14). However, tertiary alcohol did not react with benzoyl chloride under similar reaction conditions (Entry 15). This prompted us to examine the chemoselective acylation between secondary and tertiary alcohols.

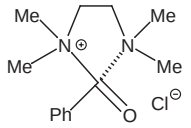
2-Methylpentane-2,4-diol (**3**) having both secondary and tertiary hydroxyl groups was reacted with benzoyl chloride in the presence of TMEDA at –78°C to give specifically the monobenzoate **4** of the secondary hydroxyl group in 99% yield (Scheme 4).



Scheme 4

The details of the reaction mechanism are not clear at present; however, we suppose that a benzoyl chloride–TMEDA complex **5** (Figure) plays a significant role for the very fast benzoylation. ^1H NMR spectra of the benzoyl chloride–TMEDA complex **5** showed that both signals of methyl and methylene of TMEDA displayed evident downfield shift (2.37 from 2.24, 2.60 from 2.38 ppm, respectively) compared with TMEDA alone, which sug-

gested steady complexation of benzoyl chloride and TMEDA.[8]



5

Figure. Structure of benzoyl chloride-TMEDA complex

In summary, the present fast acylation of hydroxyl groups has the following synthetic advantages: 1) excellent chemical yield, 2) high efficiency (1.1 equivalents of benzoyl chloride and 0.6 equivalent of TMEDA), and 3) simple operation. Further studies towards synthetic applications and to clarify the detailed reaction mechanism are under way in our laboratory.

All reactions were carried out under argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz on a JEOL GSX-400 spectrometer, respectively. The chemical shifts are reported in ppm (δ) relative to TMS in $CDCl_3$. IR spectra were recorded in cm^{-1} on a JASCO FT/IR-300E spectrometer. CH_2Cl_2 was distilled from CaH_2. TLC were performed on Wakogel B-5F silica gel with EtOAc and hexane as eluent.

2-Benzoyloxy-4-phenylbutane (2a); Typical Procedure

To molecular sieves 4Å (40 mg) was added a solution of TMEDA (21.4 mg, 0.184 mmol) in CH_2Cl_2 (1 mL) and a solution of **1a** (45.7 mg, 0.304 mmol) in CH_2Cl_2 (1 mL) at r.t. under argon atmosphere. Benzoyl chloride (47.0 mg, 0.334 mmol) dissolved in CH_2Cl_2 (0.5 mL) was then added at –78°C. After stirring for 20 min at –78°C the mixture was quenched with a phosphate buffer (pH 7) and the organic materials were extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by TLC on silica gel to give **2a**; yield: 74.9 mg (97%).

2-Benzoyloxy-4-phenylbutane (2a)

^{1}H NMR: δ = 1.38 (d, 3 H, *J* = 6.2 Hz), 1.96 (m, 1 H), 2.09 (m, 1 H), 2.74 (m, 2 H), 5.20 (m, 1 H), 7.19 (m, 2 H), 7.28 (m, 3 H), 7.44 (m, 2 H), 7.56 (m, 1 H), 8.04 (m, 2 H).

^{13}C NMR: δ = 20.11, 31.83, 37.74, 71.15, 125.91, 128.29, 128.32, 128.42, 129.51, 130.76, 132.75, 141.51, 166.16.

IR (neat): ν = 713, 1116, 1277, 1451, 1717 cm^{-1}.

2-(4-Nitrobenzoyl)-4-phenylbutane (2b)

^{1}H NMR: δ = 1.41 (d, 3 H, *J* = 6.6 Hz), 2.00 (m, 1 H), 2.12 (m, 1 H), 2.74 (m, 2 H), 5.24 (m, 1 H), 7.18 (m, 3 H), 7.27 (m, 2 H), 8.15 (d, 2 H, *J* = 8.8 Hz), 8.27 (d, 2 H, *J* = 8.8 Hz).

^{13}C NMR: δ = 20.00, 31.81, 37.41, 72.57, 123.42, 126.02, 128.26, 128.47, 130.59, 136.06, 141.16, 150.44, 164.20.

IR (neat): ν = 712, 1117, 1275, 1452, 1718 cm^{-1}.

2-(4-Methoxybenzoyl)-4-phenylbutane (2c)

^{1}H NMR: δ = 1.36 (d, 3 H, *J* = 6.3 Hz), 1.93 (m, 1 H), 2.06 (m, 1 H), 2.73 (m, 2 H), 3.84 (s, 3 H), 5.17 (m, 1 H), 6.91 (d, 2 H, *J* = 9.2 Hz), 7.17–7.28 (m, 5 H), 7.99 (d, 2 H, *J* = 9.2 Hz).

^{13}C NMR: δ = 20.11, 20.14, 31.81, 37.77, 55.34, 55.37, 70.69, 113.49, 123.15, 125.84, 128.29, 128.36, 131.47, 141.56, 163.19, 165.88.

IR (neat): ν = 1257, 1510, 1606, 1708 cm^{-1}.

2-(4-Methylbenzoyl)-4-phenylbutane (2d)

^{1}H NMR: δ = 1.36 (d, 3 H, *J* = 6.2 Hz), 1.93 (m, 1 H), 2.06 (m, 1 H), 2.39 (s, 3 H), 2.70 (m, 2 H), 5.16 (m, 1 H), 7.14–7.27 (m, 7 H), 7.93 (d, 2 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 20.06, 21.53, 31.76, 37.71, 70.80, 125.83, 127.99, 128.26, 128.34, 128.94, 129.48, 141.50, 143.30, 166.15.

IR (neat): ν = 754, 1109, 1276, 1612, 1712, 2976 cm^{-1}.

2-(2-Methylbenzoyl)-4-phenylbutane (2e)

^{1}H NMR: δ = 1.37 (m, 3 H), 1.93 (m, 1 H), 2.07 (m, 1 H), 2.61 (s, 3 H), 2.73 (m, 2 H), 5.18 (m, 1 H), 7.16–7.36 (m, 7 H), 7.39 (m, 1 H), 7.89 (m, 1 H).

^{13}C NMR: δ = 20.13, 21.74, 31.89, 37.80, 70.91, 125.65, 125.91, 128.31, 128.42, 130.27, 130.36, 131.61, 131.71, 139.85, 141.51, 167.25 cm^{-1}.

IR (neat): ν = 739, 1078, 1257, 1715, 2976 cm^{-1}.

2-Acetoxy-4-phenylbutane (2f)

^{1}H NMR: δ = 1.25 (d, 3 H, *J* = 6.2 Hz), 1.81 (m, 1 H), 1.92 (m, 1 H), 2.02 (s, 3 H), 2.63 (m, 2 H), 4.94 (m, 1 H), 7.18 (m, 3 H), 7.27 (m, 2 H).

^{13}C NMR: δ = 19.98, 21.28, 31.79, 37.53, 70.52, 125.87, 128.28, 128.37, 141.51, 170.70.

IR (neat): ν = 700, 1244, 1373, 1736 cm^{-1}.

1-Benzoyloxy-3-phenylpropane (2g)

^{1}H NMR: δ = 2.10 (m, 2 H), 2.79 (t, 2 H, *J* = 7.3 Hz), 4.34 (t, 2 H, *J* = 6.6 Hz), 7.21–7.31 (m, 5 H), 7.43 (m, 2 H), 7.55 (t, 1 H, *J* = 7.3 Hz), 8.03 (m, 2 H).

^{13}C NMR: δ = 30.28, 32.29, 64.24, 126.00, 128.31, 128.40, 128.43, 129.51, 130.36, 132.83, 141.15, 166.56.

IR (neat): ν = 720, 1120, 1278, 1527, 1720 cm^{-1}.

1-Benzoyloxy-1-phenylethane (2h):

^{1}H NMR: δ = 1.68 (d, 3 H, *J* = 6.6 Hz), 6.13 (q, 1 H, *J* = 6.6 Hz), 7.26–7.46 (m, 7 H), 7.55 (m, 1 H), 8.08 (m, 2 H).

^{13}C NMR: δ = 22.39, 72.90, 126.03, 127.88, 128.32, 128.54, 129.63, 130.55, 132.89, 141.78, 165.81.

IR (neat): ν = 712, 1068, 1109, 1271, 1450, 1716 cm^{-1}.

1-Benzoyloxy-2-methyl-1-phenylpropane (2i)

^{1}H NMR: δ = 0.89 (d, 3 H, *J* = 6.6 Hz), 1.05 (d, 3 H, *J* = 6.6 Hz), 2.25 (m, 1 H), 5.73 (d, 1 H, *J* = 7.33 Hz), 7.22–7.55 (m, 8 H), 8.09 (d, 2 H, *J* = 7.0 Hz).

^{13}C NMR: δ = 18.39, 18.81, 33.82, 81.40, 126.87, 127.66, 128.17, 128.32, 129.56, 130.54, 132.83, 139.71, 165.75.

IR (neat): ν = 712, 1107, 1271, 1719, 2964 cm^{-1}.

***trans*-1-Benzoyloxy-2-phenylcyclohexane (2j)**

^{1}H NMR: δ = 1.38–2.01 (m, 7 H), 2.30 (m, 1 H), 2.84 (m, 1 H), 5.18 (m, 1 H), 7.10 (m, 1 H), 7.21–7.29 (m, 6 H), 7.42 (m, 1 H), 7.80 (d, 2 H, *J* = 7.0 Hz).

^{13}C NMR: δ = 24.73, 25.83, 32.33, 33.83, 49.82, 76.81, 126.35, 127.39, 128.02, 128.23, 129.29, 130.62, 132.42, 143.08, 165.80.

IR (KBr): ν = 712, 1111, 1273, 1714, 2935 cm^{-1}.

***trans*-1,2-Dibenzoyloxycyclohexane (2k)**

^{1}H NMR: δ = 1.49 (m, 2 H), 1.63 (m, 2 H), 1.82 (m, 2 H), 2.23 (m, 2 H), 5.24 (m, 2 H), 7.36 (m, 4 H), 7.48 (m, 2 H), 7.97 (m, 4 H).

^{13}C NMR: δ = 23.45, 30.17, 74.23, 128.25, 129.56, 130.17, 132.81, 165.99.

IR (KBr): ν = 715, 1117, 1282, 1713, 2946 cm^{-1}.

***cis*-1,2-Dibenzoyloxycyclohexane (2l)**
^{1}H NMR: δ = 1.58 (m, 2 H), 1.88 (m, 4 H), 2.12 (m, 2 H), 5.40 (m, 2 H), 7.41 (m, 4 H), 7.54 (m, 2 H), 8.01 (m, 4 H).

^{13}C NMR: δ = 21.86, 28.01, 71.88, 128.33, 129.63, 130.47, 132.89, 165.77.

IR (KBr): ν = 711, 1118, 1282, 1451, 1722, 2942 cm^{-1}.

1-Benzoyloxy-4-bromobenzene (2m)
^{1}H NMR: δ = 7.11 (d, 2 H, *J* = 8.8 Hz), 7.49–7.55 (m, 4 H), 7.64 (t, 1 H, *J* = 7.3 Hz), 8.19 (m, 2 H).

^{13}C NMR: δ = 118.95, 123.52, 128.61, 129.16, 130.17, 132.50, 133.76, 149.97, 164.82.

IR (KBr): ν = 706, 805, 875, 1059, 1216, 1282, 1486, 1732 cm^{-1}.

1-Benzoyloxy-2-methylbenzene (2n)
^{1}H NMR: δ = 2.24 (s, 3 H), 7.13–7.29 (m, 4 H), 7.51 (m, 2 H), 7.63 (t, 1 H, *J* = 8.8 Hz), 8.22 (d, 2 H, *J* = 8.4 Hz).

^{13}C NMR: δ = 16.19, 16.22, 121.97, 126.06, 126.95, 128.56, 128.61, 129.46, 130.11, 130.16, 130.27, 131.14, 133.53, 133.57, 149.51, 164.82.

IR (neat): ν = 707, 1064, 1112, 1173, 1266, 1491, 1735 cm^{-1}.

4-Benzoyloxy-2-methyl-2-pentanol (4)
^{1}H NMR: δ = 1.25 (s, 3 H), 1.27 (s, 3 H), 1.39 (d, 3 H, *J* = 6.2 Hz), 1.76 (dd, 1 H, *J* = 15.0, 3.3 Hz), 2.06 (dd, 1 H, *J* = 15.0, 8.8 Hz), 2.12 (br, 1 H), 5.42 (m, 1 H), 7.43 (m, 2 H), 7.55 (t, 1 H *J* = 8.8 Hz), 8.03 (m, 2 H).

^{13}C NMR: δ = 21.75, 29.63, 29.93, 49.06, 69.33, 69.98, 128.34, 129.45, 130.47, 132.91, 166.16.

IR (neat): ν = 714, 1117, 1281, 1715, 2974, 3448 cm^{-1}.

Acknowledgement

This work was partially supported by the Inamori Foundation, the Itoh Science Foundation, the Sasakawa Foundation (to T. S.), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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Article Identifier:
1437-210X,E;1999,0,07,1141,1144,ftx,en;F10498SS.pdf