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A novel and efficient macrolactonization of ω-hydroxycarboxylic acids using 2-methyl-6-nitrobenzoic anhydride (MNBA)

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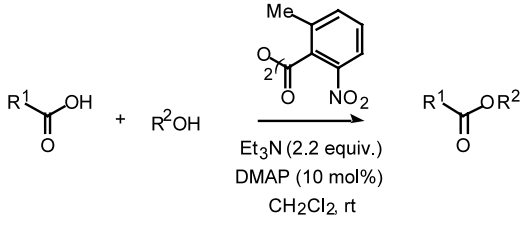
Abstract—A variety of lactones were prepared in high yields at room temperature from the corresponding ω-hydroxycarboxylic acids using 2-methyl-6-nitrobenzoic anhydride in the presence of 4-(dimethylamino)pyridine. A similar reaction also occurs with triethylamine when using a catalytic amount of 4-(dimethylamino)pyridine 1-oxide as an effective promoter for the intramolecular condensation reaction. These methods were successfully applied to the synthesis of *erythro*-aleuritic acid lactone and the efficiency of the cyclizations is compared to those of other reported mixed anhydride methods.

The macrocyclic framework is one of the most basic structures for natural and unnatural useful organic molecules. Recently, several effective C–C bond forming reactions such as transition metal-promoted coupling and olefin metathesis have been widely studied for producing cyclic compounds.[1,2] However, macrolactonization is still the most popular method for producing cyclic compounds including carboxylic ester moieties since there are some effective methods for constructing the ester linkage.[3]

In a previous communication, we developed a new condensation reaction (Scheme 1) for the synthesis of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride (MNBA) with triethylamine in the presence of 4-(dimethylamino)pyridine (DMAP).[4] This protocol is quite effective and the desired carboxylic esters are produced in excellent yields with higher chemoselectivities compared with those obtained by the Yamaguchi esterification method.[5] The reaction of nearly equal amounts of carboxylic acids and alcohols smoothly proceeds at room temperature, therefore, it is assumed that the MNBA method might be successfully applied to the intramolecular reaction for producing the macrocyclic compounds under mild conditions.



Scheme 1. Efficient esterification using MNBA.

We would now like to report a novel and efficient lactonization of ω-hydroxycarboxylic acids using MNBA, an effective condensation reagent, by the promotion of DMAP or 4-(dimethylamino)pyridine 1-oxide (DMAPO).

First, 15-hydroxypentadecanoic acid is employed as a model substrate for optimizing the reaction conditions (see Table 1). When a solution of 15-hydroxypentadecanoic acid in dichloromethane was slowly added to the reaction mixture of MNBA (1.0 equiv.), triethylamine (2.2 equiv.) and 10 mol% DMAP in dichloromethane for over a 15 h period at room temperature, the corresponding monomeric lactone was obtained in 65% yield accompanied by 6% diolide and 1% triolide (entry 1). Though the yield of the desired 15-pentadecanolide increased to 84 or 86% using 20 or 30 mol% DMAP, respectively, under the same reaction conditions, the ratio of monomer to dimer and trimer was not satisfactory, as shown in entry 2 or 3. Furthermore, employing an excess amount of triethylamine decreased the ratio to some extent (entry 4). On the other hand, better selectivity was observed when a slight excess amount of

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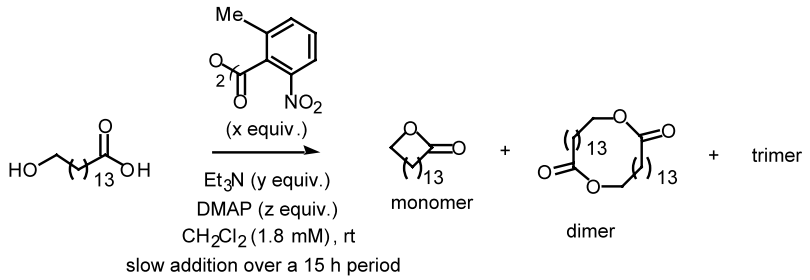
Table 1. Isolated yields of 15-pentadecanolide and product-selectivities



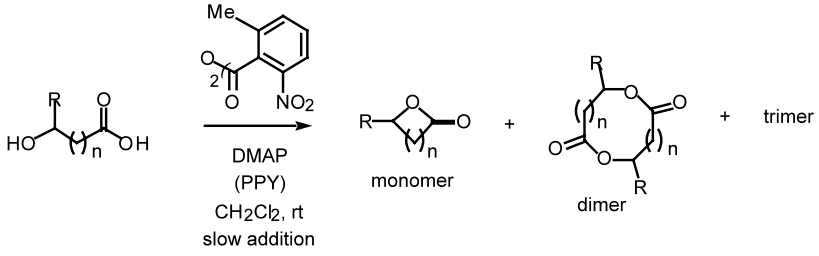
Entry	*x*	*y*	*z*	Yield (%)			Selectivity[a]
				Monomer	Dimer	Trimer	
1	1.0	2.2	0.1	**65**	6	1	10.1
2	1.0	2.2	0.2	**84**	5	Trace	16.8
3	1.0	2.2	0.3	**86**	3	Trace	26.3
4	1.0	3.3	0.2	**82**	6	1	11.3
5	1.2	2.2	0.2	**88**	3	Trace	32.1
6	1.2	0	2.4	**92**	1	Trace	**96.0**

[a] Ratios of yields of monomer to that of dimer and trimer.

MNBA was used (entry 5). Therefore, we finally used a stoichiometric amount of DMAP (2.4 equiv.) to MNBA (1.2 equiv.) in the absence of triethylamine, and the desired monomeric lactone was produced in high yield with an excellent selectivity (entry 6). In this case, DMAP does not only work as an activator for the dehydration condensation but also as a base to generate the corresponding 2-methyl-6-nitrobenzoyl pyridinium salt.

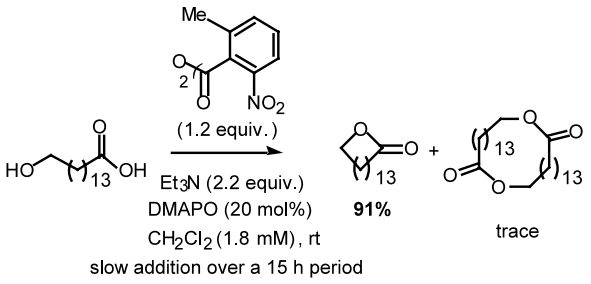
Table 2 shows the yields of the several macrolactones synthesized by the present method using MNBA and DMAP. All reactions were carried out at room temperature by adding a solution of ω-hydroxycarboxylic acids to a mixture of MNBA and DMAP in dichloromethane. Each concentration in Table 2 shows the molar amounts of ω-hydroxycarboxylic acids to the total volume of the dichloromethane solvent. Although a small amount of diolide formed in the case of using 12-hydroxyundecanoic acid as shown in entry 1, from 14- to 17-membered ring macrolactones were obtained in high yields and the undesired dimers and trimers were scarcely produced (entries 3–5 and 7). Since the reaction rate was not sufficiently fast when a secondary ω-hydroxycarboxylic acid was employed for the reaction, an excess amount of reagents were required to

Table 2. Isolated yields of a variety of macrolactones



Entry	R	*n*	Conc. (mM)	Time (h)	Yield (%)		
					Monomer	Dimer	Trimer
1[a]	H	10	1.0	15	**88**	5	1
2[b]	$C_{16}H_{13}$	10	2.0	15	**86**	1	Trace
3[a]	H	11	1.0	15	**75**	1	Trace
4[a]	H	12	1.0	15	**89**	Trace	Trace
5[a]	H	13	1.8	15	**92**	1	Trace
6[c]	H	13	1.8	12	**91**	3	0
7[a]	H	14	1.8	15	**92**	Trace	Trace

[a] 2.4 equiv. DMAP and 1.2 equiv. MNBA were used.
[b] 3.5 equiv. DMAP and 1.3 equiv. MNBA were used.
[c] 2.4 equiv. PPY and 1.2 equiv. MNBA were used.



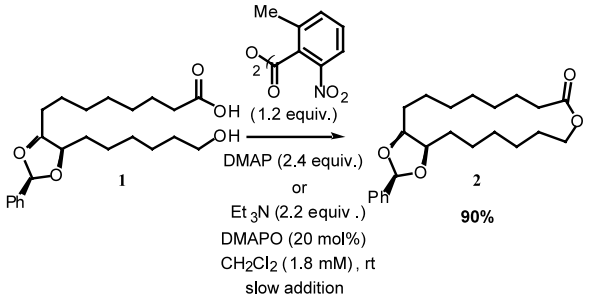
Scheme 2. Efficient macrolactonization using MNBA with triethylamine and a catalytic amount of DMAPO.

produce the excellent product-selectivity (entry 2). It is also noted that these reactions could be performed by the promotion of other derivatives of DMAP such as 4-pyrrolidinopyridine (PPY, see entry 6).

Next, we tried to investigate other activators for the present reaction to improve the efficiency for producing the desired compounds with a higher ratio of monomers to dimers. After screening several basic compounds including inorganic solid bases, it was proved that substituted pyridine 1-oxides are quite effective catalysts for the reaction forming large ring-size lactones with triethylamine in the presence of MNBA (Scheme 2). For example, the desired 15-pentadecanolide and 16-hexadecanolide were obtained in 91 and 92% yields, respectively, accompanied by only a trace and 1% of the corresponding dimers when 20 mol% DMAPO was employed as a catalyst for the reactions with triethylamine (2.2 equiv.) at room temperature. 4-Pyrrolidinopyridine 1-oxide (PPYO), a derivative of DMAPO, was also proved to be effective for the macrolactonization and the desired 15-pentadecanolide was produced in good yield (95%) from 15-hydroxypentadecanoic acid at room temperature. As far as we know, the present method is the first successful example utilizing pyridine 1-oxides for the effective synthesis of macrolactones.[6,7]

Finally, we applied the present protocol to the synthesis of a functionalized macrocyclic molecule (Scheme 3). The *seco* acid **1** having benzylidene acetal was prepared from commercially available *erythro*-aleuritic acid (*erythro*-9,10,16-trihydroxyhexadecanoic acid)[8] by treating with $PhCH(OMe)_2$ and TsOH. Macrolactonization of the *seco* acid **1** was then tried using MNBA with an excess amount of DMAP (Method A), and the corresponding monomeric lactone **2** was obtained in 90% yield with excellent product-selectivity. When PPY was used for the reaction under the same reaction conditions, **2** was also obtained in 87% yield. Furthermore, it was found that the reaction using MNBA with triethylamine and a catalytic amount of DMAPO (Method B) cleanly took place to produce the desired monomeric lactone **2** in 90% yield. Successive facile deprotection of **2** with $AcOH/H_2O$ produced the *erythro*-aleuritic acid lactone.[9]

In order to compare the efficiency of our new protocols with other mixed anhydride methods, the macrolactonization of **1** was further examined. These data are summarized in Table 3. Although the MNBA methods (A and B) provided excellent results at room temperature as mentioned above (entries 1 and 2), the desired lactone **2** was obtained in moderate yield with lower selectivity by the Yamaguchi protocol at the same temperature (entry 3). The yield increased to 70% when the reaction was carried out at refluxing temperature in



Scheme 3. Synthesis of protected *erythro*-aleuritic acid lactone **2** using MNBA.

Table 3. Isolated yields of the protected *erythro*-aleuritic acid lactone **2** and product-selectivities obtained by several mixed anhydride methods

Entry	Method	Yield (%)			Selectivity[e]
		Monomer	Dimer	Trimer	
1	MNBA, DMAP[a]	**90**	2	Trace	**45.8**
2	MNBA, DMAPO[b]	**90**	2	Trace	**45.0**
3	Yamaguchi[c]	52	5	1	8.2
4	Yamaguchi[d]	70	9	1	6.7

[a] *Method A*: A solution of **1** (0.380 mmol) in dichloromethane (84.6 mL) was slowly added to a solution of reagents in dichloromethane (135.8 mL) over a 16.5 h period at rt.

[b] *Method B*: A solution of **1** (0.360 mmol) in dichloromethane (108.0 mL) was slowly added to a solution of reagents in dichloromethane (151.0 mL) over a 16 h period at rt.

[c] A solution of MA derived from **1** (0.360 mmol) in toluene (36.0 mL) was slowly added to a solution of DMAP (2.16 mmol) in toluene (180.0 mL) over a 9 h period at rt.[5a]

[d] A solution of MA derived from **1** (0.360 mmol) in toluene (36.0 mL) was slowly added to a solution of DMAP (2.16 mmol) in toluene (180.0 mL) over a 9 h period at reflux temperature.[5a]

[e] Ratios of yields of monomer to that of dimer and trimer.

toluene according to the original procedure, but the product-selectivity is not sufficient for producing **2** with high purity (entry 4). The Lewis acid-mediated macrolactonization of **1** via MA generated in situ from (4-trifluoromethyl)benzoic anhydride (TFBA)[10] using 5 mol% $Cl_2Ti(OTf)_2$, $Hf(OTf)_4$ or 20 mol% $Sc(OTf)_3$ was not so effective, therefore, **2** was produced in moderate yield (24, 40 or 60%) with lower product-selectivity (8.6, 7.9 or 13.1).[11–13]

Two typical experimental procedures are described for the reaction of protected *erythro*-aleuritic acid **1**.[8] *Method A*: To a solution of MNBA[14] (157.8 mg, 0.456 mmol) and DMAP (111.4 mg, 0.912 mmol) in dichloromethane (135.8 mL) at room temperature was slowly added a solution of **1** (149.2 mg, 0.380 mmol) in dichloromethane (84.6 mL) with a mechanically driven syringe over a 16.5 h period. After addition of the solution, the reaction mixture was additionally stirred for 1 h at room temperature. The reaction mixture was concentrated to ca. 20 mL by evaporation of the solvent under reduced pressure and then saturated aqueous sodium hydrogencarbonate was added at 0°C. Usual work up and purification of the mixture by TLC on silica gel afforded 128.2 mg (90%) of protected *erythro*-aleuritic acid lactone **2**, 4.4 mg (1.5%) of diolide and 1.8 mg (0.4%) of triolide.

Method B: To a solution of MNBA (148.7 mg, 0.432 mmol), triethylamine (80.1 mg, 0.792 mmol) and DMAPO[15] (9.9 mg, 0.072 mmol) in dichloromethane (151.0 mL) at room temperature was slowly added a solution of **1** (141.3 mg, 0.360 mmol) in dichloromethane (108.0 mL) with a mechanically driven syringe over a 16 h period. After addition of the solution, the reaction mixture was additionally stirred for 1 h at room temperature. Same treatment of the reaction mixture as mentioned above afforded 120.8 mg (90%) of **2**, 4.9 mg (1.8%) of diolide and 0.7 mg (0.2%) of triolide.

Thus, we developed a new and convenient method for the synthesis of a variety of macrolactones with high product-selectivities via mixed anhydrides generated from ω-hydroxycarboxylic acids and MNBA using basic catalysts. One of the features of the present protocol is the very simple procedure for giving the desired products, that is, slowly adding ω-hydroxycarboxylic acids to the mixture of MNBA and the promoters at room temperature produces the desired macrolactones in excellent yields with high purity.[16] Other applications of the present protocol for the syntheses of useful complex molecules are now in progress.

Acknowledgements

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14. MNBA was synthesized from 2-methyl-6-nitrobenzoic acid. 2-Methyl-6-nitrobenzoic acid was purchased from Tokyo Kasei Kogyo Co., Ltd (TCI). A solution of 2-methyl-6-nitrobenzoic acid (5.00 g, 27.6 mmol) and thionyl chloride (20.1 mL, 276 mmol) in dichloromethane (50 mL) was stirred for 15 h at room temperature. The solvent and thionyl chloride were distillated under reduced pressure at 50°C and then dichloromethane (40 mL), 2-methyl-6-nitrobenzoic acid (5.00 g, 27.6 mmol) and pyridine (2.40 mL, 30.4 mmol) were successively added at 0°C. After the reaction mixture had been stirred for 24 h at room temperature, cooled water was added at 0°C. The mixture was extracted with dichloromethane, and the organic layer was washed with saturated aqueous copper(II) sulfate, saturated aqueous sodium hydrogencarbonate, cold water and brine, dried over sodium sulfate. Filtration of the mixture and evaporation of the solvent under reduced pressure produced 8.80 g of the crude MNBA. First recrystallization of the crude product from dichloromethane (ca. 90 mL) at 0°C gave 7.70 g of pure MNBA (81%) as a white solid: mp 178–180°C; IR (KBr): 1820 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06 (2H, d, $J=8.1$ Hz), 7.64 (2H, d, $J=7.6$ Hz), 7.53 (2H, dd, $J=7.6$, 8.1 Hz), 2.57 (6H, s). Anal: calcd for $C_{16}H_{12}N_2O_7$: C, 55.82; H, 3.51; N, 8.14. Found: C, 55.81; H, 3.39; N, 8.07%.
15. (a) DMAPO was prepared according to the procedure for the synthesis of its derivatives. See: Ife, R. J.; Dyke, C. A.; Keeling, D. J.; Meenan, E.; Meeson, M. L.; Parsons, M. E.; Price, C. A.; Theobald, C. J.; Underwood, A. H. *J. Med. Chem.* **1989**, *32*, 1970–1977; (b) Concerning the purification, we followed the modified method of: Mukaiyama, S.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2221–2222.
16. For example, the conventional Yamaguchi method requires a stepwise operation,[5a] namely, ω-hydroxycarboxylic acids are first treated with 2,4,6-trichlorobenzoyl chloride and triethylamine to generate the corresponding mixed anhydrides. After filtration of the mixture under an inert gas to remove the triethylammonium chloride formed, the filtrate containing mixed anhydrides is slowly added to the solution of an excess amount of DMAP in a suitable solvent at reflux temperature.