Alumina sulfuric acid as a novel heterogeneous system for esterification of carboxylic acids in solvent free conditions

Hashem Sharghi*, Mona Hosseini Sarvari* and Razieh Eskandari

Department of Chemistry, College of Science, Shiraz University, Shiraz 71454, Iran

Neat chlorosulfonic acid reacts with alumina to give alumina sulfuric acid (ASA) in which sulfuric acid is immobilised on the surface of alumina via a covalent bond. Carboxylic acids can be readily converted to their corresponding esters with a combination of ASA and alcohols in solvent free conditions.

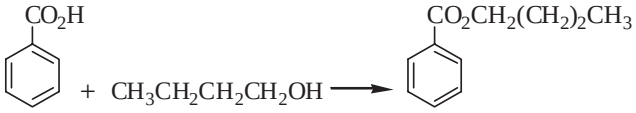
Keywords: alumina sulfuric acid, carboxylic acids, esterification

Esters are common intermediates in natural product chemistry due to their stability and accessibility for easy interconversion.[1] It has long been known that the process of esterification may be speeded up by the addition of a strong acid, such as sulfuric acid. The classical methods for the synthesis of esters are not suitable for acid sensitive compounds and have the disadvantages of the corrosiveness of strong acid and accompanying side reactions such as carbonisation, oxidation, *etc*. A large number of useful and reliable esterification methods catalysed by a variety of acids, ion exchange resin, zeolites, solid acid catalysts, *etc*., have been reported.[2-12] However, some of the reported methods are associated with certain drawbacks such as harsh reaction conditions, tedious experimental procedures, long reaction times, poor yields, complex side reactions and narrow range of applicability. Therefore, there still exists a need for novel and facile methods for efficient esterification reaction. In view of the rapidly increasing demands of green and sustainable chemistry, the practical esterification should be improved at best to meet the following requirements: (1) the carboxylic acid and alcohol reactant to be mixed in the ratio of 1:1; (2) no need of special technology to remove the liberated water; (3) easy separation of the catalyst; and (4) mild reaction conditions.[13] In addition, there is current research and general interest in heterogeneous systems because of the importance such systems have in industry and in developing technologies.[14] Therefore in continuation of our studies on the development of novel synthetic methodologies in solvent free conditions,[15] we have found that alumina reacts with chlorosulfonic acid to give alumina sulfuric acid **(I)** (ASA). It is interesting that the reaction is easy and clean without any workup procedure because HCl gas is evolved from the reaction vessel immediately (Scheme 1).

We hope that alumina sulfuric acid **(I)** would be a superior proton source to all of the reported acidic solid supports or acidic resins such as polystyrene sulfuric acid and Nafion-H[16] for running reactions under heterogeneous conditions. Therefore we were interested in using this inorganic acidic resin **(I)** for esterification reactions under simple and heterogeneous conditions without recourse to any technique to remove the formed water (Scheme 2).

To establish simple and suitable conditions for esterification reactions, the reaction of benzoic acid (**1a**) with *n*-butanol (**2a**) was chosen as a model, and its behaviour was studied under a variety of conditions via TLC and ^{1}H NMR spectroscopy (Table 1).

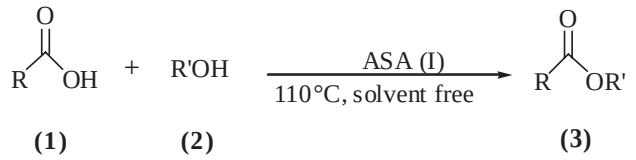
Table 1 Esterification of benzoic acid (**1a**) (1 mmol) with *n*-butanol (**2a**) (2 mmol) under various reaction conditions



1a **2** **3a**

Entry	Condition	Time/h	Yield/%[a]
1	$AlCl_3$-NaI/CH_3CN/reflux	2	71[17]
2	Al_2O_3/110°C	12	No reaction
3	ASA(0.1 g)/80°C	5	23
4	ASA(0.1 g)/110°C	3.5	40
5	ASA(0.2 g)/80°C	2.5	88
6	ASA(0.2 g)/110°C	1.5	95
7	ASA(0.2 g)/110°C/CH_2Cl_2	8	Trace
8	No catalyst	12	No reaction

[a]Yields refer to isolated products.



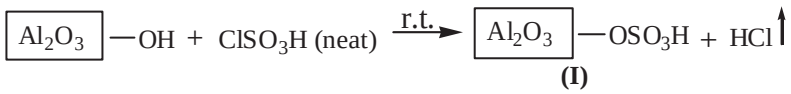
(1) **(2)** **(3)**

Scheme 2

According to Table 1, the best results were obtained using 0.2 g of ASA, when carried out at 110°C for 1.5 h (entry 6). The result also shows the importance of using ASA. In the absence of ASA (entry 8), the attempted esterification reaction did not afford the corresponding product.

In a typical reaction, alcohol was added to a mixture of ASA and carboxylic acid and mixed uniformly with shaking. The reaction mixture was kept at 110°C in an oil bath with occasional shaking for certain period of time until the reaction was completed. The product was isolated by simple extraction of the solid by ethyl acetate followed by usual work up. Several structurally varied aromatic and aliphatic carboxylic acids underwent esterification with a wide range of alcohols. The results are presented in Table 2.

According to Table 2, aromatic carboxylic acids that were substituted by an electron donating group, *e.g.*, *p*-methylbenzoic acid (entry 3), gave similar yields to those that



(I)

Scheme 1

* Correspondent. E-mail: shashem@susc.ac.ir; hossaini@susc.ac.ir

Table 2 Esterification of carboxylic acids with alcohols using ASA

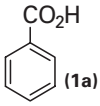
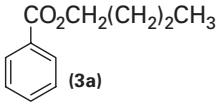
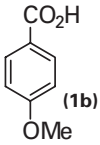
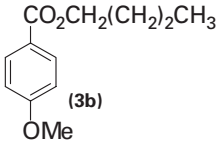
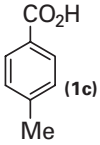
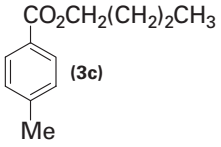
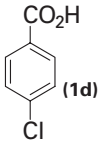
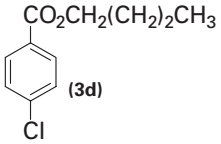
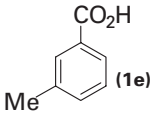
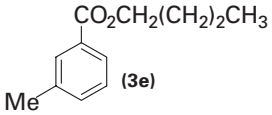
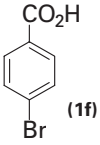
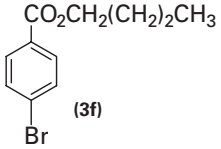
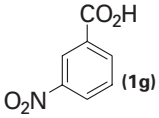
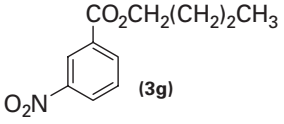
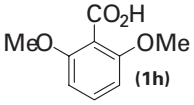
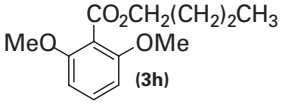
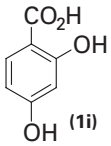
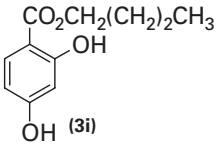
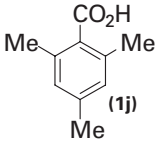
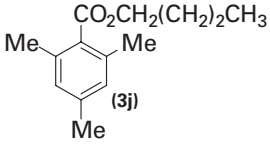
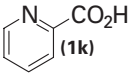
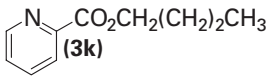
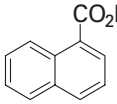
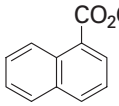
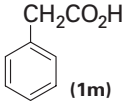
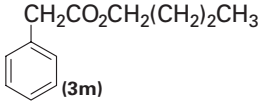
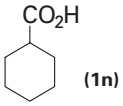
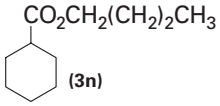
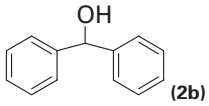
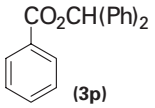
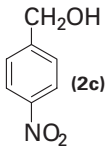
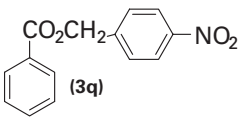
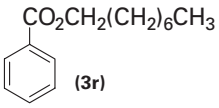
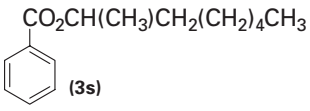
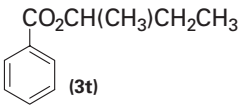
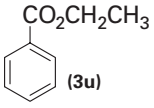
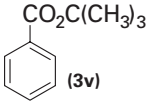
Entry	Acids **1a–o**	Alcohol **2a–h**	Product[a]	Time/h	Yield/%[b]
1	 **(1a)**	$CH_3CH_2CH_2CH_2OH$ **(2a)**	 **(3a)**	1.5	95
2	 **(1b)**	**(2a)**	 **(3b)**	1.5	73
3	 **(1c)**	**(2a)**	 **(3c)**	1.45	80
4	 **(1d)**	**(2a)**	 **(3d)**	3.5	83
5	 **(1e)**	**(2a)**	 **(3e)**	2	76
6	 **(1f)**	**(2a)**	 **(3f)**	2.5	63
7	 **(1g)**	**(2a)**	 **(3g)**	3	92
8	 **(1h)**	**(2a)**	 **(3h)**	4	67
9	 **(1i)**	**(2a)**	 **(3i)**	3	90
10	 **(1j)**	**(2a)**	 **(3j)**	5	53
11	 **(1k)**	**(2a)**	 **(3k)**	2	74

Table 2 *continued*

Entry	Acids1 **a–o**	Alcohol **2a–h**	Product[a]	Time/h	Yield/%[b]
12	 **(1l)**	**(2a)**	 **(3l)**	1.45	96
13	 **(1m)**	**(2a)**	 **(3m)**	1.45	95
14	 **(1n)**	**(2a)**	 **(3n)**	1.5	95
15	$CH_3(CH_2)_{16}CO_2H$ **(1o)**	**(2a)**	$CH_3(CH_2)_{16}CO_2CH_2(CH_2)_2CH_3$ **(3o)**	1.5	95
16	**(1a)**	 **(2b)**	 **(3p)**	4	90
17	**(1a)**	 **(2c)**	 **(3q)**	5	31
18	**(1a)**	$CH_3(CH_2)_6CH_2OH$ **(2d)**	 **(3r)**	3.5	81
19	**(1a)**	$CH_3(CH_2)_5CH(OH)CH_3$ **(2e)**	 **(3s)**	5	15[c]
20	**(1a)**	$CH_3CH_2CH(OH)CH_3$ **(2f)**	 **(3t)**	5	36
21	**(1a)**	CH_3CH_2OH **(2g)**	 **(3u)**	2	54[c,d]
22	**(1a)**	$(CH_3)_3COH$ **(2h)**	 **(3v)**	10	10[c,e]

[a]Products were characterised by their IR and NMR spectra. [b]Yields refer to isolated products. [c]The reaction was carried out at reflux condition. [d]Ethanol with benzoic acid was reacted in 5:1 molar ratio. [e]*t*-Butanol with benzoic acid was reacted in 40:1 molar ratio.

possessed electron-attracting groups, *e.g.*, *m*-nitrobenzoic acid (entry 7). When 2,6-dimethoxybenzoic acid (entry 8), was subjected to the present method, estrification took place smoothly in good yield. However, 2,4,6-trimethylbenzoic acid has increased steric hindrance toward esterification and the amount of product was decreased in carrying out the reaction (entry 10). This procedure is also good enough for the acylation of heterocyclic compounds (entry 11). Finally, the esterification reaction proceed smoothly with primary, secondary and tertiary aliphatic alcohols with the reactivity of the alcohols decreasing in the order primary>secondary> tertiary. The yields of the products also showed a trend in the same order as that of the reactivity.

In conclusion, alumina sulfuric acid (ASA) is a good proton source in terms of convenience, cheapness, easy production, and insolubility to all organic solvents. Practical and efficient esterification of carboxylic acids with alcohols were achieved by the present methodology. The cheapness and availability of the reagents, easy procedure and workup make this method attractive.

Experimental

Starting materials were obtained from Fluka company. IR spectra recorded on Perkin Elmer spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance DPX FT 250 and 62.9 MHz instrument, in $CDCl_3$.

Preparation of silica-sulfuric acid: A 500 ml suction flask was used. It was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (14 ml, 210 mmol) and a gas inlet tube for conducting HCl gas over adsorbing solution *e.g.* water. Into it was charged alumina (51 g, 510 mmol). Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After the addition was complete the mixture was shaken for 1 h. A white solid (ASA) of 67.0 g was obtained.

Esterification of carboxylic acids: Alcohol (2 mmol) was added to stirred mixture of ASA (0.2 g, 0.6 mmol) and appropriate carboxylic acid (1 mmol). The reaction mixture was heated in an oil bath at 110°C with occasional shaking for a certain period of time (Table 2) as required to complete the reaction (monitored by TLC). The reaction mixture was poured into water and extracted two times with EtOAc (25 ml), the organic layer was washed with saturated solution of sodium bicarbonate (30 ml) and dried over Na_2SO_4 and evaporated in a vacuum to give a residue, which was almost pure ester product. The crude product was isolated in a pure state by silica gel column chromatography.

Benzhydryl benzoate (**3p**): IR (KBr): 3055, 1712, 1600, 1450, 1110. ^{1}H NMR (250MHz, $CDCl_3$): δ = 5.26 (1H, s), 6–7.98 (13H, m), 8.39 (2H, d). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 77.85, 128.79, 128.86, 129.07, 129.02, 130.37, 130.53, 133.76, 140.96, 166.09.

4-Nitro benzyl benzoate (**3q**): IR (KBr): 3116, 2931, 1731, 1600, 1446, 1110. ^{1}H NMR (250MHz, $CDCl_3$): δ = 5.38 (2H, s), 7.35–7.51 (5H, m), 7.99 (2H, d), 8.1(2H, d). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 65.57, 124.26, 128.72, 128.96, 129.86, 130.13, 133.87, 143.76, 166.49.

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