N-Benzyl-2-(6-methyl)pyridinecarbamoyl Chloride: A New Useful Reagent for the Direct Esterification of Carboxylic Acids and Selective Benzoylation of Diols

Jae In Lee* and Su Jin Park

Department of Chemistry, College of Natural Science, Duksung Women's University, Seoul 132-714, Korea
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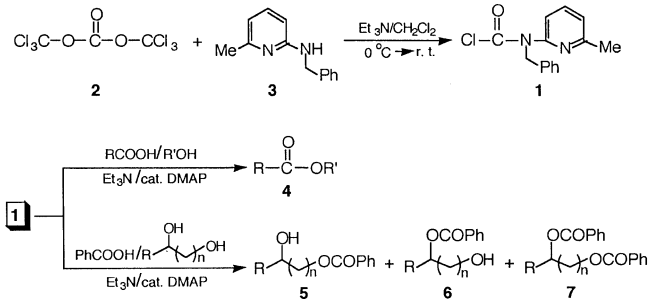
The esterification of carboxylic acids is a well-established reaction and many useful methods have been reported in the literature.[1] Among them the use of phosgene (diphosgene)[2] or its derivatives is the most common, but it is toxic and required for prolonged reaction time or the use of excess base. Several types of active carbonates derived from phosgene (or its equivalents) and *N*-hydroxysuccinimide,[3] *N*-hydroxyphthalimide,[4] 1-hydroxybenzotriazole,[5] and 2-hydroxypyridine[6] have been utilized for the preparation of carboxylic esters avoiding these limitations. Active ureas containing imidazole[7] or its activated salt,[8] 1,2-benzisoxazol-3-ol,[9] and 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine[10] have been also useful for the esterification of carboxylic acids. However, it is requisite to use 2 equiv of active moiety for the preparation of active carbonates or ureas from phosgene or its equivalents. Synthetic utility of active moiety for the preparation of carboxylic esters is further extended to the selective acylation of diols and some methods involving active esters or amides have been developed. The direct condensation of carboxylic acids and diols using diethyl azodicarboxylate[11] affords to give the corresponding hydroxy esters, but yields are low in case of secondary-secondary diols. The use of alternative reagents such as dialkyl acylphosphonate,[12] 1-(benzoyloxy)benzotriazole,[13] 3-acyl-1,3-thiazolidine-2-thione,[14] acetylimidazole,[15] and acid chloride[16] for the acylation of diols shows high selectivities, but it required for additional step to convert carboxylic acids into the corresponding active esters or amides.

In connection with our study on the synthetic utility of active carbamoyl chloride[17] we now wish to report the use of *N*-benzyl-2-(6-methyl)pyridinecarbamoyl chloride **1** for the direct esterification of carboxylic acids and selective benzoylation of diols. The reagent **1** was prepared in 97% yield by addition of an equimolar 2-benzylamino-6-methylpyridine **3** and triethylamine in methylene chloride to a solution of one-third equivalent of bis(trichloromethyl) carbonate[18] **2** in methylene chloride (Scheme 1). The reagent **1** was separated by dissolving in anhydrous tetrahydrofuran after evaporation of methylene chloride, followed by filtering off triethylamine hydrochloride. The purification of the crude filtrate by silica gel column chromatography or Kugelrohr vacuum distillation (bp 145-153 °C/0.10 mmHg) afforded to give **1** and showed no sign of decomposition when kept for three months in a refrigerator.

The effect of some bases was examined for the esterification of carboxylic acids with **1** and triethylamine to find out an optimum condition. Without additional base the reaction



Scheme 1

of phenylacetic acid, benzyl alcohol, and **1** with triethylamine gave benzyl phenylacetate in only 38% yield after 24 h. Addition of bases such as pyridine (1 equiv), triethylamine (1 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv), and tetramethylguanidine (0.5 equiv) effected a small increase in the rate of esterification and thus benzyl phenylacetate was obtained in 73%, 73%, 60%, 68% yield, respectively, after 24 h. However, subsequent addition of 0.1 equiv of 4-dimethylaminopyridine (DMAP) exceedingly accelerated the rate of esterification and benzyl phenylacetate was obtained in 92% yield after 0.7 h. Thus, the esterification of carboxylic acids using **1** proceeded smoothly in the presence of 1 equiv of triethylamine and 0.1 equiv of DMAP in contrast with diphosgene reagent which required 5 equiv of pyridine for the preparation of carboxylic esters. The rate enhancement is presumably due to the initial formation of activated *N*-acylpyridinium salt between **1** and DMAP.

Various carboxylic esters were efficiently prepared in high yields by this method (Table 1). The reaction of the most primary/secondary aliphatic carboxylic acids (**4a-4c**, **4l-4n**) and alcohols with **1** gave the corresponding esters within 1.5 h with the recovery of **3**. There were not observable side products such as the corresponding amide and carbamate in contrast with active carbonate or urea reagents which afforded to give the corresponding active esters or amides in some cases. However, the steric hindrance of carboxylic acids and alcohols influenced fairly on the yields and thus the treatment of trimethylacetic acid/benzyl alcohol (**4d**) with 0.5 equiv of DMAP gave benzyl trimethylacetate in 60% yield after 24 h. Furthermore, the reaction of benzoic acid/*tert*-butanol (**4g**) with 0.1 equiv of DMAP didn't proceed at all and **1** was recovered in 94% yield after 24 h. It is interesting to note that reaction pathway of esterification of substituted benzoic acids depends largely on the nature of substituents. The reaction of *p*-chlorobenzoic acid (**4h**) or *p*-

Table 1. Preparation of carboxylic esters using **1**

Entry	RCOOH	R'OH	Equiv of	Reaction	Isolated
4	R	R'	DMAP	time, h	yield, %[b]
a	$C_6H_5CH_2$	$C_6H_5CH_2$	0.1	1	92(92)
b		$(CH_3)_2CH$	0.1	1	93(92)
c	$(CH_3)_2CH$	*c*-C_6H_{11}	0.1	1.5	94(93)
d	$(CH_3)_3C$	$C_6H_5CH_2$	0.5	24	60
e	C_6H_5	CH_3CH_2	0.1	5	89(91)
f		$(CH_3)_2CH$	0.3	16	92(97)
g		$(CH_3)_3C$	0.1	24	94[c]
h	*p*-Cl-C_6H_4	CH_3CH_2	0.1	3	92(94)
i	*p*-O_2N-C_6H_4	CH_3CH_2	0.1	2	97(95)
j	*p*-CH_3O-C_6H_4	CH_3CH_2	0.1	24	53
			0.2	24	84[d]
k	$HOOC(CH_2)_4$	CH_3CH_2[a]	0.2	2	90(91)
l	$C_6H_5CO(CH_2)_2$	$(CH_3)_2CH$	0.1	0.5	91(93)
m	$C_6H_5CONHCH_2$	CH_3CH_2	0.1	0.3	92(93)
n	$CH_3CH(Br)$	$C_6H_5CH_2$	0.1	1.5	89(93)

[a]2 equiv of ethyl alcohol were used. [b]All products were purified by silica gel column chromatography and gave satisfactory spectral data. The numbers in parentheses indicate the recovery yield of 2-benzylamino-6-methylpyridine. [c]Recovery yield of *N*-benzyl-2-(6-methyl)pyridinecarbamoyl chloride. [d]1.8 equiv of *p*-methoxybenzoic acid were used.

Table 2. Selective benzoylation of diols with **1**

Entry	Diol	Reaction time, h	Product, isolated yield,%		
			1° benzoate **5**	2° benzoate **6**	dibenzoate **7**
a	$HO(CH_2)_2OH$	3	83		11
b	$HO(CH_2)_3OH$	3	74		22
c	$CH_3CH(OH)(CH_2)_2OH$	3.5	87[a]	4[a]	6
d	$C_6H_5CH(OH)CH_2OH$	6	79	7	8

[a]^{1}H NMR (300 MHz) yield.

nitrobenzoic acid (**4i**) having electron withdrawing group and ethyl alcohol with 0.1 equiv of DMAP gave the corresponding esters in 92% and 97% yield, respectively, within 3 h. However, the reaction of *p*-methoxybenzoic acid (**4j**) having electron donating group and ethyl alcohol with 0.1 equiv of DMAP gave a mixture of ethyl *p*-methoxybenzoate and *p*-methoxybenzoic anhydride, which converted into the corresponding ester slowly, in 25% and 63% yield, respectively, after 4 h. Thus, 1.8 equiv of *p*-methoxybenzoic acid and 0.2 equiv of DMAP were required for the ethyl *p*-methoxybenzoate formation in high yield because reaction proceeded *via* the intermediary of carboxylic anhydride as a major pathway.

The esterification of aromatic carboxylic acids using **1** proceeded more sluggish than that of aliphatic carboxylic acids. We anticipated that this would allow selective benzoylation of unsymmetrical diols at the less hindered site. As shown in Table 2, the primary hydroxyl groups of the diols were selectively benzoylated in high yields. The reaction of 1,2-ethanediol with equimolar amounts of benzoic acid and triethylamine using **1** in the presence of 0.1 equiv of DMAP gave 83% of the monobenzoate (**5a**) along with 11% of the dibenzoate (**7a**). However, better selectivities were observed in the benzoylation of unsymmetrical diols such as 1,3-butanediol and 1-phenyl-1,2-ethanediol. The treatment of 1,3-butanediol with equimolar amounts of benzoic acid and triethylamine using **1** in the presence of 0.1 equiv of DMAP gave 91% of the monobenzoate (**5c/6c**, 96/4 mixture of the primary monobenzoate and the secondary monobenzoate, determined by 300 MHz NMR analysis) along with 6% of the dibenzoate (**7c**).

In conclusion, the present method provides an efficient method for the preparation of carboxylic esters and shows high selectivity toward the direct benzoylation of diols. The reagent **1** is conveniently prepared, very stable, and therefore would be utilized in many synthetic applications.

Experimental Section

Melting points were determined on Mel temp II and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM 360L (60 MHz) or JMN-LA 300 (300 MHz) using $CDCl_3$ as a solvent. FT-IR spectra were recorded with a Bruker vector 22 spectrometer. Mass spectra were measured with VG-TRIO 2 GC/MS (low resolution) or JMS AX505WA (high resolution). Tlc was carried out on a Merck silica gel 60F-254 and silica gel (silica gel 60, E. Merck, 0.063-0.200 mm) was used for column chromatography.

Preparation of *N*-benzyl-2-(6-methyl)pyridinecarbamoyl chloride 1. To a bis(trichloromethyl) carbonate (1.2495 g, 4.21 mmol) in methylene chloride (20 mL) was added a mixture solution of 2-benzylamino-6-methylpyridine (2.3792 g, 12.0 mmol) and triethylamine (1.67 mL, 12.0 mmol) in methylene chloride (16 mL) over a period of 15 min at 0 °C. After 15 min cooling bath was removed and stirring was continued for an additional 0.5 h. Methylene chloride was evaporated under vacuum and the mixture was dissolved in anhydrous tetrahydrofuran (40 mL), followed by filtering off triethylamine hydrochloride. The crude product was purified by silica gel column chromatography using 20% EtOAc/*n*-hexane as an eluant to afford **1** (3.0347 g, 97%) as a colorless oil: bp 145-153 °C/0.10 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, J_1 = 7.8, J_2 = 7.8 Hz, 1H), 7.21-7.31 (m, 5H), 7.08 (d, J = 7.6 Hz, 1H), 6.88-7.01 (m, 1H), 5.16 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 152.6, 149.0, 138.2, 135.8, 128.5, 128.3, 127.8, 122.6, 120.1, 54.5, 24.2; FT-IR (film) 3032, 1731 (C=O), 1597, 1496, 1455, 1372, 1195, 743, 701 cm^{-1}; MS *m/z* (%) 262 (M^+ + 2, 4), 260 (M^+, 12), 225 (17), 197 (100), 182 (4), 91 (25); HRMS Calcd for $C_{14}H_{13}ClN_2O$ 260.0762, Found 260.0721.

Preparation of isopropyl phenylacetate 4b. (General procedure) To a phenylacetic acid (272.3 mg, 2.0 mmol) in methylene chloride (3 mL) was added triethylamine (279 μL, 2.0 mmol) by microsyringe at room temperature. After 2 min a solution of **1** (521.4 mg, 2.0 mmol) in methylene chloride (3 mL) was added to the reaction mixture, followed by isopropyl alcohol (153 μL, 2.0 mmol) and DMAP (24.4 mg, 0.2 mmol). After being stirred for 1 h, the reaction mixture

was extracted with methylene chloride (3 × 20 mL), washed with 0.1 N-HCl (30 mL), and sat. $NaHCO_3$ (30 mL). The organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography using 20% EtOAc/*n*-hexane as an eluant to give **4b** (331.5 mg, 93%) with the recovery of **3** (364.8 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 7.24 (br s, 5H), 4.93 (septet, J = 6.0 Hz, 1H), 3.60 (s, 3H), 1.23 (d, J = 6.0 Hz, 6H); FT-IR (film) 3056, 2983, 1728 (C=O), 1455, 1375, 1266, 1107, 739 cm^{-1}.

Selective benzoylation of 1-phenyl-1,2-ethanediol. To a stirred solution of benzoic acid (256.5 mg, 2.1 mmol) and triethylamine (293 μL, 2.1 mmol) in methylene chloride (3 mL) was added **1** (521.4 mg, 2.0 mmol) in methylene chloride (3 mL), followed by 1-phenyl-1,2-ethanediol (276.3 mg, 2.0 mmol) and DMAP (24.4 mg, 0.2 mmol) at room temperature. After being stirred for 6 h, the reaction mixture was extracted with methylene chloride (3 × 20 mL), washed with 0.1 N-HCl (30 mL), and sat. $NaHCO_3$ (30 mL). The organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The crude product was subjected to silica gel column chromatography using 20% EtOAc/*n*-hexane as an eluant to afford the primary monobenzoate **5d** (383.0 mg, 79%), the secondary monobenzoate **6d** (34.5 mg, 7%), and the dibenzoate **7d** (56.3 mg, 8%). 2-(Benzoyloxy)-1-phenylethanol (primary monobenzoate): mp 64-65 °C (lit.[13] 65-66 °C); R_f = 0.44 (30% EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.3 Hz, 2H), 7.54-7.56 (m, 1H), 7.31-7.45 (m, 7H), 5.03 (dd, J_1 = 7.9, J_2 = 3.8 Hz, 1H), 4.46 (dd, J_1 = 11.6, J_2 = 3.9 Hz, 1H), 4.37 (dd, J_1 = 11.6, J_2 = 7.8 Hz, 1H), 3.25 (s, 1H); FT-IR (film) 3427 (broad OH), 3062, 1714 (C=O), 1602, 1451, 1278, 1068, 699 cm^{-1}. 2-(Benzoyloxy)-2-phenylethanol (secondary monobenzoate): oil; R_f = 0.33 (30% EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.11 (m, 2H), 7.55-7.56 (m, 1H), 7.31-7.44 (m, 7H), 6.10 (dd, J_1 = 7.5, J_2 = 4.0 Hz, 1H), 4.01-4.05 (m, 1H), 3.93-3.95 (m, 1H), 2.06 (s, 1H); FT-IR (film) 3417 (broad OH), 2933, 1714 (C=O), 1601, 1452, 1270, 1114, 700 cm^{-1}. 1,2-Bis (benzoyloxy)-1-phenylethane (dibenzoate): mp 92-94 °C (lit.[13] 91-93 °C); R_f = 0.60 (30% EtOAc/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.65-8.04 (m, 4H), 6.97-7.53 (m, 11H), 6.24 (t, J = 6.0 Hz, 1H), 4.55(d, J = 6.0 Hz, 2H); FT-IR (film) 3056, 1722 (C=O), 1602, 1452, 1265, 1110, 738 cm^{-1}.

2-(Benzoyloxy)-1-ethanol (5a). ^{1}H NMR ($CDCl_3$) δ 7.90-8.22 (m, 2H), 7.20-7.71 (m, 3H), 4.32-4.62 (m, 2H), 3.62-4.15 (m, 2H), 2.87 (s, 1H); FT-IR (film) 3454 (broad OH), 3056, 2956, 1716 (C=O), 1602, 1452, 1267, 1122, 1070, 738 cm^{-1}.

1,2-Bis(benzoyloxy)ethane (7a). ^{1}H NMR ($CDCl_3$) δ 7.81-8.22 (m, 4H), 7.15-7.64 (m, 6H), 4.54 (s, 4H); FT-IR (film) 3054, 2986, 1721 (C=O), 1602, 1452, 1265, 1098, 738 cm^{-1}.

3-(Benzoyloxy)-1-propanol (5b). ^{1}H NMR ($CDCl_3$) δ 7.82-8.12 (m, 2H), 7.17-7.60 (m, 3H), 4.46 (t, J = 6.0 Hz, 2H), 3.79 (t, J = 6.0 Hz, 2H), 2.92 (s, 1H), 2.02 (quintet, J = 6.0 Hz, 2H); FT-IR (film) 3454 (broad OH), 3055, 2963, 1716 (C=O), 1602, 1452, 1267, 1121, 1071, 739 cm^{-1}.

1,3-Bis(benzoyloxy)propane (7b). ^{1}H NMR ($CDCl_3$) δ 7.81-8.10 (m, 4H), 7.13-7.54 (m, 6H), 4.46 (t, J = 6.0 Hz, 4H), 2.25 (quintet, J = 6.0 Hz, 2H); FT-IR (film) 3059, 2967, 1718 (C=O), 1602, 1452, 1268, 1110, 738 cm^{-1}.

4-(Benzoyloxy)-2-butanol (5c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, J = 8.3 Hz, 2H), 7.53-7.56 (m, 1H), 7.41-7.44 (m, 2H), 4.54-4.59 (m, 1H), 4.37-4.41 (m, 1H), 3.97-3.99 (m, 1H), 3.87 (s, 1H), 1.89-1.93 (m, 2H), 1.26 (d, J = 6.3 Hz, 3H); FT-IR (film, 96/4 mixture of 5c/6c) 3418 (broad OH), 3061, 2969, 1715 (C=O), 1602, 1452, 1383, 1279, 1116, 1071, 1027, 912, 713 cm^{-1}.

3-(Benzoyloxy)-1-butanol (6c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, J = 8.3 Hz, 2H), 7.53-7.56 (m, 1H), 7.41-7.44 (m, 2H), 5.36-5.37 (m, 1H), 3.64-3.73 (m, 2H), 1.84-1.87 (m, 2H), 1.40 (d, J = 6.3 Hz, 3H), 2.34 (s, 1H).

1,3-Bis(benzoyloxy)butane (7c). ^{1}H NMR ($CDCl_3$) δ 7.87-8.23 (m, 4H), 7.20-7.72 (m, 6H), 5.40 (sextet, J = 6.0 Hz, 1H), 4.46 (t, J = 6.0 Hz, 2H), 2.23 (q, J = 6.0 Hz, 2H), 1.52 (d, J = 6.0 Hz, 3H); FT-IR (film) 3055, 2985, 1716 (C=O), 1602, 1452, 1266, 1112, 739 cm^{-1}.

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