

## Efficient photolytic esterification of carboxylic acids with alcohols in perhalogenated methane

Jih Ru Hwu,\* Chuan-Yi Hsu and Moti L. Jain

*Organosilicon and Synthesis Laboratory, Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan*

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**Abstract**—Condensation of carboxylic acids and alcohols to give esters was accomplished with selectivity under photolytic conditions in 66–99% yields by use of  $\text{CCl}_4$  or  $\text{BrCCl}_3$  at room temperature.

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During our studies on photochemical reactions of various organic compounds, we found that carboxylic acids can be easily converted to the corresponding esters in the presence of alcohols and carbon tetrachloride. Esterification is a fundamental transformation in organic synthesis.<sup>1</sup> Although many methods have been developed for its accomplishment,<sup>2</sup> a few of them proceed under photolytic conditions.<sup>3,4</sup> Herein we report the applicability, selectivity, and advantages of the photochemical conversion of carboxylic acids and alcohols to esters in the presence of a perhalogenated methane.

The general procedure for photolytic esterification is as follows. A mixture containing a carboxylic acid (1.00 mmol) and an alcohol (from 1.00 mmol to excess) in  $\text{CCl}_4$  (4.0–8.0 mL) was irradiated by UV light with a medium-pressure mercury lamp (450 W) for 2.5–78 h. After the solvent was removed, the residue was purified by column chromatography to give the pure ester in 66–99% yields. Dimethylformamide and chloroform can be applied as the co-solvents for substrates with low solubility in  $\text{CCl}_4$ .

As shown in Table 1, the method was applicable to aliphatic and aromatic carboxylic acids, such as decanoic acid (entry 1), *N,N*-phthaloyl-D-phenylalanine

(entry 2), *N*-benzoylglycine (entries 3 and 4), and benzoic acid (entries 5 and 6). When phenylacetic acid was used as the substrate for esterification, it reacted smoothly with both primary and secondary alcohols of various types (see Table 2). Examples include methanol, isopropanol, allyl alcohol, benzyl alcohol, norborneol (entry 6), and pregnenolone (entry 7).

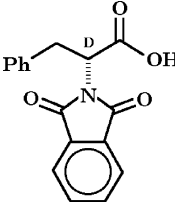
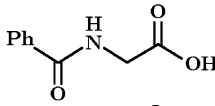
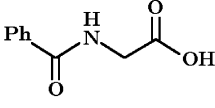
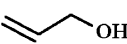
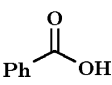
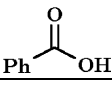
For 1,4-butanediol as a primary alcohol, the photolytic method led it to a mono-ester as the major product in 86% yield and a diester as the by-product in 8.0% yield (see entry 1 in Table 3). Esterifications of 1,3-butanediol and 2,3-*O,O*-dibenzyl-L-ascorbic acid, both of which possess 1°- and 2°-hydroxyl groups, took place preferentially at the primary position (see entries 2 and 3). When glycerol was used as the substrate, mono- and diesters were obtained as a mixture in 73% and 20% yields, respectively (see entry 4). The secondary hydroxyl group therein did not react with phenylacetic acid. These examples indicate unanimously that selectivity greatly favors a primary hydroxyl group rather than a secondary hydroxyl group during esterification of a carboxylic acid with an alcohol.

In addition, we found that the photolytic esterification proceeded successfully by using 10 equiv of  $\text{BrCCl}_3$  to replace  $\text{CCl}_4$ . As shown in entry 3 of Table 2, phenylacetic acid reacted with isopropanol in the presence of  $\text{BrCCl}_3$  and UV light to give the corresponding ester in a quantitative yield. These results are complementary to those reported by Lee et al.,<sup>3</sup> who used  $\text{CBr}_4/\text{MeOH}$  (0.42%) for esterifications. On the other hand, we found that  $\text{BrCCl}_3$  functioned as a Br-donor<sup>5,6</sup> during the photolysis of phenylacetic acid in the absence of an

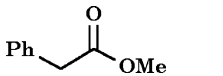
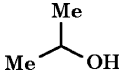
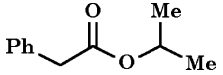
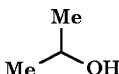
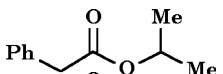
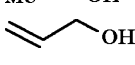
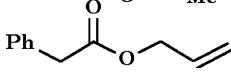
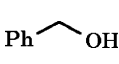
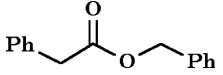
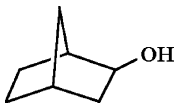
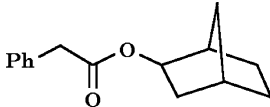
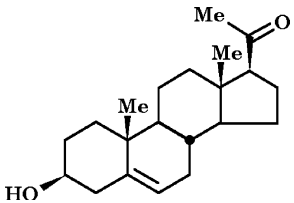
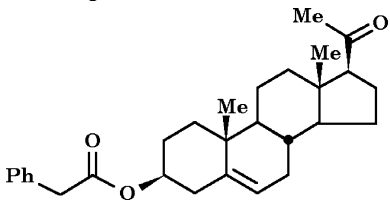
**Keywords:** Photolysis; Esterification; Carboxylic acid; Alcohol; Ester; Carbon tetrachloride.

\* Corresponding author. Tel.: +886-35725813; fax: +886-35721594; e-mail: [jrhwu@mx.nthu.edu.tw](mailto:jrhwu@mx.nthu.edu.tw)

**Table 1.** Condensation of carboxylic acids with alcohols in the presence of CCl<sub>4</sub> to give the corresponding esters under UV irradiation
$$\text{R}^1\text{CO}_2\text{H} + \text{R}^2\text{OH} \xrightarrow[\text{CCl}_4]{h\nu} \text{R}^1\text{CO}_2\text{R}^2$$

Entry	R <sup>1</sup> CO <sub>2</sub> H	R <sup>2</sup> OH <sup>a</sup>	Times (h)	Yield (%)
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COOH	MeOH	12	99
2		MeOH	12	92
3		MeOH	2.5	99
4 <sup>b</sup>			12	66
5		EtOH	72	99
6		MeOH	72	99

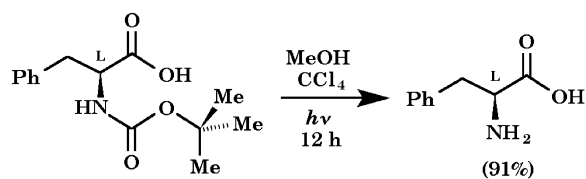
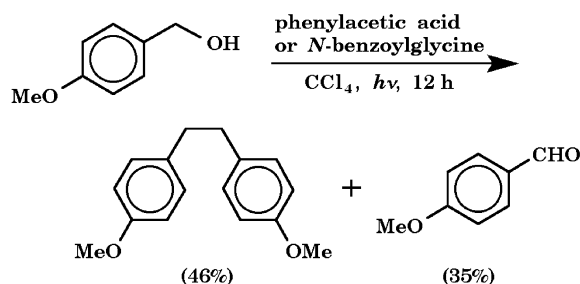
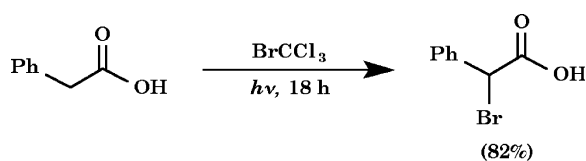
<sup>a</sup> Alcohols were used in a large excess (33–400 equiv).<sup>b</sup> DMF was used as the co-solvent.**Table 2.** Photolytic esterification of phenylacetic acid with alcohols of various types in the presence of CCl<sub>4</sub> to give the corresponding esters
$$\text{Ph-CH}_2\text{-CO}_2\text{H} + \text{ROH} \xrightarrow[\text{CCl}_4]{h\nu} \text{Ph-CH}_2\text{-CO}_2\text{R}$$

Entry	ROH	Equivalent	Product	Time (h)	Yield (%)
1	MeOH	Excess		3.0	99
2		Excess		15	99
3 <sup>a</sup>		Excess		8.0	99
4		10		6.0	93
5		1.5		12	75
6		1.5		78	67
7		2.0		76	69

<sup>a</sup> BrCCl<sub>3</sub> (10 equiv) was used to replace CCl<sub>4</sub>.

**Table 3.** Selectivity among primary, secondary, and tertiary hydroxyl groups in the photolytic esterification of carboxylic acids in the presence of CCl<sub>4</sub>

Entry	ROH	Equivalent	Product	Time (h)	Yield (%)
	$\text{Ph-CH}_2\text{-COOH} + \text{ROH} \xrightarrow[\text{CCl}_4]{h\nu} \text{Ph-CH}_2\text{-COOR}$				
1		2.0		10	86 + 8.0
2		2.0		10	73
3		1.0		12	84
4 <sup>a</sup>		10		12	73 + 20
5		Excess	None	72	None

<sup>a</sup> CHCl<sub>3</sub> was used as the co-solvent.**Scheme 1.** Photolysis of a mixture containing a carboxylic acid and an alcohol.

alcohol (see Scheme 1).  $\alpha$ -Bromophenylacetic acid was thus isolated in 82% yield.

To realize limitation of the photolytic esterification, we treated carboxylic acids with various alcohols in the presence of CCl<sub>4</sub>. Our results indicate that this photochemical method was not applicable to 2,2,2-trichloroethanol. Moreover, as shown in Scheme 1, irradiation of 4-methoxybenzyl alcohol with phenylacetic acid or *N*-benzoylglycine in CCl<sub>4</sub> produced 1,2-bis[*p*-methoxyphenyl]ethane (46%) as a coupling dimer and 4-methoxybenzaldehyde (35%). On the other hand, photolysis of *N*-*tert*-butoxycarbonyl-L-phenylalanine in the presence of excess methanol and CCl<sub>4</sub> resulted in deprotection of the *tert*-butoxycarbonyl group<sup>7</sup> instead of esterification.

In a series of control experiments, we detected pH values of the reaction media during the photolytic conversion of phenylacetic acid and methanol to the corresponding ester in CCl<sub>4</sub>. The pH value was 4.3 initially and dropped to 0.30 after 3.0 h. These results indicate that acids were generated during photolysis. Most likely the acid was HCl and produced in situ. Under the photolytic conditions, the first step could be  $\text{CCl}_4 \rightarrow \cdot\text{CCl}_3 + \cdot\text{Cl}$ .<sup>8,9</sup>

The second step would be  $\cdot\text{Cl} + \text{RR}'\text{CHOH} \rightarrow \text{HCl} + \text{RR}'\text{C}\cdot\text{OH}$ .<sup>10,11</sup> To provide evidence in support of our assumption, we added phenyl *N-tert*-butylnitronone<sup>12–14</sup> and 2,2'-azobis(isobutyronitrile),<sup>15</sup> individually, as a radical quencher in 2.0 equivalents. The photolytic esterification of phenylacetic acid with methanol was retarded completely. Therefore we believe that the reaction mechanism involves radical intermediates.

Furthermore, we found that photolytic esterification of phenylacetic acid did not proceed with *tert*-butanol or phenol. Thus one can envisage two legitimate reasons. First, *tert*-butanol and phenol lack an  $\alpha$ -H to be abstracted by  $\cdot\text{Cl}$ . As a consequence, the catalyst HCl could be not generated. Second, the steric effect imparted by a tertiary butyl group may slow down the esterification with *tert*-butanol.

We bore out the feasibility in the conversion of phenylacetic acid to the corresponding methyl ester with HCl in different forms, including  $\text{HCl}_{(\text{g})}$ ,  $\text{HCl}_{(\text{fuming})}$ , and  $\text{HCl}_{(\text{aqueous, 0.50–2.0 N})}$ . Furthermore, performance of the photolytic transformation in the media containing  $\text{NaHCO}_3_{(\text{s})}$  did not produce any ester. These data corroborate an acid-catalyzed mechanism for the photolytic esterification. An intriguing point is that the acid was generated photochemically from  $\text{CCl}_4$  and alcohols in situ under controlled conditions.

In conclusion, esterification of carboxylic acids with various alcohols in carbon tetrachloride can be accomplished efficiently by exposure of the solution to UV light. The acids include alkyl, aromatic, and amino acids. The photolytic esterification showed selectivity between primary and secondary alcohols, yet no reaction occurred to a tertiary alcohol. Performance of these esterifications involves simple manipulation; mineral or Lewis acids/bases are not required as the external catalyst.

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