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An Efficient Procedure for Esterification of certain Aromatic Acids and its Synthetic Utilities

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ABSTRACT: The esterification of aromatic acids can be promoted by mineral acid (H_2SO_4) under standard conditions. The desired product was separated by simple extraction method. Here we have used ethyl acetate as extracting solvent for the product and water (equimolar quantity). As these esters is the important and initial step for the synthesis benzoflavone (7, 8). So, in this work we have studied the first step for flavone synthesis. And synthesized couple of derivatives with different substituents of aromatic acids and it may lead to the further synthetic route for the formation different moieties of benzoflavones rings having promising biological activities and the structural analysis of these derivatives was confirmed by ^{1}H NMR, ^{13}CNMR and GCMS analysis.

Keywords: Esterification, acetylation, mineral acid, extraction method, aromatic acids.

INTRODUCTION

A Well-known process, esterification of aromatic carboxylic acids with alcohols in the presence of mineral acids as a catalyst has been the subject of studied by many researchers (Gui *et al*., 2004; Bharadwaj *et al.*, 2009; Haslam, 1980). These esterified products are used in the formation foods preservatives, (Otera and Nishikido 2009) synthesis of drug moiety, conserving solvents, additives in perfumes, plasticizers, pharmaceuticals and cosmetics products as aromatic esters (Cebrián-García *et al.*, 2018; Maki *et al.*, 2005) are active compounds for that synthetic route many research workers have been synthesized different catalyst (Mäki-Arvela *et al.*,1999; Larock *et al.*, 1989). Which is homogeneous and heterogeneous catalyst. Although the mineral acids such as hydrochloric acid (HCl) orthophosphoric acid (Dijs *et al*., 2002; Fiorio *et al*., 2019; Corma *et al.*, 1989) and Sulphuric acid (H_2SO_4) can be given as the instance of the homogenous catalysts, and also mixed oxide like ZnO and TiO_2 transition metal-based oxides as heterogeneous catalyst (Ram and Charles1997; Manabe *et al.*, 2001) in the acid form, can assist as a heterogeneous catalyst (Lahousse *et al*., 1993; Won *et al*., 2007). So, many of the research workers, have synthesized esters (Jia *et al*., 2018), but in this protocol our protocol is to express the synthetic rout for the synthesis benzoflavones (7,8). For that synthesis required aromatic esters. So as per green synthetic rout we have explore mineral acids for the synthesis of esters. So as a important intermediate for the synthesis of flavones purpose.

As per previous literature (Dupont, 2011; Park and Kazlauskas 2001) many of these researchers worked on the esterification of fatty acids (Raut and Bhagat 2022; Fang *et al.*, 2006; Peng *et al.*, 2010) by exploring ionic liquid-based catalyst and also synthesizing fuel additives by using ionic liquid based recoverable heterogeneous photocatalyst (Turhanen *et al.*, 2019; Raut and Bhagat 2021).

In present work, we have stimulated by these results, and as an allowance of our previous works (Won *et al*.,2007; Ju-Eun *et al*., 2007; Behloul *et al.*, 2006), this research articles existing a extremely competent method for the synthesis of aromatic esters by the esterification of aromatic acid (Ghodke *et al*., 2022) with Phenols and Naphthol's using mineral acid (few drops of H_2SO_4) under mild reaction conditions (Moore *et al.*, 2016). The product separation was done by extraction method, as extracting solvent is ethyl acetate and water. As the excess mineral acid were removed while extraction with extracting solvent (ethyl acetate) and water.

So, as per the green approach for the synthesis of aromatic esters with the utilization of mineral acid (can be easily removed by extraction method). In this work, we have explored the green approach for the synthesis of aromatic esters.

MATERIAL AND METHODS

Benzoic acid (99.5 %), 2-methyl benzoic acid (99.9%), 4-methyl benzoic acid (98%), Chlorobenzoic acid (97%), bromobenzoic acid (98%), iodobenzoic acid (97%), 2-nitrobenzoic acid (99.9%), 4-nitro benzoic acid, 2-Methoxy benzoic acid (97%) and 4-methoxy benzoic acid (98%) were purchased from SD Fine-Chem Ltd. Methanol (98%), Acetonitrile (99%) and

ethyl acetate (98%) were procured from Avra chemical Pvt. Ltd. Acetic acid, zinc chloride Were acquired from Sisco Research Laboratories Pvt. Ltd.

CHARACTERIZATION TECHNIQUE

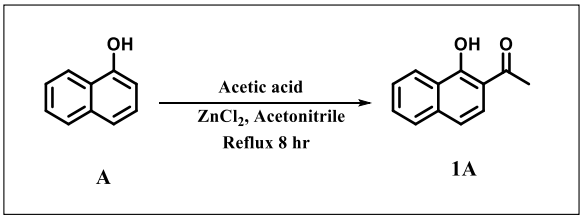
The Chemical structure of synthesized compounds was confirmed by spectral data. ^{1}H-NMR spectra were recorded on BRUKER AVANCE NEO 500 MHz spectrometer using DMSO and $CDCl_3$ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatograph.

STEPWISE SYNTHESIS

A) Acetylation of Naphthol
B) Esterification of aromatic acids

A) Acetylation of Naphthol

The synthesis (1A) compound acquired by adapting the protocol from the literature (Zhou and Chen 2018). To a 50 mL round bottom flask a mixture of hot glacial acetic acid (17 mmol) and fused Zinc chloride ($ZnCl_2$) was added and reflux it till dissolve the 1mmol of compound (A) was added and refluxed for 8 h (Park and Kazlauskas 2001). Then after completion of reaction, the reaction mixture was cooled and poured in ice acidulated water. The solid part of reaction mixture was filtered and washed with distilled water and recrystallized by aq. Ethanol.



Scheme 1. Synthesis of compound 1A.

Confirmation of 1A compound was characterized by ^{1}H NMR, ^{13}C NMR and GCMS.

^{1}HNMR(500MHz,$CDCl_3$):δ11.3(s,1H),8.33(d,1H),8.07(d,1H),7.8(d,1H),7.69(q,2H),7.64(d,1H),2.62(s,3H)^{13}CNMR(100MHz,$CDCl_3$):202.6,163.0,133.4,129.1,127.5,127.5,125.3,124.4,121.2,122.9,26.6 GCMS: Cal.m/z: 186.07 Found m/z: 187.01

Plausible mechanism of acetylation of naphthol. The stepwise mechanism of acetylation of naphthol from the literature (Larock *et al.*, 1989).

i) In step first, Lewis's acid zinc chloride approaches towards the -OH functional group of naphthol. Similarly, the acetic acid also comes in interaction with $ZnCl_2$. Via Chelation effect (Behlou *et al.*, 2006).

ii) Due to chelation, the electrophilic character of carbonyl carbon of acetic acid enhances.

iii) In step second, the nucleophilic attack of pi-bond on the carbonyl carbon of acetic acid to formed the unstable tetrahedral intermediate.

iv) In last step, the rearrangement of unstable tetrahedral intermediate via removal of water molecule and restoration of aromaticity to get the desired product.

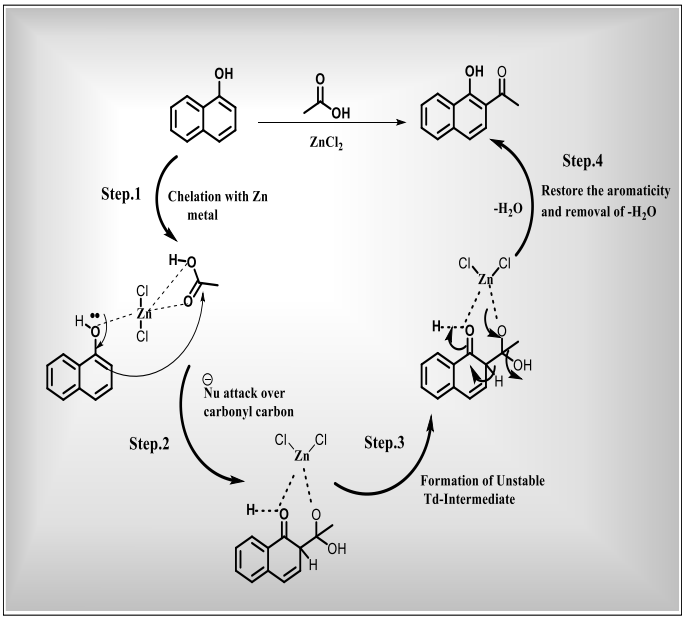
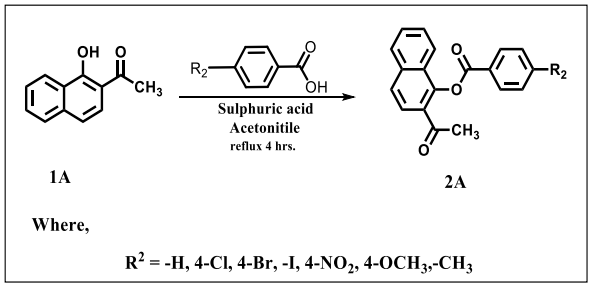


Fig. 1. Plausible mechanism of acetylation of naphthol.

B) Esterification of compound 1A with different aromatic acids

The synthesis of esterified products was achieved from following literature (Hoydonckx *et al.*, 2004; Rajabi *et al.*, 2015). To a 50 mL round bottom flask stoichiometric amount of compound 1A (10 mmol) and substituted aromatic acid (10 mmol) was dissolved in acetonitrile and refluxed for 30 min till it dissolve. Then few drops of H_2SO_4 was added to RBF and kept it for 4 h. after completion of reaction, the reaction mixture was filtrate and taken in separating funnel and desired product extracted by evaporation of ethyl acetate. Which was confirmed ^{1}H NMR ^{13}C NMR and GCMS.



Scheme 2. Esterification of aromatic acids.

Plausible mechanism of esterification of aromatic acids. The stepwise plausible mechanism of esterification of aromatic acid with naphthol is as follows from the literature (Fiorio *et al*., 2019).

Step 1. Protonation: The donation of proton from mineral acid to carbonyl oxygen of aromatic acid. Via protonation the electrophilic nature of aromatic acid enhances. This protonated from of aromatic acid can resonate in other canonical forms which can act as a electrophile.

Step 2. Nucleophilic attack: The loan pair present over the oxygen of naphthol attack over the carbonyl carbon of protonated aromatic acid. And generation of unstable tetrahedral intermediate.

Step 3. Rearrangement of tetrahedral intermediate: As the generation of tetrahedral intermediate (unstable di-hydroxy compound) in previous step. Which is highly unstable and highly energetic is susceptible to become stable via eliminating the water molecule.

Step 4. Deprotonation: The generation intermediate in step 3. Which undergoes deprotonation to from the desired product.

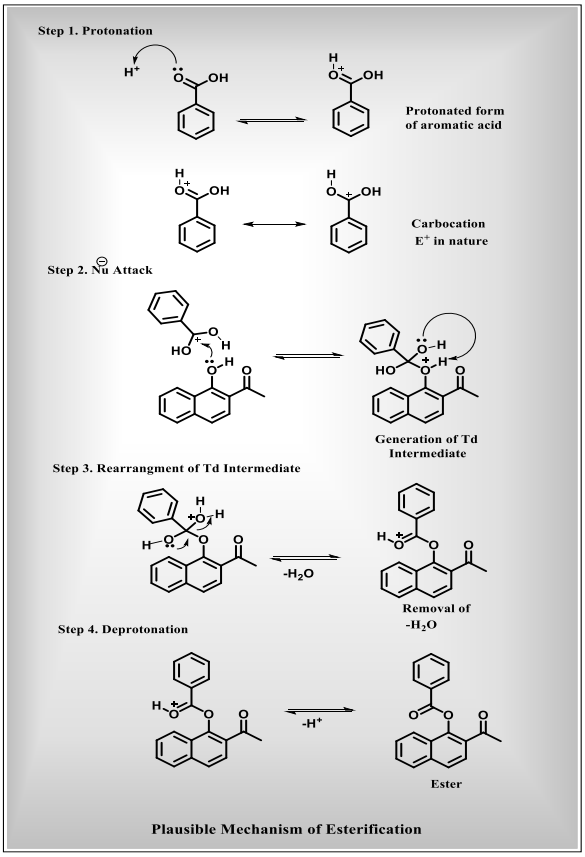


Fig. 2. Plausible mechanism of esterification of aromatic acids.

Confirmation of compounds by ^{1}H NMR ,^{13}CNMR and GCMS

1) 2-acetylnaphthalen-1-yl benzoate (2a)

^{1}HNMR(500MHz,$CDCl_3$):δ8.4(d,1H),8.16(d,2H),8.10(d,1H),7.627.64(m,3H),7.69,7.72(m,2H),7.787.82(m,2H),2.62(s,3H).^{13}CNMR(100MHz,$CDCl_3$):202.6,165.2,158.9,133.9,130.3,128.,127.5,124.9,121.2,121.8,119.9,26.3 GCMS: Cal m/z: 290.09, Found m/z : 291.0

2) 2-acetylnaphthalen-1-yl 4-chlorobenzoate (2b)

^{1}HNMR(500MHz,$CDCl_3$):δ8.42(d,1H),8.10(d,1H),8.03(d,2H),7.82(d,1H),7.78(d,1H),7.69(m,1H),7.64(d,1H),7.62(d,2H),2.62(s,3H).GCMS:Cal.m/z:324.06,Found m/z: 323.09

3) 2-acetylnaphthalen-1-yl 4-bromobenzoate (2c)

^{1}HNMR(500MHz,$CDCl_3$):δ8.4(d,1H),8.10(d,1H),7.86(d,2H),7.82(d,1H),7.78(d,1H),7.7(d,2H),7.69(d,1H),7.64(d,1H),2.62(s,3H) GCMS: Cal.m/z: 368.01 Found m/z: 367.09

4) 2-acetylnaphthalen-1-yl 4-iodobenzoate (2d)

^{1}HNMR(500MHz,$CDCl_3$):δ8.423(d,1H),8.10(d,1H),7.92(d,2H),7.95(d,2H),7.82(d,1H),7.78(d,1H),7.69(d,1H),7.64 (d,1H),2.6(s,3H) GCMS: Cal.m/z: 415.09 Found m/z: 414.19

5) 2-acetylnaphthalen-1-yl 4-nitrobenzoate (2e)

^{1}HNMR(500MHz,$CDCl_3$):δ8.42(d,2H),8.38(d,2H),8.10(d,1H),7.82(d,1H),7.78(m,1H),7.69(m,1H),7.64(d,1H), 2.62 (s,3H). GCMS: Cal.m/z:355.08, Found m/z: 354.11

6) 2-acetylnaphthalen-1-yl 3-nitrobenzoate (2f)

^{1}HNMR(500MHz,$CDCl_3$):δ8.71(s,1H),8.55(d,1H),8.45(d,1H),8.42(d,1H),8.10(d,1H),7.82(d,1H),7.78(m,1H),7.69(m,1H),7.64(d,1H),2.61(s,3H)GCMS:Cal.m/z: 355.08, Found m/z: 355.10

7) 2-acetylnaphthalen-1-yl 2-methoxybenzoate (2g)

^{1}HNMR(500MHz,$CDCl_3$):δ8.40(d,1H),8.25(d,1H),8.10(1H),7.82(d,1H),7.78(t,1H),7.69(t,1H),7.64(d,1H),7.60(d,1H),7.57(d,1H),7.22(d,1H),3.90(s,3H),2.6(s,3H)^{13}CNMR(100MHz,$CDCl_3$):202.6,169.1,158.9,134.9,133.4,131.3,129.1,127.5,127.3,124.9,121.8,114.2,55.8,26.3.GCMS:Cal.m/z: 320.10, Found m/z: 319.01

8) 2-acetylnaphthalen-1-yl 4-methoxybenzoate (2h)

^{1}HNMR(500MHz,$CDCl_3$):δ8.4(d,1H),8.11(d,1H), 8.13(d,2H),7.82(d,1H),7.78(d,1H),7.69(t,1H),7.64(d,1H),6.89(d,2H),3.81(s,3H),2.62(s,3H).GCMS:Cal.m/z: 320.10, Found m/z: 321.01

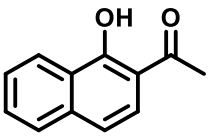
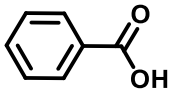
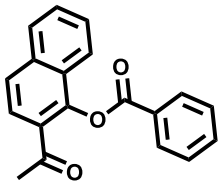
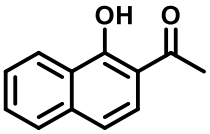
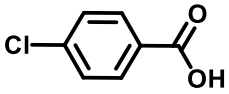
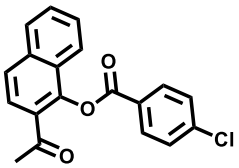
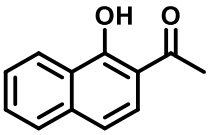
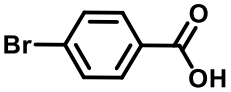
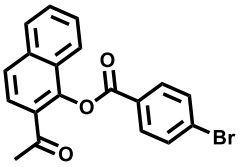
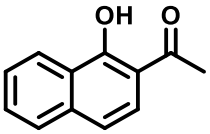
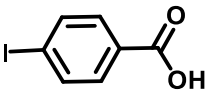
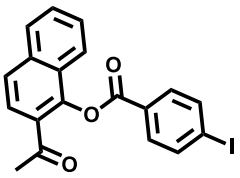
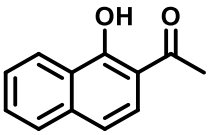
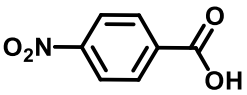
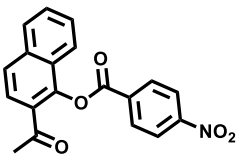
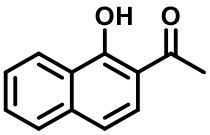
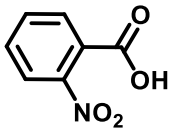
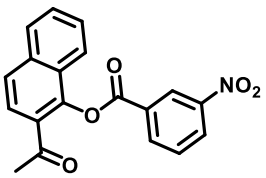
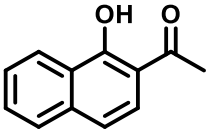
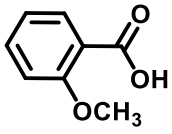
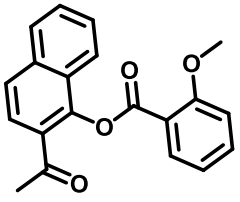
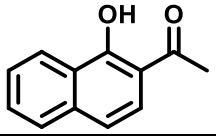
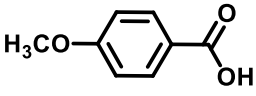
9) 2-acetylnaphthalen-1-yl 4-methyl benzoate (2i)

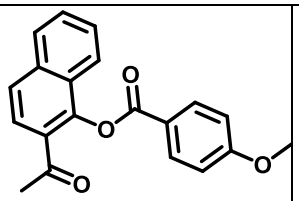
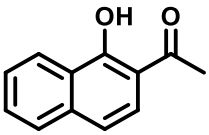
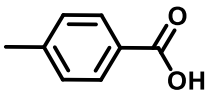
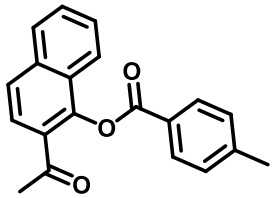
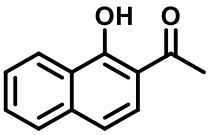
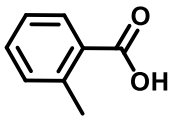
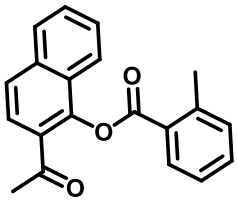
^{1}HNMR(500MHz,$CDCl_3$):δ8.40(d,1H),8.06(d,1H),7.82(d,1H),7.78(d,1H),7.69(d,1H),7.64(d,1H),7.42(d,2H),2.61(s,3H),2.42(s,3H)^{13}CNMR(100MHz,$CDCl_3$):202.6,165.2,158.9,143.6,133.4,128.9,129.1,127.5,127.3,124.9,121.9,120.3,120.3,26.3,21.3GCMS:Cal.m/z: 304.11, Found m/z: 303.01

10) 2-acetylnaphthalen-1-yl 2-methyl benzoate (2j)

^{1}HNMR(500MHz,$CDCl_3$):δ8.39(d,1H),8.0(d,1H),7.82(d,1H),7.78(d,1H),7.69(t,1H),7.64(d,1H),7.32(t,1H),7.20(d,2H),2.62(s,3H),2.53(s,3H).GCMS:Cal.m/z: 304.11, Found m/z: 304.31

Table 1: Scope of compound 1A.

Sr. No.	1A	Aromatic acid	Product	Time (h)	Yield %
1.			 (2a)	4	73
2.			 (2b)	4	82
3.			 (2c)	4	79
4.			 (2d)	4	77
5.			 (2e)	4	84
6.			 (2f)	4	81
7.			 (2g)	4	71
8.				4	73

			 **(2h)**		
9.			 **(2i)**	4	80
10.			 **(2j)**	4	78

CONCLUSIONS

The esterification of different aromatic acids has been carried out with mineral acids (Few drops of H_2SO_4) as a catalyst. To know the role of different substituents on the aromatic ring. We have synthesized the couple of derivatives. In synthetic route the separation of product was done by simple extraction method with two solvent and brine solutions. Here we have used ethyl acetate (Ester extracting solvent) and water to remove the excess mineral acid. This esterification reaction is a promising and efficient protocol to synthesize several novel esters of substituted aromatic carboxylic acids with different phenols and naphthol's.

FUTURE SCOPE

On the basis of previous literature, esterification is the important process for the synthesis of basic intermediates.

So, in future, we can synthesize the naphthoflavone followed by Baker Venkataraman rearrangement (these intermediates) will be utilized for the synthesis of naphthoflavones.

From further naphthoflavone, we can synthesize pyrazoles, pyrazolines and benzoflavones (7,8) which will be biological active moiety.

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Conflict of Interest. None.

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