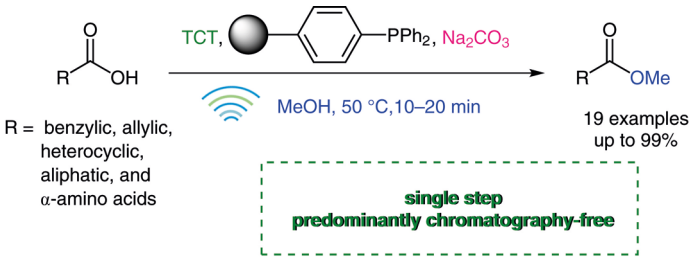
Synlett S. Jaita et al. Letter

# Ultrasound-Assisted Methyl Esterification of Carboxylic Acids Catalyzed by Polymer-Supported Triphenylphosphine

**Subin Jaita**
**Wong Phakhodee**
**Mookda Pattarawarapan***

Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai 50200, Thailand
mookdap55@gmail.com




Received: 16.04.2015
Accepted after revision: 09.06.2015
Published online: 09.07.2015
DOI: 10.1055/s-0034-1381117; Art ID: st-2015-d0276-l

**Abstract** A convenient and efficient sonochemical method for methyl esterification of carboxylic acids catalyzed by polymer-supported triphenylphosphine (PS-$Ph_3P$) is reported. In the presence of 1:0.1:2 molar ratio of 2,4,6-trichloro-1,3,5-triazine/PS-$Ph_3P$/$Na_2CO_3$, methyl esters of various carboxylic acids bearing reactive hydroxyl groups as well as acid- or base-labile functionalities could be rapidly prepared (within 10–20 min) in good to excellent yields without necessity to pre-activate the acids. Using the polymer-bound phosphine also allows easy isolation of the products which, in most of the cases, were obtained in high purities without column chromatography.

**Key words** esterification, carboxylic acids, esters, phosphorus, chemoselectivity

Methyl esterification of carboxylic acids is an important synthetic process which has been used in various applications such as in the synthesis of biodiesels, fragrance materials, and surfactants.[1] Moreover, the method is generally applied in facilitating the purification and characterization of structurally complex molecules as well as in the protection of carboxyl group(s) during a synthetic sequence.[2] Thus, numerous methods for generating methyl esters have been developed to achieve high conversion with functional-group compatibility under mild conditions.

Generally, methyl esters can be prepared either by methylation of the carboxyl oxygen or through nucleophilic substitution on the carboxyl carbon by methanol. In the former method, apart from the direct use of iodomethane,[3] various reagents such as diazomethane ($CH_2N_2$),[4] trimethylsilyldiazomethane ($TMSCHN_2$),[5] dimethyl sulfate,[6] polymer-supported methyl sulfonate,[7] and dimethyl carbonate[8] have been applied as electrophilic methyl-group equivalents.

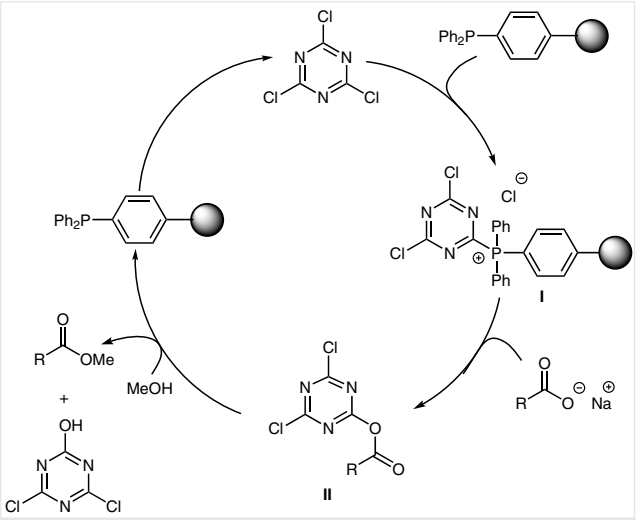
A relatively more straightforward method toward methyl esters is through the direct condensation between carboxylic acids and methanol since the starting materials are inexpensive, easy to handle, and readily available. The well-known classical approach for such transformation is the Fisher esterification.[9] This acid-catalyzed reaction is, however, reversible and requires removal of water and/or use of a large excess of alcohol to achieve high conversions. Incompatibility with acid-sensitive functionalities also limits its use to those simple carboxylic acids.

Alternatively, carboxylic acids may be converted into other more active species such as acid halides, anhydrides, or active esters before treatment with alcohols. In addition to commercially available coupling reagents, some examples of acid-activating systems including 2,4,6-trichloro-1,3,5-triazine (TCT) and its derivatives,[10] $Ph_3P$/trichloroisocyanuric acid,[11] imidazole carbamate/urea,[12] $Ph_3P$-$I_2$/imidazole,[13] $POCl_3$-DMAP,[14] $Ph_3P$-$I_2$/cat. $Zn(OTf)_2$,[15] and Mitsunobu-type reagents[16] have been developed for esterification of carboxylic acids. Nevertheless, the methods still suffer limitations such as requirement of an additional activation step, costly reagents, long reaction times, and/or harsh reaction conditions.

Ultrasonic technology has become a highly attractive energy source for organic reactions due to the safety and simplicity of the instrumental set-up.[17] Due to the cavitation effect which leads to enhancement in mass-transfer rate and mixing between the phases, reactions carried out under ultrasonic irradiation have often been reported with higher yields, better selectivity, and shorter reaction times in comparison with the traditional stirring methods.

In our ongoing studies with the TCT/$Ph_3P$-mediated nucleophilic substitution of carboxylic acids,[18] we herein report a facile, convenient, and economical approach for rapid conversion of carboxylic acids into their methyl ester derivatives using a combination of TCT, polymer-supported triphenylphosphine (PS-$Ph_3P$), and $Na_2CO_3$ under ultrasonic irradiation. The reaction is most likely to proceed via the

formation of triazinephosphonium chloride (**I**) which undergoes displacement with a carboxylate anion to provide an acyloxytriazine **II**. This reactive species then further reacts with methanol to afford the desired methyl ester with concomitant release of the hydroxyl derivative of TCT (Scheme 1).



**Scheme 1** Proposed mechanism for TCT/PS-$Ph_3P$-catalyzed methyl esterification

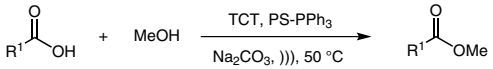
Since alcohols are weaker nucleophiles than carboxylate ions, a one-step condensation procedure in which carboxylic acids were activated in the presence of methanol and inorganic bases was investigated. In a preliminary study, it was found that the methyl ester of 4-methylbenzoic acid (0.271 mmol) could be obtained in 98% yield after ten minutes sonication of the acid in methanol (0.5 mL) at 50 °C in the presence of 1:0.1:2 molar ratio of TCT/PS-$Ph_3P$/$Na_2CO_3$. Although other carbonate bases including $K_2CO_3$ and $Cs_2CO_3$ gave comparative yields, $Na_2CO_3$ was selected as the base for further investigation due to its lower cost and ready availability.

Reaction in the absence of the phosphine catalyst gave a complex mixture which provided only 27% of the corresponding ester. Under vigorous stirring at 50 °C, the corresponding ester was obtained in 35% yield. Thus a significant improvement in both the product yield and the reaction rate results from using catalytic quantities of the polymer-bound phosphine under ultrasonic irradiation.

The one-step condensation between methanol and a series of carboxylic acids including aromatic acids, α,β-unsaturated acid, aliphatic acids, as well as N-protected α-amino acids was further evaluated.[19–21] According to Table 1, benzoic acids with either electron-donating groups or electron-withdrawing substituent(s) gave the corresponding methyl esters in good to excellent yields although electron-deficient and sterically hindered acids required slightly longer times for completion of the reaction (Table 1, entries 1–10). Nicotinic acid also reacted efficiently (Table 1, entry 11). 4-Hydroxybenzoic acid containing a reactive phenolic hydroxy group provided the respective product in moderate yield indicating good chemoselectivity of the method (Table 1, entry 12). The sonochemical conditions were also applicable to α,β-unsaturated acids as well as aliphatic acids (Table 1, entries 13–16). Methyl ester derivatives of β-aryl acids were afforded in high yields without decarboxylation as may be observed under Fischer esterification conditions (Table 1, entries 15 and 16).[22]

O-Methylation of N-protected α-amino acids was also attempted. *N*-Benzoyl glycine and Boc-Gly-OH reacted readily to give the desired products without removal of the acid-sensitive benzoyl or Boc groups (Table 1, entries 17 and 18). Similarly, Fmoc-Gly-OH (Table 1, entry 19) was converted into its corresponding methyl ester in good yield.

**Table 1** Methyl Esterification of Carboxylic Acids




| Entry | $R^1CO_2H$ | Time (min) | Yield (%)[a] | Purity (%)[c] |
|---|---|---|---|---|
| 1 | PhCOOH | 10 | 90 | 100 |
| 2 | 4-$MeC_6H_4COOH$ | 10 | 98 | 100 |
| 3 | 4-$MeOC_6H_4COOH$ | 10 | 92 | 100 |
| 4 | 2-$MeOC_6H_4COOH$ | 20 | 82 | 100 |
| 5 | 3,4-$(MeO)_2C_6H_3COOH$ | 10 | 99 | 100 |
| 6 | 3-$Me_2NC_6H_4COOH$ | 30 | 85 | 98 |
| 7 | 4-$ClC_6H_4COOH$ | 20 | 97 | 100 |
| 8 | 2-$ClC_6H_4COOH$ | 20 | 94 | 100 |
| 9 | 2-$IC_6H_4COOH$ | 20 | 92 | 100 |
| 10 | 4-$O_2NC_6H_4COOH$ | 20 | 96 | 100 |
| 11 | nicotinic acid | 20 | 80 | 95 |
| 12 | 4-$HOC_6H_4COOH$ | 20 | 70[b] | 88 |
| 13 | PhCH=CHCOOH | 10 | 82 | 100 |
| 14 | $Ph(CH_2)_4COOH$ | 10 | 97 | 100 |
| 15 | 2-$MeOPhCH_2COOH$ | 20 | 90 | 100 |
| 16 | 4-$HOPhCH_2COOH$ | 10 | 77[b] | 90 |
| 17 | benzoylglycine | 20 | 87[b] | 92 |
| 18 | Boc-Gly-OH | 20 | 80[b] | 95 |
| 19 | Fmoc-Gly-OH | 10 | 85[b] | 93 |

[a] Unless otherwise indicated, the yield was obtained after filtration of the crude reaction through a short pad of silica, followed by solvent evaporation.
[b] Yield obtained after column chromatography.
[c] Purity of the isolated product after the filtration method based on GC–MS.

It is noted that we did not observe any residual TCT after reaction which could be due to the formation of monosubstituted acyloxytriazine **II** or possibly methanolysis of the unreacted TCT. Since most methyl esters are less polar than

other unreacted carboxylic acids (if any) and the byproduct(s) from TCT, isolation of the ester products could be readily conducted by filtration through a short silica plug. With this procedure, only the polar components are retained on the silica gel, while the desired methyl esters are isolated in high purities (>95% based on GC–MS). Nevertheless, flash chromatography was necessary in the cases where the reaction gave high polarity products (Table 1, entries 17–19) or complex mixtures (Table 1, entries 12 and 16).

In summary, using a TCT/PS-$Ph_3P$/$Na_2CO_3$ combination, methyl esters of carboxylic acids could be rapidly prepared in a single step without requirement for an additional acid pre-activation reaction. Under the weakly basic conditions, the reaction is compatible with a range of carboxylic acids including those containing a reactive hydroxyl group and N-protected α-amino acids bearing acid- or base-sensitive protecting groups. This easy-to-operate sonochemical method offers an excellent alternative to the existing esterification procedures with additional benefits in terms of functional-group compatibility and selectivity. Investigations into the scope of the methodology with a series of alcohols are currently under way.

## Acknowledgment

The Center of Excellence for Innovation in Chemistry (PERCH-CIC), and the National Research University Project under Thailand's Office of the Higher Education Commission, Chiang Mai University are gratefully acknowledged for financial support.

## References and Notes

(1) (a) Leung, G.; Strezov, V. In *Biomass Processing Technologies*; Strezov, V.; Evans, T. J., Eds.; CRC Press: Boca Raton, **2014**, 213. (b) Salvi, B. L.; Panwar, N. L. *Renewable Sustainable Energy Rev.* **2012**, *16*, 3680. (c) McGinty, D.; Letizia, C. S.; Api, A. M. *Food Chem. Toxicol.* **2012**, *50*, S479. (d) Foster, N. C. *SODEOPEC: Soaps, Detergents, Oleochemicals and Personal Care Products*; Spitz, L., Ed.; AOCS Publishing: Urbana (IL, USA), **2004**, 261. (e) Cox, M. F.; Weerasooriya, U. *Surfactant Sci. Ser.* **2003**, *114*, 467. (f) Nakamura, M. *J. Oleo Sci.* **2001**, *50*, 445. (g) Opdyke, D. L. J. *Food Cosmet. Toxicol.* **1974**, *12*, 939.

(2) Otera, J. *Esterification: Methods, Reactions, and Applications*; Wiley-VCH: Weinheim, **2003**, 1–326.

(3) (a) Mal, D.; Jana, A.; Ray, S.; Bhattacharya, S.; Patra, A.; De S, R. *Synth. Commun.* **2008**, *38*, 3937. (b) Avila-Zarraga, J. G.; Martinez, R. *Synth. Commun.* **2001**, *31*, 2177. (c) Mal, D. *Synth. Commun.* **1986**, *16*, 331.

(4) (a) Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590. (b) Olias, J. M.; Rios, J. J.; Valle, M. *J. Chromatogr. A* **1989**, *467*, 279. (c) Eisenbraun, E. J.; Morris, R. N.; Adolphen, G. *J. Chem. Educ.* **1970**, *47*, 710.

(5) Presser, A.; Huefner, A. *Monatsh. Chem.* **2004**, *135*, 1015.

(6) Heravi, M. M.; Ahari, N. Z.; Oskooie, H. A.; Ghassemzadeh, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1701.

(7) Yoshino, T.; Togo, H. *Synlett* **2005**, 517.

(8) Rajabi, F.; Saidi, M. R. *Synth. Commun.* **2004**, *34*, 4179.

(9) Fischer, E.; Speier, A. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3252.

(10) (a) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037. (b) Kunishima, M.; Morita, J.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. *Synlett* **1999**, 1255. (c) Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. *Tetrahedron* **1999**, *55*, 13159. (d) Kaminski, Z. J. *Biopolymers* **2000**, *55*, 140. (e) Wetosot, S.; Duangkamol, C.; Pattarawarapan, M.; Phakhodee, W. *Monatsh. Chem.* **2015**, *146*, 959.

(11) Rodrigues, R. d C.; Barros, I. M. A.; Lima, E. L. S. *Tetrahedron Lett.* **2005**, *46*, 5945.

(12) Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572.

(13) Morcillo, S. P.; Alvarez de Cienfuegos, L.; Mota, A. J.; Justicia, J.; Robles, R. *J. Org. Chem.* **2011**, *76*, 2277.

(14) Chen, H.; Xu, X.; Liu, L.; Tang, G.; Zhao, Y. *RSC Adv.* **2013**, *3*, 16247.

(15) Mamidi, N.; Manna, D. *J. Org. Chem.* **2013**, *78*, 2386.

(16) (a) Lanning, M. E.; Fletcher, S. *Tetrahedron Lett.* **2013**, *54*, 4624. (b) Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* **2008**, *73*, 4882. (c) Fitzjarrald, V. P.; Pongdee, R. *Tetrahedron Lett.* **2007**, *48*, 3553. (d) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855. (e) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967. (f) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (g) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

(17) (a) Varma, R. S. *Green Chem. Lett. Rev.* **2007**, *1*, 37. (b) Serpone, N.; Colarusso, P. *Res. Chem. Intermed.* **1994**, *20*, 635. (c) Cintas, P.; Luche, J. L. *Green Chem.* **1999**, *1*, 115. (d) Puri, S.; Kaur, B.; Parmar, A.; Kumar, H. *Curr. Org. Chem.* **2013**, *17*, 1790. (e) Suprarukmi, D. D.; Sudrajat, B. A.; Widayat, *Procedia Environ. Sci.* **2015**, *23*, 78.

(18) Jaita, S.; Kaewkum, P.; Duangkamol, C.; Phakhodee, W.; Pattarawarapan, M. *RSC Adv.* **2014**, *4*, 46947.

(19) General Procedure
The carboxylic acid (0.271 mmol), TCT (0.050 g, 0.271 mmol), PS-$Ph_3P$ (0.009 g, 0.027 mmol, loading 3.0 mmol/g), and $Na_2CO_3$ (0.057 g, 0.542 mmol) were added to MeOH (0.5 mL). Then the mixture was sonicated in an ultrasonic bath (Elmasonic S 30H) at 50 °C for the specified time. After completion, the crude mixture was filtered through a short pad of silica to obtain the product after solvent evaporation. Whenever necessary, the product was further purified by flash chromatography.

(20) Methyl Cinnamate (Table 1 Entry 13)
Colorless oil (0.036 g, 82% yield); $R_f$ = 0.48 (5% EtOAc–hexane). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 16.0 Hz, 1 H), 7.53–7.50 (m, 2 H), 7.38–7.36 (m, 3 H), 6.44 (dd, J = 16.0, 0.8 Hz, 1 H), 3.80 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 167.4, 144.9, 134.4, 130.3, 128.9, 128.1, 117.8, 51.7. LRMS (EI): m/z (rel. intensity) = 162 (25) [$M^+$], 131 (100), 103 (61), 77 (33).

(21) (9H-Fluoren-9-yl)methyl (Methoxycarbonyl)glycinate (Table 1 Entry 19)
Colorless oil (0.0717 g, 85% yield); $R_f$ = 0.46 (40% EtOAc–hexane). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.6 Hz, 2 H), 7.60 (d, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.31 (t, J = 7.6 Hz, 2 H), 5.43 (br s, 1 H), 4.41 (d, J = 6.8 Hz, 2 H), 4.23 (t, J = 6.8 Hz, 1 H), 3.99 (d, J = 5.2 Hz, 2 H), 3.75 (s, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 170.5, 156.4, 143.8, 141.3, 127.7, 127.1, 125.1, 120.0, 67.2, 52.4, 47.1, 42.7. LRMS (EI): m/z (rel. intensity) = 311 (3) [$M^+$], 178 (100), 165 (28).

(22) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. *Chem. Eur. J.* **2006**, *12*, 9314.