Synthetic Communications<sup>®</sup>, 38: 3208–3214, 2008 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397910802109299



# Convenient Method for the Preparation of Carboxylic Esters Using (Chloromethylene)dimethylammonium Chloride

Hitoshi Nagao, Makoto Michida, and Teruaki Mukaiyama Center for Basic Research, Kitasato Institute, Tokyo, Japan

**Abstract:** (Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) works as an efficient condensation reagent in the formation of carboxylic esters from carboxylic acids and alcohols under mild conditions in a one-pot procedure. Secondary alcohols are converted successively into the corresponding esters in moderate to high yields with inversion of configurations.

Keywords: Condensation, inversion, mild conditions, one-pot, Vilsmeier reagent

Preparation of carboxylic esters is one of the most fundamental and frequently used important reactions in organic chemistry. For instance, conversion of secondary alcohols into the corresponding esters with carboxylic acids by oxidation–reduction condensation using a phosphorus reagent system such as  $Ph_3P$ -DEAD-RCO<sub>2</sub>H (Mitsunobu reaction<sup>[1–3]</sup>) is considered quite useful in the construction of chiral centers via the inversion of configuration by Sn2 displacement. However, this conventional method has some disadvantages in the process. That is, first, isolation of the desired product from the coproduct such as triphenylphosphine oxide or diethyl hydrazinedicarboxylate is often difficult. Second, azodicarboxylate, such as diethyl azodicarboxylate, is a poisonous compound. Therefore, to develop a reaction more efficient and convenient for the preparation of various esters under absolute stereochemical control is still an important topic.

Received February 6, 2008.

Address correspondence to Teruaki Mukaiyama, Center for Basic Research, Kitasato Institute, 6–15–5 (TCI), Toshima, Kita-ku, Tokyo 114–0003, Japan. E-mail: mukaiyam@abeam.ocn.ne.jp

## **Preparation of Carboxylic Esters**

(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent), which is easily derived from N.N-dimethylformamide and a chlorinating reagent, is frequently used not only as a formulating reagent  $[^{[4,5]}]$  but also as an activating reagent for carboxylic acids to form esters<sup>[6]</sup> and amides.<sup>[7]</sup> Although the Vilsmeier reagent has a powerful ability to dehydrate carboxylic acids, only a few examples have been reported on the dehydration from an alcoholic moiety.<sup>[8-10]</sup> Of the few methods, Barrett et al. reported that secondary alcohols were converted into the corresponding esters in an inverted fashion when the Vilsmeier reagent and potassium benzoate were used in combination.<sup>[8]</sup> This method requires tough reaction conditions (e.g., reflux for 3 days in THF), and the esterification of chiral 1-phenylethyl alcohol proceeded with partial inversion (ee = 51%). Recently, our laboratory reported that (chloromethylene)dimethylammonium chloride was a useful reagent for the preparation of inverted alkyl aryl sulfides from various chiral alcohols.[11]

In this communication, we report a convenient method for the preparation of esters from various primary and secondary alcohols via (alkoxymethylene) dimethylammonium chloride under mild conditions (Scheme 1).

In the first place, we tried esterification of (S)-(-)-1-phenylethyl alcohol with 1.5 equivalents of Vilsmeier reagent using 3.0 equivalents of triethylamine in THF at room temperature (Table 1). When benzoic acid was used, the desired ester was obtained in 66% yield with 90% ee (entry 1). The yield and enantiomeric excess further increased when benzoic acids with electron-withdrawing groups were used (entries 3–6). The best result of all was obtained when 2,4-dinitrobenzoic acid was used (entry 6), and the yield was 96% with almost complete inversion of stereochemistry (95% ee). It is noteworthy that the reaction proceeded with clean inversion of configuration even when the easily epimerizable substrate was used.

Next, the effect of solvents was examined (Table 2). When the solvents such as dichloromethane, acetonitrile, or acetone were used, the yield of the desired ester was obtained in low (entries 1–3). On the other hand, the esterification of (S)-(–)-1-phenylethyl alcohol gave the ester in low enantiomeric purities when solvents such as diethylether or



Scheme 1. Preparation of carboxylic esters from alcohol.

	OH Ph Me + 1 (1.5 eq.)	ArCO <sub>2</sub> H <b>2</b> (1.0 eq.)	CIHC=N <sup>+</sup> Me (1.5 eq.) Et <sub>3</sub> N (3.0 ec THF, rt, 16	$\begin{array}{ccc} P_2 C \Gamma & & & \\ \hline & & & \\ \hline q. ) & & Ph & Me \\ h. & & 3 \end{array}$	۸r
Entry	ArCO <sub>2</sub>	H	Product	Yield $(\%)^a$	Ee $(\%)^b$
1	C 2a	O₂H	3a	66	90
2	MeO-	−CO <sub>2</sub> H	3b	55	72
3	Br	-CO <sub>2</sub> H	3c	80	85
4		O <sub>2</sub> H	3d	82	93
5	$O_2N - 2e$	−CO <sub>2</sub> H	3e	85	93
6	$O_2N \longrightarrow 2f$	NO₂ −CO₂H	3f	96	95
7		O <sub>2</sub> H	3g	44	96
8	NC 2h	CO₂H	3h	80	90

Table 1. Esterfication of (S)-(-)-1-phenylethyl alcohol using various carboxylic acids

<sup>a</sup>Isolated yield.

<sup>b</sup>Determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or AS-H) with hexane/2-propanol as an eluent.

1,4-dioxane were used (entries 7 and 8). Low enantioselectivities and yields are because the present reaction proceeded by either a mixed Sn2/Sn1 pathway or partially via the corresponding benzylic chloride.

## Table 2. Effect of solvents

OH 人 +		$\begin{array}{c} CIHC=N^{+}Me_{2}CI^{-}\\ (1.5 \text{ eq.}) \end{array}$		
Ph´ `Me		Et <sub>3</sub> N (3.0 eq.)	Ph Me NO <sub>2</sub>	
<b>1a</b> (1.5 eq.)	<b>2f</b> (1.0 eq.)	Solv., rt, 16 h.	3f	
Entry	Solvent	Yield $(\%)^a$	Ee $(\%)^b$	
1	$CH_2Cl_2$	28	92	
2	CH <sub>3</sub> CN	39	95	
3	Acetone	54	96	
4	Toluene	81	86	
5	AcOEt	79	98	
6	THF	96	95	
7	Et <sub>2</sub> O	91	25	
8	1,4-dioxane	46	6	

<sup>a</sup>Isolated yield.

<sup>b</sup>Determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or AS-H) with hexane/2-propanol as an eluent.

As a result, tetrahydrofuran was found to be the most effective solvent of the present reaction (entry 6).

Then, esterification of various alcohols was tried with 2,4-dinitrobenzoic acid in THF at room temperature for 16 h (Table 3). The reactions of primary and secondary alcohols proceeded smoothly to provide the corresponding esters in moderate to good yields (entries 1–9). The desired 2,4-dinitrobenzoates were obtained in good yields with almost complete inversion of the stereochemistry when chiral secondary alcohols were used (entries 5–9). However, when a tertiary alcohol having an ester group at the quaternary center was tried, the corresponding ester was obtained in only 9% yield (entry 12).

In conclusion, it is noted that a convenient and efficient method for the preparation of inverted alkyl carboxylates from various chiral secondary alcohols was established using the readily available Vilsmeier reagent under mild conditions.

## **TYPICAL EXPERIMENTAL PROCEDURE**

Experimental procedure is exemplified in the following (Table 1, entry 6): To a stirred solution of DMF (117  $\mu$ L, 1.37 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), oxalyl chloride (108  $\mu$ L, 1.24 mmol) was added dropwise at

он	+ $O_2 N = C O_2 H$	CIHC=N <sup>+</sup> (1.5	<sup>t</sup> Me <sub>2</sub> Cl <sup>-</sup>	NO <sub>2</sub>	
R' R' 1 (1.5 eq.)	2f(1.0  eq.)	Et <sub>3</sub> N ( THF, ri	3.0 eq.) R F t, 16 h.	$R R' NO_2$	
Entry	RR'OH	Product	Yield $(\%)^a$	Ee $(\%)^{b}$	
1	Ph 1b	3i	76		
2	Ph <sup>^^</sup> OH 1c	3j	65	_	
3	С>-ОН 1d	3k	87		
4	OH le	31	74	_	
5	Ph <sup>¯</sup> Me 1f	3m	92	95	
6	OH Ph 1g	3n	94	96	
7	OH Ph 1h	30	86	99	
8	OH Me <sup>L</sup> CO <sub>2</sub> Me 1i	3р	76	96	
9	$ \begin{array}{c} O \\ O \\ O \\ I \\ J \end{array} $	3q	65	95	
10	Me Me MeO <sub>2</sub> C <sup>×</sup> OH 1k	3r	9	_	

 Table 3. Esterification of various alcohols

<sup>a</sup>Isolated yield.

<sup>b</sup>Determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H, Chiralpak AD-H or AS-H) with hexane/2-propanol as an eluent.

## **Preparation of Carboxylic Esters**

0°C under an argon atmosphere. The mixture was stirred for 5 min at the same temperature, and solvent was evaporated. The obtained white solid was cooled down to 0°C and suspended in dry THF (3.0 mL). (S)-(-)-1-Phenylethyl alcohol (151.2 mg, 1.24 mmol), triethylamine (346.7 uL, 2.49 mmol), and 2.4-dinitorobenzoic acid (176.1 mg, 0.83 mmol) were added sequentially. After the reaction mixture was stirred for 16h at room temperature, it was guenched with water. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na2SO4, filter, and concentrated. The product purified by column chromatography crude was (hexane/EtOAc = 3/1) to afford the desired product **3f** (250.8 mg, 96%, 95% ee) as a coloress solid. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ 8.77 (d, J = 2.1 Hz, 1H), 8.50 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.41–7.29 (m, 5H), 6.16 (q, J = 6.6 Hz, 1H), 1.69 (d, J = 6.6 Hz, 1H). The enantiomeric purity was determined by HPLC analysis using DAICEL Chiralpak AD-H, hexane/2-propanol = 20/1,  $\lambda = 254 \text{ nm}$ , flow rate = 1.0 mL/min, retention times = 19.1 min (R) and  $24.6 \min(S)$ .

## REFERENCES

- Mitsunobu, O.; Yamada, M. Preparation of esters of carboxylic and phosphoric acid via quaternary phosphonium salts. *Bull. Chem. Soc. Jpn.* 1967, 40, 2380–2382.
- Mitsunobu, O.; Eguchi, M. Preparation of carboxylic esters and phosphoric esters by the activation of alcohols. *Bull. Chem. Soc. Jpn.* 1971, 44, 3427– 3430.
- 3. Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, 1–28.
- 4. Campagine, E.; Monroe, P. A.; Arnwine, B.; Archer, W. L. Thiosemicarbazones of thiophene derivatives. J. Am. Chem. Soc. 1953, 75, 989–991.
- Treibs, W.; Neupert, H.-J.; Hiebsch, J. Über bi- und polycyclische azulene, XXXVII: Synthesen und eigenschaften von azulen-aldehyden. *Chem. Ber.* 1959, 92, 141–154.
- 6. Stadler, P. A. Eine einfache Veresterungsmethode im Eintopf-Verfahren. *Helv. Chim. Acta.* **1978**, *61*, 1675–1681.
- 7. Zaoral, M.; Arnold, Z. A novel peptide synthesis. *Tetrahedron Lett.* **1960**, 9–12.
- Barrett, A. G. M.; Koike, N.; Procopiou, P. A. Nucleophilic substitution of (alkoxy-methylene)dimethylammonium chloride with carboxylate salts: A convenient procedure for the synthesis of esters with inversion of configuration. J. Chem. Soc., Chem. Commun. 1995, 1403–1404.
- Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. A novel cyclodehydration reaction of hydroxy-phenols using imidate esters as leaving groups. *Tetrahedron Lett.* 1993, 7483–7486.

- Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. N,N,N',N'-Tetramethylchloroformamidinium chloride as an efficient condensation reagent for a novel– esterification applicable to the macrolide synthesis. *Chem. Lett.* 1982, 1891–1894.
- 11. Kawano, Y.; Kaneko, N.; Mukaiyama, T. A convenient method for the preparation of alkyl aryl sulfides from alcohols and (chloromethylene)-dimethylammonium chloride. *Chem. Lett.* **2005**, *34*, 1612–1613.

Copyright of Synthetic Communications is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.