Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(12):203-207
(http://derpharmachemica.com/archive.html)

Ultrasonic assisted Synthesis of methyl esters of carboxylic acids by using most convenient, safe and cost effecting reagent $NaHSO_4$

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ABSTRACT

A most efficient, safe and cost effective reagent for esterification of amino acids and carboxylic acids of aromatic and aliphatic by using $NaHSO_4$ is discussed. This method is very much useful for aromatic carboxylic acids as well as aliphatic acids. Great advantage of this reagent is very safe in handling and it is not health hazard like HCl, H_2SO_4 and other acid catalyzed reactions. It is not expensive like other esterification reagents. Esterification reactions with $NaHSO_4$ help in easy to isolation of the desired esters. Because of its low price, it reduces the cost of synthesis also.

Key words: Esterification aromatic carboxylic acids, aliphatic carboxylic acid esters, acids, esters of amino acids etc.

INTRODUCTION

Esterification of carboxylic acids to the corresponding esters is a synthetically important transformation both in industry and academic laboratories. Therefore, numerous new reagents and methods have been developed for the esterification of carboxylic acids. Functionalized esters are industrially important intermediates in organic synthesis and other chemicals intermediates. These reactions have limited utility in the presence of other acid sensitive functional groups. When compared with health hazard and expensive reagents this is most safe and cost effecting method. However the application of ultrasonic assisted synthesis of esters of carboxylic acids in presence of N-Boc groups is low yielding reaction because the reaction is often accompanied by the deprotection of these functional groups. It is well known that the esterification depends on the reactivity of carboxylic acid. Since it is mono sodium salt of sulfuric acid it is sufficiently acidic to catalyze esterification. Ultrasonic synthesis is most effective method for this reagent to synthesize aromatic esters of carboxylic acids. In most cases, the use of different acid catalysts under a wider range of reaction conditions yields the corresponding esters quantitatively, without producing of unwanted products. $NaHSO_4$ much safer than the other esterification reagents in handling where as other reactions include exothermic in nature so that numerous safety precautions have to be taken. Especially with ultrasonic method is very efficient for the esterification reaction which gives good yields comparable to or better than the other esterification reagents. We conducted a brief study of esterification by using ultrasonic method in presence of $NaHSO_4$.

MATERIALS AND METHODS

General spectral data were obtained at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR spectrophotometer and the chemical shift are reported in δ ppm relative to TMS as internal standard in D_2O solvents. Compound mass (m/z)

values were observed by mass spectrophotometer (MS-EI). Completion of reaction was monitored by thin layer chromatography (TLC) and was visualized by UV light of 254 nm.

Experimental procedure

General Information

The reactions were carried out with the help of a standard ultrasonic bath instrument (Bandelin Company, RK510H model) producing irradiation at 40 kHz in sealed tube (aldrich). Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light and Ninhydrin spray. ^{1}H NMR and ^{13}C NMR spectra were determined in D_2O solution on 300 and 75 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. MS(ESI) spectra were obtained on a mass spectrometer.

General experimental procedure for esterification of amino acids of aromatic and aliphatic compounds.

A suspension of carboxylic acid of aromatic or aliphatic compound (1 eq), Sodium bisulphate (5 eq) in methanol was taken in a sealed tube (Aldrich). Heated the reaction mixture to 70 ^{0}C for 5 h in an ultrasonic bath. After completion of the reaction (monitored by TLC), concentrated the reaction mixture to dry. Crude was diluted in THF and filtered. Filtrate was purged with dry HCl at 10 ^{0}C; obtained precipitate was filtered and dried under nitrogen atmosphere to get HCl salt of carboxylic acid methyl ester.

Methyl 4-aminobenzoate (1).

^{1}H NMR (300MHz, D_2O): δ 7.86 (d, 1H), 7.83 (d, 1H), 7.32 (d, 1H), 7.29 (d,1H), 3.72 (s,3H); ^{13}C NMR (75MHz, D_2O) δ 167.9, 135.2, 131.2, 129.6, 123, 52.8; MS(ESI): m/z 152.21$[M+H]^+$

Methioninemethylester (2).

^{1}H NMR (300MHz, D_2O): δ 4.51(t, 1H), 3.79(s, 3H), 3.30(d, 2H); ^{13}C NMR (75MHz, D_2O) δ 169.2, 54.0, 51.6, 35.7; MS(ESI): m/z 139.01$[M+H]^+$

Methyl 3-aminobenzoate (3).

^{1}H NMR (300MHz, D_2O): δ 7.9-7.83(m, 2H), 7.51(m, 2H), 3.77(s, 3H); ^{13}C NMR (75MHz, D_2O) δ 167.6, 131.4, 130.6, 130.2, 130.1, 128.0, 123.9, 53.0; MS(ESI): m/z 152.11$[M+H]^+$

Proline methyl ester (4).

^{1}H NMR (300MHz, D_2O): δ 4.39(m, 1H), 3.76(s, 3H), 2.35(m, 2H), 2.03(m, 2H), 1.98(m, 2H); ^{13}C NMR (75MHz, D_2O) δ 170.5, 59.7, 53.9, 46.4, 28.4, 23.4; MS(ESI): m/z 130.12$[M+H]^+$

6-Aminocaproicacid methyl ester (5).

^{1}H NMR (300MHz, D_2O): δ 3.62(s, 3H), 2.93(t, 2H), 2.35(t, 2H), 1.61-1.55(m, 4H), 1.33(m, 2H); ^{13}C NMR (75MHz, D_2O) δ 177.4, 52.3, 39.4, 33.5, 26.5, 25.2, 23.8; MS(ESI): m/z 146.11$[M+H]^+$

α –Alanine methyl ester (6):

^{1}H NMR (300MHz, D_2O): δ 4.14(m, 1H), 3.76(s, 3H), 1.49(m, 3H); ^{13}C NMR (75MHz, D_2O) δ 171.3, 53.7, 48.9, 15.2; MS(ESI): m/z 104.09$[M+H]^+$

Glycine methyl ester (7).

^{1}H NMR (300MHz, D_2O): δ 4.03(s, 2H), 3.92(s, 3H); ^{13}C NMR (75MHz, D_2O) δ 168.8, 53.5, 40.2; MS(ESI): m/z 90.12$[M+H]^+$

Dimethy iminodiacetate (8).

^{1}H NMR (300MHz, D_2O): δ 4.06(s, 4H), 3.77(s, 6H); ^{13}C NMR (75MHz, D_2O) δ 167.5, 53.6, 47.2; MS(ESI): m/z 162.09$[M+H]^+$

Methyl 4-(aminomethyl)benzoate (9).

^{1}H NMR (300MHz, D_2O): δ 7.96(d, 2H), 7.64(d, 2H), 4.08(s, 2H), 3.84(s, 3H); ^{13}C NMR (75MHz, D_2O) δ 166.0,

147.8, 130.0, 128.3, 126.6, 51.5, 45.5; MS(ESI): m/z 166.03$[M+H]^+$

β-Alanine methyl ester (10).
^{1}H NMR (300MHz, D_2O): δ 3.86(s, 3H), 3.22(t, 2H), 2.77(t, 2H); ^{13}C NMR (75MHz, D_2O) δ 173.2, 52.7, 35.2, 31.2; MS(ESI): m/z 104.01$[M+H]^+$

Methyl 4-(aminomethyl)cyclohexanecarboxylate (11).
^{1}H NMR (300MHz, D_2O): δ 3.59(s, 3H), 2.79(m, 2H), 2.29(m, 1H), 1.94-1.90(m, 2H), 1.78-1.75(m, 2H), 1.57(m, 1H), 1.38-1.26(m, 2H), 1.04-0.92(m, 2H); ^{13}C NMR (75MHz, D_2O) δ 179.4, 52.3, 44.9, 42.6, 34.8, 28.5, 27.7; MS (ESI): m/z 172.13$[M+H]^+$

γ-Aminobutyric methyl ester (12).
^{1}H NMR (300MHz, D_2O): δ 3.63(s, 3H), 2.97(t, 3H), 2.45(m, 2H), 1.89(t, 2H); ^{13}C NMR (75MHz, D_2O) δ 175.7, 52.4, 38.8, 30.6, 22.1; MS(ESI): m/z 118.21$[M+H]^+$

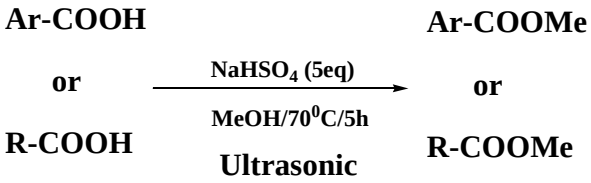
Aspartic acid dimetyl ester(13).
^{1}H NMR (300MHz, D_2O): δ 4.44(dd, 1H), 3.77(s, 3H), 3.68(s, 3H), 3.10(dd, 2H); ^{13}C NMR (75MHz, D_2O) δ 171.7, 169.4, 54.0, 53.1, 49.3, 33.7; MS(ESI): m/z 162.09$[M+H]^+$

Phenylalanine methyl ester(14).
^{1}H NMR (300MHz, D_2O): δ 7.37-7.34(m, 3H), 7.23(d, 1H), 7.21(d, 1H), 4.36(t, 1H); ^{13}C NMR (75MHz, D_2O) δ 170.1, 133.8, 129.5, 128.2, 54.2, 53.7, 35.7; MS(ESI): m/z 180.11$[M+H]^+$

Leucine methyl ester(15).
^{1}H NMR (300MHz, D_2O): δ 4.1(t, 1H), 3.78(s, 3H), 1.82(m, 1H), 1.65(m, 2H), 0.89(m, 6H); ^{13}C NMR (75MHz, D_2O) δ 171.4, 53.6, 51.6, 38.9, 24.0, 21.6, 21.1; MS(ESI): m/z 146.31$[M+H]^+$

RESULTS AND DISCUSSION

Esterification of aromatic and aliphatic carboxylic acids using anhydrous sodium bisulphate as an acid catalyst in ultrasonic is an efficient, safe and simplest synthetic process. Comparatively this process is faster and safer than other methods. Simple amino acids, benzoic acids and hetero aromatic acids have given excellent yield when compared with substituted acid and protected compounds. The observed time for esterification is 5 hours with sodium bisulphate (5 eq) is used if less than that it took more than 7 hours. Reaction was performed by using ultrasonic instrument in methanol. Isolation of product is very convenient and simple. Since it is a low price reagent it reduces the cost of synthesis. Reaction was performed in reflux condition. The main advantage of this study is to choose suitable, safe, cost effecting acid catalyst for esterification where safety is concerned. Completion of the reaction was monitored by TLC and products were characterized by proton NMR and MS-EI data.



Scheme: Esterification of carboxylic acids by using $NaHSO_4$

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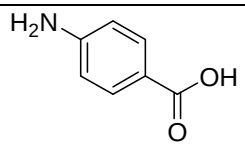
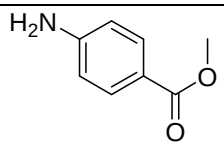
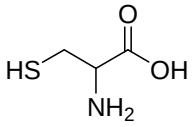
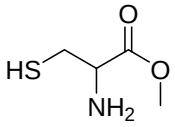
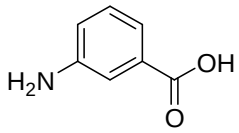
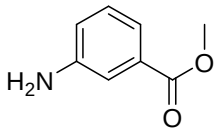
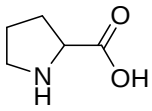
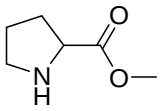
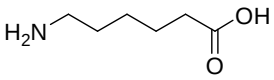
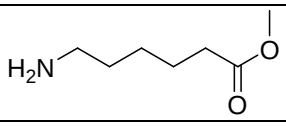
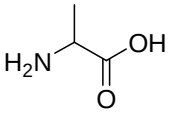
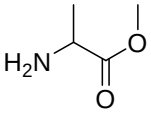
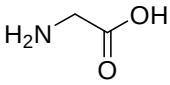
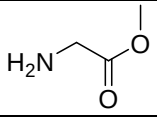
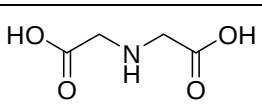
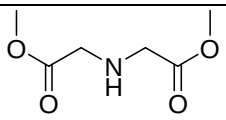
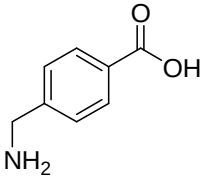
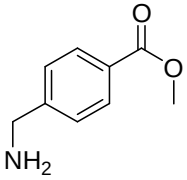
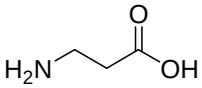
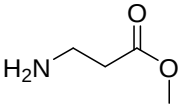
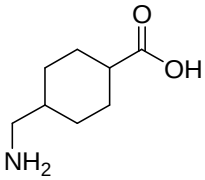
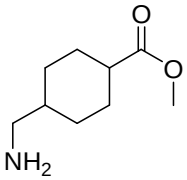
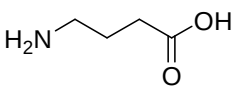
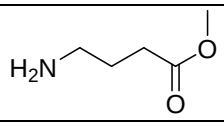
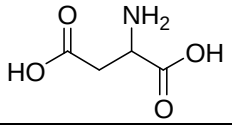
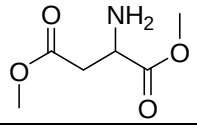
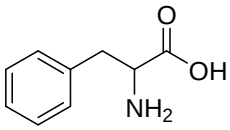
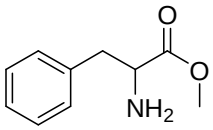
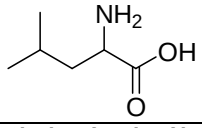
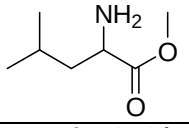
1			70	5	95
2			70	5	98
3			70	5	94
4			70	5	90
5			70	5	93
6			70	5	91
7			70	5	99
8			70	5	90
9			70	5	95
10			70	5	95
11			70	5	96
12			70	5	90

13			70	5	91
14			70	5	89
15			70	5	90

[a] *we made all compounds as HCl salt and analyzed by ^{1}HNMR, ^{13}C NMR and MS(ESI) for comparison with reported data. References have given as in order from compound1 to 15.*

CONCLUSION

In conclusion, we have developed a safe and cost effecting synthetic procedure for esterification of aromatic and aliphatic carboxylic acids at high yields by using sealed tube under ultrasonic bath. This method is very useful where safety is more concern. Reaction time is less and high yields are the main advantages. Since most of the compounds data was recorded as its HCl salt, so we also made HCl salt of all compounds and analyzed for comparison of the data.

Acknowledgements
The authors would like to thank the Management, K L University for providing facilities required to carry out this work.

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