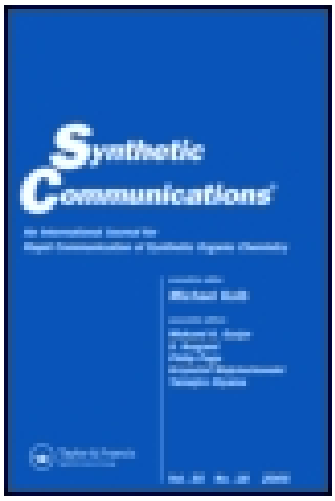

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Modified Yamaguchi Reagent: Convenient and Efficient Esterification

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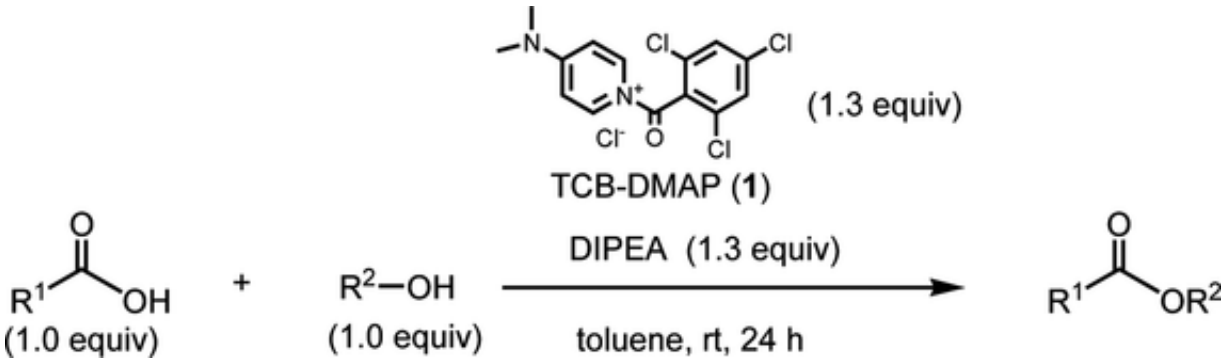
Abstract

A convenient and efficient esterification method that used a modified Yamaguchi reagent (TCB-DMAP) and avoided to use not only intractable acid chloride but also acid anhydrides was proposed. The reaction mechanism was described by FT-IR spectroscopy and supported by a density functional theory calculation.



KEYWORDS: DMAP, acylation, esterification, condensation, acylpyridinium salt.

INTRODUCTION

The effectiveness of 4-dimethylaminopyridine (DMAP) as a highly nucleophilic base catalyst has been reported by both Steglich and Höfle–Litvinenko–Kirichenko.[1] Because DMAP can be utilized in a variety of group-transfer reactions, such as the acylation of alcohols and amines, it has been studied widely.[2] Notably, Yamaguchi and co-workers

have reported a convenient method for the preparation of carboxylic esters and lactones in the presence of triethylamine and DMAP using 2,4,6-trichlorobenzoyl chloride as a bulky acid moiety for the formation of the intermediary mixed anhydride.[3] Recently, a regioselective version of the Yamaguchi esterification method was reported by SantaLucia and Dhimitruka.[4] In addition, Shiina and co-workers developed an effective esterification method using 2-methyl-6-nitrobenzoic anhydride, a reagent similar to the Yamaguchi reagent.[5] It is estimated that these esterification methods proceed *via* intermediates including a mixed anhydride and an *N*-acylpyridinium salt with an activated acyl group.[6] Generally, acid chlorides and acid anhydrides are intractable in condensation reactions, such as peptide bond formation and esterification, because acid chlorides react with both carboxylates and nucleophiles, such as alcohols and amines.

We demonstrate a convenient and practical protocol for these esterification methods *via* mixed anhydride and an *N*-acylpyridinium salt with an activated acyl group. For this purpose, we prepared the modified Yamaguchi reagent 2′,4′,6′-trichlorobenzoyl-4-dimethylaminopyridinium chloride (TCB-DMAP) (**1**), which is a stable crystal in atmosphere and hence handled easily. In addition, we report the development of an effective method for monitoring esterification by IR spectroscopy and density functional theory (DFT) calculation[7], and we apply the results to clarify the esterification mechanism in the presence of TCB–DMAP.

RESULTS AND DISCUSSION

First, we prepared TCB-DMAP by the following method. To a solution of DMAP (5.5 mmol) in 20 mL of dry THF was added 2,4,6-trichlorobenzoylchloride (5mmol), and the mixture was stirred for 24 h. The precipitate was collected by suction filtration, washed with THF, and recrystallized from THF-CH_2Cl_2 mixed solvent to give TCB-DMAP (90% yield). This reagent is very stable crystal avoiding humidity. It has been stored in the desiccator for several years, and the activity is no change at all.

A typical procedure for esterification is as follows. TCB-DMAP (0.26 mmol) was added to a solution of carboxylic acid (0.20 mmol) and *N′,N′*-diisopropylethylamine (DIPEA) (0.26 mmol) in anhydrous toluene (2 mL) and stirred for a minute. *l*-menthol (0.20 mmol) was added to the mixture over a period of 1 min and then stirred for 24 h at room temperature. In every case, this reaction proceeded at room temperature to give the corresponding carboxylic esters in high yields from equimolar amounts of carboxylic acids and alcohols, such as the benzyl, allyl, and secondary aliphatic alcohols (Table 1). This method is also applicable to various carboxylic acids including □,□-unsaturated and aromatic carboxylic acids, with alcohols (benzyl, allyl and secondary aliphatic alcohols) using TCB-DMAP to obtain the corresponding carboxylic esters. Therefore, various carboxylic esters can be obtained in good to high yields under mild reaction conditions.

In addition, this method was applied to the synthesis of 3*R*-[3*R*-(3*R*-hydroxybutyryloxy)butyryloxy] butyric acid (**23**), a pheromone of *Linyphia triangularis*[8], which was obtained in an overall good yield (Scheme 1).

The DMAP-supported reaction pathway in the esterification reaction using TCB-DMAP was then studied by evaluating the time-dependent changes in the FT-IR spectrum. Specifically, the absorption bands associated with C=O bond stretching were observed (Figure 1). TCB-DMAP in acetonitrile displays a stretching vibration at 1751.2 cm^{-1} corresponding to the C=O bond stretching of the *N*-acylpyridinium salt. The FT-IR spectrum of a mixture of phenylpropionic acid, TCB-DMAP, and DIPEA in acetonitrile showed the presence of the mixed anhydride, 2,4,6-trichlorobenzoic phenylpropionic anhydride **(II)** (1818.3 cm^{-1}), and the acylpyridinium salt, 4-dimethylamino-1-(3-phenylpropionyl)pyridinium salt **(III)** (1767.7 cm^{-1}). The IR spectral changes that occurred upon addition of *l*-menthol to the mixture are shown in Figure 1. The increase in the new absorbance corresponding to a stretching band at 1724.4 cm^{-1} is due to the accumulation of the product (−)-menthyl 3-phenylpropionate **(IV)** in the reaction mixture. Concurrently, the intensity of the bands for **(II)** and **(III)** decreased dramatically. These spectral changes were associated with the absorption bands of the alternatively synthesized mixed anhydride (2,4,6-trichlorobenzoic phenylpropionic anhydride) and *N*-acylpyridinium salt (4-dimethylamino-1-(3-phenylpropionyl)pyridinium chloride) and their conversion to the product ester **(IV)**. In this way, the carboxylate anion attacks the carbonyl group of TCB-DMAP, which is the most activated site at the beginning of the reaction. These results suggest that the esterification mechanism with TCB-DMAP favors the formation of a mixed anhydride derived from the carboxylic acid and the 2,4,6-trichlorobenzoyl group that is released from TCB-DMAP, followed by subsequent reacylation of DMAP to form the *N*-acylpyridinium salt.

Further, we have discussed for absorption of IR spectrum by use of quantum calculation. Molecular orbital calculations for mixed anhydride (**II**), DMAP, and *l*-menthol were also performed using DFT, as implemented in the DMol3 package from Accelrys Inc (Figure 2). The delocalized lowest unoccupied molecular orbital (LUMO) was observed near the C1, and 2,4,6-trichlorophenyl groups. The localized LUMO orbital was observed on C15. Therefore, nucleophiles such as DMAP or alcohols are more likely to attack the localized carbonyl carbon C15 than the delocalized C1 (Figure 2). In addition, the energy levels of the highest occupied molecular orbital (HOMO) of DMAP and *l*-menthol were also calculated. The energy levels of the HOMO for DMAP and the HOMO for *l*-menthol were −5.7 and −7.0 eV, respectively. Thus, the nucleophilicity of the N-atom of the pyridine ring of DMAP with respect to C15 is greater than that of the hydroxyl group of *l*-menthol. Therefore, in this DMAP-catalyzed esterification, nucleophilic alcohol does not react to C15 of the mixed anhydride. The released DMAP attacks C15 and gives *N*-acylpyridinium salt.

CONCLUSIONS

In conclusion, we demonstrated a modified Yamaguchi esterification method using TCB-DMAP which avoided the use of acid chlorides and acid anhydrides. Due to the crystal stability of TCB-DMAP, this protocol provides a convenient one-pot procedure that is easily handled. Furthermore, we elucidated the mechanism of this esterification reaction using the modified Yamaguchi reagent by time-dependent FT-IR spectroscopy and DFT calculations. This esterification proceeds *via* a mixed anhydride and an acylpyridinium

salt. These results support the catalytic mechanism for DMAP that has been proposed on the basis of other studies completed to date.[9]

EXPERIMENTAL

^{1}H NMR spectra were recorded on a 500 NMR spectrometer operating at JAOL ECA500, respectively in $CDCl_3$ unless otherwise noted. Coupling constant (*J*) values are reported in Hertz. Mass Spectra (MS) were performed at JAOL JMS-700 MStation at the University of Kitasato using chemical ionization or electron impact techniques. HPLC experiments were performed on a LC solution (□ = 254 nm) system using a wakosil-II 3C18 HG (3.0 mm φ x 75 mm) column. Assay yields calculated by HPLC using an internal standard method under 40 ºC, 0.8 mL/min. The calibration curve was prepared from various concentrations of each esters. Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Compounds were visualized located by UV (254 nm) and spraying the TLC plate with a solution of phosphomolybdic acid followed by heating until color developed. Optimized geometry and molecular orbital were calculated by DFT method using the Materials Studio DMol3 package of Accelrys Inc. First, optimized geometry was obtained using the Perdew-Wong GGA functional (PWC) and double numerical puls d-functional (DND) basis set. Second, the optimized geometry obtained were further calculated for molecular orbital using the Becke exchange puls Lee-Young-Parr correlation (B3LYP) and the double numerical plus polarization (DNP) basis set.

General Method

To a solution of carboxylic acid (0.20 mmol) and DIPEA (0.26 mmol) in 2 mL of anhydrous toluene was added TCB-DMAP (**1**) (0.26 mmol) and stirred for 1 min. The mixture was added alcohol (0.20 mmol) over 1 min and stirred for 24 h at room temperature. The portion (50 □L) of the mixture was added coumarin as internal standard substance, and diluted with 2 mL of acetonitrile / H_2O (5 : 1). The solution was analyzed by HPLC using an internal method of coumarin.

Synthesis Of (*R*)-(−)-2-{(*R*)-(−)-2-Carboxy-1-Methylethoxy Carbonyl}-1-Methylethyl (*R*)-(−)-3-Hydroxybutyrate (23)

(**22**) (0.418 mmol) was dissolved in 10 mL of EtOH. To the solution was added Pd/C (5%) (10 mg), and stirred under H_2 for 24 h. The residue was filtrated and concentrated in vacuo to give colorless oil (**23**) (>99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.25 (d, 3H, *J*=6.9 Hz), 1.30 (m, 6H), 2.41-2.64 (m, 6H), 4.29 (m, 1H), 5.37 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.5, 171.9, 170.0, 68.1, 67.8, 64.9, 43.1, 41.2, 40.8, 22.4, 20.2, 20.1; HRMS $[M+H]^+$ calcd for $C_{12}H_{21}O_7$ 277.1287, found 277.1291; $[\square]_D^{24}$ = -23.8 (c 1.0, $CHCl_3$)

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

ACKNOWLEDGMENTS

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REFERENCES

1. (a) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97; (b) Steglich, W.; Höfle, G. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981; (c) Höfle, G.; Steglich, W. *Synthesis* **1972**, 619; (d) Höfle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

2. (a) Berry, D. J.; DiGiovanna, C. V.; Metrick, S. S.; Murugan, R. *Arkivoc* **2001**, (i), 201; (b) Murugah, R.; Scriven, E. F. V. *Ald. chem. Acta.* **2003**, *36*, 21; (c) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4826; (d)Scriven, E. F. V *Chem. Soc. Rev.* **1983**, *12*, 129; (e) Hassner, A.; Krepski, L. R. Alexanian, V. *Tetrahedron* **1978**, *34*, 2069; (f) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368; (g) Su, D. W.; Wang, Y. C.; Yan, T. H. *Tetrahedron Lett.* **1999**, *40*, 4197; (h) Ranarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494; (i) Wolfe, M. S. *Synthetic Communications* **1997**, *27*, 2975.

3. (a) Inanaga, J.; Hirata, K.; Saeki, H., Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613; (c) Ghosh, K. A.; Swanson, L. *J. Org. Chem.* **2003**, *68,* 9823; (d) Nagamitsu,T.; Takano, D.; Marumoto, K.; Fukuda, T.; Furuya, K.; Otoguro, K.; Takeda, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *J. Org. Chem.* **2007**, *72,* 2744; (e) Nagamitsu,

T.; Takano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *Org*. *Lett*. **2004**, *6*, 1865.

4. Dhimitruka, I.; StantaLucia, J. Jr. *Org*. *Lett*. **2006**, *8*, 47.

5. (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem*. *Lett*. **2002**, 286; (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett*. **2002**, *43*, 7535; (c) 2-Methyl-6-nitrobenzoic anhydride (MNBA) is commercially available from Tokyo Kasei Kogyo Co., Ltd. (TCI, M1434).

6. Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J*. *Org*. *Chem*. **2004**, *69*, 1822-1830.

7. (a) Delly, B. *J. Chem. Phys.* **1990**, *92*, 508; (b) Delly, B. *J. Chem. Phys.* **2000**, *113*, 7756; (c) Perdew, J. P.; Wang, Y. *Phys. ReV. B* **1992**, *45*, 13244; (d) Beck, A. D. *J. Chem. Phys.* **1988**, *88*, 2547; (e) Lee, C.; Yang, W.; Parr, R. G. *Phys. ReV. B* **1988**, *37*, 786.

8. (a) Quang, D. N.; Hashimoto, T.; Toyota, M.; Asakawa, Y. *J. Nat. Prod.* **2003**, *66*, 1613; (b) Schulz, S.; Toft, S. *Science*, **1993**, *260*, 1635.

9. Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem*. *Eur*. *J*. **2005**, *11*, 4751.

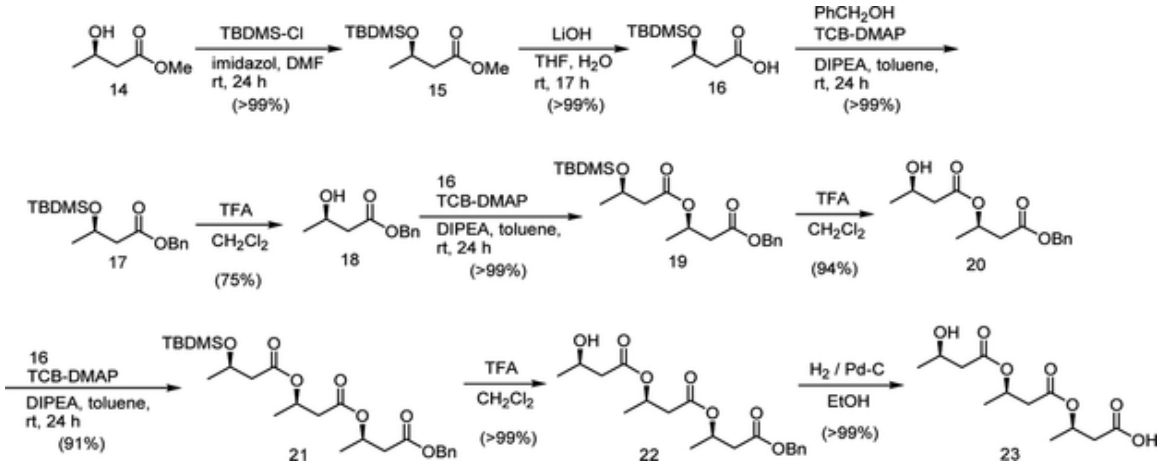
Table 1 Synthesis of various esters by TCB-DMAP

entry	R^1COOH	R^2OH	Product	A (%)[a]
1	$Ph(CH_2)_2COOH$	(-)-Menthyl-OH	**2**	99
2	$Ph(CH_2)_2COOH$	BnOH	**3**	94
3	$Ph(CH_2)_2COOH$	1-Phenylethyl-OH	**4**	88
4	$Ph(CH_2)_2COOH$	(*E*)-Cinnamyl-OH	**5**	93
5	PhCOOH	(-)-Menthyl-OH	**6**	95
6	PhCOOH	BnOH	**7**	88[b]
7	PhCOOH	1-Phenylethyl-OH	**8**	88
8	PhCOOH	(*E*)-Cinnamyl-OH	**9**	77
9	(*E*)-PhCH=CHCOOH	(-)-Menthyl-OH	**10**	>99
10	(*E*)-PhCH=CHCOOH	BnOH	**11**	91
11	(*E*)-PhCH=CHCOOH	1-Phenylethyl-OH	**12**	90
12	(*E*)-PhCH=CHCOOH	(*E*)-Cinnamyl-OH	**13**	84

[a]Assay yields calculated by HPLC using an internal standard method of coumarin

[b]Isolated yield

Scheme 1 Synthesis of a *Linyphia triangularis* pheromone



Scheme 2 Detailed proposed mechanism esterification using TCB-DMAP

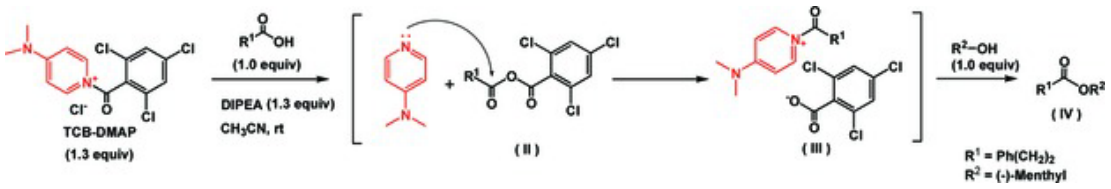


Figure 1 IR spectra of the intermediates generated in esterification using TCB-DMAP.

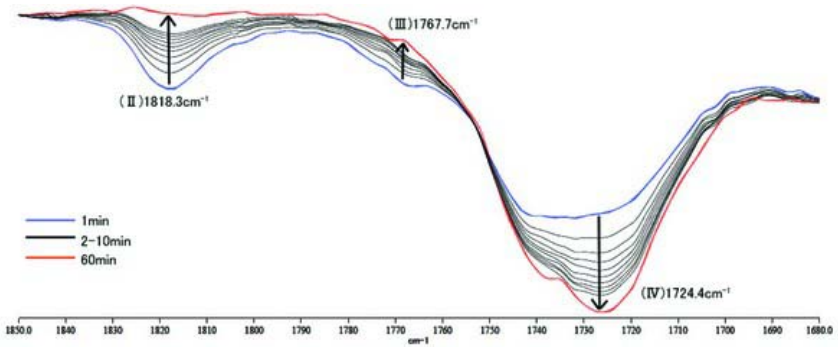


Figure 2 Delocalized LUMO+1 of the mixed anhydride (II). Method : B3LYP/DNP(6-31G*)//B3LYP/DNP(6-31G*)