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An unprecedented and highly chemoselective esterification method

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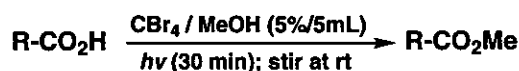
Abstract—A series of carboxylic acids was transformed to their corresponding methyl esters under $\text{CBr}_4/\text{CH}_3\text{OH}$ (0.05 eq., 5 ml) reaction conditions. The rate of esterification is decreased with increasing bulkiness of the alcohol. Chemoselectivity can be achieved between phenylacetic and benzoic acids, $sp^3\text{-C}$ and $sp^2\text{-C}$ acids as well as between $sp^3\text{-C}$ and $sp\text{-C}$ tethered carboxylic acids. © 2000 Elsevier Science Ltd. All rights reserved.

The transformation of a carboxylic acid to an ester is a common and useful method for protecting carboxyl groups.^{1–6} The selective esterification of a carboxyl group is an important tool in organic synthesis. Although many effective and reliable reactions for the preparation of esters have been reported, there is still a need for simple and selective esterification methods. Several selective esterification procedures have been reported in the literature.^{7–14} Recently, our laboratory reported effective and selective methods for hydrolysis of trialkylsilyl ethers,^{15,16} acetals/ketals¹⁷ and tetrahydropyranyl ethers.¹⁸ Under the reaction conditions for desilylation of silyl esters, we found that α -unsubstituted carboxylic acids were esterified to their corresponding esters.¹⁹ Therefore, we investigated esterification of different carboxylic acids under these reaction conditions. Herewith, we wish to report a mild, highly efficient and selective esterification method for carboxylic acids under CBr_4/MeOH (or EtOH) reaction conditions (Scheme 1).

A typical procedure for esterification of a carboxylic acid is as follows: A solution of the carboxylic acid (1.0 mmol), CBr_4 (0.05 mmol) and anhydrous CH_3OH (5 ml) in a Pyrex culture tube is irradiated directly by a TLC lamp at room temperature (UVItec Limited, 8 watt, 254 nm) for 30 minutes and then stirred without irradiation at room temperature. After the reaction is complete (by TLC), the organic solvent is removed directly under reduced pressure. Further purification is achieved by flash chromatography with ethyl acetate/hexane as eluant. A series of carboxylic acids were esterified under these reaction conditions and the results are shown in Table 1.

Primary and secondary tethered carboxylic acids were converted into their esters with high yields (Entries 1–6). Benzoic acid, $sp^2\text{-C}$ tethered and α -amino acids undergo esterification slowly even after a prolonged reaction time (Entries 7, 8 and 10). It is interesting to note that the rate of esterification becomes much slower when the methanol is replaced with a more sterically hindered alcohol, such as ethanol or isopropanol. A mixture of phenylacetic and benzoic acids were investigated for selective esterification. The results showed that phenylacetic acid was selectively transformed to its methyl or ethyl ester whereas benzoic acid was stable under the reaction conditions (Scheme 2).

The results led us to investigate further this highly chemoselective esterification process which distinguishes between $sp^3\text{-C}$ and $sp^2\text{-C}$ tethered carboxylic acids. A mixture of 8-bromo-1-octanoic acid and 2,4-hexadienoic acid in CBr_4/MeOH (10%/10 ml) was investigated under the reaction conditions (Scheme 3). The $sp^3\text{-C}$ tethered primary acid was converted into its methyl ester in 98% yield, whereas the $sp^2\text{-C}$ tethered carboxylic acid was stable under the reaction conditions for 24 hours and a 96% recovery was obtained after chromatography. The $sp^3\text{-C}$ tethered secondary carboxylic acid was also converted into its methyl ester in 97% yield, whereas the $sp^2\text{-C}$ tethered carboxylic acid was resistant under the reaction conditions for 50 hours and a 99% recovery was obtained after chromatography.



Scheme 1.

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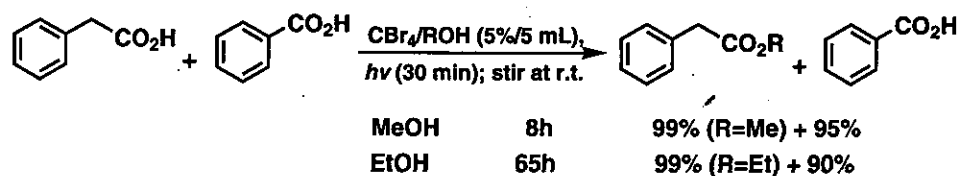
Table 1. Esterification of carboxylic acids

| Entry | Substrate | Product | R' | Time (h) | Yield ^a |
|-------|---|--|-------------|----------|-------------------------|
| 1 | | | Me | 13 | 90% |
| | | | Et | 48 | 85%(10%) ^b |
| | | | <i>i</i> Pr | 48 | N.R.(95%) ^b |
| 2 | | | Me | 24 | 98% |
| | | | Et | 67 | 98% |
| | | | <i>i</i> Pr | 48 | Trace(90%) ^b |
| 3 | | | Me | 7 | 96% |
| | | | Et | 48 | 90% |
| 4 | | | Me | 72 | 40% ^c |
| | | | Et | 189 | N.R.(95%) ^b |
| 5 | | | Me | 2 | 96% |
| | | | Et | 68 | 99% |
| 6 | | | Me | 25 | 95% |
| | | | Et | 79 | 84%(13%) ^b |
| 7 | | | Me | 72 | 14%(80%) ^b |
| | | | Et | 330 | 64%(34%) ^b |
| 8 | | | Me | 48 | N.R.(99%) ^b |
| | | | Et | 390 | N.R.(95%) ^b |
| 9 | | | Me | 140 | 93% |
| | | | Et | 330 | 64%(34%) ^b |
| 10 | AcNH-CH ₂ -CO ₂ H | AcNH-CH ₂ -CO ₂ R' | Me | 240 | 60%(32%) ^b |

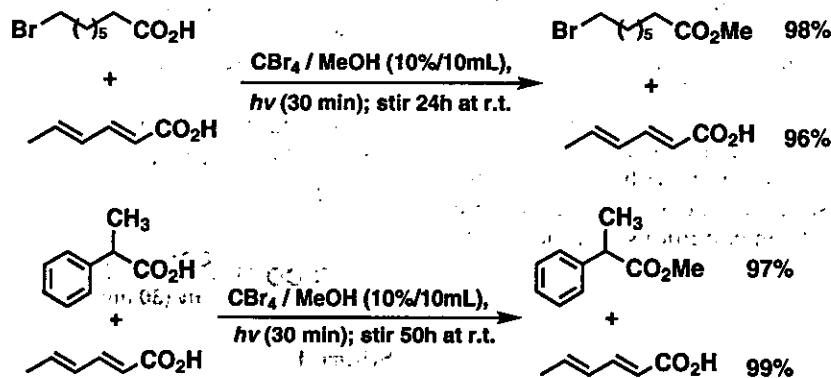
(a) The yields were determined after chromatographic purification.

(b) The yield of recovered starting material after chromatography.

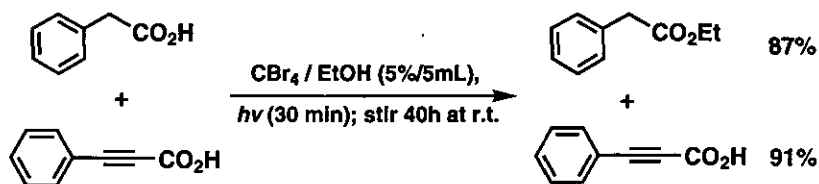
(c) The yield is low because the product is highly volatile.



Scheme 2.



Scheme 3.



Scheme 4.

We further investigated this highly chemoselective esterification process between phenylacetic and phenylpropionic acids (Scheme 4). The sp^3 -C tethered primary carboxylic acid was converted into its ethyl ester in 87% yield, whereas the sp -C tethered carboxylic acid was resistant under the reaction conditions for 40 hours and a 91% recovery was obtained after chromatography:

In conclusion: these reaction conditions provide a highly chemoselective method for the esterification of a carboxylic acid. This method enables the esterification of an sp^3 -C tethered carboxylic acid, whereas sp^2 -C and sp -C tethered carboxylic acids were stable under the reaction conditions. Our previous investigations have shown that numerous functionalities are hydrolyzed by this reaction system (e.g. acetals/ketals, silyl ethers, tetrahydropyranyl ethers, etc.). These results lead us to investigate the mechanism of this highly chemoselective method and studies are underway.

Acknowledgements

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- The results for selective desilylation of silyl esters will be submitted for publication soon.

