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One-pot esterification and Ritter reaction: chemo- and regioselectivity from *tert*-butyl methyl ether

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ABSTRACT

tert-Butyl methyl ether (TBME) has been effectively used as a reagent for esterification of carboxylic acids. By varying amounts of sulfuric acid, a remarkable regioselectivity in esterification has been demonstrated. Additionally, under the present reaction conditions, one-pot esterification and Ritter reaction are achieved in almost quantitative yield.

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Esterification of carboxylic acid is an important transformation in organic synthesis, which has been well reviewed.¹ Esters are key intermediates in the synthesis of polymers, perfumes, and pharmaceutical intermediates or final products.² Acid-catalyzed esterifications³ at reflux condition is most common procedure adopted for esterification. This is a reversible reaction, which is equilibriumcontrolled therefore, does not always furnish quantitative yield.⁴ Therefore there are number of attempts to achieve quantitative conversion by using a variety of conditions such as alkaline, neutral and acidic conditions.⁵

The classic reagents for esterification under alkaline conditions are strong electrophiles such as alkyl iodides⁶ or the corresponding mesylates or tosylates.^{7–10} Haworth methylation, which employs DMS and LiOH in THF¹¹ proceeds well to furnish almost quantitative yield of the product without any side reactions. It is important to note that these classic hard electrophiles such as methyl iodide and alkyl sulfonates are carcinogens and genotoxic, and dimethyl sulfate is extremely hazardous.^{12–14} Besides these reagents, several reagents such as diazomethane,¹⁵ trimethylsilyl diazomethane,¹⁶ and methyl triazien,¹⁷ and dialkyl formamide dimethyl acetal¹⁸ are known to convert carboxylic acids to esters under neutral conditions. Cyclic imides such as *O*-methyl caprolactam,¹⁹ isourea ethers ,²⁰ modified thiazynes and *S*-propargyl xanthates²¹ are few more reagents that are used successfully for the esterification. The Mitsunobu reaction,^{22,23} triethyl or trimethyl orthoformates have also been used as esterification reagents under neutral conditions.²⁴ Lewis acid-catalyzed esterification with Mg(ClO₄)₂²⁵ has been reported. Further, asymmetric acyl transfer reactions mediated by organo catalysts²⁶ and enzymes for the formation of optically active esters have been documented in the literature.²⁷ Interestingly, there are no attempts to use ether as a reagent for esterification except one report, which uses THF and acid chloride.²⁸ In this paper, we are disclosing a regioselective synthesis of methyl or *tert*-butyl ester of carboxylic acid by using TBME, which is achieved by varying the reaction conditions.

TBME is a common organic solvent which is a safe alternative to tetrahydrofuran in the Grignard reaction.²⁹ Apart from this, TBME has been reported as a butylating agent for active aromatic systems,³⁰ There is a report on the use of TBME as a *tert*-butyl esterification agent under microwave conditions.³¹ Other than these reports, to the best our knowledge, there are no reports on the utility of TBME in organic synthesis. Therefore, we thought that it is reasonable to exploit this unsymmetrical molecule in organic synthesis and decided to investigate the esterification of carboxylic acids.

Initial experiments of benzoic acid **1a** with TBME and two equivalent of H_2SO_4 under reflux condition furnished exclusively methyl benzoate **1b** in good yield (73%, entry 1, Table 1). On the other hand, the reaction of **1a** at 0–5 °C furnished the corresponding *t*-butyl ester **1c** as a major product along with the corresponding methyl ester **1b** in minor amount (entry 2, Table 1). However, increasing the amount of acid to 4 or 5 equiv and performing the reaction at reflux condition has resulted in formation of mixture





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Table 1

Optimization of esterification of benzoic acid with TBME and H₂SO₄^a



Entry	H ₂ SO ₄ (mmol)	Reaction condition	1a:1c ^b	Yield ^c (%)
1	180	Reflux	100:0	73
2	480	0−5 °C	20:80	87
3	900	Reflux	72:28	85
4	360	rt	70:30	87
5	900	10-15 °C	75:25	83
6	18	Reflux	100:0	90
7	9	Reflux	100:0	40

^a Benzoic acid (80 mmol), TNBE (50 ml) are used for the experiments.

 $^{\rm b}$ Ratio based on $^1{\rm H}$ NMR integration of CH₃ and (CH₃)₃ protons. $^{\rm c}$ Isolated yield, all reactions were carried out for 16 h.

Table 2

Esterification of with TBME and H₂SO₄ under reflux conditions



^a All the reaction were carried in 10 g scale and yield refers to isolated yield.

of methyl ester **1b** and *tert*-butyl ester **1c** (72:28 ratio, 85%, entry 3 and 4, Table 1). Nevertheless, decreasing the amount of acid to 18% and performing the reaction at reflux temperature has produced the ester **1b** exclusively in 90% (entry 6, Table 1). In the optimized

conditions, the carboxylic acids were heated at reflux with about 18% sulfuric acid (0.1 equiv w/v), to furnish the corresponding methyl esters (Table 2, entries 1-12).³³ Interestingly, when the reaction of carboxylic acid with TBME was carried out at colder temperature (0–5 °C), *t*-butyl esters are formed as the major product (Scheme 1).

This reaction is generalized and the results are tabulated in Table 3. As seen in Table 3, benzoic acid and substituted benzoic acids furnished the corresponding *t*-butyl ester as the major product (Table 3, entries 13–16). Based on the above observation, it is evident that the regio- and chemoselectivity is temperature and quantity of sulfuric acid dependent. However, we were not able to obtain *tert*-butyl ester exclusively under these reaction conditions.

Further to take advantage of the present observation, we continued our investigation to accomplish Ritter reaction and esterification in one-pot using TBME as the reagent. Esterification and the Ritter reaction³² are two complementary reactions. In esterification, water is formed as a by product while in the Ritter reaction water is one of the reactants. Therefore, we decided to examine whether it is possible to accomplish both esterification and the Ritter reaction in one-pot. If this is successful, it would also drive the esterification to completion. Thus, when cyano acetic acid was reacted with TBME under similar conditions, it was completely converted to *tert*-amido methyl ester in almost quantitative yield



Scheme 1. Esterification with TBME.

Table 3	
Esterification of with TBME at 0-5 °C	

Entry	Substrates	Products	Yield (%) ^a
13	CO ₂ H	COOR 1b: R= CH ₃ 4: D= tot bot d	1b:1c 12:49
14	CO ₂ H CI 14a	COOR CI 14b: R= CH ₃ 14c: R= <i>tert</i> -butyl	14b:14c 10:51
15	C ₆ H ₅ CO ₂ H 15a	COOR 15b: R= CH ₃ 15c: R= <i>tert</i> -butyl	15b:15c 5:75
16	CO ₂ H	COOR 16b : R= CH ₃ 16c : R= <i>tert</i> -butyl	16b:16c 7:34

^a All reaction were carried at 80 mmol scale and yield. Ratio by ¹H NMR by integrating methyl signal and *tert*-butyl signal.

Table 4

Esterification and Ritter reaction with TBME



^a All the reaction were carried out at 10 g batches and yield refers to isolated yield.

^b Yield of esters.

^c 70% perchloric acid (1:1, W/V) was used.

(Scheme 2). This reaction is indeed a general one and a variety of nitriles reacted well to furnish the corresponding tert-amido methyl ester in almost quantitative yields (entries 17-22, Table 4). It is interesting to note that cyano acids produces the corresponding tert-amido methyl ester (entry 17, Table 4), whereas ethyl ester of cyano acetic acid underwent a trans esterification to produce the corresponding tert-amido methyl esters in almost quantitative yield (entries 18 and 19, Table 4). The concomitant esterification and Ritter reaction is highly chemoselective, where, complete addition of TBME and water from the esterification occurs to the substrates. Methyl ester and tert-amides were formed exclusively. This facile reaction also works well for intermolecular Ritter reactions. As seen in entries 21 and 22 of Table 4, benzyl cyanide (21a) or CH₃CN reacted well with benzoic acid (1a) under similar condition to furnish ester and amides in quantitative vields..33

Further, we observed that TBME can also be used for esterification of anhydrides. Phthalic anhydride, and maleic and succinic anhydride reacted smoothly with TBME to furnish the corresponding esters in good yield (Table 4, entries 23–26).³³ Using perchloric acid as a catalyst, phthalic anhydride was converted almost exclusively to *tert*-butyl methyl diester (Table 4, entry 25) in average yield.



Scheme 2. Esterification and Ritter reaction with TBME.



Scheme 3. Tentative mechanism.

Tentatively, we propose the following reaction mechanism (scheme 3) for the esterification and Ritter reaction based on water liberation in esterification and water consumption in Ritter reaction. The mechanism also explains higher yield of cyano acids in the reaction.

To sum up, we have developed a new reaction condition for esterification and esterification- Ritter reactions using TBME as solvent and reagent. These reactions are regioselective and chemoselective for both substrates.

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Supplementary data

Supplementary data (spectral data and ¹H and ¹³C NMR of corresponding products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.100.

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- 33. Experimental procedures: Procedure for methyl ester (Table 2): To a well-stirred mixture of acid (80 mmol) in TBME (50 mL) was added sulfuric acid (1.8 g, 1 mL) at room temperature and refluxed for 16-18 h. The reaction mixture was cooled and added to 20% sodium carbonate solution (100 mL). The reaction mass was extracted in TBME/CH₂Cl₂ (50 mL \times 2). The combined organic layer was washed with water (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to obtain methyl ester (73-97%) as the only product. Most examples gave NMR pure product. Where minor impurities are formed, the product was purified over silica gel using ethyl acetate: petroleum ether (1:9). General procedure for tert-butyl ester (Table 3). To a well-stirred mixture of acid (80 mmol) in TBME (50 mL) at 0-5 °C, was added sulfuric acid (10 g, 5.5 mL) at the same temperature and maintained for 4-5 h then was allowed to warm to room temperature and was stirred for 8-10 h. The reaction mixture was added to 20% sodium carbonate solution (100 mL). The reaction mass was extracted in TBME or dichloromethane (50 mL \times 2). The combined organic layer was washed with water (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to obtain tert-butyl ester (34-75%) as the major product. The percentage ratio of product is calculated by ¹H NMR integration of methyl proton and tert-butyl methyl protons. General procedure for cyano acids (Table 4). To a well-stirred mixture of cyano acid (80 mmol, or anhydride) in TBME (50 mL) at about 10 °C was added sulfuric acid (18 g, 10 mL), the mixture was then stirred at room temperature for 10-12 h. The reaction mixture was added to 20% sodium carbonate solution (100 mL). The reaction mass was extracted in TBME or dichloromethane (50 mL \times 2). The combined organic layer was washed with water (100 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the product (94-98%). Most examples gave NMR pure products. Where minor impurities were formed, the product was purified over silica gel using ethyl acetate: petroleum ether (1:9).