A New Condensation Reaction for the Synthesis of Carboxylic Esters from Nearly Equimolar Amounts of Carboxylic Acids and Alcohols Using 2-Methyl-6-nitrobenzoic Anhydride

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Various carboxylic esters were obtained in excellent yields with high chemoselectivities from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride with triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine.

Synthesis of carboxylic esters is one of the most fundamental and important process for producing natural and unnatural useful compounds in organic chemistry. In order to perform high yielding esterification with equimolar reactions of carboxylic acids and alcohols under mild conditions, coupling reactions between activated derivatives of carboxylic acids and alcohols have been employed.[1]

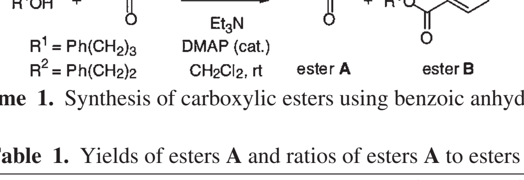
In 1992, we developed a unique method for the preparation of carboxylic esters starting from silyl carboxylates and alkyl silyl ethers *via* active intermediary mixed anhydrides prepared *in situ* from silyl carboxylates with 4-(trifluoromethyl)benzoic anhydride by using a catalytic amount of Lewis acid such as $Sn(OTf)_2$ or $TiCl_2(ClO_4)_2$.[2] Further, in 1994, we extended this method to the reaction between nearly equimolar amounts of free carboxylic acids and alcohols by varying the combination of Lewis acids.[3] The corresponding carboxylic esters or lactones are obtained in high yields by treating nearly equimolar amounts of free carboxylic acids and alcohols or ω-hydroxycarboxylic acids with substituted benzoic anhydrides possessing electron withdrawing group(s) in the presence of catalytic amounts of $TiCl_2(OTf)_2$ and chlorotrimethylsilane. Yamamoto *et al.* found in 1995 that $Sc(OTf)_3$ is an effective Lewis acid for the promotion of this reaction and that the desired carboxylic esters including medium sized lactones were produced in high yields.[4] Our group achieved the total synthesis of cephalosporolide D, a natural product consisting of a distinctive 8-membered ring lactone, by the dehydrating cyclization reaction of the seco acid using 4-(trifluoromethyl)benzoic anhydride in the presence of a catalytic amount of $Hf(OTf)_4$ in 1998.[5]

Although other effective esterification reactions using acidic catalysts were recently reported,[6] it is also required to develop efficient reactions which proceed under basic conditions since acid-sensitive protective groups such as acetals or silyl ethers are sometimes needed in the total synthesis of complex molecules. Yamaguchi *et al.* developed an effective mixed anhydride method for the synthesis of carboxylic esters from carboxylic acids and alcohols using 2,4,6-trichlorobenzoyl chloride.[7] In this reaction, carboxylic acids are transformed to the corresponding mixed anhydrides by the reaction with 2,4,6-trichlorobenzoyl chloride and triethylamine, followed by the second reaction of the mixed anhydrides with alcohols to give the desired carboxylic esters.

However, Yamaguchi method was conventionally carried out using an excess amount of 4-(dimethylamino)pyridine (DMAP) and it requires stepwise operation, namely, carboxylic acids are treated with 2,4,6-trichlorobenzoyl chloride and triethylamine at first to generate the corresponding mixed anhydrides. After filtration of the mixture under inert gas to remove triethylammonium chloride formed, the filtrate containing mixed anhydrides is secondly used for the acylation of alcohols with an excess amount of DMAP (usually, 2 molar amounts).

Therefore, we planned to develop more simple and effective esterification using carboxylic anhydrides instead of using acid chlorides in the presence of a catalytic amount of basic promoter.

In the first place, the reaction of 1.1 molar amounts of 3-phenylpropanoic acid with 1.0 molar amount of 3-phenylpropanol was examined in the presence of 1.1 molar amounts of 4-substituted benzoic anhydride, 1.1 molar amounts of triethylamine and 10 mol% of DMAP (Scheme 1, Table 1). When benzoic anhydride was used as a dehydrating reagent, 3-phenylpropyl 3-phenylpropanoate was obtained in 69% yield along with a small amount of 3-phenylpropyl benzoate, the undesirable carboxylic ester (Entry 1). Though the desired carboxylic ester was obtained with higher chemoselectivity by using 4-methoxybenzoic anhydride, the reaction proceeded very slowly (Entry 2). It was proven that electron withdrawing groups increase the reactivities of benzoic anhydrides and the desired carboxylic ester was obtained in good yields within shorter time (Entry 3), however, the chemoselectivities were rather low compared to the result using benzoic anhydride. Then, we tried to introduce substituents on the 2- and 6-positions of the aromatic ring of benzoic anhydride to give hindrance near the carboxyl group. Methyl or methoxy group existing on 2- and 6-positions increases the chemoselectivity, however, the reaction proceeded sluggishly (Entries 4 and 5). 2,4,6-Trichlorobenzoic anhydride



Scheme 1. Synthesis of carboxylic esters using benzoic anhydrides.

Table 1. Yields of esters **A** and ratios of esters **A** to esters **B**

Entry	X_n	Time/h	Yield of **A**/%	**A/B**
1	H	8	69	100/1
2	4-MeO	20	62	170/1
3	4-CF_3	1	70	19/1
4	2,4,6-Me_3	70	56	>200/1
5	2,6-$(MeO)_2$	18	82	>200/1
6	2,4,6-Cl_3	1	77	27/1
7	2-Me-6-NO_2	1	67	>200/1

which might afford the same mixed anhydride in the Yamaguchi protocol gave lower selectivity as shown in Entry 6. On the other hand, we found that 2-methyl-6-nitrobenzoic anhydride was a quite effective dehydrating reagent for producing the carboxylic ester with high chemoselectivity in the presence of a catalytic amount of DMAP (Entry 7).

Several examples of carboxylic esters obtained by the present method under the optimized conditions (standard ratio; 1.0 mol. of R^1OH; 1.2 mol. of R^2COOH; 1.2 mol. of 2-methyl-6-nitrobenzoic anhydride; 2.2 mol. of triethylamine and 10 mol% of DMAP, in dichloromethane at rt) are listed in Table 2.[8] Including benzyl and allyl alcohols, primary aliphatic alcohols were successfully employed and the corresponding carboxylic esters were obtained in excellent yields with complete chemoselectivities (Entries 1–3). The reaction of secondary aliphatic alcohols also gave the desired carboxylic esters in high yields with perfect selectivities (Entries 4–6). It is noteworthy that acid sensitive alcohols could be converted to the desired esters in high yields without forming undesirable by-products (Entries 7 and 8). This protocol is also applicable to other carboxylic acids such as cyclohexane carboxylic, (*E*)-cinnamic and benzoic acids, and various aliphatic, α,β-unsaturated and aromatic carboxylic esters were obtained in good to high yields under the mild reaction conditions (Entries 9–14).

Table 2. Yield of various carboxylic esters using 2-methyl-6-nitrobenzoic anhydride and a catalytic amount of DMAP

Entry	R^1	R^2	Yield of **A**/%	
			[**A**/**B**]	[**A**/**C**^{d}]^c
1	Bn	$Ph(CH_2)_2$	95 [>200/1]	(90)^c [15/1]
2	$CH_2=CHCH_2$	$Ph(CH_2)_2$	92 [>200/1]	(85)^c [10/1]
3	$Ph(CH_2)_3$	$Ph(CH_2)_2$	94 [>200/1]	(58)^c [2/1]
4	$Ph(CH_2)_2CHCH_3$	$Ph(CH_2)_2$	95 [>200/1]	(92)^c [152/1]
5	Menthyl	$Ph(CH_2)_2$	90 [>200/1]	(88)^c [>200/1]
6	5α-Cholestan-3β-yl	$Ph(CH_2)_2$	83 [>200/1]	(86)^c [70/1]
7	$C_9H_{19}C(CH_3)_2$	$Ph(CH_2)_2$	94^a [>200/1]	(51)^{c,e} [>200/1]
8	$THPO(CH_2)_5$	$Ph(CH_2)_2$	98 [>200/1]	(62)^c [6/1]
9	$Ph(CH_2)_3$	c-C_6H_{11}	96 [143/1]	(89)^c [14/1]
10	$Ph(CH_2)_2CHCH_3$	c-C_6H_{11}	quant.^{b} [>200/1]	(97)^c [187/1]
11	$Ph(CH_2)_3$	(*E*)-PhCH=CH	98 [187/1]	(82)^c [7/1]
12	$Ph(CH_2)_2CHCH_3$	(*E*)-PhCH=CH	95 [>200/1]	(87)^c [22/1]
13	$Ph(CH_2)_3$	Ph	92 [42/1]	(85)^c [11/1]
14	$Ph(CH_2)_2CHCH_3$	Ph	88^b [>200/1]	(98)^c [>200/1]

[a] 3 equiv of carboxylic acid, 3 equiv of 2-methyl-6-nitrobenzoic anhydride and 5 equiv of triethylamine were used. [b] 1.3 equiv of carboxylic acid and 1.3 equiv of 2-methyl-6-nitrobenzoic anhydride were used. [c] the data obtained by Yamaguchi protocol according to the procedure in Ref. 7a. [d] The undersired 2,4,6-trichlorobenzoates (**C**) of the corresponding alcohols. [e] 38% of 2-methylundecan-2-ol was recovered.

Further, we compared our results with those obtained according to Yamaguchi procedure using 2,4,6-trichlorobenzoyl chloride.[7a] These data are presented in the right column of Table 2. We observed the formation of considerable amounts of the undesired alkyl 2,4,6-trichlorobenzoates (**C**) in many cases (Entries 1 (6%), 2 (9%), 3 (29%), 8 (10%), 9 (6%), 11 (12%), 12 (4%) and 13 (8%)), though our method gave almost perfect chemoselectivities except Entry 13 (2%). It is noted that maximum yield of the desired ester **A** is limited to *ca.* 70% by Yamaguchi method in Entry 3 since the reaction proceeded without high chemoselectivity.

One of features of the present protocol using 2-methyl-6-nitrobenzoic anhydride is the quite simple procedure for the synthesis of a variety of carboxylic esters, that is, only mixing carboxylic acids, 2-methyl-6-nitrobenzoic anhydride, triethylamine, a catalytic amount of DMAP and alcohols at room temperature gave the desired compounds in excellent yields with high purity.

The authors dedicate this paper to Professor Teruaki Mukaiyama on the celebration of his 75th birthday.

References and Notes

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8 A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid with 4-phenyl-2-butanol; to a solution of triethylamine (66.1 mg, 0.65 mmol) in dichloromethane (1.5 mL) were added DMAP (2.5 mg, 0.020 mmol), 2-methyl-6-nitrobenzoic anhydride[9] (82.9 mg, 0.24 mmol) and 3-phenylpropanoic acid (36.3 mg, 0.24 mmol). After having been stirred for 10 min, a solution of 4-phenyl-2-butanol (30.1 mg, 0.20 mmol) in dichloromethane (2.0 mL) was added. The reaction mixture was stirred for 20 h at room temperature and then saturated aqueous ammonium chloride was added. Usual work up and purification of the mixture by TLC on silica gel afforded 53.9 mg (95%) of 1-methyl-3-phenylpropyl 3-phenylpropanoate.

9 2-Methyl-6-nitrobenzoic anhydride was prepared from 2-methyl-6-nitrobenzoic acid and 2-methyl-6-nitrobenzoyl chloride with pyridine according to the procedure for the preparation of 4-trifluoromethylbenzoic anhydride. See Ref. 2b.